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PLEURAL DISEASES AND MESOTHELIOMA (YCG LEE, SECTION EDITOR)

Management of malignant pleural effusions

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Abstract Malignant pleural effusions (MPE) are a common occurrence in many advanced malignancies. They are a significant cause of morbidity and mortality; symptoms can be debilitating to patients and impair quality of life, especially as many of these patients are already functionally impaired by their underlying cancer and medical treatment. MPE generally represent advanced stage malignancy and the primary goal of therapy is palliation of symptoms. The purpose of this article is to review the therapeutic options available in the treatment of MPE and discuss clinical factors affecting management decision-making.

Keywords Malignant · Pleural disease · Effusion · Thoracentesis · Chest tube · Pleural catheter · Thoracoscopy · Pleuroscopy · Pleurodesis · Poudrage

Introduction

Pleural effusions are a common complication of advanced malignancies and are associated with significant morbidity and mortality. The incidence of MPE is estimated to be greater than 150,000 cases per year in the United States [1, 2]. Over 75% of patients with MPE are symptomatic, though a significant number may be asymptomatic with only evidence of pleural fluid on clinical examination or chest imaging [3]. Common presenting symptoms include dyspnea, cough, orthopnea, and chest pain. Median survival ranges from 3–12 months and depends on the type and stage of the malignancy [4–8].

Treatment for MPE has traditionally included recurrent therapeutic thoracentesis, drainage by chest tube thoracostomy, and pleurodesis. While these modalities remain viable therapeutic options, they are imperfect. Development of new therapies, including long-term indwelling pleural catheters and pleuroscopy, have expanded the spectrum of interventions allowing physicians to offer outpatient [9] and cost-effective [10] therapies that decrease hospital stay, decrease discomfort, and allow patients to maximize time at home or in hospice care [11].

Etiology and pathogenesis

Lung cancer is the most common cause of MPE and is the etiology in more than one-third of cases, followed by cancers of the breast, lymphoma, ovary, and stomach. Combined, these comprise almost 80% of MPE, though the primary site of origin is unknown in 7% of cases [12]. These data, however, likely underestimate the role of mesothelioma as a cause of MPE given the increasing incidence of mesothelioma and the higher prevalence of the disease in certain parts of the world [13••]. Most MPE are exudates, though 2%–5% are transudates [14, 15].

MPE are diagnosed by the discovery of malignant cells in pleural fluid or pleural biopsy. MPE commonly result from disruption of normal Starling forces regulating pleural fluid absorption by obstruction of mediastinal lymphatics, which drain the pleural space [16]. There is a strong relationship between mediastinal metastasis and development of MPE

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[3, 9, 17]. Other causes of MPE include direct invasion (eg, lung cancer, breast cancer, chest wall neoplasms), hematogenous spread of tumor to the pleura (eg, metastasis, non-Hodgkin's lymphoma), or increased capillary permeability caused by tumor invasion-related local inflammatory changes or vascular endothelial growth factor production [16, 18–20]. Malignancy involving the pleura, however, does not always result in the development of MPE, as MPE are only present in 60% of such cases [17, 21].

Paramalignant effusions develop secondary to tumor effect, such as from thoracic duct obstruction (eg, Hodgkin's lymphoma), bronchial obstruction, pneumonia, atelectasis, trapped lung, pulmonary embolism, or secondary to chemotherapy or radiation treatment [3]. Since pleura is not directly affected, pleural fluid cytology and pleural biopsy are negative for malignant cells.

Therapeutic considerations

While not all patients with MPE are symptomatic, the majority have symptoms that decrease their quality of life. Dyspnea with exertion affects more than 90% of symptomatic patients while cough and chest discomfort (ie, pleuritic pain, chest pressure or heaviness) affect over 50% of patients [22]. In addition to the quantity of pleural fluid, the rate of accumulation is an important factor in the severity of symptoms [3]. As MPE represent advanced disease and portend poor overall prognosis, therapies are considered palliative rather than curative. Systemic chemotherapy can reduce pleural fluid production, though response is heavily dependent upon cancer etiology. Therapeutic options focus on fluid drainage or reduction in fluid production (Table 1). When evaluating therapeutic options, the patient's symptoms, functional status, life expectancy, and underlying etiology of malignancy must be considered (Fig. 1).

Pleural drainage

Therapeutic thoracentesis

Removal of a large volume of pleural fluid by thoracentesis is generally the first therapeutic intervention tried for patients with symptomatic MPE. Patient response to large volume thoracentesis is also important in determining the future management of their MPE. Up to 50% of patients may not have significant symptom relief due to comorbid conditions, generalized deconditioning from their malignancy, or incomplete reexpansion of the lung (aka "trapped lung").

Table 1 Treatment options for malignant pleural effusions

Treatment	Advantages	Disadvantages
Observation	• Noninvasive	• Most patients progress and require therapeutic intervention
Periodic therapeutic thoracentesis	• Rapid relief of symptoms	• Multiple procedures required
	• Good option for patients with limited life expectancy or slow reaccumulation rate	• Recurrent procedural risk (ie, pneumothorax)
		• Requires periodic medical visits
Tunneled pleural catheter	• Effective control of symptoms	• Drainage may require assistance from a caregiver
	• Allows outpatient management	• Risk of catheter infection
	• Minimally invasive	• Low and slow pleurodesis rate compared to chemical pleurodesis options
	• Possible spontaneous pleurodesis pleurodesis	
	• Can be used with trapped lung or failed pleurodesis	
Chest tube thoracotomy with pleurodesis	• Permanent relief of symptoms	• 5–7 day hospitalization
	• High pleurodesis success rate	• Invasive
		• Higher associated morbidity
Medical thoracoscopy or VATS with pleurodesis	• Permanent relief of symptoms	• 5–7 day hospitalization
	• High pleurodesis success rate	• Invasive
	• Able to perform concurrent diagnostic and therapeutic interventions	• Higher associated morbidity
		• Must tolerate single-lung ventilation (VATS)
Pleuroperitoneal shunt	• Can be used after failed pleurodesis	• Risk of shunt occlusion
	• Recirculation of chyle with chylothorax	• Requires frequent manual pumping

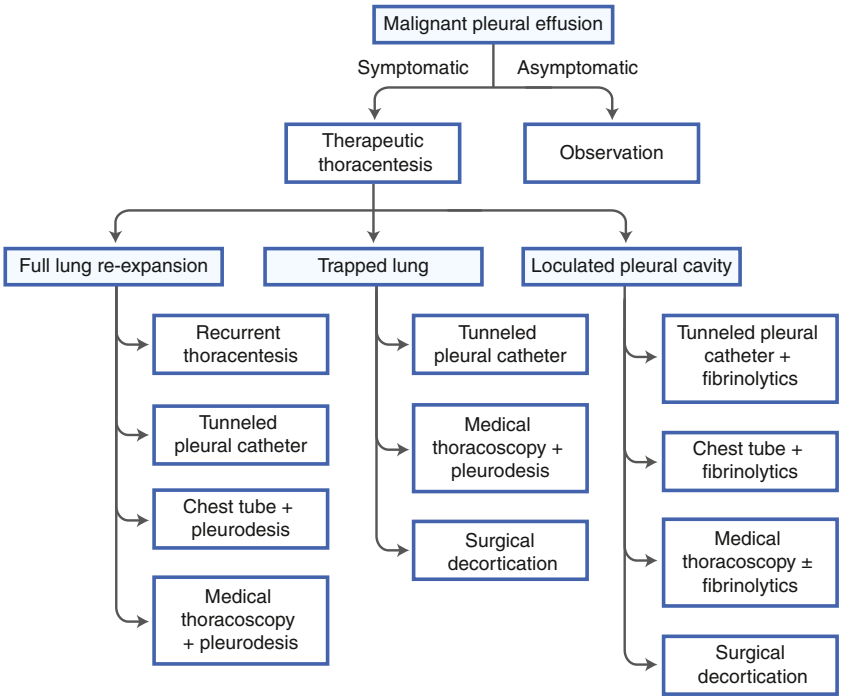

Fig. 1 Treatment considerations for malignant pleural effusions

Lack of symptom relief following fluid removal discourages additional, more invasive therapeutic options given the lack of benefit. Trapped lung may result from pleural-based malignancy or metastasis, pleural loculations, or bronchial obstruction with post-obstruction collapse. In addition, radiographic evidence of lung reexpansion and apposition of the parietal and visceral pleura after removal of pleural fluid is an important predictor of success if considering future pleurodesis [23–25].

There are no absolute contraindications to thoracentesis, though relative contraindications include bleeding diathesis, use of anticoagulation, positive pressure ventilation, or minimal effusion size. While the volume of fluid that can safely be removed is unknown, caution must be taken due to the risk of reexpansion pulmonary edema. This is a rare (< 1%) but well-described complication associated with the rapid reexpansion of the lung [26–28]. Large volume drainage has been shown to be safe if the patient is symptom-free during the procedure and manometry pressures remain less than -20 cm H_2O during the removal of a large quantity of fluid [23]; however, as most clinicians do not routinely measure pleural pressures during thoracentesis, it is recommended not to remove more than 1.5 L at a time and to avoid use of excessive negative pressure, such as from a vacuum bottle [13••, 29].

A total of 98%–100% of patients will have reaccumulation of pleural fluid and recurrence of associated symptoms within 30 days of thoracentesis [30, 31]. Therefore, recurrent thoracentesis may be a viable therapeutic approach for patients who have limited life expectancy or who are poor candidates for more definitive but invasive interventions. However, the physician should have a candid discussion with the patient regarding procedural-related risks such as infection, bleeding, pneumothorax, and the development of adhesions which may interfere with other therapeutic modalities.

Tunneled pleural catheter

Indwelling tunneled pleural catheters (TPC) have become commonly used for palliative drainage of MPE since its initial approval in 1997 for commercial use by the U.S. Food and Drug Administration. The role of TPC is constantly evolving as it provides physicians a minimally invasive, potentially less expensive, outpatient treatment option.

The most common catheter system in use (PleurX; CareFusion, San Diego, CA, USA) is a 15.5 Fr silicone rubber catheter measuring 66 cm in length with fenestrations along the distal 24 cm and a proximal valve. The catheter is tunneled subcutaneously in a procedure akin to a combination of a thoracentesis and modified Seldinger technique [32, 33]. A polyester cuff along the tunneled portion of the catheter induces fibrotic tissue formation preventing infection and securing the catheter in place. Insertion can be performed under conscious sedation on an outpatient basis in an ambulatory procedure unit. Pleural fluid can be drained via vacuum or drainage bottles by the patient, a family member, or visiting home nurse. The catheter is removable should the patient develop spontaneous pleurodesis or in the event of a complication.

Multiple studies have shown TPC to be effective in drainage of recurrent MPE [9, 10, 34, 35]. A recent meta-analysis

of 19 studies involving TPC showed symptomatic improvement in 95.6% of patients and development of spontaneous pleurodesis in 45.6% (range 11.8–76.4%) after an average of 52 days [36•]. Given the non-invasive nature of the therapy, this catheter system has commonly been used in patients with poor prognosis (< 6 months) as well as patients who are not optimal candidates for traditional pleurodesis due to a trapped lung or who have failed prior pleurodesis [37, 38•, 39]. However, the role of TPC is expanding with the demonstration of utility in patients who otherwise would qualify for traditional pleurodesis [40].

Currently only one study compares TPC to pleurodesis; there was no difference in survival or quality-of-life but a decreased length of hospitalization (1.0 vs 6.5 days) when compared to pleurodesis with doxycycline. Costs associated with hospitalization were clearly in favor of TPC use [41]. However, given the high cost associated with the disposable drainage bottles, a recent cost analysis estimated a similar cost between TPC and talc pleurodesis ($9011.60 vs $8170.80, respectively) with cost effectiveness favoring the TPC when life expectancy was less than 6 weeks [42•]. Of course, the decision to use a TPC versus pleurodesis should focus on patient preference, comfort, and quality of life rather than cost. TPC-related complications are relatively rare, but include catheter malfunction (9.1%), dislocation (2.2%), obstruction (3.7%), and pneumothorax (3.9%); cellulitis (3.4%) and empyema (2.8%) have also been reported [9]. Tumor seeding along the catheter tract is rare, but most notable with mesothelioma.

Pleuroperitoneal shunt

Largely supplanted now by TPC, pleuroperitoneal shunts are used in patients with refractory malignant effusions, failed chemical pleurodesis, trapped lung, or who are not pleurodesis candidates. Pleuroperitoneal shunts transfer fluid from the pleural space to the peritoneal cavity actively when manually pumped (Denver shunt) or passively (LeVeen shunt). Palliation is achieved in 80%–90% of properly selected patients [15]. This method of pleural fluid drainage is particularly useful with chylothorax as it allows recirculation of chyle.

Infection and shunt occlusion are the most significant complications associated with pleuroperitoneal shunts. Shunt occlusion, usually from clotting of the catheter, occurs in up to 25% of cases with a median length of patency of 2.5 months [43, 44].

Pleurodesis

Pleurodesis eliminates the potential pleural space by inducing inflammation and fibrosis causing the visceral and parietal pleura to adhere together. This process can be incited by the introduction of a chemical sclerosant, by mechanical abrasion of the pleural surface, or by prolonged use of a chest tube. Chemical sclerosants are most commonly introduced through a chest tube, via medical thoracoscopy, or by other surgical intervention. Patients selected for pleurodesis should have significant symptom relief and evidence of full lung reexpansion after removal of pleural fluid. Lung reexpansion is paramount as trapped lung has been associated with chemical pleurodesis failure [45]. The pleurodesis process commonly takes 5–7 days during which time the patient is hospitalized for chest tube drainage and pain control. The chest tube is removed after pleural fluid output diminishes and the patient can then be discharged.

Chest tube thoracostomy

Chest tube thoracostomy is an inpatient procedure performed under local anesthesia or conscious sedation. Its use in MPE is primarily for drainage of the pleural cavity and demonstration of lung reexpansion before instillation of a chemical sclerosant. Typically a 24–32 Fr chest tube is used, though smaller bore tubes have been used for chemical pleurodesis [46–48]. Large bore chest tubes are associated with greater patient discomfort but have traditionally been used because of the concern of obstruction of smaller bore tubes by fibrin plugs. However, several randomized trials have compared small versus large bore chest tubes without significant difference in pleurodesis outcome [46, 49–51]. Pleurodesis is performed by mixing the sclerosing agent of choice with 50–100 mL of sterile saline and then instilling it into the pleural cavity through the chest tube. The chest tube is clamped for 1–2 h and then reconnected to suction. No benefit in distribution of sclerosant or outcome or has been shown from rotating the patient [52, 53].

Medical thoracoscopy

Medical thoracoscopy, also referred to as pleuroscopy, is another diagnostic and therapeutic tool gaining popularity amongst pulmonologists and thoracic surgeons [54, 55•]. The procedure can be performed under local anesthesia with conscious sedation in an endoscopy suite or procedure room. General anesthesia, intubation, and single-lung ventilation are not required. The patient is placed in the lateral decubitus position and one or more trocars are inserted into the pleural space, allowing introduction of the thoracoscope. There are different sizes of trocars (typical diameter 5–13 mm) and a variety of thoracoscopes, including semi-rigid versus rigid telescopes in addition to direct (0°), oblique (30 or 50°), and periscope (90°) visualization options. Visually guided biopsies of parietal pleura, lysis of adhesions (mostly with rigid thoracoscope), and administration of

chemical sclerosants can be performed before a chest tube is placed through the trocar site at the completion of the procedure.

The procedure requires the patient to tolerate spontaneous breathing under conscious sedation with one lung partially collapsed. Presence of adhesions will influence trocar placement, and adhesiolysis with the telescope or biopsy forceps may be required to allow complete drainage of the pleural cavity and uniform distribution of the sclerosant for pleurodesis. Potential complications include pneumothorax, subcutaneous emphysema, fever, and pain. Reports of major complications such as empyema, sepsis, or death are rare [56, 57].

Surgical interventions

While similar in many ways to medical thoracoscopy, video-assisted thoracic surgery (VATS) has several distinct and clinically important differences. The equipment is similar in concept to rigid medical thoracoscopes, though usually slightly larger in size. VATS permits a greater number of diagnostic and therapeutic options compared to medical thoracoscopy, such as diagnostic biopsy of lung parenchyma and select hilar lymph nodes. However, it requires a higher level of surgical expertise and is performed in an operating room, which requires greater ancillary and logistical support. VATS also requires at least two trocars, general anesthesia, and single-lung ventilation through a double-lumen endotracheal tube. Despite its increased complexity, it remains a valuable tool in the evaluation and pleurodesis of the pleural cavity.

Thoracotomy and decortication can be used for the treatment of MPE with loculations and/or trapped lung. It has a significantly higher associated mortality rate and is generally reserved for the limited population of patients with significant symptoms, prolonged life expectancy, and who have failed other therapeutic interventions. Variations of pleurectomy (radical pleurectomy and decortication, lung-sparing total pleurectomy, and extrapleural pneumonectomy) have been used to treat malignant mesothelioma. While successful at achieving pleurodesis, these surgical interventions are associated with a high morbidity and mortality; as such, their use in malignant mesothelioma is now discouraged [58, 59•].

Pleurodesis agents and administration

The ideal sclerosing agent is chosen based on factors such as efficacy, accessibility, ease of administration, and safety profile. A number of chemical sclerosants have been utilized in pleurodesis, including talc, bleomycin, tetracycline, doxycycline, iodoprovidone, and mustine. Talc is now generally accepted as the agent of choice [13••, 60]; meta-analysis suggests successful pleurodesis is more likely with talc compared to other agents or chest tube drainage alone (RR 1.34, CI 1.16–1.55) [61]. Success rates with talc are reported to be 81%–93% [62–65], as compared to 80%–85% with tetracycline/doxycycline [66–68] and 70%–79% with bleomycin [64, 69].

Chemical sclerosing agents can be administered either through a chest tube (slurry) or insufflated into the pleural cavity during medical thoracoscopy or VATS (poudrage). Several studies have demonstrated similar or better pleurodesis rates with talc poudrage compared to talc slurry, though these data are not completely conclusive [70–73]. The largest of these trials randomized 501 patients to talc poudrage versus talc slurry with 30-day pleurodesis rates of 78% versus 71%, respectively [70]. However, subgroup analysis showed increased success with talc poudrage (82% versus 67%) in patients with lung or breast cancers compared to other primary malignancies. Despite this controversy, medical thoracoscopy or VATS-administered talc poudrage has specific situational advantages over talc slurry. Diagnostic biopsy and therapeutic pleurodesis can be performed simultaneously; in addition, procedural removal of adhesions and direct visualization permits confirmation of adequate drainage of the pleural cavity and widespread dispersal of the sclerosing agent.

Other factors have been shown to be associated with pleurodesis outcomes. Low pleural fluid pH has been shown to be a poor prognostic indicator for pleurodesis success with receiver operating curve thresholds for pH of 7.28–7.34 [74, 75]. Other predictors of poor pleurodesis results include trapped lung [45], large tumor bulk lining the pleural surfaces [76], and elevated adenosine deaminase levels [75]. Predictors of successful pleurodesis include pleural fluid output of <200 mL/day when treated by talc slurry [77] as well as MPE secondary to lung adenocarcinomas that are positive for epidermal growth factor receptor (EGFR) mutation when treated with Tarceva [78].

The most common complications associated with chemical pleurodesis are fever and pain [11]. Other potential complications include local site infection, empyema, arrhythmias, cardiac arrest, myocardial infarction, and hypotension. Doxycycline is commonly associated with more pleuritic pain than talc. Acute respiratory distress syndrome (ARDS), acute pneumonitis, and respiratory failure have been described with use of talc. ARDS has been described in up to 1%–9% of cases of talc pleurodesis [79], though recent investigation has shown that this may be related to the use of ungraded talc as opposed to large particle talc (> 15 μm). Janssen and colleagues prospectively treated 558 patients using large particle talc without a single occurrence of ARDS, demonstrating that use of graded large particle talc is preferable [79].

Intrapleural fibrinolytics

Fibrinolytics instilled into the pleural cavity have been used for treatment of non-malignant loculated effusions, such as with parapneumonic effusions and empyema. Fibrin deposits along the pleura in MPE can lead to loculations hindering pleurodesis and resulting in dyspnea and trapped lung. Streptokinase [80] and urokinase [81] have been used with loculated MPE with an increase in pleural fluid output and improvement in dyspnea. The only prospective randomized control trial used streptokinase and a 10 Fr drainage tube in patients with MPE; this resulted in increased pleural fluid drainage, increased number of patients with lung reexpansion (96% vs 74%), and increased success with doxycycline pleurodesis (74% vs 56%) [82].

Future directions

Multimodality interventions

The ultimate goal of therapeutic intervention for MPE is to provide rapid onset of symptom relief with minimally invasive interventions and minimal hospital length-of-stay. To this end, Reddy and colleagues recently evaluated patients with recurrent, symptomatic MPE who underwent medical thoracoscopy with talc poudrage; the chest tube was removed after 24 h and drainage was continued via TPC [83]. Patients were potentially discharged if stable after the chest tube was discontinued. Using this multimodality approach, pleurodesis was successfully achieved in 92% of patients and the TPC was removed at a mean of 16.7 days. Mean length of hospitalization was only 3.2 days post procedure. While only a pilot study, combination therapy has the potential to provide permanent symptom relief while minimizing hospital length-of-stay.

Subcutaneous implantable pleural port

Recently, Kriegel and colleagues described their experience using an 8.5 Fr fenestrated pleural catheter attached to an implantable access port (Celsite ST, Laboratoires Braun, France) [84]. The access port is positioned in a subcutaneous compartment created along the mid-axillary line over the 10th to 12th ribs with the catheter inserted between the third to fifth intercostals space and directed towards the lung base via fluoroscopic guidance. The procedure can be performed as an outpatient and allows access of the port with a Huber needle and drainage bottle to remove pleural fluid.

One hundred and sixty-eight devices were implanted in 137 patients. Ninety-eight percent had complete or partial relief of their dyspnea, and 36.8% developed spontaneous pleurodesis within 2 months. Median patient survival time was 344 days. Complications included infection (1 empyema, 2 cellulitis) and 3 mechanical complications. Catheter occlusion was also described which was resolved with instillation of urokinase. Though additional studies using this device are required, the potential advantage over a TPC is that the external catheter and valve are implanted subcutaneously, similar to implanted ports used for chronic infusion therapy (eg, Portacath, Infusaport). Such devices have the potential to decrease infection risk and improve patient comfort and aesthetics.

Intrapleural chemotherapy

Administration of chemotherapeutic agents directly into the pleural space has the potential to control the underlying malignancy and/or the MPE by producing high drug concentrations localized at the malignancy site while minimizing systemic toxicity [85]. Ideal agents would have a slow clearance rate from the intrapleural cavity, allowing greater exposure of cancer cells to the cytotoxic agent. In addition, ideal agents have limited tissue penetration to decrease systemic absorption; however, the utility of intrapleural chemotherapy may therefore be limited in patients with bulky disease. A phase II trial of intrapleural paclitaxel demonstrated a 370-fold increase in intrapleural versus serum drug levels [86]. Chemotherapeutics studied include paclitaxel, cisplatin, carboplatin, etoposide, cytarabine, and docetaxel [85, 87–91]; unique agents such as *Staphylococcus aureus* superantigen have also been tried [92]. The majority of studies to date are phase I and II trials evaluating safety and dosing rather than efficacy. A phase III trial using intrapleural cisplatin versus observation noted a decrease in significant MPE development in non-small cell lung cancer patients with cytologically positive pleural fluid (8% vs 42%, $P=0.008$) [90]; however, the trial was stopped early due to poor enrollment. Given current indwelling methods allowing chronic access to the pleural cavity, intrapleural chemotherapy remains a potential mechanism of drug administration, though further studies are needed.

Conclusions

There are a number of palliative treatment options available for patients with MPE. Pleurodesis offers the potential for permanent relief of symptoms for patients able to tolerate the procedure. Newer modalities, such as TPC, can provide less invasive yet long-term solutions for patients with poor functional status and still has the potential for eventual pleurodesis. TPC also offers palliation for patients with trapped lung who are unable to undergo pleurodesis. Ultimately a multitude of factors must be considered when evaluating patients with MPE, including functional status,

symptoms, and overall prognosis in order to choose the most efficacious, cost-effective, and minimally invasive means to meet the patient's goals of care.

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•• Of major importance

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