PATHOGENESIS AND MANAGEMENT OPTIONS OF MALIGNANT PLEURAL EFFUSION: A REVIEW ARTICLE

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ABSTRACT
Malignant pleural effusion is a common complication of many advanced malignancies and is associated with reduced life expectancy. The pathogenesis of malignant effusion depends on the type of cancer. This review briefly discusses the pathogenesis and various management options.

Keywords: Malignant pleural effusion, Tunnelled indwelling pleural catheter, Pleurodesis.

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INTRODUCTION

Pleural effusion complicates many advanced stage intrathoracic and extrathoracic malignancies. The diagnosis of a malignant effusion usually portends as a poor prognosis with an estimated median survival of between 3 and 12 months after diagnosis[1]. Currently, the most common metastatic tumour to the pleura is lung cancer in men and breast cancer in women[1]. Together, both malignancies account for 50-65% of all malignant effusions[4]. Lymphomas, tumours of the genito-urinary tract and gastrointestinal tract account for a further 25%[1]. In approximately 5-10% of malignant pleural effusion, no primary tumour site can be identified[2]. Mesothelioma accounts for about 3% of cases in old case series [3]. However, there are no recent data to reflect the impact of mesothelioma in light of its increasing incidence. The optimal management of malignant pleural effusion continues to provide formidable challenges to chest physicians around the world.

This article briefly discusses the pathogenesis and management options of malignant pleural effusion with a special emphasis on the use of the tunnelled indwelling pleural catheters (TIPIC) to provide outpatient management.

Pathogenesis:
Malignant pleural effusion (MPE) is defined by the discovery of cancer cells in the pleural space. The pathogenesis of MPE is often multifactorial and depends on both the type of malignancy and patient comorbidities[4]. In general, the development of MPEs could result from either direct or indirect effects of the underlying malignancies. Metastatic MPEs result from direct extension of malignant cells from an adjacent cancer (such as malignancies of the lung, breast, and chest wall), invasion of the pulmonary vasculature with embolization of tumour cells to the visceral pleura, or hematogenous metastases from distant tumours to the parietal pleura[9]. This metastatic spread subsequently results in obstruction of lymphatic stomata along parietal pleural membranes and causes impairment of pleural fluid drainage. Furthermore, pleural tumour deposits also stimulate the release of chemokines that increase vascular and pleural membrane permeability, thereby promoting pleural effusion[6,7]. Patients with cancer can also develop pleural effusion even in the absence of cancer cells in the pleural space through the indirect effects of the underlying malignancy. These effusions termed as paramalignant or paraneoplastic effusions. They result from various mechanisms such as bronchial obstruction, mediastinal lymph node metastasis, concurrent superior vena cava syndrome, pulmonary embolism, and the effect of radiochemotherapy.

Management principles:
Significant morbidity is associated with the development of a MPE. The majority of patients who present with malignant pleural effusion are asymptomatic, although up to 25% are asymptomatic with an incidental finding of effusion on physical examination or by chest radiography[10]. Dyspnea is the most common presenting symptom[8]. Chest pain occurs due to parietal pleural involvement, ribs or intercostal structure infiltration. Patients may also experience cough, decreased exercise tolerance and weight loss. The development of a malignant effusion can have a profound impact on the overall quality of life experienced by cancer patients in the terminal stages of their illness[9].

The optimal management of MPEs has long been a challenge for physicians caring for patients with end stage cancer. Current management strategies vary widely amongst institutions, and range from surgical procedures requiring hospitalization to treatment on an outpatient basis. Furthermore, management of malignant effusions depend on several factors: symptoms and performance status of the patient, the primary tumour type and its response to systemic therapy, as well as degree of lung re-expansion following pleural fluid evacuation[10]. Arguably, the ideal management of MPEs would effectively palliate patient symptoms while minimizing complications, cost, and time in hospital[4,10]. In addition, the effective management of malignant effusions is complicated by their extremely high rates of symptomatic recurrence[11]. For instance, an early study described the re-accumulation of pleural fluid within 4.2 days of initial drainage[12], while a 30 day recurrence rate of 98% has been reported elsewhere[13]. Therefore, the management of an MPE requires both, short-term palliation of symptoms and a means to prevent or control recurrence of the effusion.

Management Strategies:
Options for management include observation, therapeutic pleural aspiration, and intercostal tube drainage, in addition to instillation of sclerosant, thoracoscopy and pleurodesis or placement of an indwelling pleural catheter[1]. Advantages and disadvantages of available management strategies briefly reviewed with special emphasis on the use of tunnelled pleural catheter to provide outpatient management.

Observation:
Observation is recommended if the patient is asymptomatic and the tumour type is known[1]. However, the majority of patients will become symptomatic in due course and interventions will need to be undertaken.

Therapeutic Pleural Aspiration:
Repeat therapeutic thoracentesis in the past have been advocated as a viable option for frail patients with a very limited life expectancy for the rapid relief of dyspnea and avoidance of hospitalization. However, due to high recurrence rate of MPEs, this strategy is not recommended if life expectancy is more than one month[11].

Intercostal Tube Drainage and Instillation of Sclerosant:
Chest tube drainage with instillation of a sclerosing agent to induce pleurodesis is also an effective strategy and has long been used in the management of malignant effusions[1,5]. In fact, intercostal drainage without pleurodesis is associated with a high rate of effusion recurrence and should be avoided[1]. Small bore intercostal catheters (10-14 F) are recommended.
to be used for effusion drainage and pleurodesis\(^\text{[1]}\). While the chest tube drains the pleural space allowing pleural apposition, a chemical agent such as talc, doxycycline or bleomycin provokes an inflammatory response within the pleural space ultimately leading to pleurodesis\(^\text{[14]}\). Successful pleurodesis rates of 71% to 96% have been reported for procedures using talc as a sclerosant\(^\text{[5]}\). However, chemical pleurodesis is limited by several disadvantages. This includes the need for hospitalization with a median stay of approximately 7 days\(^\text{[15]}\), thus, often perceived to be a major disadvantage by terminally ill patients. Furthermore, re-accumulation of fluid requiring a second procedure and common procedural side effects such as chest pain are also recognized as disadvantages\(^\text{[9]}\). In addition, a significant subset of patients with an MPE fails to respond to chemical pleurodesis. Poor response is usually attributable to factors preventing adequate apposition of pleural surfaces including a large intrapleural tumour burden, endobronchial obstruction or pleural loculations leading to trapped lung\(^\text{[5,16,17]}\). Dresler et al. found that up to 30% of patients considered for pleurodesis were ultimately deemed poor candidates due to the presence of trapped lung\(^\text{[17]}\).

**Thoracoscopy and Pleurodesis:**

Pleurodesis to eliminate the pleural space is a widely accepted and an effective way to manage recurrent effusions. However, the optimal way to achieve pleurodesis has been a matter of some debate, and the literature reflects significant variability in both technique and outcome\(^\text{[18]}\). Insufflation of a sclerosing agent such as talc during medical or surgical thoracoscopy is a common means to achieve pleurodesis and treat MPEs. This modality is effective with short term rates of successful pleurodesis ranging from 71% to 97%\(^\text{[3]}\). Thoracoscopy has added benefits of facilitating lysis of adhesions or loculations when present to enhance lung re-expansion and providing a diagnostic tool when the aetiology of an MPE is uncertain. However, thoracoscopy is a relatively more invasive and a costly procedure. Careful selection of patients with a high performance status (i.e., Eastern Cooperative Oncology Group, ECOG<2) is often required due to the need for increased sedation or even general anaesthesia\(^\text{[5]}\). These patients need to be either fully functioning or at worse, they are amputulary and capable of self-care and are up-and-about>50% of waking hours. Furthermore, thoracoscopic has less to offer in patients with a known malignant pleural effusion, and a clearly trapped lung on the chest X-ray\(^\text{[4]}\).

Although a number of sclerosing agents are available for use in chemical pleurodesis, sterile talc has been shown to be the most effective in a number of studies, including a recent meta-analysis\(^\text{[1,19]}\). Talc was first used as a sclerosant in 1935 and continues to be widely utilized. However, data on the efficacy of talc are primarily limited to small scale, single center clinical studies. Many of these studies are limited by the use of variable definitions of pleurodesis, short post-procedure follow up, and limited data on long-term symptom control or impact on patient quality of life. In addition, the safety of talc has been questioned. Adverse effects associated with talc instillation in the pleural space range from fever, dyspnea, and chest pain to the development of acute respiratory failure and ARDS\(^\text{[5]}\). However, the development of ARDS is believed to be related to the systematic absorption of talc particles through the pleural membranes. Thus, talc particle size appears to be a significant factor, with increased complications observed with smaller particle size\(^\text{[5]}\). In fact, the use of large-particle talc for pleurodesis in malignant pleural effusion is safe and not associated with the development of acute respiratory distress syndrome\(^\text{[20]}\). The elegant prospective cohort, open label and multicenter study by Janssen et al.\(^\text{[20]}\) confirmed this finding. In this study, 558 patients underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc in 13 European hospitals, and one in South Africa. The primary end-point was the occurrence of ARDS after talc pleurodesis, which did not occur in any patients. This data supports the safety of large particle talc for pleurodesis. Therefore, graded talc should always be used in preference to ungraded talc as it reduces the risk of arterial hypoxemia complicating talc pleurodesis\(^\text{[1]}\). Presently, only one large randomized prospective trial has addressed both, the efficacy and safety of talc pleurodesis in relation to the appropriate mode of instillation. Dresler et al. compared thoracoscopic talc poudrage and thoracostomy with talc slurry in 482 patients with MPE. Based on the primary end-point of lack of radiographic recurrence at 30 days, the efficacy of the two modalities was found to be similar. However, significant treatment associated morbidity was observed, with respiratory failure in 4% of patients who received talc slurry and 8% who underwent talc poudrage. In addition, a Kaplan-Meier estimator used to evaluate the distribution of recurrence after 30 days demonstrated a roughly 50% rate of MPE recurrence by 4 months post pleurodesis\(^\text{[17]}\). When talc is not available, bleomycin can be used as an alternative sclerosant with a modest efficacy rate\(^\text{[1]}\).

**Placement of an Indwelling Pleural Catheter:**

Insertion of tunnelled indwelling pleural catheters (TIPC) to control recurrent and symptomatic malignant pleural effusions is effective. Over the last decade, several studies documented the efficacy and safety of this strategy to provide outpatient management for malignant pleural effusion\(^\text{[14-19]}\). They are silicone catheters which are designed for long-term use as they are tunnelled in the subcutaneous tissue to prevent infection and tube displacement\(^\text{[11]}\). They can be inserted at the bedside with local anaesthesia as an outpatient procedure with or without ultrasonographic guidance. Upon catheter insertion, initial fluid drainage is performed under physician observation. Drainage is limited only by patient symptoms such as chest tightness or persistent cough indicating lung re-expansion. Following Post-procedure chest X-ray, patients are able to go home without the need for hospitalization. In order to ensure proper care of the tunnelled pleural catheter and successful home drainage, all patients should be provided with community homecare services\(^\text{[14]}\). Home care nurses ideally should receive special training in the management of the catheter and provide home pleural drainages on a schedule individualized to each patient, typically three times per week. Pleural fluid drainage
can be performed in the patient’s home on an intermittent basis with the frequency of drainage determined by the rate of fluid re-accumulation. Catheters are routinely removed when pleural drainage is less than 50 ml on three separate occasions and no change in the chest X-ray is observed[14].

Current guidelines published by the British Thoracic Society advocate the use indwelling pleural catheter for controlling recurrent malignant effusions when length of hospitalization is to be kept to a minimum (reduced life expectancy). Moreover, where patients are known or are suspected to have trapped lung, and where expertise and facilities exist for out-patient management of these catheters. The presence of an indwelling catheter also commonly leads to pleurodesis at least in part due to the mechanical irritation and inflammation caused by the catheter itself[9]. Spontaneous pleurodesis was reported in 40% to 58% of patients after 2 to 6 weeks in recent studies[11,21].

The advantages associated with the outpatient management of MPEs have been well described. Indwelling pleural catheters are consistently associated with significant symptom control, high rates of spontaneous pleurodesis and low risk of complications[4,9,11,14,21,22]. Putnam et al. published a prospective randomized trial comparing an indwelling Pleurx® to doxycycline pleurodesis in 144 patients with malignant pleural effusion. This study demonstrated that the two modalities were equivalent with respect to symptom control, safety and overall efficacy[15]. A number of studies have demonstrated that indwelling pleural catheters are effective in the management of MPEs associated with trapped lungs[16] and in patients with MPE irrespective of their suitability for talc pleurodesis[10]. A recent cost-effectiveness study has also demonstrated the comparability of the Pleurx® catheter and talc pleurodesis[23].

Potential catheter related complications and the significant infrastructure requirements are considered the two primary disadvantages of indwelling catheters in the treatment of MPEs. Tremblay and Michaud reported catheter related complications such as empyema (3.2%), pneumothorax (2.4%), cellulitis (1.6%), dislodged catheters (1.2%), bleeding (0.8%) and rare tumour seeding (0.4%)[21]. However, overall complication rates are relatively low and compare favourably to other treatment modalities[9,11,21]. A more significant limitation to the use of chronic indwelling catheters is the infrastructure needed for the long term care of these patients. An outpatient based MPE program requires sufficient clinic time for both the initial catheter placement and the follow up visits. Frequent scheduled follow-up is necessary both to assess symptom control and to monitor for complications. Ideally, a mechanism should be in place to rapidly address catheter related complications and thus avoid emergency department visits and unnecessary hospitalizations. Considerable community resources are also required to facilitate catheter management and pleural drainages in the patient’s home. Infrastructure requirements and resource availability may be factors limiting the utility of outpatient based malignant effusion management in many institutions[14]. Although experience with using the TIPC for MPE is becoming more widespread, there is little existing high-quality evidence comparing the efficacy and safety of the TIPC to other available treatments[24]. Prospective randomized studies comparing the TIPC to pleurodesis are needed before the TIPC can be definitively recommended as a first-line treatment of MPE[24].

CONCLUSION

The presence MPEs in cancer patients represents a significant source of morbidity and causes significant impairment of quality of life. Up to date and despite considerable research, the optimal management strategy remains a matter of some debate. As discussed, the significant safety concerns with intrapleural talc make it less attractive as a palliative therapy except if large particle talc is to be used. In contrast, indwelling catheters are associated with successful palliation of symptoms, high rates of pleurodesis and relatively fewer serious complications. However, the use of TIPC as a first line treatment of MPE cannot be recommended at this time due to lack of high-quality studies. More randomized comparative studies are still needed to solve this debate.

REFERENCES


