УДК 618.14-006.6:611.018.21]:57.085.23

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INTERACTIONS OF VASCULAR CANCER-ASSOCIATED FIBROBLASTS WITH MICROCIRCULATORY PARAMETERS OF ENDOMETRIOID ENDOMETRIAL CARCINOMA AND VASCULOGENIC MIMICRY

Introduction

Approximately 142,000 women worldwide develop endometrial cancer each year, and approximately 42,000 women die from this cancer. The typical age curve of endometrial cancer incidence shows that most cases are diagnosed after menopause, with the highest incidence occurring in the seventh decade of life. The appearance of symptoms in the early stages explains why most women with endometrial cancer have early stage disease. With all stages combined, the overall 5-year survival rate is about 80% [1].

Tumor neoangiogenesis is essential for spread to adjacent and distant organs. The development of vascular network is responsible for the metastatic development of cancerous tissues. Tumor cells can invade in both lymphatic and blood vessels, sprouting into heterogeneous tissues, circulating intravascularly and developing appropriate metastasis risks [2, 3]

It is known that tumors need sufficient blood supply for growth. When the diameter of a solid tumor is greater than 2 mm, the formation of new blood vessels is necessary to maintain sufficient blood supply; otherwise, tumors will undergo necrosis due to ischemia and hypoxia. Tumour angiogenesis is the proliferation of blood vessels penetrating the cancerous growth for the supply of nutrients and oxygen. Angiogenesis is a requisite not only for continued tumour growth, but also for metastasis. VM is a model of microcirculation which is different from classic form of tumor angiogenesis as it does not depend on endothelial cells and can provide sufficient blood supply for tumor growth [4]. Moreover, VM is associated with high tumor grade, invasion, metastasis, and poor prognosis in patients with malignant tumors. CD105 and CD146 are angiogenic biomarkers that are useful to determine the microvessel density within a tumor [5]. Angiogenesis is an important step for tumor growth and progression in almost all malignancies [3]. Numerous investigations have focused on the pathological role, clinical significance, and predictive value of angiogenesis in patients with cancer. In human cancer tissues, the most representative method for (semi-)quantification of angiogenesis is the measurement of microvessel density using endothelium-specific markers.

Goal

The aim of this research is to identify features of the clinical course; there may be different relationships between different signaling molecules of angiogenesis and microcirculatory vascular network of endometrial cancer in the tumor microenvironment.

Material and methods of research

This single-centre, retrospective, observational study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and approved by the Ethical Committee of Gomel State Medical University (protocol No. 1 of 26.01.2024).

The study was carried out by examining specimen from a total of 189 patients divided into two groups, one with progression of cancer (n = 40) and the other, without progression

of cancer(n=149). Correlations were revealed between the number of vasculogenic mimicry vessels and CD105+, CD146+ vessels, tumor expression of Fibulin-1, BMP4 and clinico-morphological parameters (grade and clinical stage). When testing statistical hypotheses in this study, p was taken as 0.05. Then, the obtained results were analyzed using a non-parametric Spearman and other tests in GraphPad Prism 8.

The results of the research and their discussion

In the group with unfavorable outcome there were weak correlations between the degree of differentiation and Fibulin-1 expression (r=0.34 CI 0.18-0.48; p<0.001), which may be associated with multiple functions of extracellular matrix protein Fibulin-1 and stromal changes at different degrees of tumor differentiation. Weak direct correlations between the grade and CD146+ vessels surrounded by vascular cancer-associated fibroblasts (r=0.45 CI 0.31-0.57; p<0.001) were also determined, which may be a manifestation of specific relationships between the extracellular matrix and vascular tumor-associated fibroblasts.

Moderately expressed direct correlations were observed between CD105+-positive microcirculatory vessels and clinical stage according to FIGO (r=0.63 CI 0.52-0.72; p<0.001), these correlations may be related to activation (appearance of CD105 expression) of endothelium in the process of cancer progression. Inverse moderately expressed correlations between vasculogenic mimicry and BMP-4 expression may be related to modulating effect of BMP-4 on tumor stroma.

Weakly significant direct correlations were observed between CD105+-positive microcirculatory vessels and vasculogenic mimicry (r=0.43 CI 0.13-0.65; p=0.006), and between Fibulin-1 expression and CD146+ vessels surrounded by vascular cancer-associated fibroblasts (r=0.35 CI 0.03-0.63; p=0.026). Moderately significant direct correlations were observed between CD105+-positive microcirculatory vessels and CD146+ vessels surrounded by vascular cancer-associated fibroblasts (r=0.64 CI 0.42-0.80; p<0.001), as well as Fibulin-1 expression. A significant direct correlation was observed between CD146+ vessels surrounded by vascular cancer-associated fibroblasts and vasculogenic mimicry (r=0.64 CI 0.42-0.80; p<0.001). The above-mentioned correlations may indicate remodeling of the vascular component of the tumor microenvironment leading to changes in the biological potential of endometrial endometrioid carcinoma in cases of unfavorable disease outcome.

Conclusion

In cases of unfavorable outcome, changes in the micro vessels of endometrial endometrioid carcinoma with the appearance of a strong correlation between vascular cancer-associated fibroblasts and vasculogenic mimicry were determined.

LITERATURE

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