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В учебном пособии представлены этиология, патогенез, современные классификации, диагностика и лечение заболеваний сердечно-сосудистой системы, суставов, диффузных заболеваний соединительной ткани, заболеваний крови.

Материал подготовлен в соответствии с типовой программой для высших учебных заведений по специальности «Лечебное дело»

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THE LIST OF ABBREVIATIONS

ACE inhibitor — angiotensin-converting enzyme inhibitor
ACPA — anti-citrullinated protein antibody
ACR — American College of Rheumatology
AECA — anti-endothelial cell antibody
AIHA — autoimmune haemolytic anaemia
ALL — acute lymphoblastic leukemia
ALT — alanine aminotransferase
AML — acute myeloid leukemia
ANA — antinuclear antibody
ANCA — antineutrophil cytoplasmic antibodies
APS — antiphospholipid syndrome
AST — aspartate aminotransferase
BM — bone marrow
BMI — body mass index
BMT — bone marrow transplantation
CBC — complete blood (cell) count
CHCC — Chapel Hill Consensus Conference
CHF — congestive heart failure
CK — creatinine kinase
CK-MB — creatinine kinase-MB isoenzyme
CT — computed tomography
CTD — connective tissue disease
CTGF — connective tissue growth factor
DAT — direct antiglobulin test
DCM — dilated cardiomyopathy
DIC — disseminated intravascular coagulation
DM/PM — dermatomyositis/polymyositis
DMARD — disease modifying anti-rheumatic agents
EBV — Epstein-Barr virus
ECG — electrocardiography
ELISA — enzyme-linked immunosorbent assays
ESR — erythrocyte sedimentation rate
ET — endothelin
EULAR — European League Against Rheumatism
FDA — Food and Drug Administration
G6PD — glucose-6-phosphate dehydrogenase
GCA — giant cell arteritis
GFR — glomerular filtration rate
GI — gastrointestinal
GM-CSF — granulocyte-macrophage colony-stimulating factor

Hb — haemoglobin
HCM — hypertrophic cardiomyopathy
HCV — hepatitis C virus
HF — heart failure
HIV — human immunodeficencies virus
HLA — human leukocyte antigen
HSP — Henoch Schonlein purpura
HUS — hemolytic uremic syndrome
IC — immune complex
ICD — implantable cardioverter defibrillator
IDA — iron deficiency anaemia
Ig G — immunoglobulin G
IgM — immunoglobulin M
IV — intravenous
LcV — leukocytoclastic vasculitis
LDH — lactic dehydrogenase
LV — left ventrical
LVEF — left ventricular ejection fraction
MCV — mean cell volume
MPA — microscopic polyangiitis
MRI — magnetic resonance imaging
NF-κB — nuclear factor κB
NSAID — non-steroidal anti-inflammatory drugs
PAN — panarteritis nodosa
PB — peripheral blood
PBC — primary biliary cirrhosis
PCR — polymerase chain reaction
PDGF — platelet derived growth factor
PET — positron emission tomography
PMR — polymyalgia rheumatica
PNH — paroxysmal nocturnal hemoglobinuria
RA — rheumatoid arthritis
RBCs — red blood cells
RCM — restrictive cardiomyopathies
RF — rheumatoid factor
RV — right ventricular
SCD — sudden cardiac death
SLE — systemic lupus erythematosus
SSc — systemic sclerosis
TA — Takayasu arteritis
TGF-β — transforming growth factor β
TNF-α — tumor necrosis factor α
TTP — thrombotic thrombocytopenic purpura

CARDIOMYOPATHY. MYOCARDITIS

CARDIOMYOPATHY

Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and functionally abnormal, and in which coronary artery disease, hypertension, valvular and congenital heart disease are absent or do not sufficiently explain the observed myocardial abnormality (European Society of Cardiology, 2008).

Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability. Cardiomyopathies usually are associated with failure of myocardial performance, which may be mechanical (e.g. diastolic or systolic dysfunction) or a primary electrical disease prone to life-threatening arrhythmias.

The first classifications of cardiomyopathies from 1980 and 1996 described them as heart muscle diseases, with dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and nonclassifiable cardiomyopathies. Furthermore, the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) classification from 1996 listed among the specific cardiomyopathies inflammatory cardiomyopathy as a new and distinct entity, which was defined histologically as myocarditis in association with cardiac dysfunction. Infectious and autoimmune forms of inflammatory cardiomyopathy were recognized. Viral cardiomyopathy was defined as viral persistence in a dilated heart without ongoing inflammation. If it was accompanied by myocardial inflammation, it was termed inflammatory viral cardiomyopathy (or viral myocarditis with cardiomegaly). This entity was further elucidated in a World Heart Federation consensus meeting in 1999 by quantitative immunohistological criteria (< 14 infiltrating cells/mm^2) and the etiology by molecular biological methods, e.g., polymerase chain reaction, as viral, bacterial, or autoimmune (nonmicrobial).

The development of molecular genetics, with the discovery of a genetic background in several forms of cardiomyopathies previously alluded to as «of unknown origin», was the origin of a debate on a new classification based on genomics. A genomic/postgenomic classification was postulated taking the underlying gene mutations and the cellular level of expression of encoded proteins into account, thus distinguishing cytoskeleton (cytoskeletalopathies, e.g., DCM or ARVC), sarcomeric (sarcomyopathies as in HCM and RCM) and ion channel (channelopathies, e.g., long or short QT syndrome and Brugada's syndrome) cardiomyopathies. Such a classification of cardiomyopathies was proposed in 2006 by the American Heart Association (AHA), which took the rapid evolution of molecular genetics in cardiology into account. It also introduced several recently

described diseases, and is unique in that it incorporated ion channelopathies even without hemodynamic dysfunction as a «primary» cardiomyopathy.

Two fundamental forms of cardiomyopathy are recognized:

1) a primary type, consisting of heart muscle disease predominantly involving the myocardium and/or of unknown cause;

2) a secondary type show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders (table 1).

In many cases it is not possible to arrive at a specific etiologic diagnosis, and thus it is often more desirable to classify the cardiomyopathies into one of three morphologic types (dilated, restrictive, and hypertrophic) on the basis of differences in their pathophysiology and clinical presentation. An important additional consideration is whether or not the particular cardiomyopathy in question (whether primary or secondary) has a genetic basis.

Table 1 — Etiologic classification of cardiomyopathies

Primary myocardial involvement:
• genetic; • mixed (genetic and nongenetic); • acquired
Secondary myocardial invovlement
Accumulation of abnormal substances between myocytes (ie, extracellular). †Genetic (familial) origin. ‡Accumulation of abnormal substances within myocytes (ie, intracellular). Infiltrative Amyloidosis (primary, familial autosomal dominant†, senile, secondary forms) Gaucher disease† Hurler's disease† Hunter's disease† Storage‡ Hemochromatosis Fabry's disease† Glycogen storage disease† (type II, Pompe) Niemann-Pick disease† Toxicity Drugs, heavy metals, chemical agents Endomyocardial Endomyocardial fibrosis Hypereosinophilic syndrome (Löeffler's endocarditis) Inflammatory (granulomatous) Sarcoidosis Endocrine Diabetes mellitus† Hyperthyroidism Hypothyroidism Hyperparathyroidism Pheochromocytoma Acromegaly

Cardiofacial
- Noonan syndrome†
- Lentiginosis†

Neuromuscular/neurological
- Friedreich's ataxia†
- Duchenne-Becker muscular dystrophy†
- Emery-Dreifuss muscular dystrophy†
- Myotonic dystrophy†
- Neurofibromatosis†
- Tuberous sclerosis†

Nutritional deficiencies
- Beriberi (thiamine), pallagra, scurvy, selenium, carnitine, kwashiorkor

Autoimmune/collagen
- Systemic lupus erythematosis
- Dermatomyositis
- Rheumatoid arthritis
- Scleroderma
- Polyarteritis nodosa

Electrolyte imbalance

Consequence of cancer therapy
- Anthracyclines: doxorubicin (adriamycin), daunorubicin
- Cyclophosphamide
- Radiation
- Metazoal myocarditis
- Spirochetal
- Rickettsial
- Metabolic
- Familial storage disease
- Glycogen storage disease
- Mucopolysaccharidoses
- Hemochromatosis
- Fabry's disease
- Deficiency
- Electrolytes
- Nutritional
- Connective tissue disorders
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Rheumatoid arthritis
- Progressive systemic sclerosis
- Dermatomyositis
- Infiltrations and granulomas
- Amyloidosis
- Sarcoidosis
- Malignancy
- Neuromuscular
- Muscular dystrophy
- Myotonic dystrophy
- Friedreich's ataxia
- Sensitivity and toxic reactions
- Alcohol
- Radiation
- Drugs
- Peripartum heart disease

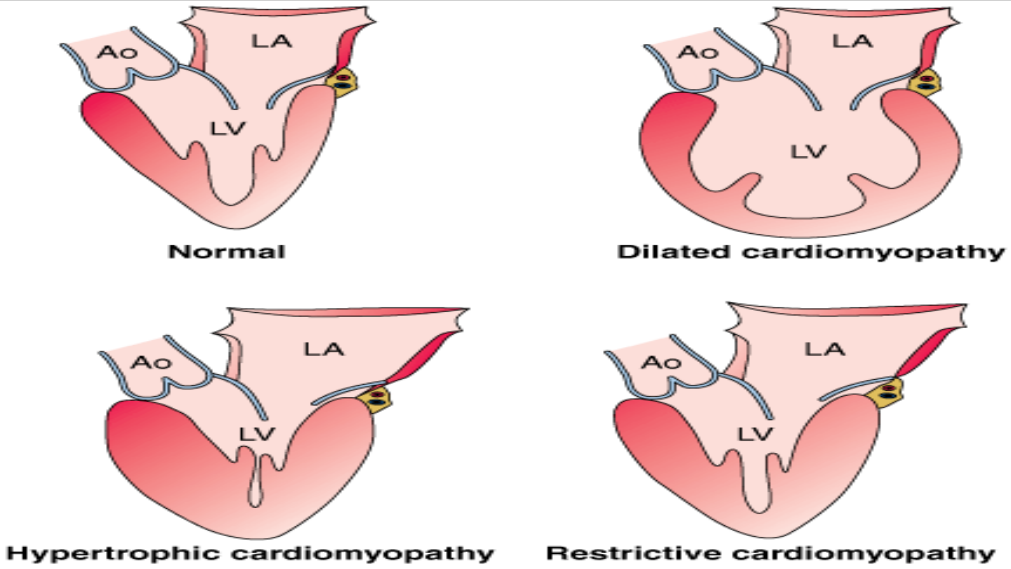


Figure 1 — The main types of cardiomyopaties:
A_o — aorta, LA — left atrium, LV — left ventricle

From: Harrison's Principles of Internal Medicine / A. C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

PRIMARY CARDIOMYOPATHIES

GENETIC

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a clinically heterogeneous but relatively common autosomal dominant genetic heart disease (1:500 of the general population for the disease phenotype recognized by echocardiography) that probably is the most frequently occurring cardiomyopathy.

Hypertrophic cardiomyopathy (HCM) is characterized by LV hypertrophy, typically of a nondilated chamber, without obvious cause, such as hypertension or aortic stenosis (figure 1).

The patients with outflow gradient have hypertrophic obstructive cardiomyopathy. The patients without outflow gradient have hypertrophic non-obstructive cardiomyopathy.

Two features of HCM have attracted the greatest attention: (1) asymmetric LV hypertrophy, often with preferential hypertrophy of the interventricular septum; and (2) a dynamic LV outflow tract pressure gradient, related to narrowing of the subaortic area. About one-third of patients with HCM demonstrate an outflow tract pressure gradient at rest and a similar fraction develop one with provocation. The ubiquitous pathophysiologic abnormality is diastolic dysfunction, which can be detected by Doppler tissue imaging and results in elevated LV end-diastolic pressures; the latter may be present despite a hyperdynamic, nondilated LV.

The pattern of hypertrophy is distinctive in HCM and usually differs from that seen in secondary hypertrophy (as in hypertension or aortic stenosis). Most patients have striking regional variations in the extent of hypertrophy in different portions of the left ventricle, and the majority demonstrate a ventricular septum whose thickness is disproportionately increased when compared with the free wall. Other patients may demonstrate symmetric hypertrophy, while others have mid-ventricular cavity obstruction or disproportionate involvement of the apex or LV free wall. In the disproportionately hypertrophied portions of the left ventricle, there is a bizarre and disorganized arrangement of myocytes, with disorganization of the myofibrillar architecture, along with a variable degree of myocardial fibrosis and thickening of the small intramural coronary arteries.

Hemodynamics

In contrast to the obstruction produced by a fixed narrowed orifice such as valvular aortic stenosis the pressure gradient in HCM, when present, is dynamic and may change between examinations and even from beat to beat. Obstruction appears to result from narrowing of the LV outflow tract by systolic anterior movement (SAM) of the mitral valve against the hypertrophied septum.

Three basic mechanisms are involved in the production and intensification of the dynamic intraventricular obstruction: (1) increased LV contractility, (2) decreased ventricular preload, and (3) decreased aortic impedance and pressure (afterload). Interventions that increase myocardial contractility such as exercise and sympathomimetic amines and those that reduce ventricular preload such as the strain phase of the Valsalva maneuver, sudden standing, or nitroglycerin, reduce LV end-diastolic volume and, thereby, may cause an increase in the gradient and the murmur. Conversely, elevation of arterial pressure by squatting, sustained handgrip, augmentation of venous return by passive leg raising, and expansion of the blood volume (as during pregnancy) all increase ventricular volume and ameliorate the gradient and murmur.

Genetic considerations

About half of all patients with HCM have a positive family history compatible with autosomal dominant transmission. More than 400 mutations of 11 different genes that encode sarcomeric proteins have been identified; these account for ~60 % of cases. The most common are mutations of the cardiac myosin heavy chain gene on chromosome 14. Others involve myosin heavy chains; cardiac troponins C, I, and T; cardiac myosin-binding protein C; actin; myosin light chains; and titin. Certain mutations are associated with more malignant prognoses. Many sporadic cases of HCM probably represent spontaneous mutations. Echocardiographic studies have confirmed that by the age of 20, when full expression has usually occurred, about one-half of the first-degree relatives of patients with familial HCM have evidence of the disease. However, in many of these relatives the extent of hypertrophy is mild, no outflow tract pressure gradient is present, and symptoms are not prominent. Since the hypertrophic characteristics may not be ap-

parent in childhood, a single normal echocardiogram in a child does not exclude the presence of the disease. Screening by echocardiography of first-degree relatives between the ages of 12 and 20 should be carried out every 12–24 months, unless the diagnosis is established or excluded by genetic testing.

Genetic testing

Although not yet routinely available, genetic testing may allow a definitive diagnosis of HCM with a genetic cause to be established by identifying a mutation in a gene encoding a sarcomeric protein. Genetic testing can identify family members who are at risk for developing HCM and who, therefore, require echocardiographic screening and follow-up. It can also exclude the disease in family members.

Clinical features

The clinical course of HCM is highly variable. Many patients are asymptomatic or mildly symptomatic and may be relatives of patients with known disease. Unfortunately, the first clinical manifestation may be sudden cardiac death (SCD), frequently occurring in children and young adults during or after physical exertion. Indeed, HCM is the most common cause of SCD in young competitive athletes. In symptomatic patients, the most common complaint is dyspnea, largely due to diastolic ventricular dysfunction, which impairs ventricular filling and leads to elevated LV diastolic, left atrial, and pulmonary capillary pressures. Other symptoms include syncope, angina pectoris, and fatigue. Symptoms are not closely related to the presence or severity of an outflow pressure gradient.

Physical examination

Most patients demonstrate a double or triple apical precordial impulse and a fourth heart sound. Those with intraventricular pressure gradients may have a rapidly rising arterial pulse. The hallmark of obstructive HCM is a systolic murmur, which is typically harsh, diamond-shaped, and usually begins well after the first heart sound. The murmur is best heard at the lower left sternal border as well as at the apex, where it is often more holosystolic and blowing in quality, no doubt due to the mitral regurgitation that usually accompanies obstructive HCM.

Laboratory and instrumental evaluation

The ECG commonly shows LV hypertrophy and widespread deep, broad Q waves. The latter suggest an old myocardial infarction but actually reflect severe septal hypertrophy. Many patients demonstrate arrhythmias, both atrial (supraventricular tachycardia or atrial fibrillation) and ventricular (ventricular tachycardia), during ambulatory (Holter) monitoring. Chest roentgenography may be normal, although a mild to moderate increase in the cardiac silhouette is common.

The ECG signs of hypertrophic cardiomyopathy:

• short PR interval;

• various rhythm disturbances, including ventricular tachycardia, ventricular fibrillation;

• left atrial hypertrophy;
• left anterior hemiblock or left bundle branch block;
• left ventricular hypertrophy;
• prolonged QT interval;
• deep T wave inversion anteriorly.

The mainstay of the diagnosis of HCM is the echocardiogram, which demonstrates LV hypertrophy, often with the septum 1.3 times the thickness of the posterior LV free wall. The septum may demonstrate an unusual «ground-glass» appearance, probably related to its myocardial fibrosis. SAM of the mitral valve, often accompanied by mitral regurgitation, is found in patients with pressure gradients. The LV cavity typically is small in HCM, with vigorous motion of the posterior wall but with reduced septal excursion. An uncommon form of cardiomyopathy characterized by apical hypertrophy is associated with giant negative T waves on the ECG and a «spade-shaped» LV cavity; it usually has a benign clinical course. CMRI is superior to echocardiography in providing accurate measurements of regional hypertrophy and in identifying sites of regional fibrosis.

Although cardiac catheterization is not required to diagnose HCM, the two typical hemodynamic features are an elevated LV diastolic pressure due to diminished compliance and, in some patients, a systolic pressure gradient, usually between the body of the left ventricle and the subaortic region. When a gradient is not present, it can be induced in some patients by provocative maneuvers, such as infusion of isoproterenol, inhalation of amyl nitrite, the Valsalva maneuver, or a premature ventricular contraction.

Hypertrophic cardiomyopathy: treatment

Since sudden cardiac death often occurs during or just after physical exertion, competitive sports and very strenuous activities should be prescribed.

• β-adrenergic blockers ameliorate angina pectoris and syncope in one-third to one-half of patients (table 2). Although resting intraventricular pressure gradients are usually unchanged, these drugs may limit the increase in the gradient that occurs during exercise. It does not appear that β-adrenergic blockers offer any protection against sudden cardiac death.

• Amiodarone appears to be effective in reducing the frequency of supraventricular as well as of life-threatening ventricular arrhythmias, and data suggest that it may reduce the risk of SCD.

• Nondihydropyridine calcium channel blockers (verapamil and diltiazem) may reduce the stiffness of the left ventricle, reduce the elevated diastolic pressures, increase exercise tolerance, and, in some instances, reduce the severity of outflow tract pressure gradients.

• Disopyramide has been used in some patients to reduce LV contractility and the outflow pressure gradient; it may reduce symptoms as well.

• Atrial fibrillation is poorly tolerated, and a strong effort should be made to restore and then maintain sinus rhythm. Slowing of the heart rate with a β-

adrenergic blocker or ablation of the AV node and insertion of a pacemaker may be indicated when sinus rhythm cannot be sustained.

- Surgical myotomy/myectomy of the hypertrophied septum usually abolishes intraventricular obstruction and provides lasting symptomatic improvement in about three-quarters of severely symptomatic patients with large pressure gradients who are unresponsive to medical management.
- The insertion of an ICD should be considered in patients with a high-risk profile for SCD.

Dehydration should be avoided, and diuretics used with caution.

Digitalis, diuretics, nitrates, dihydropyridine calcium blockers, vasodilators are best avoided, particularly in patients with known LV outflow tract pressure gradients. Alcohol ingestion may produce sufficient vasodilatation to exacerbate an outflow pressure gradient.

Infarction of the interventricular septum induced by ethanol injections into the septal artery (alcohol septal ablation) can also reduce obstruction and improve symptoms. However, it should be carried out only by experts.

Table 2 — Management of hypertrophic cardiomyopathy

Groups of the patients	**Methods of treatment (class of the drugs)**	**The drug**	**The dosage**
Without outflow gradient	β-adrenergic blockers	Carvedilol	The initial dose is 3.125 mg twice daily, then may be increased to 12.5 and 25 mg twice daily gradually
		Metoprolol	25–50 mg twice daily
		Bisoprolol	2.5–5 mg daily
	Nondihydropyridine calcium channel blockers	Verapamil	40–80 mg 3-times daily
		Diltiazem	60–90 mg 2–3-times daily
With outflow gradient	β-adrenergic blockers	See above	
	Antiarrhytmic drugs	Disopyramide	100 mg 3-times daily
		Amiodarone	200 mg 3-times daily for 1 week, then 200 mg 2-times daily for 1 week, then 200 mg daily (in symptomatic arrhythmias and for control of ventricular rate in atrial fibrillation)
With outflow gradient not responding to medical treatment	Dual chamber pacemaker		
	Septal ablation		
	Myotomy-myectomy		
	Implantable cardioverter-defibrillator		
	Mitral valve replacement		
	Heart transplantation		

Prognosis

The natural history of HCM is variable, although many patients never exhibit any clinical manifestations. Atrial fibrillation is common late in the course

of the disease; its onset often leads to the development of or an increase in symptoms. Infective endocarditis occurs in < 10 % of patients. However, endocarditis prophylaxis is currently recommended only in HCM patients with a prior episode of infective endocarditis. Progression of HCM to left ventricular dilatation and dysfunction (DCM) with wall thinning and disappearance of a preexisting outflow pressure gradient (so-called burnt out HCM) occurs in 5–10 % of patients and may be associated with nonresponsive CHF requiring cardiac transplantation.

The major cause of mortality in HCM is sudden cardiac death, which may occur in asymptomatic patients or interrupt an otherwise stable course in symptomatic ones. Patients at increased risk of SCD include those with a history of resuscitation, recurrent syncope, ventricular tachycardia on ambulatory monitoring or at electrophysiologic testing, marked ventricular hypertrophy (ventricular septal thickness > 30 mm), failure of blood pressure to rise during exercise, a family history of sudden cardiac death, and certain genetic mutations.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

ARVC/D is a familial cardiomyopathy characterized by progressive fibrofatty replacement of the right ventricle and, to a much lesser degree, of the LV myocardium. It is most commonly inherited in an autosomal dominant manner and is caused by multiple mutations of several genes encoding proteins that constitute desmosomes, structures that maintain normal contacts between cells. It has been suggested that abnormalities in the desmosomes cause detachment of myocytes with consequent myocyte apoptosis and fibrofatty replacement. Among the desmosomal protein genes, the most common gene mutation occurs in plakophilin-2 (PKP-2). Mutations in the cardiac ryanodine receptor gene (RyR2) and other genes have also been described.

On clinical examination, patients may manifest RV failure with jugular venous distention, hepatomegaly and edema. Clinical manifestations usually develop during the second decade and include ventricular tachyarrhythmias as well as varying degrees of RV failure; both of these complications may be fatal.

The ECG typically shows QRS prolongation localized to the right precordial leads and left bundle branch block-type ventricular tachycardia. CTI and CMRI typically show RV dilatation, RV aneurysm, and fatty replacement.

Restriction from competitive sports and antiarrhythmic therapy with beta blockers or amiodarone may be useful. Implantation of an ICD may be required. If RV failure becomes intractable, cardiac transplantation may be necessary.

MIXED (GENETIC AND NONGENETIC)

Dilated cardiomyopathy

About one in three cases of congestive heart failure is due to dilated cardiomyopathy (DCM). LV and/or right ventricular (RV) systolic pump function is impaired, leading to

progressive cardiac dilatation (remodeling). Symptoms of heart failure (HF) typically appear only after remodeling has been ongoing for some time (months or even years).

Although no cause is apparent in many cases, DCM is either familial or the end result of myocardial damage produced by a variety of known or unknown infectious, metabolic, or toxic agents. DCM may be the late consequence of acute viral myocarditis, possibly mediated in part through an immunologic mechanism. Although DCM may occur at any age, it most commonly becomes apparent clinically in the third or fourth decades. A reversible form of DCM may be found with alcohol abuse, pregnancy, thyroid disease, cocaine use, and chronic uncontrolled tachycardia.

Genetic considerations

One-fifth to one-third of patients have familial forms of DCM. Mutations in > 20 genes that are transmitted in an autosomal dominant fashion have been described. Most common are mutations in genes encoding sarcomeric proteins, such as cardiac actin, myosin, heavy chain tropomyosin and troponins T, I, and C. It is believed that the abnormal proteins cause contractile dysfunction by impairing the production and/or transmission of force.

Patients with genetic DCM may also exhibit skeletal myopathies, particularly Duchenne's and Emery-Dreyfuss muscular dystrophy. Mutations in the gene encoding the nuclear envelope protein lamin A/C are also inherited in an autosomal dominant manner; they are responsible for the development of DCM associated with atrioventricular (AV) conduction disorder and other electrophysiologic disturbances that may cause sudden cardiac death (SCD). An X-linked autosomal recessive disorder caused by the dystrophin gene occurs in young males and is associated with a rapid downhill course; mutations in mitochondrial genes have also been reported in DCM.

Clinical features

Symptoms of left- and right-sided CHF usually develop gradually. Some patients have LV dilatation for months or even years before becoming symptomatic. Although vague chest pain may be present, typical angina pectoris is unusual and suggests the presence of ischemic heart disease. Syncope due to arrhythmias and systemic embolism (often emanating from a ventricular thrombus) may occur.

Physical examination

Variable degrees of cardiac enlargement and findings of CHF are noted. In patients with advanced disease, the pulse pressure is narrow and the jugular venous pressure is elevated. Third and fourth heart sounds are common, and mitral or tricuspid regurgitation may occur.

Laboratory and instrumental examinations

The chest roentgenogram demonstrates enlargement of the cardiac silhouette due to LV dilatation, although generalized cardiomegaly is often seen.

The lung fields may demonstrate pulmonary vascular redistribution and interstitial or, in advanced cases, alveolar edema. The electrocardiogram (ECG) often shows sinus tachycardia or atrial fibrillation, ventricular arrhythmias, left atrial abnormality, low voltage, diffuse nonspecific ST-T-wave abnormalities, and sometimes intraventricular and/or AV conduction defects. Echocardiography, computed tomographic imaging (CTI), and cardiac magnetic resonance imaging (CMRI) show LV dilatation, with normal, minimally thickened, or thinned walls, and systolic dysfunction. Circulating levels of brain natriuretic peptide are usually elevated.

Cardiac catheterization and coronary angiography are often performed to exclude ischemic heart disease, and bedside hemodynamic monitoring may be helpful in the management of selected acutely decompensated patients. Angiography reveals a dilated, diffusely hypokinetic left ventricle, often with some degree of mitral regurgitation. Cardiac CTI may distinguish between DCM and proximal coronary artery disease and, thereby, reduce the need for invasive procedures. Transvenous endomyocardial biopsy is usually not necessary in idiopathic or familial DCM; however, it may be helpful in the recognition of secondary cardiomyopathies, such as amyloidosis and acute myocarditis (see below).

Dilated cardiomyopathy: treatment

- Standard therapy of heart failure is indicated (table 3).
- Patients should be considered for chronic anticoagulation because systemic embolization is a concern.
- Alcohol should be avoided because of its cardiotoxic effects, as should calcium channel blockers and nonsteroidal anti-inflammatory drugs.
- Antiarrhythmic agents are best avoided owing to the risk of proarrhythmia.
- Cardiac resynchronization therapy (biventrical pacing). Use of the resynchronization therapy should be considered in patients with HF in III–IV NYHA class with ejection fraction (EF) < 35 % and QRS duration of ≥ 120 ms.
- Insertion of an implantable cardioverter defibrillator (ICD) should be employed in DCM as in HF of other etiologies. The current guidelines recommend ICD implantation in selected symptomatic patients with left ventricular EF < 30–35 %, not earlier than 40 days after myocardial infarction, who receive optimal pharmacotherapy.
- Left ventricular assist devices (LVAD). These are pump like devices the blood and the pump with pressure working like venrtricles.
- In some patients revascularization procedures can be considered, which in order to be effective must be performed in patients with viable myocardium.
- In patients with advanced disease who are refractory to other therapies, cardiac transplantation should be considered.

Indications for the cardiac transplantation:

- end stage heart disease with a poor (6–12 months) prognosis refractory to the medical and surgical therapy;

- functional class of HF III or IV;
- age < 60 years;
- pulmonary vascular resistance < 3 RU;
- strong self-motivation.

Contrindications for the cardiac transplantation:

- malignancy;
- active infection;
- advanced insulin dependent diabetes;
- kidney and liver dysfunction;
- advanced peripheral vascular disease;
- active alcoholism.

Most patients pursue an inexorably downhill course, and the majority, particularly those > 55 years, die within 4 years of the onset of symptoms. Spontaneous improvement or stabilization occurs in about one-quarter of patients. Death is due to either progressive HF or ventricular tachy- or bradyarrhythmia; SCD is a constant threat.

Table 3 — Management of dilated cardiomyopathy

Class of the drug	**The drug**	**The dosage**
Diuretics	Furosemide (loop diuretic)	20–160 mg once daily
	Spironolactone (potassium sparing diuretic)	25–200 mg once daily
	Hydrochlorthiazide (thiazide diuretic)	25 mg once daily
Angiotensin converting enzyme (ACE) inhibitor	Captopril	12.5–25 mg 3-times daily
	Enalapril	2.5–5 mg 2-times daily
	Lisinopril	2.5–5 mg once daily
	Ramipril	1.2–2.5–5 mg 1–2-times daily
Angiotensin II receptor antagonists	Losartan	25–50 mg once daily
	Valsartan	80 mg once daily
Digitalis	Digoxin	0.125–0.25 mg once daily (only for the patients who remain symptomatic on diuretics and ACE inhibitors as well as for heart failure patients who require rate control in atrial fibrillation)
β-adrenergic blockers	See in table 2	
Antiarrhytmic drugs	See in table 2	
Anticoagulants	Warfarine	2.5–5.0–7.5 mg (under control of International Normalization Ratio – INR)

Primary restrictive nonhypertrophied cardiomyopathy

The hallmark of the restrictive cardiomyopathies (RCMs) is abnormal diastolic function; the ventricular walls are excessively rigid and impede ventricular filling. In late stages systolic function is also impaired. Myocardial fibrosis, hypertrophy, or in-

filtration due to a variety of causes are responsible. Myocardial involvement with amyloid is a common cause of secondary restrictive cardiomyopathy, although restriction is also seen in the transplanted heart, in hemochromatosis, glycogen deposition, endomyocardial fibrosis, sarcoidosis, hypereosinophilic disease, and scleroderma; following mediastinal irradiation; and in neoplastic infiltration and myocardial fibrosis of diverse causes. In many of these conditions, particularly those with substantial concomitant endocardial involvement, partial obliteration of the ventricular cavity by fibrous tissue and thrombus contributes to the abnormally increased resistance to ventricular filling. Thromboembolic complications are frequent in such patients.

Clinical features

The inability of the ventricles to fill limits cardiac output and raises filling pressures; thus, exercise intolerance and dyspnea are usually prominent. As a result of persistently elevated systemic venous pressure, these patients commonly have dependent edema, ascites, and an enlarged, tender, and often pulsatile liver. The jugular venous pressure is elevated and does not fall normally (or may rise) with inspiration (Kussmaul's sign). The heart sounds may be distant, and the third and fourth heart sounds are common. In contrast to constrictive pericarditis, which RCM resembles in many respects, the apex impulse is usually easily palpable, and mitral regurgitation is more common.

Laboratory and instrumental examinations

In patients with infiltrative cardiomyopathies, the ECG often shows low-voltage, nonspecific ST-T-wave abnormalities and various arrhythmias. Pericardial calcification on X-ray, which occurs in constrictive pericarditis, is absent. Echocardiography, CTI, and CMRI typically reveal symmetrically thickened LV walls and normal or slightly reduced ventricular volumes and systolic function; the atria are usually dilated. Doppler echocardiography typically shows diastolic dysfunction. Cardiac catheterization shows a reduced cardiac output, elevation of the RV and LV end-diastolic pressures, and a dip-and-plateau configuration of the diastolic portion of the ventricular pressure pulses resembling constrictive pericarditis.

Differentiation of RCM from constrictive pericarditis is of importance because the latter is often curable by surgery. Helpful in the differentiation of these two conditions are RV transvenous endomyocardial biopsy (by revealing myocardial infiltration or fibrosis in RCM) and CTI or CMRI (by demonstrating a thickened pericardium in constrictive pericarditis but not in RCM).

Restrictive cardiomyopathy: treatment

Management is usually disappointing, except for hemochromatosis and Fabry's disease. Chronic anticoagulation is often recommended to reduce the risk of embolization from the heart (table 3). Diuretics may give some relief of the symptoms.

Eosinophilic endomyocardial disease

Also called Loeffler's endocarditis and fibroplastic endocarditis, this condition occurs in temperate climates. It appears to be a subcategory of the hypereosinophilic syndrome in which the heart is predominantly involved, with cardiac damage being the apparent result of the toxic effects of eosinophilic proteins. Typically, the endocardium of either or both ventricles is thickened markedly, with involvement of the underlying myocardium. Cardiac imaging typically reveals ventricular thickening, especially of the posterobasal LV wall. Mitral regurgitation is frequently present on Doppler echocardiography. Large mural thrombi may develop in either ventricle, thereby compromising the size of the ventricular cavity and serving as a source of pulmonary and systemic emboli. Hepatosplenomegaly and localized eosinophilic infiltration of other organs are usually present. Management usually includes diuretics, afterload-reducing agents, and anticoagulation. The use of glucocorticoids and hydroxyurea appears to improve survival. Surgical treatment with resection of fibrotic tissue and mitral valve repair or replacement may be helpful in selected patients.

Cardiac amyloidosis

Involvement of the heart is the most frequent cause of death in primary amyloidosis and hereditary amyloidosis, with deposition of amyloid in the cardiac interstitium. On gross pathologic examination, the heart is firm, rubbery, and noncompliant and has a waxy appearance. Clinically significant cardiac involvement is uncommon in the secondary form. Focal deposits of amyloid in the hearts of elderly persons (senile cardiac amyloidosis), although common, are usually clinically insignificant.

Four clinical presentations (alone or in combination) are seen: (1) diastolic dysfunction, (2) systolic dysfunction, (3) arrhythmias and conduction disturbances, and (4) orthostatic hypotension. The two-dimensional echocardiogram may be helpful in establishing the diagnosis of amyloidosis and may show a thickened myocardial wall with a diffuse, hyperrefractile «speckled» appearance. CMRI typically shows late gadolinium enhancement of the subendocardium. Aspiration of abdominal fat or biopsy of the myocardium or other organs permits the ante mortem diagnosis to be established in over three-quarters of cases.

Chemotherapy, often with alkylating agents such as melphalan, together with glucocorticoids, appears to have improved survival in individual cases. Heart transplantation (often combined with bone marrow transplantation or liver or kidney transplantation for hereditary amyloidosis) may help selected patients. However, the overall prognosis is poor, especially in the primary form with advanced cardiac involvement.

Other restrictive cardiomyopathies

Iron-overload cardiomyopathy (hemochromatosis) is often the result of multiple transfusions or a hemoglobinopathy, most frequently — thalassemia; the familial (autosomal recessive) form should be suspected if cardiomyopathy occurs in the presence of diabetes mellitus, hepatic cirrhosis, and increased skin pigmentation. The diagnosis may be confirmed by endomyocardial biopsy. CMRI shows a reduced T2* signal as iron levels rise. Phlebotomy may be of

some benefit if employed early in the course of the disease. Continuous subcutaneous administration of deferoxamine or other iron chelators may reduce body iron stores and result in clinical improvement.

Myocardial sarcoidosis is generally associated with other manifestations of systemic disease. It may cause restrictive as well as congestive features, since cardiac infiltration by sarcoid granulomas results not only in increased stiffness of the myocardium but also in diminished systolic contractile function. A variety of arrhythmias, including high-grade AV block, have been noted. A common cardiac manifestation of systemic sarcoidosis is RV overload due to pulmonary hypertension as a result of parenchymal pulmonary involvement. Many patients are treated empirically with glucocorticoids.

The carcinoid syndrome results in endocardial fibrosis and stenosis and/or regurgitation of the tricuspid and/or pulmonary valve; morphologically similar lesions have been seen with the use of the anorexic agents fenfluramine and phentermine.

Table 4 — Differential diagnosis of tne main types of cardiomyopathies

Method of examination	**Type of cardiomyopaty**		
	dilated	**restrictive**	**hypertrophic**
Chest roentgenogram	• moderate to marked cardiac silhouette enlarge; • pulmonary venous hypertension ment	• mild cardiac silhouette enlargement	• mild to moderate cardiac silhouette enlargement
Electrocardiogram	• ST-segment and T-wave abnormalities	• low voltage, conduction defects	• ST-segment and T-wave abnormalities • left ventricular hypertrophy • abnormal Q waves
Echocardiogram	• left ventricular dilatation and dysfunction	• increased left ventricular wall thickness • normal or mildly reduced systolic function	• asymmetric septal hypertrophy (ASH) • systolic anterior motion (SAM) of the mitral valve
Radionuclide studies	• left ventricular dilatetion and dysfunction (RVG)	•normal or mildly reduced systolic function (RVG)	• vigorous systolic function (RVG) • perfusion defect (^{201}Tl or technetium sestamibi)
Cardiac catheterization	• left ventricular dilatation and dysfunction • elevated left- and often right-sided filling pressures • diminished cardiac	• normal or mildly reduced systolic function • elevated left- and right-sided filling pressures	• vigorous systolic function • dynamic left ventricular outflow obstruction • elevated left- and

	output		right-sided filling pressures

Note: RVG, radionuclide ventriculogram; 201Tl, thallium 201.

Key Messages:

- The primary cardiomyopathies are not the result of congenital, acquired valvular, hypertensive, coronary arterial, or pericardial abnormalities.
- Systolic or diastolic heart failure is differentiate between dilated, restrictive, or hypertrophic types of cardiomyopathy.
- Dilated cardiomyopathy is characterized by left and/or right ventricular enlargement, impaired systolic function, congestive heart failure, arrhythmias, emboli.
- Restrictive cardiomyopathy is characterized by endomyocardial scarring or myocardial infiltration resulting in restriction to left and/or right ventricular filling.
- Hypertrophic cardiomyopathy is characterized by disproportionate left ventricular hypertrophy, typically involving septum more than free wall, with or without an intraventricular systolic pressure gradient; usually of a nondilated left ventricular cavity.
- In patients with advanced disease who are refractory to other therapies, cardiac transplantation should be considered.

MYOCARDITIS

The term myocarditis describes inflammatory disorders of the heart muscle of varied infectious and non-infectious origin. In acute myocarditis, infectious strains usually cause myocardial inflammation with subsequent disturbance of left ventricular or right ventricular function.

Etiology and pathogenesis of myocarditis

Viruses:

✓ Adenoviruses.
✓ Enteroviruses (Coxsackie A/B, Echo).
✓ Cytomegalovirus.
✓ Erythroviruses.
✓ Herpesviruses.
✓ Influenza A/B.
✓ HIV.
✓ Hepatitisvirus C.
✓ Poliovirus.
✓ Varicella zoster.
✓ Arboviruses.
✓ Mixed infections.

(Auto-)Immune activation:

✓ Postinfectious.

✓ Influenza vaccination.
✓ SLE (systemic Lupus erythematosus).
✓ Sarcoidosis.
✓ Sjögren's syndrome.
✓ Churg-Strauss syndrome.
✓ Wegener's granulomatosis.
✓ Takayasu arteritis.
✓ Inflammatory bowel disorders.
✓ Giant cell myocarditis.

Bacteria:

✓ Mycobacteria.
✓ Chlamydia.
✓ Streptococci.
✓ Mycoplasma.
✓ Legionella spp.
✓ Salmonella spp.
✓ Rickettsia spp.
✓ Corynebacteria.
✓ Borrelia spp.

Protozoa:

✓ Trypanosoma cruzi.
✓ Toxoplasma gondii.
✓ Trichinosis/trichinellosis.
✓ Echinococci.

Toxins:

✓ Anthracyclines.
✓ Catecholamines.
✓ Cytokines.
✓ Cocaine.
✓ Alcohol.
✓ Chemotherapeutic drugs.

Allergic/hypersensitive:

✓ Penicillin.
✓ Tricyclic antidepressants.
✓ Clozapine.
✓ Antirheumatic drugs.
✓ Sulfonamides.
✓ Cephalosporins.

Physical pathogens:

✓ Arsenic.
✓ Lithium.
✓ Irradiation.
✓ Hypothermia.

✓ Heat stroke.

Parasites:

✓ Schistosomiasis.

✓ Larva migrans.

Fungal infections:

✓ Aspergillus.

✓ Candida.

✓ Cryptococus.

✓ Histoplasmodium spp.

In Western industrialized countries these pathogens are primarily viruses, whereas in developing countries the cause may be bacterial, protozoal, or fungal infections.

Acute myocardial injury can result from either direct virus-mediated lytic processes or are caused by the emerging antiviral immune response. In fulminant cases of myocarditis, resulting myocyte necrosis may cause a significant loss of contractile tissue, which is accompanied by rapidly developing cardiac failure and early death of the host (early phase). Cytokines released by macrophages and activation of natural killer cells that directly kill virus-infected heart cells through perforin or granzyme-mediated lysis contribute to early myocardial lesions and impaired myocardial function.

Myocardial processes triggered by infectious and non-infectious causes also underlie the chronic-inflammatory myocardial disorders. If the immune system does not eliminate the infectious pathogen early on-owing to insufficient activation, e.g. on the basis of a genetic predisposition-chronic infection develops, which may or may not be accompanied by inflammation. If the inflammatory response does not spontaneously resolve after successful elimination of the pathogen, chronic-inflammatory cardiomyopathy is present. In addition to such postinfectious inflammatory processes, accompanying cellular or humoral inflammations in systemic diseases may cause lasting injury to the myocardium.

Clinical symptoms of myocarditis

The clinical spectrum of myocarditis ranges from an asymptomatic state, with the presence of myocarditis inferred only by the finding of transient electrocardiographic ST-T-wave abnormalities, to a fulminant condition with arrhythmias, acute heart failure, and early death. In some patients, myocarditis simulates an acute coronary syndrome, with chest pain, ECG changes, and elevated serum levels of troponin, but it typically occurs in patients younger than those with coronary atherosclerosis.

Most patients with myocarditis initially have such non-specific symptoms that these are often categorized in the context of the preceding infection and not as being of cardiac origin. Patients with viral myocarditis may give a history of a preceding upper respiratory febrile illness or a flu-like syndrome, and viral nasopharyngitis or tonsillitis may be evident.

The physical examination is often normal, although more severe cases may show a muffled first heart sound, along with a third heart sound and a murmur of

mitral regurgitation. A pericardial friction rub may be audible in patients with associated pericarditis.

Cardiac involvement is often considered as the differential diagnosis only when cardiac symptoms, such as palpitations, angina, and/or exertional dyspnea, persist for a long period after the underlying infection has resolved, or if they develop de novo in the course of the recovery. At this point in time, the electrocardiography results and laboratory chemical findings that are characteristic of acute myocarditis such as the changes to the ST segment and raised cardiac enzymes that are typical for acute myocardial involvement are no longer present.

Diagnostic evaluation of myocarditis

Diagnostic evaluation starts to collect data on the extent of myocardial injury, even when using imaging methods (echocardiography, angiography, magnetic resonance imaging [MRI]); excludes specific cardiac disorders such as ischemic cardiomyopathy or valve deficiencies; or provides clues for a suspected diagnosis of infectious myocarditis; it can't, however, diagnose the cause of the existing disorder.

The effects of virus-induced inflammatory processes on myocardial functioning and the disease course can be identified by:

- the medical history;
- the isolation of virus from the stool, pharyngeal washings, or other body fluids;
- changes in specific antibody titers laboratory tests;
- ECG/long-term ECG. The ECG signs of myocarditis are:
  - ✓ sinus tachycardias and other arrhythmias;
  - ✓ first, second or third degree block;
  - ✓ widened QRS complexes;
  - ✓ irregularity of QRS waveform;
  - ✓ prolonged QT interval;
  - ✓ ST segment elevation or depression;
  - ✓ T wave inversion in any lead.
- echocardiography;
- computed tomography (CT)/magnetic resonance imaging (MRI): exhibits contrast enhancement;
- diagnostic catheterization;
- endomyocardial biopsy.

Acute «infarct-like» changes on the ECG, a positive troponin-T/I measurement, raised NT-proBNP, and a finding of edema, or early contrast enhancement, in patients with clinically suspected myocarditis indicates, non-specifically, virus-associated or inflammatory cell-associated injury to the myocardium. However, they do not provide any information on the type of infectious pathogen or the inflammation, nor as to whether the infectious strain has been completely eliminated or the inflammation subsided. Since the toxic,

infiltrative, or infectious-inflammatory processes that are responsible for the clinical phenotype «myocarditis» take place at the cellular level, they cannot be identified at all or only unsatisfactorily by means of non-invasive clinical diagnostic modalities, including MRI.

Identifying infectious agents of myocarditis

With the exception of borreliosis, which is accompanied by cardiac symptoms in 8 % of cases, non-viral infections are not of major importance in the Western world. 10 % to 15 % of virus associated cases of myocarditis are caused by enteroviruses. Other pathogens include adenoviruses, herpesviruses, erythroviruses, cytomegalovirus, HIV, and hepatitis viruses; the prevalence rates differ by geographical location. Non-infectious autoimmune processes in systemic disease affect some 10 %.

Molecular biology diagnostic testing for the causative agent is done by means of polymerase chain reaction (nPCR) and identifies relevant infectious pathogens with a very high degree of sensitivity. Qualitative diagnosis of viral pathogens is complemented by quantitatively determining the viral load (real-time PCR) and sequencing for the purpose of identifying the viral subtypes or quality assurance. Acute or latent infections and infections that replicate actively in the myocardium can be differentiated from one another by parallel analyses of blood composition (peripheral cells, plasma, serum) and confirmation of transcriptional activity. Since different viruses and viral subtypes respond differently to antiviral medications and are in some cases not completely eliminated-merely blocked in their continual replication — this information is important for making a tailored decision regarding treatment and the success thereof.

Tissue-based diagnostics and diagnostic evaluation of inflammation

An AHA/ACCF/ESC joint scientific statement recommended that endomyocardial biopsy should be performed (Class I indication) in patients with heart failure and (I) a normal sized or dilated left ventricle, < 2 weeks of symptoms, and haemodynamic compromise and also in (II) patents with a dilated ventricle, 2 weeks to 3 months of symptoms, new ventricular arrhythmias or Mobitz type II second degree or third degree heart block, or who fail to respond to usual care within 1–2 weeks.

Endomyocardial biopsy processing: EMB usually is performed safely under fluoroscopic guidance. Fluoroscopy is generally better than 2-dimensional echocardiography to guide EMB because it provides more information to the operator about the course of the bioptome and site of biopsy. The echocardiographic technique without fluoroscopy has been used primarily to biopsy intracardiac masses. Samples should be obtained from > 1 region of the right ventricular septum. The number of samples obtained should range from 5 to 10, depending on the studies to be performed, and each sample should be 1 to 2 mm^3 in size. The samples are submitted for light microscopic examination, for transmission electron mi-

croscopy, are suitable for culture, polymerase chain reaction (PCR), or reverse transcriptase PCR (rtPCR) for the identification of viruses.

Endomyocardial biopsy-based criteria of viral myocarditis are inflammation present by immunohistology and viral genomes present by polymerase chain reaction.

In cases with an acute inflammatory disease course, the histology or immunohistology specimens often contain focal or diffuse cell infiltration by lymphocytes and/or macrophages, more rarely, by eosinophils or giant cells. In contrast to borderline myocarditis, active lymphocytic myocarditis is characterized by inflammatory cell-associated acute myocardial cell necrosis (figure 2). The density of the inflammatory cell infiltrate determines the acute and long-term disease course; the clinical relevance of the extent of inflammation and the inflammatory cell subtypes is not known. Giant cell myocarditis, idiopathic eosinophilic myocarditis, inflammatory processes in granulomatous disorders, and allergic medication-induced types of myocarditis are rare and found in less than 20 % of acute cases of myocarditis.

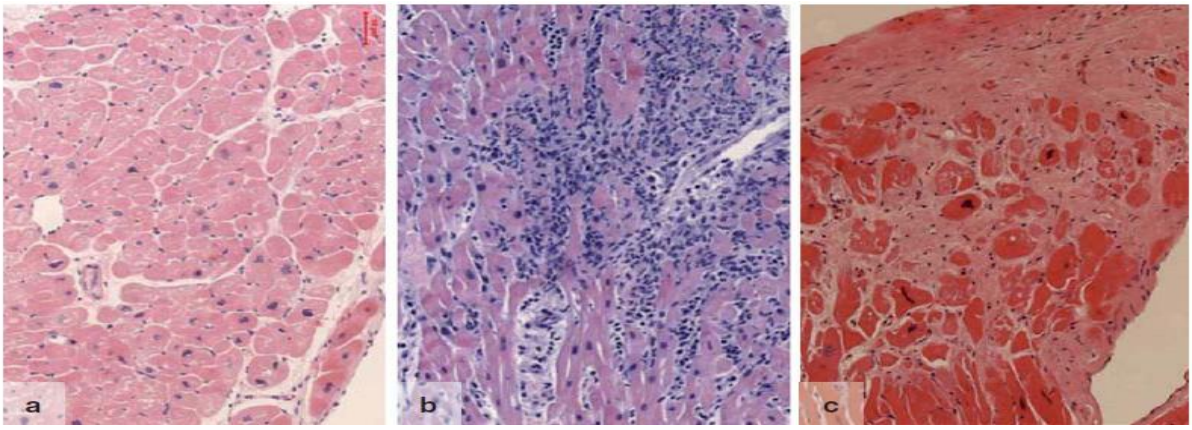


Figure 2 — Diagnostic evaluation of inflammation in a myocardial biopsy specimen (histology and immunohistology):
a) normal myocardium; b) acute lymphocytic myocarditis with focal cell infiltrates and necrosis of myocytes, c) advanced postinflammatory dilated cardiomyopathy with hypertrophy of the cardiomyocytes and pronounced fibrosis/scarring

From: Kühl, U. Myocarditis / U. Kühl, H.-P. Schultheiss // Dtsch Arztebl Int. — 2012. — Vol. 109. — P. 361–368.

In case of a biventricular biopsy, virus genome (12.6 % versus 7.1 %) or inflammation (18.7 % versus 7.9 %) is slightly more commonly found in the specimens from the left ventricle. Left ventricular biopsy is as safe as right ventricular biopsy.

The Dallas criteria of myocarditis were proposed in 1986 and provided a histopathological categorization by which the diagnosis of myocarditis could be established. Dallas criteria myocarditis requires an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event. A number of investigators have shown that virus may be present in the myocar-

dium without Dallas criteria myocarditis. These criteria have been used exclusively by American investigators over the last 2 decades. Sampling error, variation in expert interpretation, variance with other markers of viral infection and immune activation in the heart, and variance with treatment outcomes all suggest that the Dallas criteria are no longer adequate.

Treatment of myocarditis

Exercise may be deleterious in patients with acute myocarditis, and strenuous activity should be proscribed until the ECG and LV function have returned to normal.

The cornerstone of any therapeutic approach is to treat the heart failure or arrhythmia, which — independent of the actual cause — is done symptomatically in accordance with general, evidence-based guidelines. If the left ventricular ejection fraction (LVEF) is 40 % recommend that an angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker and/or a β-adrenergic blocking agent be used according to the current AHA/ACCF and ESC guidelines for the management of heart failure.

Specific treatment depends on the results of the diagnostic myocardial biopsy, while also taking into account the disease course so far and the individual patient's current clinical symptoms.

Patients with fulminant myocarditis may require mechanical cardiopulmonary support or cardiac transplantation; however, the majority of these patients survive, and many demonstrate substantial recovery of LV function.

Acute disease course

Virally induced acute myocarditis is initially cardioprotective and aims rapidly to eliminate the viral infection, before irreversible myocardial injury has developed. Whether early inhibition of the inflammation or early antiviral therapy has a beneficial effect on the disease course is not known as data are lacking. If anti-inflammatory treatment is given before the virus has been completely eliminated, the result may be virus persistence and an unfavorable disease course over the longer term.

Frequently administered anti-inflammatory drugs are immunoglobulins, corticosteroids, azathioprine, and cyclosporine, which are administered on top of regular heart failure medication. The immunosuppressive therapy in patients with biopsy-proven, virus-negative inflammatory cardiomyopathy is an effective and safe option in addition to supportive treatment for recovery of cardiac failure.

Since acute viral inflammatory cardiomyopathies after spontaneous viral elimination and receding inflammation often improve spontaneously within weeks or months during treatment with ACE inhibitors, beta blockers, and diuretics (60 %), watchful waiting is justified in patients who can be stabilized and whose biopsy results are known.

Indications for early implantation of a mechanical circulatory support device or implantable cardioverter defibrillator (ICD) should be defined with

caution and undertaken only if symptoms are persistent. A wearable LifeVest defibrillator can be used as an interim measure.

If progressive deterioration of cardiac pump function develops in spite of optimal drug treatment or if intractable arrhythmias are present in a specific finding of inflammation, speedy and if possible etiologically targeted treatment is required.

Giant cell and eosinophilic myocarditis and acute heart failure in necrotizing myocarditis are among the treatable disorders that require immediate treatment because of their high mortality. If treatment is initiated too late then often the only remaining option is that of mechanical circulatory support or — as the method of last resort — heart transplantation, because of the rapidly developing irreversible myocardial injuries.

Specific treatment regimens

Giant Cell Myocarditis, a rare myocarditis of unknown cause, is characterized by rapidly progressive CHF and ventricular tachyarrhythmia and occurs most commonly in the third or fourth decades; approximately two-thirds of patients die within 1 year. At necropsy, the distinctive features include cardiac enlargement, ventricular thrombi, grossly visible serpiginous areas of necrosis in both ventricles, and microscopic evidence of giant cells within an extensive inflammatory infiltrate. The etiology of giant cell myocarditis has not been identified, although an autoimmune cause appears to be likely. While treatment with immunosuppressive therapy may help some patients, cardiac transplantation is often necessary (table 5).

Table 5 — Management of inflammatory cardiomyopathies

Types of myocarditis (disease stage)	**Pathomechanism and infectious strain**	**Therapeutic option**	**The drugs and dosage**
Acute viral myokarditis (early phase)	Direct cytopathic myocardial injury	Antiviral therapy?	Interferon alpha/beta, ganciclovir/valaciclovir
	Congenital immune response (macrophages, natural killer cells, cytokines)	Antiviral therapy? Intravenous immunglobulins? Immunoadsorption	Sea above
Giant cell myocarditis	Autoimmune mechanisms	Immunosuppression treatment	Oral steroids 3 (anti-CD3-antibodies) 5 mg/day i.v. for 7 days 10 mg/kg body weight for 3 days
			Ciclosporin — targeted trough level: 100–120 μg/mL
			Methylprednisolone 1 mg/kg body weight (1 week) Reduction: 10 mg/ 4 weeks
Chronic/autoimmune	Autoimmune mecha-	Methylprednisolone	1 mg/kg body weight

Types of myocarditis (disease stage)	Pathomechanism and infectious strain	Therapeutic option	The drugs and dosage
myocarditis, eosinophilic myocarditis	nisms Adaptive immune response (T/B cells, antibody production)		(2 weeks), then reduction by 10 mg each week for 4 weeks to a maintenance dose of 10 mg (duration of treatment 6 months)
		Azathioprine	50–150 mg/day (6 months)
Chronic viral cardiomyopathy	Enterovirus	Interferon-β	A dose of initially 2×10^6 IU IFN-ß is administered subcutaneously every other day and increased at weekly intervals, first to 4×10^6 IU and then to $6–8 \times 10^6$ IU; this is continued for 24 weeks
	Adenovirus	Interferon-β	Sea above
	Erythro-/Parvovirus	Intravenous immunglobulins (acute infection) Type I interferons (chronic infection)	
	Human herpesvirus type 6A/B	Valaclovir/ganciclovir	
	Cytomegalovirus	Valaclovir/ganciclovir Foscanet Cidofovir	
	Epstein-Barr virus	Vala-/Ganciclovir Foscanet Cidofovir	
	Herpes simplex virus	Aciclovir	
	Varicella	Aciclovir	
	Respiratory syncytial virus	Ribavirin	
	Hepatitis C virus	Pegylated interferon-α + ribavarin	
	HIV	Antiretroviral medications	

For *giant cell myocarditis* an aggressive treatment regimen with anti-CD3-antibodies, ciclosporin (trough level 100–120 μg/mL), and cortisone is required. In the following period, cortisone can be reduced stepwise in two-week intervals by 10 mg each time down to a maintenance dose of 5–10 mg/day. This regimen is maintained with continued ciclosporin for a minimum of 12 months.

Eosinophilic myocarditis is — like chronic lymphocytic myocarditis and autoimmune myocarditis — treated with cortisone and azathioprine, with the cortisone being stepped down at fortnightly intervals from an initial dose of 1 mg/kg body weight by 10 mg each time until a maintenance dose of about 10 mg has been reached and then gradually tapered off after 6 months (table 5).

Granulomatous myocarditis with a fulminant course is usually identified post mortem. Other granulomatous disorders with myocardial involvement, such

as sarcoidosis or rheumatoid arthritis, respond well to cortisone but often require a lengthy course of treatment. The prognosis of giant cell myocarditis can be improved only by early immunosuppression treatment. Too few data to enable reliable assessment of mortality are available for eosinophilic and granulomatous myocardial diseases, although individual positive case reports exist.

Myocarditis in Patients with HIV

Many HIV-infected patients have subclinical cardiac involvement, including pericardial effusion, right-sided chamber enlargement, arrhythmias, and neoplastic involvement. Overt clinical manifestations are seen in 10 % of HIV patients. The most common finding is LV dysfunction that in some cases appears to be due to infection of the myocardium by the virus itself. In other patients, the heart is affected by one of the various opportunistic infections common in HIV-AIDS, such as toxoplasmosis; by cardiac involvement by neoplastic disorders; or by toxicity from anti-HIV drugs.

Bacterial Myocarditis

Bacterial involvement of the heart is uncommon, but when it does occur, it is usually as a complication of infective endocarditis in which abscess formation involves the valve rings and interventricular septum.

Diphtheritic myocarditis develops in over one-quarter of patients with diphtheria; it is one of the more serious complications and the most common cause of death in this infection. Cardiac damage is due to the liberation of a toxin that inhibits protein synthesis and leads to a dilated, flabby, hypocontractile heart. The conduction system is frequently involved as well. Cardiomegaly and severe CHF typically appear after the first week of illness. Prompt therapy with antitoxin is critical; antibiotic therapy is also indicated but is of less urgency.

Lyme Carditis

Lyme disease is caused by a tick-borne spirochete and is most common in the Northeast, upper Midwest, and Pacific Coastal regions of the United States during the summer months. About 10 % of patients develop symptomatic cardiac involvement during the acute phase of the disease. AV conduction abnormalities are the most common manifestations of involvement and may lead to syncope. Concomitant myopericarditis is not uncommon, and mild, asymptomatic LV dysfunction may occur.

Intravenous ceftriaxone or penicillin is indicated in all but the mildest forms of Lyme carditis, in which case oral amoxicillin or doxycycline is employed. Hospitalization with ECG monitoring is indicated in patients with second- or third-degree AV block. A temporary pacemaker may be needed for symptomatic AV block, but permanent pacing is rarely required. Although glucocorticoids are often given, their effectiveness in reversing AV block is uncertain. Long-term cardiac manifestations of Lyme disease are uncommon.

The rationale for *immunoadsorption* is to lower cardiotoxic antibodies in the patient's plasma, and with serial treatments over 5 or more days, extract antibodies and immune complexes from the heart as well. The plasma is separated from cellular components by a centrifuge or column and passed through an immunoadsorbtion column. IgG and to a lesser degree IgA and IgM are non-specifically adsorbed during repetitive sessions. Plasma IgG levels are partially restored by infusion of 0.5 g/kg polyclonal IgG >.18 h after the last apheresis treatment.

Accumulating experimental and clinical data indicate that cellular transplantation may improve myocardial function. Mesenchymal stem cells (MSCs) have anti-apoptotic, anti-fibrotic properties, are non-immunogenic, and possess immunomodulatory properties.

Prognosis of myocarditis

Acute myocarditis mostly does not sufficiently respond to symptomatic medication for heart failure, and mortality is high in spite of treatment. The long-term disease course depends on the pathogen, the extent and type of inflammation, and the initial injury to the myocardium. Focal borderline myocarditis often undergoes spontaneous clinical healing if no serious heart failure developed initially. The early mortality of fulminant lymphocytic myocarditis requiring intensive care is in excess of 40 % in the first 4 weeks. Untreated giant cell and eosinophilic myocarditis also have an extremely poor prognosis, with 4 year survival rates of less than 20 %. Granulomatous necrotizing myocarditis is lethal if overlooked and untreated. Non-fulminant active myocarditis has a mortality rate of 25 % to 56 % within 3 to 10 years, owing to progressive heart failure and sudden cardiac death, especially if symptomatic heart failure manifests early on. In addition to impaired left ventricular (LV) and right ventricular (RV) function, virus persistence, chronic inflammation, and cardiodepressive autoantibodies are independent predictors of a poor prognosis.

Key Messages:

- Viral infections are the most common triggers of inflammatory cardiomyopathies (including myocarditis) and can, if persistent, damage the myocardium even without accompanying inflammation.
- Since the pathophysiological processes in myocarditis take place at the cellular and subcellular levels, myocardial biopsy is the only method by which the causative strain can be identified and/or inflammation can be confirmed – both of which are important for differential treatment.
- Cases of subacute myocarditis that initially is accompanied by non-specific symptoms are frequently identified and cardiologically evaluated only at an advanced stage.
- Because the clinical course of myocarditis is unpredictable, all patients with etiologically unexplained heart failure have to undergo myocardial biopsy, before irreversible and thus untreatable damage to the myocardium has developed.

• Numerous chronic viral infections and postinfectious or autoimmune inflammations of the myocardium are treatable.

CASE REPORT No.1

A 19-year-old and otherwise healthy woman presented to her primary care physician with a report of increasing dyspnea on exertion of 2 or 3 days' duration.

She had had an upper respiratory tract infection 3 weeks previously. Chest radiography showed mild cardiac enlargement, and transthoracic echocardiography revealed a small circumferential pericardial effusion.

The patient was treated with ibuprofen for presumed postviral pericarditis.

Two days later, the patient was found unconscious in her shower. Electrocardiography revealed diffuse ST segment elevation throughout the precordial leads, with 1.0-mm PR-segment depression in leads I and II (figure 3).

She underwent immediate coronary catheterization, which showed normal coronary arteries, and was subsequently transferred to a tertiary referral center for further evaluation.

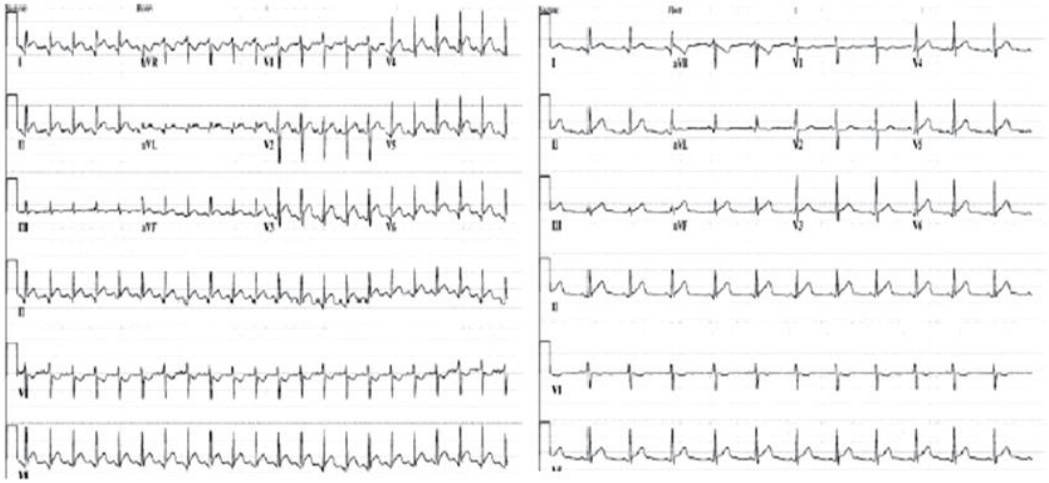


Figure 3 — Electrocardiograms:
Left: at hospital admission — sinus tachycardia at 130 beats/min, with diffuse ST-segment elevation and 1,0 mm of PR-segment depression in leads I and II.
Right: two days after admission, normal sinus rhytm at 85 beats/min and resolution of ST-segment abnormalities

On arrival, she was intubated and sedated, with a heart rate of 125 beats/min and a blood pressure of 94/60 mm Hg. Cardiopulmonary examination showed an S3 gallop with no audible murmur or rub. The patient's jugular venous pressure was elevated at 8 cm H_2O, and scattered crackles were found on lung examination. Echocardiography revealed a left ventricular ejection fraction (LVEF) of 15 % to 20 % with generalized hypokinesis and small pericardial effusion.

Laboratory findings included a white blood cell count of 27.2×10^9/L (reference ranges shown parenthetically) ($3.5–10.5 \times 10^9$/L), a creatinine kinase-MB isoenzyme fraction level of 22 ng/mL (<6.2 ng/mL; to convert to μg/L, multiply

by 1.0), and a troponin T level of 0.9 ng/mL (<0.01 ng/mL; to convert to μg/L, multiply by 1.0). Emergent right heart catheterization with endomyocardial biopsy was performed. The biopsy specimen showed active lymphocytic myocarditis. Inotropic support was initiated with dobutamine; gentle afterload reduction was initiated with nitroglycerin. The patient was weaned from hemodynamic support and extubated; low doses of β-blocker and angiotensin-converting enzyme inhibitor were initiated. At 6-week follow-up, her left ventricle ejection fraction had roved to 66%. Subsequently, endomyocardial tissue was analyzed with polymerase chain reaction and found to be positive for Epstein-Barr virus.

JOINTS DISEASES. RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a common autoimmune disease that can lead to serious functional limitations, joint destruction, extra-articular disease, poor quality of life, and premature death. It is characterised by polyarticular inflammation of synovial tissue, which causes pain, swelling, and stiffness of the joints of the hands, wrists, and feet in particular. It also results in functional limitations and may progress to joint destruction and extra-articular disease.

Rheumatoid arthritis has an estimated prevalence of 0.5–1.1 % and an incidence of 20–50 per 100 000 person years in northern Europe and North America. Lower prevalences (0.1–0.7 %) have been reported in southern Europe, South America, Asia, and the Middle East, with very low prevalences in some parts of Africa. The disease is more prevalent in women than in men (3:1 to 2:1). Cohort studies suggest that prevalence rises with age and peaks at 65–74 years.

The pathogenic mechanisms

Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia («swelling»), autoantibody production (rheumatoid factor and anti-citrullinated protein antibody [ACPA]), cartilage and bone destruction («deformity»), and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.

Genetic and environmental factors

Rheumatoid arthritis involves a complex interplay among genotype, environmental triggers, and chance.

Twin studies implicate genetic factors in rheumatoid arthritis, with concordance rates of 15 to 30 % among monozygotic twins and 5 % among dizygotic twins. Genomewide analyses make it clear that immune regulatory factors underlie the disease.

The long-established association with the human leukocyte antigen (HLA)-DRB1 locus has been confirmed in patients who are positive for rheumatoid factor or ACPA.

Smoking and other forms of bronchial stress (e.g., exposure to silica) increase the risk of rheumatoid arthritis among persons with susceptibility *HLA-DR4* alleles.

Infectious agents (e.g., Epstein-Barr virus, cytomegalovirus, proteus species, and *Escherichia coli*) and their products (e.g., heat-shock proteins) have long been linked with rheumatoid arthritis.

Rheumatoid arthritis appears to be associated with periodontal disease: *Porphyromonas gingivalis* expresses *PADI4,* which is capable of promoting citrullination of mammalian proteins.

The gastrointestinal microbiome is now recognized to influence the development of autoimmunity in articular models, and specific (and potentially tractable) clinical bacterial signatures that are associated with autoantibody-positive rheumatoid arthritis are emerging.

The greater risk of rheumatoid arthritis among women than among men has long been recognized.

Synovial immunologic processes and inflammation

Synovitis occurs when leukocytes infiltrate the synovial compartment. Leukocyte accumulation primarily reflects migration rather than local proliferation. Cell migration is enabled by endothelial activation in synovial microvessels, which increases the expression of adhesion molecules (including integrins, selectins, and members of the immunoglobulin superfamily) and chemokines. Accordingly, neoangiogenesis, which is induced by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which limits cellular egress, are characteristic features of early and established synovitis. These microenvironmental changes, combined with profound synovial architectural reorganization and local fibroblast activation, permit the buildup of synovial inflammatory tissue in rheumatoid arthritis.

Adaptive immune pathways

The genetics of rheumatoid arthritis and the presence of autoantibodies clearly place adaptive immunity at the center of early pathogenesis. Autoreactive T cells against citrullinated self-proteins have been identified. Humoral adaptive immunity is integral to rheumatoid arthritis. Synovial B cells are mainly localized in T-cell-B-cell aggregates. The role of B cells and their progeny in the pathogenesis of rheumatoid arthritis goes beyond autoantibody production to include autoantigen presentation and cytokine production (e.g., interleukin-6, TNF-α, and lymphotoxin-β).

Activation of the innate immune system

A variety of innate effector cells, including macrophages, mast cells, and natural killer cells, are found in the synovial membrane, whereas neutrophils reside mainly in synovial fluid. Macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating

factor (GM-CSF) enhance maturation of these cells, their efflux from the bone marrow, and trafficking to the synovium. In particular, macrophages are central effectors of synovitis; clinically effective biologic agents consistently reduce macrophage infiltration in the synovium. Macrophages act through release of cytokines (e.g., TNF-α and interleukin-1, 6, 12, 15, 18, and 23), reactive oxygen intermediates, nitrogen intermediates, production of prostanoids and matrix-degrading enzymes, phagocytosis, and antigen presentation.

Cytokines and intracellular signaling pathways

Cytokine production that arises from numerous synovial cell populations is central to the pathogenesis of rheumatoid arthritis (table 6).

Table 6 — Key molecules and signal mediators implicated in the pathogenesis of rheumatoid arthritis

Molecule or signal mediator	**Functions**
Cytokines	
TNF-α	Activates leukocytes, endothelial cells, and synovial fibroblasts, inducing production of cytokines, chemokines, adhesion molecules, and matrix enzymes; suppression of regulatory T-cell function; activation of osteoclasts; and resorption of cartilage and bone; mediates metabolic and cognitive dysfunction
Interleukin-1α and 1β	Activate leukocytes, endothelial cells, and synovial fibroblasts; induce matrix-enzyme production by chondrocytes; activate osteoclasts; mediate fever; enhance glucose metabolism; and reduce cognitive function
Interleukin-6	Activates leukocytes and osteoclasts; is involved in B-lymphocyte differentiation; regulates lipid metabolism, acute-phase response, and anemia of chronic disease; and is implicated in hypothalamic-pituitary-adrenal axis dysfunction and fatigue
Interleukin-7 and 15	Promote and maintain T-cell and natural killer-cell activation and T-cell memory, block apoptosis, and maintain T-cell-macrophage cognate interactions
Interleukin-17A and 17F	Act synergistically to enhance activation of synovial fibroblasts, chondrocytes, and osteoclasts
Interleukin-18	Promotes activation of Th1, neutrophils, and natural killer cells
Interleukin-21	Activates Th17 and B-cell subsets
Interleukin-23	Expands Th17
Interleukin-32	Activates cytokine production by several leukocytes and promotes osteoclast differentiation
Interleukin-33	Activates mast cells and neutrophils
Growth and differentiation factors	
BLyS (B-lymphocyte stimulator) and APRIL (proliferation-inducing ligand)	Activate B cells and have a role in the maturation of B cells and enhancement of autoantibody production
GM-CSF and M-CSF	Enhance differentiation of granulocyte and myeloid-lineage cells in the bone marrow and synovium

RANKL (receptor activator of NF-κB ligand)	Promotes maturation and activation of osteoclasts
Intracellular signaling molecules and transcription factors	
JAK (Janus kinase)	Tyrosine kinase that regulates cytokine-mediated leukocyte maturation and activation, cytokine production, and immunoglobulin production
Syk (spleen tyrosine kinase)	Tyrosine kinase that regulates immune-complex-mediated and antigen-mediated activation of B and T cells and other Fc receptor-bearing leukocytes
PI3K (phosphatidylinositol 3-kinase)	Mediates signals that drive proliferation and cell survival
BTK (Bruton's tyrosine kinase)	Plays important role in the activation of B cells, macrophages, mast cells, and neutrophils, through regulation of B-cell receptor and Fc receptor signaling as appropriate
NF-κB	Helps integrate inflammatory signaling and is important for cell survival

Mesenchymal tissue responses

The normal synovium contains mesenchymal-derived, fibroblast-like synoviocytes (FLSs) and resident macrophages. In rheumatoid arthritis, the membrane lining is expanded, and FLSs assume a semiautonomous phenotype characterized by anchorage independence, loss of contact inhibition, and the expression of high levels of disease-relevant cytokines and chemokines, adhesion molecules, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs). FLSs thereby contribute directly to local cartilage destruction and the chronicity of synovial inflammation.

Synovial hyperplasia could also reflect increased influx of mesenchymal cells. The molecular mechanisms that sustain synovial hyperplasia are incompletely understood.

Structural damage

Cartilage damage

A hyperplastic synovium is the major contributor to cartilage damage in rheumatoid arthritis.

Chondrocytes physiologically regulate matrix formation and cleavage: under the influence of synovial cytokines (particularly interleukin-1 and 17A) and reactive nitrogen intermediates, cartilage is progressively deprived of chondrocytes, which undergo apoptosis. These processes ultimately lead to the destruction of the surface cartilage and the radiographic appearance of joint-space narrowing.

Bone erosion

Bone erosion occurs rapidly (affecting 80 % of patients within 1 year after diagnosis) and is associated with prolonged, increased inflammation. Synovial cytokines, particularly macrophage colony-stimulating factor and receptor activator of NF-κB ligand (RANKL), promote osteoclast differentiation and invasion of the periosteal surface adjacent to articular cartilage. Osteoclasts have the acidic enzymatic machinery necessary to destroy mineralized tissues, including

mineralized cartilage and subchondral bone; destruction of these tissues leads to deep resorption pits, which are filled by inflammatory tissue.

Mechanical factors predispose particular sites to erosion. Thus, «mechanically vulnerable» sites such as the second and third metacarpals are prone to erosive changes.

Systemic consequences of rheumatoid arthritis

Rheumatoid arthritis is associated with increased rates of cardiovascular illness (standardized mortality rate, approximately 1.5), including myocardial infarction, cerebrovascular events, and heart failure.

Effective therapies decrease cardiovascular risk and favorably modify vascular physiology. Statin drugs also reduce surrogates of vascular risk and inflammatory factors in patients with rheumatoid arthritis, and risk adjustment for statin use in patients with rheumatoid arthritis is now advocated.

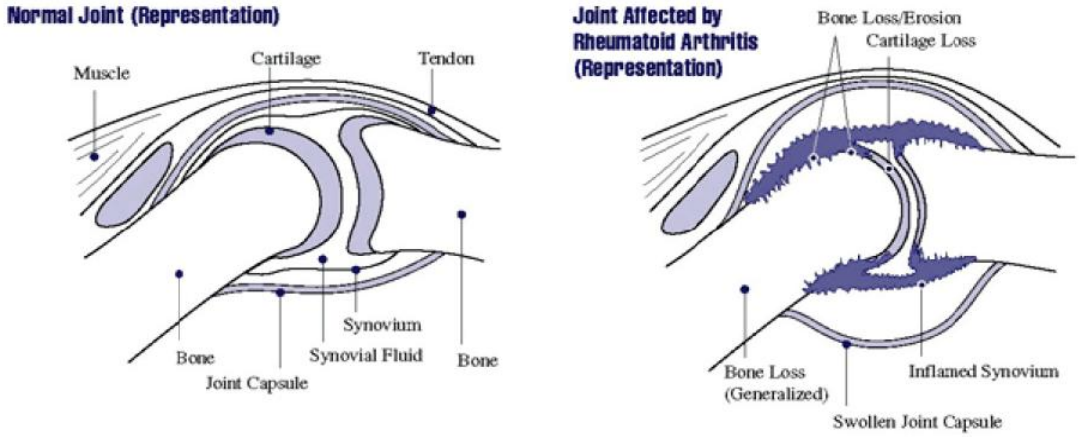


Figure 4 — Joint affected by rheumatoid arthritis:
The joint capsule is lined with a type of tissue called synovium, which produces synovial fluid that lubricates and nourishes joint tissues. In rheumatoid arthritis, the synovium becomes inflamed, causing warmth, redness, swelling, and pain. As the disease progresses, the inflamed synovium invades and damages the cartilage and bone of the joint. Surrounding muscles, ligaments, and tendons become weakened. Rheumatoid arthritis also can cause more generalized bone loss that may lead to osteoporosis (fragile bones that are prone to fracture)

From: the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (http://www.niams.nih.gov/Health_Info/Rheumatic_Disease/default.asp).

Inflammation in rheumatoid arthritis also affects the brain (fatigue and reduced cognitive function), liver (elevated acute-phase response and anemia of chronic disease), lungs (inflammatory and fibrotic disease), exocrine glands (secondary Sjögren's syndrome), muscles (sarcopenia), and bones (osteoporosis).

The risk of lymphoma is increased among patients with rheumatoid arthritis and is strongly associated with inflammatory disease activity.

The higher rates of lung cancer among patients with rheumatoid arthritis than among other persons may be explained in part by the association between smoking

and rheumatoid arthritis. However, inflammation increases the risk of lung cancer regardless of smoking, perhaps because of the long-known extraarticular effects of rheumatoid arthritis on fibrotic remodeling of interstitial lung tissue.

Diagnostic algorythm of RA

1. History

Rheumatoid arthritis can affect any joint, but it is usually found in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as in the wrists and knee. Articular and periarticular manifestations include joint swelling and tenderness on palpation, with morning stiffness and severe motion impairment in the involved joints.

Patients have pain, stiffness, and limited joint movement. Presentation may be classic, with symmetrical polyarthritis of the small joints of the hands and feet, but monoarthritis or oligoarthritis, including large joints as first manifestation, is not uncommon. Observational studies suggest that patients who present with monoarthritis or oligoarthritis are as likely to develop progressive joint damage as those who present with polyarthritis.

Patients often report general symptoms, such as morning stiffness (not only in the affected joints, lasting more than an hour), fatigue, fever, sweats, and weight loss. In early disease, functional limitations are determined by the presence of active synovitis, but in the long run joint damage is also a contributory factor.

Signs of inflammatory arthritis:

- pain;
- swelling;
- loss of function of the affected joint (flexion or rotation, resistance to hyperextension);
- sometimes heat;
- occasionally redness;
- morning stiffness (not only in swollen joints);
- squeeze test: put tangential pressure on the metatarsophalangeal and metacarpophalangeal joints; if tender, suspect synovitis;
- general symptoms such as fatigue, fever, weight loss, and sweats.

Table 7 — Extra-articular manifestations of rheumatoid arthritis

EXTRA-ARTICULAR FEATURES	
Musculoskeletal	
Rheumatoid nodules	Usually seen at sites of pressure or friction such as the extensor surfaces of the forearms below the elbow, scalp, sacrum, scapula, Aschilies tendon, as well as on the fingers and toes
Bursitis	The olecranon and other bursae may become swollen
Tenosynovitis	Particulary affecting the flexor tendons in the palm of the hand and may contribute to flexion deformities

Muscle wasting	Around affected joints especially in the hands
Neurological: carpal tunnel syndrome, atlanto-axial subluxation, polyneuropathy, mono-neuritis complex	
Ocular: Sjogren's syndrome, scleritis, keratoconjuctivitis	
Hematological: anemia, eosinophilia, thrombocytosis (or thrombocytopenia)	
Pulmonary: pleural effusion, diffuse fibrosing alveolitis, rheumatoid nodules in the lungs, Caplan's syndrome	
Cardiac: pericarditis, myocarditis, aortitis, heart block	
Lymphatic: lymphadenopathy, splenomegaly, Felty's syndrome	
Skin: vasculitis, leg ulcer	
Systemic: fever, weight loss, susceptibility to infection, amyloidosis	

2. Examination

Synovitis can be clinically diagnosed by examination of the joints. Palpation shows swelling within the joint, sometimes with bulging and pain on pressure. Movement, particularly (over)extension or rotation, is limited, and force is reduced – for example, when bunching a fist. Because the small joints of the feet may be difficult to assess separately, inflammation may be easier to detect if the metatarsal joints are squeezed together. Heat and redness may be apparent, but absence of these signs does not preclude inflammation. In later stages of disease, rheumatic nodules or deformation might be seen, typically with ulnary deviation of the metacarpophalangeal joints. No single test or set of criteria is available to diagnose rheumatoid arthritis.

Investigations in newly diagnosed patients include measurement of acute phase reactants (to calculate disease activity), a full blood count, and autoantibody tests. When an infectious cause or crystal induced (poly) arthritis is suspected, aspiration of synovial fluid or synovial biopsy may be helpful. Ultrasound may show synovitis in joints that are clinically difficult to assess and may help guide synovial fluid aspiration. Additional radiological and laboratory assessments might be needed to exclude alternative diagnoses. Radiographs of hands, wrists, and feet are recommended early in the disease to assess early structural damage and should be repeated annually to monitor disease severity and response to treatment. In research settings, changes on ultrasound and magnetic resonance imaging seem to be predictive of future progression, but it is unclear if and how these modalities should be integrated into daily practice.

3. Biomarkers and Autoantibodies

Laboratory studies, observational trials, and randomised trials have shown that rheumatoid factor, directed against IgG, and antibodies against citrullinated proteins are seen in about two thirds of patients with rheumatoid arthritis. Several observational studies have shown that the presence of autoantibodies predicts a more severe disease course. In patients with undifferentiated arthritis, the presence of anti-citrullinated protein antibodies predicts progression to

rheumatoid arthritis. Patients with and without these autoantibodies seem to differ genetically from one another, suggesting that anti-citrullinated protein positive and negative arthritis may be two distinct disease entities. Both types of autoantibody can be present years before the onset of the disease.

Current RA Biomarkers

For decades, rheumatoid factor (RF), IgG, IgA, and IgM auto-antibodies directed against Fc portion of IgG have been considered the primary serologic marker for the diagnosis of inflammatory arthritis.

Acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are markers of inflammation that are not specific for RA; nonetheless, they have proven to be the best validated biomarkers to date. Though elevations in one or both can be helpful, their ubiquitous nature in many inflammatory states, as well as their absence in as many as 40 % of patients with active RA, prevents them from becoming a gold standard for the diagnosis of RA. The recent advent of highly specific biomarkers for RA, not available at the time the 1987 criteria were developed, offers a significant opportunity to classify patients with RA early in the disease process.

Anti-citrullinated protein antibodies (ACPA), most commonly measured by commercial assays for antibodies against cyclic citrullinated peptides (anti-CCP), have been identified as important for both the diagnosis and subsequent prognosis in RA. Although the presence of anti-CCP Abs (antibodies) offers better specificity than RF (95 % to 97 % vs 65 % to 75 %), the two tests have similar sensitivity for diagnosis, with minimal benefit gained from the combination of the two in established RA.

4. Instrumental methods

Radiography has long been the standard for detection of joint damage in established RA. It is readily available, low-cost, and reliably demonstrates many of the more advanced changes, such as erosions, joint space narrowing, and juxta-articular bone loss.

Stages of X-ray examination in RA:

I — periarticular osteoporosis (osteopenia);

II — loss of articular cartilage («joint space»);

III — bone erosions;

IV — subluxation and ankylosis.

Ultrasonography

Contrast-enhanced computed tomography

Positron emission tomography (PET) imaging

Scintigraphy and SPECT imaging (figure 5).

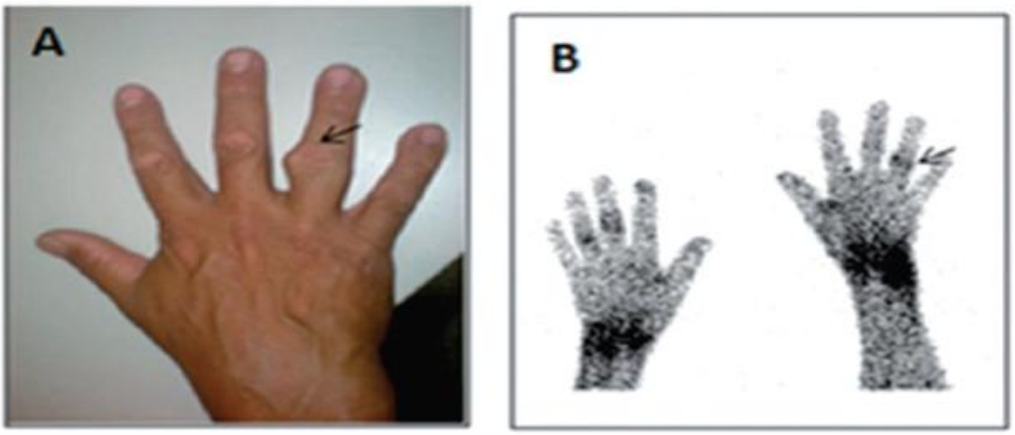


Figure 5 — Examination joints in rheumatoid arthritis:
A — right hand with fourth PIP joint swelling and capsular bulging;
B — hand scintigraphy scan showing increase in uptake of ^{99m}Tc-anti-TNF-α
in the fourth right PIP (arrow), third and fourth left PIP and wrists

From: 99mTc-anti-TNF-α scintigraphy in RA: a comparison pilot study with MRI and clinical examination / L. Roimicher [et al.] // Rheumatology (Oxford). — 2011. — Vol. 50. — P. 2044–2050.

Magnetic resonance imaging (MRI)

MRI is capable of demonstrating the broad spectrum of findings seen in rheumatoid arthritis.

Synovitis: Synovitis is one of the earliest abnormalities detected in RA. The synovial lining should be barely perceptible in normal patients with minimal or no contrast enhancement with Gadolinium administration. Thickening, increased water content producing high signal on T2-weighted images, or more than minimal contrast enhancement suggests synovitis.

Bone Marrow Edema: Bone marrow edema or osteitis, albeit non-specific, also occurs in early RA. On fat-suppressed T2-weighted images, it appears as a high signal in the subchondral bone.

Erosions: Erosions, when they develop in early RA, strongly imply that irreversible joint damage has developed.

Other Findings: Tendinopathy is a common finding in RA. Most commonly this takes the form of tenosynovitis, which exhibits MR evidence of fluid in the tendon sheath or increased thickness or enhancement of the tendon sheath synovium. Tendonitis may also occur. Joint effusions occur in RA often in association with synovitis. Fibrotic pannus may also be present in RA, but is more common in long-standing disease. Loss of cartilage and joint space narrowing occur late in long-standing disease.

Classification criteria for RA have been developed for the use in research populations only, although they are sometimes used in clinical practice. Until recently, the 1987 classification criteria of the American College of Rheumatology (ACR) were used.

American College of Rheumatology classification criteria (1987):

1) morning stiffness for at least one hour;
2) synovitis in three or more joints;
3) synovitis in hands or wrists;
4) symmetrical distribution;
5) subcutaneous nodules;
6) positive rheumatoid factor;
7) radiographic changes on radiographs of hands or wrists.

At least 4 items should be present; items 1–4 should be of at least 6 weeks' duration.

The new criteria for classification of Rheumatoid Arthritis have been recently released (2010).

The new scoring system of the 2010 ACR/EULAR criteria, similar to prior criteria, includes four domains: symptom duration, number of joints involved, types of joints involved, and laboratory biomarkers of inflammation and autoimmunity (table 8). They incorporate the anti-Citrullinated Protein antibody testing and the other classic criteria in a score system (the diagnosis of definite rheumatoid arthritis is made by a total score ≥6).

Table 8 — 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis

Points	Joint involvement	Serology	Duration	Acute phase reactants
0	1 large joint	RF and CCP are negative	< 6 weeks	ESR or CRP is normal
1	2–10 large joints		≥ 6 weeks	ESR or CRP is abnormal
2	1–3 small joints	RF or CCP low titer positive	The patient receives scores in 4 domains. A total score of 6 or greater (of a possible 10) indicate to definite RA.	
3	4–10 small joints	RF or CCP high titer		
5	> 10 joints (at least 1 small joint)			

In the new criteria set, classification as «definite RA» is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis. This new classification system redefines the current paradigm of RA by focusing on features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features.

Differential diagnosis of RA

RA in initial phase is not a straight forward diagnosis, other conditions have similar presentation and they should be ruled out.

Rheumatic fever: migratory arthritis, raised ASO titer, dramatic response to aspirin, carditis and erythema marginatum may occur in adults.

SLE: butterfly rash, discoid rash, photosensitivity, alopecia, higher titer of anti-DNA, renal involvement (proteinuria), CNS involvement.

Osteoarthritis: eldery patients; no systemic features; joint pain is relieved by rest; morning stiffness is much less and for short period; it spares wrist and metacarpophalangeal joints and commonly involves distal interphalangeal joints to produce Heberden nodes; it mostly involves spine, hip and knee.

Gouty arthritis: intermittent and monoarticular in early stage, gouty tophy, the presence of synovial urate crystals.

Others: septic arthritis, polymyalgia rheumatica, seronegative arthritis, postinfectional arthritis.

Treatment of RA

The ultimate goal of treatment is sustained clinical and radiological remission after cessation of anti-rheumatic drugs.

The European League Against Rheumatism (EULAR) recommendations concluded that treatment should aim to suppress the disease activity as soon as possible, reduce symptoms, and retard the progression of joint damage and associated functional limitations (table 9).

In practice, clinical remission denotes absence of inflammation as determined by joint and laboratory evaluation and the patient's assessment.

EULAR/ACR remission committee proposed *new remission criteria* that include no more than one swollen and one painful joint on examination, a patient's global assessment of less than 10 mm on a 0–100 mm visual analogue scale, and normal concentrations of acute phase reactants.

Table 9 — Management of rheumatoid arthritis

Class of the drugs	The drug	The dose
DMARDs (disease modifying anti-rheumatic agents)		
DMARDs	Methotrexate (*first line treatment)*	7.5 mg (tab. 2.5 mg) once a week (if patients has no response in 1 month the dose can be increased to 15 mg)
Synthetic DMARDs	Sulfasalazine	500 mg twice daily (maximum 3 g)
	Cyclophosphamide	1–2 mg/kg
	Hydroxychloroquine	200–400 mg daily
	Ciclosporin A	2.5–4 mg/kg
	Azathioprine	Initial dose is 1 mg/kg, maximum 2.5–3 mg/kg
Methotrexate to be safe and effective in combination with other DMARDs		
Corticosteroids		
Corticosteroids	Prednisolon	7.5–15 mg/day
Biological agents: anticytokines or cytokine receptor antagonists		
TNF-α inhibitors	Infliximab	3–10 mg/kg q 4–8 weeks i.v.
	Adalimumab	40 mg qwk-q2wk
	Golimumab	50 mg q4wk
	Certolizumab	400 mg at week 1-2-4
	Etanercept	25 mg biw; 50 mg qwk
IL-6 receptor blockade, IL-1 blockade		
Inhibitors of cellu-	Abatacept	10-mg/kg i.v. infusion at weeks 0,2 and 4 and

lar activation T-cell modulation		every 4 weeks thereafter, the average dose, based on body weight, ranging from 500 to 1000 mg
B-cell modulation	Rituximab	Twice infusions on 1000 mg separated by 14 days

Early introduction of DMARDs prevents joint damage. Methotrexate is the first line treatment.

Evidence from randomised controlled trials shows that the combination of methotrexate and a TNF-α inhibitor is better than either drug alone at reducing clinical symptoms and progression of joint damage in patients with early disease and in those who do not respond to conventional DMARDs. Five TNF-α blocking agents are currently licensed for the treatment of rheumatoid arthritis (table).

An increased incidence of tuberculosis was seen in patients treated with TNF-α inhibitors, mainly as a result of reactivation of latent infections. Screening before starting treatment and anti-tuberculosis pretreatment if appropriate have greatly reduced this complication.

There is no convincing evidence that the overall risk for cancer is higher for patients given anti-TNF-α than for other patients with rheumatoid arthritis.

Expert guidelines recommend TNF-α inhibitors as the first choice of biological agent. If a patient does not respond to a first anti-TNF-α agent, then to the second one — rituximab, abatacept, or tociluzimab — can be considered, preferably in combination with methotrexate.

An evidence based approach to treatment

Start treatment with a single DMARD, preferably methotrexate (although NICE recommends adding another DMARD), combined with short-term glucocorticoids. If no response is seen, consider introducing a TNF-α blocker rather than switching to a combination of traditional DMARDs. Some guidelines recommend TNF-α blockers and methotrexate as initial treatment in high risk patients. Consider cautiously reducing and stopping treatment in patients in stable clinical remission, with prompt reintroduction if the diseases recurs.

Combination therapy for pain management in RA includes at least 2 drugs from the following classes: analgesics, nonsteroidal antiinflammatory drugs (NSAID), opioids, opioid-like drugs, and neuromodulators (antidepressants, anticonvulsants, and muscle relaxants).

Arthroscopic synovectomy is a safe and successful procedure in ankle joints affected by RA. The best clinical outcomes are achieved when the procedure is performed early in the disease course and when there is no evidence of cartilage degeneration.

Key Messages:

- Rheumatoid arthritis is an autoimmune disease that is characterized by synovial inflammation and hyperplasia, autoantibody production (rheumatoid factor and

anti-citrullinated protein antibody), cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.

- Rheumatoid arthritis can affect any joint, but it is usually found in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as in the wrists and knee.
- Morning stiffness in and around the joints, lasting at least 1 h before maximal improvement is a typical sign of rheumatoid arthritis.
- Radiography has long been the standard for detection of joint damage in rheumatoid arthritis. It demonstrates changes, such as erosions, joint space narrowing, and juxta-articular bone loss.
- Positive rheumatoid factor is usually found in seropositive rheumatoid arthritis.
- The new scoring system of the 2010 ACR/EULAR criteria incorporate the anti-Citrullinated Protein antibody (ACPA).
- Patients with ACPA-positive disease have a less favorable prognosis than those with ACPA-negative disease.
- Methotrexate is the first line drug, but in high risk patients early combination of methotrexate with prednisone or a tumour necrosis factor inhibitor improves outcomes.

CASE REPORT No.2

A 42-year-old female, a known case of rheumatoid arthritis for ten years was admitted with a history of passing reduced quantity of cola-colored urine for three days and anuria for one day, along with cough, shortness of breath and blood-mixed sputum.

She had received various regimens of methotrexate, hydroxychloroquine and steroids for seven years, which she had stopped for the last two and a half years and was taking tramadol hydrochloride and paracetamol as and when required.

There was no history of fever or drug intake in the recent past. She exhibited swan neck deformities of hands, pallor, and palpable purpuric rash over both lower limbs, bilaterally scattered crepts in the chest and splenomegaly.

On lab investigation she was found to have pancytopenia, deranged renal functions and 2+ proteinuria and active sediments in urine. Anti-neutrophilic cytoplasmic antibody-perinuclear and cryoglobulins in serum were found positive. Immunofixation showed cryoglobulins to be of mixed variety of Immunoglobulin M and G (IgM and IgG) with no prominent "M" band found on electrophoresis. Antibody against Hepatitis -C virus and its RNA (Anti-HCV and HCV RNA) were negative in serum. Rheumatoid factor and Antinuclear antibody were positive; but ds-DNA was negative. She had hypo-complementemia as well. Anti-glomerular basement membrane antibody was negative. Prothrombin time and Partial thromboplstin time were normal. Bone marrow biopsy did not reveal evidence of hematological malignancy. Upper gastrointestinal endoscopy did not show evidence of varices. Serial X-rays of chest revealed frequently changing fluffy shadows, suggestive of pulmonary hemorrhage. Provisional clinical diagnosis made was small-vessel vasculitis mediated by either anti-neutrophilic cytoplasmic antibody or cryoglobulinemia or secondary to

rheumatoid vasculitis itself, in presence of rheumatoid arthritis and Felty syndrome.

Empiric treatment was started and a diagnostic procedure was performed when the patient stabilized.

She was given one session of heparin-free hemodialysis and plasma filtration was initiated. Daily two liters of plasma was replaced with 5 % albumin, normal saline (0.9 %) and fresh frozen plasma in total, for seven days. Pulse of methylprednisolone was given (750 mg) for three days. It was followed by oral prednisolone (50 mg once daily with plan of weekly tapering of 10 mg/week). Cyclophosphamide could not be started in view of pancytopenia. With this treatment pulmonary hemorrhage resolved, rash and urine output improved and she became symptomatically better but she relapsed within three days of stopping plasma filtration.

Five more sessions of plasma filtration were given. Injection granulocyte colony stimulating factor (G-CSF) was administered, which resulted in surge of total leucocyte count to 54,000/mm^3 within a day and marginal increase in platelets. A pulse of cyclophosphamide (750 mg) was given simultaneously. TLC dropped to pretreatment levels within a week and injection G-CSF was repeated. After one month of treatment, patient's skin, pulmonary and renal manifestations remained in remission but platelet count dropped to 27,000/ mm^3. She died of massive upper gastrointestinal bleeding, possibly due to steroid-induced ulcer.

OSTEOARTHRITIS. GOUT

OSTEOARTHRITIS

Osteoarthritis (OA), the most common musculoskeletal disorder, is complex, multifaceted, and characterized by degradation of articular cartilage and alterations in other joint tissues.

The likelihood of developing osteoarthritis increases with age. Epidemiological studies have revealed that there are both endogenous and exogenous risk factors for osteoarthritis (table 10). Genetic factors unquestionably play a role.

Table 10 — Endogenous and exogenous risk factors for osteoarthritis

Endogenous risk factors	Exogenous risk factors
Age	Macrotrauma
Sex	Repetitive microtrauma
Heredity	Overweght
Ethnic origin	Resective joint surgery
Post-menopausal changes	Lifestyle factors (alcohol, nicotin)

Etiology of osteoarthritis

Osteoarthritis is classified as either primary (idiopathic) or secondary.

The most common localisation of the affected joints are the knee and coxal (gonartrosis and coxartrosis) ones.

Among the various structures making up the joint, the hyaline joint cartilage is the main target of the harmful influences that cause osteoarthritis and the structure in which the disease begins. 95 % of hyaline cartilage consists of extracellular matrix.

Etiologies of secondary osteoarthritis:

- post-traumatic;
- congenital/malformation;
- malposition (varus/valgus);
- postoperative;
- metabolic;
- rickets;
- hemochromatosis;
- chondrocalcinosis;
- ochronosis;
- endocrine disorders;
- acromegaly;
- hyperparathyroidism;
- hyperuricemia;
- aseptic osteonecrosis.

Pathophysiology of osteoarthritis

The dynamic equilibrium between the continual, ongoing formation and breakdown of the cartilaginous matrix is regulated by an interplay of anabolic influences (e.g., insulin-like growth factors I and II) and catabolic influences (e.g., interleukin-1, tumor necrosis factor alpha, and proteinases). To a limited extent, these mechanisms can eliminate or compensate for the harmful influences that cause osteoarthritis by stimulating and modifying the metabolic activity of chondrocytes. When these harmful influences exceed the system's ability to compensate, however, matrix degradation occurs; this is the first step in the development of osteoarthritis, which can progress to advanced disease. The reason why the cartilage degenerates is not yet well understood. Mechanical and enzymatic factors are thought to impair chondrocyte function and damage the matrix.

Genetic predisposition

Genetic predisposition may have an effect on OA in a variety of ways, by e.g. influencing susceptibility to the disease, age at onset, progression, subtype and, probably, response to treatment. Identifying susceptibility genes may be useful in helping to explain the disease's mechanisms, since it may uncover the primary biological events causing OA. Genetic predisposition may influence the type of reactivity of some innate functions involved in the inflammatory response.

Biomechanical reactivity

The biological events induced by mechanical factors may destabilise the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix and subchondral bone.

Cytokines, growth factors and metalloproteinases

Cytokines and growth factors involved in OA may be released from different cellular sources, such as chondrocytes, synovial cells or osteocytes. It is almost certain that cytokines are involved in OA development and progression, and that blocking cytokines is useful in protecting cartilage from damage. IL-1 and TNF are the most important and best studied cytokines in OA.

Adipokines

Adipokines include a variety of pro-inflammatory peptides or cytokines which contribute to the «low-grade inflammatory state» of obese subjects. The best known of this family are leptin, adiponectin and resistin.

Subchondral bone

An increasing body of evidence shows that subchondral bone is actively involved in the pathogenesis of OA through several possible mechanisms, including a defect in its role as a shock absorber; abnormal osteocyte function; increased production of bonederived products, cytokines, and MMPs.

Symptoms and signs of osteoarthritis

Persons suffering from osteoarthritis complain of limited movement and pain when they initiate movement or start to walk. In advanced disease, they may complain of nocturnal or permanent joint pain.

Diagnostic evaluation of osteoarthritis

The major elements of the diagnostic evaluation are the history, physical examination, imaging studies, and, in some cases where special questions arise, laboratory testing.

History

Patients suffering from osteoarthritis often complain of pain on movement, typically occurring when movement is initiated or when the patient begins to walk. The pain is often described as a dull ache. As osteoarthritis progresses, the pain becomes continuous, and the functionality of the joint is severely impaired.

Specific historical features of osteoarthritis:

- pain;
- pain at the beginning of movement;
- pain during movement;
- permanent / nocturnal pain;
- need for analgesics;
- loss of function;
- stiffness;
- limitation of range of movement;
- impairment in everyday activities;
- need for orthopedic aids;
- other symptoms;
- crepitation;

- elevated sensitivity to cold and/or damp;
- stepwise progression.

Physical examination

Each stage of the disorder has its own characteristic physical findings.

Joint pain is the leading symptom, usually becoming worse when the affected joint is put in motion and improving when it is at rest. Persistent pain at rest, or at night, can be a sign of advanced osteoarthritis.

The physical examination should incorporate all relevant findings, including findings on inspection and palpation (figure 6), testing of the range of movement, and special functional tests when needed (e.g., ligament stability, meniscus tests, gait analysis).

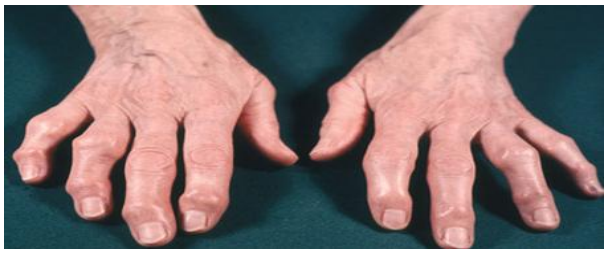


Figure 6 — Severe osteoarthritis of the hands
Osteoarthritis affecting the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bouchard's nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base.

From: Harrison's Principles of Internal Medicine / A. C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

The physical examination of the joint ligaments consists of the following:

- testing of the lateral ligaments with varus or valgus stress;
- testing of the anterior and posterior cruciate ligaments with the drawer test.

Likewise, the menisci should be diagnostically tested manually, and the femoropatellar joint should be assessed for signs of irritation and for normal patellar mobility. In the Zohlen test, the patient’s knee is extended, and the examiner gently presses the patella into the trochlear groove while asking the patient to tense the extensor muscles of the thigh (quadriceps femoris). If this maneuver causes pain, the test is positive. Limping revealed by gait analysis may be due to shortening of one leg.

Physical examination includes:

- generally relevant data;
- inspection and palpation;
- examination of the range of motion;
- special functional tests (e.g., meniscus tests, gait analysis).

Imaging studies of osteoarthritis

X-ray imaging studies are used both for primary diagnosis and to assess the progression of the disease (figure 7).

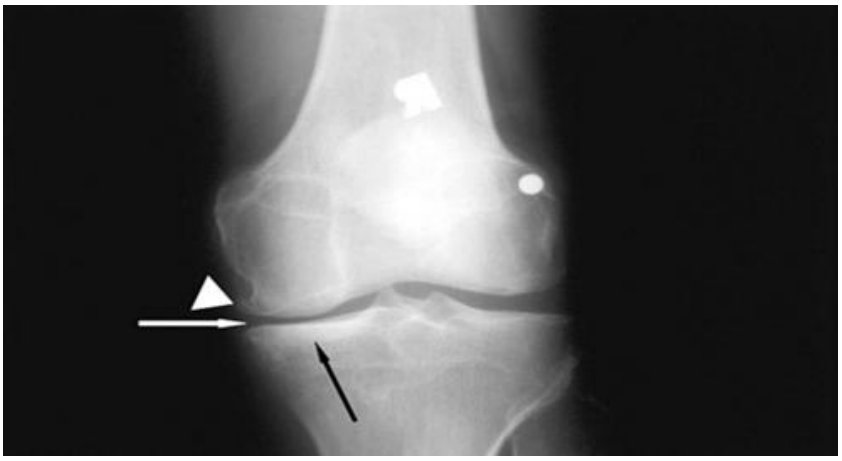


Figure 7 — X-ray of knee with medial osteoarthritis:
Note the narrowed joint space on medial side of the joint only (*white arrow*),
the sclerosis of the bone in the medial compartment providing evidence of cortical thickening (*black arrow*), and the osteophytes in the medial femur (*white wedge*)

From: Harrison's Principles of Internal Medicine / A.C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

Plain films should be obtained in standardized fashion in at least two planes (a-p and lateral). Special functional plain films can be obtained as well to answer specific diagnostic questions. The typical radiological signs of osteoarthritis that can be seen on plain films are incorporated in the staging system of Kellgren.

The staging of osteoarthritis of the knee, after Kellgren and Lawrence

Stage 0:

- no abnormality.

Stage 1:

- incipient osteoarthritis, beginning of osteophyte formation on eminences.

Stage 2:

- moderate joint space narrowing, moderate subchondral sclerosis.

Stage 3:

- >50% joint space narrowing, rounded femoral condyle, extensive subchondral sclerosis, extensive osteophyte formation.

Stage 4:

- joint destruction, obliterated joint space, subchondral cysts in the tibial head and femoral condyle, subluxed position.

Supplementary radiological studies can include MRI, to demonstrate the hyaline cartilage, as well as ^{99m}Tc bone scanning, to assess metabolic activity in the subchondral bone. These tests do not appear to yield much additional useful information. Ultrasonography is a good way to demonstrate the soft tissues and fluid-filled spaces, but it is highly examiner-dependent, and much experience is needed for the proper assessment of its findings.

Staging of osteoarthritis

The clinical symptoms and signs of osteoarthritis and its radiological correlates follow a typical course as the disease progresses and can thus be incorporated into a clinically useful staging system. The WOMAC osteoarthritis index, for example, reflects the clinical severity of the disease. Though not commonly used in routine clinical practice, the WOMAC index permits a valid, reproducible assessment of the degree of impairment by pain and loss of function. A number of different joint-specific scoring systems have been developed; they vary with respect to the weighting of subjective and objective criteria.

Treatment of osteoarthritis

Osteoarthritis is not a curable disease at present, as the mechanism by which it arises and progresses remains incompletely understood. Therefore, the goal of treatment is to alleviate the signs and symptoms of the disease and, if possible, to slow its progression.

The therapeutic spectrum ranges from general measures to physiotherapy, orthopedic aids and orthoses, pharmacotherapy, and finally surgery and rehabilitation.

Surgery is indicated when the patient's symptoms accord with the physical and radiological findings and all conservative treatments have been exhausted.

Conservative treatment

Conservative treatment is provided in stepwise fashion, as recommended by the European League Against Rheumatism (EULAR).

EULAR stepwise recommendations for the conservative treatment of osteoarthritis of the knee:

1. Optimal management requires a combination of non-pharmacological and pharmacological treatment modalities.
2. The treatment of knee osteoarthritis should be tailored according to risk factors, severity of pain, presence or absence of joint effusion, and degree of osteoarthritic damage.
3. Non-pharmacological treatment: weight loss, orthopedic aids, physical and physiotherapeutic measures.
4. Paracetamol is the analgesic of first choice for long-term use, if effective (table 11).
5. Topical applications (e.g., non-steroidal anti-inflammatory drugs [NSAID]) are effective.
6. Opioid analgesics can be used effectively if paracetamol or NSAID are ineffective or poorly tolerated.
7. Symptomatic slow-acting drugs for osteoarthritis (SYSADOA) are an effective symptomatic treatment (table 11).

8. Intra-articular injection of corticosteroids to treat effusions and severe pain.

Table 11 — Pharmacotherapy of osteoarhtritis

The drug	The dosage
Analgesics/anti-inflammatory drugs	
Paracetamol (acetaminophen)	500 mg 2–3 times daily (maximum 3 g)
Naproxen	375–500 mg bid
Ibuprofen	600–800 mg 3–4 times a day
Specific inhibitors of COX-2	100–200 mg daily
Glucocorticoids	
Intraarticular injections varies from 3 to 5 weekly injections depending on preparation	
Opioids	
Consider for severe symptoms if surgery contraindicated or delayed; commence at low dose, titrate dose and monitor for adverse events	
Slow-acting drugs for osteoarthritis: symptomatic slow-acting drugs for osteoarthritis (SYSADOA) and disease-modifying osteoarthritis drugs (DMOAD)	
D-glucosamine sulphate	750 mg 2 times a day — 6 months
Chondroitin sulphate	1000 mg 2 times a day — 6 months
Diacerein	50 mg 2 times daily > 1 month
Anti-cytokines	
see in table 9	

When signs of inflammation arise, intra-articular glucocorticoid injections can very rapidly eliminate a joint effusion. The most suitable type of glucocorticoid for injection has been found to be the one with a long half-life, in crystalloid solution, with a small crystal size (e.g., triamcinolone acetonide or hexacetonide, at a dose of 10 mg or 40 mg, respectively). Steroid injections should be used with caution in diabetic patients who are already hyperglycemic. All joint punctures and injections must be performed with the proper sterile technique, as described in the guidelines.

The AAOS guidelines

Intra-articular corticosteroid injections are recommended for no more than short-term use.

There is a heterogeneous group of medications that, unlike the COX-2 inhibitors, do not inhibit prostaglandin synthesis.

Slow-acting drugs for osteoarthritis (SADOA) can be given either orally or directly into the joint. Their effect, as the term SADOA implies, is of gradual onset. The mechanisms of action of the individual agents have not yet been fully elucidated; they range from inhibition of inflammation and nociceptor blockade to a potential alteration of the viscoelastic properties of cartilaginous tissue.

For the sake of completeness, mention is also made of other treatment approaches such as ointments, herbal and homeopathic remedies, leeches, and special diets containing gelatin and amino sugars. The efficacy of these treatments seems questionable.

Physiotherapeutic measures

Physiotherapy for knee osteoarthritis includes exercise therapy as well as physical measures, including the following:

- ultrasound application (to relieve pain and support endogenous healing processes);
- electrotherapy;
- muscle stimulation;
- application of heat and cold;
- transverse friction (a special massage technique);
- acupuncture;
- stretching/walking;
- traction.

Orthopedic aids and orthoses

Sometimes, an orthopedic aid or orthosis is necessary. Orthopedic aids include, among others, cushioned heels (providing a shock-absorbing function) and wedges to elevate the inner or outer side of the shoe, thereby correcting the axis to a certain extent and taking mechanical stress off the affected part of the joint. Some patients initially do not want to accept these aids, but can be made more amenable to them by adequate patient education and the active involvement of orthopedic technicians and shoemakers. Knee orthoses are also intended to relieve pain and improve joint function.

Further treatment options:

- bone-stimulating treatments;
- joint surface restoration;
- corrective osteotomy near the knee joint.

Surgery is indicated only when all conservative measures have been tried without success, in patients with advanced osteoarthritis and severe subjective impairment from their symptoms.

Joint-preserving surgical treatment options:

- symptomatic;
- lavage;
- shaving;
- debridement;
- bone-stimulating;
- drilling;
- microfracturing;
- abrasion arthroplasty;
- joint surface restoration;
- autologous chondrocyte transplantation (ACT);
- autologous osteochondral transplantation (OCT);
- corrective osteotomy near the joint.

Surgery

The overwhelming majority of intra-articular operations are performed through an arthroscope. The main advantages of arthroscopic procedures are minimal operative trauma and a very low infection rate (under 0.1 %).

The goal of bone-stimulating techniques is to open the subchondral cartilage and thereby bring pluripotential stem cells to the joint surface, where they are then supposed to form fiber bundles under the influence of mechanical and biological forces. Studies have not revealed any significant differences between the various methods that are used.

Autologous chondrocyte transplantation was described in 1984 by Brittberg. In this technique, cartilage cells are taken from the joint, enzymatically isolated and cultured ex vivo, and then put back into the joint at the site of the cartilage defect, which is prepared ("freshened up") before the cultured cells are added. Long-term results are not yet available to document the survival of the reimplanted cartilage cells.

Symptomatic, joint-preserving surgical techniques:

- lavage;
- shaving;
- debridement.

In autologous osteochondral transplantation (OCT), also called mosaicplasty, cylinders of cartilage and bone are taken from a part of the joint that is not affected, and then inserted into the cartilage defect with press-fit technology. In principle, OCT can be performed through an arthroscope, unless the defect is too large. The reported results of OCT are, in general, very promising.

Corrective osteotomy near the knee joint can be performed in the frontal, sagittal, or transverse plane, in either the distal portion of the femur or the proximal portion of the tibia (i.e., just above or just below the knee). The goal of such operations is to «tip» the affected portion of the joint out of the zone of excessive mechanical stress, redirecting the weight-bearing axis toward the portion of the joint that is still largely intact.

Bone-stimulating surgical techniques:

- drilling;
- microfracturing;
- abrasion arthroplasty.

Methods of restoring the joint surface:

- autologous chondrocyte transplantation (ACT);
- autologous osteochondral transplantation (OCT).

Key Messages:

- Osteoarthritis is characterized by degradation of articular cartilage and alterations in other joint tissues.
- Patients suffering from osteoarthritis often complain of pain on movement, typically occurring when movement is initiated or when the patient begins to walk.

- The typical radiological findings of osteoarthritis are joint space narrowing, subchondral sclerosis, subchondral cysts, and peripheral osteophytes.
- Optimal management of osteoarthritis requires a combination of non-pharmacological and pharmacological treatment modalities.
- Paracetamol is the analgesic of first choice for long-term use in osteoarthritis.
- Symptomatic slow-acting drugs for osteoarthritis (SYSADOA) are an effective symptomatic treatment. This group includes hyaluronic acid, D-glucosamine sulphate, chondroitin sulphate, and diacerein.

GOUT

Gout is a type of inflammatory arthritis induced by the deposition of monosodium urate crystals in synovial fluid and other tissues and is associated with hyperuricemia.

Hyperuricemia is defined as a serum urate level of 6.8 mg per deciliter (404 μmol per liter) or more, the limit of urate solubility at physiologic temperature and pH. Hyperuricemia is caused by the overproduction of urate or, more commonly, by renal urate underexcretion.

However, not all persons with hyperuricemia have gout. Data from NHANES 2007-2008, in which the definition of hyperuricemia was a sUA level greater than 7.0 mg/dL for men and greater than 5.7 mg/dL for women, showed the mean sUA level to be 6.1 mg/dL in men and 4.9 mg/dL in women, corresponding to gout prevalences of 21.2 % and 21.6 % respectively.

Purine metabolism and hyperuricemia

Purines are crucial for a range of normal physiologic functions. They are the essential building blocks for nucleic acids (deoxyribonucleic and ribonucleic acid), extra- and intracellular messengers (adenosine triphosphate and G-protein coupled reactions), metabolic regulators (cyclic adenosine monophosphate), coenzymes, antioxidants, and neurotransmitters. Uric acid is the end product of purine degradation. It exists as the urate ion at physiologic pH and has a very narrow window of solubility. The enzyme xanthine oxidase is required for the conversion of xanthine to urate. Humans lack the enzyme urate oxidase (uricase), which converts urate in other species to the highly soluble compound allantoin.

The transition from hyperuricemia to the formation of uric acid crystals and subsequent inflammation is dependent on several factors in the local microenvironment, including both pH and temperature. Once crystals form, an intense inflammatory response is triggered. There is an initial interaction with mononuclear cells, which results in a release of inflammatory cytokines and chemokines, resulting in neutrophil recruitment and activation. Once neutrophils migrate to the site of inflammation, there is aggressive phagocytosis of the uric acid crystals, de-

layed phagocytic apoptosis, and, ultimately, neutrophil death with massive enzyme and mediator release, which leads to the clinical acute gouty attack.

Pathophysiologic effects of uric acid in renal disease

Association of uric acid with chronic kidney disease dates back to 1890s. Uric acid and renal disease association first emerged in the context of the high prevalence of renal dysfunction – the so-called gouty nephropathy — in patients with gout. Hyperuricemia induces endothelial dysfunction and inflammation, extensive tubular crystal deposition, alters glomerular hemodynamics and contributed to the progression of established renal injury.

Risk factors of gout

Genomewide association studies have identified common polymorphisms in several genes involved in renal urate transport that are associated with gout, including *SLC2A9, ABCG2, SLC17A3,* and *SLC22A12*. Rare X-linked inborn errors of metabolism can cause gout.

The prevalence increases with age and is higher among men than among women, with a ratio of 3 or 4 to 1 overall. However, this sex disparity decreases at older ages, at least in part because of declining levels of estrogen, which has uricosuric effects in women. The rising incidence and prevalence of gout are probably related to the aging of the population, increasing levels of obesity, and dietary changes.

The use of thiazide diuretics, cyclosporine, and low-dose aspirin (< 1 g per day) can cause hyperuricemia, whereas high-dose aspirin (≥ 3 g per day) is uricosuric.

Factors that are associated with hyperuricemia and gout include insulin resistance, the metabolic syndrome, obesity, renal insufficiency, hypertension, congestive heart failure, and organ transplantation. The uricosuric effects of glycosuria in diabetes may reduce the risk of gout.

The risk of incident gout is increased in persons with an increased intake of dietary purines (particularly meat and seafood), ethanol (particularly beer and spirits), soft drinks, and fructose and is decreased in those with an increased intake of coffee, dairy products, and vitamin C (which lower urate levels).

Triggers for recurrent flares include recent diuretic use, alcohol intake, hospitalization, and surgery. Urate-lowering therapy, which reduces the risk of gout attacks in the long term, can trigger attacks in the early period after its initiation, presumably as a result of mobilization of bodily urate stores.

Clinical symptoms of gout

Gout has two clinical phases.

The first phase is characterized by intermittent acute attacks that spontaneously resolve, typically over a period of 7 to 10 days, with asymptomatic periods between attacks.

With inadequately treated hyperuricemia, transition to the second phase can occur, manifested as chronic tophaceous gout, which often involves polyarticular attacks, symptoms between attacks, and crystal deposition (tophi) in soft tissues or joints. Although the prevalence of tophaceous gout varies among popula-

tions. Recurrent attacks are common. Approximately two thirds of patients with at least one gout attack in the previous year had recurrent attacks.

Diagnostic evaluation of gout

The presence of monosodium urate crystals and/or tophus and response to colchicine have the highest clinical diagnostic value.

The diagnostic standard remains synovial fluid or tophus aspiration with identification of negatively birefringent monosodium urate crystals under polarizing microscopy. Crystals are detectable during attacks and also potential between attacks, primarily in the previously inflamed joints in patients with hyperuricemia.

Hyperuricemia may not be present during acute gout attacks and therefore may not be a helpful criterion for diagnosis.

A typical presentation that is strongly suggestive of the diagnosis includes rapid development of severe pain (i.e., within 24 hours), erythema, and swelling in a characteristic joint distribution — for example, in the first metatarsophalangeal joint (podagra).

The differential diagnosis of acute gout includes other crystal-induced arthritides (e.g., calcium pyrophosphate dihydrate) and a septic joint. Joint aspiration with Gram's staining and culture must be performed if a septic joint is suspected, even if monosodium urate crystals are identified. Older adults, particularly women, may present with polyarticular involvement, which may be mistaken for rheumatoid arthritis; a tophus may be mistaken for a rheumatoid nodule. Tophaceous deposits that are not clinically apparent may be visualized by plain radiography or another imaging method. A diagnosis of gout should include prompt evaluation for potentially modifiable risk factors (e.g., dietary habits) and associated coexisting illnesses (e.g., hypertension and hyperlipidemia) that may require intervention.

Treatment options of gout

Acute gout

The main aim of therapy for acute gout is rapid relief of pain and disability caused by intense inflammation. Options for managing acute attacks are in table 12.

Table 12 — Management of acute gout

The drug	The dosage
Nonsteroidal antiinflammatory drugs (NSAIDs)	
Indomethacin	25–50 mg 1–2 times daily
Ibuprofen	800 mg 1–2 times daily
Diclofenac	50 mg 1–2 times daily
Colchicine: 1.2 mg at the onset of a flare, followed by 0.6 mg 1 hour later	
Glucocorticoids	
Prednison	30–50 mg/d as the initial dose and gradually tapered with the resolution of the attack
Methylprednisolone	25–50 mg intraarticular
Triamcinolone	20–40 mg intraarticular
Adrenocorticotropic hormone — ?	
Corticotropin	40–80 IU intramuscular injection in a single dose or every 12 h for 1–2 days

The choice of agent, dose, and duration of therapy is guided by consideration of coexisting illnesses that preclude the safe use of a particular regimen, as well as the severity of gout. Adjunctive measures include applying ice to and resting the affected joint.

NSAIDs and colchicine are first-line agents for acute attacks. Oral colchicine has long been used, although it has only recently (in 2009) been approved by the Food and Drug Administration (FDA) for use in patients with acute gout.

The relative efficacy of colchicine as compared with NSAIDs is unknown. In head-to-head studies, various NSAIDs have had similar benefits for acute gout, and a controlled trial showed the efficacy of tenoxicam over placebo.

The dose and duration of therapy for acute gout should be sufficient to eradicate the profound inflammatory response. Although randomized trials have generally studied the effects of short courses of treatment on pain reduction, clinical experience suggests that 7 to 10 days of treatment may be necessary to ensure the resolution of symptoms. Increased doses of antiinflammatory drugs are typically prescribed for the first few days, with a reduction in the dose once symptoms begin to improve. Flares should be treated without interruption of urate-lowering therapy. A «medications in the pocket» strategy should be considered for patients with established gout so that therapy can be started promptly at the onset of symptoms that are consistent with typical attacks.

There is evidence that attacks of gout are caused by the activation of the NLRP3 inflammasome by urate crystals, leading to the release of interleukin-1β. For this reason, interleukin-1 antagonists are being studied as potential options for patients in whom other treatments are not feasible.

Hyperuricemia

Pharmacologic approaches

The purpose of lowering serum urate levels is to prevent acute flares and the development of tophi. However, gout does not develop in all patients with hyperuricemia, and antihyperuricemic therapies are not without risk.

Recommendations that are based on both consensus and evidence support the consideration of urate-lowering therapy in patients with hyperuricemia who have at least two gout attacks per year or tophi (as determined by either clinical or radiographic methods). However, the severity and frequency of flares, the presence of coexisting illnesses (including nephrolithiasis), and patient preference are additional considerations.

Urate-lowering therapy should not be initiated during acute attacks but rather started 2 to 4 weeks after flare resolution, with a low initial dose that is increased as needed over a period of weeks to months, and with close monitoring of urate levels, renal function, and adverse effects. The dose should be adjusted as necessary to maintain a serum urate level below 6 mg per deciliter (357 μmol per liter), which is associated with a reduced risk of recurrent attacks and tophi. It is uncertain whether

a more stringent target of less than 5 mg per deciliter (297 μmol per liter) results in greater disease control. Therapy is generally continued indefinitely (table 13).

Table 13 — Management of hyperuricemia

The drug	The dosage
Xanthine oxidase inhibitors	
Allopurinol	300 mg daily (up to 800 mg)
Febuxostat	40–80 mg daily
Uricosuric agents	
Probenecid	250 mg (up to 500) twice daily
Sulfinpyrazone	100 mg daily
Benzbromarone (has become restricted in some European countries)	200 mg daily
Uricase agents	
Pegloticase	8 mg i.v. twice in month

Xanthine oxidase inhibitors block the synthesis of uric acid and can be used regardless of whether there is overproduction of urate. In this class of drugs, the one most commonly prescribed to lower urate levels is allopurinol, which is effective in decreasing flares and tophi, particularly among patients in whom target urate levels are achieved. As compared with a daily dose of 300 mg of allopurinol, febuxostat at daily doses of 80 mg and 120 mg was 2.5 and 3 times as likely, respectively, to achieve serum urate levels of less than 6 mg per deciliter in a 52-week trial. In another study involving patients with renal impairment (defined as a creatinine clearance of 30 to 89 ml per minute), daily doses of 80 mg and 40 mg of febuxostat were superior to 300 mg of allopurinol (or 200 mg in patients with moderate renal impairment) for lowering serum urate to a level below 6 mg per deciliter. There was no increase in cardiovascular risk or hypersensitivity associated with the use of either dose of febuxostat, as compared with allopurinol, although the trial was not powered for such comparisons.

Uricosuric drugs block renal tubular urate reabsorption. Although these drugs can be used in patients with underexcretion of urate (accounting for up to 90 % of patients with gout), they are used less frequently than xanthine oxidase inhibitors and are contraindicated in patients with a history of nephrolithiasis.

Uricase converts uric acid into soluble allantoin. Pegloticase, a polyethylene glycolated (pegylated) modified porcine recombinant uricase, was approved by the FDA in 2010 for chronic gout that is refractory to conventional treatments. The approval was based on data from two double-blind, randomized, placebo-controlled, 6-month trials showing the drug's urate-lowering and tophus-reducing effects. However, pegloticase must be administered intravenously, and infusion reactions were common. Rasburicase, which is approved for use in preventing the tumor lysis syndrome, is not appropriate for use in patients with gout because of its immunogenicity and short half-life.

Lifestyle, Nutrition, and Adjunctive Therapies

Observational data indicate that nonpharmacologic approaches, such as avoiding alcohol or modifying one's diet, can reduce serum urate levels but may not be sufficient to control established gout.

In one randomized trial involving persons without gout, 500 mg of vitamin C per day for 2 months resulted in serum urate levels that were 0.5 mg per deciliter (30 μmol per liter) lower than in those receiving placebo.

The intake of dairy milk reduced serum urate levels by approximately 10 % during a 3-hour period in a small, randomized, crossover trial involving healthy volunteers. Whether these approaches would have similar effects in persons with gout, or with a longer duration of therapy, is not known.

Losartan and fenofibrate, which have uricosuric effects, may be considered in patients with gout who have hypertension or hypertriglyceridemia, respectively, although it is not known whether their use reduces the frequency of gout attacks.

Key Messages:

- Gout is a type of inflammatory arthritis induced by the deposition of monosodium urate crystals in synovial fluid and other tissues.
- Hyperuricemia is caused by the overproduction of urate or, more commonly, by renal urate underexcretion.
- A typical presentation of gout includes rapid development of severe pain (i.e., within 24 hours), erythema, and swelling in a characteristic joint distribution — in the first metatarsophalangeal joint.
- Crystal deposition (tophi) in soft tissues or joints can occurs in gout.
- NSAIDs and colchicine are first-line agents for acute attacks of gout.
- Urate-lowering therapy should not be initiated during acute attacks but rather started 2 to 4 weeks after flare resolution.
- Three classes of drugs are approved for lowering urate levels: xanthine oxidase inhibitors (including allopurinol, febuxostat), uricosuric agents (including probenecid, sulfinpyrazone, and benzbromarone), and uricase agents (pegloticase).

CASE REPORT No.3

A healthy and well-nourished 42-year-old woman came to us for a consultation. She had sustained torsional injury to her right knee from a fall at age 18. In anamnesis, she had undergone a tuberosity transfer procedure on the right knee because of lateralization of the patella. A total of three arthroscopic procedures had been performed because of medial meniscal damage in the right knee. She had been asymptomatic for a long time thereafter, but then presented to us again because she had been suffering for six months from very severe pain related to weight-bearing on the right knee, localized in the medial compartment of the knee. She could walk for only 15 minutes without crutches. On clinical examination, the most prominent finding was tenderness over the medial joint

space, with a medial meniscus sign. The right knee joint was freely mobile, with stable ligaments. Further findings included a joint effusion of considerable size and mild retropatellar crepitations. The X-rays (knee in two planes, axial patellar view and whole-leg radiograph) showed osteoarthritis of the knee, more severe on the medial side, with narrowing of the joint space and osteophyte formation, a well-centered patella, and mild valgus deviation of the axis. Knee arthroscopy revealed an area of stage 4 cartilaginous damage in the anteromedial tibial plateau measuring 5 × 5 mm, as well as the radial tear of the medial meniscus. The medial meniscus was partially resected, and microfracturing of the medial tibial plateau was performed. After six weeks of partial weight-bearing (15 kg), the patient was fully mobile and was asymptomatic for months thereafter.

SYSTEMIC LUPUS ERYTHEMATOSUS. SYSTEMIC SCLEROSIS

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that predominantly affects women and typically has manifestations in multiple organs.

Pathogenesis of systemic lupus erythematosus

Immune-system aberrations, as well as heritable, hormonal, and environmental factors, contribute to the expression of organ damage. Immune complexes, autoantibodies, autoreactive lymphocytes, dendritic cells, and local factors are all involved in clinical manifestations of systemic lupus erythematosus.

Genetic influences

Genetic factors confer a predisposition to the development of SLE (figure 8). Although in rare cases SLE may be associated with the deficiency of a single gene (e.g., the complement components C1q and C4), the disease more commonly results from the combined effect of variants in a large number of genes. Some genes have been associated with several autoimmune diseases (e.g., *STAT4* and *PTPN22* with rheumatoid arthritis and diabetes); others appear to increase the risk of SLE specifically. A recent largescale replication study confirmed some of these associations and identified *TNIP1*, *PRDM1*, *JAZF1*, *UHRF1BP1*, and *IL10* as risk loci for SLE.

Environmental influences

Epigenetic changes such as DNA hypomethylation have been attributed to medications known to cause SLE (figure 8). Smoking and exposure to ultraviolet light have been implicated in epidemiologic studies. The possibility that viruses may trigger SLE has been considered during the past 40 years. The faster seroconversion to Epstein-Barr virus (EBV) infection and higher viral load in patients with SLE than in normal subjects.

Female hormones and sex

Hormones contribute through unknown mechanisms to the increased prevalence of SLE among women. Pregnancy may aggravate SLE, and although it is not clear whether rising levels of estradiol or progesterone play a role, a link between pregnancy outcome and the status of the disease at conception has been noted.

Epigenetic regulation of gene expression

DNA accessibility to transcription factors, and thus gene expression, is regulated by DNA methylation and histone modifications (acetylation and methylation). Hydralazine and procainamide inhibit DNA methylation and can induce manifestations of lupus in healthy persons.

Immune cells and cytokines

In the patients with SLE antigen receptor-mediated activation in T and B cells is altered, a reduction in the number of naive B cells is observed, and the number of plasma cells is increased in the peripheral blood.

Interferon-α, CD40 ligand, free nucleosomes, and autoantibody-DNA complexes cause differentiation and activation of normal dendritic cells and stimulate their cytokine production. Dendritic cells secrete large amounts of type I interferon (interferon-α).

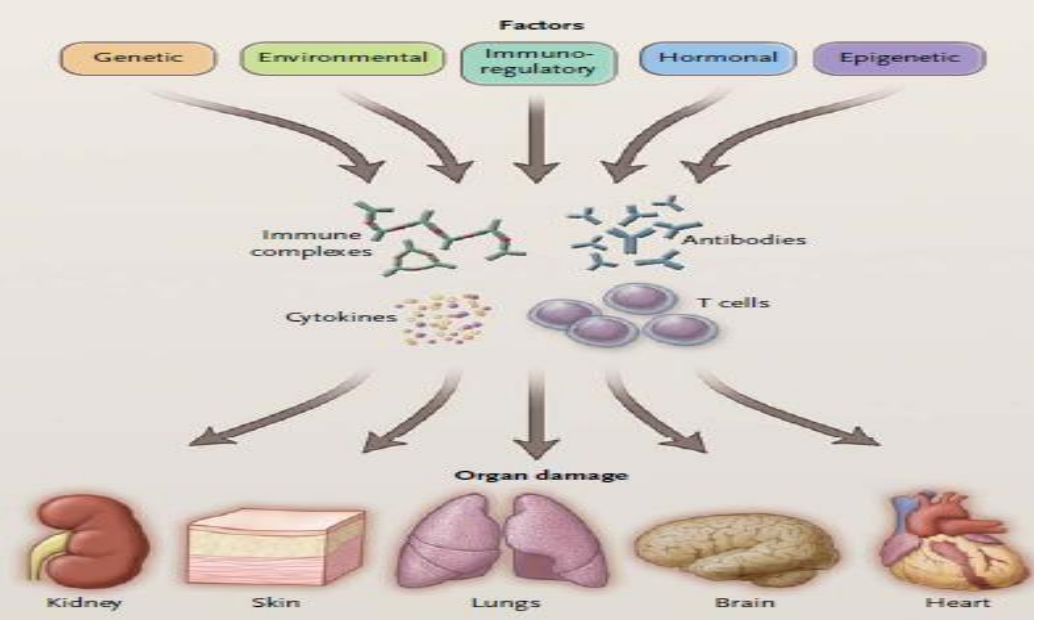


Figure 8 — Overview of the pathogenesis of systemic lupus erythematosus: Genetic, environmental, hormonal, epigenetic, and immunoregulatory factors act either sequentially or simultaneously on the immune system. The action of pathogenic factors results in the generation of autoantibodies, immune complexes, autoreactive or inflammatory T cells, and inflammatory cytokines that may initiate and amplify inflammation and damage to various organs. The affected target organ may be further damaged by local factors

From: Tsokos, G. C. Mechanisms of disease systemic lupus erythematosus / G. C. Tsokos // N Engl J Med. — 2011. — Vol. 365. — P. 2110–2121.

Tissue injury in SLE

Immune complexes are central players in the tissue injury in SLE. They are formed in large amounts as antinuclear antibodies bind to the abundant nuclear material in blood and tissues, and they are not cleared promptly because the Fc and complement receptors are numerically and functionally deficient. In addition to activating complement, immune complexes may alter the function of Fc receptors.

In the kidney, immune complexes accumulate in the subendothelial and mesangial areas first, followed by deposition in the basement membrane and subepithelial areas. Anti-DNA and anti-nucleosome antibodies contribute to lupus nephritis, and anti-chromatin-chromatin immune complexes are present in the mesangium of patients with lupus nephritis.

Immune complexes may accumulate in the skin and the central nervous system. Anti-NMDAR antibodies in the cerebrospinal fluid and the brain in patients with SLE have been linked to neurocognitive defects. Proinflammatory cytokines that are present in the cerebrospinal fluid of patients with SLE (interleukin-6, interferon-α, and interleukin-1) compromise the blood-brain barrier.

Anti-Ro antibodies may alter the function of myocytes and cells of the conduction system and link to heart block.

Anti-blood-cell antibodies activate complement and cause cytopenias.

Some patients with SLE have antibodies against phospholipids and β_2-glycoprotein. The presence of such antibodies is linked to thrombotic events and fetal loss in mice and is known as the antiphospholipid syndrome.

Atherosclerosis-attributed vascular events are significantly more frequent in patients with SLE than in matched healthy persons. Several factors contribute to this increased frequency, including antibodies to lipoproteins, oxidized lipoproteins, hypertension, and the metabolic syndrome.

Diagnostic of Systemic Lupus Erythematosus

Table 14 — American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus (SLE)*

Criterion	Definition
Malar rash	A rash on the cheeks and nose, often in the shape of a butterfly
Discoid rash	A rash that appears as red, raised, disk-shaped patches
Photosensitivity	A reaction to sunlight that causes a rash to appear or get worse
Oral ulcers	Sores in the mouth
Arthritis	Joint pain and swelling of two or more joints
Serositis	Inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain, which is worse with deep breathing (pericarditis)
Kidney disorder	Persistent protein or cellular casts in the urine
Neurologic disorder	Seizures or psychosis
Blood disorder	Anemia (low red-cell count), leukopenia (low whitecell count), lymphopenia (low level of specific white cells), or thrombocytopenia (low platelet count)
Immunologic disorder	Positive test for anti-double-stranded DNA, anti-Sm, or antiphospholipid antibodies
Abnormal antinuclear antibodies	Positive antinuclear-antibody test
* Four of the 11 criteria are needed for the formal diagnosis of SLE.	

Prospects for new therapies of SLE

Patients with SLE are treated with nonsteroidal antiinflammatory drugs, antimalarial agents, glucocorticoids, and immunosuppressive drugs, including cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil. The choice of the drug is determined largely by the severity of the disease and the function of the involved organ.

Treatment approaches for SLE*

Aspirin†
Glucocorticoids†
Immunosuppressive agents
Cyclophosphamide
Methotrexate
Azathioprine
Mycophenolate mofetil
Modulation of B-cell function or numbers
Reestablishment of tolerance
B-cell depletion
B-cell-directed cytokines
Blockade of B-lymphocyte stimulator (belimumab)†
TACI-immune globulin (atacicept)
Blockade of the interleukin-6 receptor (tocilizumab)
Interruption of T-cell — B-cell interaction
Blockade of CD40 ligand
CTLA4-immune globulin
Blockade of inducible costimulator
Reestablishment of tolerance in T cells
Autoantigen-derived peptides
Blockade of type I interferon
Inhibition of toll-like receptor
Hydroxychloroquine†
Hormone manipulation (dehydroepiandrosterone)
Modulation of cell signaling
Spleen tyrosine kinase (fostamatinib)
Janus kinase
Rho kinase
Calcium/calmodulin-dependent protein kinase IV
Calcineurin (dipyridamole)
Mammalian target of rapamycin (sirolimus)

* CTLA4 denotes cytotoxic T-lymphocyte-associated antigen 4, and TACI transmembrane activator and calcium-modulator and cyclophilin-ligand interactor.

† These approaches have been approved by the Food and Drug Administration for use in patients with lupus.

In addition to having antiinflammatory effects, inhibitors of cyclooxygenase-2 have been claimed to promote the death of autoreactive T cells. The antimalarial agent hydroxychloroquine has therapeutic value and limited toxicity. It inhibits the function of toll-like receptors that contribute to autoimmunity.

Cyclophosphamide pulses (intravenous infusions every month or bimonthly at lower doses) are effective in the treatment of lupus nephritis, although there

are serious potential side effects, including bone marrow suppression, infections, and gonadal suppression.

Mycophenolate mofetil has considerable therapeutic value with few side effects, but its long-term effects with respect to the preservation of kidney function are unproven.

B-lymphocyte stimulator (BLyS) is a cytokine that is involved in the survival of B cells, germinalcenter formation, and T-cell-dependent and T-cell-independent immunoglobulin-class witching. Blockade of BLyS with an anti-BLyS antibody resulted in a small but significant beneficial clinical effect within the first year of treatment in patients with mild or moderate disease. This antibody (belimumab) is approved by the Food and Drug Administration for use in the treatment of lupus.

Interleukin-6 promotes antibody production in humans and mice with lupus and is present in the urine of patients with lupus nephritis. A monoclonal antibody against the interleukin-6 receptor (tocilizumab) was judged to be promising in a phase 1 clinical trial.

Complement activation inhibition of C5 with an antibody (eculizumab), which has proved efficacy in the treatment of paroxysmal nocturnal hemoglobinuria, is being considered.

The proinflammatory cytokines interleukin-17 and interleukin-23 are important in the pathogenesis of nephritis in lupus-prone mice. Given that interleukin-17-producing cells are found not only in the peripheral blood but also in the inflamed kidney in patients with SLE, blockade of interleukin-17, interleukin-23, or both may warrant evaluation.

Efforts to block the interaction between T and B cells have led to the use of a fusion molecule of cytotoxic T-lymphocyte-associated antigen with immunoglobulin (abatacept), which in a phase 2 trial failed to meet set end points. Inducible costimulator, a regulatory molecule, and its ligand, B7-related peptide 1, represent another costimulatory pair, and disruption of the interaction with a human antibody is currently in a phase 1 trial. In addition, the costimulatory pair CD40-CD40 ligand is important in the production of autoantibodies, but the use of antibodies to disrupt the interaction had considerable side effects in clinical trials.

The mammalian target of rapamycin (mTOR), which plays a role in several key metabolic pathways, is increased in T cells of patients with SLE, and treatment of cells with rapamycin (i.e., sirolimus) corrects the signaling process.

ANTIPHOSPHOLIPID SYNDROME (APS) is an autoimmune disorder of acquired hypercoagulability characterized by the association of vascular thromboses (venous, arterial, small vessels) and/or pregnancy morbidity (foetal loss, premature birth or recurrent embryonic losses) and persistent elevated serum levels of Antiphospholipid antibodies (anticardiolipin, lupus anticoagulant or anti- B2glycoprotein I).

Antiphospholipid antibodies are associated with autoimmune diseases such as systemic lupus erythematosus. Patients often exhibit positive lupus anticoagulant activity but they infrequently suffer from the typical systemic lupus erythematosus

(SLE) that satisfies diagnostic criteria. When they occur in isolation, this is known as primary antiphospholipid syndrome. The main antiphospholipid antibodies implicated in thrombosis and atherosclerosis are the anticardiolipin antibody, the lupus anticoagulant, and Ig G antibodies against plasma phospholipid-binding protein such as B2-glycoprotein I and prothrombin. Lupus anticoagulants were strong risk factors for both arterial and venous thrombosis and they are better predictors of thrombosis than anticardiolipin antibodies. Separate analysis of the different types of thrombosis showed anticardiolipin antibodies were associated with cerebral stroke and myocardial infarction but not with deep vein thrombosis.

Clinical features of APS

APS predominantly presents as a prothrombotic disorder with either vascular thrombosis or pregnancy complications. Bleeding is quite uncommon and, when present, is usually secondary to significant thrombocytopenia, dysfunctional platelets, hypoprothrombinemia, or an underlying disease.

As per the revised clinical criteria for APS, vascular thrombosis is defined by 1 or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ. Venous thromboembolism is the most common clinical presentation and affects between 30 % and 70 % of APS patients. The deep veins of the extremities are most commonly affected, followed by axillary, retinal, hepatic, and cerebral venous sinus thrombosis.

Pregnancy morbidity includes 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; 1 or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, preeclampsia, or placental insufficiency; or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

Clinical studies have linked LA positivity with an increased risk for ischemic stroke. In addition, APAs are also linked with various neurologic disorders like dementia, migraines, chorea, seizures, transverse myelopathy, mononeuritis multiplex, and myasthenia gravis.

Thrombocytopenia (platelets 100–150 $\times$ $10^3\mu$) is found in approximately 20 % of patients with APS and is found in more than 40 % of patients with an underlying autoimmune disease. Autoantibodies directed against platelet glycoproteins have been implicated as a cause for thrombocytopenia in patients with APS.

Among APAs, LA positivity is recognized as the strongest risk factor for thromboembolic events or pregnancy morbidity. Anticardiolipin antibodies show clinically significant association only at moderate to high titers, and the IgG isotype appears to carry more clinical significance than the IgM isotype for both aCL and anti-B2GPI antibodies. Patients with “triple positivity” are at highest risk.

Antiphospholipid antibodies are seen in conjunction with autoimmune diseases like SLE, rheumatoid arthritis, and Behçet syndrome. Antiphospholipid antibodies are also identified in patients with hematolymphoid malignancies,

monoclonal gammopathy of undetermined significance, Waldenstrom macroglobulinemia, and liver disease. Certain infections such as hepatitis C, human immunodeficiency virus syndrome, HTLV-1 associated spastic paraparesis, Q fever, and malaria may also be associated with APAs.

The term *primary antiphospholipid syndrome* has been used when APS occurs in the absence of an underlying disease. In conjunction with other medical illnesses, the term *secondary antiphospholipid syndrome* has been used. However, the most recent international consensus statement on classification criteria for APS advises against this terminology because the clinical consequences in both groups appears to be the same.

In rare cases, APS leads to rapid multiorgan failure due to generalized thrombosis. If the patient experiences clinical involvement of at least 3 different organ systems with histologic evidence of thrombosis, it is termed catastrophic antiphospholipid syndrome.

Laboratory findings of APS

To establish a diagnosis of APS, in addition to the clinical findings there should be a positive laboratory test result indicating the presence of APAs (positive LA, aCL, or anti-B2GPI antibodies). Enzyme-linked immunosorbent assays for other APA specificities (including IgA B2GPI antibody, IgA cardiolipin antibody, prothrombin antibodies, phosphatidylserine antibodies, and phosphatidylcholine antibodies) are also available but are not currently recommended due to uncertain clinical significance. Laboratory testing should be limited to patients who have a significant probability of having APS. Lupus anticoagulant testing is also often performed in patients who have an unexplained prolonged activated partial thromboplastin time.

The International Society on Thrombosis and Haemostasis subcommittee recommends categorizing patients according to clinical characteristics into low, moderate, and high priority for LA testing to minimize the risk of a false positive as follows: low, venous or arterial thromboembolism in elderly patients; moderate, accidentally found prolonged activated partial thromboplastin time in asymptomatic subjects, recurrent spontaneous early pregnancy loss, unprovoked venous thromboembolism in young patients; and high, unprovoked venous thromboembolism and unexplained arterial thrombosis in young patients (< 50 years), thrombosis at unusual sites, late pregnancy loss, any thrombosis or pregnancy morbidity in patients with autoimmune diseases (SLE, rheumatoid arthritis, autoimmune thrombocytopenia, autoimmune hemolytic anemia). Any positive laboratory test needs to be repeated 12 or more weeks following the initial positive laboratory result. This helps to exclude transient APAs, which are often secondary to intercurrent infection or other acute illness.

Treatment and prognosis of APS

Patients with APS may be treated in an outpatient setting. Patients with catastrophic antiphospholipid syndrome require intense observation and treatment, often in an intensive care unit.

In general, treatment regimens for APS must be individualized according to the patient's current clinical status and history of thrombotic events.

Asymptomatic individuals who have positive laboratory tests do not meet APS criteria and do not require specific treatment. Patients with significant thrombotic events or obstetric complications are treated with anticoagulant therapy. Even if the venous or arterial occlusion occurred many years before, long-term treatment with oral anticoagulant therapy is often used. Low-dose aspirin is used widely in this setting as well; however, its effectiveness remains unproven.

Hydroxychloroquine, with its intrinsic antithrombotic properties, might be useful in some patients. Steroids or intravenous immunoglobulin has proved benefit in LA patients with hypoprothrombinemia syndrome (LA antibodies directed against prothrombin) who either have bleeding or need surgery.

Immunosuppressive medications, such as cyclophosphamide, are effective in reducing elevated antibody levels; however, the antibody titers rise significantly following discontinuation.

Patients with catastrophic antiphospholipid syndrome need intensive treatment with corticosteroids, immunosuppression, intravenous IgG, and/or plasma exchange.

Pregnant APS patients with no history of thrombosis benefit from low-dose heparin; however, those with a history of thrombosis need therapeutic anticoagulation with low-molecular-weight heparin. Planned pregnancy enables change from long-term warfarin to aspirin and heparin before pregnancy is attempted.

Key Messages:

- Systemic lupus erythematosus (SLE) is a multisystemic, autoimmune, inflammatory disorder predominantly affecting young females. Its onset may be abrupt or insidious, presenting with a broad range of clinical and immunological features.
- A rash on the cheeks and nose, often in the shape of a butterfly is characterized to SLE.
- Positive LE-cells, test for anti-double-stranded DNA, antinuclear-antibody test, anti-Sm, or antiphospholipid antibodies is characterized to SLE.
- Patients with SLE are treated with nonsteroidal antiinflammatory drugs, antimalarial agents, glucocorticoids, and immunosuppressive drugs, including cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil.
- Antiphospholipid syndrome is an autoimmune disorder of acquired hypercoagulability characterized by the association of vascular thromboses (venous, arterial, small vessels) and/or pregnancy morbidity (foetal loss, premature birth or recurrent embryonic losses) and persistent elevated serum levels of Antiphospholipid antibodies (anticardiolipin, lupus anticoagulant or anti-B2glycoprotein I).

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is characterized by endothelium dysfunction and microvascular damage, chronic inflammation, and excessive accumulation of structurally normal extracellular matrix proteins in the skin and organs of affected patients.

The prevalence of SSc is 5–24: 100 000 and its incidence 1-5: 100 000. As in most connective tissue diseases women are more often affected than men (4–14:1). The peak incidence lies between the third and fifth decade.

Etiology and pathophysiologic aspects of SSc

The etiology of SSc is unknown

There are three major processes involved in the pathophysiology of the disease: (I) microvascular dysfunction and damage, (II) disturbances of cellular and humoral immunity, and (III) overproduction of extracellular matrix proteins leading to excessive tissue fibrosis.

Microvascular dysfunction and damage. According to the vascular hypothesis, disturbed endothelial and contractile vessel function is regarded as the initiating process, while others emphasize the presence of a primarily dysregulated inflammatory immune processes. Endothelium dysfunction or damage precedes the accumulation of extracellular matrix proteins in the time course of the disease. Elevated levels of markers of endothelial activation and damage such as endothelin-1, soluble intercellular all adhesion molecule 1 (sICAM), soluble vascular all adhesion molecule 1 (sVCAM-1), thrombomodulin, and von Willebrand factor antigen were found by different groups, whereas nerve growth factor does not seem to be involved. Elevated levels of endothelin-1 (ET-1) might not only contribute to vasospasm and EC-damage, but directly induce profibrogenic effects by coregulating collagen I synthesis and seem to be correlated with the degree of capillary microscopic abnormalities. Impairment of endothelial cell differentiation from bone marrow-derived mesenchymal stem cells became evident.

Disturbances of cellular and humoral immunity. Functional and/or morphologic abnormalities in endothelial cells (EC), T- and B-lymphocytes, and fibroblasts (FB) have been described. Activation of EC results in up-regulation of adhesion molecules, leukocyte trepping, and migration. Perivascular infiltration with monocytes and accumulation of T-cell urge fibrosis via overproduction of fibroblast stimulating cytokines (f.ex. IL-4, TGF-β) and growth factors (such as CTGF and PDGF).

Overproduction of extracellular matrix proteins. Once chronic tissue hypoxia is induced, fibrosis might be enhanced and perpetuated by over-expression of genes directly regulating fiber matrix components production in the activated fibroblasts (FB) or post-translational modification processes of the extracellular matrix. Activated FB are considered to be the effector cells responsible for tissue fibrosis.

Nearly all cells involved in the complex pathophysiology of SSc are able to produce tissue growth factor β (TGFs) and it is considered as one of the strongest inducers of collagen synthesis.

Platelet derived growth factor (PDGF) induces migration, differentiation, and transformation of various cell lines involved in SSc-pathophysiology and participates in the complex regulation of apoptosis and the metabolism of O2 radicals. Activation of the PDGF-receptor α by autoantibodies has been shown to markedly increase typ I collagene gene expression in SSc-fibroblasts.

Although the significance of the antinuclear antibodies for the pathogenesis remains unclear, their presence and the presence of certain subtypes is helpful for establishing early diagnosis and predicting certain disease pattern and organ involvement.

Diagnostic and classification criteria of SSc table15.

Table 15 — American College of Rheumatology (ACR) classification criteria for SSc

Original ACR-Classification of SSc	
Major criterion	**Minor criterion**
Proximal scleroderma (proximal to metacarpophalangeal joints)	Sclerodactyly
	Digital pitting scars of fingertips or loss of substance of the distalfinger pad
	Bilateral basilar pulmonary fibrosis
SSc is based on the presence or absence of the major criterion, or 2 or more minor criteria.	
Modified ACR-classification	
Original criteria plus	Definitively or extremely dilated capillaries
	Moderate or extensive capillary loss
	Presence of visible teleangiectases
	Presence of anticentromere antibodies
For limited SSc sensitivity of ACR criteria is low. Adding capillary microscopic data, presence of teleangiectases, and serologic data markedly improved sensitivity	

In a recent Delphi exercise, 4 signs/symptoms have been identified as necessary for the very early diagnosis of SSc: Raynaud's phenomenon (RP), puffy swollen digits turning into sclerodactily, antinuclear antibodies and specific SSc antibodies (anticentromere and antitopoisomerase-I antibodies), and abnormal capillaroscopy with scleroderma pattern.

The most commonly used by the clinician simply differentiates between:

- *a limited cutaneous variant (lcSSc)* affecting hands, forearms, feet, lower legs, as well as the face and the neck;
- *a diffuse cutaneous form (dcSSc)* additionally affecting the skin of the upper arms, the thighs, and the trunk.

CREST-syndrome is now considered to be a variant of lc-SSc, defined by the presence of skin calcification, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and teleangiectasia.

In general, the manifestation of skin fibrosis and organ involvement as well as overall survival varies between dcSSc and lcSSc, with dcSSc usually progressing more rapidly and showing a poorer prognosis. Nevertheless, prognosis not always depends on the degree and the extent of skin fibrosis, and there are variants of lcSS with isolated pulmonary hypertension or significant lung fibrosis or renal crisis with a poor prognosis. Even cases with diffuse organ involvement but without scleroderma (termed SSc sine scleroderma) have been described.

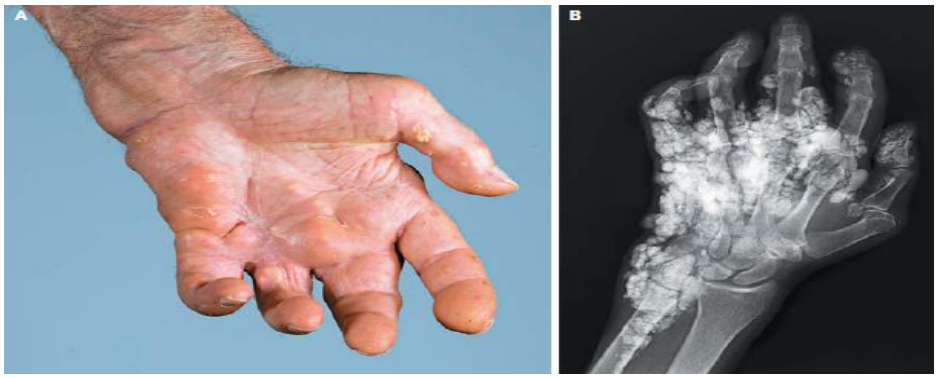


Figure 9 — Calcinosis cutis in systemic sclerosis:
Physical examination revealed extensive soft-tissue calcification involving both hands and all the fingers, with bilateral flexion deformities and unhealed ulcers of the distal digits that drained calcific deposits (Panel A). Extensive calcinosis cutis was also observed on plain radiographs of the hands (Panel B)

From: Makol, A. Images in clinical medicine. Calcinosis cutis in systemic sclerosis / A. Makol, S. R. Ytterberg // N. Engl. J. Med. — 2011. — Vol. 364. — P. 2245

In lcSSc swollen fingers and hands, joint tenderness, and Raynaud's phenomenon (RP) often precede dermal sclerosis, development of teleangiectasia, and digital ulcers for many years, whereas in dcSSc a more rapid onset of vascular acro-symptoms, skin fibrosis, and organ involvement is typical.

RP, although being the initial and heralding symptom in > 90 % of patients, is often not present at the time of consultation. Thus, frequency, duration and distribution of RP should especially be asked for and should be recorded by the patients in RP-dairies.

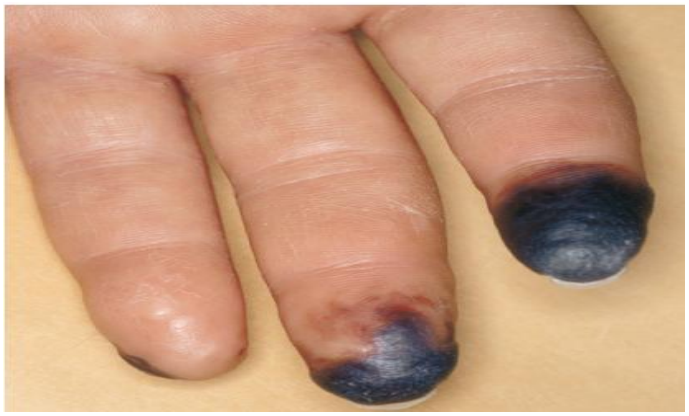


Figure 10 — Digital necrosis
Sharply demarcated necrosis of the fingertip in a patient with limited cutaneous SSc.

From: Harrison's Principles of Internal Medicine / A. C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

Patients with RP and hallmark antibodies such as ANA, anticentromer or antitopoisomerase I (SCL-70) but without any other disease manifestations must be considered at high risk and might be classified as having «prescleroderma» or

«suspected secondary RP». These patients should be kept under close surveillance. Even in RP without positive autoantibodies long time follow-up revealed a conversion rate of approximately 1 % per year.

Malaise, fatigue, sleep difficulties, arthralgias, stiff joints, acral swelling, and myalgias are early unspecific symptoms of SSc.

Skin manifestation should be scored according to the modified Rodnan-Skin-Score (RSS). For this purpose in 17 distinct skin areas a skin fold is tried to be formed between thumb and index finger. Grad 0 refers to normal skin, whereas grad 4 is defined as complete inability to mobilize the skin.

Digital ulcers (DU), erosions, and scars as well as their infection status should be followed and documented carefully.

Male sex, presence of pul-involvement of the esophagus, diffuse skin sclerosis, anti-Scl70 antibodies, young age at onset of Raynaud's phenomenon (RP), and elevated erythrocyte sedimentation rate (ESR) have a significant impact on the appearance of DU with the highest probability for male patients with early onset of RP, ESR > 30 mm, anti-Scl70 antibodies, and PAH.

Deep tendon friction rubs are rare and seem to indicate aggressive disease. Typically, contractures develop as the result of fibrosis affecting tendons, and periarticular structures.

Muscle weakness might be a secondary phenomenon. About 20 % of all the patients develop myositis, which often indicates overlap-syndrome.

Nearly 90 % of patients with SSc have evidence of gastrointestinal tract (GI) involvement. The GI-tract might be affected in all parts with dysphagia and choking due to esophageal dysmotility and heartburn due to gastric reflux being the leading clinical symptoms.

Severe cases often progress to malabsorption and wasting. Microstomia and thickening of the frenulum of the tongue might be indicative for the diagnosis.

Prognostically, the most important organ manifestations are lung and renal involvement. Pulmonary involvement is seen in more than 70 % of patients. About 15–20 % of the cases develop severe pulmonary fibrosis and pulmonary arterial hypertension (PAH) with often progressive right ventricular failure. Dyspnoe on exertion and fatigue are the leading symptoms but lack specificity.

Cardiac involvement might manifest itself with arrhythmias, conduction blocks, diastolic heart failure, pericarditis, and pericardial effusion. Myocardial involvement consists of patchy myocardial fibrosis and myocardial band necrosis, probably caused by coronary vasospasm and reperfusion injury.

Renal involvement is common in SSc, with most patients manifesting only mild renal dysfunction. A rare but serious complication is renal crisis, affecting about 1–2 % of patients. Renal crisis leads to rapidly progressing renal failure and malign hypertension, pulmonary edema, and sometimes microangiopathic hemolytic anemia and thrombocytopenia. Major risk factors for renal crisis include diffuse skin involvement, glucocorticoid treatment, particularly in higher doses, and the presence of anti-RNA-polymerase antibodies.

Diagnostic methods of SSc

Digital perfusion

Digital skin perfusion can easily be examined noninvasively by determination of digital occlusion pressure, light reflex or transmission rheography, thermography, or laser Doppler perfusion imaging, also allowing to determinate the tendency for vasospasms by performing a standard cold test (f.e. bathing the hands for 2–3 min in cold water of 15 °Celcius).

If digital pulse curves do not completely normalize after bathing the hands in warm water (40 °Celcius) and sublingual application of nitroglycerine (0.2–0.4 mg) arterial occlusion must be assumed.

Capillary microscopy

Brown and O'Leary were the first who used capillary microscopy to describe microvasculature involvement in Raynaud's phenomenon. Their observations were made at the nailfolds, because here the most distal rows of the capillaries run almost parallel to the skin surface.

Capillary nailfold microscopy (CNM) should be performed at constant room temperature of 20–22 °C after appropriate acclimatization of the patient in an upright sitting position with comfortably fixed arms and fingers.

In clinical routine CNM, focussing on morphologic aspects of the most distal capillary row it suffices to identify patterns of microvasculature alterations which are (more or less) typical for patients with SSc or those «at risk» for the development of SSc.

The technique is cheap, safe, non-invasive and is of prognostic value, especially in the presence of RP.

Soft tissue and skeletal imaging

Plain radiographs of the hand and feet might reveal tissue calcifications, acro-osteolysis, articular erosions, malposition, and contractures (figure 11).

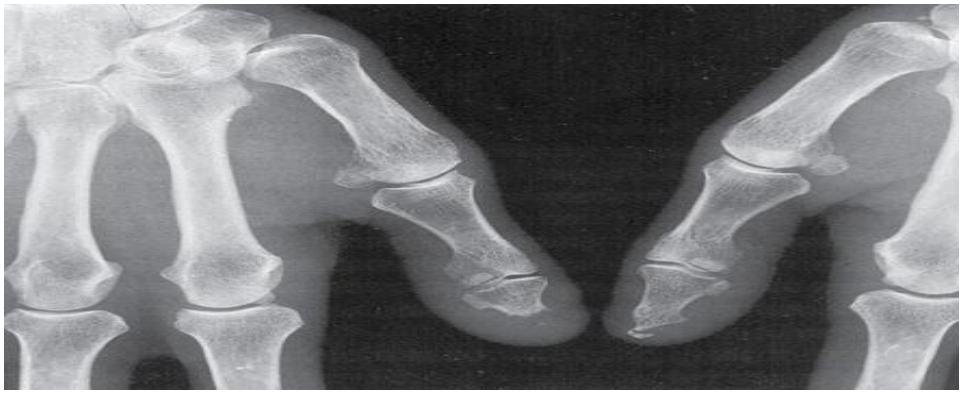


Figure 11 — Acro-osteolysis:
Note dissolution of terminal phalanges in a patient with long-standing limited cutaneous SSc.

From: Harrison's Principles of Internal Medicine / A. C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

Angiography

Severe ischemia of the hand in SSc might be an indication for angiography, especially when the diagnosis is not yet clear or if there is evidence of occlusive lesions of conducting vessels indicated by pulselessness or a pathologic Allen test. Angiographically, arterial lesions in Ssc were described most frequently in small-caliber vessels rather than in proper digital arteries, the superficial palmar arch, and/or the common digital arteries. Lesions are usually smooth and the compensatory collateral circulation is poorly developed. Lesions of the forearm arteries in Ssc are — for unknown reasons — almost exclusively restricted to the ulnar artery. Lesions in the lower extremities are usually not limited to the digits, but include the plantar arch, the crural arteries, or the dorsalis pedis artery.

Although spatial resolution is much higher in DSA, contrast enhanced MR-angiography can also demonstrate small vessel damage in patients with SSc if special acquisition protocols are used.

GI-tract diagnostic

GI-tract involvement can be screened for by esophago-gastro-duodenoscopy and bariumsulfate contrast flouroscopy, whereas esophageal pressure measurement and pH-metry are often used optionally. Bacterial overgrowth might best be diagnosed by the H2 breathing test.

Deep duodenal or jejunal biopsy is recommended in cases with malabsoption syndrome and wasting. Colocsopy and mucosa biopsies can rule out malignancy and amyloidosis.

Lung disease

Spirometry and carbon monoxide diffusing capacity (DLCO) are helpful to detect restrictive ventilation dysfunction and pulmonary fibrosis. If suspected, high resolution computed tomography (HR-CT) is the diagnostic measure of choice. In addition, lung function parameters can be important for the timely detection of developing PAH and should be performed every 6–12 months. A DLCO < 55 % predicted, an annual DLCO reduction > 10 % or a forced vital capacity (FVC): DLCO ratio > 1.6 should raise the suspicion of PAH and trigger further evaluation (echocardiography).

Bronchoscopy and bronchoalveolary lavage (BAL) might be useful for the detection of alveolitis, but the overall predictive value of BAL for prediction of progressive ventilator failure seems to be low.

Pulmonary arterial hypertension

Early detection of PAH is essential as it indicates a poor prognosis and therapeutic possibilities have changed dramatically in recent years. Echocardiography with estimation of systolic pulmonary arterial pressure (sPAP) should be performed in all symptomatic patients with SSc and in 12 month-intervals even in asymptomatic patients. Systolic right ventricular pressure can be estimated by measuring the velocity of tricuspid regurgitation and adding estimated right atri-

al pressure. In the absence of a pulmonic valve disease this value correlates with the sPAP. PAH can be suspected when tricuspid regurgitation velocity exceeds 2.9–3.4 m/sec, corresponding to an estimated sPAP of 37–50 mmHg, or when other echocardiographic variables suggestive of PH are pres-reduced RV function, pericardial effusion and others).

Cardiac disease

Spiroergometry and the 6 min walking test are helpful to characterize functional capacity. To exclude arrhythmias and conduction blocks a plain ECG and a Holter-ECG is recommended, while echocardiography is diagnostic for pericardial effusion and assessment of systolic and diastolic cardiac function.

Renal function

For the monitoring of renal function analyses of the serum creatinine concentration and of the urine proteincreatinine quotient (alternatively urine albumin creatinine quotient) are advocated every 6–12 months. Patients with risk factors for renal crisis should even be screened in shorter intervals.

Table 16 — Recommendations for organ-specific clinical and diagnostic workup for SSc

Organ system	Diagonostic measure
GI-tract	• Esophago-gastro-duodenoscopy, coloscopy • Esophageal manometry • Esophageal contrast • H2-breathing test • Antinuclear antibodies (ANA) • Anti-Centromer antibodies (esophageal disease) • Anti-To antibodies (small bowel) • AMA-Type M2 antibodies (Primary biliary cirrhosis)
Lung	• Chest X-ray • Bodyplethysmography • DLCO (carbon monoxide diffusing) • HR-CT • TTE (Pulmonary hypertension?) • Pulmonary function tests (VC, TLC, FVC, DLCO) • Anti-Scl-70 (Anti-Topoisomerase-1) (interstitial lung fibrosis) • Anti-Centromer antibodies (PAH — Pulmonary arterial hypertension) • Anti-Fibrillarin antibodies (PAN) • Anti-To antibodies (PAN) • Antinuclear antibodies (ANA)
Kidneys	• Blood pressure • Renal ultrasound • GFR (MDRD or Cockroft-Gault-formula) • Urine protein or urinealbumin • Urine-protein or urinealbumin • Antinuclear antibodies (ANA) • Anti-RNA-Polymerase

Organ system	Diagonostic measure
Heart	• ECG • TTE (diastolic, systolic, or right heart dysfunction?) • Spiro-ergometry • 6-min walking test • Holter-ECG • Coronary angiography • ABI (ankle brachial index) • Antinuclear antibodies (ANA)
Vessels	• ABI • Digital plethysmography • Capillary microscopy • Duplex scanning • Angiography • Antinuclear antibodies (ANA)
Skin	• Anti-RNA-Polymerase antibodies • SS-A (Ro) antibodies (Sjörgren syndrome)
Muscle	• Anti-Fibrillarin antibodies • Anti-PM-Scl antibodies • Anti-U1-RNA antibodies (mixed connective tissue disease)

Associated diseases of SSc

Primary biliary cirrhosis (PBC)

The prevalence of PBC in SSc is at least 1–3 %. PBC is seen in lcSSc (predominantly) as well as in dcSSc. The hallmark antibodies of PBC (AMA-M2) show antimitochondrial activities and are found in 6–25 % of SSc-patients.

If AMA are positive and transaminases and cholestase parameters are elevated diagnosis might be proved by endoscopic retrograde cholangiography and liver biopsy.

Sjorgren's syndrom

Sjorgren's Syndrome (SS) might occur as a primary disease or is associated with connective tissue diseases, including SSc. SS predominantly causes xerostomia and xerophthalmia. Prevalence of SS in SSc was reported between 14 and 29 % and manifests predominantly in lcSSc. Diagnosis might be proven histologically by biopsy of the enoral mucosa of the lips.

Malignoma

There are several malignomas associated with SSc, the most important is skin cancer. The cause of the increased cancer risk is not well understood. Smokers are overrepresented and in patients treated with cytostatic substances treatment associated cancerogenesis must be distinguished. One should keep also in mind that scleroderma-like skin lesions might manifest as a paraneoplastic syndrome.

Accelerated atherosclerosis

Atherosclerotic disease of coronary or peripheral arteries in SSc patients is not uncommon and often not paralleled by clinical symptomatology. Although impairment of markers of endothelium function and increased intima-media thickness have been described in SSc, generalized premature atherosclerosis has not been confirmed yet in SSc.

In clinical routine care, all patients should undergo non-invasive testing for atherosclerotic vascular disease in regular intervals (for example ABI, carotid and peripheral artery duplex scanning, cardiac stress tests).

Scleroderma overlap syndromes

Many patients with scleroderma have a positive antinuclear antibody, and there can be family histories of other connective tissue diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Some patients have features of scleroderma and other autoimmune conditions. Recent reports of scleroderma overlap with rheumatoid arthritis suggest distinct features of diffuse scleroderma with positive Scl-70, pulmonary fibrosis, and later seropositive erosive rheumatoid arthritis. SLE rarely occurs with scleroderma. Sjogren's syndrome symptoms are common in scleroderma. In primary Sjogren syndrome, anticentromere antibody positive patients have more Raynaud phenomenon. Antibodies that occur in scleroderma that are thought to be specific are present in other connective tissue diseases. For instance, Scl-70 antibody is reported in as many as 35 % of patients with scleroderma but can be present in 25 % of patients with SLE. Myositis or myopathy can be features of scleroderma. Scleroderma overlap with polymyositis is frequently anti-PM Scl antibody positive, whereas anti-Jo-1 does not normally occur in the overlap of scleroderma and polymyositis but is usually exclusively positive in polymyositis with arthritis and alveolitis. A better prognosis is found with PM Scl antibody in myositis. Vasculitis is not a typical feature of scleroderma, but has been reported. Eosinophilic fasciitis is rare, and the onset could be associated with simvastatin.

Treatment of SSc

Vasculopathy, autoimmunity, and fibrosis are therapeutic targets in systemic sclerosis.

According to European League against Rheumatism (EULAR) and EULAR Scleroderma Trials and Research Group (EUSTAR)-treatment recommendations for SSc vasoactive therapies such as prostacyclins, endothelin receptor blockers, selective phosphodiesterase inhibitors and calcium channel blockers (especially of the dihydropyridine type) were graded with the highest level of evidence (I A), whereas immunosuppressants, ACE inhibitors, and prokinetics were graded I B (table 17).

Table 17 — EULAR recommendations for the therapy of SSc

THE HIGHEST LEVEL OF EVIDENCE (I A): VASOACTIVE THERAPIES	
Prostacyclins	Epoprostenol i.v. 2–40 ng/kg bw/min
Endothelin receptor blockers	Bosentan 62.5 mg twice daily p.o. for 4 weeks; thereafter 125 mg twice daily p.o.
	Tadalafil 40 mg p.o. once daily
Selective phosphodiesterase inhibitors	Sildenafil 3 × 20/25 mg p.o. per day
Calcium channel blockers (especially of the dihydropyridine type)	Nifedipine up to 4 × 20 mg per day
EVIDENCE GRADE I B	
Immunosuppressants	
Cyclophosphamide	Bolus therapy 800–1400 mg/month i.v. or oral therapy 1–2 mg/kg/d
Azathioprine	2 mg/kg/d per os
Methotrexate	15–25 mg/week per os
Mycophenolate mofetil	1–2 g/day
Prednison	up to 10 mg daily
ACE inhibitors	
Captopril	25–50 mg 2–3 times daily
Enalapril	5–10 mg twice daily
Lisinopril	2.5–5 mg once daily
Prokinetics	
Autologous stem cell transplantation	

Further therapeutic options in SSc

2–9 % of the patients die as a result of infections. Patients with SSc should therefore be vaccinated for pneumococcal infections every 3–5 years and also for influenza, especially in the presence of lung fibrosis and PAH or in patients treated with immunosuppressants. In case of bacterial infections early and aggressive antibiotic treatment is indicated.

A retrospective analysis compared 20 SSc patients treated with hormone replacement therapy (HRT) with 41 matched controls. No patients under HRT developed PAH but 8 matched controls did. This is an interesting observation, but up-to-date, controlled studies are missing.

Vitamin D is an important mediator of bone composition. It also has some immunological properties. Vitamin D deficiency is associated with osteoporosis, hypertension and accelerated atherosclerosis. As recently shown, SSc patients often have vitamin D deficiency even under supplementation. Therefore, vitamin D levels should be controlled and vitamin D should be supplemented with sufficient doses.

Patients with SSc often have multiple gastrointestinal (GI) symptoms. Esophageal motility might be enhanced by procinetic substances like metoclopramide. In a recently published study of 51 consecutive patients nearly half of the patients suffered from small intestinal bacterial overgrowth. The presence of ≥ 5 gastrointestinal symptoms was highly predictive for this complication. On the other hand, rotating antibiotics provided beneficial effects leading to a marked reduction of GI symptoms.

Key Messages:

- Systemic sclerosis is a connective tissue disease characterized by inflammation and fibrosis of multiple organs (skin, gastrointestinal tract, lung, kidney and heart).
- A limited cutaneous variant (lcSSc) affecting hands, forearms, feet, lower legs, as well as the face and the neck, and a diffuse cutaneous form (dcSSc) additionally affecting the skin of the upper arms, the thighs, and the trunk.
- In lcSSc swollen fingers and hands, joint tenderness, and Raynaud's phenomenon often precede dermal sclerosis, development of teleangiectasia, and digital ulcers for many years, whereas in dcSSc a more rapid onset of vascular acro-symptoms, skin fibrosis, and organ involvement is typical.
- CREST-syndrome considered to be a variant of lc-SSc, defined by the presence of skin calcification, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and teleangiectasia.
- Treatment recommendations for SSc vasoactive therapies such as prostacyclins, endothelin receptor blockers, selective phosphodiesterase inhibitors and calcium channel blockers (especially of the dihydropyridine type) were graded with the highest level of evidence.

CASE REPORT No.4

A 30-year-old Caucasian man was admitted in intensive care unit because of bilateral acute ischemia of the two legs. He was regularly treated for Basedow disease. Smoking was the only risk factor of atherosclerosis disease. Physical examination showed a skinny patient. Peripheral pulses of the legs were absent. Arterial pressure was normal. The electrocardiogram showed a QS pattern in leads V1, V2, V3, and V4. Echocardiography revealed an apical large thrombus measuring 38 by 18 mm associated with a thinning left ventricular wall, suggesting painless myocardial infarction. It also demonstrated a markedly reduced left ventricular ejection fraction (19 %). The patient was immediately brought to the cardiovascular surgical department where bilateral Embolectomy to Fogarty probe was effectuated. Then amputation of the right leg was done because of so late consultation. Intravenous heparin was administrated with oral aspirin. Haematological tests showed normal levels of C, S and ATIII Protein. While FT4, FT3 were high, TSH was low. The patient was found to have a positive Lupus anticoagulant LA and a false positive VDRL. Anticardiolipin antibodies were also tested and subsequently came back positive for anticardiolipin antibody of the IgM isotype with a low level (19.25 MPL). The patient had no evidence for infection or any other triggering event before the MIs.

The patient was also found to have a false positive VDRL. Antinuclear antibodies, anti DNA, anti Sm, anti SSA and anti SSB were negative. This was consistent with a primary antiphospholipid syndrome. Unfortunately, the patient died 15 days after his admission because of the failure of many of his organs (heart failure, acute renal failure, cytopenia).

CASE REPORT No.5

The patient is a 48-year-old female of mixed heritage, who worked as housemaid. She reported that edema of her lower limbs and deterioration of her general state of health began one year ago. She sought medical care 6 month ago, when bilateral pleural effusion was evidenced, and thoracocentesis and pleural biopsy (discrete chronic and unspecific pleuritis) were performed. Now she was admitted to a hospital complaining of pain and increased abdominal volume.

On admission, she complained of diffuse abdominal pain, increased abdominal volume, dyspnea on mild exertion, and asthenia. She reported significant weight loss (approximately 25 kg in 10 months). The physical examination showed an emaciated, tachycardic, tachypneic patient, with reduced respiratory sounds in both pulmonary bases, diffuse abdominal pain on palpation, shifting dullness and positive fluid wave test, and edema of lower limbs.

Diagnostic investigation was initiated, and the major diagnostic hypothesis was neoplasm of unknown origin. Upper digestive endoscopy and colonoscopy ruled out neoplasm of the upper and low digestive tract. The chest, abdomen, and pelvis tomographies showed large volume ascites, bilateral pleural effusion, and pericardial effusion.

The diagnosis of systemic lupus erythematosus was established based on abnormal antinuclear antibody (ANA) titers, presence of specific autoantibodies (anti-Sm and anti-DNA), serositis, and lymphopenia. Prednisone, at the dose of 1 mg/kg, was initiated. Initially, the lower limb edema and ascites worsened, requiring repeated relief paracentesis. Due to significant and persistent hypoalbuminemia, with no significant proteinuria, normal liver function tests, and adequate protein intake, protein-losing enteropathy was investigated by use of Tc-99m albumin scintigraphy.

Azathioprine at the dose of 100 mg/day was added for four weeks, and the cavity effusions and lower limb edema subsided, and her serum albumin levels normalized.

Protein-losing enteropathy is rarely seen in patients with systemic lupus erythematosus. This clinical condition should be suspected in the presence of persistent hypoalbuminemia despite normal liver function, adequate protein intake, and no significant proteinuria.

DERMATOMYOSITIS. POLYMYOSITIS

Dermatomyositis is an idiopathic inflammatory myopathy with characteristic skin manifestations.

Polymyositis includes the inflammatory myopathy without the cutaneous findings.

Although the disorder is rare, with a prevalence of one to 10 cases per million in adults and one to 3.2 cases per million in children, early recognition and treatment are important ways to decrease the morbidity of systemic complications.

The average age at diagnosis is 40, and almost twice as many women are affected as men. The average age of onset in juvenile dermatomyositis is between five and 14 years. This subgroup of patients has a better prognosis than adult patients. Modern therapy has reduced mortality from near 50 percent to less than 10 percent.

The etiology of dermatomyositis remains unknown; some studies have reported an association with histocompatability antigens, environmental agents (e.g., virus, drugs) and autoimmunity.

Classification of dermatomyositis/polymyositis

Dermatomyositis:

- Without muscle weakness (amyopathic dermatomyositis or dermatomyositis sine myositis)
- With muscle weakness
- Adult
  - ✓ Associated with cancer
  - ✓ Not associated with cancer
- Pediatric

Polymyositis:

- Adult
- Pediatric
- Inclusion-body myositis
- Overlap (myositis associated with a connective tissue disease)

Manifestations of dermatomyositis/polymyositis

Cutaneous

Cutaneous manifestations of dermatomyositis are generally grouped as pathognomonic, characteristic, compatible, less common and rare (table 18).

Table 18 — Cutaneous manifestations of dermatomyositis

Pathognomonic manifestations:
Gottron's papules: violaceous erythematous papules overlying the dorsal interphalangeal or metacarpophalangeal, elbow or knee joints.
Gottron's sign: symmetric, nonscaling, violaceous erythematous macules or plaques, often atrophic, in the same distribution as Gottron's papules.
Characteristic manifestations:
shawl sign/V-sign;
heliotrope;
periungual telangiectasias;
mechanic's hand.
Compatible manifestations:
poikiloderma atrophicans vasculare;
calcinosis cutis.
Less common manifestations:
facial swelling;
malignancy;
erythroderma;
lichen planus;
cutaneous vasculitis;
panniculitis.
Rare manifestations:
follicular hyperkeratosis;
papular mucinosis;
hypertrichosis;
malignant erythema;
urticaria/urticarial vasculitis;
partial lipodystrophy;
malignant atrophic papulosis (Degos' disease);
zebra-like striping;
vulvar/scrotal involvement.

The primary lesion appears as a violaceous, macular erythema with a symmetric distribution. This may progress and become poikilodermatous (atrophic with telangiectasia and pigmentary changes) and indurated (as a result of mucin deposition).

Pathognomonic manifestations include Gottron's papules and Gottron's sign. Gottron's papules, violaceous papules overlying the dorsal interphalangeal or metacarpophalangeal areas, elbow or knee joints, occur in approximately 70 percent of patients with dermatomyositis. Gottron's sign is erythematous or violaceous, often atrophic, macules or plaques in the same symmetric distribution pattern but sparing the interphalangeal spaces - just the opposite dermatologic distribution pattern on the hand that is observed in patients with systemic lupus erythematosus.

Heliotrope, a macular rash with periorbital edema, is considered a characteristic finding of dermatomyositis, as are periungual telangiectasias. The rash occurs early in the course of the disease in 30 to 60 percent of patients. The characteristic

lesions of the shawl sign and the V-sign appear as erythematous, poikilodermatous macules distributed in a «shawl» pattern over the shoulders, arms and upper back and in a V-shaped distribution over the anterior neck and chest. Mechanic's hand and may be associated with an increased risk of interstitial lung disease.

Poikiloderma atrophicans vasculare (poikilodermatomyositis), a circumscribed violaceous erythema with associated telangiectasia, hypopigmentation and superficial atrophy, is most commonly found over the posterior shoulders, back, buttocks and a V-shaped area of the anterior neck and chest, and is often a late finding. Calcium deposition (calcinosis cutis) occurs in approximately 30 to 70 percent of cases of juvenile dermatomyositis and in only 10 percent of adult cases. The calcinosis is most commonly present on the buttocks, elbows, knees or traumatized areas, and is associated with increased disease activity and duration. Skin findings may be subtle even in patients with severe myositis and are not a measure of the severity of the disease.

Systemic symptoms of dermatomyositis/polymyositis

Patients with dermatomyositis may also present with many systemic symptoms (table 19). The most common are proximal muscle weakness, dysphonia or dysphagia. Other possible symptoms include respiratory muscle weakness, visual changes and abdominal pain. An important association with internal malignancy has been demonstrated and will be discussed in further detail.

Table 19 — Systemic manifestations and complications of dermatomyositis

Systemic manifestations:
common: proximal muscle weakness, dysphonia, dysphagia;
less common: respiratory muscle weakness, visual changes, abdominal pain.
Systemic complications/associations:
cardiomyopathy;
cardiac conduction defects;
aspiration pneumonia secondary to respiratory muscle weakness;
diffuse interstitial pneumonitis/fibrosis;
large-bowel infarction secondary to vasculopathy has occurred in juvenile patients with myositis;
muscle atrophy;
muscle calcification;
ocular complications including iritis, nystagmus, cotton-wool spots, optic atrophy, conjunctival edema and pseudopolyposis; internal malignancy.

Subtypes of dermatomyositis

JUVENILE DERMATOMYOSITIS

While the clinical presentation of juvenile dermatomyositis is usually different from the presentation of the adult type, the skin lesions are similar, with the exception of an increased incidence of calcinosis cutis in juvenile patients. Common findings include low-grade fever, increased risk of gastrointestinal manifestations, and

symmetric arthritis of the large and small joints. Asymptomatic cardiac conduction delays or right bundle branch block may be found in 50 percent of this group.

Patients may exhibit weakness of the truncal muscles that requires them to use their arms to push themselves up from a prone position (i.e., Gower's sign). There does not appear to be any association between juvenile dermatomyositis and malignancy.

OVERLAP SYNDROME

A number of patients with dermatomyositis also meet the criteria for one of the connective tissue disorders. To be a true overlap syndrome, the patient must meet the diagnostic criteria for each separate disorder. Overlap syndrome occurs more frequently in females than in males, with a 9:1 ratio. 11 to 40 percent of patients with dermatomyositis have been reported to have a concomitant diagnosis of a connective tissue disorder.

These disorders include rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Sjögren's syndrome, polyarteritis nodosa and mixed connective tissue disease, and these patients may present with polyarthritis, sicca syndrome, sclerodactyly, Raynaud's phenomenon and late symptoms of myositis. Patients are also more likely to have positive nonmyositis-associated antibodies (such as double-stranded DNA, antinuclear antibodies [ANA], Scl-70, Jo-1 precipitating antibodies, PM-Scl, Ku antibodies or extractable nuclear antigen antibodies). ANA are found in up to 80 percent of patients with dermatomyositis or polymyositis, but this finding does not aid in distinguishing myositis from scleroderma or other rheumatologic diseases. Precipitating autoantibodies to the Mi-2 antigen are specific for dermatomyositis but are found in only about 20 percent of patients with dermatomyositis. In patients with overlap syndrome, myositis tends to respond better to treatment with corticosteroids than it does in patients with an idiopathic etiology.

AMYOPATHIC DERMATOMYOSITIS

This classification has been controversial because it does not strictly meet the criteria put forth by Bohen and Peter. Amyopathic patients essentially have pathognomonic skin changes without clinical or laboratory evidence of muscle involvement. This condition has been reported in approximately 2 to 11 percent of patients with dermatomyositis. Patients most commonly present with lethargy, pruritus, fatigue, photosensitivity or arthralgias. In some cases, myositis developed later; in others, myositis that was not found by standard methods was suspected on the basis of magnetic resonance imaging (MRI).

DERMATOMYOSITIS/MALIGNANCY

Although an increased risk of malignancy has not been associated with juvenile dermatomyositis, it has been demonstrated in adults with dermatomyositis. One study suggested a 6.5-fold increased risk of malignancy. This risk appears to be the highest in patients diagnosed with dermatomyositis after 45 years of age. The most commonly reported malignancies are ovarian and gastric can-

cer, and lymphoma. Other reported malignancies include lung, male genital organ, nonmelanoma skin, Kaposi's sarcoma, mycosis fungoides and melanoma.

Skin changes are not different in patients with or without malignancy. Therefore, careful investigation for malignancy should be initiated at the time dermatomyositis is diagnosed. In women with dermatomyositis, there is a significant association with ovarian cancer, and some authors recommend that the work-up for dermatomyositis include a comprehensive gynecologic evaluation, including a cancer antigen (CA-125) baseline screen, mammography and transvaginal ultrasonographic evaluation of the ovaries at baseline, and gynecologic examinations at 6- to 12-month intervals for at least two years.

Table 20 — Differential diagnosis of dermatomyositis

HIV infection (at onset of immunodeficiency)
Lichen planus
Polymorphous light eruption
Seborrheic dermatitis
Systemic lupus erythematosus
Psoriasis
Contact dermatitis
Atopic dermatitis
Trichinosis (caused by periorbital swelling and edema)
Alcohol
Drug effects*
Penicillamine, nonsteroidal anti-inflammatory agents (nifluric acid and phenylbutazone), hydroxyurea (Hydrea), pravastatin (Pravachol), clofibrate (Atromid-S) and ipecac

HIV-human immunodeficiency virus

**A partial listing of drugs that can cause myositis*

Evaluation of dermatomyositis/polymyositis

A complete history should be obtained and a physical examination performed, including a thorough review of systems, with an emphasis on myositis-related presentations and evidence of skin changes (table 21).

Table 21 — Evaluation of dermatomyositis

History and physical examination
Chest radiograph
Serum aldolase, LDH, ALT, AST, CBC with differential, CK, ANA/ENA in appropriate clinical setting, routine serum chemistry
Stool guaiac (three samples)
Urinalysis, urine myoglobin
Muscle biopsy
Skin biopsy*
Electromyography

LDH — lactic dehydrogenase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CBC — complete blood count; CK — creatine kinase; ANA — antinuclear antibody; ENA — extractable nuclear antigens.

**Skin biopsy findings of dermatomyositis are not specific for dermatomyositis but may help exclude other skin conditions that can have clinical appearances similar to the early cutaneous changes of dermatomyositis*.

Laboratory manifestations of dermatomyositis

- Muscle enzyme elevation

✓ Serum aldolase, ALT, LDH, CK,* AST, carbonic anhydrase isoenzyme III†

- Autoantibodies

✓ ANA levels: elevated in 60 to 80 percent of patients with classic DM/PM
✓ Antisynthetase antibodies
✓ Jo-1: most common antisynthetase found; 20 % of patients with DM may have positive result
✓ Anti-EJ: may be more associated with typical skin lesions
✓ SRP: occurring in 5 percent of patients, associated with polymyositis, acute-onset, severe, treatment-resistant forms of classic DM/PM with cardiac involvement
✓ Mi-2 antibodies (a nuclear protein complex)
✓ Anti-PM-Scl antibodies: associated with overlap of scleroderma and DM/PM
✓ Anti-Ku antibodies: associated with overlap of scleroderma or SLE with DM/PM

- ESR: elevated in approximately 50 percent of patients, does not correlate well with disease activity
- Rheumatoid factor: elevated in 20 percent of patients, most often in those with overlap syndromes
- Neopterin and factor VIII-related antigen (von Willebrand factor): reported to correlate with juvenile DM
- EMG: myopathic pattern, 10 percent are false-negative

CK — creatinine kinase; AST — aspartate aminotransferase; ALT — alanine aminotransferase; LDH — lactic dehydrogenase; ANA — antinuclear antibody; DM — dermatomyositis; PM — polymyositis; SRP — signal recognition particle; SLE — systemic lupus erythematosus; ESR — erythrocyte sedimentation rate; EMG — electromyography.

** Used to follow course of disease.*

† More sensitive but not widely available

Table 22 — Classification criteria for polymyositis and dermatomyositis*

1. Skin lesions: • heliotrope: red-purple edematous erythema on the upper palpebral; • Gottron's sign: red-purple keratotic, atrophic erythema or macules on the extensor surface of finger joints; • erythema on the extensor surface of extremity joints, slight raised red-purple erythema over elbows or knees.
2. Proximal muscle weakness (upper or lower extremity and trunk).
3. Elevated serum creatine kinase or aldolase level.
4. Muscle pain on grasping or spontaneous pain.
5. Myogenic changes on electromyography (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials).
6. Positive anti-Jo-1 antibody test (histidyl-tRNA synthetase).
7. Nondestructive arthritis or arthralgias.
8. Systemic inflammatory signs (temperature: more than 37 °C [98.6°F] at axilla, elevated serum C-reactive protein level or accelerated erythrocyte sedimentation rate of more than 20 mm per hour by Westergren).
9. Pathologic findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen)

** Patients presenting with at least one finding from item 1 and four findings from items 2 through 9 are said to have dermatomyositis. Patients presenting with at least four findings from items 2 through 9 are said to have polymyositis.*

Treatment of dermatomyositis/polymyositis

The goal is to improve function and prevent disability. The treatment regimen must be instituted early and requires a team approach between the physical therapist, dermatologist and family physician. Other subspecialist involvement may be required, depending on the particular manifestations of the disease. Before the development of treatment, mortality from complications of dermatomyositis was approximately 50 percent, so patient education is particularly important.

NONPHARMACOLOGIC AND TOPICAL THERAPY

Physical therapy is directed at preventing atrophy and contractures, and is particularly necessary in patients with calcinosis and muscle involvement. Technique should focus initially on passive stretching and splinting, with inclusion of more aggressive strength-building therapy once inflammation is controlled. The use of a broad-spectrum sunscreen is recommended in all patients with dermatomyositis and has the greatest benefit in patients who are photosensitive. Sun-avoidance techniques should be used, including the use of protective clothing. For control of severe pruritus, antihistamines (such as hydroxyzine or doxepin) are recommended. For further control of the erythematous and pruritic skin changes, a class I (superhigh potency) or class II (high potency) topical corticosteroid is recommended.

SYSTEMIC PHARMACOLOGIC THERAPY

Prednisone remains the initial oral pharmacologic agent, given in a single daily dose of 0.5 to 1.5 mg per kg until the serum creatine kinase (CK) level is normalized and then slowly tapered over the following 12 months. An alternate regimen is 40 to 60 mg of prednisone per day (1 to 2 mg per kg in children) in divided doses until the CK level has been normalized, at which point the drug can be consolidated to a single daily dose. If the CK level remains within normal limits, that dose may be reduced by one fourth every three to four weeks. Prednisone should continue to be tapered until a maintenance dosage of 5 to 10 mg per day is reached. This low dosage should be continued for one year. If the CK level increases, a higher dosage of prednisone is warranted. If no improvement in objective muscle strength occurs after three months of prednisone therapy, other immunosuppressive therapy should be considered. The latter will be necessary in approximately 25 percent of patients.

It is important to be aware of steroid myopathy, which may mimic a worsening dermatomyositis. Differentiating steroid myopathy from worsening dermatomyositis is based on evaluation of neck flexor strength-neck flexor strength would be unchanged if steroid myopathy were developing.

Methotrexate is considered the first-line adjuvant therapy in patients who do not respond to prednisone (table 23). Oral therapy should be initiated at a dosage of 7.5 to 10 mg per week and increased by 2.5-mg increments until a goal of 25 mg per week is reached. In children, a dosage of 1 mg per kg has been used. As the methotrexate dosage increases, the dosage of steroid should be de-

creased. Alternate intravenous dosing initiated at 10 mg per week should be increased by 2.5 mg per week until a total dosage of 0.5 to 0.8 mg per kg is reached. It is important to also give 1 to 3 mg per day of folic acid to minimize the side effects of methotrexate. Adverse effects include stomatitis, hepatic fibrosis, cirrhosis, nausea, abdominal pain, neutropenia, pruritus, fever, pneumonitis and other gastrointestinal symptoms. A liver biopsy should be considered before treatment is initiated. Methotrexate should be used only by physicians who are familiar with the drug's actions and side effects.

Serum immunoglobulin has been used with success for treatment of patients with refractory dermatomyositis. Because of the limited duration of improvement and its high cost, this agent has not become a primary therapy.

Table 23 — Treatment modalities for dermatomyositis

Treatment modality	Dosage	Side effects	Comments
Oral prednisone	0.5 to 1.5 mg per kg daily until serum creatine kinase normalizes, then slowly taper over 12 months	Gastrointestinal symptoms, adrenal suppression, immunosuppression, avascular necrosis, osteoporosis	Initial pharmacologic agent; consider adjunctive therapy if no improvement in objective muscle strength after three months of therapy
Methotrexate	Oral: 7.5 to 10 mg per week, increased by 2.5 mg per week to total of 25 mg per week Intravenous: 10 mg per week, increased by 2.5 mg per week to total of 0.5 to 0.8 mg per kg Children: 1 mg per kg. As dosage increases, taper off steroid dose. Give 3 mg daily of folic acid to minimize side effects of methotrexate	Stomatitis, hepatic fibrosis, cirrhosis, nausea, abdominal pain, neutropenia, thrombocytopenia, pruritus, fever, pneumonitis, and gastrointestinal symptoms	First-line adjuvant therapy in patients unresponsive to steroids. Pretreatment liver biopsy for those with underlying liver disease
Azathioprine	2 to 3 mg per kg per day tapered to 1 mg per kg per day once steroid is tapered to 15 mg per day. Reduce dosage monthly by 25-mg intervals. Maintenance dosage is 50 mg per day	Lymphoma, nausea, vomiting, hepatotoxicity, leukopenia, oral ulcers, Thrombocytopenia	Screen patients for thiopurine methyltransferase deficiency before therapy (0.3 to 11 percent of white population)
Cyclophosphamide	Oral: 1 to 3 mg per kg per day Intravenous: 2 to 4 mg per kg per day, in conjunction with prednisone	Increased risk for malignancy, leukopenia, thrombocytopenia, hemorrhagic cystitis, anorexia, nausea, vomiting, alopecia, sterility, congestive heart failure and stomatitis	In refractory cases only

Treatment modality	Dosage	Side effects	Comments
Cyclosporine	2.5 to 10 mg per kg per day*	Impairs T-cell proliferation; nephrotoxicity, lymphoma, hypertension, hypertrichosis, gingival hyperplasia, hepatotoxicity, paresthesias, fatigue, hyperesthesias, depression and seizures	Maintain whole blood level of 200 to 300 ng per mL; may have rapid response to therapy
Hydroxychloroquine	200 mg twice daily in adults; 2 to 5 mg per kg per day in children	Myopathy, differentiated by biopsy; hematologic toxicity, hepatotoxicity, antimalarial retinopathy, dizziness, ataxia and weight loss	Adjunctive treatment to reduce rash
Intravenous immunoglobulin	2 g per kg in divided doses once per month for three months	Pancytopenia, death, lymphoma	Showed improvement in 70 percent of patients; limited by high cost
Total body irradiation	15 rads biweekly over five weeks for total of 150 rads	Pancytopenia, death, lymphoma	Only case studies
Topical steroids	Class I (super-high potency) or class II (high potency) topical steroid is recommended	—	For further control of the erythematous and pruritic skin changes
Physical therapy	—	—	Directed at preventing atrophy and contractures; technique should focus initially on passive stretching and splinting; more aggressive strength-building therapy once inflammation is controlled
Sun avoidance	—	—	Broad-spectrum sunscreen, protective clothing, avoiding ultraviolet light exposure
Antihistamines	—	—	For control of severe pruritus
Thymectomy and plasmapheresis	—	—	Investigational

* *Cyclosporine dosing is highly subjective; it is used only as an adjunct to oral steroid therapy in a dosage of 2.5 to 10 mg per kg per day, then tapered to the lowest effective dosage over two weeks.*

Prognosis of dermatomyositis/polymyositis

Poor prognostic indicators include recalcitrant disease, delay in diagnosis, older age, malignancy, fever, asthenia-anorexia, pulmonary interstitial fibrosis, dysphagia and leukocytosis. Malignancy, cardiac and pulmonary dysfunction, and infection are the most common causes of death. With early treatment, survival rates as high as 80

and 73 percent at five and eight years, respectively, have been reported. Poor prognostic indicators in juvenile dermatomyositis are late onset of treatment, initial treatment with a dosage of prednisone that is too low, recalcitrant disease and pharyngeal involvement. Up to two thirds of this patient population develop severe complications of calcinosis cutis with mortality rates between 3 and 10 percent.

Key Messages:

- Polymyositis-dermatomyositis is a systemic autoimmune disease which belongs to the class of idiopathic inflammatory myopathies.
- Polymyositis-dermatomyositis can be associated with other connective tissue disorders (overlap syndrome) and malignancy.
- Patient management includes sunscreen, antihistamines, and oral corticosteroids.
- Poor prognostic indicators include poorly responsive disease, delay in diagnosis and the presence of malignancy.

CASE REPORT No.6

The patient was a 64-year-old male from China. Prior to admission in January 2012, the patient had experienced tinnitus in the right ear for one year and bloody nasal mucus for two months.

A tumor was identified on the right and top wall of the nasopharynx by magnetic resonance imaging (MRI) and nasopharyngeal mirror. MRI also revealed that the right pharynx was absent and the right base of the skull had been destroyed by the tumor. Pathological results of the tumor confirmed that it was nasopharyngeal undifferentiated non-keratinizing carcinoma. Two hard lymph nodes in the right neck, with an approximate diameter of 2 cm, were identified by physical examination. Comprehensive examination of the patient was performed. Abdominal computer tomography (CT) revealed multiple nodules in the liver, indicative of metastasized lesions. The diameter of these nodules ranged between 2 and 3 cm. In addition, CT revealed a thicker than normal cardia tube wall. Gastroscopy was performed and a large neoplasm was identified surrounding almost the entire diameter of the cardia. Pathological analyses were consistent with the diagnosis of cardia adenocarcinoma. *In situ* Epstein-Barr virus (EBV)-encoded small RNA (EBER) detection demonstrated that the nasopharyngeal carcinoma cells were positive and cardia carcinoma cells were negative for EBER.

The present study reports a case in which synchronous nasopharyngeal undifferentiated non-keratinizing carcinoma and cardia adenocarcinoma were diagnosed. During the therapy course, progressive painless symmetric proximal muscle weakness and a skin rash emerged and were accompanied with dysphasia. In addition, suspected dermatomyositis (DM) was diagnosed. The

coexistance of multiple primary cancers with DM is extremely rare and indicative of poor prognosis.

SYSTEMIC VASCULITIS

Systemic vasculitis is a heterogeneous group of diseases, characterized by inflammation and fibrinoid necrosis of blood vessel walls.

These are relatively uncommon disorders, with a reported annual incidence of 40 to 54 cases per 1 million persons. The incidence appears to be affected by geography, age, and seasonal challenges.

Vasculitis may be primary in origin (with no identifiable cause) or it may be secondary to infection, malignancy, or autoimmune disease. Vessels of any type, in any organ can be affected, resulting in a broad spectrum of signs and symptoms.

Classification of systemic vasculitis

Early attempts to classify systemic vasculitis into discrete categories were based primarily on blood vessel size, and indeed that approach still underpins more recent classification schemes. These schemes include those of the American College of Rheumatology and of the international consensus conference held in Chapel Hill, North Carolina, USA that gave rise to the Chapel Hill nomenclature.

Today, most physicians use the Chapel Hill nomenclature, which is based on clinical and histopathological features of vasculitis (figure 12).

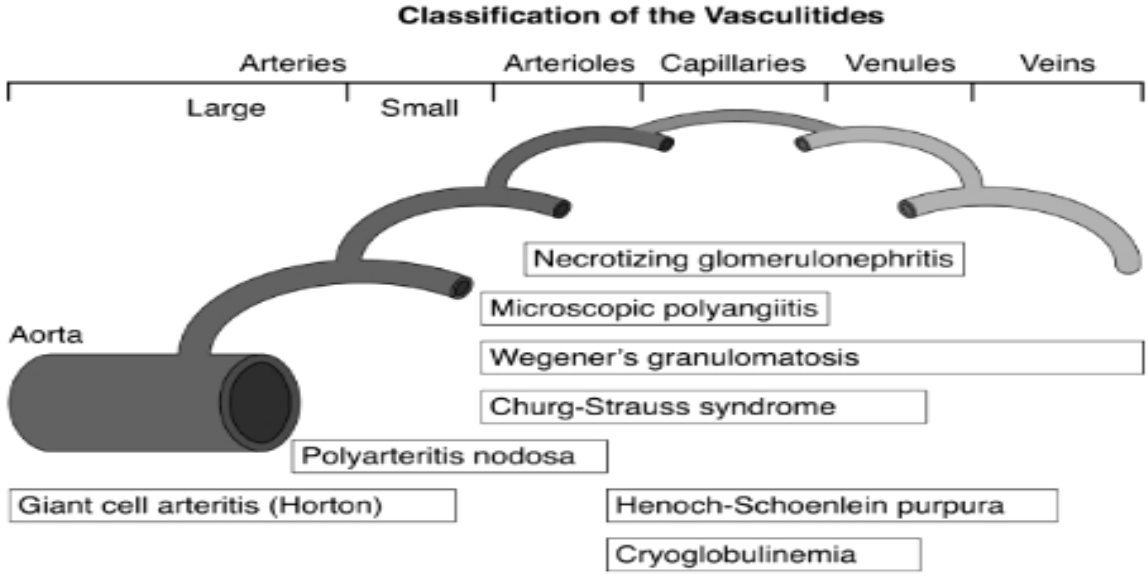


Figure 12 — Classification of systemic vasculitis

From: Guillevin, L. Vasculitis: mechanisms involved and clinical manifestations / L. Guillevin, T. Dörner // Arthritis Research & Therapy. — 2007. — Vol. 9. — P. 2–9.

In essence, classification schemes, including the Chapel Hill nomenclature, recognize two major groups of systemic vasculitides:

• large vessel vasculitis, which consists of giant cell arteritis (GCA) and Takayasu arteritis, both of which involve the aorta and its major branches;

• necrotizing vasculitis, which encompasses the rest of vasculitides. Necrotizing systemic vasculitides include polyarteritis nodosa and Kawasaki disease, which affect medium-sized arteries, and a large group of disorders in which vasculitis affects arterioles, capillaries and venules. Within this latter group there are four disorders, namely Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis and necrotizing glomerulonephritis, which are characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCAs);

• other types of small vessel vasculitis include Henoch-Schönlein purpura, which is characterized by IgA-dominant immune deposits in the small blood vessels, and essential cryoglobulinaemic vasculitis, in which cryoglobulin immune deposits are responsible for small blood vessel vasculitis (table 24).

Table 24 — Clinical classification of vasculitis (modification of the classification of the American College of Rheumatology (ACR) and that of the Chapel Hill Consensus Conference (CHCC))

Vessels predominantly or exclusively involved	**Vasculitis**
Aorta and branching vessels	— Takayasu's arteritis — Giant cell arteritis (e.g. temporal arteritis) — (Mesaortitis luetica, direct infection of vasa vasorum)
Medium-sized blood vessels (medium-sized and small arteries and veins)	***1. Polyarteritis nodosa group:*** — Classic (systemic) PAN — Cutaneous PAN (without visceral involvement) — Kawasaki syndrome / infantile PAN ***2. Nodose vasculitis in panniculitis:*** — Erythema induratum Bazin — Erythema nodosum leprosum
Small-sized blood vessels (postcapillary venules, arterioles, rarely capillaries)	***1. Systemic ANCA-associated vasculitis*** (also involving medium-sized vessels such as small arteries, but mostly small vessels. LcV of postcapillary venules is most frequent form of cutaneous involvement inWegener granulomatosis): — Wegener granulomatosis — Microscopic polyangiitis — Churg-Strauss syndrome ***2. Immune complex-associated vasculitis (most common form of LcV)*** *2.1. Immune complex-mediated damage of vessel wall as main pathogenic factor for LcV:* *— LcV with predominantly perivascular deposition of IgA-containing immune complexes (Henoch-Schönlein Purpura) (HSP)* *— LcV with predominant perivascular deposition of IgG/IgM-containing immune complexes* (hypersensitivity vasculitis, necrotizing or allergic vasculitis) — Cutaneous LcV (without apparent systemic involvement)

Vessels predominantly or exclusively involved	Vasculitis
	— IgG/IgM-associated LcV with systemic involvement — *Serum-sickness* *2.2. Immune complex-mediated damage of vessel wall as major, but not the only pathogenic factor* *— Cryoglobulinemic vasculitis (intravascular gelation in addition to immune complex-mediated damage of vessel wall)* *— Urticarial vasculitis (factors causing urticae and/or disturbances in complement in addition to immune complex-mediated damage of vessel wall)* — normocomplementemic urticarial vasculitis (NUV) — hypocomplementemic urticarial vasculitis (HUV) — syndrome of hypocomplementemic urticarial vasculitis (HUVS) ***3. Complex forms of LcV (immune complexes may be present, but other major pathogenic factors come into effect):*** — LcV in conjunction with connective tissue disease (Sjögrens' syndrome, SLE, RA) — Acral LcV and vasculopathy in SLE — LcV in conjunction with neutrophil dermatosis (M. Behcet) — Erythema elevatum et diutinum — Granuloma faciale ***4. Vasculitis combined with coagulopathy:*** — Bacteremia, sepsis, pupura fulminans (Shwartzman-reaction) ***5. Vasculitis due to direct infection of endothelial cells^*** *— e.g.* infection with certain rickettsia *EJD, vol.*

Vasculitides that occur in autoimmune diseases usually affect small-sized vessels, as in the case with SLE, systemic sclerosis and Sjögren's syndrome.

Pathogenesis of vasculitis

Various pathogenic mechanisms have been implicated in the induction of vasculitis, including cell-mediated inflammation, immune complex-mediated inflammation and autoantibody-mediated inflammation.

Progress in the classification of systemic vasculitides has facilitated better understanding of the pathogenesis underlying these inflammatory conditions, which can involve cell-mediated inflammation, immune complex (IC)-mediated inflammation, and ANCA-mediated inflammation. Of central importance is that various inflammatory pathways lead to endothelial cell activation, which may induce complications such as vessel occlusion and tissue destruction in a predisposed host, and longstanding disease.

Investigations into ANCA vasculitides have pioneered the field and expanded our understanding of the pathogenesis of vessel inflammation.

VASCULITIS INVOLVING PREDOMINANTLY LARGE BLOOD VESSELS (AORTA AND BRANCHING VESSELS)

Takayasu arteritis (nonspecific aortoarteritis):

• granulomatous inflammation of the aorta and its major branches;

• usually occurs in patients younger than 50.

This idiopathic process has a strong female predilection, affecting females ten times more than men.

Takayasu arteritis (TA) is a necrotising and obliterative segmental, large-vessel panarteritis of unknown cause, involving elastic arteries including the aorta and its branches. T-cell-mediated panarteritis starts in the adventitial vasa vasorum and progresses inwards, with the unknown antigen triggering monoclonal T-cell expansion. This inflammatory process begins with perivascular cuffing of the vasa vasorum in the early stage of the disease followed by fibrosis and calcifications. Destruction and fibrosis coexist with the former, causing aneurysmal formation and the latter leading to narrowing of the aorta and its branches, resulting in significant stenosis. Takayasu artertitis is also known as "pulseless disease" from the frequent involvement of subclavian arteries with substantial stenosis and subsequently diminished peripheral pulses.

Clinical presentation of Takayasu arteritis

Two phases, early acute and late chronic, are seen in TA.

In the early phase, so-called «B» symptoms, such as weight loss, fatigue, night sweats, anorexia and malaise, are common.

Chronic phase symptoms are determined by the organs involved, with fewer constitutional symptoms, and with claudication, cerebrovascular insufficiency, carotid artery pain and renal artery involvement.

Aortic aneurysm or stenosis has been reported in up to one-third of the cases. In the order of frequency, aneurysmal formation is seen in descending, abdominal and ascending aortic segments. Stenosis of the aorta is even more frequent, occurring in 53 % of cases, mostly affecting the abdominal aorta (up to 70 % of aortic stenosis cases).

Diagnosis of Takayasu arteritis

Takayasu arteritis, ACR criteria:

1) age at disease onset ≤ 40 years (development of symptoms or findings related to Takayasu arteritis at age ≤ 40 years);

2) claudication of extremities (development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities);

3) decreased brachial artery pulse (decreased pulsation of 1 or both brachial arteries);

4) blood pressure difference > 10 mm Hg (difference of > 10 mm Hg in systolic blood pressure between arms);

5) bruit over subclavian arteries or aorta (bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta);

6) angiographic (CT, MR) evidence of stenosis: arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular displasia, or similar causes; changes usually focal or segmental.

The presence of at least 3 of the 6 criteria are suggestive for Takayasu arteritis.

Laboratory tests such as erythrocyte sedimentation rate and C-reactive protein are elevated in 70 % of patients in the acute and 50 % of patients in the chronic stage of the disease.

Imaging findings of Takayasu arteritis

All clinically available imaging modalities play an important role in the diagnosis and follow-up of TA. Until recently, digital subtraction angiography (DSA) was the procedure of choice, but this has been subsequently replaced by cross-sectional imaging as the major disadvantages of DSA are the high radiation dose, substantial contrast material burden and difficulty in assessing cases of long-segment stenosis and aortic wall abnormalities such as arterial calcification, wall inflammation or chronic fibrosis. Additionally, transoesophageal echocardiography and intravascular US are tools that provide high-resolution images of subtle changes in aortic segments that may appear normal with other imaging techniques, although usually only the proximal aorta can be assessed.

Computer tomography

Acute stage: CT angiography (CTA) early findings in the vessel wall and lumen, such as circumferential vessel wall thickening, thrombosis, stenosis, occlusion, vessel ectasia, aneurysms and ulcers (figure 13). The «double ring» appearance of the thickened aortic wall at contrast-enhanced CT is an early stage finding with a poorly enhanced internal ring of swollen intima and an enhancing outer ring of the inflamed media and adventitia.

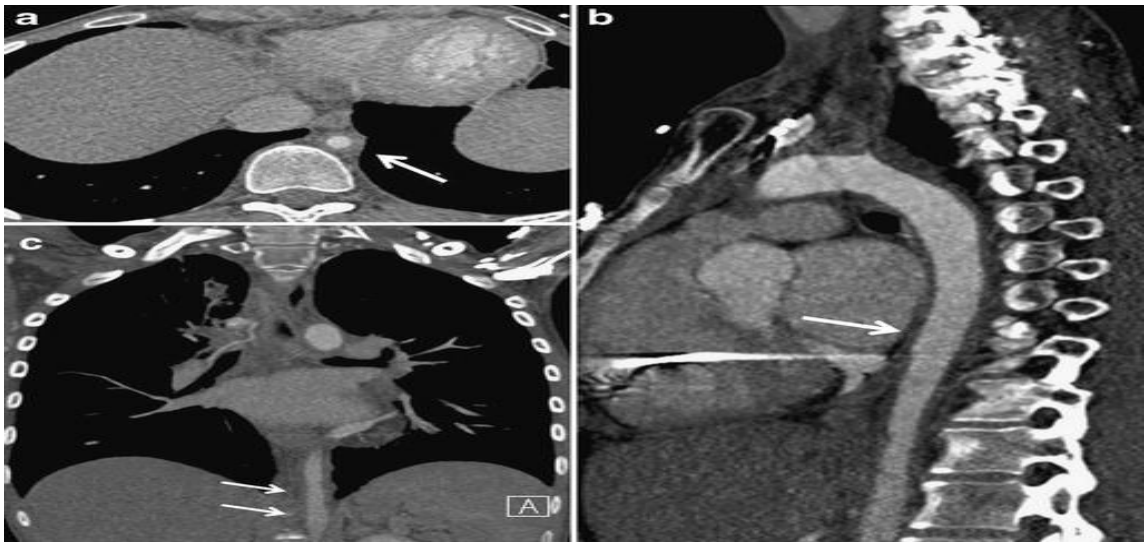


Figure 13 — Computer tomography angiography in Takayasu arteritis: Axial (a), sagittal (b) and coronal (b) images of CTA of the torso demonstrate circumferential wall thickening.

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

That milder degrees of inflammation or wall oedema may not be apparent with CTA is of note. It is considered less sensitive than other modalities such as MR or PET-CT for evaluating the degree of inflammation in the aortic wall.

Since CTA is performed using iodinated contrast, it offers the additional advantage of allowing rapid exclusion of aortic pathologies that may clinically mimic acute aortitis, including aortic dissection, intramural haematoma and penetrating atherosclerotic ulcer.

Chronic stage

Chronic findings include long-standing, burned out aortitis such as linear arterial wall calcification that can be seen after a minimum of 5 years of inflammatory involvement in the aorta or any of the involved vessels, except the ascending aorta. CT can also be used to assess the progression of a potential thoracic aortic aneurysm. High specificity and sensitivity of CT angiography (95 % and 100 %, respectively) as well as high availability make it the imaging modality of choice for the evaluation of TA.

Magnetic resonance imaging

A major strength of MR imaging is its ability to depict wall abnormalities before luminal changes occur. Gadolinium-enhanced fat-suppressed T1-weighted images are preferred to assess thickening and enhancing of the arterial wall and T2-weighted images for showing high signal of the vessel wall representing mural oedema (figure 14). MR angiography may show stenosis at multiple levels, mural thrombi, thickening of aortic valve cusps and pericardial effusions. Signal alterations within the pericardial effusion, reflecting fluid and granulation tissue, can be seen as well. Cine MRI can detect cardiovascular and haemodynamic changes, such as aortic regurgitation in patients with TA; MR angiography demonstrates the anatomical location, degree, extent of stenosis and vascular dilation, and patency of collateral vessels and surgical bypass grafts.

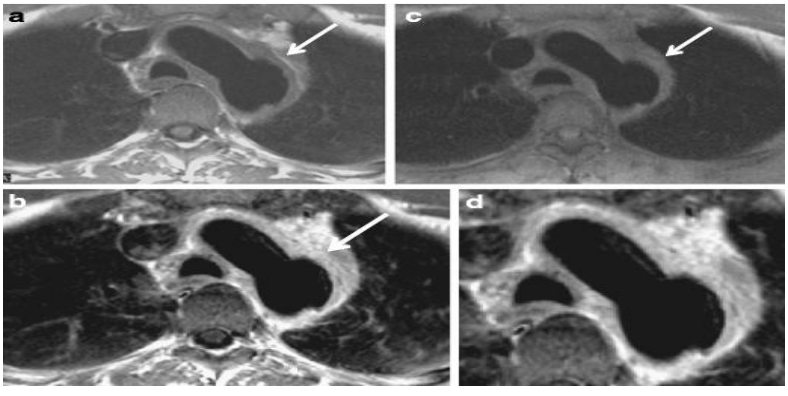


Figure 14 — Magnetic resonance angiography in Takayasu arteritis: Spin-echo T1-weighted (a), post-gadolinium enhanced (b) and proton density (c) images of the aortic arch show diffuse and relatively uniform thickening of the aortic arch with focal aneurysmal dilatation

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

Both contrast-enhanced MRI and CTA play an important role in the early diagnosis of TA, i.e., by demonstrating crescentic or ring-like aortic thickening of more than 3 mm, as well as for assessing disease activity.

Nuclear imaging

PET-CT may help to identify vasculitis in patients referred for whole-body imaging for constitutional symptoms and fever of unknown origin, as well as to monitor treatment response. The circumferential region of increased metabolic activity in the vessel wall is characteristic of the active phase of TA (Figure 15). FDG-PET has a reported sensitivity of up to 92 % and a specificity of 89–100 % for the detection of large vessel vasculitis among untreated patients with elevated serum markers. Recently, the use of 18-fluorodeoxyglucose (18F-FDG) PET, either alone or in combination with contrast-enhanced CTA or MRA, has emerged as a potential tool for the initial diagnosis and assessment of disease activity of aortitis caused by Takayasu arteritis. PET-CT may also be useful for monitoring treatment response, reflected in decreases in vessel wall metabolic activity. However, the main limitations of these studies are the small sample size, heterogeneous patient population and inconsistent reference standards.

Hybrid imaging with 18F-FDG PET and either CTA or MRA allows more precise anatomic localisation of disease activity with increased uptake of 18F-FDG thought to be a surrogate marker of increased activity of inflammatory cells. The presence of wall thickening, arterial stenosis, luminal thrombus and aneurysm cannot be assessed by PET alone; CTA and MRA are complementary to PET for complete evaluation of the patient with aortitis.

Complications and therapy of Takayasu arteritis

To prevent the known complications of TA such as stenosis, aneurysm formation or occlusion, early treatment with corticosteroids is indicated to suppress inflammatory response. The usual regimen includes high-dose oral steroids (40–60 mg daily), usually for as long as 1–2 years. Unfortunately, up to 50 % of patients relapse during tapering and require additional immunosuppression. Serum markers have limited value in follow-up since disease progression has been shown in the presence of normal serum marker levels.

Revascularisation in cases of aortic stenosis or aneurysm is performed when there is secondary vascular organ insufficiency or risk of rupture. Usually the intervention is done in chronic cases after the acute phase inflammation has subsided.

Giant cell (temporal) arteritis:

• granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery;

• often involves the temporal artery;

• usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.

Giant cell arteritis (GCA), also known as temporal arteritis, is an elastic vessel systemic granulomatous vasculitis affecting the aorta as well as its secondary and tertiary branches (large and medium-sized vessels) and usually involves superficial cranial arteries. Aortic involvement occurs in 15 % of GCA patients. As opposed to predominately young patients affected by TA, GCA is usually seen in patients over 50 years old with an incidence peaking in the 8th decade of life. Female predilection is less frequent (3:2 female:male ratio). A higher than usual incidence of the disease is seen in Northern Europe (Scandinavia in particular), with lesser frequency in Southern Europe, making genetic predisposition in certain populations likely. A strong relationship between GGA and polymyalgia rheumatica has been shown.

Pathogenesis of giant cell arteritis

In GCA vasculitis is essentially a T-cell driven process that is triggered by exposure to antigens, most probably infectious agents. Dendritic cells present in the adventitia and media of the blood vessel wall are potent antigen-presenting cells that can prime naïve T cells. In patients with GCA they are responsible for activating $CD4^+$ T cells, which orchestrate vascular injury by recruiting macrophages and monocytes to the vessel walls. These cells induce systemic inflammation via the release of cytokines, such as interleukin-1 and interleukin-6. Tissue resident T cells also release interferon-γ, which is a key proinflammatory cytokine that has been implicated in the pathogenesis of GCA. Sustained inflammation mediated by T cells, macrophages and the proinflammatory cytokines released by these cells leads to extensive intimal thickening and vessel occlusion (figure 15). Platelet-derived growth factor and vascular endothelial growth factor play key roles in the subsequent development of the lumen-occlusive arteritis that characterizes GCA.

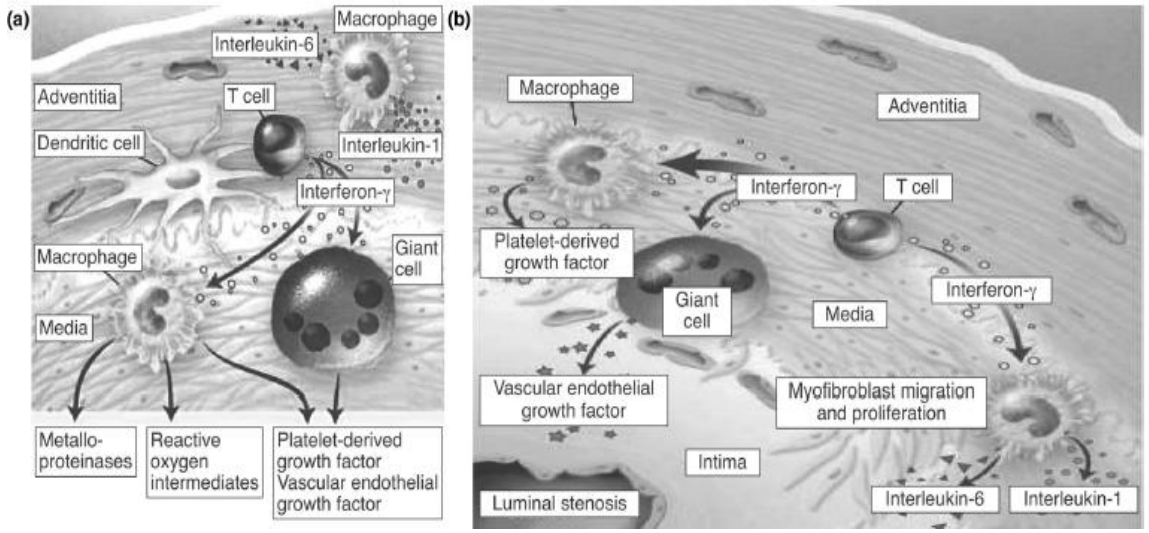


Figure 15 — Pathogenesis of giant cell arteritis

From: Guillevin, L. Vasculitis: mechanisms involved and clinical manifestations / L. Guillevin, T. Dörner // Arthritis Research & Therapy. — 2007. — Vol. 9. — P. 2–9.

Clinical presentation of giant cell arteritis

GCA has acute and chronic stage pathophysiology. During the acute stage constitutional symptoms such as weight loss, night sweats, malaise and fever are extremely common, affecting half of the patients. In up to 90 % of patients with biopsy-proven disease, scalp tenderness is present. Cranial symptoms (tenderness, headache), jaw claudication, visual changes and neurologic changes are all commonly seen.

Vascular inflammation most commonly involves external carotid branches, especially the superior temporal artery and the vertebral arteries. Extracranial arteries are involved in 25 % of cases such as the aorta, coronary arteries and mesenteric arteries. Five-year survival can be affected in cases of widespread disease. Aortic stenosis is less common than in TA, although annuloaortic ectasia or ascending aortic aneurysms that can extend into the aortic arch are more common than in TA. Thoracic aortic aneurysms are usually seen in the late stages of the disease.

Diagnosis of giant cell arteritis

ACR criteria:

1) age at disease onset ≥ 50 years (development of symptoms or findings starting at age 50 or older);

2) new headache (new onset or a new type of localized pain in the head);

3) claudication of jaw, tongue, or on deglutition (development or worsening of fatigue or discomfort in muscles of mastication, tongue or swallowing muscles while eating);

4) temporal artery abnormality (temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries) (figure 16);

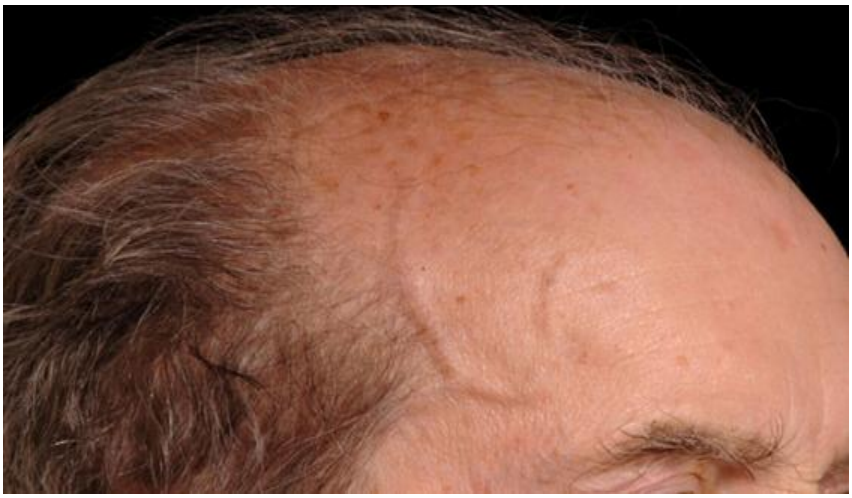


Figure 16 — Temporal artery inflammation in giant cell arteritis: The temporal artery is tender, enlarged and have decreased pulsation.

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin. Exp. Immunol. — 2010. — Vol. 160. — P. 143–160.

5) scalp tenderness or nodules (development of tender areas or nodules over the scalp, away from the temporal artery or other cranial arteries) (figure 17);

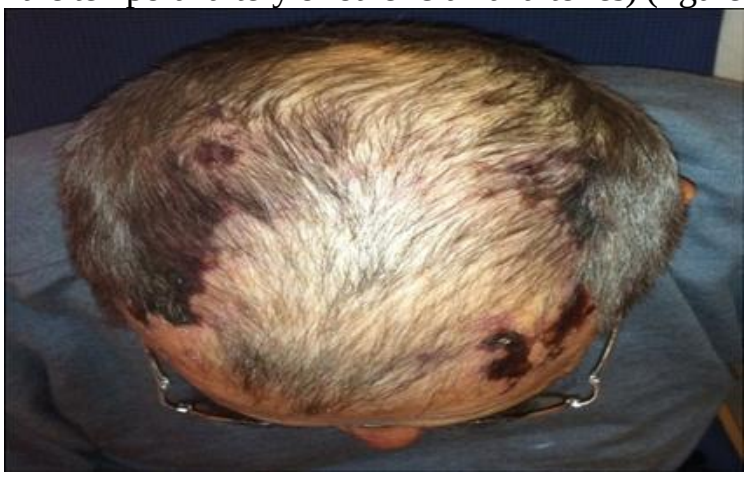


Figure 17 – Scalp necrosis in giant cell arteritis

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

6) abnormal artery biopsy (biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells) (figure 18).

The presence of at least 3 of the 6 criteria are suggestive for giant cell arteritis.

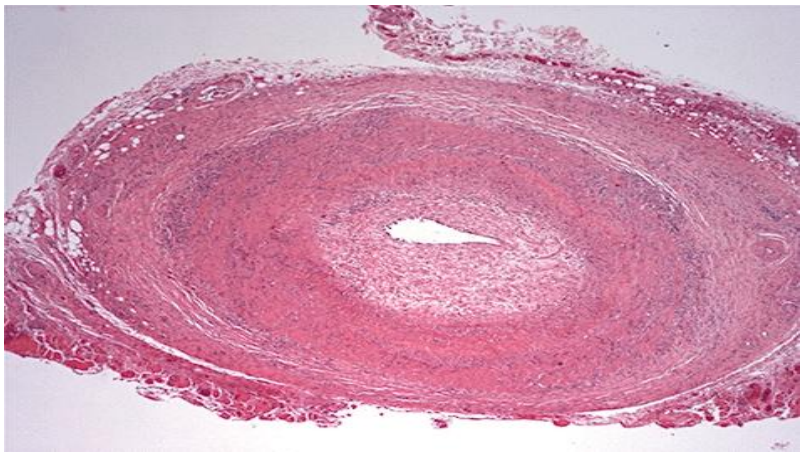


Figure 18 — Biopsy of the artery from a patient with giant cell arteritis: Intense inflammatory infiltrate in the adventitia and media, and proliferation of the intima with narrowing of the lumen of temporal artery.

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

Imaging findings of giant cell arteritis CT, MRI, PET-CT and ultrasound

Although no imaging findings are required for diagnosis, imaging might be helpful in diagnosing GCA.

Long segment involvement with significant wall thickening and smooth tapering proximal and distal to the lesion on CT and MR are classic radiological findings. The most frequently affected arteries are the subclavian, axillary, femoral, popliteal, tibial and peroneal, with rare involvement of coronary arteries. CT and in particular MR angiography are able to demonstrate vessel wall oedema, which reflects disease activity. CT angiography can reveal luminal changes similar to TA such as stenosis, occlusion, dilatation, aneurysm formation, calcification and mural thrombi.

An association between the history of GCA and the development of aortic aneurysm, particularly thoracic aortic aneurysm, has been described. The frequency of aortic involvement in GCA is unknown, but it has been suggested that all patients with temporal GCA and symptoms of extracranial vascular involvement undergo an imaging study to evaluate the aorta and large thoracic vessels.

FDG PET has been shown to be sensitive for extracranial vasculitis but not for intracranial vasculitis on account of its poor spatial resolution. FDG PET reveals abnormal uptake in the aortic arch or large thoracic arteries in more than half of the affected patients (sensitivity 56 %, specificity 98 %, positive predictive value 93 %, negative predictive value 80 %).

Ultrasonography is useful in assessing cranial vessels, showing an increased diffuse, circumferential intima-media complex (IMC) thickness in transverse sections (dubbed the ‘macaroni sign’), reflecting inflammatory oedema, increased vascularity or both. In contrast, atherosclerotic lesions are usually characterised by a localised thick IMC pattern.

Complications and therapy of giant cell arteritis

Aortic aneurysm complicated by acute dissection or aortic valve insufficiency is associated with decreased survival (on average 1.1 years). The standard therapy, high-dose oral steroids (40–60 mg daily) for 1–2 years, results in rapid improvement but a high relapse rate.

A typical regime for GCA is to maintain patients above 40 mg prednisolone for 1 month, and then reduce by 5 mg per week until they reach 20 mg, then by 2.5 mg every 2 weeks until they reach 15 mg, and then reduce subsequently as for PMR. All patients should have prophylaxis against osteoporosis started early in their treatment course, and gastroprotection considered.

In the presence of acute or threatened visual loss many rheumatologists would also consider giving 500 mg intravenous methylprednisolone immediately at presentation and possibly for the next 2 days, on the basis of reducing the threat to the contralateral eye. Three days of intravenous methylprednisolone may allow a reduced cumulative prednisolone dose and a higher frequency of sustained remission according to a small study although intravenous glucocorticoids did not show convincing evidence of benefit in unselected GCA patients without threatened visual loss.

Unlike TA, additional immunosuppressive therapy does not affect the course of the disease, but the approach to revascularisation is similar to TA.

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are two inflammatory rheumatic diseases that often coexist in the same patient, suggesting shared disease mechanisms. GCA is vasculitis affecting large-sized and medium-sized blood vessels whereas PMR produces inflammatory-type pain and stiffness of the neck, shoulder and/or hip girdle areas. Both are usually accompanied by laboratory evidence of systemic inflammation. GCA is a medical emergency and prompt diagnosis and treatment are required to prevent blindness.

Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is characterised by continuous, aching pain in the shoulders, neck and upper arms, and to a lesser extent in the hips, thighs and lower back, associated with marked stiffness after rest. Early morning stiffness typically lasts at least an hour but it may be hard to pin patients down as to the exact duration of their early morning stiffness; some patients say they are stiff ‘all day’. In these cases, asking about the *severity* of stiffness in the morning and evening can be helpful. Apart from severe limitation of active movement, clinical signs of PMR are few, apart from non-specific features of systemic inflammation such as fever, pallor or weight loss. Symptoms are generally at their worst during the small hours of the morning or on waking, and may greatly improve towards the afternoon. In contrast, degenerative arthritis is usually worst towards the end of the day and there is short-lived ‘gelling’ rather than prolonged stiffness. This is a key point for clinical practice.

It is important to remember that the clinical syndrome of PMR may be a presenting feature of rheumatoid arthritis (RA). In most series of prospectively-followed PMR patients about 10 % of patients presenting with PMR-like symptoms are later diagnosed with 'late-onset' rheumatoid arthritis. This may represent an overlap of disease phenotype. A non-erosive synovitis of the small joints of the hands or feet may occur in PMR, is usually a presenting symptom and is very glucocorticoid responsive.

The differential diagnosis of PMR is of critical importance, especially for young or otherwise atypical cases, such as those with normal inflammatory markers. Screening for hypothyroidism should be routine and there should be a low threshold for investigation of possible malignancy or infection. Deep-seated or occult infections such as subacute bacterial endocarditis or osteomyelitis are important differentials because of the potentially catastrophic consequences of misdiagnosis of these conditions as PMR. Other treatable causes include statin-related myalgia and osteomalacia.

Diagnosis of polymyalgia rheumatica

Inflammatory markers

Elevation of IL-6, ESR, CRP and PV.

Imaging

Ultrasound in PMR may demonstrate glenohumeral joint synovitis, subdeltoid bursitis, biceps tenosynovitis, hip synovitis and trochanteric bursitis. These abnormalities have recently been incorporated into the new ACR/EULAR provisional classification criteria and musculoskeletal ultrasound is being incorporated into routine clinical practice at some centres.

Other imaging modalities, including MRI and FDG-PET, show abnormalities in PMR which may shed light onto its possible anatomical basis; however, in practice these are likely to remain research tools.

Treatment of polymyalgia rheumatica

PMR is treated with medium-dose glucocorticoids (most patients respond to 15 mg prednisolone daily; some require 20 mg). The patient's weight should be taken into account when starting glucocorticoids; lighter patients may respond to 12.5 mg.

Clinical response should be assessed on the basis of patient symptoms as well as inflammatory markers. Provided there is a clinical response, the glucocorticoids are usually maintained at the same dose for a few weeks and then gradually tapered, initially reducing by 2.5 mg every 2–4 weeks. Once on 10 mg, reduction is usually done at a rate of around 1mg per month; some patients need a slower reduction of 0.5 mg every month. All patients should have prophylaxis against osteoporosis started early in their treatment course.

VASCULITIS INVOLVING PREDOMINANTLY MEDIUM-SIZED BLOOD VESSELS (MEDIUM-SIZED AND SMALL ARTERIES AND VEINS)

Panarteritis nodosa:

• necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.

Pathogenesis of panarteritis nodosa

Immune complex (IC) formation is usually considered to be the major pathological event in polyarteritis nodosa. In polyarteritis nodosa antibody-mediated IC deposition can lead to renal infarction. Micro-aneurisms are another manifestation that can occur as a consequence of IC formation in the medium-sized necrotizing systemic vasculitides, which can also lead to blood vessel occlusion.

It has been suggested that the interaction of ICs, Fcγ receptors and adhesion molecules leads to disturbances in transmigration and activation of polymorphonuclear neutrophils, with consequent vessel damage.

Diagnosis of panarteritis nodosa

Panarteritis nodosa, ACR criteria:

1) weight loss ≥ 4 kg (loss of 4 kg or more of body weight since illness began, not due to dieting or other factors);

2) livedo reticularis (Mottled reticular pattern over the skin of portions of the extremities or torso);

3) testicular pain or tenderness (pain or tenderness of the tesicles, not due to infection, trauma or other causes);

4) myalgias, weakness or leg tenderness (diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles);

5) mononeuropathy or polyneuropathy (development of mononeuropathy, multiple mononeuropathies, or polyneuropathy);

6) diastolic blood pressure ≥ 90 mm Hg (development of arterial hypertension with the diastolic BP higher than 90 mmHg);

7) elevated BUN or creatinine (elevation of blood urea nitrogen ≥ 40 mg/dl or creatinine > 1.5 mg/dl, not due to dehydration or obstruction);

8) hepatitis B virus (presence of hepatitis B surface antigen or antibody in serum);

9) arteriographic abnormality (arteriogram showing aneurysms or occlusion of the visceral arteries, not due to arteriosclerosis, fibromuscular displasia, or other noninflammatory causes) (figure 19);

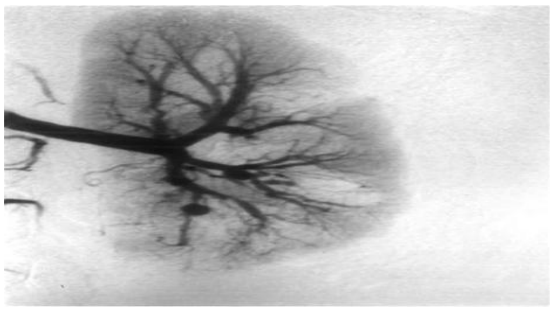


Figure 19 — A renal angiogram of patient with polyarteritis nodosa: There are large and small aneurysms, perfusion defects, arterial cutoff and lack of crossing of peripheral renal arteries

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

10) biopsy of small or medium-sized artery containing PAN (histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall) (figure 20).

For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present.

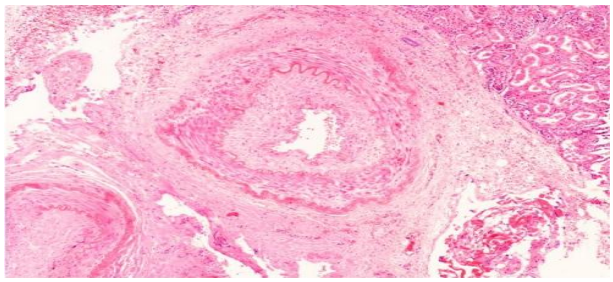


Figure 20 — Late vasculopathy associated with polyarteritis nodosa: Very abnormal medium-sized arteries are present, consistent with healed vasculitis with internal elastic lamina rupture, fibrosis and intimal thickening but no active vasculitis

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

Patients with polyarteritis nodosa present with a multi-system illness with constitutional features such as weight loss, fever, myalgia, development of a rash, neuropathy or abdominal ischaemia. Polyarteritis nodosa is associated commonly with hepatitis B infection.

Treatment of panarteritis nodosa

Induction

Hepatitis B-associated polyarteritis nodosa should be managed in conjunction with a hepatologist. High-dose glucocorticoids are given for 2 weeks followed by anti-viral agents (such as vidarabine, interferon-alpha and lamivudine) and then plasmapheresis. This protocol facilitates seroconversion to hepatitis B immune status, which would prevent relapse.

In those patients who do not have hepatitis B infection, combination therapy of cyclophosphamide and high-dose glucocorticoids (such as prednisolone 1 mg/kg/day) is usually indicated, unless patients have a favourable prognosis as defined using the five-factor score. Oral or pulsed high-dose cyclophosphamide is given for at least 3 months and glucocorticoids are tapered over the next 4 months to a minimum of 15 mg/day.

Intravenous methylprednisolone is used for fulminant disease. Short duration (6 × monthly pulses) of high-dose cyclophosphamide is associated with higher relapse rates and lower event-free survival than long duration (12 × monthly pulses) treatment in patients with polyarteritis nodosa; however, there is no significant difference in mortality. Pulsed cyclophosphamide has been used with equal efficacy to continuous oral daily cyclophosphamide in polyarteritis nodosa and had a lower incidence of adverse events over a 12-month period.

Maintenance

Once remission is achieved, steroids can be reduced gradually to 10 mg/day or less. Polyarteritis nodosa has a low relapse rate and maintenance treatment is usually not needed. In cases of relapse, maintenance treatment with azathioprine or methotrexate could be considered.

VASCULITIS OF SMALL SIZED VESSELS

Wegener’s granulomatosis:

• granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (*e.g.* capillaries, venules, arterioles, and arteries);

• necrotizing glomerulonephritis is common.

Pathogenesis of Wegener’s granulomatosis

Autoantibodies play a central role in the ANCA-related vasculitis that is characteristic of Wegener's granulomatosis (figure 21).

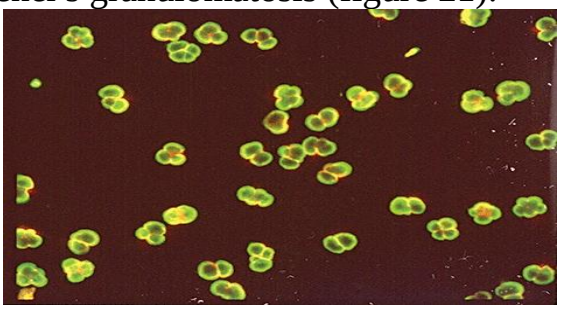


Figure 21 — Indirect immunofluorescence pattern of perinuclear anti-neutrophil cytoplasm antibody (p-ANCA) from a patient with microscopic polyangiitis

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

These antibodies are directed against enzymes that are contained in the granules of neutrophils and monocytes. In Wegener's granulomatosis they primarily target proteinase 3, which is a neutral serine protease. Proteinase 3-ANCA can contribute to vasculitis in the small blood vessels, causing adverse clinical sequelae such as pauci-immune glomerulonephritis and pulmonary haemorrhage. An enhancing effect of ANCAs on leucocyte diapedesis caused by their interaction with the endothelium was recently demonstrated in a study involving passive transfer of immunoglobulin; this procedure resulted in microvascular haemorrhage.

Diagnosis of Wegener's granulomatosis

Wegener's granulomatosis, ACR criteria:

1) nasal or oral inflammation (development of painful or painless oral ulcers or purulent or bloody nasal discharge);

2) abnormal chest radiograph (chest radiograph showing the presence of nodules, fixed infiltrates, or cavities) (figure 22);

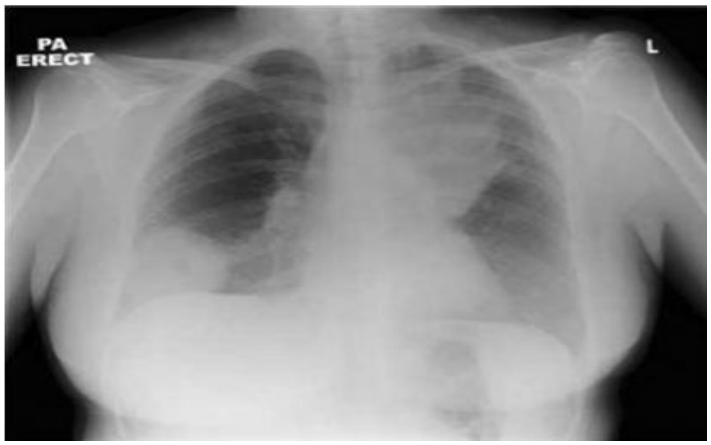


Figure 22 — Plain chest radiograph of a patient with Wegener's granulomatosis: Extensive consolidation in the left upper lobe and a large granulomatous lesion in the right lower zone

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

3) urinary sediment (microhematuria (> 5 red blood cells per high power field) or red cell casts in urine sediment);

4) granulomatous inflammation on biopsy (histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present.

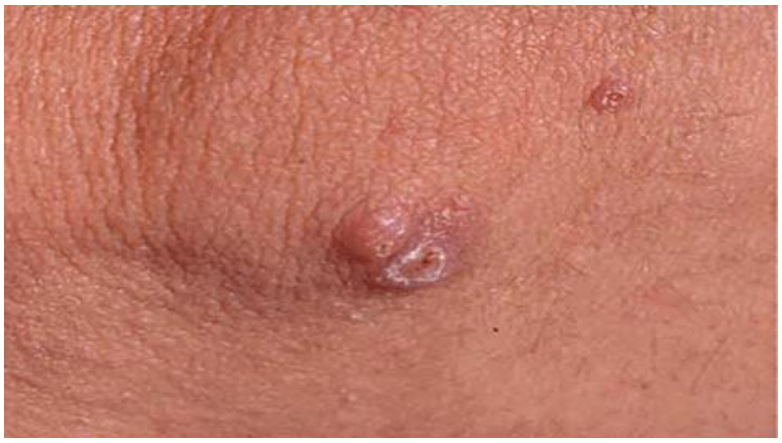


Figure 23 — Nodulopapular lesions on the elbow in a patient with Wegener's granulomatosis

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

Treatment of Wegener’s granulomatosis

Corticosteroids and immunosuppressants such as cyclophosphamide are the mainstay of treatment for vasculitis.

A common approach to treatment, and one supported by data from the European Vasculitis Study Group on ANCA-associated vasculitis and Wegener's granulomatosis, is to use short-term cyclophosphamide over a 3-month to 6-month period as induction therapy, and then to switch patients to maintenance therapy with either azathioprine or methotrexate. This is in addition to background corticosteroid therapy.

Treatment of Wegener's granulomatosis with the anti-tumour necrosis factor-α agent infliximab has also shown early promise.

Co-trimoxazole is commonly added to therapeutic programs for the treatment of WG, particularly in those with upper respiratory tract involvement, serving both as prophylaxis against opportunistic infection and as a possible disease-modifying agent.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is defined as vasculitis with immunoglobulin (Ig)A-dominant immune deposits affecting small vessels and typically involving the skin, gut, and glomeruli and associated with arthralgias or arthritis.

The etiology of HSP is unclear. It is frequently associated with upper respiratory tract infection, which is consistent with its peak occurrence in the winter and fall. Patients usually present with a 2- to 3-week history of fever, headache, myalgia, arthralgia, and abdominal pain preceding the typical cutaneous purpura. Group A streptococci, mycoplasma, and a variety of other infectious agents and drugs have been reported as potential triggers.

Pathogenesis of Henoch-Schönlein purpura

Immune complex (IC) formation is usually considered to be the major pathological event in Henoch-Schönlein purpura.

The pathogenetic mechanisms underlying HSP are poorly understood. Widespread abnormalities in IgA have been described including raised serum IgA concentrations, IgA immune complexes, IgA class antibodies such as IgA rheumatoid factor (RF), IgA ANCA (antineutrophil cytoplasmic antibody), and IgA AECA (antiendothelial cell antibody). IgA deposits are also found in skin biopsies and deposited within glomeruli.

Complement abnormalities have been described in association with HSP: C2 deficiency, homozygous null C4 phenotypes, and C4B deficiency. Other abnormalities including glomerular C3 and properdin deposition, low CH50 and properdin, and raised C3d concentrations in the acute phase of the disease have suggested complement activation.

CHCC definition:

• vasculitis, with lgA-dominant immune deposits, affecting small vessels (*i.e.* capillaries, venules, or arterioles);

• typically involves skin, gut, and glomeruli, and is associated with arthralgia or arthritis.

According to the new EULAR/PRINTO/PRES definition, a patient is classified as having HSP in the presence of purpura (commonly palpable) or petechiae with lower limb predominance (mandatory criterion) plus one of the four following criteria:

1) abdominal pain;

2) histopathology showing typical leukocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit;

4) arthritis or arthralgia;

5) renal involvement (proteinuria or hematuria or presence of red blood cell casts).

In cases of purpura with atypical distribution, a demonstration of IgA is required at biopsy.

Manifestations of Henoch-Schönlein purpura

Henoch-Schönlein purpura typically affects children between the age of 3 and 10 years.

Skin involvement is typically with purpura which is generally symmetrical, affecting the lower limbs and buttocks in the majority of cases; the upper extremities are involved less frequently (figure 24). The abdomen, chest, and face are generally unaffected. New crops of purpura may develop for several months after disease onset, though these generally fade with time. Lesions can be induced by mild trauma. Angioedema and urticaria can also occur.

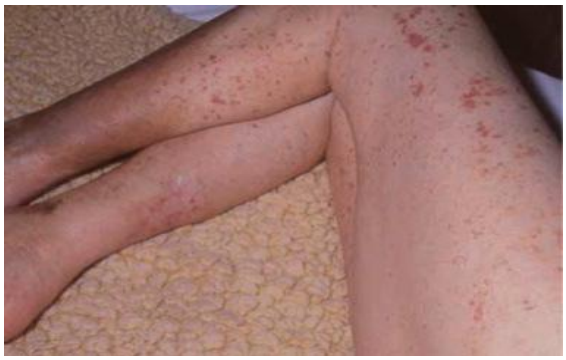


Figure 24 — Henoch–Schonlein purpura:
Purpuric rash on calves with coalescence of lesions on the thighs secondary to pressure. There are haemosiderin deposits from previous episodes of purpura and a scar on the right calf from a healed ulcer

From: An approach to the diagnosis and management of systemic vasculitis / A. Miller [et al.] // Clin Exp Immunol. — 2010. — Vol. 160. — P. 143–160.

Around two-thirds of children have joint manifestations at presentation. The knees and ankles are most frequently involved. Symptoms, which take the form of pain, swelling, and decreased range of movement, tend to be fleeting and resolve without the development of permanent damage.

Three-quarters of children develop abdominal symptoms ranging from mild colic to severe pain with ileus and vomiting. Hematemesis and melena are sometimes observed. Other complications include intestinal perforation and intussusception. The latter may be difficult to distinguish from abdominal colic, and the incidence of intussusception is significant enough to warrant exclusion by ultrasound where suspected. Acute pancreatitis is also described, although it is a rare complication.

Other organs less frequently involved include the central nervous system (cerebral vasculitis), gonads (orchitis may be confused with torsion of the testis), and the lungs (pulmonary hemorrhage). Many cases follow an upper respiratory tract infection, and the onset of the disorder may be accompanied by systemic symptoms, including malaise and mild pyrexia.

Multiple organ involvement may be present from the outset of the disease or, alternatively, an evolving pattern may develop, with different organs becoming involved at different time points over the course of several days to several weeks. One complication worth emphasizing for pediatric nephrologists is the rare but well-recognized complication of ureteric obstruction.

Around one-third of children have signs and symptoms for < 14 days, one-third for 2–4 weeks, and one-third for > 4 weeks. Recurrence of symptoms occurs in around one-third of cases, generally within 4 months of resolution of the original symptoms. Recurrences are more frequent in those patients with renal involvement.

Reports of HSP nephritis indicate that between 20–61 % of cases are affected with this complication. Renal involvement is normally manifest between a few days and a few weeks after first clinical presentation, but it can occur up to 2 months or

(rarely) more following presentation. Patients with bloody stools appear to have an increased risk of renal disease. Renal involvement can present with varying degrees of severity, including isolated microscopic hematuria, proteinuria with microscopic or macroscopic hematuria, acute nephritic syndrome (hematuria with at least two of hypertension, raised plasma creatinine and oliguria), nephrotic syndrome (usually with microscopic hematuria), or a mixed nephritic-nephrotic picture.

Diagnosis of Henoch-Schönlein purpura

Henoch-Schönlein purpura, ACR criteria:

1) palpable purpura (slightly raised «palpable» hemorrhagic skin lesions, not related to thrombocytopenia);

2) age ≤ 20 at disease onset (patient 20 years or younger at onset of first symptoms);

3) bowel angina (diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhoea);

4) wall granulocytes on biopsy (histologic changes showing granulocytes in the walls of arterioles or venules).

For purposes of classification, a patient shall be said to have Henoch-Schönlein purpura if at least 2 of these 4 criteria are present.

Diagnosis is usually straightforward clinically, with the typical skin rash (predominantly lower limb purpura) being the main clue, often accompanied by abdominal pain and arthralgia or overt arthritis. No single laboratory test is available for the diagnosis of HSP. Immunological investigations including complement levels and anti-nuclear antibodies are normal. The IgA level is elevated in approximately one-half of children, and a small number exhibit ANCA positivity. Coagulation studies are normal (although factor XIII may be low; see below), and platelet numbers are normal or occasionally increased. Where significant nephritis is present at presentation, renal function and electrolytes may be correspondingly abnormal. Diagnosis of HSP is often made on the basis of clinical signs and symptoms and can be confirmed with direct immunofluorescence of the skin biopsy sample, which demonstrates leukocytoclastic vasculitis with perivascular immunoglobulin A, immunoglobulin C3, and fibrin deposits.

The renal lesion of HSP nephritis is characteristically a focal and segmental proliferative glomerulonephritis. Severe cases with rapidly progressive glomerulonephritis usually demonstrate a high percentage of crescentic glomerular changes on renal biopsy. Indications for diagnostic renal biopsy in children with HSP are:

- nephritic/nephrotic presentation (urgent);
- raised creatinine, hypertension or oliguria (urgent);
- heavy proteinuria (urine albumin/urine creatinine ratio persistently > 100 mg/mmol) on an early morning urine sample at 4 weeks; serum albumin not necessarily in the nephrotic range;
- persistent proteinuria (not declining) after 4 weeks;
- consider biopsy for persistent impaired renal function [glomerular filtration rate (GFR) < 80 ml/min/1.73 m^2].

The differential diagnosis of HSP includes sepsis (particularly meningococcal septicaemia), other systemic vasculitides [systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), WG, MPA, hypersensitivity vasculitis, and

cutaneous leukocytoclastic vasculitis], all of which can present with similar clinical features. Isolated cutaneous leukocyclastic vasculitis does not typically present with a history of a hypersensitivity reaction to drugs or infections and hence should be differentiated clinically from true hypersensitivity vasculitis. Cutaneous leukocytoclastic vasculitis can occur with arthralgia and thus mimic HSP, but it is not associated with the other systemic features of HSP, such as renal involvement. Thus, the diagnosis of true cutaneous leukocytoclastic vasculitis is one of exclusion after screening for features of systemic features.

Familial Mediterranean fever can also mimic or occur in association with HSP in areas where this is endemic.

Treatment of Henoch-Schönlein purpura

Henoch-Schönlein purpura is usually benign and resolves spontaneously, so treatment is mostly supportive, including adequate hydration. The large majority of cases of HSP require symptomatic treatment only. Arthropathy is managed with rest and analgesia.

Treatment to prevent renal disease

The efficacy of corticosteroids to prevent complications such as abdominal pain is still debated. Prophylactic corticosteroid does not prevent the onset of HSP nephritis.

Prednisone treatment (1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks) was effective in reducing the intensity of abdominal pain and joint pain. Prednisone did not prevent the development of renal symptoms, but it was effective in treating them if present; renal symptoms resolved in 61% of the prednisone patients after treatment, compared with 34% of the placebo patients, although it should be noted that the renal involvement in the patients in this study was relatively mild.

Treatment of rapidly progressive glomerulonephritis

For patients with rapidly progressive glomerulonephritis (RPGN) with crescentic change on biopsy, uncontrolled data suggest that treatment may comprise aggressive therapy with corticosteroid, cyclophosphamide and, possibly, plasma exchange, as for other causes of crescentic nephritis. Other therapies, such as cyclosporine A, azathioprine, and cyclophosphamide, have been reported to be effective.

Treatment of HSP nephritis that is not rapidly progressive

Many would advocate corticosteroids. Others advocate the addition of cyclophosphamide to corticosteroids in HSP nephritis in which biopsy shows diffuse proliferative lesions or sclerosis, but with < 50 % crescentic change, in patients who have ongoing heavy proteinuria. A typical regimen would comprise 8 weeks of oral cyclophosphamide (2 mg/kg/day) with intravenous pulsed methylprednisolone, followed by daily prednisolone, and converting to alternate day prednisolone and azathioprine for a total of 12 months. In patients with > 6 months duration of proteinuria an angiotensin converting enzyme (ACE) inhibitor may be indicated to limit secondary glomerular injury, although again the evidence to support this therapy is lacking.

Outcome of Henoch-Schönlein purpura

The majority of patients with HSP make a full and uneventful recovery with no evidence of ongoing significant renal disease. Renal involvement is the most serious long-term complication of HSP.

Disease activity items recorded routinely in assessment of systemic vasculitis

1. General
Arthralgia or arthritis
Myalgia
Fever > 38,0 °C
Weight loss > 2 kg
2. Cutaneous
Infarct
Purpura
Ulcer
Gangrene
Other skin vasculitis
3. Mucous membranes/eyes
Mouth ulcers/granulomata
Genital ulcers
Adnexal inflammation
Significant proptosis
Red eye (epi)scleritis
Red eye conjunctivitis/blepharitis/keratitis
Blurred vision
Sudden visual loss
Uveitis
Retinal change (vasculitis/thrombosis/retinal exudates/haemorrhage)
4. ENT (ear/nose/throat)
Bloody nasal discharge/nasal discharge/crusts/ulcers and/or granulomata
Paranasal sinus involvement
Subglottic stenosis
Conductive hearing loss
Sensorineural hearing loss
5. Chest
Wheeze
Nodules or cavities
Pleural effusion/pleurisy
Infiltrate
Endobronchial involvement
Massive haemoptysis/alveolar haemorrhage
Respiratory failure

6. Cardiovascular
Loss of pulses
Valvular heart disease
Pericarditis
Ischaemic cardiac pain
Cardiomyopathy
Congestive cardiac failure
7. Abdominal
Peritonitis
Bloody diarrhoea
Ischaemic abdominal pain
8. Renal
Hypertension
Proteinuria > 1+
Haematuria ≥ 10 rbc/hpf
Raised creatinine (> 125 μmol/l)
Rise in creatinine > 30 % or fall in GFR (glomerular filtration rate) > 25 %
9. Nervous system
Headache
Meningitis
Organic confusion
Seizures (not hypertensive)
Stroke
Cord lesion
Cranial nerve palsy
Sensory peripheral neuropathy
Motor mononeuritis multiplex

Table 25 — Summary of drugs and treatments used for systemic vasculitis

Vasculitis	Drug/treatment	Indication
Small vessel		
Antineutrophilic cytoplasmicantibody–associated small vessel vasculitis (Churg-Strauss syndrome, microscopic polyangiitis, Wegener granulomatosis)	Prednisolone	First-line therapy in conjunction with cyclophosphamide in generalized disease; first-line therapy in localized/early disease
	Methylprednisolone	Severe vasculitis with rapidly progressive glomerulonephritis
	Methotrexate	First-line therapy in conjunction with steroids in localized/early disease
	Cyclophosphamide	First-line therapy in generalized disease, aggressive local disease, and life-threatening disease
	Plasmapheresis	Progressive severe renal disease
	Intravenous immune globulin	Refractory disease
	Azathioprine Biologic therapy (infliximab, rituximab, antithymocyte globulin)	Refractory or relapsing disease

Vasculitis	Drug/treatment	Indication
	Interferon alfa	
Cutaneous leukocytoclastic angiitis	Antihistaminics plus nonsteroidal anti-inflammatory drugs	Symptom control in absence of systemic disease
	Prednisolone	Severe cutaneous or systemic disease
Essential cryoglobulinemic vasculitis	Interferon alfa plus oral ribavirin	Hepatitis C-related cryoglobulinemic vasculitis
	Therapy same as antineutrophilic cytoplasmic antibody-associated vasculitis	Nonviral-related cryoglobulinemic vasculitis
Henoch-Schönlein purpura	Steroids plus cyclophosphamide	Henoch-Schönlein purpura with nephritis (most cases without renal involvement resolve spontaneously)
Medium vessel		
Kawasaki disease	Intravenous immune globulin with aspirin	First-line therapy
	Intravenous immune globulin plus heparin infusion	Second-line therapy in patients who do not initially respond to intravenous immune globulin and aspirin combination
	Methylprednisolone followed by prednisolone	Second-line therapy
Polyarteritis nodosa	Prednisolone	First-line therapy
	Methylprednisolone	Fulminant disease
	Cyclophosphamide	First-line therapy (used in combination with steroids in non-hepatitis B-associated polyarteritis nodosa)
	Antiviral agents (interferon alfa plus lamivudine	Hepatitis B-associated polyarteritis nodosa
	Plasmapheresis	Hepatitis B-associated polyarteritis nodosa
	Bisphosphonate	Bone protection with long-term steroid
Large vessel		
Giant cell arteritis and Takayasu arteritis	Prednisolone	First-line in active Takayasu arteritis and in giant cell arteritis without eye symptoms
	Methylprednisolone	Consider in giant cell arteritis with significant visual disturbance
	Methotrexate	Adjunct to steroids for maintenance therapy Reduces risk of first or second relapse Decreased cumulative dose of steroids Allows earlier discontinuation of steroids
	Azathioprine	Adjunct to prednisolone for maintenance therapy
	Bisphosphonate	Bone protection with long-term steroid
	Aspirin	In conjunction with maintenance therapy for prevention of cerebrovascular and cardiovascular

Vasculitis	Drug/treatment	Indication
		ischemic events

Key Messages

- Vasculitis refers to a heterogenous group of disorders in which there is inflammation and damage in blood vessel walls, leading to tissue necrosis. Vasculitis may be limited to skin or other organs, or may be a multisystem disorder with multiple manifestations.
- The traditional management approach is to start with systemic glucocorticoid therapy at immunosuppressive dose, followed by cytotoxic immunosuppressive drugs (methotrexate, azatioprine, cyclophosphamide or mycofenolate mofetil).
- Nonreversible vascular lesions (such as occlusion or stenosis) may require surgical treatment (stent or bypass), however this must be done only when a complete control of the inflammatory activity has been reached.

CASE REPORT No.7

A 65-year-old man was admitted to department for diffuse abdominal pain, nausea, vomiting, diarrhea, painful joints and rectal tenesmus.

He initially had an urticarial rash, followed by palpable purpura involving the lower extremities. The diarrheic stools evolved towards melena. Endoscopic examination of the upper gastrointestinal tract showed hiatal hernia, superficial erosions in the stomach and multiple areas of deep and superficial ulcerations disseminated from the second to the third portion of the duodenum. Terminal ileum intubation at colonoscopy showed redness, edema, swelling, petechiae and ecchymosis, irregular erosions and ulcers. Endoscopic biopsy specimens showed non-specific inflammation. Computed tomography showed moderate ascites, small pleural effusion, mesenteric lymphadenopathy and small bowel wall thickening at the level of the second duodenum, proximal jejunum and segments of ileum. The urine analysis revealed microscopic hematuria with nephrotic range proteinuria, red cells and cellular casts. Therapy with corticosteroids and pulses of cyclophosphamide was started with significant clinical improvement.

Three weeks after the first admission, the patient developed an acute peritonitis due to an intestinal perforation and acute mesenteric ischemia of the small bowel. The patient had a Henoch-Schönlein type vasculitis with acute mesenteric ischemia and perforation of the small bowel.

ANAEMIA

The World Health Organization defines anaemia as a haemoglobin (Hb) concentration below 13 g/dl in men over 15 years of age, below 12 g/dl in non-pregnant women over 15 years of age, and below 11 g/dl in pregnant women.

Table 26 — Reference values for laboratory tests

Analyte	SI Units	Conventional Units
Erythrocyte count female	4.00–5.20 × 10^{12}/L	4.00–5.20 × 10^{6}/mm^3
Erythrocyte count male	4.30–5.60 × 10^{12}/L	4.30–5.60 × 10^{6}/mm^3
Reticulocyte count female	0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte count male	0.008–0.023 red cells	0.8–2.3% red cells
Hemoglobin female	120–158 g/L	12.0–15.8 g/dL
Hemoglobin male	133–162 g/L	13.3–16.2 g/dL
Hematocrit female	0.354–0.444	35.4–44.4
Hematocrit male	0.388–0.464	38.8–46.4
Mean corpuscular hemoglobin (MCH)	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	9.00–12.95 fL	9.00–12.95 μm^3
Platelet count (PLT)	165–415 × 10^{9}/L	165–415 × 10^{3}/mm^3
Leukocytes count (WBC)	3.54–9.06 × 10^{9}/L	3.54–9.06 × 10^{3}/mm^3

Classification anemia according to the morphology:

- **microcytic (MCV < 80 fl)** — iron deficiency anaemia, thalassemia minor, sideroblastic anemia;
- **macrocytic (MCV > 100 fl):**

✓ ***megaloblastic*** — vitamin B_{12} and folate deficiency anemia:

✓ ***macrocytic nonmegaloblastic*** — due to alcohol excess, liver cirrhosis, hypothyroidism, myelodisplastic syndrome;

- **normocytic (MCV 80–100 fl)** — aplastic anemia, hemolytic anemias, anemia in chronic diseases (connective tissue diseases, renal failure).

IRON DEFICIENCY ANEMIA

Iron deficiency anaemia (IDA) occurs in 2–5% of adult men and postmenopausal women in the developed world and is a common cause of referral to gastroenterologists. Gastrointestinal (GI) blood loss from colonic cancer or gastric cancer, and malabsorption in coeliac disease are the most important causes that need to be sought.

Iron metabolism and homeostasis

Iron in the form of heme is vital to many metabolic functions including oxygen transportation in hemoglobin. Iron is also a component of multiple enzymes, including cytochromes, necessary for energy generation and drug metabolism. Through the donation or acceptance of an electron, iron exists in either a reduced ferrous (Fe^{2+}) or an oxidative ferric (Fe^{3+}) state. The majority of functional iron is contained in hemoglobin, with smaller quantities found in myoglobin and cytochromes. The liver, which is the site of production of iron transport proteins, contains the largest non-functional iron stores either as ferritin or hemosiderin. Ferritin is both diffuse and soluble, and is the primary iron storage protein. Hemosiderin is similar in structure, but has more iron relative to protein and is insoluble. Iron is also stored in reticuloendothelial cells of the bone marrow and spleen.

Most body iron (ie, 2.6g of 3–4g) circulates as haemoglobin (Hb), which is recycled when red cells senesce. One gram is stored in the liver, and 0.4 g in myoglobin and cytochromes. Small amounts (3 mg) circulate bound to plasma transferrin. Men and nonmenstruating women lose about 1 mg of iron per day. Menstruating women lose from 0.6 to 2.5 percent more per day. An average 132-lb (60-kg) woman might lose an extra 10 mg of iron per menstruation cycle, but the loss could be more than 42 mg per cycle depending on how heavily she menstruates. A pregnancy takes about 700 mg of iron, and a whole blood donation of 500 cc contains 250 mg of iron.

Dietary iron is absorbed mainly in the duodenum. Only ferrous iron is absorbed, and it is transported across the apical membrane of the enterocyte by divalent metal transporter 1. It is then transferred across the enterocyte to the basolateral membrane by an unknown mechanism. Iron is exported across the basolateral membrane of enterocytes by ferroportin, then bound to transferrin in the plasma and transported for use in target organs and/or storage.

Body stores of iron are tightly regulated to provide adequate iron for cellular needs without developing toxicity from excess. Because the body lacks a mechanism to excrete excessive iron, homeostasis is tightly controlled by limiting enteric iron uptake through impaired efflux from enterocytes. Iron efflux is regulated by hepcidin, a recently discovered hormone produced by hepatocytes. When iron stores are adequate or high, hepcidin is released and binds to intestinal ferroportin causing internalization and destruction of ferroportin. The reduction in ferroportin causes absorbed dietary iron to remain in the enterocyte, where it is lost by enterocyte shedding. Conversely, when iron stores are low, hepcidin production and secretion are suppressed, increasing iron efflux from enterocytes into the blood (figure 25).

Tight homeostasis of iron is critical, as excessive iron accumulation in hepatocytes can cause pathologic damage, termed hemochromatosis. Subsequently, increased fibrosis and cirrhosis can occur. In contrast, iron deficiency leads to depletion of body iron stores, and ultimately, iron deficiency anemia and other metabolic dysfunctions. The duodenum’s ability to absorb dietary iron is very

limited, but can be upregulated. However, the upregulation in iron absorption secondary to chronic blood loss and resulting iron deficiency may be insufficient to restore adequate iron homeostasis, even after blood loss has been arrested.

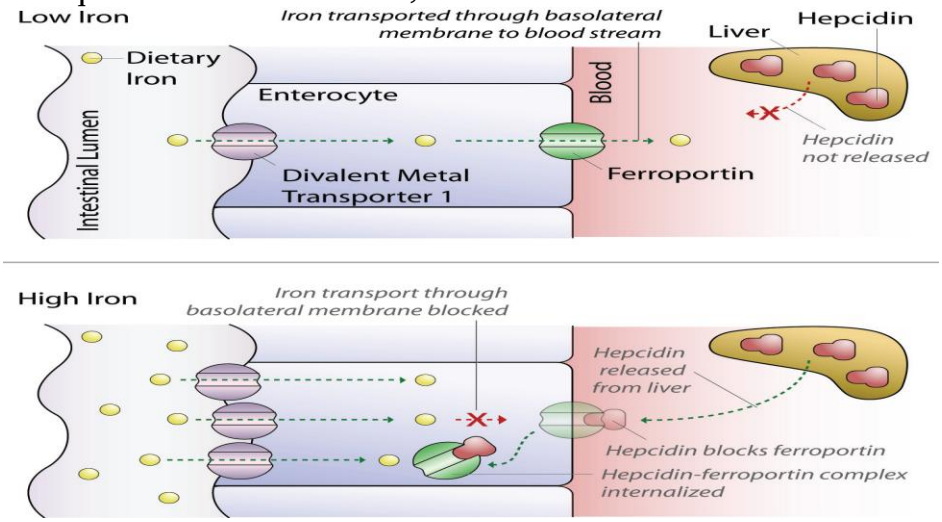


Figure 25 — Mechanism of intestinal iron absorption at low and high serum iron levels

From: Iron deficiency anemia / D. Naigamwalla [et al.] // Can Vet J. — Vol. 53. — P. 250–256.

Causes of iron deficiency anemia

Iron deficiency results when either dietary intake does not meet the body's requirement or when there is chronic external (non-resorptive) blood loss. High iron content is found in meat products (such as liver, heart, and muscle), but also in brewer's yeast, wheat germ, egg yolks, oysters, some dried beans, and some fruits. Green vegetables, cereals, fish, and fowl have an intermediate amount of iron. Foods low in iron include milk, milk products, and most non-green vegetables.

During acute blood loss, body iron stores are generally sufficient for accelerated erythropoiesis and subsequent iron uptake is adequate for restoring iron homeostasis. Iron deficiency anemia only develops over weeks to months of chronic or recurrent blood loss. Gastrointestinal hemorrhage can result from primary gastrointestinal disease (benign or malignant neoplasm, ulceration, arteriovenous fistula), ulcerogenic drugs (most commonly non-steroidal anti-inflammatory agents and corticosteroids) or secondary to systemic diseases such as renal and hepatic diseases, bleeding disorders, and hypoadrenocorticism. Surgical resection of the entire duodenum will result in iron malabsorption.

Pathogenesis of iron deficiency anemia

Iron deficiency anemia may be classified into 3 stages: storage iron deficiency, iron deficient erythropoiesis, and iron deficiency anemia. Initially during blood loss, iron body stores are preferentially utilized for accelerated erythropoiesis. After depletion of body iron stores, erythropoiesis and production of other iron-

containing proteins (such as myoglobin) become limited, leading to an overt iron deficiency anemia. Anemia is exacerbated as iron-deficient erythrocytes have a shortened survival due to their fragility, which accelerates reticuloendothelial cell sequestration and destruction. The observed erythrocyte morphologic changes with the underlying iron deficiency reflect the severely hampered hemoglobin synthesis and are characterized by hypochromasia and microcytosis (figure 26). Furthermore, the hemoglobin-deficient erythroid precursors are thought to undergo additional mitoses while attempting to achieve ideal cytoplasmic hemoglobin levels, thereby exaggerating the microcytosis.

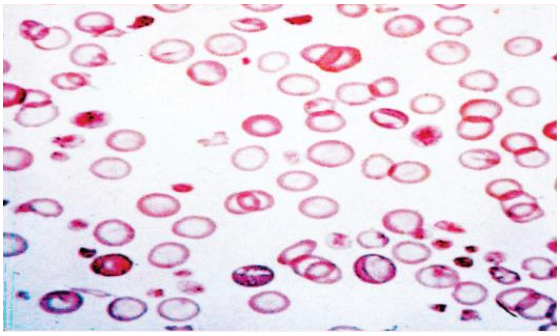


Figure 26 — Blood smear of a patient with severe iron deficiency anemia: A hypochromia of erythrocytes.

From: Iron deficiency anemia / D. Naigamwalla [et al.] // Can Vet J. — Vol. 53. — P. 250–256.

While normocytic normochromic erythrocytes contain approximately 1/3 hemoglobin, red blood cell indices of patients with iron deficiency anemia demonstrate progressive decreases in mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume. Early iron deficiency states may not be suspected as the anemia may be initially normocytic and normochromic.

Initially, reticulocytosis is present due to increased production and release of reticulocytes secondary to anemia. However, as iron stores are depleted and the iron deficiency becomes more severe, the absolute reticulocyte count becomes inadequate for the degree of anemia. Furthermore, due to the lack of heme and reduced hemoglobin synthesis, the red blood cells become more fragile which can result in mild hemolysis, worsening the anemia.

Disease states with functional iron deficiency can occur when iron is not available for heme synthesis despite normal to increased body stores of iron. One example is anemia of inflammatory disease, which can be mistaken for iron deficiency anemia based on the hemogram. In this condition, serum iron levels are decreased secondary to iron sequestration in the liver, spleen, and bone marrow, which results in a functional iron deficiency, defective heme synthesis, and the formation of some microcytic and possibly hypochromic erythrocytes despite adequate body iron stores.

Physical examination findings of iron deficiency anemia

Clinical signs are variable and may be due to the underlying disease process, anemia, or both. However, since iron deficiency anemia develops gradually, many patients adapt and compensate for even the most severe anemia and do not demonstrate major clinical signs beyond pallor.

Clinical signs:

- **anemic syndrome** occur due to anemia and can include lethargy, decreased exercise tolerance, weakness, weight loss, retarded growth, and generalized malaise;
- **syderopenic syndrome** occur due to a lack of other iron-containing proteins such as myoglobin, cytochrome C, and metabolic enzymes and include signs of advanced tissue iron deficiency — cheilosis (fissures at the corners of the mouth), angular stomatitis, atrophy of the papillae of the tongue, brittle of nails and hair, koilonychia (spooning of the fingernails).

Evidence of blood loss, such as melena, hematuria, or bleeding from other sites may be noted by the owners or at the time of the examination.

Physical examination results may be normal with the exception of pallor, or may reflect the underlying disease process. If the anemia is severe, bounding pulses, arrhythmia, and a systolic heart murmur may be noted. Melena or hematochezia may be noted on examination of feces, on digital rectal examination, or on the thermometer but may only be visible intermittently. While patients can develop a severe compensatory cardiomegaly to increase cardiac output, tachypnea and tachycardia are unusual with iron deficiency anemia.

Diagnostic approach to iron deficiency anemia

The diagnostic approach to iron deficiency anemia includes identifying the underlying disease or trigger with a thorough history, physical examination, and diagnostic evaluation.

The history should include a thorough review of medications, diet, concurrent medical conditions, fecal characteristics, and careful questioning of the owner for possible sources of blood loss.

In many cases, further diagnostic evaluation is necessary, including complete blood (cell) count (CBC) with reticulocyte count, fecal occult blood test, serum iron parameters, coagulation parameters, biochemical profile (including albumin, globulins, and hepatic and renal parameters), urinalysis and abdominal imaging.

Iron status is investigated by measuring serum iron parameters (table 27):

- serum iron concentration;
- total iron binding capacity (TIBC) is a measure of the plasma's ability to carry iron and represents the maximum concentration of iron that can be bound by plasma transferrin;
- iron saturation (IS) reflects the amount of iron bound to transferrin and is low (< 20%) in cases of iron deficiency anemia;

• iron binding capacity (UIBC) measures transferrin's open iron binding sites and is elevated in iron deficiency anemia;

• serum ferritin correlates well with body iron stores and is decreased ih iron deficiency anemia.

Table 27 — Clinical Chemistry of iron status

Parameter	SI Units	Conventional Units
Iron	7–25 μmol/L	41–141 μg/dL
Iron-binding capacity	45–73 μmol/L	251–406 μg/dL
Iron-binding capacity saturation	0.16–0.35	16–35 %
Ferritin Female	10–150 μg/L	10–150 ng/mL
Ferritin Male	29–248 μg/L	29–248 ng/mL

Typically serum iron concentration is very low in patients with iron deficiency anemia. However, mildly low to low normal serum iron values can also be observed with anemia of inflammatory disease.

Serum iron can be transiently elevated by intravascular red blood cell lysis, recent blood transfusion, and iron supplementation, which can complicate interpretation of laboratory data. Exogenously administered corticosteroids have also been shown to increase serum iron levels by an undetermined mechanism.

Table 28 — Expected serum parameters in iron deficiency anemia

Hematocrit	↓ to ↓↓↓
MCV	↓ to ↓↓↓
MCHC	↓
Serum iron	↓ to ↓↓↓
Serum TIBC	normal to ↑
Serum ferritin	↓ to ↓↓
Stainable iron in marrow	absent
Reticulocytes	normal to ↓

Ferritin is also an acute phase protein, and hyperferritinemia can occur with underlying disease, such as inflammatory disease, neoplasia, liver disease, or hemolytic disease. Nevertheless, low serum ferritin concentrations can be helpful in differentiating iron deficiency anemia from anemia of inflammatory disease.

Diagnostic imaging may be warranted to further investigate iron deficiency anemia. Abdominal ultrasonography is recommended to visualize abdominal organs and to assess the gastrointestinal tract for evidence of ulceration, wall thickening, or masses. Examples of typical gastrointestinal tumors that can cause ulceration and chronic blood loss include leiomyoma, leiomyosarcoma, carcinoma, and round cell tumors. If primary gastrointestinal disease is suspected, and no abnormalities are noted with abdominal imaging, gastroduodenal or colonic endoscopy (or both), or exploratory laparotomy may be indicated to assess for ulceration and to obtain biopsies.

Differential diagnosis of iron deficiency anemia

The differential diagnosis for microcytic anemia includes iron deficiency, thalassemia, sideroblastic anemias, some types of anemia of chronic disease, and lead poisoning (rare in adults). Patients with sideroblastic anemia will have almost to complete saturation of the serum transferrin, which can differentiate them from patients with iron deficiency. Differentiating between iron deficiency and anemia of chronic disease can sometimes be difficult, especially in early iron deficiency or when the conditions coexist. Patients with lead poisoning will have characteristic signs and symptoms of lead poisoning.

Therapeutic approach to iron deficiency anemia

The general principles of treating patients with iron deficiency anemia include preventing further blood loss, correcting the anemia if severe, initiating iron supplementation, and addressing the underlying disease.

A red blood cell products transfusion may be necessary prior to receiving results from diagnostic evaluation if the patient is severely anemic and demonstrating signs of hypoxemia. Blood samples for CBC, and ideally serum biochemical profile, coagulation profile, and iron parameters should be obtained prior to the administration of a blood transfusion.

Oral iron therapy is usually the first-line therapy for patients with IDA. In stable patients, oral iron therapy is usually preferred over parenteral iron administration due to its low cost and higher safety. Both ferrous and ferric forms are available but only the ferrous form is recommended due to superior absorption. Ferrous sulfate is used most frequently but ferrous gluconate and fumarate can also be used. Care must be taken when determining the dosage to be administered, as published doses are expressed as either milligrams of iron salt or elemental iron. The usual recommended dose of oral iron for the treatment of IDA in adults is 100–200 mg of elemental iron daily or in 2 to 3 divided doses. Bone marrow response to iron is limited to 20 mg per day of elemental iron. An increase in the hemoglobin level of 1 g per dL (10 g per L) should occur every two to three weeks on iron therapy; however, it may take up to four months for the iron stores to return to normal after the hemoglobin has corrected. Ferrous sulfate in a dose of 325 mg provides 65 mg of elemental iron, whereas 325 mg of ferrous gluconate provides 38 mg of elemental iron. Sustained-release formulations of iron are not recommended as initial therapy because they reduce the amount of iron that is presented for absorption to the duodenal villi.

One of the more common side effects of oral iron supplemenation is gastrointestinal irritation, which can be minimized by dividing the dose several times a day. Interaction with other drugs is recognized and should be avoided. For instance iron can bind tetracycline and other drugs thereby decreasing the efficacy of both; these and other drugs should be administered several hours apart if given concurrently. Moreover, the bioavailability of iron is decreased if

administered concurrently with antacids, eggs, or milk. Foods rich in tannates (e.g. tea) or phytates (e.g. bran, cereal), or medications that raise the gastric pH (e.g. antacids, proton pump inhibitors, histamine H_2 blockers) reduce absorption and should be avoided if possible.

Iron supplementation is generally needed to restore iron homeostasis and should be based on the degree of anemia, underlying pathology, red blood cell count, serum iron panel, and erythrocyte morphology. These same parameters are used to monitor further iron supplementation needs. Supplemental iron is beneficial in treating iron deficiency anemia but is not recommended for other forms of anemia and in fact may be harmful, as iron overload may occur.

Several months of iron supplementation may be necessary for red blood cell parameters to return to normal, and therapy should be continued beyond normalization of red blood cell parameters as body iron stores take much longer to be replenished. While serum iron would be expected to be normal or even high when being actively supplemented with iron, red blood cell indices should be monitored closely to gauge response to therapy and resolution of functional iron deficiency. Body iron stores are rarely assessed post-treatment, but measurement of serum ferritin and other iron parameters is warranted after termination of iron supplementation to ensure normalization.

Parenteral forms of iron other than red blood cell products can be administered if oral supplementation causes side effects, is ineffective due to malabsorption. A single dose of iron can also be administered parenterally prior to initiation of oral supplementation.

Several intravenous iron preparations are available in humans, including iron gluconate, iron sucrose, iron dextran, and ferric carboxymaltose; iron sucrose is considered the safest of the preparations. In humans, an initial test dose is given; if no adverse effects are noted, the remainder of the dose is administered over several hours. Adverse reactions from rapid infusion can include hypotension, tachycardia, dyspnea, and phlebitis.

In conclusion, iron is a vital element for multiple metabolic functions, most notably oxygen transport by hemoglobin. Iron deficiency anemia typically develops following chronic blood loss after iron body stores have been exhausted. Iron deficiency anemia is characterized by microcytosis and hypochromasia with inadequate regeneration, and low serum iron, iron saturation, and ferritin. Samples for diagnostic testing should be obtained prior to treatment. Therapy for iron deficiency anemia includes preventing further blood loss, oral and/or parenteral iron supplementation, and treating the underlying disease. With appropriate therapy, patients with iron deficiency anemia can have a good prognosis as long as the underlying disease can be addressed.

Major reasons for inadequate response to oral iron therapy

Inadequate iron intake:

- patient not taking oral iron therapy;
- patient taking an iron supplement or multivitamin tablet with insufficient iron content.

Inadequate iron absorption:

- concomitant consumption of inhibitors of iron absorption (e.g. tea, calcium, antacids, tetracycline, within 2 hours of iron ingestion);
- coexisting inflammation with functional iron deficiency;
- intestinal mucosal disorders (e.g. coeliac disease, inflammatory bowel disease);
- impaired gastric acid secretion (including use of proton pump inhibitors);
- gastric/intestinal bypass procedures;
- *Helicobacter pylori* colonisation;
- controlled-release iron formulations may contribute (i.e. potential for limited iron absorption in some patients)†.

Ongoing iron losses or need in excess of dose absorbed:

- occult, undiagnosed or recurrent gastrointestinal blood loss (e.g. peptic ulcer, malignancy, angiodysplasia, small bowel lesion, parasites);
- other source of recurrent blood loss (e.g. menorrhagia due to uterine pathology or an inherited bleeding disorder such as von Willebrand disorder);
- multiple sources of recurrent blood loss (e.g. hereditary haemorrhagic telangiectasia);
- ongoing urinary iron losses (e.g. significant valve haemolysis);
- renal failure responding to erythropoietin-stimulating agents.

Coexisting condition interfering with bone marrow response:

- superimposed infection, inflammation, malignancy or renal failure;
- concomitant B_{12} or folate deficiency;
- coexisting primary bone marrow disease or suppression.

Incorrect diagnosis or more than one cause of anaemia:

- anaemia of chronic disease or renal failure;
- haemoglobinopathy;
- other causes of anaemia (e.g. haemolysis, myelodysplastic syndromes, congenital anaemia, endocrine disorders).

* More than one factor is often present. † Role is unclear (limited available data show efficacy comparable to that of non-controlled-release formulations).

Indications for intravenous (IV) iron therapy in patients with iron deficiency anaemia (IDA)

IV iron should be considered in patients with confirmed IDA* and one or more of the following:

- demonstrated intolerance, non-compliance or lack of efficacy with oral iron, despite modification of dose, timing and frequency;

• pregnancy (beyond the first trimester) and postpartum, for the above reasons or to avoid imminent decompensation / transfusion (e.g. in women who present late and/or display severe anaemia);

• intestinal malabsorption (e.g. inflammatory bowel disease);

• ongoing iron (i.e. blood) losses that exceed absorptive capacity;

• a clinical need for a rapid iron supply (i.e. in patients where optimisation of erythroid response is important to prevent physiological decompensation / transfusion);

• chronic renal impairment receiving concomitant erythropoietin-stimulating agent therapy.

* Prescribed in consultation with an expert in the use of IV iron and the relevant patient group.

PERNICIOUS ANEMIA (BIERMER'S DISEASE)

Pernicious anemia (also known as Biermer's disease) is due to an autoimmune atrophic gastritis, predominantly of the fundus, and is responsible for a deficiency in vitamin B12 (cobalamin) due to its malabsorption.

Its prevalence is 0.1% in the general population and 1.9 % in subjects over the age of 60 years. Pernicious anemia represents 20–50 % of the causes of vitamin B_{12} deficiency in adults.

Pernicious anemia is a macrocytic anemia due to cobalamin deficiency, which is the result of intrinsic factor deficiency. Pernicious anemia is associated with atrophic body gastritis, whose diagnostic criteria are based on the histologic evidence of gastric body atrophy associated with hypochlorhydria. Its prevalence is 0.1 % in the general population and 1.9 % in subjects over the age of 60 years. Pernicious anemia represents 20–50 % of the causes of vitamin B_{12} deficiency in adults. Given its polymorphism and broad spectrum of clinical manifestations, pernicious anemia is a great pretender. Its diagnosis must therefore be evoked and considered in the presence of neurological and hematological manifestations of undetermined origin. Biologically, it is characterized by the presence of anti-intrinsic factor antibodies.

Pathogenesis of pernicious anemia

Pathologically, PA is characterized by at least the following elements:

• the destruction of the gastric mucosa, especially fundic, by a process of cell-mediated autoimmunity;

• a fundic atrophy accompanied by a reduction in gastric acid secretion, a reduction in intrinsic factor (IF) secretion, and vitamin B12 malabsorption, which is corrected by the addition of IF;

• the presence of various antibodies, including antibodies detectable in both plasma and gastric secretions in the form of anti-IF antibodies and antigastric parietal cell (anti-GPC) antibodies, the latter being specifically directed against the hydrogen potassium adenosine triphosphatase (H^+/K^+-ATPase) proton pump.

PA-associated type A atrophic gastritis is restricted to the fundus and gastric body. Early lesions are characterized by chronic inflammation in the submucosa that extends into the lamina propria of the mucosa between gastric glands, with a loss of both gastric and zymogene cells. In advanced stages of the disease, gastric atrophy is recognizable macroscopically. The architecture of the gastric body and fundus is comparable to newsprint paper because of the dramatic reduction or absence of gastric glands. In particular, the parietal cells and zymogenic cells are absent from the gastric mucosa and are replaced by intestinal metaplasia.

A major breakthrough in understanding the pathogenesis of type A atrophic gastritis has been the identification of the gastric enzyme H^+/K^+-ATPase as the target antigen recognized by anti-GPC antibodies. This proton pump is responsible for acid secretion in the stomach and is the major protein of the secretory canaliculi of GPCs. The H^+/K^+-ATPase molecule is a heterodimer consisting of a 92 kDa α subunit and a highly glycosylated β subunit with an apparent molecular weight of 60–90 kDa.

The potential role of *Helicobacter pylori* in the pathogenesis of autoimmune gastritis and PA has been explored and postulated in recent years.

Antibodies and their clinical interest

Anti-GPC antibodies, directed against the H^+/K^+-ATPase (or gastric proton pump) antigen located in the secretory canaliculi of parietal cells and in gastric microsomes, are present at a high frequency of approximately 80–90 %, especially in early stages of the disease. They are, however, unspecific and can be found at low frequency in other autoimmune diseases (e.g. Hashimoto's disease or diabetes) or in elderly subjects, even those free of any atrophic gastritis.

In the later stages of the disease, the incidence of anti-GPC antibodies decreases due to the progression of autoimmune gastritis and a loss of GPC mass, as a result of the decrease in antigenic rate. In recent studies, an average incidence of 55 % of anti-GPC antibodies was documented in patients with advanced PA.

Anti-IF antibodies do not appear to have a clearly defined pathogenic role in the development of gastritis. By contrast, they have a well-documented role in the onset of PA, via the vitamin B_{12} deficiency they induce.

Two types of autoantibodies have been described:

- the blocking autoantibodies (type I), which inhibit the binding of vitamin B_{12} to the IF and thereby prevent the formation of the vitamin B_{12}/IF complex;
- the binding autoantibodies (type II), which bind to IF-vitamin B_{12} complexes, thus preventing their absorption by the intestinal mucosa. They are found in one-third of cases and only in patients who already have anti-type I antibodies.

Clinical manifestations of pernicious anemia

Anemia is the most frequently encountered clinical sign during PA, together with accompanying functional manifestations, depending on their severity. It can often include a hemolytic component with subicterus. Other hematological manifestations have also been commonly reported: neutropenia, thrombocytopenia, pancytopenia, intramedullary hemolytic component due to ineffective erythropoiesis, and pseudothrombotic microangiopathy.

Main clinical manifestations of vitamin B_{12} deficiency

Neuropsychiatric manifestations:
Frequent:
combined sclerosis of the spinal cord;
polyneuritis;
ataxias;
Babinski.
Rare:
cerebellar syndrome;
cranial nerve impairment;
sphincter dysfunctions.
Others:
memory impairments;
dementia;
atherosclerosis;
Parkinsonism;
depression.
Digestive manifestations:
Frequent:
Hunter's glossitis;
hemolytic icterus.
Others:
abdominal pain;
GI (gastrointestinal) transit disorders.
Other manifestations:
vaginal mucosa atrophy;
urogenital infections (especially mycoses);
rebellious or recurrent cutaneous–mucosal ulcers;
thrombosis (venous thromboembolism and ischemic heart disease);
subfertility and recurrent spontaneous abortions/male infertility.

Glossitis (Hunter's glossitis) — characterized by a slick or bald tongue, papillary atrophy, and burning sensation on contact with certain foods — is usually associated with this disease, although much less described in a recent series devoted to PA.

Vitamin B_{12} deficiency can be responsible for neurological impairment, which can occur in the absence of any anemia or macrocytosis (30 % of PA cases). Neurological signs usually generate a clinical picture of combined sclerosis of the spinal cord. Disorders are usually predominant in the lower limbs. Large nerve fiber damage is responsible for ataxia, paresthesia, tendinous areflexia, and deep sensitivity disorders with Romberg's signs. However, neurological signs are inconsistent along with a highly variable clinical spectrum ranging from optic neuritis to manifestations of depression. It should also be kept in mind that neurological manifestations may only partially regress despite prolonged and high-dose vitamin B_{12} therapy, leading to — at times — irreversible sequelae.

Association of pernicious anemia with other autoimmune diseases

Genetic susceptibility to PA appears to be genetically determined, although the mode of inheritance remains unknown. Evidence for the role of genetic factors includes familial co-occurrence of PA and its association with other autoimmune diseases. A certain number of autoimmune diseases occur at a higher frequency in patients with PA — around 30 % in the authors' experience — or among family members of PA patients. They can precede the disease or occur after its onset.

The association of PA with autoimmune diseases such as type 1 diabetes (insulin dependent), autoimmune thyroiditis (particularly Hashimoto's thyroiditis), or vitiligo is common. Other associations have also been frequently described, e.g. Sjogren's syndrome, celiac disease, and Addison's adrenal insufficiency. Cases of multiple autoimmune syndrome including PA have also been documented.

Neoplastic complications of pernicious anemia

The somewhat subtle progression from autoimmune gastritis to PA can take 20–30 years or even more, given that vitamin B12 stores can last 5–10 years depending on the individual. Nonetheless, it should be emphasized that the diagnosis of PA is important, not only because of the consequences of anemia but also because of neurological complications and especially because of a susceptibility to all types of gastric tumors – from common carcinoid tumors to more rare adenoma carcinomas and non-Hodgkin's malignant lymphomas (of low grade). The prevalence of gastric carcinoid tumors in patients with PA varies from 4–7 % depending on the series.

Thus, surveillance by upper endoscopy is recommended, quarterly during the first year in the presence of neoplastic lesions, and less frequently thereafter in the absence of macroscopic or histological recurrence. In the absence of such lesions, biannual endoscopic surveillance is suggested, with multiple biopsies.

Diagnostic criteria of pernicious anemia

The diagnosis of PA is classically (or historically) established in clinical routine by demonstrating the absence of IF by the study of gastric juice — a rate

of secretion of IF < 200 U/hour after stimulation with pentagastrin (normal being > 2000 U/hour) is specific to PA; or indirectly by performing a Schilling test which highlights abnormal absorption of radioactive cobalamin, which is corrected after administration of IF. It should be kept in mind that the Schilling test and lack of IF secretion remain the gold standard for diagnosis of PA.

- CBC (complete blood count): genuine aregenerative, normochromic, and macrocytic anemia; generally associated with moderate leukopenia and thrombopenia.
- Blood smear: large red blood cells, anisocytosis, Howell–Jolly bodies, and globular-shape cells in the form of ovalocytes; large-size granulocytes with hypersegmentation of the nuclei (shift to the right in Arneth's formula).
- Biology: elevated serum levels of LDH (lactate dehydrogenase) and free bilirubin and decreased levels of haptoglobin (hemolysis by ineffective intramedullary erythropoiesis).
- Spinal smear: rich and bluish spinal fluid due to cytoplasmic hyperbasophilia; increased medullary erythroblastosis with megaloblastic erythroblasts. All stages of erythroid maturation are represented but the asynchrony of nucleocytoplasmic maturation is marked by immature nuclei and an already acidophilic cytoplasm.

It should also be noted at this juncture that incipient PA may be associated in young women with a tendency for microcytosis due to iron deficiency linked to achlorhydria-induced iron malabsorption, menstrual bleeding, and a failure to exhaust the 10-year reserves of vitamin B_{12}.

Other criteria commonly used to diagnose PA vary in specificity and sensitivity, routine availability, or invasiveness. These include:

- the presence of serum anti-IF antibodies for which sensitivity is only 50% (only one out of two patients with true PA has these antibodies);
- the presence of histological lesions of autoimmune fundic gastritis (as discussed above), especially in the absence of *H. pylori* (in collected samples);
- hypergastrinemia or increased serum chromogranin A in response to achlorhydria, which strongly points to PA in the absence of proton pump inhibitor use.

Differential diagnosis of vitamin B_{12} deficiency

The primary differential diagnosis of vitamin B12 deficiency in adults is food-cobalamin malabsorption (syndrome of nondissociation of vitamin B_{12} from its carrier proteins), an entity that is the primary etiology of vitamin B_{12} deficiency in elderly subjects.

In practice, this disorder is characterized by an inability to release vitamin B_{12} from ingested food and/or from intestinal transport proteins, particularly in the presence of hypochlorhydria in which absorption of unbound vitamin B_{12} is normal.

Low vitamin B_{12} intake is uncommon in industrialized countries, aside from strict vegans and newborns of vegan women. Other vitamin B_{12} malabsorption syndromes comprise the genetic defects of proteins involved in vitamin B_{12} metabolism such as IF deficiency/defects or transcobalamin II deficiency/defects.

Ultimately, one should bear in mind that PA is a great pretender due to the similarity of presentation with other clinical conditions that can result in vitamin B_{12} deficiency. The diagnosis should be considered when faced with any hematological and neurological manifestations.

Treatment of vitamin B_{12} deficiency and optimal management

In most countries, treatment of vitamin B_{12} deficiency related to PA is based on parenteral vitamin B_{12} administered intramuscularly under the form of cyanocobalamin, hydroxocobalamin, or methylcobalamin. A certain superiority of hydroxocobalamin is nevertheless recognized and related to better tissue uptake and storage than the other forms.

Attitudes regarding the dosage and frequency of administration are very different from one group to another. In the United States and the United Kingdom, the doses range from 100–1000 μg/month for life. In France, cobalamin therapy involves acute treatment at a dose of 1000 μg daily for 1 week, followed by 1000 μg per week for 1 month, then a monthly dose of 1000 μg for life.

With regard to curative treatment by orally administered cobalamin (1 % of free vitamin B_{12} is absorbed passively, independently of the IF and of its receptor [cubilin]), a therapeutic scheme has yet to be definitely validated, given the present state of knowledge. In PA, the doses conventionally administered should in all cases greatly exceed those required physiologically, ranging from 1000–2000 μg/day of cyanocobalamin. In the authors' experience of oral administration, this therapeutic mode should be reserved for primarily hematological consequences of vitamin B_{12} deficiency. Currently, it is always recommended to use the parenteral route in severe neurological forms. Alternatively, the oral route could curtail or avoid the inconvenience related to discomfort of injections and of likely higher costs. It can also be particularly useful in patients under anticoagulant or antiplatelet agent therapy in whom intramuscular injections are contraindicated.

It is nesessary for annual monitoring of these patients to ensure therapeutic adherence (the vitamin has to be administered for life) and to detect neoplastic complications of PA (endoscopy at least twice yearly in the absence of detectable lesions) as well as associations with other autoimmune disorders.

FOLATE DEFICIENCY ANEMIA

The history of folate deficiency may mimic the history of vitamin B_{12} deficiency in regard to poor nutritional intake or absorption. In addition, 35 percent of patients with alcoholism and macrocytic anemia are folate deficient, which can be caused by poor nutritional intake, malabsorption, hepatobiliary dysfunction, and possibly increased folate catabolism. Some medications that are used to treat seizure disorders, cancer, and autoimmune diseases can lead to folate deficiency. For example, methotrexate directly inhibits dihydrofolate reductase, which leads to a functional folate deficiency. Other medications that affect folate metabolism include 5-fluorouracil, hydroxyurea, pyrimethamine, trimethoprim / sulfame-

thoxazole, pentamidine, and phenytoin. Medications can also affect folate absorption, including metformin and cholestyramine. Supplementing with folate may be necessary when treating a patient with such medications.

Diagnosis of folate deficiency anemia

Peripheral Blood Smear

Macrocytosis is reported in terms of mean corpuscular volume (MCV).

The presence of macro-ovalocytes having an MCV > 115 fl, anisocytosis, poikilocytosis and hypersegmented neutrophils suggests a megaloblastic disorder associated with a nutritional deficiency, i.e. folate deficiency (figure 27).

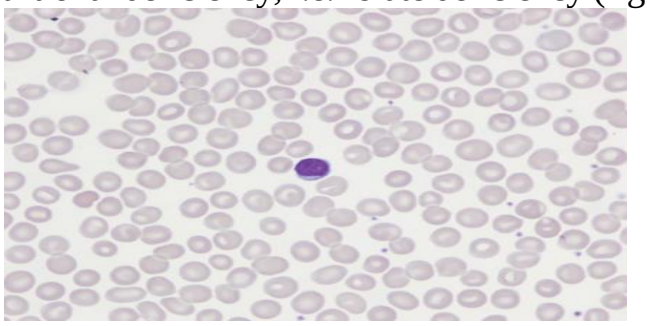


Figure 27 — Peripheral blood smear of a patient with vitamin B_{12} deficiency and folate deficiency:
Macro-ovalocytosis (MCV 134 fl) of erythrocytes in the peripheral blood smear.

From: Harrison's Principles of Internal Medicine / A.C. Fauci [et al.] // 17th Edition. — USA: The McGraw-Hill Companies, Inc., 2008.

Reticulocyte Count

A reticulocyte count should be obtained if there is evidence of hemolysis on the peripheral smear, i.e. increased polychromasia, nucleated RBCs, spherocytes or schistocytes. The presence of increased polychromasia of the macrocytes on the peripheral smear and a reticulocyte count of > 10 % should raise suspicion of hemolysis or an acute bleed. These large polychromatophilic erythrocytes noted on the peripheral smear represent reticulocytes, immature RBCs that are larger than mature RBCs, and are indicative of increased erythropoiesis or RBC production and, if present in increased number, can raise the MCV. Additionally, the reticulocyte maturation parameters performed on the peripheral blood may also be helpful to differentiate megaloblastic from nonmegaloblastic causes of the macrocytosis. An elevated reticulocyte maturation value is more suggestive of a megaloblastic rather than a non-megaloblastic anemia.

Bone marrow examination

Macrocytosis associated with a megaloblastic marrow is usually accompanied by anemia due to ineffective erythropoiesis. The bone marrow is hypercellular, showing evidence of abnormal proliferation and maturation of multiple myeloid cell lines. These abnormalities are most evident in the erythroid precursors with

large megaloblastic erythroblasts present in increased numbers throughout the marrow. Similar morphologic abnormalities can be seen in the other myeloid elements, e.g. large or giant metamyelocytes and other granulocytic precursors. This ineffective erythropoiesis is accompanied by intramedullary hemolysis causing an elevated lactate dehydrogenase and indirect bilirubin in the serum. However, the reticulocyte count is low due to the abnormal maturation process. More severe degrees of abnormal proliferation and maturation are seen with myelodysplasia and myeloid leukemias. It is imperative that a hematologist or hematopathologist examine the marrow in order to appreciate these important, subtle, hematopoietic abnormalities. Patients with macrocytosis who are not anemic and have no other abnormalities noted on the peripheral blood smear do not usually need a bone marrow examination.

Serum folate levels

Serum folate levels are not useful because they fluctuate rapidly with dietary intake — serum folate levels can decrease within a few days of dietary folate restriction. Pregnancy, certain anticonvulsant drugs, and alcohol intake may also cause a decrease in serum levels despite adequate tissue stores. Serum folate levels tend to be increased in patients with vitamin B_{12} deficiency, presumably because of impairment of the methionine synthase pathway and accumulation of methyltetrahydrofolate, the principal form of folate in the serum.

RBC folate

RBC folate levels more accurately correlate with folate stores and should be performed if folate deficiency is suspected. RBC folate levels remain constant throughout the lifespan of the cell and are not affected by short-term dietary changes that can alter serum levels. It should be noted that low RBC folate levels have been reported with alcohol use, pregnancy and anticonvulsant medications. Another important cause of low RBC folate levels is vitamin B_{12} deficiency.

Methylmalonic acid (MMA) and homocysteine serum concentrations

Cobalamin and folate are cofactors in several important metabolic pathways in the cell. The hydroxylated form of cobalamin plays an important role in the metabolism of homocysteine and MMA. The conversion of homocysteine to methionine requires both vitamin B_{12} and folate as cofactors. However, the metabolism of L-methylmalonyl CoA to succinyl CoA, an enzymatic pathway involved in oxidative phosphorylation reactions within the cell, only requires vitamin B_{12}. These metabolites provide early information regarding the cellular state of vitamin B_{12} and folate and can be used to distinguish folate from vitamin B_{12} deficiency, since most patients with folate deficiency have normal MMA or mildly elevated levels. It should be kept in mind that nearly 50 % of those with elevation of these metabolites will have normal serum vitamin B_{12} levels. This

emphasizes the low sensitivity of using vitamin B_{12} levels, particularly in the presence of other signs or symptoms.

Treatment of folate deficiency

In folate deficiency, the serum folate level is very sensitive to dietary folate intake and responds well to short-term treatment. Long-term treatment is not warranted except with chronic conditions such as malnutrition, exfoliative dermatitis or hemolysis. A complete blood cell count 10–14 days after starting the treatment for folate deficiency should reveal a rise in hemoglobin and a decrease in MCV. A full hematologic response should occur within 8 weeks. During treatment, further monitoring of the complete blood cell count or measuring folate levels or their metabolites is not necessary.

HEMOLYTIC ANEMIA

Hemolysis is the destruction or removal of red blood cells from the circulation before their normal life span of 120 days. While hemolysis can be a lifelong asymptomatic condition, it most often presents as anemia when erythrocytosis cannot match the pace of red cell destruction. Hemolysis also can manifest as jaundice, cholelithiasis, or isolated reticulocytosis.

Pathophysiology

There are two mechanisms of hemolysis. Intravascular hemolysis is the destruction of red blood cells in the circulation with the release of cell contents into the plasma. Mechanical trauma from a damaged endothelium, complement fixation and activation on the cell surface, and infectious agents may cause direct membrane degradation and cell destruction.

The more common extravascular hemolysis is the removal and destruction of red blood cells with membrane alterations by the macrophages of the spleen and liver. Circulating blood is filtered continuously through thin-walled splenic cords into the splenic sinusoids (with fenestrated basement membranes), a spongelike labyrinth of macrophages with long dendritic processes. A normal 8-micron red blood cell can deform itself and pass through the 3-micron openings in the splenic cords. Red blood cells with structural alterations of the membrane surface (including antibodies) are unable to traverse this network and are phagocytosed and destroyed by macrophages.

History and physical examination

Anemia most often is discovered through laboratory tests, but the history and physical examination can provide important clues about the presence of hemolysis and its underlying cause. The patient may complain of dyspnea or fatigue (caused by anemia). Dark urine and, occasionally, back pain may be reported by patients with intravascular hemolysis. The skin may appear jaundiced or pale. A resting tachycardia with a flow murmur may be present if the anemia

is pronounced. Lymphadenopathy or hepatosplenomegaly suggest an underlying lymphoproliferative disorder or malignancy; alternatively, an enlarged spleen may reflect hypersplenism causing hemolysis. Leg ulcers occur in some chronic hemolytic states, such as sickle cell anemia.

Diagnostic testing

Hematologic tests

Along with anemia, a characteristic laboratory feature of hemolysis is reticulocytosis, the normal response of the bone marrow to the peripheral loss of red blood cells. In the absence of concomitant bone marrow disease, a brisk reticulocytosis should be observed within three to five days after a decline in hemoglobin. In a minority of patients, the bone marrow is able to chronically compensate, leading to a normal and stable hemoglobin concentration. The anemia of hemolysis usually is normocytic, although a marked reticulocytosis can lead to an elevated measurement of mean corpuscular volume, because the average mean corpuscular volume of a reticulocyte is 150 fL.

Review of the peripheral blood smear is a critical step in the evaluation of any anemia. Along with an assessment for pathognomonic red blood cell morphologies, such as spherocytes or schistocytes, examination of the white blood cells and platelets for coexisting hematologic or malignant disorders is essential.

Chemistry tests

The destruction of red blood cells is characterized by increased unconjugated bilirubin, increased lactate dehydrogenase, and decreased haptoglobin levels. Lactate dehydrogenase and hemoglobin are released into the circulation when red blood cells are destroyed. Liberated hemoglobin is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The hemoglobin-haptoglobin complex is cleared quickly by the liver, leading to low or undetectable haptoglobin levels.

Urinary tests

In cases of severe intravascular hemolysis, the binding capacity of haptoglobin is exceeded rapidly, and free hemoglobin is filtered by the glomeruli. The renal tubule cells may absorb the hemoglobin and store the iron as hemosiderin; hemosiderinuria is detected by Prussian blue staining of sloughed tubular cells in the urinary sediment approximately one week after the onset of hemolysis. Hemoglobinuria, which causes red-brown urine, is indicated by a positive urine dipstick reaction for heme in the absence of red blood cells.

Types of hemolytic anemia see in the table 29.

Table 29 — Overview of hemolytic anemias

Type	Etiology	Associations	Diagnosis	Treatment
Acquired*				

Type	Etiology	Associations	Diagnosis	Treatment
Immune-mediated	Antibodies to red blood cell surface antigens	Idiopathic, malignancy, drugs, autoimmune disorders, infections, transfusions	Spherocytes and positive DAT	Treatment of underlying disorder; removal of offending drug; steroids, splenectomy, IV gamma globulin, plasmapheresis, cytotoxic agents, or danazol; avoidance of cold
Microangiopathic	Mechanical disruption of red blood cell in circulation	TTP, HUS, DIC, pre-eclampsia, eclampsia, malignant hypertension, prosthetic valves	Schistocytes	Treatment of underlying disorder
Infection	Malaria, babesiosis, Clostridium infections		Cultures, thick and thin blood smears, serologies	Antibiotics
Hereditary†				
Enzymopathies	G6PD deficiency	Infections, drugs, ingestion of fava beans	Low G6PD activity measurement	Withdrawal of offending drug, treatment of infection
Membranopathies	Hereditary spherocytosis		Spherocytes, family history, negative DAT	Splenectomy in some moderate and most severe cases
Hemoglobinopathies	Thalassemia and sickle cell disease		Hemoglobin electrophoresis, genetic studies	Folate, transfusions

DAT = direct antiglobulin test; IV = intravenous; TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic uremic syndrome; DIC = disseminated intravascular coagulation; G6PD = glucose-6-phosphate dehydrogenase.

**Other select causes of acquired hemolysis (not discussed in this article) include splenomegaly, end-stage liver disease/spur cell (acanthocyte) hemolytic anemia, paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, insect stings, and spider bites.*

†Other select causes of inherited hemolysis (not discussed in this article) include Wilson's disease and less common forms of membranopathy (hereditary elliptocytosis), enzymopathy (pyruvate kinase deficiency), and hemoglobinopathy (unstable hemoglobin variants).

HEREDITARY DISORDERS

The mature red blood cell, while biochemically complex, is a relatively simple cell that has extruded its nucleus, organelles, and protein-synthesizing machinery. Defects in any of the remaining components — enzymes, membrane, and hemoglobin — can lead to hemolysis.

ENZYMOPATHIES

The most common enzymopathy causing hemolysis is G6PD deficiency. G6PD is a critical enzyme in the production of glutathione, which defends red cell proteins (particularly hemoglobin) against oxidative damage. This X-linked disorder predominantly affects men. More than 300 G6PD variants exist worldwide, but only a minority cause hemolysis (table 30).

Table 30 — Agents that Precipitate Hemolysis in Patients with G6PD Deficiency

Acetanilid	Phenylhydrazine
Furazolidone	Primaquine
Isobutyl nitrite	Sulfacetamide
Methylene blue	Sulfamethoxazole
Nalidixic acid	Sulfapyridine
Naphthalene	Thiazolesulfone
Niridazole	Toluidine blue
Nitrofurantoin	Trinitrotoluene
Phenazopyridine	Urate oxidase

Most patients have no clinical or laboratory evidence of ongoing hemolysis until an event — infection, drug reaction or ingestion of fava beans — causes oxidative damage to hemoglobin. The oxidized and denatured hemoglobin cross-links and precipitates intracellularly, forming inclusions that are identified as Heinz bodies on the supravital stain of the peripheral smear. Heinz bodies are removed in the spleen, leaving erythrocytes with a missing section of cytoplasm; these «bite cells» can be seen on the routine blood smear. The altered erythrocytes undergo both intravascular and extravascular destruction. Older red blood cells are most susceptible, because they have an intrinsic G6PD deficiency coupled with the normal age-related decline in G6PD levels.

Hemolysis occurs two to four days following exposure and varies from an asymptomatic decline in hemoglobin to a marked intravascular hemolysis. Even with ongoing exposure, the hemolysis usually is self-limited, as the older G6PD-deficient cells are destroyed. There is no specific therapy other than treatment of the underlying infection and avoidance of implicated medications. In cases of severe hemolysis, which can occur with the Mediterranean-variant enzyme, transfusion may be required.

G6PD activity levels may be measured as normal during an acute episode, because only nonhemolyzed, younger cells are assayed. If G6PD deficiency is suspected after a normal activity-level measurement, the assay should be repeated in two to three months, when cells of all ages are again present.

MEMBRANOPATHIES

Hereditary spherocytosis is an autosomal dominant disorder caused by mutations in the red blood cell membrane skeleton protein genes. With a weakened protein backbone anchoring its lipid bilayer, the membrane undergoes a progressive deterioration in structure, resulting in a spherocyte, the characteristic abnormality seen on peripheral smear. As with AIHA, the spherocytes are unable

to pass through the splenic cords and are degraded and ingested by the monocyte-macrophage system.

Although there is marked variability in phenotype, hereditary spherocytosis is typically a chronically compensated, mild to moderate hemolytic anemia. The diagnosis is based on the combination of spherocytosis noted on peripheral smear, a family history (in 75 percent of cases), and a negative DAT. The mean corpuscular hemoglobin concentration frequently is elevated.

Splenectomy effectively arrests the extravascular hemolysis and prevents its long-term complications, such as cholelithiasis and aplastic crises. Because of the inherent risk of infections and sepsis, however, splenectomy generally is reserved for use in patients older than five years with moderate to severe disease, characterized by hemoglobin concentrations of less than 11 g per dL (110 g per L) and jaundice. Partial splenectomy has been demonstrated to be effective in decreasing hemolysis while maintaining the phagocytic function of the spleen.

HEMOGLOBINOPATHIES

Chronic hemolysis can be a characteristic of disorders of hemoglobin synthesis, including sickle cell anemia and thalassemias.

The thalassemias are a heterogeneous group of inherited multifactorial anemias characterized by defects in the synthesis of the alpha or beta subunit of the hemoglobin tetramer ($\alpha_2\beta_2$). The deficiency in one globin chain leads to an overall decrease in hemoglobin and the intracellular precipitation of the excess chain, which damages the membrane and leads to clinically evident hemolysis in the severe forms of alpha thalassemia (hemoglobin H disease) and beta thalassemia (intermedia and major). Beta thalassemia can be diagnosed by hemoglobin electrophoresis, which shows elevated levels of hemoglobins A_2 and F, while diagnosis of alpha thalassemia requires genetic studies. Thalassemias are characterized by hypochromia and microcytosis; target cells frequently are seen on the peripheral smear.

Sickle cell anemia is an inherited disorder caused by a point mutation leading to a substitution of valine for glutamic acid in the sixth position of the β chain of hemoglobin. Membrane abnormalities from sickling and oxidative damage caused by hemoglobin S, along with impaired deformability of sickle cells, lead to splenic trapping and removal of cells. Some degree of intravascular hemolysis occurs as well. Hemoglobin electrophoresis reveals a predominance of hemoglobin S. Sickle cells are observed on the peripheral smear.

ACQUIRED DISORDERS

Once the diagnosis of hemolysis is made on the basis of laboratory and peripheral smear findings, it is necessary to determine the etiology. While most forms of hemolysis are classified as predominantly intravascular or extravascular, the age of onset, accompanying clinical presentation, and co-existing medical problems usually guide the clinician to consider either an acquired or a hereditary cause.

IMMUNE HEMOLYTIC ANEMIA

Immune hemolytic anemias are mediated by antibodies directed against antigens on the red blood cell surface. Microspherocytes on a peripheral smear and a positive direct antiglobulin test are the characteristic findings. Immune hemolytic anemia is classified as autoimmune, alloimmune, or drug-induced, based on the antigen that stimulates antibody- or complement-mediated destruction of red blood cells.

Autoimmune hemolytic anemia

Autoimmune hemolytic anemia (AIHA) is diagnosed in the presence of anemia, usually macrocytic and of variable intensity, reticulocytosis, and a positive direct and/or indirect antiglobulin test, after ruling out other types of hemolytic anemia. A positive direct antiglobulin test alone is not sufficient to diagnose AIHA and may be positive in many patients without anemia or negative in some patients with AIHA.

AIHA may be classified into two major categories according to the optimal temperature of antibody activity: warm-reacting autoantibodies (usually IgG) optimal around 37 degrees C and cold-reacting autoantibodies, optimal at 4 degrees C (usually IgM). This classification guides the selection of tests and treatment.

When warm autoantibodies attach to red blood cell surface antigens, these IgG-coated red blood cells are partially ingested by the macrophages of the spleen, leaving microspherocytes, the characteristic cells of AIHA. These spherocytes, which have decreased deformability compared with normal red blood cells, are trapped in the splenic sinusoids and removed from circulation.

Cold autoantibodies (IgM) temporarily bind to the red blood cell membrane, activate complement, and deposit complement factor C3 on the cell surface. These C3-coated red blood cells are cleared slowly by the macrophages of the liver (extravascular hemolysis). Less frequently, the complete complement cascade is activated on the cell surface, resulting in the insertion of the membrane attack complex (C5b to C9) and intravascular hemolysis.

Aetiologies of autoimmune haemolytic anaemia

Autoantibody (incidence)

Warm antibody AIHA (1:100000)
Primary (idiopathic)
Secondary
Lymphoproliferative disease (lymphoma)
Autoimmune diseases (SLE, colitis ulcerosa)
Acute leukaemia
Solid malignancy (ovarian carcinoma)
***Cold antibody AIHA* (1:1000000)**
Primary (idiopathic): frequently herald of occult lymphoma

Secondary
Lymphoproliferative disease (M. Waldenstrom, lymphoma)
Infection (mycoplasma, EBV)
***Biphasic haemolysins* (rare)**
Idiopathic
Secondary
Postviral, siphilis
Mixed forms with warm and cold antibodies
Idiopathic
Secondary
Autoimmune diseases (SLE)

The direct antiglobulin test (DAT), also known as the direct Coombs' test, demonstrates the presence of antibodies or complement on the surface of red blood cells and is the hallmark of autoimmune hemolysis (figure 28).

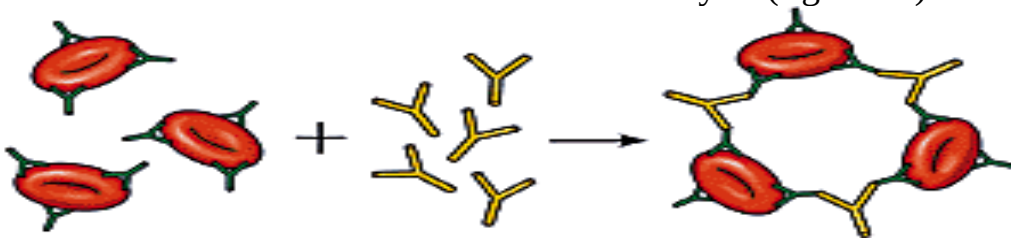


Figure 28 — Direct antiglobulin test:
The presence of autoanti-bodies or complement on the surface of the red blood cell

From: Zeerleder, S. Autoimmune haemolytic anaemia – a practical guide to cope with a diagnostic and therapeutic challenge / S. Zeerleder // The Netherlands Journal of Medicine. — 2011. — Vol. 69. — P. 177–184.

The patient's red blood cells are mixed with rabbit or mouse antibodies against human IgG or C3. Agglutination of the patient's antibody- or complement-coated red blood cells by anti-IgG or anti-C3 serum constitutes a positive test. Red blood cell agglutination with anti-IgG serum reflects warm AIHA, while a positive anti-C3 DAT occurs in cold AIHA.

Although most cases of autoimmune hemolysis are idiopathic, potential causes should always be sought. Lymphoproliferative disorders (e.g. chronic lymphocytic leukemia, non-Hodgkin's lymphoma) may produce warm or cold autoantibodies. A number of commonly prescribed drugs can induce production of both types of antibodies. Warm AIHA also is associated with autoimmune diseases (e.g. systemic lupus erythematosus), while cold AIHA may occur following infections, particularly infectious mononucleosis and *Mycoplasma pneumoniae* infection. Human immunodeficiency virus infection can induce both warm and cold AIHA.

Complications of autoimmune hemolytic anemia

Thromboembolism (pulmonary embolism, venous thromboembolism) may be related to coexistent antiphospholipid antibodies. To recommend anticoagulant prophylaxis in general for patients with hemolytic episodes from AIHA.

Lymphoproliferative Disorders

Patients with lymphoproliferative disorders are well known to have a higher risk for development of AIHA; this is particularly true of chronic lymphocytic leukemia. Interestingly, there may also be an increased risk for future development of lymphoproliferative disorders (B-cell non-Hodgkin lymphomas, myeloid malignancies) in patients with AIHA.

Therapy of autoimmune hemolytic anemia

The standard therapeutic approaches to treatment of AIHA include corticosteroids, splenectomy and immunosuppressive drugs.

Refractory cases may require splenectomy, intravenous gamma globulin, plasmapheresis, cytotoxic agents, or danazol. All of the aforementioned therapies are generally ineffective for cold AIHA, which is managed most effectively by avoidance of the cold and treatment of any underlying disorder.

Transfusion therapy in AIHA is challenging, and the most compatible red blood cells (i.e. those with the least cross-reacting antibodies) should be given.

Intravenous immune globulin (IVIG)

For patients with initial hepatomegaly and lower initial hemoglobin levels.

Danazol

Danazol, which has been used more in refractory cases of immune thrombocytopenia, has also been used in AIHA.

Newer Immunosuppressives

The use of mycophenolate mofetil (500 mg per day initially, then 1000 mg per day) in patients with refractory AIHA showed excellent results.

Monoclonal Antibodies

Monoclonal antibody therapy, specifically rituximab, is a safe and effective therapy for refractory AIHA.

In warm antibody AIHA, standard first line therapy are glucocorticosteroids with or without high dose immunoglobulins, whereas splenectomy is considered second-line therapy. Response rates of primary AIHA to corticosteroid therapy are high. After initial remission, the dose should be tapered down slowly and with caution, and in some cases, low-dose maintenance therapy is required. The efficacy of standard therapy is low in secondary AIHA that develops in lymphoma patients, posttransplant patients, or tumor patients. Among other immunosuppressive treatments, rituximab (anti-CD20) appears to be highly

effective in patients with warm antibody AIHA refractory to standard therapy. Mycophenolate mofetil is quite effective in AIHA patients with an underlying autoimmune or lymphoproliferative disease.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Paroxysmal nocturnal hemoglobinuria is a rare, clonal hematopoietic stem cell disease that manifests as bone marrow failure, hemolytic anemia, smooth muscle dystonias and thrombosis. The median survival in untreated patients ranges from 10 to 20 years.

Pathogenesis of paroxysmal nocturnal hemoglobinuria

PNH originates from a multipotent hematopoietic stem cell that acquires a mutation in a gene called phosphatidylinositol glycan anchor biosynthesis, class A (*PIG-A*). The *PIG-A* gene product is required for the biosynthesis of the glycosylphosphatidylinositol (GPI) anchor, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells. Consequently, the PNH stem cell and all of its progeny have a reduction or absence of GPI anchor proteins (GPI-APs). Two of these proteins, CD55 and CD59, are complement regulatory proteins; the absence of these proteins is fundamental to the pathophysiology of PNH. CD55 inhibits C3 convertases and CD59 blocks C9 incorporation into the membrane attack complex (MAC). The absence of CD55 and CD59 makes PNH cells vulnerable to complement mediated intravascular and extravascular hemolysis, although it is the intravascular hemolysis that most contributes to the morbidity of the disease. Intravascular hemolysis releases free hemoglobin into the plasma. Free plasma hemoglobin scavenges nitric oxide and depletion of nitric oxide at the tissue level contributes to numerous PNH manifestations.

Diagnosis of paroxysmal nocturnal hemoglobinuria

PNH remains a clinical diagnosis.

The diagnosis of PNH requires the presence of hemolysis (usually demonstrated by elevated levels of lactate dehydrogenase, an elevated reticulocyte count, and anemia) and documented deficiency of GPI-AP on two or more blood cell lineages. GPI-AP deficiency on blood cells is usually documented by flow cytometry using fluoresceinated monoclonal antibodies directed against individual GPI-AP.

Treatment of paroxysmal nocturnal hemoglobinuria

Targeted Complement inhibition

Eculizumab, a monoclonal antibody that inhibits the terminal stage of the complement cascade, has been shown to decrease hemolysis and thrombosis and to markedly improve the quality of life in patients with PNH.

Newer and even more targeted complement inhibitors are in clinical development and will likely be useful in treating a large number of complement mediated conditions.

Bone Marrow Transplantation

BMT is the only curative therapy for PNH with success rates ranging from 50 to 70%. BMT should not be offered as initial therapy for most patients with classical PNH.

Key Messages

- Iron deficiency anemia (IDA) is usually caused by chronic blood loss from colonic cancer or gastric cancer, and malabsorption in coeliac disease and is characterized by a microcytic, hypochromic, potentially severe anemia.
- Increasing dietary iron intake alone is inadequate to treat frank IDA. All patients should have iron supplementation both to correct anaemia and replenish body stores.
- Patient taking an iron supplement must not take concomitant consumption of inhibitors of iron absorption (e.g. tea, calcium, antacids, tetracycline, within 2 hours of iron ingestion).
- Parenteral iron can be used when oral preparations are not tolerated.
- Blood transfusions should be reserved for patients with or at risk of cardiovascular instability due to the degree of their anaemia.
- Pernicious anemia is normochromic and macrocytic anemia, with Howell-Jolly bodies, generally associated with moderate leukopenia and thrombopenia, elevated bilirubin.
- Pernicious anemia is considered in the presence of neurological and hematological manifestations of undetermined origin.
- Treatment of pernicious anemia is based on the administration of parenteral vitamin B_{12}.
- Common acquired causes of hemolytic anemia are autoimmunity, microangiopathy, and infection.
- The diagnosis of autoimmune haemolytic anaemia (AIHA) is based on the presence of anaemia, signs of haemolysis with reticulocytosis, low haptoglobin, increased lactate dehydrogenase, elevated indirect bilirubin, and a positive direct antiglobulin test (Coombs test).
- The standard therapeutic approaches to treatment of AIHA include corticosteroids, splenectomy and immunosuppressive drugs.

CASE REPORT No.8

A 47 year old women was admitted to hospital because a haemoglobin level of 6.4 g/dl had attracted attention when she was donating blood. She complained of fatigue and occasionally frontal headaches. On physical examination

she appeared to have a normal nutritional condition but her skin was pale and she had brittle nails. Despite the severity of the anaemia she appeared well. Pulse frequency and blood pressure were normal. Blood smear showed a strikingly microcytotic hypochromic red blood cell morphology (mean corpuscular volume 56 fl, mean corpuscular haemoglobin 15.5 pg/cell, mean cell haemoglobin concentration 27.5 g/dl). According to this, serum iron was below 5 μg/l, serum transferrin was elevated to 3.97 g/l and less than 10 % saturated, and serum ferritin concentration was 3 mg/l. Erythrocyte count was normal (4.14×10^{12}/l), indicating enduring iron deficient erythropoiesis rather than bleeding. In fact, the guaiac smear test was negative and endoscopies of the gastrointestinal tract revealed no abnormalities. Gynaecological examination excluded uterine bleeding. Exploring her food patterns she confessed to regular eating of crayons for more than nine years to compensate for a sulky taste. She had such a craving for clean white crayons that she had increased her intake to 20 packages per month. Three days after cessation, oral iron absorption tests were normal. Starting treatment with an oral iron preparation resulted in reticulocytosis with a peak of 7.8 % after 10 days.

This exceptional case of severe iron deficiency anaemia related to long term ingestion of large amounts of purchasable crayons clearly meets the diagnostic criteria of adult pica. Pica comes from the Latin word for magpie, a bird known for its large and indiscriminate appetite, and implies a qualitative eating disorder defined by oral ingestion of non-food items for at least one month. Pica is most common in those with developmental disabilities, including autism and mental retardation, and in children. Apart from sporadic cases due to a specific underlying psychiatric disorder, pica also features a culture bound syndrome worldwide. Iron deficiency is one peculiar finding quite commonly associated with pica. Anaemia, dwarfism, and hypogonadism have been related to clay eating among children and women from rural areas in Turkey and Iran. Eating of chalk among children and Black pregnant and non-pregnant women in middle Georgia reflects another example of a socioculturally transmitted form of pica without other apparent psychopathology. The basis of the bizarre behaviour in pica still remains obscure. Specific nutritional deficiencies of particular trace elements may trigger the unusual cravings for non-food items. Some of these materials bind iron in the gastrointestinal tract, worsening the deficiency. Pica has recently been identified as a predominant risk factor for anaemia in pregnant women in a large case control study from the Sudan. The type of crayon ingested by our patient consisted of pure calcium sulphate. It is conceivable that the bioavailability of dietary iron was markedly impaired in the presence of abundant calcium sulphate. Albeit a rare condition in Central Europe, adult pica should be considered for differential diagnosis of chronic iron deficiency anaemia, particularly if other causes of abnormal iron absorption have been excluded.

CASE REPORT No.9

A 29-year-old male patient was admitted to the hospital with an eight-day history of fever and productive cough, followed by jaundice and passing dark urine for three days. The patient was previously healthy and was not using any drugs. There was no family history of hemolytic attacks. Upon physical examination, the patient appeared ill, febrile, dyspneic with yellowish discoloration of the sclera. Blood pressure was 110/60 mmHg, pulse rate was 110/minute and temperature 39.8 °C. Chest examination showed bilateral basal crepitations. The rest of the examination was unremarkable. Initial investigations showed a hemoglobin level of 6.3 g/dL, mean cell volume (MCV) 94 fL (normal MCV can be explained by early occurrence of hemolysis), total leukocyte count 43,100/mm^3, with 74.6% neutrophils, 15 % lymphocytes, 9 % monocytes, platelets 738,000/mm^3, and erythrocyte sedimentation rate (ESR) 75 mm/hour. A peripheral blood film showed marked leucocytosis and agglutination. Chest X-ray showed bilateral basal opacities. Reticulocyte count was 3.4 %. Lactate dehydrogenase (LDH) was 2,758 U/liter (normal 240–480). Haptoglobin was < 5.8 mg/dL (normal 27–139). Total bilirubin was 64 μmol/L (normal 3.5–24), of which 20.2 μmol/L was direct (normal 0–7). Other blood chemistry, liver profile, and coagulations studies were within normal limits. Malaria parasite smear was negative, urine dipstick and microscopy were normal. A tuberculin skin test was negative. Blood culture, urine analysis, urine culture, and *Brucella* serology were negative. Hepatitis A IgM antibodies, hepatitis C antibody, hepatitis B markers and antibodies to human immunodeficiency virus were likewise negative. The patient was transfused two units of packed red cells, after which his hemoglobin increased to 8.5 gm/dL.

Based on this information, the following diagnoses were considered: acute intravascular hemolysis complications from an *M. pneumoniae* infection, hemolytic uremic syndrome and leukemia. The patient was treated for community-acquired pneumonia, and was started on 2 g ceftriaxon once daily intravenously, plus azithromycin 500 mg once daily orally. Hemolytic anemia workup was initiated. G6PD deficiency was not found. Serum vitamin B_{12}, red blood cell folate and hemoglobin electrophoresis all gave results within normal limits. Direct Coombs' test was strongly positive and cold agglutinin titer was high, with anti-I specificity. A bone marrow biopsy was performed in order to rule out the possibility of an underlying leukemia. It revealed increased erythropoesis, but no changes indicative of a hematological malignancy. An acute hemolysis complicating an *M. pneumonia* infection then seemed the most likely diagnosis, and this was later confirmed serologically. Antimycoplasma antibody titer by complement fixation was high 1:10,240. Ceftriaxon treatment was stopped and azithromycin continued for five days. The patient responded well, fever subsided and hemoglobin reached 10.3 gm/dL, while the leukocyte count declined to normal values. The patient was discharged in good health after a 12-day hospital stay. Six months later, he remained clinically well, with no recurrence of jaundice.

HEMOBLASTOSIS. ACUTE LEUKEMIAS. AGRANULOCYTOSIS

Acute leukemias are characterized by recurring chromosomal aberrations and gene mutations which are critical to disease pathogenesis. It is now evident that epigenetic modifications including DNA methylation and histone modifications contribute significantly to the leukemogenic phenotype. An additional layer of epigenetic complexity is the pathogenetic role of microRNAs in leukemias, and their key role in the transcriptional regulation of tumor suppressor genes and oncogenes. The genetic heterogeneity of acute leukemias poses therapeutic challenges, but pharmacologic agents that target components of the epigenetic machinery hold promise as a part of the therapeutic arsenal for this group of diseases.

The myeloid leukemias are a heterogeneous group of diseases characterized by infiltration of the blood, bone marrow, and other tissues by neoplastic cells of the hematopoietic system.

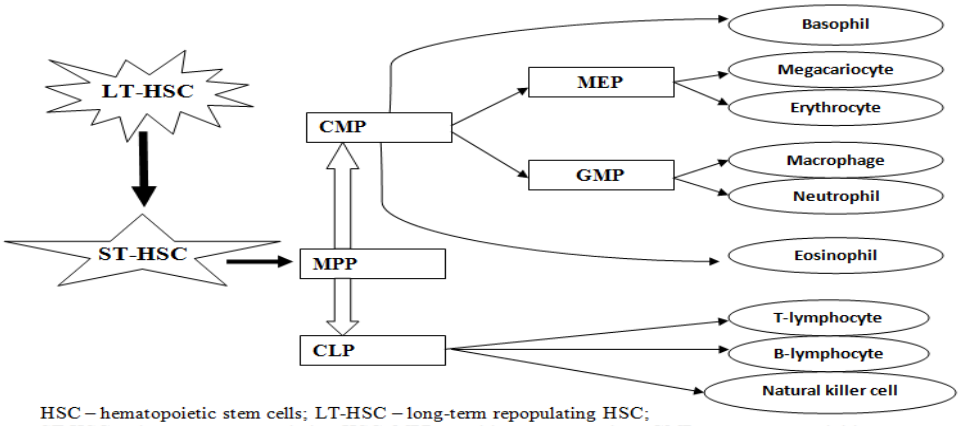
Acute lymphoblastic leukemia (ALL), a clonal expansion of hematopoietic blasts, is a highly heterogeneous disease comprising many entities for which there are distinct treatment strategies. Although ALL is a success story in pediatric oncology, results in adults lag behind those in children. An expansion of new drugs, more reliable immunologic and molecular techniques for the assessment of minimal residual disease, and efforts at more precise risk stratification are generating new aspects of adult ALL therapy.

Agranulocytosis is a rare and serious disease often caused by drugs. Its mortality rate is around 10 %. The most common manifestations are infections such as tonsillitis, pharyngitis, stomatitis or pneumonia.

Haematopoiesis

Haematopoiesis is the development of the cellular components of the blood. The formation and development of blood cells is initiated by the haematopoietic stem cells (HSCs). HSCs are primitive cells capable of self-renewal and differentiation. Due to the self-renewal capability, at least one of the daughter cells possesses the same HSC characteristics as the mother cell after cell division. During the entire life of an individual, the stem cell pool is maintained due to the self-renewal capability of the HSCs and supplies cells for multilineage haematopoiesis. Currently it is considered that long-term repopulating HSCs (LT-HSC) differentiate into a short-term repopulating HSC (ST-HSC) and, as schematically shown in figure 29, they will differentiate further into multipotent progenitor cells (MPP) only capable of differentiating into the myeloid lineage or the lymphoid lineage.

The common myeloid progenitors (CMP) give rise to megakaryocyteerythroid progenitors (MEP), which differentiate into megakaryocytes and erythrocytes, and granulocytemonocyte progenitors (GMP), which differentiate into macrophages and neutrophil granulocytes. The eosinophilic and basophilic granulocytes differentiate directly from the CMP. The common lymphoid progenitors (CLP) differentiate into T- and B-lymphoid cells and natural killer cells. The progeny that arises from HSCs progressively loses its self-renewal capacity and gradually becomes more restricted to one lineage. HSCs require intrinsic and extrinsic factors for their activities provided by the stem cell niche. The interaction of HSCs with the stem cell niche determines whether the HSCs remain in a quiescent state or proliferate to progenitor cells and differentiate into mature blood cells.



HSC – hematopoietic stem cells; LT-HSC – long-term repopulating HSC; ST-HSC – shortg-term repopulating HSC; MPP – multipotent progenitor; CMP – common myeloid progenitor; CLP – common lymphoid progenitor; MEP – megakaryocyte-erythroid progenitor; GMP – granulocyte-macrophage progenitor.

Figure 29 — Development of haematopoietic stem cells

Leukemogenesis

• Acute leukemias, arising from neoplastic transformation of uncommitted or partially committed hematopoietic stem cells, are characterized by recurring chromosomal aberrations and gene mutations which are critical to disease pathogenesis.

• The recurring chromosomal translocations in acute myeloid leukemia (AML) result in the generation of chimeric fusion proteins, which in many cases function as transcriptional regulators. These include AML1-ETO (generated by t(8;21)), CBFB-MYH11 (generated by inv(16) or t(16;16)), PML-RARA (generated by t(15;17)), MOZ-CBP (generated by t(8;16)), MORF-CBP (generated by t(10;16)), MOZ-TIF (generated by inv(8)), and MLL fused with various partners (generated by t(11q23)). They contribute to leukemogenesis, at least partially by causing transcriptional deregulation via epigenetic modifications.

• Epigenetic modifications including DNA methylation or demethylation and histone changes lead to activation or repression of gene expression. Aberrant epigenetic changes occur frequently in acute leukemias. Fusion genes resulting from chromosome translocations may be regulators or mediators of the epigenetic machinery.

• MicroRNA regulation may also contribute significantly to leukemogenesis. Some microRNAs function as oncogenes or tumor suppressor genes in acute leukemias. microRNA signatures correlate with cytogenetic and molecular subtypes of acute leukemias, and some microRNA signatures are associated with outcome or survival of acute leukemias.

• It is evident that not only do microRNAs themselves function in an epigenetic manner by post-transcriptional regulation of expression of target genes, but they can also be targets of the epigenetic machinery and effectors of DNA methylation and histone modifications. These functions may all be involved in leukemogenesis.

A first step in the leukemogenic process is likely to be a mere clonal expansion. Several gene mutations may play a role at this stage. Their identity may depend on whether they target a hematopoietic stem cell or a progenitor. In the first case the initial hit should provide a proliferation boost, in the second the hit should bestow self-renewal on the proliferating progenitor.

Then, because of increasing proliferation and genetic instability, a cell from the affected clone (or clones) undergoes various additional mutations (including many background mutations), leading to an oligoclonal malignant tumor. Some of the early mutations may not be present in the clone that eventually becomes leukemic.

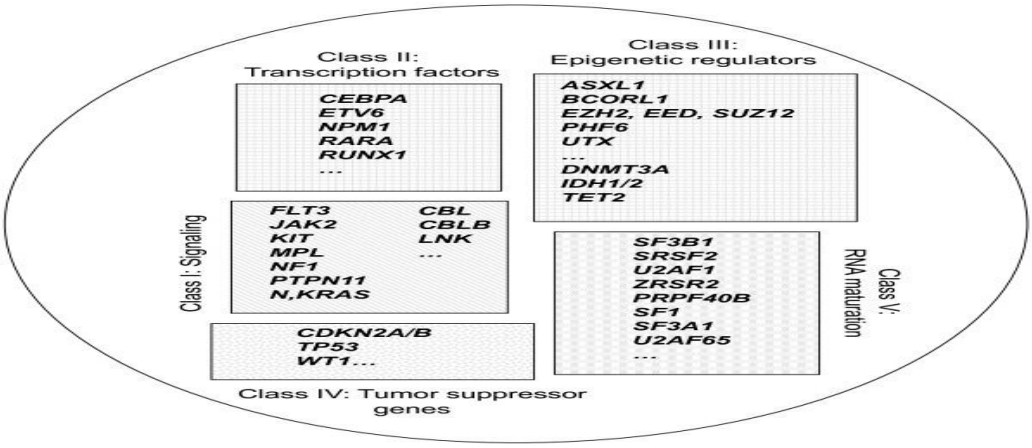


Figure 30 — Schematic representation of five classes of leukemogenic genes

From: Leukemogenesis: more than mutant genes / J. Chen [at al.] // Nat Rev Cancer. — 2010. — Vol. 10. — P. 23–36.

Classification of leukemias

French-American-British classification for leukemias (includes Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia and Myelodysplastic syndrome) has been widely accepted due to its objectiveness and good reproducibility.

French-American-British (FAB) Classification

M0: Minimally differentiated leukemia
M1: Myeloblastic leukemia without maturation
M2: Myeloblastic leukemia with maturation
M3: Hypergranular promyelocytic leukemia
M4: Myelomonocytic leukemia
M4Eo: Variant: Increase in abnormal marrow eosinophils
M5: Monocytic leukemia
M6: Erythroleukemia (DiGuglielmo's disease)
M7: Megakaryoblastic leukemia
L1: Pre-B ALL
L2: T cell ALL
L3: B cell ALL

Myelodysplastic syndrome (MDS) requires a careful light microscopic examination of optimally stained peripheral blood and bone marrow smears and trephine biopsy sections, with the diagnosis being based on the presence of dysplastic features of hematopoietic lineage. FAB group distinguished the following MDS types: 1) refractory anemia (RA); 2) refractory anemia with ring sideroblasts (RAS); 3) refractory anemia with excess of blasts (RAEB); 4) chronic myelomonocytic leukemia (CMML); and 5) RAEB *in transformation* (RAEB-t).

WHO classification of leukemias was formulated in 1997 with a purpose of further enhancing the objectivity. However, the requirement of cytogenetics and immunophenotyping makes it difficult for many countries to put WHO classification in routine use.

The recent World Health Organization (WHO) classification reflects the fact that an increasing number of acute leukemias can be categorized based upon their underlying cytogenetic or molecular genetic abnormalities, and that these genetic changes form clinico-pathologic-genetic entities.

In general, the classification stratifies neoplasms according to their lineage (myeloid, lymphoid, histiocytic/dendritic) and distinguishes neoplasms of precursor cells from those comprised of functionally mature cells.

Lymphoid neoplasms are derived from cells that frequently have features that recapitulate stages of normal B-, T-, and NK-cell differentiation and function, so to some extent they can be classified according to the corresponding normal

counterpart, although additional features, such as genotype, clinical features and even location of the tumor figure into the final classification listing as well.

Five major subgroups of *myeloid neoplasms* are based mainly on their degree of maturation and biologic properties: myeloproliferative neoplasms (MPNs) which are comprised primarily of mature cells with effective proliferation; myeloid (and lymphoid) neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB and FGFR1, defined largely by the finding of significant eosinophilia and specific genetic abnormalities; myelodysplastic/myeloproliferative neoplasms (MDS/MPN), comprised mainly of mature cells with both effective and ineffective proliferation of various lineages; myelodysplastic syndromes (MDS), in which immature and mature cells are found with abnormal, dysplastic and ineffective maturation, and acute myeloid leukemia (AML), comprised of precursor cells with impaired maturation. Genetic abnormalities play an important role as diagnostic criteria for further sub-classification of some myeloid neoplasms, particularly of AML. Although therapy-related MDS and AML (t-MDS/AML) often have genetic defects identical to those found in de novo AML and de novo MDS, they are classified separately from de novo AML and MDS in order to emphasize their unique clinical and biologic properties.

GUIDELINES FOR USING THE REVISED WHO CLASSIFICATION OF MYELOID NEOPLASMS

Specimen requirements:

— PB (peripheral blood) and BM (bone marrow) specimens collected prior to any definitive therapy;

— PB and cellular BM aspirate smears and/or touch preparations stained with Wright-Giemsa or similar stain;

— BM biopsy, at least 1.5 cm in length and at right angles to the cortical bone, is recommended for all cases if feasible;

— BM specimens for complete cytogenetic analysis and, when indicated, for flow cytometry, with an additional specimen cryopreserved for molecular genetic studies. The latter studies should be performed based on initial karyotypic, clinical, morphologic, and immunophenotypic findings.

Assessment of blasts:

— blast percentage in PB and BM is determined by visual inspection;

— myeloblasts, monoblasts, promonocytes, megakaryoblasts (but not dysplastic megakaryocytes) are counted as blasts when summing blast percentage for diagnosis of AML or blast transformation; count abnormal promyelocytes as «blast equivalents» in APL;

— proerythroblasts are not counted as blasts except in rare instances of «pure» acute erythroleukemia;

— flow cytometric assessment of $CD34^+$ cells is not recommended as a substitute for visual inspection; not all blasts express CD34, and artifacts introduced by specimen processing may result in erroneous estimates;

— if the aspirate is poor and/or marrow fibrosis is present, IHC on biopsy sections for CD34 may be informative if blasts are $CD34^+$.

Assessment of blast lineage:

— multiparameter flow cytometry (at least 3 colors) is recommended; panel should be sufficient to determine lineage as well as aberrant antigen profile of neoplastic population;

— cytochemistry, such as myeloperoxidase or nonspecific esterase, may be helpful, particularly in AML, NOS, but it is not essential in all cases;

— IHC on biopsy may be helpful; many antibodies are now available for recognition of myeloid and lymphoid antigens.

Assessment of genetic features:

— complete cytogenetic analysis from BM at initial diagnosis when possible;

— additional studies, such as FISH, RT-PCR, mutational status, should be guided by clinical, laboratory, and morphologic information;

— mutational studies for mutated *NPM1*, *CEBPA*, and *FLT3* are recommended in all cytogenetically normal AML; mutated *JAK2* should be sought in *BCR-ABL1*-negative MPN, and mutational analysis for *KIT*, *NRAS*, *PTNP11*, etc, should be performed as clinically indicated.

Correlation/reporting of data:

— all data should be assimilated into one report that states the WHO diagnosis;

— WHO indicates World Health Organization; PB (peripheral blood); BM (bone marrow); IHC (immunohistochemistry); AML (acute myeloid leukemia); APL (acute promyelocytic leukemia); NOS (not otherwise specified); FISH (fluorescence in situ hybridization); RT-PCR (reverse transcriptase–polymerase chain reaction); and MPN (myeloproliferative neoplasm).

WORLD HEALTH ORGANIZATION CLASSIFICATION OF NEOPLASTIC DISEASES OF HEMATOPOIETIC AND LYMPHOID TISSUES

Myeloproliferative neoplasms (MPN)

Chronic myelogenous leukemia, *BCR-ABL1*-positive
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*

Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
Myeloid neoplasms associated with *PDGFRB* rearrangement

Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

Chronic myelomonocytic leukemia

Atypical chronic myeloid leukemia, *BCR-ABL1*-negative

Juvenile myelomonocytic leukemia

Myelodysplastic/myeloproliferative neoplasm, unclassifiable

Provisional entity: refractory anemia with ring sideroblasts and thrombocytosis

Myelodysplastic syndrome (MDS)

Refractory cytopenia with unilineage dysplasia

Refractory anemia

Refractory neutropenia

Refractory thrombocytopenia

Refractory anemia with ring sideroblasts

Refractory cytopenia with multilineage dysplasia

Refractory anemia with excess blasts

Myelodysplastic syndrome with isolated del(5q)

Myelodysplastic syndrome, unclassifiable

Childhood myelodysplastic syndrome

Provisional entity: refractory cytopenia of childhood

Acute myeloid leukemia and related neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities

AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*

AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*

APL with t(15;17)(q22;q12); *PML-RARA*

AML with t(9;11)(p22;q23); *MLLT3-MLL*

AML with t(6;9)(p23;q34); *DEK-NUP214*

AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*

AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*

Provisional entity: AML with mutated NPM1

Provisional entity: AML with mutated CEBPA

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukemia

Acute monoblastic/monocytic leukemia

Acute erythroid leukemia

Pure erythroid leukemia

Erythroleukemia, erythroid/myeloid

Acute megakaryoblastic leukemia

Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage

Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B-myeloid, NOS
Mixed phenotype acute leukemia, T-myeloid, NOS
Provisional entity: natural killer (*NK*) *cell lymphoblastic leukemia/lymphoma*

B lymphoblastic leukemia/lymphoma

B lymphoblastic leukemia/lymphoma, NOS
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2);*BCR-ABL 1*
B lymphoblastic leukemia/lymphoma with t(v;11q23);*MLL* rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1*)
B lymphoblastic leukemia/lymphoma with hyperdiploidy
B lymphoblastic leukemia/lymphoma with hypodiploidy
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH*
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*

T lymphoblastic leukemia/lymphoma

ACUTE MYELOID LEUKEMIA (AML)

The myeloid leukemias are a heterogeneous group of diseases characterized by infiltration of blood, bone marrow, and other tissues by neoplastic cells of the hematopoietic system.

Epidemiology of acute myeloid leukemia

The incidence of acute myeloid leukemia (AML) is ~3.7 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.6 versus 3.0). AML incidence increases with age; it is 1.9 in individuals < 65 years and 18.6 in those > 65. A significant increase in AML incidence has occurred over the past 10 years.

Etiology of acute myeloid leukemia

Heredity, radiation, chemical and other occupational exposures, and drugs have

been implicated in the development of AML. No direct evidence suggests a viral etiology.

Heredity

Certain syndromes with somatic cell chromosome aneuploidy, such as trisomy 21 noted in Down syndrome, are associated with an increased incidence of AML. Inherited diseases with defective DNA repair, e.g., Fanconi anemia, Bloom syndrome, and ataxia telangiectasia, are also associated with AML. Congenital neutropenia (Kostmann syndrome) is a disease with mutations in the granulocyte colony-stimulating factor (G-CSF) receptor and, often, neutrophil elastase that may evolve into AML. Myeloproliferative syndromes may also evolve into AML.

Radiation

Survivors after the atomic bomb explosions in Japan had an increased incidence of myeloid leukemias that peaked 5–7 years after exposure. Therapeutic radiation alone seems to add little risk of AML but can increase the risk in people also exposed to alkylating agents.

Chemical and Other Exposures

Exposure to benzene, a solvent used in the chemical, plastic, rubber, and pharmaceutical industries, is associated with an increased incidence of AML. Smoking and exposure to petroleum products, paint, embalming fluids, ethylene oxide, herbicides, and pesticides, have also been associated with an increased risk of AML.

Drugs

Anticancer drugs are the leading cause of therapy-associated AML. Alkylating agent-associated leukemias occur on average 4–6 years after exposure, and affected individuals have aberrations in chromosomes 5 and 7. Topoisomerase II inhibitor-associated leukemias occur in 1–3 years after exposure, and affected individuals often have aberrations involving chromosome 11q23. Chloramphenicol, phenylbutazone, and, less commonly, chloroquine and methoxypsoralen can result in bone marrow failure that may evolve into AML.

Clinical Presentation of acute myeloid leukemia

History:

- increasing fatigue or decreased exercise tolerance (anemia);
- excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia);
- fevers or recurrent infections (granulocytopenia);
- headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed);
- early satiety (splenomegaly);
- family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia telangiectasia);

• history of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors);

• occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides).

Symptoms

Patients with AML most often present with nonspecific symptoms that begin gradually or abruptly and are the consequences of anemia, leukocytosis, leukopenia or leukocyte dysfunction, or thrombocytopenia. Nearly a half had symptoms for ≤ 3 months before the leukemia was diagnosed.

Fatigue as the first symptom, but most patients complain of fatigue or weakness at the time of diagnosis. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in ~10 % of patients. Signs of abnormal hemostasis (bleeding, easy bruising) are noted first in 5 % of patients. On occasion, bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis is the presenting symptom.

Rarely patients may present with symptoms from a mass lesion located in the soft tissues, breast, uterus, ovary, cranial or spinal dura, gastrointestinal tract, lungs, mediastinum, prostate, bones, or other organs. The mass lesion represents a tumor of leukemic cells and is called a granulocytic sarcoma, or chloroma.

Physical Findings:

• performance status (prognostic factor);

• ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia);

• fever and tachycardia (signs of infection);

• papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia);

• poor dentition, dental abscesses;

• gum hypertrophy (leukemic infiltration, most common in monocytic leukemia);

• skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia);

• lymphadenopathy, splenomegaly, hepatomegaly;

• back pain, lower extremity weakness [spinal granulocytic sarcoma, most likely in t(8;21) patients].

Diagnostic procedures of patients with acute myeloid leukemia

Patients who present with AML should have studies performed on leukemic cells leading to morphologic and cytogenetic classification.

In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic, and renal systems.

1. Hematologic Findings:

- normocytic normochromic anemia;
- leukocyte count is about 15,000/μL; fewer than 5% have no detectable leukemic cells in the blood; lack of intermediate form of leukocyte;
- in AML the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells; abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, myeloid lineage is virtually certain;
- poor neutrophil function may be noted by impaired phagocytosis and migration and morphologically by abnormal lobulation and deficient granulation.

2. Morphology

A bone marrow (BM) aspirate — *a marrow or blood blast count of 20% or more is required* in patient with suspected AML. Myeloblasts, monoblasts, and megakaryoblasts are included in the blast count.

Blood and marrow smears are morphologically examined using a May-Grünwald-Giemsa or a Wright-Giemsa stain. It is recommended that at least 200 leukocytes on blood smears and 500 nucleated cells on marrow smears be counted, with the latter containing spicules.

To identify lineage involvement some countries still rely more on cytochemistry, rather than on immunophenotyping (usually by flow cytometry), using myeloperoxidase (MPO) or Sudan black B (SBB) and nonspecific esterase (NSE) stains.

Detection of MPO (if present in ≥ 3 % of blasts) indicates myeloid differentiation, but its absence does not exclude a myeloid lineage because early myeloblasts and monoblasts may lack MPO. SBB staining parallels MPO but is less specific. NSE stains show diffuse cytoplasmic activity in monoblasts (usually > 80 % positive) and monocytes (usually > 20 % positive). In acute erythroid leukemia, a periodic acid-Schiff (PAS) stain may show large globules of PAS positivity. Iron stains may allow for the detection of iron stores, normal sideroblasts, and ring sideroblasts.

3. Immunophenotyping

Immunophenotyping using multiparameter (commonly at least 3- to 4-color) flow cytometry is used to determine lineage involvement of a newly diagnosed acute leukemia. There is no general agreement on the cutoff point for considering an acute leukemia to be positive for a marker. For most markers, a commonly used criterion is 20% or more of leukemic cells expressing the marker, whereas for selected markers (e.g. cytoplasmic CD3, MPO, TdT, CD34, CD117) a lower cutoff has been applied (10%). Quantification of expression patterns of several surface and cytoplasmic antigens is necessary for lineage assignment, to diagnose mixed phenotype acute leukemia (MPAL), and to detect aberrant immunophenotypes allowing for measurement of minimal residual disease (MRD). Flow cytometry determination of blast count should not be used as a substitute for morphologic evaluation.

4. Cytogenetics

Conventional cytogenetics analysis is a mandatory component in the diagnostic evaluation of a patient with suspected acute leukemia. Chromosome

abnormalities are detected in approximately 55 % of adult AML. Seven recurrent balanced translocations and inversions, and their variants, are recognized in the WHO category «AML with recurrent genetic abnormalities». Furthermore, several cytogenetic abnormalities are considered sufficient to establish the WHO diagnosis of «AML with myelodysplasia-related features» when 20 % or more blood or marrow blasts are present.

A minimum of 20 metaphase cells analyzed from bone marrow is considered mandatory to establish the diagnosis of a normal karyotype, and recommended to define an abnormal karyotype. Abnormal karyotypes may be diagnosed from blood specimens.

5. Molecular cytogenetics

Methanol/acetic acid-fixed cell pellets should be stored so if cytogenetic analysis fails, fluorescence in situ hybridization (FISH) is an option to detect gene rearrangements, such as *RUNX1-RUNX1T1*, *CBFB-MYH11*, *MLL* and *EVI1* gene fusions, or loss of chromosome 5q and 7q material. FISH is frequently necessary to identify *MLL* fusion partners in 11q23 translocations.

6. Molecular genetics

A marrow (and blood) specimen should routinely be taken for molecular diagnostics. Ideally, DNA and RNA should be extracted and viable cells stored; if cell numbers are limited, RNA extraction should be a priority, because RNA is suitable for molecular screening for fusion genes and leukemia-associated mutations.

Molecular diagnosis by reverse transcriptase–polymerase chain reaction (RT-PCR) for the recurring gene fusions, such as *RUNX1-RUNX1T1*, *CBFB-MYH11*, *MLLT3-MLL*, *DEK-NUP214*, can be useful in certain circumstances. RT-PCR, for which standardized protocols were published by the BIOMED-1 group, is an option to detect these rearrangements, if chromosome morphology is of poor quality, or if there is typical marrow morphology but the suspected cytogenetic abnormality is not present.

Somatically acquired mutations have been identified in several genes, for example, the *NPM1* gene, the *FLT3* gene, the *CEBPA* gene, the myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*) (*MLL*) gene, the neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) gene, the Wilms tumor 1 (*WT1*) gene, the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) gene, the runt-related transcription factor 1 (*RUNX1*) gene, the tet oncogene family member 2 (*TET2*) gene, and the isocitrate dehydrogenase 1 (NADP+), soluble (*IDH1*) gene. The frequencies of these gene mutations vary among cytogenetic groups.

AML with mutations in *NPM1* or *CEBPA* have been incorporated in the WHO classification as provisional entities. Screening for these 2 markers as well as for *FLT3* mutations should be done in clinical trials. While testing for *NPM1*, *CEBPA*, and *FLT3* is currently not considered mandatory outside clinical trials, the panel recommends that these 3 mutations be analyzed at least in patients with cytogenetically normal AML (CN-AML) who will receive treatment other than low-dose chemotherapy or best supportive care.

7. Genome-wide studies

Recent progress in genomics technology has resulted in the identification of novel genetic abnormalities and holds the promise of making the systematic characterization of cancer genomes feasible. For example, gene- and microRNA-expression profiling have proven valuable for the discovery of novel leukemia subgroups and of prognostic signatures. The introduction of genome-wide single nucleotide polymorphism (SNP)-based mapping arrays, providing both copy number and allele-specific information, led to the identification of a novel mechanism involved in the pathogenesis of AML, that is, uniparental disomy (UPD). Acquired UPD is due to a mitotic recombination event and may render a cell homozygous for a preexisting mutation located in the affected genomic region. The power of SNP genotyping as a tool for gene discovery is shown by several recent studies. While analyses of genomic copy number will continue to be informative with regard to selection of candidate leukemia genes, it is also hoped that high-throughput DNA sequence analysis will become possible at an affordable cost, which may ultimately result in the development of comprehensive, disease- and allele-specific oncogene mutation profiling strategies. Finally, functional genetic approaches, such as large-scale RNA interference screens, have great potential for the identification of novel cancer genes. An example is a recent study in which graded down-regulation of multiple candidate genes by RNA interference was used to identify *RPS14* as a causal gene for the MDS 5q-syndrome.

8. Biobanking

Within clinical trials, we strongly recommend storing patients' pretreatment leukemic marrow and blood within a biobank. A prerequisite for biobanking is the patient's informed consent that ideally should allow a broad spectrum of correlative laboratory studies that also include analysis of germline DNA. Pretreatment samples should include nucleic acid (DNA and RNA, stored at -80 °C) and viable cells (stored at -196°C). For further optional storage, we advise saving germline DNA (e.g. from a buccal swab, skin biopsy, or sputum), a plasma sample, a methanol/acetic acid-fixed cell pellet (from cytogenetic analysis), and frozen cell pellets from various time points during and after treatment (i.e. at the time of complete remission [CR], at relapse, and for MRD monitoring at defined time points during treatment and follow-up), stored under appropriate conditions.

9. Other diagnostic tests

Additional diagnostic tests and procedures in the initial work-up of a patient with AML:

- **tests to establish the diagnosis:**

✓ complete blood counts and differential count;
✓ bone marrow aspirate;
✓ bone marrow trephine biopsy;
✓ immunophenotyping;
✓ cytogenetics;

- **additional tests/procedures at diagnosis:**

✓ demographics and medical history;
✓ performance status (ECOG/WHO score);
✓ analysis of comorbidities;
✓ biochemistry, coagulation tests, urine analysis;
✓ serum pregnancy test;
✓ eligibility assessment for allogeneic HSCT;
✓ hepatitis A, B, C; HIV-1 testing;
✓ chest X-ray, 12-lead ECG; echocardiography (on indication);
✓ lumbar puncture (required in patients with clinical symptoms suspicious of central nervous system involvement);
✓biobanking;

- **prognostic/predictive marker assessment.**

Treatment options for acute myeloid leukemia

The treatment paradigm for AML generally includes remission induction, followed by consolidation with either 1–4 cycles of chemotherapy or stem cell transplantation.

Remission induction therapy

Induction chemotherapy should be started after the diagnostic work-up has been completed, preferably with minimal delay.

In AML patients the backbone of remission induction consists of an anthracycline (daunorubicin or idarubicin) or anthracenedione (mitoxantrone) and cytosine arabinoside (Ara-C). *Alternative anthracyclines, high-dose cytarabine, additional agents given with conventional induction chemotherapy.*

Typically, daunorubicin is given at a dose of 45 mg/m^2/d × 3 days, or mitoxantrone or idarubicin are given at doses of 12 mg/m^2/d × 3 days, in combination with Ara-C, which is administered as a continuous infusion at 100 or 200 mg/m^2/d × 7 days (frequently referred to as **7+3 chemotherapy**).

Allogeneic stem cell transplantation has been established as the most effective form of antileukemic therapy in patients with AML in first or subsequent remission.

New drugs are being evaluated in clinical studies, including immunotoxins, monoclonal antibodies, nucleoside analogues, hypomethylating agents, farnesyl-transferase inhibitors, alkylating agents, FMS-like tyrosine kinase 3 inhibitors, and multidrug-resistant modulators. However, determining the success of these treatment strategies ultimately requires well-designed clinical trials, based on stratification of the patient risk, knowledge of the individual disease, and the drug's performance status.

Hematopoietic growth factors

In the majority of AML patients, death results from bleeding or infectious complications. This is particularly true in eldery patients with AML. The utility

of hematopoietic growth factors (HGF) for ameliorating the myelosuppressive complications of AML therapy in eldery patients has been studied extensively.

Postremission strategies

Various types of postremission strategies have been evaluated including intensive conventional chemotherapy, prolonged maintenance treatment, and high-dose therapy followed by autologous or allogeneic hematopoietic stem cell transplantation (HSCT).

High-dose cytarabine

Maintenance therapy

Maintenance chemotherapy is generally not routinely administered outside of clinical trials for patients with non-APL AML.

Autologous hematopoietic stem cell transplantation

Autologous HSCT is considered an alternative option for postremission therapy in patients with favorable- and intermediate-risk cytogenetics, whereas it cannot be recommended to patients with high-risk cytogenetics.

Allogeneic hematopoietic stem cell transplantation

Allogeneic HSCT as a postremission strategy is associated with the lowest rates of relapse.

Relapsed AML

In the majority of patients with AML who achieve a CR, the leukemia will recur within 3 years after diagnosis. In general, the prognosis of patients after relapse is poor and treatment options are unsatisfactory.

Reinduction of remission

There is a lack of prospective controlled studies evaluating different treatments in relapsed AML, and therefore no generally established standard. A commonly accepted approach is to define a treatment that is directed at achieving a new remission and that leads to HSCT.

Salvage consolidation treatment including stem cell transplantation

Allogeneic HSCT is the preferred consolidation therapy once a new remission has been attained.

Management of special situations

Hyperleukocytosis

Hyperleukocytosis, generally defined as a WBC more than 100×10^9/L, is associated with increased induction mortality mainly due to hemorrhagic events,

tumor lysis syndrome, and infections. Hyperleukocytosis with leukostasis and, for example, pulmonary infiltrates or retinal and cerebral hemorrhages requires immediate medical treatment.

Leukapheresis is an option for the initial management of hyperleukocytosis. In general, the recommended therapy to lower WBC is hydroxyurea, given at dosages up to 50 to 60 mg/kg per day, until WBCs are less than 10–20 × 10^9/L. Until the WBC has been reduced, excessive red blood cell transfusions can lead to increased blood viscosity. Special attention should be given to the prevention of tumor lysis syndrome (e.g. hydration, control of uric acid production using allopurinol or rasburicase, control of urine pH).

Central nervous system involvement

In patients with CNS involvement, 40 to 50 mg of cytarabine should be administered intrathecally, 2 to 3 times per week until clearance of blasts, followed by 3 further injections with the same dosage. Alternatively, liposomal cytarabine (50 mg every other week) may be given for approximately 6 cycles. For prevention of arachnoiditis, dexamethasone (4 mg three times a day [tid] p.o.) may be prescribed on the days of intrathecal application. Prolonged application of intrathecal therapy does not appear to be justified, given that such therapy carries the risk of complications (e.g. leukencephalopathy). In patients with a CNS recurrence, craniospinal irradiation with or without intrathecal chemotherapy has also been shown to be effective.

Myeloid sarcoma

Myeloid sarcoma (synonyms: extramedullary myeloid tumor, granulocytic sarcoma, chloroma) is a tumor mass consisting of myeloid blasts in which the tissue architecture is effaced, occurring at an anatomical site other than the bone marrow, most commonly in skin, lymph nodes, gastrointestinal tract, bones, soft tissue, and testis. Myeloid sarcoma occurring de novo should be considered as AML and treated as such.

Supportive care

Prophylactic anti-infectious treatment

For prophylaxis and treatment of infectious diseases, prevailing institutional infectious organisms and their drug-resistance pattern should primarily be considered.

Personal hygiene, dental care, and vigorous hand washing (the latter also for family and caregivers) are very important for prevention of infections. Reasonable precautions should be undertaken to protect patients from bacteria or fungi in their environment. Although eating fresh fruits and/or vegetables is often discouraged, there is little evidence that adherence to such a «neutropenic diet» prevents infections.

Fungal prophylaxis

Invasive fungal infections are a major cause of morbidity and mortality in

patients with prolonged neutropenia.

Prophylaxis with itraconazole, posaconazole, or amphotericin, that is, drugs with antimold activity, reduced the risk of documented aspergillus infection and likely had some effect on mortality.

Antibiotic prophylaxis

Antibiotic prophylaxis should be given after chemotherapy for AML with a preference for a quinolone.

Growth factors

Numerous studies have shown that myeloid growth factors, either GM-CSF or G-CSF, accelerate neutrophil recovery by 2 to 5 days, can reduce antibiotic use, duration of fever, and number of days spent in hospital, and do not retard platelet recovery, or have a detrimental effect by stimulation of leukemic cell growth. The general use of growth factors in AML cannot be recommended. However, in individual cases (e.g. severe infection before expected neutrophil recovery), growth factor use can be considered.

Transfusion support

Platelet transfusion

The introduction of platelet transfusions has reduced mortality from hemorrhage in AML. American Society of Clinical Oncology guidelines recommend a threshold of 10×10^9/L for prophylactic platelet transfusions.

Red blood cell transfusion

Although evidence is lacking, it is generally accepted to keep the hemoglobin level above 8 g/dL, especially in thrombocytopenic patients.

Granulocyte transfusion

No good evidence exists to recommend granulocyte transfusions in the treatment of AML.

Post-remission chemotherapy of acute myeloid leukemia

To administer post-remission therapy consisting of a repeat of remission induction therapy, single-agent Ara-C, or 2 days of an anthracycline or anthracenedione (the same type of drug given at the same doses as in remission induction therapy) combined with 5 days of Ara-C, again given at the same dose as in remission induction therapy (frequently referred to as post-remission therapy).

Table 31 — Response criteria in AML

Category	Definition
Complete remission	Bone marrow blasts < 5%; absence of blasts with Auer rods; ab-

Category	Definition
(CR)[*]	sence of extramedullary disease; absolute neutrophil count > 1.0 × 10^9/L (1000/μL); platelet count > 100 × 10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)[†]	All CR criteria except for residual neutropenia (< 1.0 × 10^9/L [1000/μL]) or thrombocytopenia (< 100 × 10^9/L [100 000/μL])
Morphologic leukemia-free state[‡]	Bone marrow blasts < 5 %; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 % to 25 %; and decrease of pretreatment bone marrow blast percentage by at least 50 %
Cytogenetic CR (CRc)[§]	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)[‖]	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts n the blood, but no bone marrow examination available
Relapse[¶]	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

[*] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[†] The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

[‡] This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

[§] Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome. 112–115

↵‖ As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission. 108–110

↵¶ In cases of low blast percentages (5–10 %), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Response assessment

After conventional induction therapy with 3 days of an anthracycline and 7 days of cytarabine («3 + 7») or therapies of comparable intensity, response assessment is commonly performed between day 21 and day 28 after start of therapy.

Early response assessment

Early response assessment may be required in investigational studies to evaluate the antileukemic efficacy of a novel agent, or to guide subsequent treatment, for example, with protocols applying intensified induction regimens. It is made in 7 to 10 days after chemotherapy. Bone marrow at that time is usually hypoplastic or aplastic, documenting the antileukemia effect.

Response assessment during follow-up period

Within clinical trials, it is usually recommended that repeat marrow aspirates be performed every 3 months for the first 2 years; in some cases, surveillance continues every 6 months for the following 2 to 3 years. Most relapses occur within 1 to 3 years after the end of therapy. Standardized time points are necessary if MRD monitoring is performed. Outside clinical trials, repeat marrow aspirates may not be needed, and should be done only if blood counts become abnormal. Blood counts should be done every 1 to 3 months for the first 2 years, then every 3 to 6 months up to 5 years.

Table 32 — Selected new agents under study for treatment of adults with AML

Class of Drugs	Example Agent(s)
MDR1 modulators	Cyclosporine, LY335979
Demethylating agents	Decitabine, 5-azacytidine, zebularine
Histone deacetylase inhibitors	Suberoylanilide hydroxamic acid (SAHA), MS275, LBH589, valproic acid
Heavy metals	Arsenic trioxide, antimony
Farnesyl transferase inhibitors	R115777, SCH66336
FLT3 inhibitors	SU11248, PKC412, MLN518, CHIR-258
HSP-90 antagonists	17-allylaminogeldanamycin (17-AAG) or derivatives
BCR-ABL PDGFR/KIT inhibitors	Imatinib, dasatinib, nilotinib
Telomerase inhibitor	GRN163L
Cell cycle inhibitors	Flavopiridol, CYC202, SNS-032
Nucleoside analogues	Clofarabine, troxacitabine

Humanized antibodies	Anti-CD33 (SGN33), anti-DR4, anti-DR5, anti-KiR
Toxin-conjugated antibodies	Gemtuzumab ozogamicin
Radiolabeled antibodies	Yttrium-90-labeled human M195

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease, both in terms of its pathology and the populations that it affects. Disease pathogenesis involves a number of deregulated pathways controlling cell proliferation, differentiation, and survival that are important determinants of treatment response.

Epidemiology of acute lymphoblastic leukemia

The age-adjusted overall incidence of ALL in the United States is 1.5 per 100,000 population with peaks between ages 2 years and 5 years and again after age 50 years. ALL is more frequent among Caucasians, in affluent societies, and in urban areas, giving rise to speculation about socioeconomic factors in its etiology. Investigations also have focused on genetic variability in drug metabolism, DNA repair, and cell-cycle checkpoints that may interact with the environmental, dietary, maternal, and other external factors to affect leukemogenesis.

Clinical presentation of acute lymphoblastic leukemia

Clinical manifestations at presentation include constitutional symptoms (fevers, night sweats, weight loss), easy bruising or bleeding, dyspnea, dizziness, and infections. Extremity and joint pain may be the only presenting symptoms.

Extramedullary sites of disease are frequently involved in patients who present with leukemia, including lymphadenopathy, hepato- or splenomegaly, central nervous system (CNS) disease, testicular enlargement (is rare in adults), and/or cutaneous infiltration.

T-lineage ALL with a mediastinal mass can cause stridor and wheezing, pericardial effusions, and superior vena cava syndrome.

Diagnosis of acute lymphoblastic leukemia

Peripheral blood counts regularly show anemia and thrombocytopenia but may show leukopenia, a normal leukocyte count, or leukocytosis based largely on the number of circulating malignant cells.

As leukemic lymphoblasts lack specific morphologic and cytochemical features, the assessment of immunophenotype by flow cytometry and the identification of distinct cytogenetic-molecular abnormalities have become essential and are part of the World Health Organization Classification of Neoplastic Diseases of Hematopoietic and Lymphoid Tissues.

The ambiguous expression of myeloid markers (CD13, CD33, CD14, CD15, CDw65) with lymphoid markers is common, especially in ALL with translocations t(9;22), t(4;11), and t(12;21). Although the presence of myeloid-associated antigens lacks prognostic significance, it can be useful in distinguishing

leukemic cells from normal hematogones and in monitoring patients for minimal residual disease (MRD).

Cytogenetic-molecular abnormalities in acute lymphoblastic leukemia

The identification of cytogenetic and molecular abnormalities provides prognostic information, markers for therapy (e.g. *BCR-ABL1*) and targets for drug development, and pathobiologic insights.

The most frequent (15 to 30 %) and clinically relevant structural abnormality in adult ALL remains *translocation t(9;22)(q34;q11) (Philadelphia chromosome [Ph])* with the *BCR-ABL1* fusion. Patients with Ph-positive ALL are older, present with higher white blood cell and blast counts, and often share myeloid markers. Patients with Ph-positive ALL used to have a dismal prognosis with little chance of a cure other than stem cell transplantation (SCT).

Treatment options for acute lymphoblastic leukemia

The treatment paradigm for ALL generally includes remission induction, followed by early intensification and consolidation, CNS prophylaxis, and a prolonged maintenance phase. Algorithms were introduced of the European Working Group for Adult ALL.

Remission induction therapy

Vincristine, corticosteroids, anthracyclines (daunorubicin, idarubicin, Ara-C — cytarabine), and asparaginase remain the backbone of induction therapy.

Conventional treatments mainly mirror variations of drug combinations used in several induction protocols: 1) combinations of vincristine, steroids, and anthracyclines; 2) asparaginase and methotrexate; or 3) high-dose cytarabine.

Each of cyclophosphamide, vincristine, doxorubicin, and dexamethasone is used in conjunction with methotrexate/leucovorin and cytarabine for a total of eight cycles of therapy.

Early intensification and consolidation therapy

Cytarabine, methotrexate, cyclophosphamide, 6-mercaptopurine, and (less frequently) etoposide, tenoposide, or m-amsacrine are used mainly during early intensification.

CNS (central nervous system) prophylaxis

Central nervous system (CNS) prophylaxis is necessary to treat sanctuary sites that are shielded from systemic therapy by the blood-brain barrier. CNS prophylaxis is provided with intrathecal methotrexate and cytarabine.

Prolonged maintenance phase

Maintenance therapy with 6-mercaptopurine, methotrexate, vincristine, and prednisone continues for a total of two years.

Postremission therapy includes intensified consolidation and maintenance therapy or hematopoietic stem cell transplantation (HSCT).

Ph-positive ALL — it is a disease with a historically dismal prognosis in which HSCT has provided the only chance for a cure.

Whereas intensifying chemotherapy in older patients reduces the incidence of leukemia resistance, it also increases the incidence of death in complete remission from myelosuppression-related complications.

Table 33 — Management leukemia

Phase of leukemia	Lymphoblastic leukemia	Myelogenous leukemia
Induction	Vincristine i.v.	Daunorubicin i.v.
	Prednison oral	Cytarabine i.v.
	L-asparaginase i.v.	Etoposide i.v./oral
	Daunorubicin i.v.	Tioguanine oral
	Methotrexate (intrathecal)	
Consolidation	Daunorubicin i.v.	Cytarabine i.v.
	Cytarabine i.v.	Amsacrine i.v.
	Etoposide i.v./oral	Mitoxantrone i.v.
	Methotrexate i.v.	
Maintenance	Prednison oral	
	Vincristine i.v.	
	Mercaptopurine oral	
	Methotrexate oral	

EPIGENETIC THERAPY IN ACUTE LEUKEMIA

Because epigenetic mechanisms are critical to the pathogenesis of acute leukemias as a whole, there has been a significant interest in the clinical and translational investigation of agents that target the epigenome in these diseases.

Histone deacetylase inhibitors (HDIs)

HDIs have been associated with effects on a variety of genes including those involved with cell cycle regulation, apoptosis and angiogenesis. HDIs have been demonstrated to exert anti-tumor effects *in vitro* and *in vivo*, and are now used in clinical trials of acute leukemias. HDIs have also been demonstrated to induce differentiation and apoptosis of leukemia cell lines and primary leukemia blasts with the t(8;21).

DNA methyltransferase (DNMT) inhibitors

There are now several early phase trials utilizing DNMT inhibitors, either as single agents or in combination with other agents, that confirm the clinical activity of this group of drugs in AML, including elderly patients with AML who are unable to tolerate standard cytotoxic chemotherapy.

MiRNAs as Potential Therapeutic Targets and Tools

Because they can function as oncogenes or tumor suppressor genes in leukemogenesis, miRNAs also have the potential to serve as therapeutic targets or tools. miRNA-based cancer gene therapy offers the theoretical appeal of targeting multiple gene networks that are controlled by a single, aberrantly expressed miRNA.

AGRANULOCYTOSIS

Definition

Neutropenia may be defined as a neutrophil granulocyte count of less than 1,500/mm^3. Agranulocytosis may be defined as a neutrophil count of less than 500/mm^3.

Etiology, pathogenesis of agranulocytosis

The peripheral neutrophil count reflects the balance between several compartments. In the bone marrow, there is the mitotic pool, the maturation pool and the storage pool. Outside the bone marrow, there are circulating pools, the marginated pool adhering to the vascular endothelium and the tissue pool. Clinical trials to establish the number of neutrophils measure only the circulating pool in transit from the bone marrow to tissues. The movement is usually made in the direction of bone marrow-blood-tissue.

Out of a total of 1.2×10^9 granulocytes/kg, 20 % are precursors of the bone marrow pool, 75% are in the storage pool, 3 % in the marginated pool and 2% in the circulating pool. Under normal conditions, 1.5×10^9 granulocytes/kg are produced per day. Inflammatory processes increase this production. The granulocytes live for nine days in the bone marrow, three to six hours in blood and one to four days in tissues.

The biology of hematopoiesis is complex and is regulated by many cytokines. Some cytokines, such as G-CSF and GM-CSF (granulocyte colony-stimulating factor and granulocyte-monocyte colony-stimulating factor), together with complementary components, are able to increase the release of granulocytes from the bone marrow storage pool to circulation. This may result in a two to threefold increase in the number of leukocytes within four to five hours. The marginated pool, representing over half of the number of granulocytes in peripheral blood, may also be released to circulation. Epinephrine is one of the main elements in this process, which explains the neutrophilic response to stress and exercises. Many other mediators are involved, such as L-selectin, P-selectin, lactoferrin and acid isoferritins.

Neutropenia may occur because of decreased production of granulocytes, shift of granulocytes from the circulating compartment to the marginated or tissue pool, peripheral destruction, or a combination of these three mechanisms.

Many agents can cause neutropenia. The mechanism may directly involve the bone marrow, such as in the case of antineoplastic agents; be related to formation of antibodies and complements against hematopoietic precursors; and, more rarely,

involve peripheral destruction with neutrophil clearance. Agranulocytosis is a rare and serious disease often caused by drugs. Drug-induced neutropenia, either due to myelosuppression or antibody-mediated destruction, can be caused by almost any drug, including antibiotics, anticonvulsants, anti-inflammatories, antithyroid agents, diuretics, and phenothiazines.

Classification of neutropenias

Types of neutropenia

1. Congenital:
- severe infantile agranulocytosis (Kostmann's syndrome);
- Shwachman – Diamond – Oski syndrome;
- myelokathexis/neutropenia with tetraploid nuclei;
- cyclic neutropenia;
- Chediak – Higashi syndrome;
- reticular dysgenesis;
- dyskeratosis congenital.

2. Acquired:
- postinfectious neutropenia;
- drug-induced neutropenia;
- complement activation (haemodialysis, leukapheresis, acute respiratory distress syndrome);
- immune neutropenia;

✓ isoimmune neonatal neutropenia;
✓ alloimmune neutropenia (transfusion reaction);
✓ autoimmune neutropenia (primary);
✓ autoimmune neutropenia (secondary);
✓ autoimmune diseases;
✓ large granular lymphocyte;
✓ pure white cell aplasia;

- chronic idiopathic neutropenia;
- hypersplenism;
- nutritional deficiency (vitamin B12 or folate deficiency);
- diseases affecting the bone marrow;
- postchemotherapy;
- aplastic anaemia;
- Fanconi anaemia;
- myelodysplastic syndrome;
- acute and chronic leukaemia.

Diagnostic of agranulocytosis

The most common manifestations are infections such as tonsillitis, pharyngitis, stomatitis or pneumonia.

Serial blood counts are necessary to establish the diagnosis.

Bone marrow examination is indicated in cases of severe or persistent neutropenia, or when other hematological lineages are affected.

The diagnosis of agranulocytosis can be established by repeated neutrophil count below 500/mm^3 and a bone marrow finding of myeloid maturation arrest at the promyelocyte stage.

Cytogenetic studies should be performed prior to initiation of G-CSF therapy to detect monosomy 7 as a harbinger of MDS/AML. *ELA2* mutation analysis may be useful to establish the diagnosis, particularly if a positive antineutrophil antibody assay has falsely suggested a destructive process. In some forms of familial benign neutropenia, adequate bone marrow reserves of mature granulocytes can be demonstrated indirectly by a more than twofold increase in ANC on blood counts before and 6 hours after a single dose of prednisone 1–2 mg/kg. However, a positive result does not constitute an indication for steroid therapy, which would do more harm than good in this benign condition.

Treatment of agranulocytosis

Antibiotic therapy is used if patient has serious infection.

The goal is to keep the neutrophil count above 1000/μl, which can usually be done by giving G-CSF intravenously or subcutaneously at a dose of 5–10 μg/kg per day for 3 days, after which further doses can be given, depending on the response. The biological effect of G-CSF is not merely to stimulate proliferation and maturation of neutrophil progenitors or to release mature cells into the bloodstream.

Key Messages

- All types of acute leukemias are based upon their underlying cytogenetic or molecular genetic abnormalities. To identify lineage involvement some countries still rely more on cytochemistry, rather than on immunophenotyping (usually by flow cytometry), using myeloperoxidase (MPO) or Sudan black B (SBB) and nonspecific esterase (NSE) stains.
- Characteristic clinical symtomps of acute myeloid leukemia (AML) may be gum hypertrophy, skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia), lymphadenopathy, splenomegaly, hepatomegaly.
- In patient with suspected acute leukemia is required fewer than 5 % have no detectable leukemic cells in the blood; lack of intermediate form of leukocyte; a bone marrow or blood blast count of 20 % or more.
- The treatment for AML generally includes remission induction, followed by consolidation with either 1–4 cycles of chemotherapy or stem cell transplantation. Induction of remission consists of 7 days cytosine arabinoside (Ara-C) and 3 days an

anthracycline (daunorubicin or idarubicin) or anthracenedione (mitoxantrone) (referred to as 7+3 chemotherapy).

- The most frequent and clinically relevant structural abnormality in adult acute lymphoblastic leukemia (ALL) remains translocation t(9;22)(q34;q11) (Philadelphia chromosome [Ph]) with the BCR-ABL1 fusion.
- Vincristine, corticosteroids, anthracyclines (daunorubicin, idarubicin, Ara-C — cytarabine), and asparaginase remain the backbone of induction therapy in adult acute lymphoblastic leukemia. Postremission therapy includes hematopoietic stem cell transplantation
- Agranulocytosis is defined as a neutrophil count of less than 500/mm^3. Agranulocytosis is often caused by drugs, including antibiotics, anticonvulsants, anti-inflammatories, antithyroid agents, diuretics, and phenothiazines.
- G-CSF and GM-CSF (granulocyte colony-stimulating factor and granulocyte-monocyte colony-stimulating factor) may be given to patients with severe neutropenia.

CASE REPORT No.10

The patient, a previously healthy woman, presenting with acute renal failure and anemia, was admitted to the hospital.

Her serum creatinine (Scr) increased from 0.79–2.69 mg/dl over three days and hemoglobin decreased from 12.1–7.8 g/dl over 4 weeks. Mild compression fracture and degeneration of the lumbar vertebra and skull were observed in X-ray. The renal biopsy showed acute proximal tubular lesions induced by multiple calcium deposition. A bone marrow biopsy showed that primitive lymphocyte was up to 92.5 %. After making a diagnosis of acute lymphoblastic leukemia complicated with acute kidney injury induced by hypercalcemia, CRRT (continued renal replacement therapy) and chemotherapy were used immediately. Ten days later, the blood calcium gradually decreased from 3.88 to normal range (1.8 mmol/l) and the renal function was back to normal (Scr 0.93 mg/dl).

This unusual case shows that a patient who has a syndrome of acute renal failure, electrolyte disturbances, anemia, and elevated LDH needs bone marrow puncture to eliminate renal injury caused by acute lymphoblastic leukemia.

CASE REPORT No.11

A 53-year-old woman with a history of Graves disease presented with an absolute neutrophil count of zero, body temperature of 38.7 °C, and symptoms of an upper respiratory tract infection. She had been treated continuously with low doses of antithyroid drugs for the preceding 11 years — propylthiouracil (100 to 150 mg daily) from February 1998 until July 2003 and methimazole (5 to 30 mg daily) from July 2003 until her presentation with severe neutropenia in March 2009. The daily dose of methimazole had been stable at 15 mg for 1 year before the current presentation. A thorough hematologic evaluation, including bone marrow biopsy, did not reveal an alternative cause for the agranulocy-

tosis. After discontinuation of methimazole treatment and a short course of granulocyte colony-stimulating factor, she responded successfully with clinical improvement of her symptoms and resolved neutropenia.

POLYCYTHEMIA. MULTIPLE MYELOMA. LYMPHOMAS

Myeloproliferative neoplasia (MPNs) are clonal bone marrow stem cell disorders involving a multipotent haematopoietic stem cell, characterised by proliferation of one or more lineages of the myeloid, erythroid and megakaryocytic cell lines. This proliferation results in increased numbers of granulocytes, erythrocytes or platelets in the peripheral blood respectively.

According to the World Health Organization (WHO) 2008 criteria, MPNs are now divided in classical MPNs which carry the Philadelphia (Ph+) chromosome (chronic myeloid leukaemia) and classical MPNs which do not carry the Philadelphia (Ph-) chromosome, including essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF).

POLYCYTHEMIA VERA (PV) is a chronic myeloproliferative disorder characterized by an increased red blood cell mass (RCM), or erythrocytosis, which leads to hyperviscosity and an increased risk of thrombosis.

Epidemiology of polycythemia vera

The average age of patients diagnosed with PV is 60 years, although it can occur in persons in all age groups. PV occurs with a slight predominance in men. The incidence of PV is 2.3 per 100,000 persons per year. Untreated patients may survive for 6 to 18 months, whereas adequate treatment may extend life expectancy to more than 10 years.

Clinical features of polycythemia vera

Patients may present with complaints of pruritus after bathing, burning pains in the distal extremities (erythromelalgia), gastrointestinal disturbances, or nonspecific complaints such as weakness, headaches, or dizziness (Table 24).

Table 34 — Signs and symptoms of polycythemia vera

More common:
Hematocrit level > 52 percent (0.52) in white men, > 47 percent (0.47) in Afro-Americans and women;
Hemoglobin level > 18 g per dL (180 g per L) in white men, > 16 g per dL (160 g per L) in Afro-Americans and women);
Plethora;
Pruritus after bathing;
Splenomegaly;
Weight loss;
Weakness;
Sweating.
Less common:
Bruising/epistaxis;
Budd-Chiari syndrome;
Erythromelalgia;
Gout;
Hemorrhagic events;
Hepatomegaly;
Ischemic digits;
•Thrombotic events;
Transient neurologic complaints (headache, tinnitus, dizziness, blurred vision, paresthesias);
Atypical chest pain.

Other patients are diagnosed after an incidental finding of an elevated hemoglobin and/or hematocrit level on a complete blood count.

Diagnosis of polycythemia vera

PV should be suspected when hemoglobin and/or hematocrit levels are elevated (i.e., hemoglobin level greater than 18 g per dL [180 g per L] in white men and 16 g per dL [160 g per L] in Afro-Americans and women; hematocrit level greater than 52 percent (0.52) in white men and 47 percent (0.47) in Afro-Americans and women). PV also should be suspected in patients with portal venous thrombosis and splenomegaly with or without thrombocytosis and leukocytosis.

Criteria for polycythemia vera (PV)

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

- **major criteria:**

1) hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume;

2) presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation;

- **minor criteria:**

1) bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation;

2) serum erythropoietin level below the reference range for normal;

3) endogenous erythroid colony formation in vitro.

In making the diagnosis of PV, the physician must first exclude a secondary erythrocytosis. Once a secondary cause is ruled out, the diagnosis of PV is made using a combination of major and minor criteria defined by the Polycythemia Vera Study Group (PVSG).

Secondary causes of increased red cell mass (erythrocytosis)

- **Physiologically appropriate:**

✓ chronic pulmonary or cardiac disease;
✓ decreased 2,3-diphosphoglycerate;
✓ high oxygen affinity hemoglobinopathy;
✓ increased carboxyhemoglobin (in smokers) and methemoglobin;
✓ residence at high altitude.

- **Physiologically inappropriate:**

✓ adrenal cortical hypersecretion;
✓ hydronephrosis;
✓ tumors producing erythropoietin or anabolic steroids.

- **Relative (stress):**

- disorders associated with decreased plasma volume (e.g., diarrhea, emesis, renal diseases).

New diagnostic modalities to diagnose polycythemia vera:

- serum erythropoietin (EPO) levels are low or normal;
- bone marrow histopathology and karyotype;
- presence of endogenous erythroid colonies (EEC).

Treatment of polycythemia vera

The major goal of treatment is to prevent thrombotic events. Examples of thrombotic events include arterial and venous thrombosis, cerebrovascular accident, deep venous thrombosis, myocardial infarction, peripheral arterial occlusion, and pulmonary infarct. Of additional importance to the family physician is the symptomatic treatment of the bothersome microvascular sequelae, such as pruritus and distal extremity erythromelalgia.

Table 35 — Symptomatic treatments in polycythemia vera

Symptom	Treatment	Level of evidence
Pruritus	H_1 and H_2 blocking antihistamines (diphenhydramine, cyproheptadine, hydroxyzine, fexofenadine, terfenadine)	C
	Paroxetine	C
	Oatmeal or starch baths (in lukewarm water)	C
	Recombinant interferon alfa-2b	C
Erythromelalgia	Aspirin, 50 to 100 mg daily	C
	Myelosuppressive agents	C

PV produces microvascular sequelae, the symptoms of which, while not life threatening, can be bothersome to patients. Pruritus, particularly after bathing (aquagenic pruritus) is a common symptom and various treatment options are available. Symptoms such as transient neurologic disturbances may respond to low-dose aspirin therapy. Erythromelalgia is rare, occurring in approximately 3 percent of patients with PV. Low-dose aspirin typically is used, with myelosuppressive therapy reserved for those patients who do not respond.

Table 36 — Myelosuppressive agents for the treatment of polycythemia vera

Agent	Class	Common side effects	Uncommon side effects	Precautions
Hydroxyurea	Antimetabolite	Anemia, neutropenia, oral ulcers, skin ulcers, hyperpigmentation, nail changes	Leg ulcers, nausea, diarrhea, fever, elevated liver function test results	Renal disease
Recombinant interferon alfa-2b	Myelosuppressive	Influenza-like symptoms, fatigue, anorexia, weight loss, alopecia, headache, nausea, insomnia, body pain	Confusion, depression, autoimmunity, hyperlipidemia	Psychiatric disease, cardiovascular disease
Radioactive phosphorus (^{32}P)	Radiopharmaceutical	Anemia, thrombocytopenia, leukopenia, leukemia may develop after treatment	Diarrhea, fever, nausea, emesis	—
Busulfan	Alkylating agent	Pancytopenia, hyperpigmentation, ovarian suppression	Pulmonary fibrosis, leukemia, seizure, hepatic veno-occlusion	Seizure disorder

The use of myelosuppressive agents such as radioactive phosphorus (^{32}P), chlorambucil, busulfan, pipobroman, and hydroxyurea in conjunction with phlebotomy has been studied.

Chlorambucil, busulfan, and pipobroman, all alkylating agents, have fallen out of favor because of concerns about rates of iatrogenic leukemia. The myelosuppressive drugs such as ^{32}P had an initial advantage over phlebotomy alone regarding thrombosis rates during the first three years of treatment. However, this effect disappeared after three years, and rates of thrombosis thereafter were equivalent.

The nonalkylating myelosuppressive agent hydroxyurea is widely used in the treatment of PV, because it is less leukemogenic. Concern regarding the safety of long-term use of hydroxyurea has been noted.

Recombinant interferon alfa-2b reduces myeloproliferation and splenomegaly, and alleviates the symptom of pruritus.

The mainstay of treatment for PV is phlebotomy, which is aimed at reducing hyperviscosity by decreasing the venous hematocrit level to less than 45 percent (0.45) in white men and 42 percent (0.42) in blacks and women. A recent survey of physicians who were members of the American Society of Hematology showed that 69 percent use phlebotomy as first-line therapy for PV.

A number of new therapeutic agents have been developed. In addition to interferon alfa-2b therapy, agents that target platelet number (e.g., anagrelide), and platelet function (e.g., aspirin) are being investigated as potential therapies.

MULTIPLE MYELOMA (MM) is characterised by uncontrolled proliferation of plasma cells within the marrow (mature antibody producing B cells).

Epidemiology of multiple myeloma

The annual incidence of MM is ~4 per 100 000 inhabitants. It constitutes 1 % of malignant diseases and almost 15 % of all haematological malignancies. The incidence in blacks is twice that in whites. The peak of higher incidence is between 60 and 70 years of age. Only 15 % and 2 % of patients are younger than 50 and 40 years, respectively. It is evident that MM is an age-related disease but the ultimate cause is unknown.

It has been recently recognized that virtually all cases of MM are preceded by monoclonal gammopathy of undetermined significance (MGUS) (an asymptomatic condition with an M-protein concentration of < 3 g/dl and < 10 % bone marrow plasma cells (BMPCs). However, the cause of MGUS, the precise mechanisms that maintain the MGUS state and the mechanisms that trigger progression from MGUS to MM are still unknown.

Diagnosis of multiple myeloma

The features of end-organ damage are defined as follows: hypercalcemia, renal insufficiency, anemia, and/or bone disease manifested by osteolytic lesions or osteoporosis. Osteolytic lesions are most commonly found in the axial skeleton, skull, shoulder girdle, proximal humeri, ribs, and proximal femurs.

Additionally, patients may present with multiple extramedullary plasmacytomas at diverse sites, including the nasopharynx, larynx, and upper respiratory tract.

According to current diagnostic criteria, multiple myeloma is diagnosed in the presence of a monoclonal protein detectable in the blood or urine, light chain restricted plasma cells in the bone marrow, and myeloma-related end-organ damage.

Diagnosis is based on laboratory and radiographic findings and depends on 3 abnormal results:

- bone marrow containing more than 10 % plasma cells (normally no more than 4 % of the cells in the bone marrow are plasma cells);
- generalised osteopaenia and/or lytic bone deposits on plain film radiography;
- blood serum and/or urine containing an abnormal protein.

In about 75 % of all cases of multiple myeloma the paraprotein present (M protein) will correspond with one type of immunoglobulin. In about 60 % of cases an abnormal protein, known as Bence-Jones protein may also be found in the urine. Measuring the amount of paraprotein in the blood or urine is of value in the diagnosis of myeloma and in monitoring the response to treatment. A full list of criteria for diagnosis issued by the International Myeloma Working Group can be found elsewhere.

Staging of multiple myeloma

The clinical staging system devised by Durie and Salmon distinguishes different patient subgroups in terms of tumour mass and disease aggression and still often determines management. Patients with at least 2 lytic foci are classified in advanced disease subgroups and aggressive systemic treatment is usually indicated. Subsequently, the scientific advisers of the International Myeloma Foundation proposed a new staging system called Durie and Salmon PLUS based on the traditional Durie and Salmon system integrated by fluorodeoxyglucose (FDG)-positron emission tomography (PET) or magnetic resonance imaging (MRI) of the spine. This staging system has recently been replaced by the one based entirely on serum β2 microglobulin and serum albumin levels. However, this system cannot be used for therapeutic risk stratification and does not provide a good estimate of tumour burden.

Table 37 — Durie – Salmon PLUS staging system for symptomatic multiple myeloma

Stage	**Imaging findings (including MR and FDG PET)**
Stage I clinical criteria	< 5 focal spine lesions ± mild diffuse spine disease
Stage II clinical criteria	5–20 focal lesions ± moderate diffuse spine disease
Stage III clinical criteria	> 20 focal lesions ± severe diffuse spine disease

Table 38 — New international staging system of multiple myeloma

Stage I	Serum β2 microglobuli < 3.5 mg/l (average survival 62 months), serum albumin > 3.5 g/dl
Stage II	Not I or III[a] (average survival 44 months)
Stage III	Serum β2 microglobulin >5.5 mg/l (average survival 29 months)

[a]There are 2 categories for stage II: serum β2 microglobulin < 3.5 mg/l but serum albumin < 3.5 g/dl or serum β2 microglobulin 3.5–5.5 mg/l irrespective of the serum albumin level.

Radiology and cross-sectional imaging

Radiology plays an important role in staging, monitoring treatment response, detection of relapse and assessing complications.

Conventional radiography (skeletal survey)

Almost 80 % of patients with multiple myeloma have radiological evidence of skeletal involvement at diagnosis manifest in 4 different appearances: solitary deposit (plasmacytoma), diffuse skeletal involvement (myelomatosis), generalised osteopaenia and sclerosing myeloma. Views acquired should be posterior-anterior chest, anterior-posterior (AP) and lateral views of cervical spine (including an open mouth view), thoracic spine, lumbar spine, humeri and femora, AP and lateral views of skull and AP view of pelvis. Additional views of any symptomatic area should also be acquired. The most common sites include the vertebrae, ribs, skull and pelvis; involvement of the distal bones is unusual. In early stage disease the role of the plain radiograph is limited with myeloma deposits often not visualised.

Myeloma lesions are sharply defined as small lytic areas (average size 20 mm) of bone destruction with no reactive bone formation. At post mortem these lesions are due to nodular replacement of marrow and bone by plasma cells. Although myeloma arises within the medulla, disease progression may produce infiltration of the cortex, invasion of the periosteum and large extraosseous soft tissue masses. The pattern of destruction may be geographic, moth eaten or permeated. Pathological fractures are common.

Generalised osteopaenia may be the only bone manifestation of myeloma in up to 15 % of patients. At post mortem these patients show diffuse replacement of marrow with plasma cells but have less severe bone resorption compared with lytic deposits. Vertebral body collapse is the usual manifestation of this subtype which should not be confused with non-myelomatous osteoporosis that occurs in many older patients.

Radionuclide imaging

In multiple myeloma the osteoblastic response to bone destruction is negligible and the bone scan (using technetium-99m labelled diphosphonate) is often therefore normal or may show areas of decreased uptake (photopaenia). As a result its routine use is not recommended. However, skeletal scintigraphy may be helpful in evaluating areas not well visualised on plain film radiographs such as the ribs, sacrum, scapulae and sternum.

PET using the glucose analogue [F]FDG has the functional and morphological capacity to identify the extent and activity of multiple myeloma for staging and monitoring purposes. The ability of PET to perform whole-body examinations is a major advantage over conventional imaging techniques.

Cross-sectional imaging

A wide range of findings have been described in CT of myeloma. These include sharp, lytic foci of small and relatively homogeneous size with no sclerotic rim, diffuse faint osteolysis fan angioma-like appearance due to the presence of thickened vertical trabeculae and expansile deposits. CT can accurately depict the extent of associated soft tissue masses and can direct needle biopsy for histological diagnosis. Multidetector CT (MDCT) provides more detailed information on the risk of vertebral fractures compared with conventional radiography and MRI. In patients who are severely disabled or who are unable to undergo MRI examination this is a useful alternative imaging technique.

Magnetic resonance imaging

MRI has high sensitivity and its ability to directly visualise bone marrow. The role of MRI (and PET imaging) is acknowledged by their inclusion in the Durie-Salmon PLUS staging system.

The imaging patterns in multiple myeloma can be classified as normal, focal, diffuse and variegated.

Functional MRI

Analysis of enhancement patterns following intravenous contrast has enabled a functional component to MRI studies. Changes in microcirculation patterns using MRI circulation parameters (amplitude A, exchange rate constant k_{ep}) reflecting vascular volume and permeability allow them to be visualised.

Bone marrow angiogenesis is increased in multiple myeloma and has prognostic importance. Patients with newly diagnosed multiple myeloma have higher microvessel density at bone marrow biopsy than do control subjects.

Uncommon variants of myeloma

Extraosseous myeloma

Clinical manifestations of extraosseous myeloma are rare, occurring in less than 5 % of patients with multiple myeloma. Extraosseous myeloma deposits have been reported at multiple sites with the breast, lymph nodes and spleen most frequently involved. It may also occur in the epidural region causing cord compression. Extraosseous myeloma is more aggressive, occurs in a younger age group (average age 50 years) and is associated with worse survival than conventional myeloma.

Sclerotic myeloma

Primary sclerotic manifestations are rare and occur only in 3 % of patients. It may take the form of diffuse osteosclerosis, patchy sclerotic areas throughout the skeleton or very small numbers of focal sclerotic lesions.

Therapy of multiple myeloma

The International Myeloma Foundation and UK Myeloma Forum (with the support of the British Committee for Standards in Haematology) should be regarded as the preferred source of detailed guidance on treatment.

Treatment strategy is:

- adequate analgesia;
- rehydration;
- management of hypercalcaemia;
- management of renal impairment;
- treatment of infection.

The response categories (complete, near complete, partial, minimal, stable and progressive) are determined primarily by the level of M protein present. M protein is the level of monoclonal protein measured by protein electrophoresis in serum or 24-h urine.

Chemotherapy is indicated for management of symptomatic myeloma. High-dose therapy using melphalan and prednisolone can produce complete remission in up to 75 % of patients.

A newer class of drug, bortezomib (a proteasome inhibitor), is effective for treatment of relapsed refractory myeloma and is superior to dexamethasone in progression-free and overall survival. Other new agents entering clinical trials include conventional drugs (doxorubicin), cytokines (bevacizumab), biological agents (β-alanyl cystreamine disulfide) and agents such as arsenic trioxide.

The most serious morbidity in these patients arises from destructive bone deposits which cause severe intractable pain and pathological fractures often resulting in deformity and disability. A recently published retrospective review of outcome data from 67 myeloma patients treated with vertebroplasty showed significant improvement in rest pain, activity pain, narcotic use and mobility. The bisphosphonate group of drugs bind to bone at sites of active bone remodelling and can therefore inhibit myelomatous bone damage arresting the destructive cycle. These agents (used in conjunction with cytotoxic chemotherapy) have been found to be superior to chemotherapy alone in decreasing the incidence of pathological fractures and bone pain and may lead to prolonged survival.

Autologous transplantation has an established place in the treatment of myeloma. It is the treatment of choice for patients aged under 65 years and can be considered in older age groups (with good performance status) carrying a procedure-related mortality of less than 5 %.

Radiation therapy is reserved for patients with spinal cord compression secondary to vertebral body collapse associated with a soft tissue mass or pathological fractures elsewhere associated with a soft tissue mass. It can be very effective but permanently destroys normal bone marrow stem cells in the treatment field.

New generation of antimyeloma drugs: IMIDs, pomalidomide, proteasome inhibitors, PR-171, NPI-0052, histone deacetylase inhibitors, SAHA, LBH589,

depsipeptide, m-Tor inhibitors, rapamycin, temsirolimus, everolimus, perifosine, monoclonal antibodies, anti-IL-6-CNTO 328, anti-CS1.

Myeloma is generally considered incurable. It is a slowly progressing disease with long periods of relative inactivity. Relapse occurs in virtually all cases. On current treatment regimens patients younger than 70 years can expect a median survival of 5 years (depending on stage). Death results from bacterial infection, renal insufficiency and thromboembolism.

Supportive therapy of multiple myeloma

Patients receiving thalidomide or lenalidomide in combination with high-dose glucocorticoids and/or a cytotoxic agent should receive thromboprophylaxis, because of the increased incidence of thromboembolic events.

Peripheral neuropathy is the main adverse effect of regimens containing thalidomide and bortezomib and careful dose reductions and/or drug discontinuation should be considered. In patients receiving bortezomib herpes zoster prophylaxis with aciclovir is mandatory.

An intravenous bisphosphonate (pamidronate or zoledronic acid) can improve or prevent skeletal complications. It is recommended that bisphosphonates be administered for 1 or 2 years after the initiation of primary therapy and during treatment of the active phases of the disease. Their long-term use can result in ostenecrosis of the jaw.

In patients with a serum Hb of < 10 g/dl treatment with erythropoietin in order to maintain a serum Hb level of ~12 g/dl should be administered according to the Amerian Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) recommendations.

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by a lymphoplasmacytic infiltration in the bone marrow or lymphatic tissue and a monoclonal immunoglobulin M protein (IgM) in the serum.

Epidemiology of Waldenström macroglobulinemia

The overall incidence of Waldenström macroglobulinemia is approximately 5 cases per 1 million persons per year, and this disease accounts for approximately 1 % to 2 % of hematologic cancers. The incidence of Waldenström macroglobulinemia is highest among white people and is rare in other population groups. The median age at diagnosis varies between 63 and 68 years, and most patients (55–70 %) with a newly diagnosed disease are men.

In the WHO classification, WM is associated with lymphoplasmacytic lymphoma (LPL); it is a clinicopathologic entity characterized by a monoclonal expansion of predominantly small B-lymphocytes with variable plasmacytoid differentiation.

Clinical symptoms WM are hyperviscosity or neuropathy. Hyperviscosity syndrome is usually manifested by bleeding, blurring or loss of vision, dizziness, headache, and neurologic symptoms. Malignant infiltration of the CNS (Bing-Neel syndrome) is uncommon.

Diagnostic criteria for Waldenström macroglobulinemia

- IgM monoclonal gammopathy of any concentration;
- bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation;
- intertrabecular pattern of bone marrow infiltration;
- cell surface markers IgM^+, $CD5^{\pm}$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$ in any variations.

Treatment of Waldenström macroglobulinemia

The optimal management of patients with newly diagnosed Waldenström macroglobulinemia can be broadly divided into the following components:

1) confirmation of the diagnosis;

2) stratification of risk and determination of the need for treatment;

3) selection of the appropriate initial therapy;

4) choice of additional therapy if initial response is inadequate or the patient's disease progresses.

Initially, the standard therapy for patients with Waldenström macroglobulinemia was treatment with oral alkylating agents such as chlorambucil, melphalan, or cyclophosphamide.

Combinations of alkylating agents with or without vinca alkaloids or anthracyclines have been used. Alkylating agent–based regimens in combination with rituximab may be preferable as initial therapy for Waldenström macroglobulinemia.

DRC regimen consisting of 20 mg of *dexamethasone* administered intravenously followed by *rituximab* intravenously at 375 mg/m^2 on day 1 and *cyclophosphamide* orally at 100 mg/m^2 twice daily on days 1 to 5 every 21 days for 6 months in previously untreated patients with symptomatic Waldenström macroglobulinemia.

1. Patients with IgM MGUS or smoldering (asymptomatic) Waldenström macroglobulinemia and preserved hematologic function should be observed without initial therapy.

2. Patients with symptomatic Waldenström macroglobulinemia and modest hematologic compromise, IgM-related neuropathy requiring treatment, or hemolytic anemia unresponsive to corticosteroids should receive standard doses of rituximab alone without maintenance therapy.

3. Patients with Waldenström macroglobulinemia who have severe constitutional symptoms, profound hematologic compromise, bulky disease, or

hyperviscosity should be treated with the DRC regimen. Any patient with symptoms of hyperviscosity should first undergo plasmapheresis.

For patients who experience relapse after a response to initial therapy of more than 2 years' duration, the original therapy should be repeated. For patients who had an inadequate response to initial therapy or a response of less than 2 years' duration, an alternative agent or combination should be used. Autologous stem cell transplant should be considered in all eligible patients with relapsed disease.

LYMPHOMA

Some malignancies of lymphoid cells almost always present as leukemia (i.e. primary involvement of bone marrow and blood), while others almost always present as lymphomas (i.e. solid tumors of the immune system). However, other malignancies of lymphoid cells can present as either leukemia or lymphoma. In addition, the clinical pattern can change over the course of the illness. This change is more often seen in a patient who seems to have a lymphoma and then develops the manifestations of leukemia over the course of the illness.

The WHO classification takes into account morphologic, clinical, immunologic, and genetic information and attempts to divide non-Hodgkin's lymphomas and other lymphoid malignancies into clinical/pathologic entities that have clinical and therapeutic relevance (table 39). The relationship of lymphoid neoplasms to the immune system was being explored, and immunohistochemistry, flow cytometry, monoclonal antibodies, and molecular genetics have made lymphomas the most exciting area of pathology.

Table 39 — WHO classification of lymphoid malignancies

B Cell	T Cell	Hodgkin's Disease
Precursor B cell neoplasm	Precursor T cell neoplasm	Nodular lymphocyte-predominant Hodgkin's disease
Precursor B lymphoblastic leukemia/lymphoma (precursor B cell acute lymphoblastic leukemia)	**Precursor T lymphoblastic lymphoma/leukemia (precursor T cell acute lymphoblastic leukemia)**	
Mature (peripheral) B cell neoplasms	Mature (peripheral) T cell neoplasms	Classical Hodgkin's disease
B cell chronic lymphocytic leukemia/small lymphocytic lymphoma	T cell prolymphocytic leukemia	Nodular sclerosis Hodgkin's disease
B cell prolymphocytic leukemia	T cell granular lymphocytic leukemia	Lymphocyte-rich classic Hodgkin's disease
Lymphoplasmacytic lymphoma	Aggressive NK cell leukemia	Mixed-cellularity Hodgkin's disease
Splenic marginal zone B cell lymphoma (± villous lymphocytes)	Adult T cell lymphoma/ leukemia (HTLV-I+)	Lymphocyte-depletion Hodgkin's disease

B Cell	T Cell	Hodgkin's Disease
Hairy cell leukemia	Extranodal NK/T cell lymphoma, nasal type	
Plasma cell myeloma/ plasmacytoma	Enteropathy-type T cell lymphoma	
Extranodal marginal zone B cell lymphoma of MALT type	Hepatosplenic T cell lymphoma	
Mantle cell lymphoma	Subcutaneous panniculitis-like T cell lymphoma	
Follicular lymphoma	**Mycosis fungoides/Sézary syndrome**	
Nodal marginal zone B cell lymphoma (± monocytoid B cells)	Anaplastic large cell lymphoma, primary cutaneous type	
Diffuse large B cell lymphoma	**Peripheral T cell lymphoma, not otherwise specified (NOS)**	
Burkitt's lymphoma/ Burkitt cell leukemia	**Angioimmunoblastic T cell lymphoma**	
	Anaplastic large cell lymphoma, primary systemic type	

Note: HTLV — human T cell lymphotropic virus; MALT — mucosa-associated lymphoid tissue; NK — natural killer; WHO — World Health Organization.

About 90 % of all lymphomas are of B cell origin. Non-Hodgkin's lymphomas were separated from Hodgkin's disease by recognition of the Sternberg-Reed cells.

Etiology of lymphoma

A number of environmental factors have been implicated in the occurrence of non-Hodgkin's lymphoma, including infectious agents (table 40), chemical exposures, and medical treatments.

Table 40 — Infectious agents associated with the development of lymphoid malignancies

Infectious Agent	Lymphoid Malignancy
Epstein-Barr virus	Burkitt's lymphoma Post-organ transplant lymphoma Primary CNS diffuse large B cell lymphoma Hodgkin's disease Extranodal NK/T cell lymphoma, nasal type
HTLV-I	Adult T cell leukemia/lymphoma
HIV	Diffuse large B cell lymphoma Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma

Infectious Agent	Lymphoid Malignancy
	Multicentric Castleman's disease

Note: CNS — central nervous system; HTLV — human T cell lymphotropic virus; MALT — mucosa-associated lymphoid tissue; NK — natural killer.

In addition to infectious agents, a number of other diseases or exposures may predispose to developing lymphoma (table 41).

Table 41 — Diseases or exposures associated with increased risk of development of malignant lymphoma

Inherited immunodeficiency disease
Klinefelter's syndrome
Chédiak-Higashi syndrome
Ataxia telangiectasia syndrome
Wiscott-Aldrich syndrome
Common variable immunodeficiency disease
Acquired immunodeficiency diseases
Iatrogenic immunosuppression
HIV-1 infection
Acquired hypogammaglobulinemia
Autoimmune disease
Sjögren's syndrome
Celiac sprue
Rheumatoid arthritis and systemic lupus erythematosus
Chemical or drug exposures
Phenytoin
Dioxin, phenoxyherbicides
Radiation
Prior chemotherapy and radiation therapy

Malignancies of lymphoid cells are associated with recurring genetic abnormalities (table 42).

Table 42 — Cytogenetic translocation and associated oncogenes often seen in lymphoid malignancies

Disease	Cytogenetic abnormality	Oncogene
CLL/small lymphocytic lymphoma	t(14;15)(q32;q13)	—
MALT lymphoma	t(11;18)(q21;q21)	API2/MALT, BCL-10
Mantle cell lymphoma	t(11;14)(q13;q32)	BCL-1, IgH
Follicular lymphoma	t(14;18)(q32;q21)	BCL-2, IgH
Diffuse large cell lymphoma	t(3;-)(q27;-)[a] t(17;-)(p13;-)	BCL-6 p53
Burkitt's lymphoma, Burkitt's leukemia	t(8;-)(q24;-)[a]	C-MYC
CD30+ Anaplastic large cell lymphoma	t(2;5)(p23;q35)	ALK
Lymphoplasmacytoid lymphoma	t(9;14)(p13;q32)	PAX5, IgH

a-Numerous sites of translocation may be involved with these genes.

Note: CLL — chronic lymphoid leukemia; MALT — mucosa-associated lymphoid tissue; IgH — immunoglobulin heavy chain.

Hodgkin lymphoma (HL) — a B cell-derived cancer, is one of the most frequent lymphomas in the Western world, with an annual incidence of about 3 cases per 100 000 persons.

This lymphoid malignancy involves peripheral lymph nodes and can also affect organs such as liver, lung, and bone marrow. About 40 % of patients suffer from constitutional symptoms («B-symptoms»).

Based on differences in the histological picture and the phenotype of the tumor cells, HL is subclassified into nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted, and nodular lymphocyte-predominant HL (NLPHL). The first four subtypes are collectively called classical HL. The tumor cells of HL are very rare and usually account for only about 0.1–2 % of cells in the tissue.

In classical HL, the malignant cells are referred to as Hodgkin and Reed-Sternberg (HRS) cells, and in NLPHL they are lymphocyte-predominant (LP) cells. These malignant cells are large, and in classical HL one may distinguish mononucleated Hodgkin cells and bi- or multinucleated Reed-Sternberg cells.

The initial evaluation of a patient with Hodgkin's disease or non-Hodgkin's lymphoma is similar. In both situations, the determination of an accurate anatomic stage is an important part of the evaluation. The staging system is the Ann Arbor staging system originally developed for Hodgkin's disease (table 43).

Table 43 — The Ann Arbor staging system for Hodgkin's disease

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered «latera-lized» and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as «E» More than one extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of > 10 % of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the

Stage	Definition
	previous month Recurrent drenching night sweats during the previous month
C	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Most patients with Hodgkin's disease present with palpable lymphadenopathy that is nontender; in most patients, these lymph nodes are in the neck, supraclavicular area, and axilla. More than half the patients will have mediastinal adenopathy at diagnosis, and this is sometimes the initial manifestation. Subdiaphragmatic presentation of Hodgkin's disease is unusual and more common in older males.

One-third of patients present with fevers, night sweats, and/or weight loss - B symptoms in the Ann Arbor staging classification.

Hodgkin’s disease can present as a fever of unknown origin or with unusual manifestations: severe and unexplained itching, cutaneous disorders such as erythema nodosum and ichthyosiform atrophy, paraneoplastic cerebellar degeneration and other distant effects on the CNS, nephrotic syndrome, immune hemolytic anemia and thrombocytopenia, hypercalcemia, and pain in lymph nodes on alcohol ingestion.

Evaluation of patients with Hodgkin's disease will typically include:

• history and physical examination;
• complete blood count;
• erythrocyte sedimentation rate;
• chemistry studies reflecting major organ function;
• chest radiograph;
• CT scans of the chest, abdomen, and pelvis;
• bone marrow biopsy.

The diagnosis of Hodgkin’s disease is established by review of an adequate biopsy specimen. Most patients have nodular sclerosing Hodgkin's disease, with a minority of patients having mixed-cellularity Hodgkin's disease. Lymphocyte-predominant and lymphocyte-depleted Hodgkin’s disease are rare. Mixed-cellularity Hodgkin's disease or lymphocyte-depletion Hodgkin’s disease are seen more frequently in patients infected by HIV.

The differential diagnosis of a lymph node biopsy suspicious for Hodgkin’s disease includes inflammatory processes, mononucleosis, non-Hodgkin’s lymphoma, phenytoin-induced adenopathy, and nonlymphomatous malignancies.

Neither a positron emission tomography (PET) scan nor a gallium scan is absolutely necessary for primary staging, but one performed at the completion of therapy allows evaluation of persisting radiographic abnormalities, particularly the mediastinum.

In patients with non-Hodgkin’s lymphoma, the same evaluation described for patients with Hodgkin’s disease is usually carried out. In addition, serum levels of lactate dehydrogenase (LDH) and β2-microglobulin and serum protein electrophoresis are often included in the evaluation. Anatomic stage is assigned in the same manner as used for Hodgkin’s disease.

CT scans are routinely used in the evaluation of patients with all subtypes of non-Hodgkin’s lymphoma, but PET and gallium scans are much more useful in aggressive subtypes such as diffuse large B cell lymphoma than in more indolent subtypes such a follicular lymphoma or small lymphocytic lymphoma.

Table 44 — Staging evaluation for Non-Hodgkin’s lymphoma

Physical examination
Documentation of B symptoms
Laboratory evaluation
Complete blood counts
Liver function tests
Uric acid
Calcium
Serum protein electrophoresis
Serum β_2-microglobulin
Chest radiograph
CT scan of abdomen, pelvis, and usually chest
Bone marrow biopsy
Lumbar puncture in lymphoblastic, Burkitt's, and diffuse large B cell lymphoma with positive marrow biopsy
Gallium scan (SPECT) or PET scan in large cell lymphoma

Note: SPECT — single photon emission CT; PET — positron emission tomography.

Treatment of lymphoms

The standard therapy of lymphom is *CHOP* (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a comparable CHOP-like regimen that incorporates anthracyclines.

CHOP plus rituximab has shown better response rates than CHOP alone.

Patients with localized disease might be treated with combination chemotherapy followed by radiotherapy.

Aggressive combination chemotherapy regimens followed by autologous or allogeneic bone marrow transplantation are frequently offered to younger patients.

Patients with all stages of Hodgkin's disease are treated initially with chemotherapy. Patients with localized or good-prognosis disease receive a brief course of chemotherapy followed by radiotherapy to sites of node involvement.

The most popular chemotherapy regimens used in Hodgkin's disease include doxorubicin, bleomycin, vinblastine, and dacarbazine (*ABVD*) and mechlorethamine, vincristine, procarbazine, and prednisone (*MOPP*), or combinations of the drugs

in these two regimens. In Europe a high-dose regimen called *BEACOPP* incorporating alkylating agents has become popular and might have a better response rate in very high risk patients.

Patients who relapse after an effective chemotherapy regimen are usually not curable with subsequent chemotherapy administered at standard doses. Autologous bone marrow transplantation can cure half of patients who fail effective chemotherapy regimens.

Key Messages

- Polycythemia vera is a chronic myeloproliferative disorder characterized by increased red blood cell mass.
- Polycythemia vera should be suspected in patients with elevated hemoglobin or hematocrit levels, splenomegaly, or portal venous thrombosis. Patients may present with complaints of pruritus after bathing, burning pains in the distal extremities (erythromelalgia), gastrointestinal disturbances, or nonspecific complaints such as weakness, headaches, or dizziness.
- The mainstay of treatment for Polycythemia vera is phlebotomy, which is aimed at reducing hyperviscosity. The nonalkylating myelosuppressive agent hydroxyurea is widely used in the treatment of PV.
- Multiple myeloma is characterized by the neoplastic proliferation of a plasma cell clone that produces a monoclonal immunoglobulin. The diagnosis of Multiple myeloma requires the presence of an M-protein in serum and/or urine (protein Bence-Jones), increased bone marrow plasma cells (more than 10 %) and related organ or tissue impairment.
- The features of end-organ damage in multiple myeloma are defined as follows: hypercalcemia, renal insufficiency, anemia, and/or bone disease manifested by osteolytic lesions or osteoporosis, which are most commonly found in the axial skeleton, skull, shoulder girdle, proximal humeri, ribs, and proximal femurs.
- High-dose chemotherapy using melphalan and prednisolone can produce complete remission in up to 75 % of patients of multiple myeloma.
- In classical Hodgkin’s lymphom may distinguish mononucleated Hodgkin cells and bi- or multinucleated Reed-Sternberg cells. This lymphoid malignancy involves peripheral lymph nodes and can also affect organs such as liver, lung, and bone marrow.
- The standard therapy of lymphom is CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a comparable CHOP-like regimen that incorporates anthracyclines.
- The most popular chemotherapy regimens used in Hodgkin's disease include doxorubicin, bleomycin, vinblastine, and dacarbazine (*ABVD*) and mechlorethamine, vincristine, procarbazine, and prednisone (*MOPP*). In Europe a high-dose regimen called *BEACOPP* incorporating alkylating agents has become popular.

CASE REPORT No.12

The patient is a previously healthy 54-year-old Caucasian male who experienced severe left arm pain while lifting a heavy bag at an airport. Plain radiographs revealed a left humeral fracture. The patient was then placed in a sling for 4 weeks. During this time, he developed numbness and tingling of his right arm, prompting further imaging.

Magnetic resonance imaging (MRI) of his spine revealed a T1 destructive lesion with epidural extension from C7 to T1. Further laboratory evaluation revealed an immunoglobulin G (IgG) κ monoclonal protein of 1.6 g/dL on serum protein electrophoresis (SPEP), hemoglobin of 10 g/dL, creatinine of 0.99 mg/dL, albumin of 3.2 g/dL, calcium of 2.25 mmol/L, and a β_2-microglobulin of 2.7 mg/L. His serum free light chain (FLC) ratio was also abnormal at 32 (κ =61 mg/dL; λ = 1.88 mg/dL).

He later underwent a left humeral internal fixation. Biopsies obtained from both the T1 lesion and the left proximal humerus were consistent with a plasma cell neoplasm, as determined by CD138-positive kappa restricted plasma cells. His bone marrow biopsy demonstrated 5–10% CD138 plasma cells with aberrant expression of CD56. In addition, a fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomgraphy (^{18}F-FDG PET/CT) scan revealed additional bone marrow lesions at the left transverse process of T10, the body of L3, left posterior scapula, left inferior sacrum, and the left femur, not previously seen on a skeletal survey.

The constellation of imaging findings, pathology reports, and laboratory values led to the diagnosis of multiple myeloma with an International Staging System (ISS) score of 2. The patient received radiation therapy to the T1 lesion, left humerus, and left sacrum with improvement of his pain and neurologic symptoms. He is currently on systemic therapy with lenalidomide, bortezomib, and low dose dexamethasone.

CASE REPORT No.13

A 72 year old female non-smoker presented with shortness of breath (SOB), productive cough, and intermittent fever for 3 months. She was treated with azithromycin for community acquired pneumonia without improvement. The chest radiograph showed multiple areas of consolidation in the right lung. Initial laboratory findings revealed normal complete blood count and an unremarkable chemistry panel. A computed tomographic (CT) scan of the chest showed bilateral areas of consolidation with cavitation in the right upper lobe and diffusely distributed small nodules. No mediastinal or hilar adenopathy was noted. Antibiotic coverage was modified to intravenous doxycycline and cefotaxime. A bronchoscopy with transbronchial biopsy (TBB) was performed. The bronchoalveolar lavage (BAL) fluid revealed 240 white blood cells (WBC)/ml with 80 % lymphocytes, and the TBB showed lymphocytic inflammation. Cultures

from the BAL fluid subsequently grew group B *Streptococcus* and parainfluenza virus, which were believed to be responsible for the lymphocytic inflammation. She improved and was discharged home only to return to the hospital 2 weeks later with worsening SOB.

A repeat CT scan of the chest showed increasing consolidation in both lungs without adenopathy and a new right sided pleural effusion. Thoracentesis was performed which also revealed a lymphocytic exudate. Cultures and cytological examination of the pleural fluid were negative. The patient underwent a repeat bronchoscopy with TBB which again indicated lymphocytic infiltration. Gram stain and special stains for atypical organisms including mycobacteria, fungi, and *Pneumocystis carinii* were negative. The BAL fluid cultures were negative. Flow cytometry of the BAL fluid indicated that more than 80 % of the lymphocytes were T cells (CD3+) with a CD4 to CD8 ratio of 0.3.

At this point a clinical suspicion for a T cell lymphoproliferative disorder was raised. A positron emission tomographic (PET) scan was obtained in an attempt to identify the extent of the disease and an alternative site for tissue sampling. The PET scan revealed an isolated intense hypermetabolic uptake in the right middle and lower lung regions without other identifiable adenopathy. An open lung biopsy was recommended to the patient which she declined. A CT guided transthoracic needle biopsy of the right perihilar area was therefore undertaken which revealed CD3+, CD20−, and CD56+ cells indicating that the cells were of T and NK cell lineages. The new finding of CD56+ lymphocytes increased the likelihood of an atypical lymphoproliferative process involving NK cells, but it cannot be considered pathognomonic for a malignant process. T cell receptor (TCR) gene rearrangement was attempted but was unsuccessful due to paucity of viable cells. The patient's clinical condition deteriorated. She refused further evaluation and developed progressive respiratory failure and died.

Post mortem examination showed multiple masses in both lungs, hilar and mediastinal lymphadenopathy. On microscopic examination the lung tissues and enlarged lymph nodes contained uniform, round, small cells with a high nucleus to cytoplasm ratio supportive of a malignant process. The cells were angiocentric and angioinvasive. Special staining for leucocyte common antigen (LCA) was positive. The cells stained positive for CD3 and CD56 but negative for CD20. As CD3 is a T cell marker, CD56 is an NK cell marker, and CD20 is a B cell marker, the immunocytochemistry showed that the malignant lymphoma cells were of T and NK lineages. TCR gene rearrangement could not be done because of the lack of viable cells at post mortem examination. Based on the neoplastic morphology and the destructive nature of the CD3+ CD56+ lymphocytes, the pathological diagnosis was primary T cell lymphoma of the lung with the possibility of NK cell overlap.

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