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CHAPTER 224

Malignant Ascites

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KEY POINTS

- Ascites is an accumulation of peritoneal cavity fluids in the peritoneal cavity that can be malignant (secondary to peritoneal carcinomatosis) or nonmalignant (hepatic cirrhosis).
- Ascites is generally associated with peritoneal metastasis and obstruction of subphrenic lymphatic vessels by tumor infiltration.
- Most patients with malignancy-related ascites have a poor prognosis, and the principle of minimal disturbance should guide management, especially for those patients who are bedbound and whose life expectancy is short.
- Clinical guidelines on paracentesis related to malignancy have been published with particular attention to the need for preliminary ultrasound examination, intravenous fluid provision, and drainage time.
- Ascites secondary to chemotherapy-sensitive tumors may benefit from *chemotherapy*: a reasonable response can be expected in patients with ovarian cancer, whereas a poorer response is obtained in patients treated for gastric or colon cancer.

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Normally, a healthy person has approximately 50 mL of transudate in the peritoneal cavity. Normal fluid turnover is 4 to 5 L/hour. In malignant ascites, the fluid turnover is higher than in healthy persons.

PREVALENCE AND ETIOLOGY

Ascites is accumulation of peritoneal cavity fluid that can be malignant (from peritoneal carcinomatosis) or nonmalignant (hepatic cirrhosis). Although nonmalignant conditions are more common (80% to 90%), ascites secondary to peritoneal carcinomatosis or hepatic failure resulting from metastatic disease is not uncommon (10% to 20%). Ascites occurs in 6% of patients with cancer and has a poor prognosis. Many tumors cause ascites, most frequently ovarian cancers (up to 50%), cancer of unknown origin, and gastrointestinal cancers (stomach, colon, pancreas). Ascites may be the presenting feature of cancer, of recurrence, or of metastasis. It often signifies end-stage disease. Cardiac failure, liver failure, and renal failure are common causes of nonmalignant ascites. Some tumors cause hepatic failure from massive metastatic liver involvement.

CLINICAL SYMPTOMS AND DIAGNOSIS

The most common symptoms include abdominal discomfort, difficulty in bending forward, inability to sit upright, and dyspnea. Symptoms related to gastric compression and increased intra-abdominal pressure include heartburn, nausea, vomiting, and anorexia. Peripheral edema of the legs and genitalia is common. Patients are usually symptomatic only when the abdominal wall is tense.

The diagnosis in patients with cancer is usually clinical, and investigations are usually unnecessary. The diagnosis is based on abdominal distention, shifting dullness (detects ≈ 500 mL), and ultrasound examination (detects 100 mL). 70 Ultrasound may determine whether it is loculated by tumor adhesions. A computed tomography scan should be done to exclude bowel obstruction (use caution with oral contrast media).

PATHOGENESIS

Ascites is generally associated with peritoneal metastasis and obstruction of subphrenic lymphatic vessels by tumor infiltration. Other mechanisms include increased peritoneal permeability, increased sodium retention by hyperaldosteronism (possibly secondary to extracellular blood volume), liver metastasis leading to hypoalbuminemia, and venous obstruction (e.g., portal vein obstruction, inferior vena caval obstruction). Immune modulators, vascular permeability factors, and metalloproteinases may contribute to the condition and offer the opportunity for new therapies for malignant ascites.[1]

PROGNOSIS

When caused by cancer, ascites is associated with advanced disease. These patients have a median life expectancy of 8 to 20 weeks. In ovarian cancer, in which ascites can present early, survival of 20 to 50 weeks may occur.[2]

MANAGEMENT AND TREATMENT

Malignant ascites occurs in association with various neoplasms. It is a frequent cause of morbidity and presents significant problems for no clear evidence-based management guidelines exist. A recent guideline for symptomatic 71 malignant ascites is based on a systematic literature review. Although paracentesis, diuretics, and shunting are commonly used, the evidence is weak. Available data show good, although temporary effects of paracentesis on symptoms. Fluid withdrawal, speed, and concurrent intravenous hydration are insufficiently studied. Peritoneovenous (P-V) shunts can control malignant ascites, but they have to be balanced by the potential risks. The data about diuretics for malignant ascites are controversial. Diuretics should be considered in all patients, but each case should be evaluated individually.[3] 72

Treatment consists most effectively of removing and, if possible, preventing the return of ascites. Most people with malignancy-related ascites have a poor prognosis, and the principle of minimal disturbance should guide management, especially for patients who are bedbound and whose life expectancy is short. Although no treatment is entirely satisfactory, paracentesis generally remains the most practical effective measure.[4]

Symptomatic Treatment

Analgesia may be all that is required to overcome any discomfort or mild dyspnea, although active patients usually want the fluid drained. No randomized trials of *diuretics* in malignant ascites have been conducted. Diuretics may be effective in approximately one third of patients with malignant disease, and efficacy may be determined by plasma renin-aldosterone concentrations. Diuretics reduce malignant ascites over 2 to 3 weeks, provided high doses are used. These drugs are effective because sodium retention contributes to the ascites. Spironolactone is the key to success because it antagonizes aldosterone. Start with spironolactone, 100 to 200 mg, in addition 73 to the loop diuretic furosemide, 40 mg (or bumetanide, 1 mg) daily; if patients tolerates these doses, double the dose after 1 week. Monitor treatment by daily abdominal girth measurement, and reduce the dose once the patient is at risk of dehydration or impaired renal function (biochemical control). Reduce diuretics to the lowest dose that controls ascites. An intravenous furosemide infusion (100 mg over 24 hours) may be an alternative to paracen- 74 tesis for rapid relief of tense ascites. Patients with liver cirrhosis or liver metastasis respond better to diuretics.

Many studies on *paracentesis* in liver disease have been conducted. Removal of several liters of fluid is associated with the risk of hypotension, hypovolemia, disturbance of electrolytes, and renal impairment. Intravenous albumin reduces these risks.[5] Paracentesis is a simple, effective, and safe mechanical procedure that can provide good and immediate symptomatic relief. For an ambulatory patient, the fluid can be removed rapidly, up to 5 liters over 1 to 2 hours. In weaker patients, the fluid should be drained more slowly because hypotension can occur. The fluid reaccumulates over 1 to 3 weeks unless diuretics are used. Symptomatic benefit is maximal after the first few liters have been removed. Limit the volume of paracentesis to 75 Q1

4 to 6 liters maximum if renal or hepatic failure is present, if the serum albumin is less than 30 g/ L, or if the sodium concentration is lower than 125 mmol/L.[6]

Clinical guidelines on paracentesis related to malignancy have been published, with particular attention to the need for preliminary ultrasound examination, intravenous fluid provision, and drainage time.[4] The procedure is simple. Patients should have an empty bladder and should be in a semirecumbent position. The puncture site needs to be in an area without scars, tumor masses, distended bowel, bladder, liver, or inferior epigastric vessels. Stay 10 cm from the midline to avoid blood vessels. Use an aseptic technique, anesthetize the skin locally with 0.5% bupivacaine (Marcaine), and infiltrate the puncture site down to the peritoneum. Insert a large (14- to 16-gauge) intravenous cannula in the left or right iliac fossa. If fluid dribbles out of the puncture site after paracentesis, a colostomy bag can collect the fluid, which usually stops within a few hours. Warn the patient that this may occur, 76 and reassure the patient that this leakage is harmless. If no fluid is obtained, ascites may be pocketed, so try one further puncture site or use ultrasound guidance. This procedure is contraindicated in patients with intestinal obstruction or multiple adhesions. Other contraindications include local or systemic infection and coagulopathy (platelets <40.000 or international normalized ratio >1.4).

When ascites requires frequent drainage, a permanent drainage tube may be considered. A Pleurx (Denver Biomedical) catheter with a one-way valve can be palliative; it offers convenient home drainage, and the patient does not have to wait until symptoms arise. This catheter is well tolerated, and the infection rate is low. The drain lines can be kept in place for months, until the patient's death. One study compared the safety and efficacy of two percu- 77 taneous drainage methods over 41 months: large-volume paracentesis and Pleurx catheter placement. The Pleurx catheter provided effective palliation with complications similar to those of large-volume paracentesis, and it precluded the need for frequent hospital trips for repeated percutaneous drainage.[7]

A *P-V shunt* is indicated for a relatively fit patient who is troubled by recurrent ascites. This situation arises most commonly in patients with cancer of the breast or ovary. A shunt can provide excellent control, and it should be considered early. A P-V shunt also prevents repeated paracenteses and maintains normal serum albumin concentrations. A Denver shunt or a LeVeen shunt is commonly used. It is a multiply perforated catheter that joins a one-way valve and a reservoir that can be pumped. The shunt is easily inserted using a short general anesthetic regimen. The lower abdominal end of the shunt is inserted into the hypochondrium, and the venous end is led subcutaneously to a neck incision and is inserted into the internal jugular vein. The fluid is drained into the superior vena cava; fluid flows through the shunt on inspiration. Patients should pump the reservoir to keep fluid flowing. A P-V shunt is not indicated if the fluid is blood stained or turbid (because the shunt will quickly block) or if it is loculated. Unfortunately, 30% of shunts occlude within 3 to 6 months and need to be replaced. Complications include fever, infection, shunt blockage, and coagulopathy. Facilitating hematogenous tumor spread is a theoretical disadvantage: postmortem studies showed that despite the infusion of viable malignant cells into the venous circulation, no clinically significant metastases occurred. In nonmalignant ascites, a shunt can give good palliation; blockage occurs sooner in patients with malignant disease.[8]

Chylous ascites is a rare complication of abdominal radiation or para-aortic lymph node dissection in gynecological malignant diseases. Chylous ascites in adults is a significant management problem, with high mortality from cachexia and infection or after surgical attempts at correction. A systemic approach with subcutaneous octreotide and a fat-free diet may have good results in adults. This noninvasive approach avoids surgery. Intraperitoneal corticosteroids can also be considered: 600 mg methylprednisolone at once, at the end of the 78 tap.[9]

Etiological Treatment

Patients with ascites who have chemotherapy-sensitive tumors may benefit from *chemotherapy*: a reasonable response can be expected in ovarian cancer, although 79 responses are less dramatic in gastric or colon cancer. Intraperitoneal chemotherapy is logical because a significantly higher drug concentration is achieved than after intravenous administration and because patients with malignant ascites have reduced peritoneal drug clearance rates. In ovarian cancer, intraperitoneal chemotherapy (cisplatin, paclitaxel) may confer a survival advantage.[10] Various other agents have been used, including bleomycin, 5-flurouracil, and thiotepa, but results with these agents are disappointing, and the use of these drugs is rarely indicated.

Laparoscopic intraperitoneal hyperthermic chemotherapy for malignant ascites is carried out at 42°C for 90 minutes, with 1.5% dextrose solution as a carrier. In one 80 study, chemotherapeutic agents included cisplatin and doxorubicin or mitomycin, depending on the primary tumor. The drains were left in situ after surgery and were removed when perfusate drainage ceased. Ascites was controlled in all the treated cases in this study. This method benefited patients who were not candidates for 81 cytoreductive surgery.[11]

Clinical experience with antiangiogenic agents such as the matrix metalloproteinase inhibitors and the vascular endothelial growth factor antagonists suggests that these agents may have a role in the management of malignant ascites.[12] Targeted antibody therapy *(radioimmunotherapy)* is a novel approach that has achieved useful palliation in some cases. Monoclonal antibodies to tumor antigens (detected on malignant cells in the fluid) are coupled to a radioisotope (iodine 131) and are given intraperitoneally to deliver radiation directly to tumor-bearing areas.

Cytoreductive surgery (omentectomy, debulking) should be offered to some patients with peritoneal carcinomatosis because this approach may provide significant palliation.[13] Combined treatment with intraperitoneal hyperthermic chemotherapy has shown promising survival in patients with pseudomyxoma peritonei and peritoneal dissemination of digestive tract cancer.[14]

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CHAPTER 225

Pleural and Pericardial Effusions

Susan B. LeGrand

KEY POINTS

- Management of malignant pleural effusion (MPE) and malignant pericardial effusion (MPCE) must be based on the individual goals of care, co-morbidity, underlying malignant disease, and potential for chemotherapy response.
- If fluid removal does not improve the symptom (e.g., dyspnea, cough), then definitive treatment of the effusion has no role.
- In MPE, repeated thoracentesis is discouraged because loculations may limit therapeutic options.
- Definitive therapy of MPE with sclerotherapy or a tunneled indwelling catheter should be pursued once the diagnosis and symptomatic benefit are confirmed.
- Symptomatic pericardial effusions require pericardiocentesis. Prolonged catheter drainage (until < 25 to 30 mL/day) may provide definitive therapy. Otherwise, creation of a pericardial window is appropriate.

Effusions are common complications of malignant disease that cause significant distress but are also amenable to interventions that can yield significant improvement. Therapies are typically geared to drainage and prevention of reaccumulation of fluid.

BASIC SCIENCE

The fundamental cause of fluid accumulation in the pleural or pericardial space is imbalance between the amount secreted and the amount of fluid resorbed (Table 225-1). Vascular endothelial growth factor (VEGF), a critical protein, is under active research in malignant disease, given the need for tumors to develop a blood supply to support growth. Cancer therapies that antagonize VEGF are already in use or are under active development. These agents typically are antibodies to the VEGF receptors (bevacizumab) or chemical inhibitors of VEGF receptor tyrosine kinase function (imatinib, sorafenib, and sunitinib). Evidence supporting the role of VEGF, originally known as vascular permeability factor, in effusions includes the following: (1) increased levels seen in pleural, pericardial, and peritoneal effusions; (2) increased levels in malignant effusions relative to benign causes; and (3) animal studies that demonstrate differences in effusion volumes with transfected genes that either increase or decrease VEGF expression.[2]

The effect of VEGF appears to be local because serum levels are not increased. Cells believed to produce VEGF in the pleural space include mesothelial, inflammatory, and infiltrating tumor cells. Although the relative contribution of inflammatory cells is unknown, their role is believed to be less important because no correlation exists between VEGF levels and inflammatory cell numbers.

Matrix metalloproteinases (MMPs) and their counterparts, tissue inhibitors of metalloproteinase (TIMPs), comprise a family of endopeptidases involved in the maintenance of the extracellular matrix.[3] Two of these substances, gelatinase A (MMP-2) and gelatinase B (MMP-9), have been identified in pleural fluid. MMP-2 has been seen in transudates and exudates, whereas MMP-9 has been seen only in exudates. Evidence includes the following: (1) correlation of the ratio of MMP-2 and MMP-9 to cause; (2) expression of MMP-2 constitutively by pleural mesothelial cells and present in all pleural effusions regardless of origin; and (3) the presence of MMP-9 only in exudative

TABLE 225-1 Mechanisms of Pleural Fluid Accumulation

MECHANISM	DISORDER
Increased hydrostatic pressure	Heart failure
Decreased oncotic pressure	Nephrotic syndrome, hypoalbuminemia
Decreased pressure in pleural space	Lung collapse
Increased permeability of microvascular circulation	Malignant disease, infection
Impaired lymphatic drainage	Malignant disease
From peritoneal space (ascites)	Malignant disease, cirrhosis

From Moores DWO. Management of malignant pleural effusion. Chest Surg Clin N Am 1994;4:481-495.