Management of Malignant Pleural Effusions

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The development of pleural effusions is a common occurrence in patients with neoplastic disease. In one postmortem study, 15% of patients who died with malignancies were found to have malignant pleural effusions, and the annual incidence of malignant pleural effusions (MPE) in the United States is estimated to be >150,000 cases. The presence of a MPE often portends a poor prognosis; the mean survival after the diagnosis of a MPE ranges from 3 to 12 months, depending on the underlying tumor (lung cancer is generally associated with the shortest average survival time). Patients with MPE often have symptoms that impair their quality of life, such as dyspnea, orthopnea, cough, and chest discomfort, some or all of which can be improved with palliative therapeutic measures. The interventional pulmonologist can play an important role in the management of MPE by helping with the accurate diagnosis of the pleural malignancy, thereby guiding treatment plans for the underlying neoplasm, and also by performing pleural drainage procedures with or without pleurodesis to relieve symptoms.

Diagnosis

Pleural effusions may be the result of a primary neoplasm of the pleura, such as with malignant pleural mesothelioma (MPM), or from metastatic disease to the pleural surfaces. While nearly all neoplasms have been reported to cause MPE, more than 75% are caused by lung cancer, breast cancer, ovarian cancer, and lymphoma. Other types of neoplasms that can metastasize to the visceral or parietal pleura include sarcoma, melanoma, and carcinomas of the uterus, cervix, stomach, colon, pancreas, and bladder; the primary site of malignancy is unknown in about 6% of cases.

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Asbestos exposure remains the major known risk factor for MPM. While relatively few patients with a history of asbestos exposure develop the disease, up to 80% of patients with MPM have a history of asbestos exposure with a latent period between exposure and diagnosis of 20–60 years. Other possible risk factors include prior radiation exposure, infection with simian virus 40, and strong family history. The three main histological subtypes of MPM are epithelioid, biphasic, and sarcomatoid. The epithelioid subtype is the most common and carries the better prognosis, although the median overall survival ranges between 9 and 17 months.

Not all pleural effusions in patients with known malignancy are necessarily malignant pleural effusions. Patients with cancer can have "paramalignant" pleural effusions in which the effusion is not due to malignant involvement of the pleura. Potential causes of paramalignant effusions include local effects of tumor such as atelectasis due to endobronchial obstruction and postobstructive pneumonia with parapneumonic effusion, systemic effects of tumor such as venous thromboembolism and hypoalbuminemia, and complications of therapy such as radiation pleuritis and pleural effusion related to chemotherapy. It is therefore often important to make an accurate and specific diagnosis of MPE in order to make rational management decisions.

Medical Thoracoscopy/Pleuroscopy

The suspicion for MPE represents the leading diagnostic indication for medical thoracoscopy/pleuroscopy. Diagnostic pleuroscopy is often performed to evaluate an exudative pleural effusion for which no etiology can be identified despite performance of a thoracentesis with analysis of the pleural fluid and, if done, closed pleural biopsy. Pleuroscopy is particularly helpful and effective in diagnosing MPEs. In cases of suspected mesothelioma, for example, making the diagnosis can be difficult using cytological examination of pleural fluid and histological examination

A. Ernst and F.J.F. Herth (eds.), *Principles and Practice of Interventional Pulmonology*,
DOI 10.1007/978-1-4614-4292-9_64,

of the small samples obtained by closed-needle pleural biopsy. Pleuroscopy improves the diagnostic yield for mesothelioma to above 90%. As another example, pleuroscopy can be used in patients with known bronchogenic carcinoma who have cytologically negative pleural effusions. Since only 6% of such patients will have completely resectable tumors, medical thoracoscopy can be used to identify the small group who could potentially benefit from surgical resection while preventing surgery for the majority with unresectable disease.

The yield for diagnosing MPE by pleuroscopy ranged from 80% to 96% in reported series and a large series by Loddenkemper described a combined yield for pleural fluid cytology, closed-needle pleural biopsy, and medical thoracoscopy was 97%. The main advantage of pleuroscopy is the ability to achieve early diagnosis of MPE when pleural fluid cytology and closed-needle pleural biopsy have failed. It allows inspection of approximately 75% of the visceral pleural surface as well as of the parietal pleural surface (Fig. 64.1). Boutin reported that in 85% of patients with MPE, thoracoscopy revealed visual features suggestive of malignancy, including nodules, polypoid lesions, localized masses, thickened pleural surface, and poorly vascularized pachypleuritis. However, since appearances can be misleading – some malignancies may appear inflammatory while some inflammatory lesions can look like tumors – macroscopic diagnoses must always be confirmed by histology. Biopsies can be visually directed in instances where tumor deposits appear to be localized (Figs. 64.2 and 64.3). In addition, biopsy specimens can be obtained from multiple sites and are of greater size and depth, factors that improve the diagnostic yield (Figs. 64.4 and 64.5). The larger sample sizes increases the ability of the pathologist to make an accurate diagnosis; the pathologist, for example, can better differentiate malignant mesothelioma from adenocarcinoma and can perform special studies such as hormone receptor assays or genetic marker studies on the tissue that help determine prognosis and guide therapy.

In the past, pathologists found it difficult to make a definitive diagnosis of malignant mesothelioma without large samples obtained during open thoracotomy or autopsy. With the availability of immunohistochemistry techniques, pathologists are now better able to make the diagnosis. By permitting direct visualization of lesions, pleuroscopy facilitates the choice of biopsy sites and allows accurate assessment of the degree of involvement of the diaphragmatic, parietal, visceral, and mediastinal pleura (Fig. 64.6). Boutin reported a sensitivity of thoracoscopic biopsy of 98% for the diagnosis of malignant mesothelioma, compared with 28% for pleural fluid cytology, 24% for closed-needle pleural biopsy, and 100% for surgical biopsy.

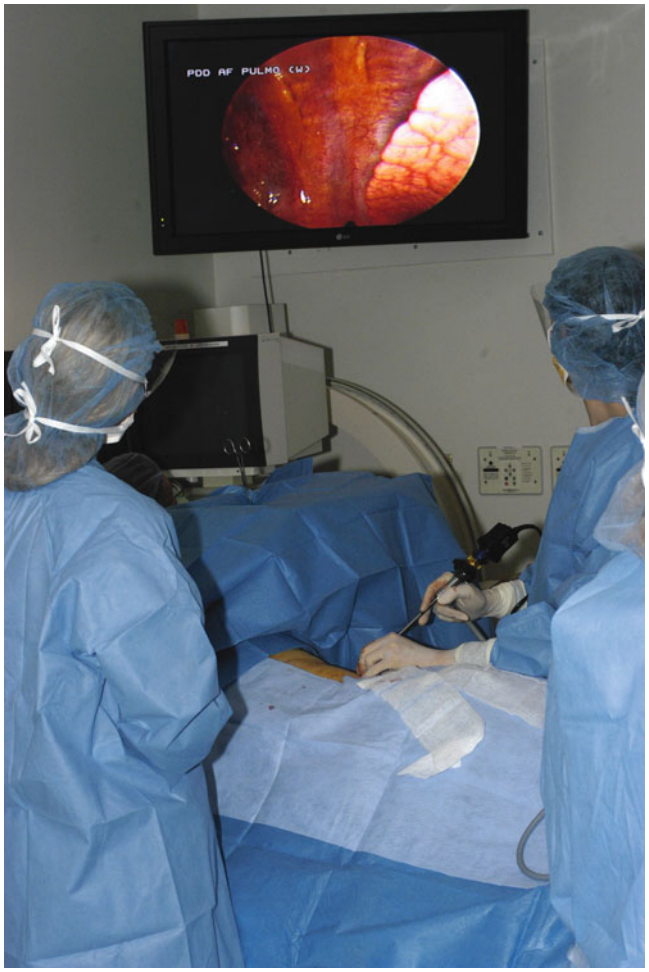

Fig. 64.1 Viewing the intrapleural space during medical thoracoscopy

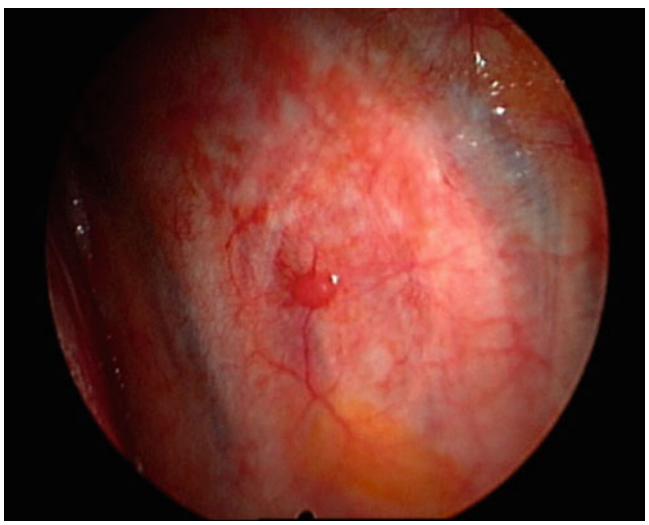

Fig. 64.2 Solitary parietal pleural tumor studding in a patient with an exudative pleural effusion of unknown etiology

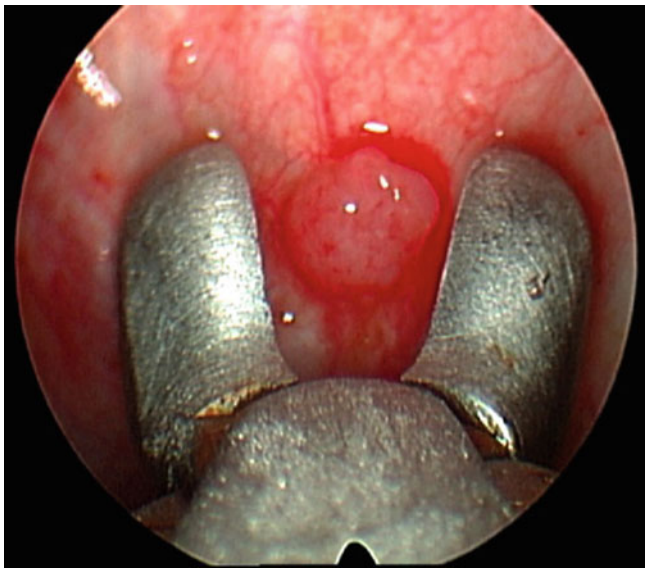

Fig. 64.3 Obtaining a biopsy of the single parietal pleural lesion under direct vision, using medical thoracoscopy. The pathology revealed adenocarcinoma from a beast primary

Bronchoscopy

The role of bronchoscopy in the diagnosis of malignant pleural effusions is limited and is not considered a routine part of the evaluation for a pleural effusion because of its low yield. A retrospective review, however, concluded that it may be useful in diagnosing bronchogenic carcinoma in patients with sizable cytology-negative pleural effusions who have hemoptysis, a lung mass, or atelectasis.

Treatment Options

While the interventional pulmonologist can play an important role in the accurate diagnosis of MPEs, an equally important, if not more frequent, role is in the treatment of MPEs. Since the presence of a MPE typically reflects advanced disease, the treatment options are generally palliative, not curative, so as to help relieve dyspnea, cough, and discomfort, thereby improving patients' quality of life.

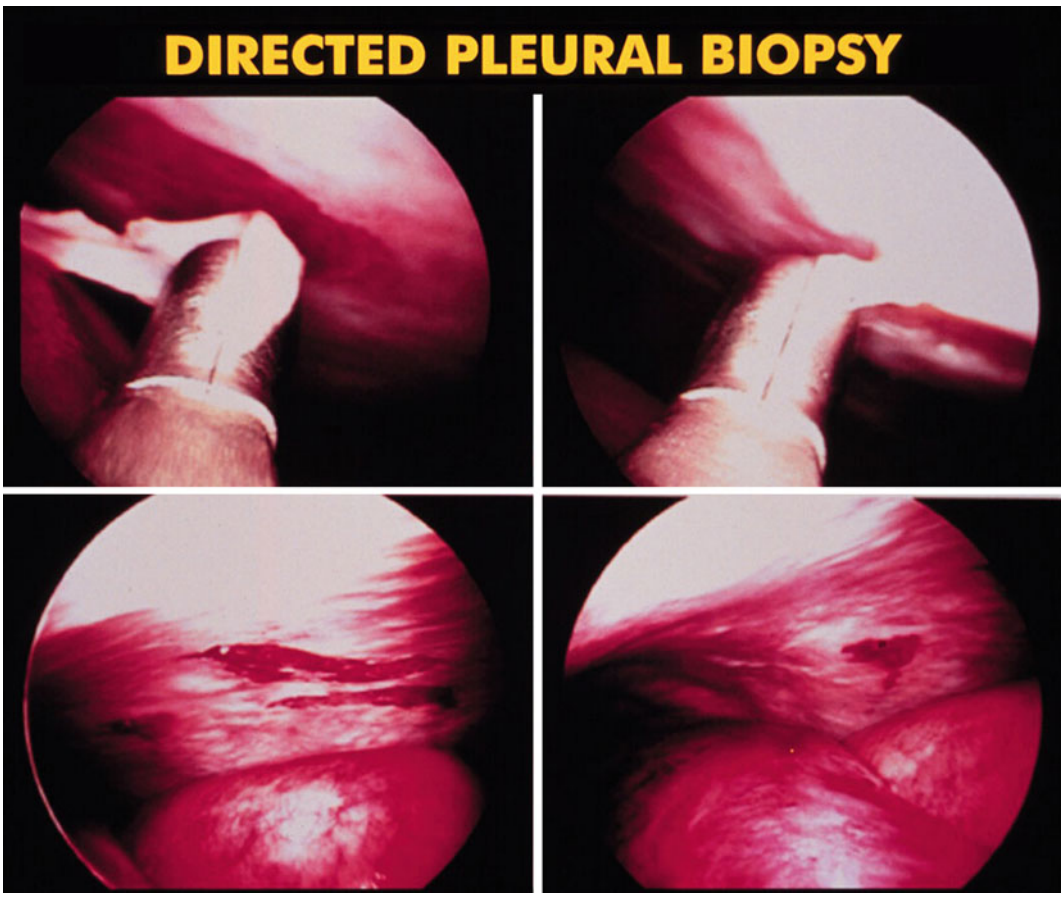

Fig. 64.4 Photo showing the sizable samples that can be obtained from the parietal pleura using medical thoracoscopy

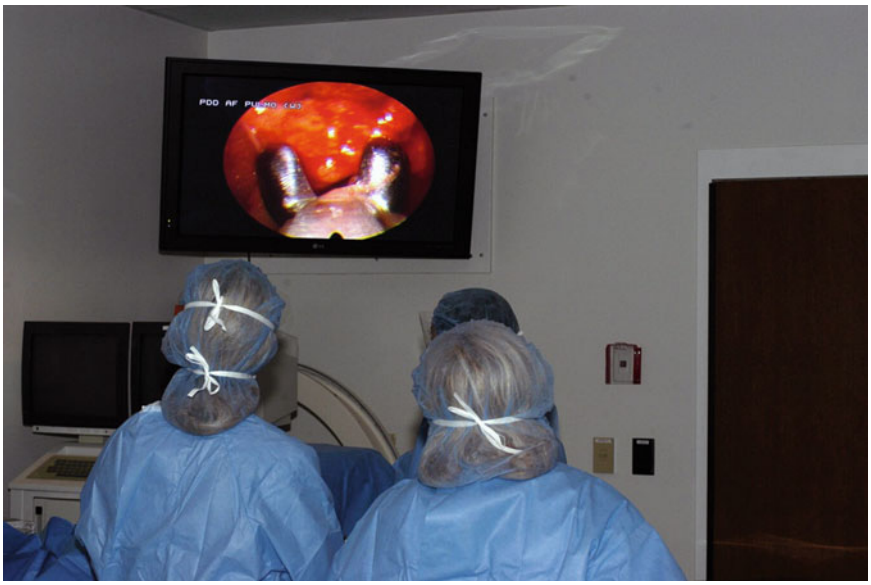

Fig. 64.5 Obtaining a parietal pleural biopsy during medical thoracoscopy

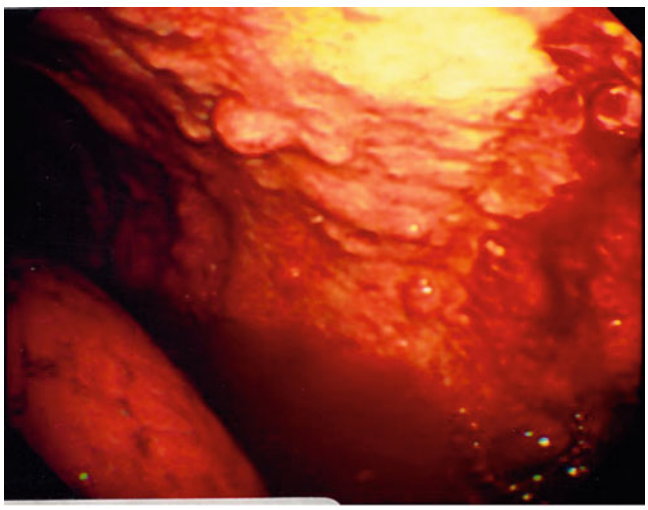

Fig. 64.6 Tumor studding along the parietal pleura. The biopsy revealed malignant mesothelioma

The cause of dyspnea, the most frequent and often the most distressing symptom, is likely multifactorial and can be due to compressive atelectasis, decreased lung compliance causing increased work of breathing, and worsened ventilation-perfusion mismatching causing hypoxemia. These problems are potentially improved by the drainage of the MPE.

Observation

Given that the treatment of a MPE is almost always palliative, directed at relieving symptoms, it is appropriate for patients without symptoms to be simply observed or treated for the underlying malignancy by an oncologist without drainage of the effusion. While many types of MPEs will not respond to chemotherapy or radiation therapy, some tumor types may respond, such as small cell bronchogenic carcinoma, lymphoma, breast adenocarcinoma, and prostate adenocarcinoma. Treatments involving drainage of the effusion, as described below, can be initiated if the MPE increases in size and begins to cause symptoms.

Therapeutic Thoracentesis

All patients with a MPE will have likely undergone a thoracentesis as part of the diagnostic evaluation. In addition to playing an integral role in the diagnosis of a MPE, thoracentesis also plays a central role in the palliative treatment when a large volume of pleural fluid is drained. Indeed, if a MPE is strongly suspected in a patient with a newly noted pleural effusion, both a diagnostic and therapeutic thoracentesis can be combined in one procedure. By draining a large volume of fluid, one can assess whether the patient's symptoms, particularly dyspnea, improve and whether the underlying lung reexpands radiographically. If symptoms significantly improve, other drainage procedures can be planned such as tube drainage and pleurodesis. If symptoms do not improve, other causes of the dyspnea should be considered, including underlying lung or heart disease, venous thromboembolism, chemotherapy- or radiation therapy-induced lung injury, tumor emboli, or pulmonary lymphangitic tumor spread. If the lung does not reexpand to touch the chest wall, one must consider pleural adhesions or lung entrapment by tumor preventing full expansion or atelectasis due to endobronchial obstruction by tumor. Such findings can affect diagnostic and treatment decisions; for example, diagnostic and therapeutic

bronchoscopy might be indicated for endobronchial tumor obstruction, or pleurodesis might not be attempted if the visceral and parietal pleural surfaces cannot be apposed because of trapped lung.

The use of ultrasound guidance for localization of the pleural effusion and to determine the optimal entry point for drainage before performing thoracentesis is becoming standard practice. Besides localizing pleural fluid, it also helps identify adhesions and fluid loculations and helps avoid puncturing visceral organs. Pleural manometry, although not yet widely adopted, can be helpful in identifying patients with trapped lung because of abnormally negative intrapleural pressures and may also help prevent reexpansion pulmonary edema by stopping drainage when intrapleural pressures exceed −20 cm H_2O (or when patients experience chest discomfort, which can be a surrogate for extremely negative intrapleural pressures.) The American Thoracic Society (ATS) and the most recent British Thoracic Society (BTS) practice guidelines continue to recommend limiting fluid withdrawal to <1.5 L during thoracentesis to avoid reexpansion pulmonary edema, in the absence of pleural manometry.

Large-volume thoracentesis is an important initial therapeutic measure for MPEs, but serial thoracentesis as the primary treatment modality is rarely a good option because of the propensity for the effusion to recur, the increased risk of multiple drainage procedures, and the increasing difficulty to completely drain the effusion because of adhesion formation and loculations with subsequent thoracenteses. In most cases, other procedures described below are generally better options because prevention of fluid reaccumulation is one of the goals of these procedures. Serial therapeutic thoracentesis should be reserved for patients with limited survival expectancy (<1 month) and poor performance status who cannot tolerate other drainage procedures.

Chest Tube Drainage and Pleurodesis

Adequate drainage of the MPE and prevention of fluid recurrence remains the main goal of the major treatment options. Prevention of fluid recurrence is most often achieved with chemical pleurodesis, which involves the instillation of a sclerosing agent into the pleural space. Several sclerosing agents have been used and described, all of which are meant to cause inflammation with fibrin deposition and consequent adhesion between the visceral and parietal pleural surfaces, thus preventing pleural fluid reaccumulation. Successful chemical pleurodesis requires the apposition of the pleural surfaces and thus reexpansion (at least partial, if not full) of the lung after pleural fluid drainage.

The two most common methods for draining the pleural fluid prior to instillation of a chemical sclerosant are chest tube drainage and thoracoscopic drainage. It had been previously assumed that large-bore chest tubes (at least a 24 F) were necessary for adequate drainage of the pleural space prior to chemical pleurodesis, but it has been shown in prospective, randomized control trials that smaller-bore chest tubes (10–14 F) provide adequate drainage with less discomfort compared to large-bore chest tubes. For chest tube drainage, the current BTS guidelines for the management of malignant pleural effusions recommend the insertion of a small-bore intercostal tube, controlled evacuation of fluid (initial drainage of 1.5 L, and 1.5 L at a time every 2 h) to prevent reexpansion pulmonary edema and radiographic confirmation of chest tube placement and lung reexpansion.

Many chemical sclerosants to achieve pleurodesis have been reported, but the most commonly used sclerosants are sterile talc, doxycycline, and bleomycin, with talc being the most commonly used. All three sclerosants can be instilled into the pleural space through a chest tube, although talc can also be instilled as a dry powder (poudrage) during medical thoracoscopy; this method will be described in the next section. The sclerosant of choice can be instilled as soon as the pleural effusion has been drained and when there is radiographic evidence of lung expansion; instillation does not need to be delayed until there is a predetermined amount of daily fluid drainage. Because the instillation of sclerosants (particularly doxycycline) is often painful to patients, lidocaine (3 mg/kg, maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration, and premedication to alleviate pain and anxiety should be considered.

There have been numerous reports describing the efficacy of various sclerosing agents for pleurodesis, but there have been few high-quality comparative effectiveness trials to determine the best sclerosing agent. Meta-analyses have consistently identified talc as having the highest efficacy (whether given as a slurry through a chest tube or by poudrage during thoracoscopy) with success rates ranging from 70% to 100%. The typical dose of talc when given as a slurry is 5.0 g diluted in 50–100 ml of normal saline. Common adverse effects of talc, likely secondary to pleural inflammation, include pain and discomfort, fever (which is common and often transient), hypoxemia (in up to 30% of patients), and dyspnea. Less common side effects include pneumonia, arrhythmias, and empyema. Acute lung injury and acute respiratory distress syndrome (ARDS) due to talc has been described by several authors and does not appear to be related to dose or method of delivery but may be related to talc particle size. The talc available in Europe (mean particle size >20 μm) has not been reported to cause ARDS, as opposed to the talc available in the United States (the only FDA-approved preparation is Sclerosol®), which contains particles <10 μm. It has been hypothesized that talc with smaller particle sizes (<10 μm) can be systemically absorbed into the vascular beds and cause an inflammatory reaction in the lung resulting in an acute pneumonitis or ARDS. The incidence of respiratory failure in patients with MPE receiving talc slurry for pleurodesis

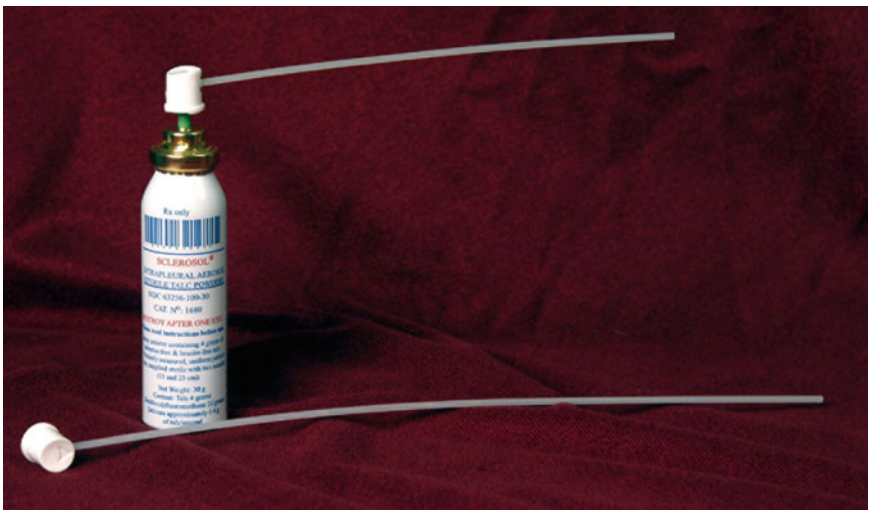

Fig. 64.7 Sterile talc that has been sterilized and packaged in a pressurized canister (Sclerosol®) for talc poudrage during medical thoracoscopy

was 4% in a prospective randomized trial. Despite the potential adverse effects, talc remains the most commonly used pleural sclerosant because of its wide availability, low expense, and good efficacy.

Tetracycline had been frequently used as a chemical sclerosant until its production ceased in the early 1990s. Doxycycline has been used as a substitute for tetracycline with successful pleurodesis rates of 60–81%. Common side effects include fever and pain, which can be severe and makes the use of intrapleural lidocaine and analgesics all the more important when using doxycycline. A typical doxycycline dose is 500 mg diluted in 50–100 ml of sterile normal saline instilled through the chest tube.

Bleomycin is an effective sclerosant with successful pleurodesis rates reported at 58–85%. Common side effects include fever, chest pain, and cough. It is not used commonly in the United States because of its relatively high cost, especially compared to talc, and its lack of demonstrated superiority over talc.

It is common practice to rotate the patient to different positions after instillation of the sclerosant to ensure intrapleural dispersion, but prospective studies have shown no advantage of rotational maneuvers over simply clamping the tube for 2 h. It has also been customary to remove the chest tube when daily pleural fluid drainage has fallen below a threshold level, such as 100–150 ml per day, but it is possible to remove it sooner as long as the chest x-ray shows adequate drainage for the effusion without diminishing effectiveness.

Thoracoscopic Drainage and Pleurodesis

Medical thoracoscopy can be used to achieve pleurodesis by completely draining the pleural space and instilling the sclerosing agent under direct vision, usually dry talc delivered as a poudrage (see Figs. 64.7 and 64.8). There are several theoretical advantages to thoracoscopic talc insufflation compared with talc slurry sclerosis. Medical thoracoscopy allows complete effusion drainage under direct visualization and optimal chest tube positioning. Talc is insufflated in a manner that allows even distribution over the entire visceral and parietal pleural surfaces. In contrast, the slurry of water-insoluble talc may gravitate to the dependent part of the pleural space shortly after instillation. Finally, in patients with an underlying malignancy but negative fluid cytology, parietal pleural biopsies of suspicious areas can be taken at the time of medical thoracoscopy, before proceeding with pleurodesis. A systematic review comparing the various treatment options to achieve pleurodesis in patients with MPE was published in the *Cochrane Database* in 2004. The comparison of thoracoscopic talc pleurodesis (TTP) and talc slurry pleurodesis favored thoracoscopic pleurodesis, with a relative risk for nonrecurrence of the effusion of 1.19 (95% CI, 1.04–1.36).

A large, multicenter randomized trial comparing talc poudrage with talc slurry was conducted by the North American Cooperative Oncology Groups in which a total of 482 patients were randomized to thoracoscopy with talc insufflation (n = 242) or tube thoracostomy with talc slurry (n = 240). Overall, no difference was detected in the percentage of patients with successful pleurodesis at 30 days (78% for TTP and 71% for talc slurry). However, in the subgroup of patients with primary lung or breast cancer, the success rate of TTP was found to be significantly higher than with talc slurry (65% vs. 50%, p = 0.014). Lung cancer and breast cancer are the first and second most common neoplasms causing malignant effusions, and these findings suggest that TTP may be a better option for a large proportion of patients

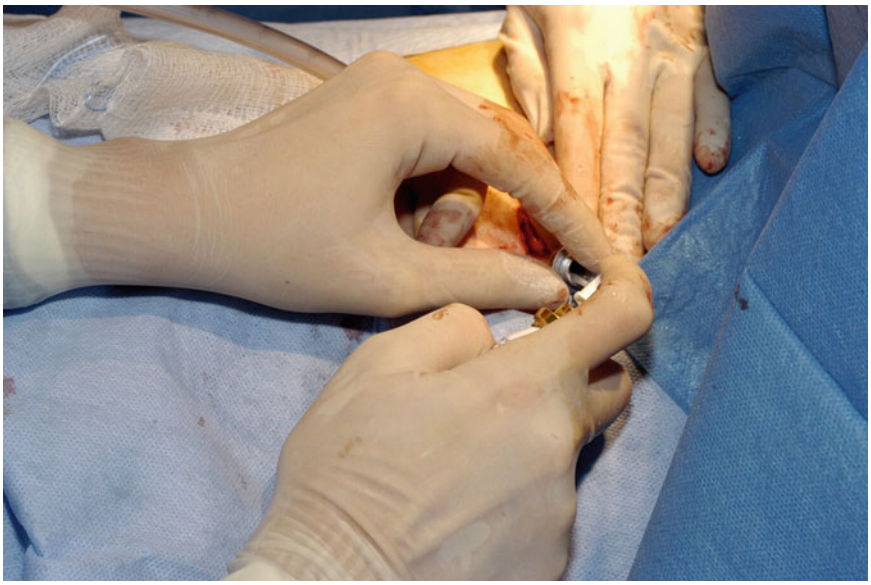

Fig. 64.8 Performing talc poudrage using Sclerosol® during medical thoracoscopy

with MPE. Moreover, a subgroup analysis of those patients with lung cancer or breast cancer who achieved lung expansion after drainage of the fluid (and therefore did not have radiographic evidence for trapped lung) and were alive at 30 days showed that TTP achieved successful pleurodesis more frequently compared to talc slurry (82% vs. 67%, $p=0.022$).

The most common side effects reported with TTP are pain and fever. In a detailed review of pleurodesis agents, pain following talc insufflation occurred in 7% of patients and fever occurred in 16% of patients. The fever has been shown to be related to the talc and not to the thoracoscopy. Empyema following TTP has been reported in 0–3% of patients, and local site infection is uncommon. Cardiovascular complications reported with TTP include arrhythmias, cardiac arrest, chest pain, myocardial infarction, and hypotension; these may be attributable to the procedure and not talc per se. Death directly related to medical thoracoscopy is extremely rare.

As described earlier, talc has been associated with acute lung injury and, rarely, ARDS and respiratory failure. In a recent single-center retrospective review of 138 patients undergoing TTP using Sclerosol®, the incidence of talc-related acute lung injury was at least 2.8% and possibly 5.6%.

Safe and successful TTP depends, in large part, on judicious patient selection. It should be demonstrated that drainage of the fluid results in symptom relief, that pleurodesis is achievable since the lung is expandable, that the patient can tolerate moderate sedation required for thoracoscopy, and that the patient can tolerate the procedure itself. In a study examining predictors of survival in patients with symptomatic MPE referred for TTP, the authors concluded that performance status, as measured by the Karnofsky score, was the best predictor. The authors proposed that a Karnofsky score ≥70 (which reflects a patient who is ambulatory and living independently) may be a reasonable marker for deciding which patients with MPE should undergo TTP. In patients with MPE, overall prognosis should thus be considered in the selection of patients for TTP. As an example, a patient with MPE who has a Karnofsky score of ≥70 and an expected prognosis of more than 6 months might be an excellent candidate for TTP, whereas other options (such as tunneled pleural catheters, which will be described later, or palliative care) should be considered for a patient with a poor performance status and an expected survival of less than 1–2 months.

It has been standard practice to hospitalize patients after pleuroscopy and talc poudrage with a chest tube in place until pleural drainage has diminished to <100–150 ml/day; this typically requires hospitalization for 6–7 days. A recent pilot study in which a tunneled pleural catheter (described in more detail below) was placed at the time of medical thoracoscopy and left in at the time of patient discharge for frequent, intermittent drainage showed that pleurodesis was achieved in 92% of 30 patients. The median duration of hospitalization following the procedure was 1.79 days, and the tunneled pleural catheter was removed at a median of 7.54 days. The placement of a tunneled pleural catheter at the time of medical thoracoscopy and talc poudrage can potentially allow earlier discharge and shortening of a hospitalization.

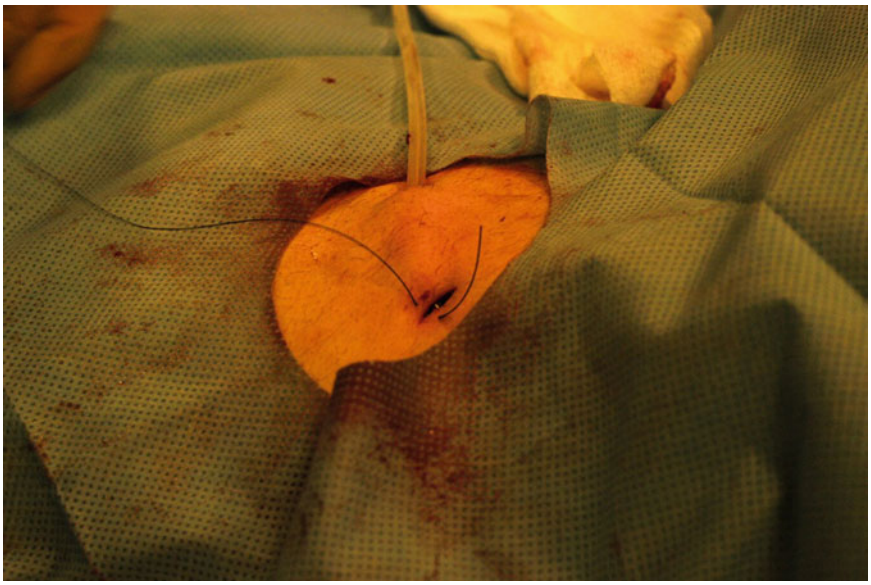

Fig. 64.9 Completing the placement of an indwelling tunneled pleural catheter

Indwelling Tunneled Pleural Catheter

Another option for the treatment of patients with symptomatic MPEs includes the placement of an indwelling tunneled pleural catheter (TPC), which can be placed at the bedside, using only local anesthesia (Fig. 64.9). A major advantage of using a TPC is that it can be placed in the ambulatory setting, making hospitalization unnecessary and allowing the patient to return home. Furthermore, it has been reported that pleurodesis can occur even without the instillation of sclerosant. It may also be useful in relieving dyspnea in patients with trapped lung in whom pleurodesis cannot be achieved. It does require knowledge of basic sterile technique and the intermittent drainage of pleural fluid through the TPC by the patient or the patient's caregiver.

There had been a previous report showing the feasibility and efficacy of using a small-bore pigtail catheter for drainage and pleurodesis in the outpatient setting. The introduction of a commercially available TPC and accessories led to its widespread adoption and case series reports of its clinical effectiveness. Symptom relief is frequently achieved, even in the presence of trapped lung, and spontaneous pleurodesis occurred in 42–58% of patients. The major risk of the TPC was infection with cellulitis (1.6%) and empyema (3.2%). Other potential complications include loculation of fluid and catheter blockage, pneumothorax, tumor seeding, and bleeding.

There are few studies comparing the effectiveness of using TPC to other methods of drainage and pleurodesis. One descriptive study showed the use of TPC to be an effective alternative method in patients with trapped lung in whom thoracoscopic talc pleurodesis was not a good option. A randomized study compared the use of TPC to doxycycline pleurodesis using a standard intercostal tube in the management of MPE and found shorter hospitalizations, a spontaneous pleurodesis rate of 46% at a median of 26.5 days, and a similar late recurrence rate (13% vs. 21%).

The use of TPC should be considered in symptomatic patients with MPE when there is trapped lung and evidence of symptom relief with fluid drainage, the patient has a poor performance status and therefore a poor candidate for medical thoracoscopy, or in patients who prefer to avoid hospitalization for chest tube drainage and pleurodesis.

Palliative/Hospice Care

All of the aforementioned therapeutic options for MPE are considered palliative since the goal is relief of dyspnea. For patients with poor performance status and extremely poor prognosis, it may be reasonable to forgo any drainage procedure and focus solely on comfort measures, using opiate analgesics and anxiolytics as required. Hospice care, either as an inpatient or outpatient, may be the most appropriate option in some circumstances.

Treatment Algorithm

See Fig. 64.10.

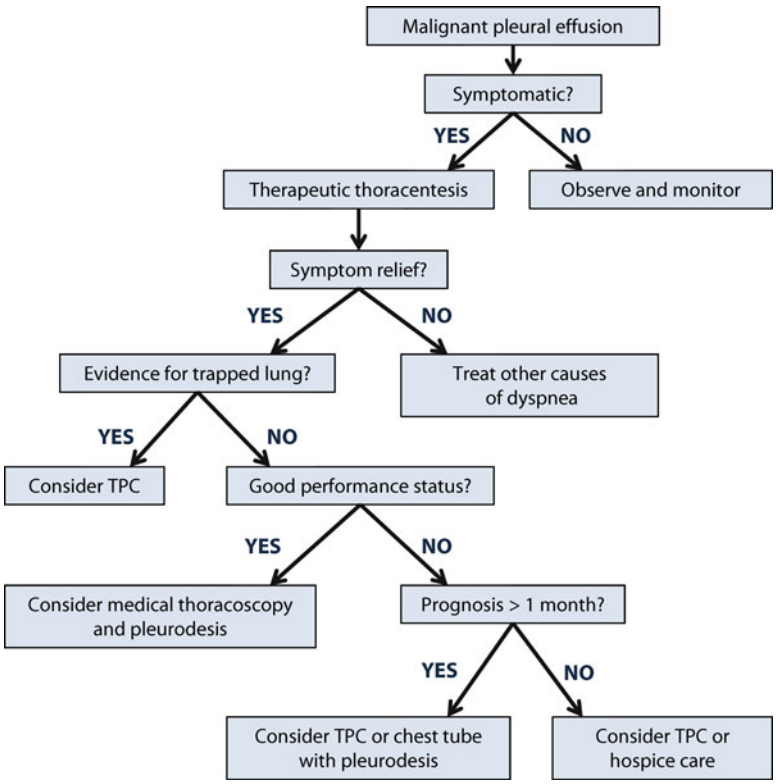

Fig. 64.10 Suggested algorithm for the treatment of patients with malignant pleural effusions (TPC = tunneled pleural catheter)

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