An Update in the Management of Malignant Pleural Effusion

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ABSTRACT

Malignant pleural effusion (MPE) usually presents in the disseminated and advanced stage of malignancy. Dyspnea is the debilitating symptom which needs palliation in these patients. Various modalities are available in the management of MPE. Careful consideration of the patient's expected survival and quality of life is needed when deciding the optimum treatment modality in such patients. In this article, different modalities of the palliative management of MPE are discussed with an attempt to derive a treatment algorithm for the management of MPE.

Key words: Malignant pleural effusion, Pleurodesant, Pleurodesis, Talc, Tube thoracostomy

INTRODUCTION

Advanced malignancies are frequently complicated by malignant pleural effusions (MPEs). They present either synchronously or as recurrence after the completion of treatment of the primary malignancy. The pathogenesis of MPE is by hematogenous or lymphatic implantation of tumor cells or by direct extension of tumor cells from adjacent organs such as lung, breast, chest wall, or pleura.

EPIDEMIOLOGY

Neoplasms of lung, breast, ovary, and lymphomas constitute more than 75% of cases of MPE.[1-4] Metastatic adenocarcinoma is the most common cause.[5] In male patients, lung cancer is the most common cause and in females, breast cancer is the most common cause [Table 1].[5,6] The presence of MPE implies disseminated or advanced disease and a reduced survival. The median survival following a diagnosis of malignant pleural effusion depends on the organ of origin of primary tumor, histological type and stage, and usually ranges from 3 to 12 months. Lung cancer has the shortest, ovarian cancer has the longest, and cancer of unknown primary has an intermediate survival.[7-10]

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PRESENTATION

The main symptom of MPE is chronic shortness of breath, although cough and pain can also be debilitating. All these greatly diminish the quality of the final phase of life for patients living with cancer. The management of dyspnea is the main complain which needs palliation in MPE. Treatment goals for these patients should focus on the relief or elimination of dyspnea, restoration of normal activity and function, minimization or elimination of hospitalization, and efficient use of medical care resources.[11-13]

Table 1: Etiology of malignant pleural effusion

Sites	Male	Female
Lung	50	15
Breast	Rare	40
Lymphoma and leukemia	20	8
Gastrointestinal	7	4
Genitourinary	6	20
Others	6	4
Unknown primary	11	9

LABORATORY DIAGNOSIS

Chest radiographs confirm the size and location of the pleural collection. Thoracentesis is usually diagnostic and also therapeutic. Exudative and hemorrhagic collections should be considered metastatic until proved otherwise. Symptomatic relief is frequently attained by removing a large amount of fluid. Cytologically malignant cells are detected in approximately 50% of proven MPEs.[14-16] A CT scan may give information about loculations of MPE, the primary disease process, and anatomy of other organs in the thorax.

MANAGEMENT

Apart from the management of the primary disease process with chemotherapy, surgery, or radiation, the main concern of MPE is palliation of dyspnea. In this article, the issues concerning the palliation of MPE will be discussed in detail.

The palliation of dyspnea in MPE is managed by the removal of fluid from the pleural space by a least invasive procedure with minimal morbidity within the limited survival period of these patients. The methods of removing fluid from the pleural space can be simple single time aspiration, tube thoracostomy, or video-assisted thoracoscopic surgery (VATS). Tube thoracostomy and VATS can be followed by pleurodesis. The aggressiveness with which treatment is done depends mainly on two factors, i.e., the extent of symptoms caused by MPE and the performance status of the patient.

Thoracentesis

Thoracentesis, or simply called aspiration of pleural fluid, is mainly used for diagnostic purposes in patients with asymptomatic MPE. Aspiration in symptomatic MPE may provide temporary relief of dyspnea, but usually failed by reaccumulation of fluid in 98–100% of patients. Repeated aspiration in these patients can be complicated with the development of iatrogenic pneumothorax, pleural fluid loculation, or contamination with subsequent empyema.[17-19] Repeated thoracenteses, therefore, should be reserved for patients who (1) have slow reaccumulation of pleural effusions after each thoracentesis, (2) have cancers that commonly respond to therapy with resolution of the associated effusions, (3) appear unlikely to survive beyond 1–3 months, and (4) cannot tolerate other more interventional procedures to control pleural fluid, such as pleurodesis.[18,19]

Tube thoracostomy

Tube thoracostomy involves making a hole in the intercostal space into the pleural cavity (blindly or with image guidance) under aseptic precautions with placement of a secured tube for continuous drainage into a water-sealed container. Tube thoracostomy can be preceded by VATS with operative visualization of the pleural cavity and pleural biopsy for diagnostic purposes. But, VATS can only be performed in those patients who can tolerate anesthesia and single lung ventilation.[20] Either large-bore (28–36 F) or small-bore (7–16 F) chest tube can be used for reliable drainage and both have equivalent results. Thoracostomy tube should not be kept for a prolonged period for fear of infection, empyema, pneumothorax, etc. The recurrence of MPE is seen in around 80% of patients within 30 days after the removal of the tube.[17] So, thoracostomy may be sufficiently therapeutic for patients with a short expected survival of 1–3 months.[18] For patients with greater survival, an alternative procedure has to be adopted to prevent reaccumulation.

A thoracostomy tube is usually inserted at the bedside under aseptic precautions in the 5th intercostal space anterior to the mid-axillary line in the triangle of safety. Loculated MPE cannot be drained by the insertion of a single chest tube. Multiple chest tubes may be needed, but this needs to be carefully decided.

Pleurodesis

Once the thoracostomy tube in the pleural space drains 150 ml per day and the lung is fully expanded which is confirmed on chest roentgenogram, the next aim is to prevent reaccumulation by another procedure.[21] Pleurodesis is the process by which the pleural space is obliterated by inflammation induced through chemical or mechanical means, to achieve definitive and long-standing pleural apposition with fibrosis. Most physicians consider an expected survival beyond 2–3 months necessary to justify the risks, discomforts, and cost of pleurodesis. So, all patients with symptomatic MPE who are with a life expectancy of 2–3 months or more should be evaluated for pleurodesis. Those patients with a very limited life expectancy can be treated only with tube thoracostomy or thoracentesis.[22]

Pleurodesis should be done in patients who are supposed to respond to the procedure. Pleurodesis usually remains unsuccessful for patients with a trapped lung, which cannot fully inflate due to scarring, adhesions, obstructive atelectasis from an endobronchial tumor, multiple pleural loculations, or extensive intrapleural tumor masses. Of the patients who are evaluated for pleurodesis, nearly 30% are unsuitable candidates for the procedure because of trapped lungs.[23]

Agents for pleurodesis

Chemical pleurodesis is the most commonly used method of pleurodesis. Many agents have been described for chemical pleurodesis including bleomycin, tetracycline/doxycycline, *Corynebacterium parvum* extract, silver nitrate, iodopovidone, quinacrine, interferons, interleukin-2, and several chemotherapeutics [Table 2].[24] All these pleurodesants are usually administered through a chest tube, after the drainage of the MPE with the drain amount less than 150 ml per 24 h. Bleomycin is the most widely administered antineoplastic agent with a success rate of 60–80%. It is associated with chest pain, fever, and nausea and is generally well tolerated, although it is costly. Tetracycline and doxycycline are also commonly used for pleurodesis and have similar clinical success rates, although they are associated with intense pleuritic pain.[25,26] There are also reports of acute renal failure, anaphylaxis, and acute respiratory distress syndrome (ARDS) after tetracycline pleurodesis.[27,28] Reports of serious adverse effects after intrapleural doxycycline administration are absent from the literature. Alternative methods of pleurodesis should always be considered if sensitivity is suspected.

Although talc is the most effective pleurodesant, it is not without complications with rare reports indicating that the incidence of ARDS can be as high as 1–9% due to intense pleuritis.[29] There are studies from across the world showing conflicting results of the deposition of talc in the alveoli of the lung with subsequent ARDS.[30-32] The literature also advocates the fact that the complication may be related to large doses of talc[33,34] although this hypothesis is questioned.[20,35,36] Some authors have the opinion that the different geographic variations in complications of talc pleurodesis are due to the size of the particles of the talc used in different studies.[37-39]

A prospective, randomized trial[40] concluded that bleomycin is as effective as talc, but the agent is extremely costly. One report of ARDS and subsequent death after bleomycin pleurodesis has been described.[41] A recent meta-analysis comparing talc, bleomycin, tetracycline/doxycycline, *C. parvum* extract, and mitozatrone did not find one agent that was significantly better than the others, although the trend was toward better success with talc.[42] Shaw *et al*.[43] in a Cochrane meta-analysis found that talc was associated with a significantly better chance of success than any other agent. The rate of complications was similar regardless of the pleurodesant. Fever and chest pain were the most common adverse events. These two meta-analyses point that talc is the most effective pleurodesant.[42,43]

Procedure of pleurdesis

Talc is used either in the form of poudrage or slurry.

Table 2: Agents of pleurodesis

Agents	Advantages	Disadvantages	Remarks
Talc	Cheap, easily available, highest efficacy	Reports of ARDS, renal failure	+++
Bleomycin	Efficacy similar to talc	Very costly, chest pain, fever nausea	++
Povidone iodine	Cheap, easily available	Anaphylaxis, randomized study required involving larger number of patients	++
Tetracycline/ doxycycline	Easily available	Very painful, ARF	++

Poudrage is defined as the surgical application of a slightly irritating powder, such as an aerosolized drug applied during a thoracoscopic procedure (i.e., talc poudrage), to the opposing pleural surfaces in order to secure adhesion. Slurry is defined as a watery mixture of insoluble matters in a liquid (usually talc in 5% dextrose with a local anesthetic) and is introduced through a chest tube.[44] Most studies report an overall effectiveness of 60–90% at 30 days for treating dyspnea and MPE.[20,45] Different studies show that the effectiveness of talc poudrage is more than 90%.[20]

To accurately compare the effectiveness of talc poudrage versus talc slurry, there have been three randomized prospective trials, all of which have shown a similar efficacy.[44,46,47] The largest trial, which included 482 patients, found that for all patients, the rate of recurrence was similar after 30 days for either group, but the success rate of poudrage was significantly higher than talc slurry in the subset of patients with lung or breast cancer. However, there was a slightly higher mortality and rate of respiratory complications in the poudrage group.[46]

Conventional pleurodesis

In the traditional approach to chest-catheter pleurodesis, a short-term catheter is inserted intrapleurally, either blindly or by image guidance for the drainage of the pleural fluid and instillation of a sclerosing agent. The tube is removed when minimal fluid remains to be drained. Many studies showed that small-bore (9–14 F) catheters are as effective as conventional large-bore (20–32 F) chest tubes.[48-54] Most experts recommend that the sclerosant be instilled only when catheter drainage has decreased to less than 150 ml/day.[8] When talc is used as a pleurodesant, it is used as a slurry. Six gram of talc is instilled, as a slurry, in a 200-ml saline solution, to which 20 ml of 7.5% ropivacaine is added to decrease associated pain. The tube is clamped for 8 h, and the patient turned in different positions. After 8 h, the drain is connected to slow suction of 20 cm of H_2O for 24 h.[44] At the end of the procedure, the patient can be discharged from the hospital. The tube is left in place,

until less than 100 ml[44] to 150 ml[22] of fluid is drained in 24 h. Chest roentgenograms are obtained 1 month after the procedure and then monthly for 3 months. Further follow-up is needed as per the type of tumor and the onset of respiratory symptoms.

Video-assisted thoracoscopic surgery pleurodesis

Talc poudrage is performed by videothoracoscopy, under general anesthesia and selective one-lung ventilation. Any residual fluid is aspirated, loculations are divided when present, pleural biopsies are taken if necessary, and lung reexpansion is confirmed. Using a disposable gas-propelled atomizer, 6 g of talc is insufflated and uniformly distributed onto the pleural surface. A chest drain is inserted and positioned toward the apex and a small-bore catheter (10 F), with a three-way stopcock is placed in the posterior costovertebral gutter. The apex chest tube is removed when the chest is expanded and the output drops below 150 ml. The patient is discharged with the small-bore catheter in place for outpatient management. Chest X-rays are obtained at 1 and 2 weeks. If pleurodesis is achieved, the pleural catheter is removed, usually 2 weeks after the procedure.[44]

A recent prospective randomized study was done to compare the efficacy, safety, and outcome of thoracoscopic talc poudrage (TTP) versus povidone iodine pleurodesis (PIP) through a thoracostomy tube as palliative treatment of MPE due to metastatic breast cancer.[55] A total of 42 patients were prospectively enrolled (22 received talc poudrage and 20 patients received pleurodesis by instilling povidone iodine through a thoracostomy tube, as a bedside procedure). There were no in-hospital deaths. TTP was associated with severe pleuritic chest pain (18% vs. 0%, $P = 0.2$), fever (18% vs. 5%), and longer hospital stay ($P = 0.009$). Both groups achieved good symptom control. The recurrence of MPE requiring intervention was not significant in the two groups (2 vs. 3 patients, P = ns). Although the study was small, it can be concluded that povidone iodine is easily available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary. Povidone iodine is a good alternative to TTP. A larger randomized study, inclusion of talc slurry as an arm, and inclusion of MPE arising out of other malignancies are necessary to come to a conclusion about the efficacy of povidone iodine.

Survival after pleurodesis

The most difficult question to answer is the improvement of survival with pleurodesis. As such, pleurodesis is purely a palliative procedure and it only decreases the mortality out of respiratory compromise and thus improving quality of life and survival. Multiple clinical factors have been used to estimate survival after pleurodesis, including the organ of origin of malignancy, cell type (adenocarcinoma, squamous, small cell, etc.), stage of the tumor, characteristics of the pleural fluid, and performance level. Unfortunately, in spite of careful selection, 32% of patients do not survive 30 days after pleurodesis.[19,56-59] The American Thoracic Society/European Respiratory Society guideline for the management of MPE recommends that pleurodesis should be limited to patients with pleural fluid pH values greater than 7.30, because of the direct correlation between low pH and poor short-term survival.[19,60-63] Among the criteria now in common use, performance status is the most important for estimating postpleurodesis survival.[64]

SURGERY FOR MALIGNANT PLEURAL EFFUSION

Thoracostomy with pleurectomy and decortication are effective means of pleurodesis. However, these operations have a mortality of 10% in excess and a high morbidity, especially prolonged air leaks.[65,66] It is only in some selected patients, with a high functional reserve and a trapped lung, that the operation may provide a benefit.

SUMMARY

MPEs present usually in a disseminated and advanced stage of malignancy. Different methods exist for the palliation of dyspnea in these patients. Careful consideration of the patient's expected survival and quality of life is needed when deciding between simple thoracentesis, thoracostomy,

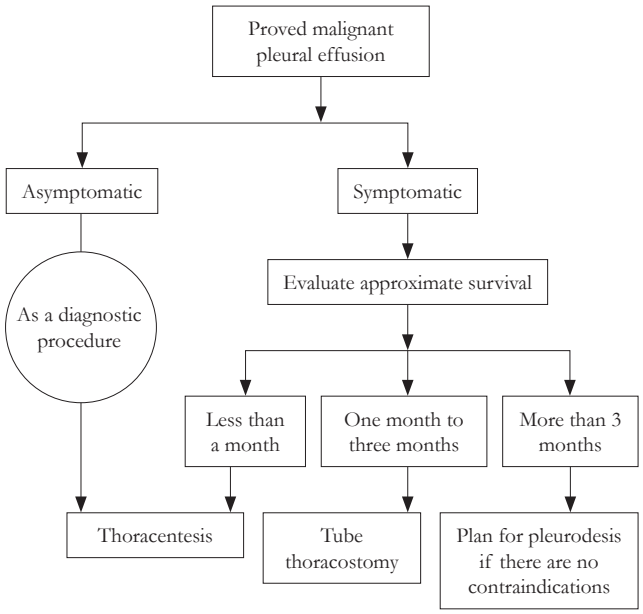

Figure 1: Flow chart in the management of malignant pleural effusion

or pleurodesis, owing to their limited survival and varying performance status [Figure 1]:

- Thoracentesis – repeated aspiration may be the only method in patients with a poor performance status with a very limited life span.
- Thoracostomy – survival of at least 1 month is required to justify the risks and morbidity of tube thoracostomy. Small-bore tube thoracostomy has similar efficacy to large-bore tube thoracostomy.
- Pleurodesis – for patients with expected survival of more than 2–3 months, pleurodesis should be considered. Talc is the most effective, cheap, and easily available pleurodesant. For patients who can tolerate general anesthesia and single lung ventilation, a VATS procedure helps in diagnosis and simultaneously draining the effusion, freeing the lung from adhesions if necessary and simultaneously performing talc pleurodesis. For patients unable to tolerate an operation but with an expandable lung, bedside tube thoracostomy to drain the effusion till the drain output is less than 100 ml followed by talc slurry pleurodesis has a similar efficacy to VATS talc poudrage.

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