Management of Malignant Pleural Effusions and Malignancy-Related Ascites

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Malignant Pleural Effusions

Background

Pleural effusion is the accumulation of fluid within the pleural space. Malignant pleural effusion (MPE) is one resulting directly from tumor in the pleural space or elsewhere in the thoracic cavity. When tumor directly invades the pleura itself, this results in increased permeability of the pleural vasculature and capillary beds. Additionally, if tumor metastasizes to or invades lymph nodes or the lymphatics, it may cause decreased fluid resorption. Both ultimately result in excess pleural fluid.¹ The diagnosis of MPE is definitively made by either cytological analysis of the pleural fluid or direct biopsy of a pleural lesion.

Lung and breast cancers are the most common causes of MPE accounting for 50 to 65% of cases. However, other malignancies and tumor of the pleura itself (mesothelioma) are also involved.^{2,3} MPEs cause more than 125,000 hospital admissions per year in the United States and are estimated to incur over \$5 billion per year in inpatient charges.⁴

The development of MPE often represents advanced or incurable metastatic disease with the average survival after diagnosis estimated between 3 and 12 months.^{5–7} This makes the goal of management primarily palliative and targeted toward symptomatic relief.

Treatment Options

Multiple treatment options are available with the goals of fluid removal and/or prevention of fluid reaccumulation. These include repeat thoracentesis, chemical pleurodesis through a chest tube or thoracoscopy, indwelling pleural catheter (IPC) placement, or less commonly pleuroperitoneal shunt.^{8,9} The two most widely used and more definitive methods of treatment are chemical pleurodesis and IPC placement, which will be discussed in more detail later. One caveat to consider is the presence of “trapped” or “untrapped” lung. Trapped lung occurs when the lung parenchyma cannot reexpand even after fluid is removed. This is most often caused by tumor or loculations in the pleura itself or endobronchial obstruction.

In some cases, MPEs caused by lymphoma, small cell lung cancer, and germ cell tumors may respond to systemic therapy without the need for direct therapy.

Pleurodesis is a procedure that induces inflammation and scarring within the pleural space in hopes of eliminating the potential space for fluid to accumulate. Chemical pleurodesis accomplishes this by using a chemical irritant. Talc is most commonly used with tetracycline, doxycycline, bleomycin, and silver nitrate and silver nitrate being less commonly used alternatives. A systematic review published in the Cochrane Database suggests using talc can achieve pleurodesis in more than 90% of patients.¹⁰ One disadvantage of this procedure is that a chest tube is typically required to remain in place 4 to 5 days to keep the pleural space collapsed.^{10,11} As mentioned, pleurodesis offers a potential cure by eliminating the pleural space. Interestingly, pleurodesis has been found to occur idiopathically (“auto pleurodesis”) in patients with IPCs after ongoing repeated drainage, although it occurs more rapidly after direct talc instillation.^{12,13}

A commonly used IPC is the PleurX Catheter (CareFusion, Illinois). The catheter consists of a fenestrated silicone catheter with a one-way valve mechanism and polyester cuff that can be attached to wall suction, a vacuum bottle, or capped when not in use (→ Fig. 1). It is inserted percutaneously into the pleural space through a subcutaneous tunnel (→ Fig. 2). This is easily performed in an outpatient setting under ultrasound guidance with or without fluoroscopy and often requires only local anesthetic with minimal sedation.^{14,15} The risk of complications is low and includes bleeding, cellulitis, catheter blockage, catheter fracture, infection within the pleural space, and reexpansion pulmonary edema (RPE).

IPCs require repeat drainage, often weekly, every other day, or even daily depending on the rate of reaccumulation and should be guided by patient symptoms. This can be performed at home by home care nurses, family members, and even patients themselves.

RPE is a known but rare complication following large volume thoracentesis. One to 1.5 L of fluid can usually be

Fig. 1 (a) PleurX Catheter kit supplied by Becton Dickinson, New Jersey. (b) Fenestrated catheter with cuff and one-way valve, and disposable vacuum bottle.

Fig. 2 Malignant pleural effusion in an 82-year-old woman with breast cancer. (a) Ultrasound demonstrating left pleural effusion. (b) Spot radiograph after PleurX Catheter placement (arrow).

safely removed, but at levels greater than that the patient should be closely monitored for chest pain, which can be a sign of RPE. Intermittent cough is not abnormal during drainage and should not be confused for symptoms of RPE. Persistent cough, chest discomfort, frothy sputum, and dyspnea are more suggestive findings of RPE and classic signs are tachypnea, tachycardia, and unilateral crackles on the affected side. If this occurs, drainage should be stopped. Treatment is primarily supportive and often only oxygen supplementation is required. However, in severe cases, intubation and mechanical ventilation may be necessary. In addition to the signs and symptoms discussed earlier, classical imaging shows unilateral pulmonary edema.

Evidence Comparing the Options

Numerous studies have attempted to compare chemical pleurodesis and IPC placement in hopes of distinguishing a superior method, as both have become recognized as viable treatment options. The decision often depends on multiple factors, including life expectancy, performance status, local expertise, underlying disease, anatomy, and patient preference.

The TIME2 trial compared patients undergoing drainage and talc pleurodesis to patients who underwent IPC placement and found no statistical difference between the groups in symptomatic relief, with both groups reporting clinically

significant improvement in dyspnea.¹⁶ Likewise, the AMPLE study randomized patients to talc slurry pleurodesis or IPC, and both demonstrated clinically significant improvement in dyspnea after only 1 day and throughout an entire 12-month follow-up period.¹⁷

However, as an outpatient procedure, placement of IPCs has been shown to result in significantly fewer inpatient hospital days. Thus, the cost to the patient and overall health system compared with chemical pleurodesis is reduced. Lastly, IPC has equal or lower perioperative morbidity compared with chemical pleurodesis.^{18–21} One advantage of chemical pleurodesis is that it results in permanent obliteration of the pleural space. Although auto pleurodesis has been observed in patients undergoing repeat drainage through IPCs, it takes longer to achieve.^{12,13}

Guidelines and Recommendations

Guidelines for the management of MPE were first published in 2000 by the American Thoracic Society and in 2010 by the British Thoracic Society.^{6,22} In 2018, the American Thoracic Society collaborated with the Society of Thoracic Surgeons and the Society of Thoracic Radiology to publish new guidelines in an attempt to provide evidence-based recommendations.²³

► **Fig. 3** outlines the treatment algorithm proposed for managing MPEs, and ► **Table 1** lists the consensus recommendations.

Fig. 3 Management algorithm guiding treatment of MPEs. IPC, indwelling pleural catheter; MPE, malignant pleural effusion. (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al; Am J Respir Crit Care Med 2018;198:839–849. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.)

Table 1 Official ATS/STS/STR clinical practice guideline recommendations for management of malignant pleural effusions

Ultrasound should be used to guide pleural interventions
Pleural interventions should not be performed in asymptomatic patients with MPE
IPC or chemical pleurodesis can be utilized in symptomatic patients with suspected expandable lung
Initial large-volume thoracentesis should be performed to assess symptomatic response and lung expansion
Talc poudrage or talc slurry can be used for chemical pleurodesis
IPC should be utilized rather than chemical pleurodesis in patients with nonexpandable lung or failed pleurodesis
IPC-associated infections should be managed with antibiotics and not removal of the catheter

Abbreviations: ATS, American Thoracic Society; IPC, indwelling pleural catheter; MPE, malignant pleural effusion; STR, Society of Thoracic Radiology; STS, Society of Thoracic Surgeons.

Malignancy-Related Ascites

Background

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Malignancy-related ascites (MA) occurs in the setting of malignancy, and similar to MPE it is likely due to tumor invasion/obstruction of the lymphatic drainage system, direct invasion of capillary beds, or cytokine release and direct invasion of capillary beds. This results in increased vascular permeability and decreased fluid resorption.^{24,25} In addition, tumor metastasis and invasion of the liver can result in MA by release of fluid into the peritoneal cavity by tumor cells themselves or obstruction of the portal veins leading to portal hypertension.

MA accounts for roughly 10% of all cases of ascites but may develop in as many as 50% of patients with cancer.^{26–28} Ovarian and gastrointestinal cancers are the most common primary malignancies associated with MA, although up to 20% of all cases have unknown primaries.^{29,30} In addition, an estimated 6% of hospice admissions may be due to ascites.³¹

Like MPE, the development of MA is an indicator of poor prognosis with the average survival time from diagnosis estimated as low as 1 to 4 months depending on the underlying primary malignancy.²⁷ Quality of life is poor due to frequent hospitalizations related to symptoms such as abdominal pain, loss of appetite, dyspnea, constipation, urinary frequency, anorexia, and vomiting. These are attributed to mass effect from the fluid on the gastrointestinal and genitourinary tracts.³² Similar to MPEs, the goal of treatment is primarily palliative and directed toward symptomatic relief.

Treatment Options

Like MPEs, multiple treatment options exist for the management of MA. These include serial paracentesis, diuretics, indwelling peritoneal catheters, peritoneovenous shunting, and intraperitoneal/systemic chemotherapy.³³

Most patients with MA undergo paracentesis every 1 to 2 weeks depending on the underlying etiology, frequency of symptoms, and rate of reaccumulation. Paracentesis is generally considered a safe procedure. There is a low risk of complications that include infection and bleeding at the puncture site, secondary peritonitis, and hypotension.^{28,34}

Multiple studies in the setting of liver disease demonstrate that up to 5 L of fluid can be removed safely.^{28,35,36} To date, there is no consensus regarding the recommended duration over which fluid is removed, with ranges varying from 30 minutes up to 24 hours.^{28,37} What is established is that patients with MA can have large volumes of fluid removed without the risk of hypotension and renal failure, unlike patients undergoing paracentesis due to portal hypertension, although it is recommended to clamp the drain every 5 L to allow for hemodynamic adjustment.³⁸ In addition, there is no evidence suggesting that patients with MA undergoing paracentesis need albumin or intravenous fluid replacement.

As with MPEs, IPCs are a well-accepted option for patients with MA. The PleurX catheter is commonly used and performed under ultrasound guidance with/without fluoroscopy. These can be managed at home by a home nurse, the patient, or family member and fluid should be drained before becoming symptomatic and resulting in costly hospitalizations.

A common catheter used at our institution is a 9.6-Fr Hickman catheter with a single lumen (→Fig. 4). The benefits of using this catheter include the ability to customize the number of fenestrations along the length of the catheter by manually cutting the fenestrations in the catheter. In addition, the total length of the catheter is nearly 19 inches longer, making the catheter customizable to the physician's desired length. Furthermore, the catheter valve cap can be used with a variety of drainage bags or syringes as opposed to the PleurX catheter, which requires its own drainage kit. Overall, the single lumen Hickman catheter provides a customizable and cost-effective alternative to the PleurX catheter.

Peritoneovenous shunts are another option that have been described and used in attempts to avoid repeated paracentesis. They are typically used in patients with longer anticipated survival and require an interventional radiologist or surgeon to place them. These shunts allow peritoneal fluid to directly enter the central venous system.³⁹ However, there are many reported serious complications.

A relatively new treatment option is targeted chemotherapy. Multiple agents are either available or currently under study. Aflibercept, the fusion protein VEGF-Trap, has been shown to be effective in symptomatic control of ascites.⁴⁰

Fig. 4 Malignancy-related ascites in a 60-year-old woman with gastric cancer. (a) Ultrasound demonstrating ascites. (b) Spot radiograph after single-lumen Hickman catheter placement (arrow).

Table 2 Recommendations on management of malignant ascites

Paracentesis is indicated for symptom reduction typically every 1–2 weeks
The use of IV fluids or albumin when removing large amounts of fluid is not sufficiently studied. IV fluid infusion should be considered if the patient is dehydrated, known to have renal impairment, or more than 5 L of fluid are being removed
It is safe to remove up to 5 L of fluid over a 4-hour period. If more than 5 L is withdrawn, clamp the tube to allow for hemodynamic stability
Permanent drains should be considered in patients who wish to avoid frequent paracentesis
No strong data are published regarding the efficacy of diuretics in symptom reduction. If there is underlying portal hypertension, diuretics may be considered and tailored to the individual patient
Intraperitoneal agents are still in early trial phases and should be considered experimental

Batimastat is a metalloproteinase inhibitor recently studied in a phase 1 study and found to inhibit the reaccumulation of ascites after drainage.³² Epithelial cell adhesion molecule and intraperitoneal catumaxomab are two additional agents currently being studied with promising early results.

Evidence Comparing the Options

Although commonly used, there is no strong evidence to suggest that the use of diuretics is effective in patients with MA. Diuretics are more effective in patients with a serum-ascites albumin gradient greater than 1.1, which is suggestive of transudative ascites due to portal hypertension rather than exudative ascites as seen with MA.

Paracentesis provides symptom control in up to 90% of patients.⁴¹ Because of ease and rapid symptom relief, repeat large volume paracentesis is a common strategy. However, studies comparing repeat paracentesis with IPC suggest that IPC is just as effective in alleviating symptoms, and more convenient and cost-effective in the long term.^{42–47}

Reported complications of peritoneovenous shunts include shunt occlusion, post shunt coagulopathy, deep vein thrombosis, catheter breakage, pulmonary edema, and leaks.⁴⁸ In one series of 89 patients that evaluated the effectiveness and morbidity associated with peritoneovenous shunt placement, 12 deaths within 30 days of surgery were directly related to a complication of shunt placement. In addition, it has proven to be effective only in symptom reduction in approximately 60% of patients.³⁹ Because of this, alternative methods are preferred.

Targeted chemotherapy is a promising new option, but further research is needed to determine the effectiveness of these agents.

Guidelines and Recommendations

Unlike MPE, there are no consensus guidelines for the evaluation and management of MA. In accordance with

Fig. 5 Management algorithm guiding treatment of malignancy-related ascites. MRI, magnetic resonance imaging; CT, computed tomography; SAAG, serum-ascites albumin gradient.

Becker et al⁴⁹ and Campbell,⁵⁰ we make the recommendations outlined in ►Table 2 and offer the management algorithm outlined in ►Fig. 5.

Disclosures

The authors have no conflict of interest.

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