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A 56-year-old Patient with Recurrent Refractory Ascites and Abdominal Pain

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Aim: to demonstrate the differential diagnosis of recurrent ascites in a patient without chronic liver disease.
Key points. The patient came to the clinic with complaints of an increase in the volume of the abdomen, shortness of breath during moderate physical activity, weight loss, and severe general weakness. The increase in the volume of the abdomen, accompanied by pain, had been occurring periodically for 12 years without any obvious cause. This condition was assessed as a manifestation of portal hypertension. Laboratory signs of systemic inflammation were noted, while liver function remained intact. Laparoscopy and therapeutic and diagnostic laparocentesis were performed repeatedly — the ascitic fluid was an exudate (serum-ascitic albumin gradient — <1.1 g/dL), an abundance of deformed mesothelial cells was also noted. According to the instrumental examinations (ultrasound, computed tomography with intravenous contrast), signs of liver cirrhosis and portal hypertension were not reliably detected. However, thickening of the parietal peritoneum and infiltration of the peritoneal sheets were noteworthy. This clinical picture was suspicious for mesothelioma/peritoneal carcinomatosis. To clarify the nature of the changes, positron emission tomography with computed tomography (PET-CT) was performed. The results showed increased accumulation of the radiopharmaceutical agent along the peritoneum. The patient underwent therapeutic and diagnostic laparoscopy with biopsy. Based on the biopsy and immunohistochemical study, a diagnosis of epithelioid mesothelioma of the peritoneum was made. Polychemotherapy was started, five courses have been completed to date. The patient's condition has improved, ascites has completely regressed, and abdominal pain practically does not bother him. In dynamics, PET-CT shows significant regression of mesothelioma foci and its metabolic activity.
Conclusion. The presence of ascites in a patient without signs of independent liver disease and portal hypertension serves as a reason for conducting an extensive differential diagnosis with a step-by-step examination to exclude malignant lesions of the peritoneum, in particular its primary tumor — mesothelioma.
Keywords: ascites, peritoneal mesothelioma, serum-ascitic albumin gradient
Conflict of interest: the authors declare no conflict of interest.

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Пациент 56 лет с рецидивирующим резистентным асцитом и болью в животе

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Цель: продемонстрировать дифференциальный диагноз рецидивирующего асцита у пациента без хронического заболевания печени.
Основные положения. Пациент обратился в клинику с жалобами на увеличение живота в объеме, одышку при умеренных физических нагрузках, снижение веса, выраженную общую слабость. Увеличение живота в объеме, сопровождающееся болью, периодически возникало на протяжении 12 лет без очевидной причины. Данное состояние расценивалось как проявление портальной гипертензии. Лабораторно отмечались признаки системного воспаления, функция печени при этом оставалась сохранной. Неоднократно проводилась лапароскопия и лечебно-диагностический лапароцентез — асцитическая жидкость представляла собой экссудат (сывороточно-асцитический альбуминовый градиент — <1,1 г/дл), также отмечалось обилие деформированных клеток мезотелия. По данным инструментальных исследований (ультразвуковое исследование, компьютерная томография с внутривенным контрастированием), признаков цирроза печени и портальной

гипертензии достоверно не выявлено, однако обращало на себя внимание утолщение париетальной брюшины и инфильтрация перитонеальных листков. Данная клиническая картина была подозрительна в отношении мезотелиомы/карциноматоза брюшины. Для уточнения характера изменений проведена позитронно-эмиссионная томография с компьютерной томографией (ПЭТ-КТ), результаты показали повышенное накопление радиофармпрепарата по ходу брюшины. Пациенту была проведена лечебно-диагностическая лапароскопия с биопсией. По данным биопсии и иммуногистохимического исследования был выставлен диагноз эпителиоидной мезотелиомы брюшины. Была начата полихимиотерапия, в настоящий момент проведено пять курсов. Состояние пациента улучшилось, асцит полностью регрессировал, боль в животе практически не беспокоит. В динамике по ПЭТ-КТ отмечается значительный регресс очагов мезотелиомы и ее метаболической активности.

Заключение. Наличие асцита у пациента без признаков самостоятельного заболевания печени и портальной гипертензии служит поводом для проведения обширного дифференциального диагноза с пошаговым обследованием для исключения злокачественного поражения брюшины, в частности ее первичной опухоли — мезотелиомы.

Ключевые слова: асцит, мезотелиома брюшины, сывороточно-асцитический альбуминовый градиент

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Clinical case

Patient M., 56-years-old male, was admitted to the V.Kh. Vasilenko Clinic of Propaedeutics of Internal Medicine, Gastroenterology and Hepatology (Sechenov University) in September 2023 with complaints of an increase in abdominal volume, abdominal pain, shortness of breath with moderate physical activity (for example, when climbing stairs to the third floor), weight loss of 8 kg in 6 months, and severe general weakness. The main complaint was an increase in abdominal volume.

It is known from the medical history that pain in the left iliac region and an increase in the volume of the abdomen first appeared in December 2011. The man was hospitalized at his place of residence, where an ultrasound examination of the abdominal organs revealed ascites. Diagnostic laparoscopy was performed: an inflammatory infiltrate in the left iliac region with fibrin deposits and hyperemia of the peritoneum were detected. The etiology of the changes was not specified, but against the background of antibacterial therapy with ceftriaxone and metronidazole, ascites regressed without the use of diuretics.

Subsequently, the patient was repeatedly hospitalized in different medical institutions due to recurrent ascites and abdominal pain. Three therapeutic and diagnostic laparoscopies were performed — no data in favor of liver cirrhosis or tumor process were found. Organic diseases of the large and small intestine, tuberculosis (according to PCR, tuberculin tests), parasitoses (helminthiasis, echinococcosis, schistosomiasis and others), vascular diseases, as well as ANCA-associated vasculitis were excluded. In laboratory tests, transient increases in systemic inflammation markers were noted — C-reactive protein (10 times), ESR, fibrinogen. Each time, a decrease in ascites and abdominal pain was observed after antibacterial therapy (fluoroquinolones, metronidazole, cephalosporins).

During an objective examination upon admission to the clinic in September 2023, attention was drawn to tense ascites, as well as pulsation and swelling of the jugular veins at the height of inspiration (positive Kussmaul's sign).

Among the possible causes of recurrent ascites, the diagnosis of cardiac liver fibrosis in congestive heart failure was considered: given the clinical picture, the patient's NT-proBNP level was examined (100 pg/mL; normal — up to 125 pg/mL), and echocardiography was performed (no signs of systolic and diastolic dysfunction were detected).

The differential diagnosis also included congenital liver fibrosis. Given the patient's advanced age and liver biopsy data, this diagnosis could be excluded.

Vascular diseases of the liver, such as Budd — Chiari syndrome, sinusoidopathy and portosinusoidal vascular disease, should also have been assumed. However, previously performed ultrasound of the abdominal organs, computed tomography (CT) did not reveal narrowing of the portal vein and hepatic vessels due to compression or thrombosis. Histological examination of the liver also did not reveal narrowing of the liver vessels.

Taking into account the clinical picture, multiple relapses of ascites, and the exclusion of cardiac and hepatic causes of the disease, the most likely cause of the patient's poor condition seemed to be peritoneal damage caused by carcinomatosis or, in fact, peritoneal mesothelioma.

According to laboratory tests, signs of systemic inflammation were noted: in the clinical blood test — a relative increase in the number of neutrophils (up to 77 %; the norm is up to 72 %),

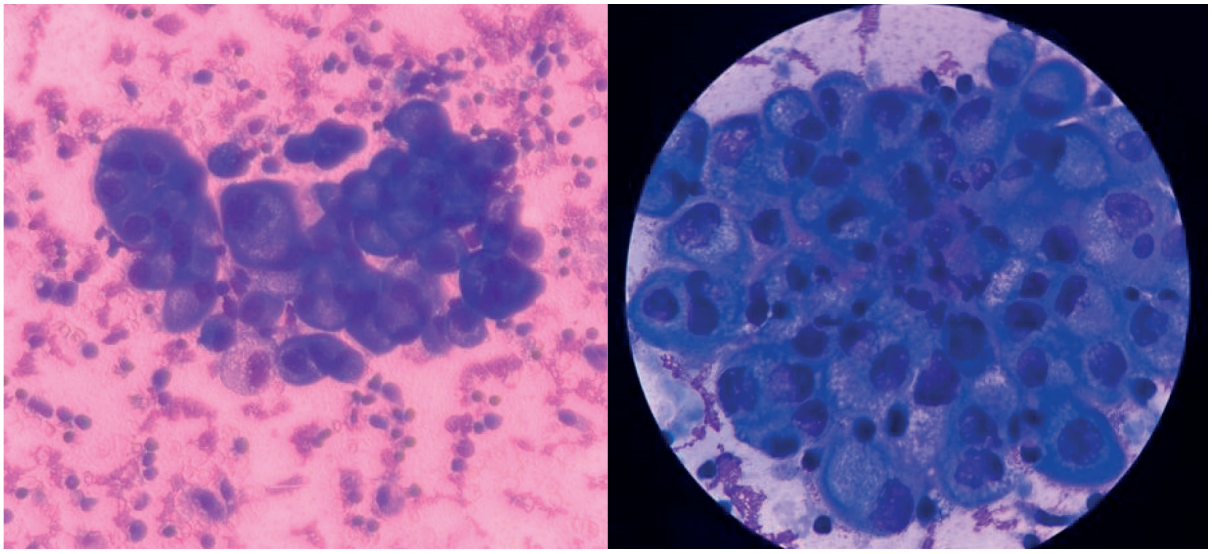

Figure 1. Cytological examination of ascitic fluid: multinucleated deformed mesothelial cells located in clusters

Рисунок 1. Цитологическое исследование асцитической жидкости: многоядерные деформированные клетки мезотелия, расположенные скоплениями

thrombocytosis (up to 533 thousand per μL); according to the biochemical analysis, liver and kidney function was not impaired, the level of C-reactive protein (96.8 mg/L; norm — 0–5 mg/L) and fibrinogen (9.52 g/L; norm — 1.0–4.0 g/L) was increased. Tumor markers (alpha-fetoprotein, CA 125, CA 19-9, CEA) were also studied — all parameters were within the normal range.

The patient underwent therapeutic and diagnostic laparocentesis: 5.5 liters of turbid yellow ascitic fluid were obtained. Laboratory count of formed elements showed leukocytes 7 thousand/mL; taking into account the calculation of the serum-ascitic albumin gradient, the obtained fluid should be assessed as inflammatory — exudate (serum-ascitic albumin gradient < 1.1 g/dL).

Cytological examination of the obtained fluid revealed a large amount of cellular material, which was predominantly represented by deformed, multinucleated mesothelial cells, suspicious of peritoneal tumors (Fig. 1).

Given the level of serum-ascitic albumin gradient and a high number of neutrophils in 1 μL of ascitic fluid, infected ascites was suspected, and the patient was prescribed empirical antibiotic therapy with broad-spectrum drugs — sulbactam and cefoperazone.

According to CT data, extensive tumor infiltrate, tumor implants in the falciform and round ligaments of the liver were noted, along the liver capsule — up to 55 mm; the pelvic peritoneum was diffusely thickened (up to 6 mm). In all parts of the abdominal cavity — a large amount of free fluid. In the V segment of the liver, a single focus up to 5 mm was

Figure 2. Multispiral computed tomography of the abdominal organs with intravenous contrast: growth of the infiltrate (mesothelioma? carcinomatosis?) is noted along the falciform, round ligament of the liver, along the liver capsule (circled with a line)

Рисунок 2. Мультиспиральная компьютерная томография органов брюшной полости с внутривенным контрастированием: отмечается разрастание инфильтрата (мезотелиома? карциноматоз?) по серповидной, круглой связке печени, по капсуле печени (обведено линией)

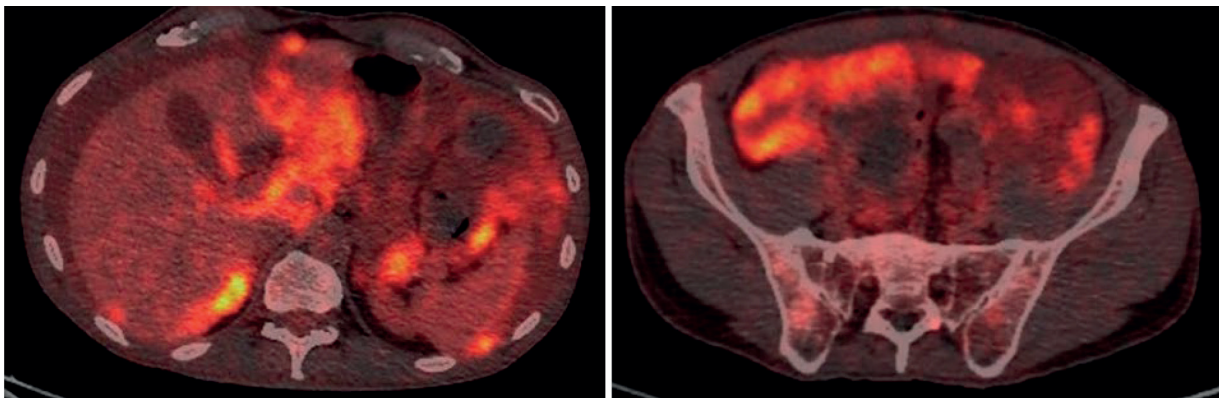

Figure 3. Positron emission tomography with computed tomography: a picture of increased metabolic activity of a radiopharmaceutical of neoplastic genesis along the peritoneum

Рисунок 3. Позитронно-эмиссионная томография с компьютерной томографией: картина повышенной метаболической активности радиофармпрепарата неопластического генеза по ходу брюшины

noted, suspicious for hepatocellular cancer or metastases (Fig. 2).

Given the positive Kussmaul sign, the patient underwent echocardiography to exclude causes for increased pressure in the right heart chambers: ejection fraction was more than 60 %, pulmonary hypertension, tricuspid valve damage, and dilation of the right heart chambers were excluded.

Additionally, to search for a possible primary tumor focus, esophagogastroduodenoscopy and colonoscopy were performed — no organic pathology was detected.

Positron emission tomography with computed tomography (PET-CT) with ^{18}F-fluorodeoxyglucose was chosen as an additional visualization method to clarify the diagnosis. The results presented PET/CT picture of increased metabolic activity of the radiopharmaceutical along the peritoneum (including along the capsule, in the porta hepatis area, in the falciform and round ligaments of the liver, in the lesser omentum, in the gastrosplenic ligament) of neoplastic genesis without an established primary lesion. Also, diffuse accumulation of the radiopharmaceutical was noticed in the area of the intrathoracic lymph nodes (Fig. 3).

Based on the data obtained, the patient was referred for diagnostic laparoscopy for peritoneal biopsy. During intraoperative visual examination of the abdominal organs, massive carcinomatosis was detected throughout the parietal peritoneum, including the small pelvis, liver, spleen, greater omentum, and mesentery of the colon. A biopsy of the greater omentum, a section of the parietal peritoneum in the plica centralis area, and the peritoneum of the umbilical region was performed.

According to the results of histological examination of the peritoneal tumor, the material revealed tumor growth consisting of cells with a large bubble-shaped nucleus and a single centrally located well-defined nucleolus. Tumor cells formed chains and solid layers, in places the connection of cells was lost, in places a tendency to form pseudo-glandular structures was detected. Pronounced edema of the stroma with mucus in places, scattered leukocyte infiltration was noted (Fig. 4).

Immunohistochemical examination revealed diffuse positive membranous-cytoplasmic staining of tumor cells in reaction with AE1/AE3 MSC, diffuse positive nuclear staining of tumor cells in reaction with WT1, and diffuse positive nuclear and cytoplasmic staining of tumor cells in reaction with calretinin. The tumor immunophenotype corresponded to mesothelioma (Fig. 5).

Taking into account the data of the morphological and immunohistochemical study, a clinical diagnosis was formulated:

Primary disease: Epithelioid mesothelioma of the peritoneum cT4N2M1, condition after diagnostic laparoscopy, biopsy on October 12, 2023.

Complications: Infected ascites.

The patient was prescribed 4–6 courses of polychemotherapy using platinum preparations (carboplatin) at a standard dose, the folic acid antagonist pemetrexed 500 mg/m^2, and the monoclonal antibody preparation — a neutralizer of the biological activity of the human vascular endothelial growth factor bevacizumab at a dose of 15 mg/kg.

At present, the patient has undergone five courses of polychemotherapy, there has been no

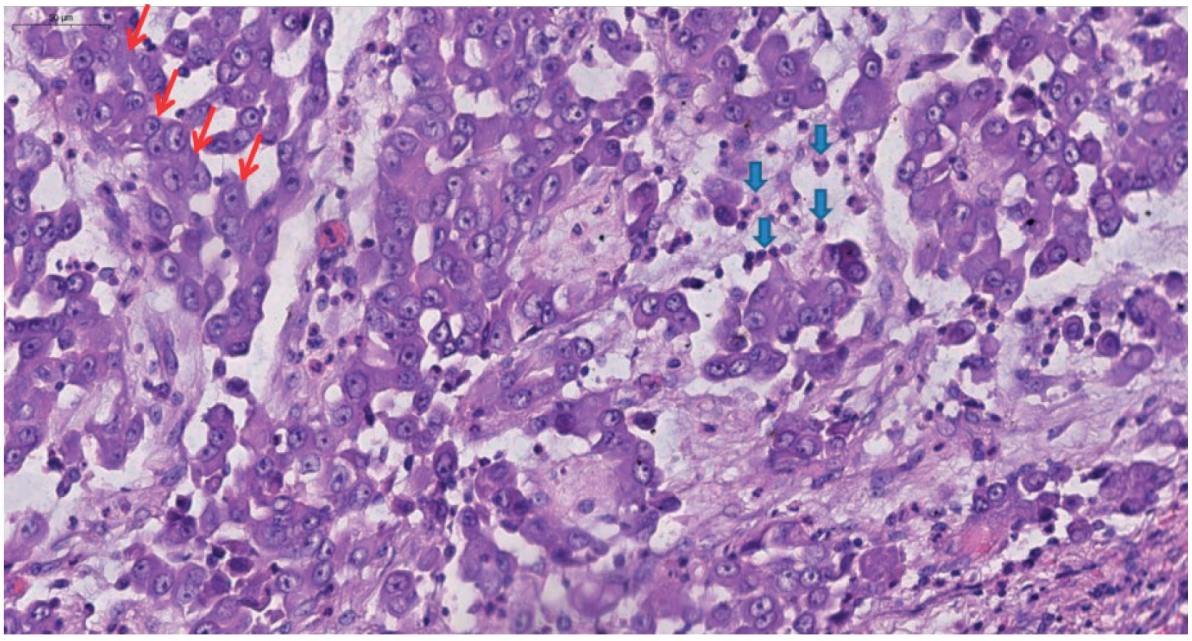

Figure 4. Large tumor cells with a large round nucleus with a single large basophilic nucleolus and abundant eosinophilic cytoplasm without clear boundaries occupy the entire area of the section with the formation of chains and focal clusters (individual cells are marked with red arrows); stroma with edema, contains a few leukocytes (shown with blue arrows); hematoxylin and eosin staining, ×250

Рисунок 4. Крупные опухолевые клетки с крупным округлым ядром с одиночным крупным базофильным ядрышком и обильной эозинофильной цитоплазмой без четких границ занимают всю площадь среза с формированием цепочек и очаговых скоплений (отдельные клетки отмечены красными стрелками); строма с отеком, содержит немногочисленные лейкоциты (показаны синими стрелками); окраска гематоксилином и эозином, ×250

side effects. Clinically, there is a pronounced regression of ascites, no abdominal pain. Also, in May 2024, the patient underwent a control PET-CT: the severity of the peritoneal lesion has significantly decreased, the level of metabolic activity has decreased, there is no accumulation of the radiopharmaceutical in the intrathoracic lymph nodes.

Discussion

Mesothelioma is a malignant tumor that develops through the transformation of mesothelial cells lining the body's natural cavities. The tumor primarily affects the pleura, peritoneum, pericardium, and testicular membranes.

In the overall structure of malignant neoplasm incidence, this pathology accounts for 0.16 %, of which peritoneal mesothelioma accounts for about 20 % [1–7].

Considering the slow growth of the tumor, the first symptoms that allow one to suspect it appear already in the late stage of the disease.

Peritoneal mesothelioma is characterized by an increase in the volume of the abdomen due to ascites and abdominal pain without clear localization, a tendency to constipation. Metastases of peritoneal mesothelioma can be detected in regional lymph nodes, lungs, liver (usually along the capsule), intestines, ovaries, brain, bone marrow, pericardium and myocardium [8].

In the described case, differential diagnosis was carried out around the causes of ascites in liver and non-liver diseases.

The most common cause of fluid accumulation in the abdominal cavity is liver cirrhosis (85 % of all cases), which is accompanied by portal hypertension syndrome. Ascites should be stopped by prescribing a salt-free diet, conservative diuretic therapy, or performing laparocentesis [9]. Along with cirrhosis, diseases such as alcoholic hepatitis, sinusoidal obstruction syndrome, Budd — Chiari syndrome, congenital liver fibrosis, and thrombosis in the portal vein system can lead to the formation of ascites. As a rule, ascitic fluid is a transudate, contains a small amount of protein, and the serum-ascitic albumin gradient is > 1.1 g/dL.

Also included in the differential diagnosis are tumor diseases: hepatocellular cancer, metastatic liver damage.

Among the tumors, one can also note malignant lesions of the peritoneum — carcinomatosis

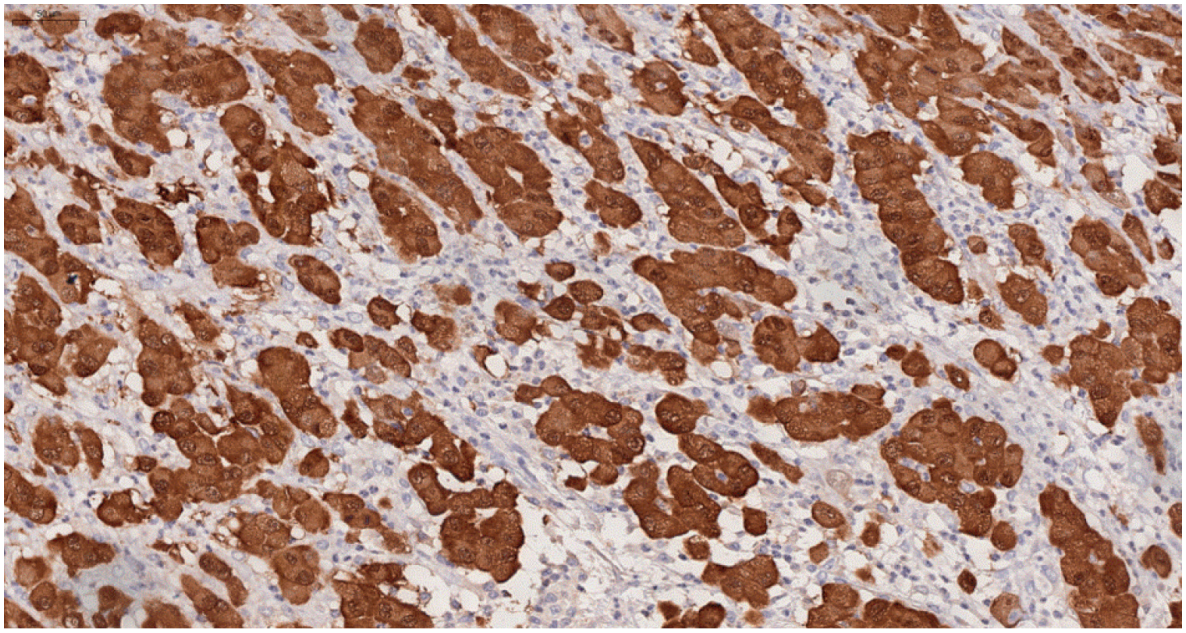

Figure 5. Immunohistochemical study with antibodies to calretinin (Clone Cal6 Leica Bond RTU), ×250; tumor cells with diffuse positive cytoplasmic and nuclear staining (stained brown)

Рисунок 5. Иммуногистохимическое исследование с антителами к кальретинину (Clone Cal6 Leica Bond RTU), ×250; клетки опухоли с диффузным позитивным цитоплазматическим и ядерным окрашиванием (окрашены в коричневый цвет)

and peritoneal mesothelioma. These conditions are quite rare; they lead to malignant ascites with constant relapses of fluid accumulation in the abdominal cavity.

In this case, diseases of the peritoneum also include infectious peritonitis due to tuberculosis, fungal diseases, and chlamydia.

Among other causes of ascites formation, one should also remember about renal and cardiovascular insufficiency. The circle of differential diseases includes diseases that are accompanied by nephrotic syndrome, due to massive loss of protein (including albumin) because of the damage to the glomerular filter. Among cardiovascular diseases in ascites, it is necessary to exclude constrictive pericarditis, long-term sluggish congestive chronic cardiovascular insufficiency.

Rare causes of fluid accumulation in the abdominal cavity include chylous ascites (due to disruption of the lymphatic system), pancreatic ascites (due to accumulation of pancreatic juice due to damage to the pancreatic duct), and hypothyroidism.

In the described clinical case, considering the complaints, clinical picture and clarifying clinical and laboratory studies, the patient was given the correct diagnosis. Despite the malignant nature of the peritoneal tumor, the patient had a slow progression of the disease, and when antitumor therapy was prescribed, a rapid and good clinical effect was observed. The patient's prognosis is determined by the response to the prescribed antitumor treatment and the possibility of performing surgical intervention (peritoneal resection) in the future.

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