RECURRENT OVARIAN CANCER: MECHANISMS OF DEVELOPMENT OF PERITONEAL MALIGNANT ASCITES.

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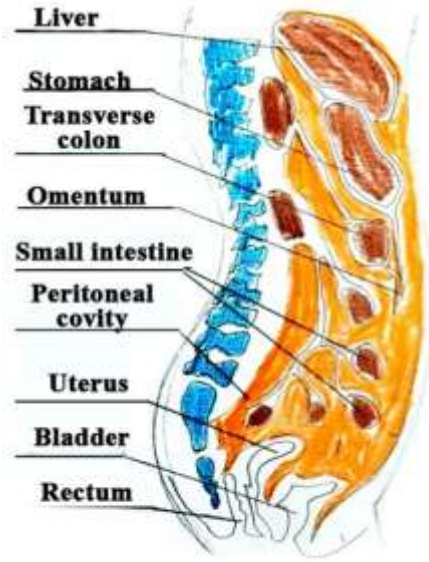
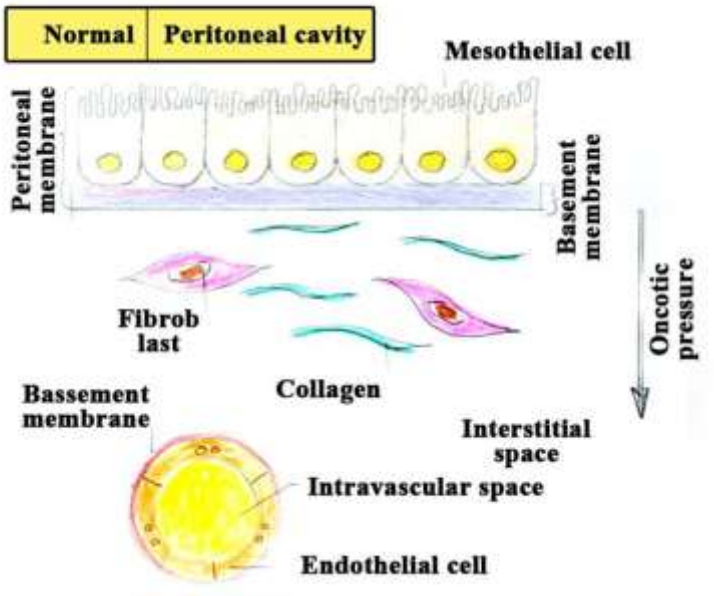
Abstract: Diagnostic approach and treatment of recurrent ovarian cancer has many unresolved issues, the relevance of which is associated with late diagnosis and ultimately low treatment effectiveness and high mortality rates. The clinical manifestation of recurrent ovarian cancer is variable even within a morphologically similar group of patients due to the high degree of heterogeneity of the tumor. Questions remain about how wide the range of molecular genetic markers is and what is the correlation between their level and the effectiveness of treatment for ovarian cancer recurrence. One of the most promising ways to obtain information about the nature of the recurrence of the tumor process in ovarian cancer (OC) can be the study of ascitic fluid (AF).

Keywords: ovarian cancer, recurrence, malignant ascites, intraperitonal metastasis

A common primary localization of cancer accompanied by ascites is OC, representing up to 38 % of cases of ascites associated with malignant tumors in women [1]. The peritoneal membrane covers the visceral organs, as well as the abdominal and pelvic regions and consists of 5 layers (Fig. 1).





First layer consists of endothelial cells that line the intravascular space of capillaries. These cells have out-cellular (extracellular) glycocalyx and a fixed anion charge that inhibits the passage of large plasma protein molecules (such as albumin) through the capillary walls. Intracellular pores provide intracellular transport through this layer. Second layer is the basal membrane. Third layer is interstitial space, it contains fibroblasts, collagen and hyaluronic acid, blocks the diffusion of macromolecules to the submesothelial basement membrane (this is layer 4). Fifth layer consists of mesothelial cells. By binding with dense compounds and secreting surface glycosaminoglycans into the abdominal space, mesothelial cells provide an effective anti-adhesive surface and a protective barrier against physical damage. Under physiological conditions, the difference in oncotic pressure across the peritoneal membrane (high in the endothelial layer and low in the mesothelial layer) restricts capillary filtration of fluid and prevents edema that occurs due to reabsorption of water into the capillaries from the interstitial space [2]

The mechanism of formation of ascites in peritoneal carcinomatosis is complex and is largely due to a combination of increased fluid flow into the abdominal cavity and a decrease in its outflow [3].

In patients with abdominal tumors, the cross-sectional area of the microvessels lining the abdominal cavity increases, and this leads to increased fluid filtration. In addition, malignant ascites have a high concentration of protein, which is secondary to increased capillary permeability [4].

In ovarian cancer, the occurrence of malignant ascites is due to increased fluid production and difficulty on evacuation through the lymphatic system. It is assumed that this occurs through several pathophysiological mechanisms: a high protein content in the ascitic fluid implies an increase in the permeability of the vessel wall. Vascular endothelial growth factor (VEGF) and inflammatory cytokines increase vascular permeability in the tumor of the microcirculatory bed and peritoneal surfaces. Along with malignant cells and mesothelial cells, VEGF also produces excess peritoneal fluid. Micrometastases disrupt normal lymphatic channels and lead to decreased lymphatic resorption [18]. This causes a decrease in the volume of circulating blood, which activates the renin-angiotensin-aldosterone pathway, leading to sodium and fluid retention. In addition, portal hypertension secondary to liver metastases can lead to further aggravation of ascites [5].

Overexpression of VEGF by the tumor provides increased capillary permeability. Growing in size, the tumor initiates a pro-inflammatory response in the abdominal cavity, which contributes to the attachment of cancer cells to the surface of the peritoneum. Disturbance of ascitic fluid reabsorption is also caused by mechanical compression of the lymphatic flow pathways, increased lymph viscosity, and retrograde lymph flow. The presence of mechanisms, including impaired lymphatic drainage, changes in vascular permeability and a decrease in intravascular oncotic pressure following hypoalbuminemia, may be aggravated by changes in sodium concentration and fluid retention due to comorbid liver disease or chronic heart failure [6]

Factors such as internal diaphragmatic pressure, the mobility of the internal organs that determine the specificity of the accumulation ascitic fluid (AF) simultaneously with the development of cancer.

In clinical practice, classification of ascites is convinient, proposed by the International Ascetic Club which distinguishes three degrees: The first degree – the fluid in the abdominal cavity is determined only by ultrasound, the second degree is manifested by a symmetrical increase of belly, the third degree-strained ascites [7].

According to the amount of fluid in the abdominal cavity, you can conduct another gradation of the degree of ascites: First degree-no more than 3 L, second degree-more than 3 L (4-6 L), third degree - from 10 to 20 L of AF [8]. Ultrasound can detect subclinical ascites or small-volume ascites (SVA) [9]

During echography, the presence of free fluid is an auxiliary factor for detecting metastases in the abdominal cavity, since it makes an anechogenic acoustic window, against which metastatic foci that are similar in echogenicity to the surrounding organs and tissues are clearly differentiated [10, 11]

Visualization of metastases in the major omentum against the background of ascites playing the role of an acoustic window also does not cause difficulties. With a minimum number of AF or its absence, special difficulties are associated with the detection of metastases up to 8-15 mm in the abdominal cavity [12].

Protein analysis allows differentiating between transudate and exudate: transudate protein content is less than 25 g / l (cirrhosis of the liver, hypoalbuminemia), exudate – more than 30 g/l (malignization, inflammation). It is common for differential diagnosis to calculate the "serum albumin/ascitic fluid albumin" gradient (SA/AFA), which allows us to assume the cause of ascites, as well as predict the risk of infection of the AF. An important indicator is the cellular composition of ascitic fluid and cytological research aimed at identifying atypic cells [13].

Peritoneal dissemination is one of the most adverse factor of malignant tumor progression. However, the prognostic factors associated with malignant ascites are not well understood. The presence of ascites in combination with edema, low levels of protein in the blood serum, and metastatic liver damage reflects the most unfavorable course of the malignant process [14].

In the model of tumor behavior, ascites are given more significance during its dissemination. Tumor cells in ascites are present either as individual cells, or, more often, as aggregates of cells, designated as " spheroids» [15]: the existing scenario of intraperitoneal dissemination events in OC is a direct spread of the tumor distally from the primary focus, involving a number of processes, including cell proliferation, epithelial‑mesenchymal transition (EMT), which results in migration of tumor cells, and, in contrast, mesenchymal‑epithelial transition (MET), which provides colonization of tumor cells with the formation of peritoneal implants. Spontaneous and iatrogenic ruptures of the tumor capsule are also important for peritoneal dissemination of OC. The formation of "spheroids", represented by complexes of tumor cells that have acquired the ability to migrate by EMT and the ability to re-differentiate and restore tissue structure by MET, eventually leads to the formation of implants on the surface of neighboring organs, and at later stages, metastases to distant organs [16]

In this case, malignant ascites represents a unique microenvironment of the tumor, providing a physical substrate for the accumulation of cellular and cell-free components. Based on morphological analysis, it is shown that two different types of cells can be distinguished from ascites: mesenchymal and epithelial cells. Both cell populations resemble stem/progenitor cells with high regenerative / proliferative potential, expressing typical markers of tumor stem cells, including CD44high, CD24low, and AC133+. These cells are also characterized by high levels of expression of genes associated with oncogenesis and metastasis, including BMP2, BMP4, TGF-β, EGFR, and integrin α2β1 [17].

The cellular component of ascites can also be subdivided into" resident cells", such as tumor and tumor‑associated fibroblasts, or stromal cells and" non-resident cells", such as

immune and mesenchymal stem cells. Each cell population has a specific role and is linked to each other by signaling via "internal" soluble factors [18].

The cell-free component of ascites provides interaction of the cellular component through soluble factors (cytokines, proteins, metabolites) and extracellular vesicles (microvesicles and exosomes) [19].

Taking into account late diagnosis, the frequency of peritoneal dissemination of primary OC reaches high values and is comparable to the proportion of diagnosis of advanced forms, which, in fact, affects the effectiveness of surgical and chemotherapeutic treatment. However, the presence of ascites in OC is not so fatal in terms of survival rates, in comparison with ascitic forms of carcinomas of other locations [20], this is probably due to differences in the molecular genetic characteristics and sensitivity spectra to chemotherapeutic agents of tumors of different locations. In any case, the presence of ascites in OC may indicate the presence of malignant cells in the abdominal cavity and is a serious prognostic sig. The degree of severity of carcinomatosis in OC is directly related to the late stages of the disease and the production of ascitic fluid [21].

The relationship between OC stages and the amount of ascitic fluid was confirmed [22]. According to Elizabeth Smile, the detection rate of malignant ascites in OC stage Ia is 29 %, and in stage Ic reaches 59 % [23]. Age, stage, degree of tumor differentiation, and cytology are important predictive markers of early OC and high risk of relapse [24]

Attention is drawn to the lack of a single concept of the mechanisms of development of malignant ascites in patients with ovarian cancer, which allows us to adequately assess the possible results of treatment for each patient. There are no reliable prognostic factors that have the necessary sensitivity and specificity when choosing treatment tactics, which makes it necessary to continue research in this direction. The use of classical prognostic factors, such as the size of the tumor, the stage of the disease, and the degree of differentiation of tumor cells, is based on statistical data and does not always allow predicting the course of ovarian cancer in a specific patient.

Conclusion. In this regard, research on this scientific problem requires further studies of the features of surgical treatment tactics depending on changes in the immuno-morphological features of the tumor process, consequently, it is planned to study the features of the immunohistochemical status of patients with malignant ascites on recurrent ovarian cancer, cytogenetic study, search for informative markers, as well as specific diagnostic tests to determine and evaluate the adequacy of the use of a particular treatment tactic.

Conducting research in this direction will allow us to determine the features of the development of malignant ascites in ovarian cancer recurrence, as well as solve the questions of the most specific IHC markers for the selection and determination of further treatment tactics for this category of patients. All together makes it advisable to conduct a new study to solve the problem.

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