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Management of malignant pleural effusions

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Abstract: Malignant pleural effusion is a common clinical problem. Evacuation of the pleural fluid and prevention of its reaccumulation are the main aims of management. Pleurodesis should be attempted early, although considerable practice variations exist in the way it is performed. There is a lack of consensus among respiratory physicians worldwide on the optimal method and agent for pleurodesis. Talc remains the most commonly used pleurodesing compound in most countries. While talc produces a higher success rate than other compounds, it generates more side-effects. The association between talc and ARDS continues to be debated. Ambulatory small-bore pleural catheter drainage followed by intrapleural instillation of a pleurodesing agent is increasingly accepted as an alternative to conventional in-patient pleurodesis. Development of novel methods to control pleural fluid formation should be made a high priority in future pleural research.

Key words: malignant, pleural effusion, pleurodesis.

INTRODUCTION

Malignant pleural effusions are common, affecting 660 patients per million population each year.¹ In Australia and New Zealand, this equates to over 13 000 patients per annum. A malignant aetiology is found in up to 50% of patients referred to respiratory units for investigation of pleural effusions.^{2,3} The diagnosis of pleural malignancy is the first indication of cancer in about 13% of patients with malignant effusions.⁴ Despite its frequent occurrence in everyday clinical practice, relatively little clinical research has been performed on the best management of malignant pleural effusions. Recommendations from published guidelines are often based on small non-randomized studies or anecdotal expert opinions.

When high-quality evidence-based data are lacking, clinical practice is often characterized by marked variations. Management of malignant pleural effusions is no exception. The recently published Inter-

national Survey on Pleurodesis Practice (ISPP),⁵ which included 859 respiratory specialists worldwide, demonstrated significant differences in the management of malignant effusions, and highlighted important areas of practice variations in performing pleurodesis.

This review, after summarizing the common presentations of malignant pleural effusions, focuses on the current controversies in the management of malignant pleural effusions.

THE CLINICAL PICTURE

Pathophysiology

Malignant pleural effusions most commonly arise from metastatic carcinomas from outside the pleura, but can also originate from primary pleural neoplasms (especially mesothelioma). Lung carcinoma, breast carcinoma, lymphoma and ovarian carcinoma are the commonest types of pleural malignancies, and account for about 80% of all malignant effusions.⁶ In some cases, pleural disease may be the only evidence of malignancy in the patient. Adenocarcinoma is the most common histological type for malignant pleural disease with an unknown primary source.⁷ In metastatic malignant disease, it is generally believed

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that the visceral pleura is involved first. Tumour can reach the visceral pleura by direct extension (from the lung, or occasionally from the breast), or via haematogenous embolization of tumour cells to the peripheral lung parenchyma. The parietal pleura is secondarily affected, presumably from shedding of malignant cells from the visceral pleura, or from direct tumour extension via pleural adhesions.

The incidence of mesothelioma varies widely across the world. In regions with a high incidence of mesothelioma, it represents a common cause of malignant effusion, as over 95% of patients with mesothelioma will develop a pleural effusion in their disease course.^{8,9} In mesothelioma, unlike metastatic carcinomas, tumour arises from the parietal surface before spreading to the visceral pleura.⁸ In fact, mesothelioma patients with only parietal involvement have earlier stage disease and better prognosis than those with mesothelioma invading both pleural surfaces.¹⁰

Malignant pleural effusion (Fig. 1) develops primarily as a result of increased vascular permeability and resultant plasma leakage.¹¹ Reduced pleural fluid outflow, secondary to tumour blockage of parietal stomas and the subsequent drainage paths, or lymphatic obstruction due to metastatic mediastinal lymphadenopathy, also contributes to fluid accumulation. Study of the molecular mechanisms of malignant effusion accumulation is a rapidly evolving field and may identify novel therapeutic targets for management of malignant effusions.¹¹ Increasing evidence from laboratory studies suggests that peripheral location of lung tumours and expression of vascular

endothelial growth factor, a potent inducer of vascular permeability, are important in the development of malignant pleural effusions.^{12,13}

Symptoms

Dyspnoea is the most common presenting symptom of malignant pleural effusions. Chest pain and constitutional symptoms from the underlying malignancy may also be present. Since the visceral pleura is devoid of sensory fibres for pain, pleuritic pain usually implies malignant infiltration of the parietal pleura. Detailed discussions of the clinical symptoms and signs of malignant pleural involvement and investigations of pleural fluid can be found elsewhere.^{14,15}

Investigations

The diagnosis of a malignant pleural effusion requires either histological or cytological demonstration of malignant cells in the pleural tissue or pleural fluid, respectively. Patients with malignancy may develop an effusion for a variety of reasons other than malignant involvement of the pleura. These effusions are sometimes termed 'para-malignant', and should be distinguished from genuine malignant effusions, as they may require different management strategies and have different prognostic implications.⁴ In a patient with an undiagnosed effusion, thoracentesis should be performed and fluid cytology should be examined by an experienced pathologist.¹⁶ The volume of fluid sent for cytology need not be large.¹⁷ The majority (95%) of malignant effusions are exudates, but exceptions are known to occur,⁶ usually in patients with concurrent causes for a transudative effusion. Pleural biopsy only minimally improves the yield for malignancy above pleural fluid cytology, but is useful to establish or exclude tuberculous pleuritis, especially in regions where tuberculosis is endemic.¹⁸ It is recommended that flow cytometry be performed to exclude lymphoma in otherwise unexplained lymphocyte-predominant effusions, as lymphoma can be difficult to diagnose using conventional methods.⁴

Ultrasonography is useful for locating sites for thoracentesis. In occasional cases, pleural masses can be identified and biopsied under ultrasound guidance.¹⁹ Contrast-enhanced computed tomography has been shown to be useful for differentiating benign and malignant pleural diseases.²⁰ Furthermore, CT-guided pleural biopsy was superior to conventional closed pleural biopsy for diagnosing pleural malignancy in a randomized study.²¹ Magnetic resonance imaging (MRI) and positron emission tomography (PET) scan may offer some additional information,²² but none of the radiological imaging modalities can provide or replace histological diagnosis, which is needed to determine whether the malignancy may be chemotherapy-sensitive. The role of radiology and surgery in the diagnosis of malignant effusions will be covered in subsequent articles in the Pleural Review Series in *Respirology*.



Figure 1 A CXR showing a complete white-out of the right hemithorax due to a large pleural effusion with mild contralateral mediastinal shift in a patient with malignant mesothelioma.

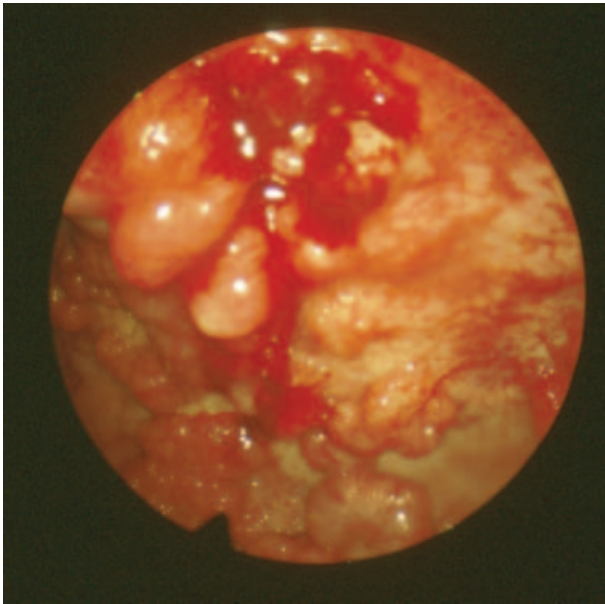


Figure 2 The parietal pleura of a patient with an undiagnosed pleural effusion who underwent thoracoscopy as a diagnostic procedure. Notice the tumour spread along the pleural surface. The biopsy revealed malignant mesothelioma. (Photo courtesy of Dr R. J. O. Davies, Osler Chest Unit, Oxford, UK.)

Thoracoscopy is the recommended procedure in patients with an undiagnosed effusion and negative pleural fluid cytology, who are suspected of having malignancy.²³ The diagnostic yield with thoracoscopy is over 90% in malignant and tuberculous pleural effusions.²⁴ Pleurodesis can be performed during the same procedure if the biopsy is positive (requiring an on-site cytologist during thoracoscopy), or if the macroscopic appearance is strongly suggestive of malignancy and adequate biopsies have been taken (Fig. 2).

MANAGEMENT

When a malignant effusion is diagnosed, the foremost management issue is the control of fluid re-accumulation to minimize any symptoms or distress to the patient.¹⁵ Pleurodesis offers the most effective control of fluid recurrence and the overall success rate is around 60–70%.⁵ A wide range of success rates for pleurodesis has been cited in the literature, and this may be explained by differences in patient selection, pleurodesing agent used, methods of pleurodesis, and definition of ‘success’. A low pleural fluid pH (< 7.20) or glucose concentration (< 60 mg/dL), often reflect a higher tumour load in the pleura, and have been associated with a lower success rate with pleurodesis, as well as poorer survival.^{25,26} Whether the larger pleural tumour load affects the creation of pleural symphysis, and if so how, is unknown. To date, no clinical or biochemical parameter reliably predicts the outcome of pleurodesis in any individual patient.²⁵ Therefore, any patient with adequate per-



Figure 3 A CXR showing a ‘trapped lung’. This patient with mesothelioma presented with a right-sided pleural effusion. After chest tube drainage, the lung failed to re-expand, creating a picture of hydropneumothorax. Pleurodesis is not indicated in such situation, and an indwelling small-bore catheter was inserted for long-term pleural fluid drainage.

formance status and symptomatic improvement from thoracentesis should be considered for pleurodesis.^{27,28} Pleurodesis is not recommended in patients who are asymptomatic from the effusion.

Patient selection

The first step is to determine if the patient has symptomatic benefits from removal of the pleural fluid. A considerable number (up to 50%) of patients with malignant effusions may not have significant improvement in breathlessness or in exercise tolerance after thoracentesis,²⁹ due to comorbidity (e.g. emphysema), general debility from the tumour, or the presence of a ‘trapped lung’ (Fig. 3). The trapped lung can be due to tumour encasement of the lung or endobronchial obstruction with distal atelectasis. Chemical pleurodesis is contraindicated in the presence of a trapped lung as it may induce fibrosis of the visceral pleura, further restricting the expansion of the underlying lung.²⁷

Pleurodesis should be reserved for patients who have a good short-term prognosis. Performance status is useful in predicting survival in patients with malignant effusions.^{30–32} Patients with a Karnofsky

performance score (KPS) > 70 have significantly better prognosis, and are more likely to derive benefits from pleurodesis.³⁰ In one study of 85 patients with malignant pleural effusions, those with a KPS \geq 70 had a median survival of 395 days, compared with 34 days in those with a KPS \leq 30.³⁰

Various methods and agents are available, but the literature does not provide firm evidence on the optimal method for pleurodesis. Not surprisingly, the ISPP uncovered significant variations among respiratory physicians worldwide in the practice pattern of performing pleurodesis,⁵ some of which are highlighted below.

When to perform pleurodesis

The timing of pleurodesis is a matter of debate. Conventional teaching suggests that one should delay performing pleurodesis until the patient has one or more episodes of symptomatic recurrence of the malignant pleural effusion.³³ Indeed, 82% of the surveyed respiratory physicians in ISPP subscribed to this practice.⁵ However, others argue that as malignant effusions inevitably re-accumulate, pleurodesis should be performed early in suitable patients.²⁶ As the disease advances, the risk of developing a trapped lung, which would preclude effective pleurodesis, increases. Delaying the pleurodesis procedure until after recurrent episodes of fluid accumulation also means that the patient has to put up with repeated periods of dyspnoea, which is entirely unnecessary had a successful pleurodesis been performed at the time of diagnosis. There are no controlled studies that compare the quality of life in patients who have pleurodesis when the effusion is first diagnosed and those who are pleurodesed after symptomatic recurrences.

Pleurodesing agents are usually delivered via a chest tube, except for dry talc, which is insufflated by thoracoscopy (either video-assisted thoracoscopy (VATS) or medical thoracoscopy). Although enthusiastic thoracoscopists have been advocating the routine application of thoracoscopic pleurodesis, the thoracoscopic approach has not been convincingly proven as being superior to chest tube pleurodesis.^{25,34} Indeed preliminary results of a large Cancer and Leukemia Group B (CALGB) trial of over 400 patients have shown no benefit of talc insufflation over talc slurry (R. W. Light, pers. comm., 2003). Open thoracotomy should not be used for pleurodesis^{35,36} because of its high mortality and morbidity risks.^{36,37}

Choice of pleurodesing agent

The most commonly used agent worldwide is talc, followed by tetracycline/doxycycline, and bleomycin.⁴ Detailed reviews of the pleurodesing agents are available elsewhere.^{28,33,38} The effectiveness of talc has been demonstrated in many studies.³⁹⁻⁴⁶ A large variety of alternative agents such as iodoprovidone,⁴⁷ silver nitrate⁴⁸ and OK432³⁸ have been suggested, though none of them have been compared with conventional agents, such as talc, in randomized trials.

None of the existing agents is perfect and physicians in general are only 'somewhat satisfied' with the agents they use.⁵ In general, chemical pleurodesing agents as well as surgical methods of pleurodesis work by provoking an acute pleural injury, which results in pleural inflammation. If the inflammatory process is sufficiently intense, chronic inflammation and fibrosis ensues, resulting in extensive pleural adhesions and eventual obliteration of the pleural cavity (successful pleurodesis).⁴⁹ Fever and pain from pleural inflammation are common with all widely employed pleurodesing agents.⁵ In simple terms, the more intense the induced pleural inflammation, the higher the likelihood of success, but at the expense of producing more pain and distress for the patient – an unfortunate 'no pain, no gain' situation.

Talc can be administered either as a dry powder (poudrage), which usually requires thoracoscopic insufflation, or as a suspension (slurry) via a chest tube. In a small randomized trial, Yim *et al.* found no advantage of thoracoscopic talc insufflation over instillation of talc slurry via tube thoracostomy.³⁴ Preliminary evidence from a large multicentre, randomized trial of the CALGB suggested no significant differences in success rates and complications whether talc was administered by insufflation or as a slurry (R. W. Light, pers. comm., 2003).

While talc is effective, potentially serious adverse effects can occasionally occur. The safety of talc pleurodesis has been one of the most debated topics in pleural research in recent years. Talc potently stimulates pro-inflammatory cytokine release into the pleural space⁵⁰ and produces chest pain and fever more commonly than bleomycin.⁵ Recently, talc-induced acute respiratory distress syndrome (ARDS) and systemic embolization have raised concerns. Talc-induced ARDS⁵¹⁻⁵⁸ can result in respiratory failure, and occasionally, death.^{51,53,54,56,58} These complications can occur with either talc insufflation or slurry, and with both high (10 g) and low (2 g) doses.⁵⁸ In the ISPP study, over 50% of physicians who used talc had observed respiratory failure after talc pleurodesis, but its actual incidence remains unknown.⁵

Talc particles have been recovered in distant organs (e.g. liver, kidney, and even the brain), following pleurodesis,^{51,57} although any long-term consequence from systemic embolization of talc particles is not known. It is currently hypothesized, but not proven, that talc preparations with small particle sizes are more likely to be absorbed systemically, and produce systemic and pulmonary inflammation.^{59,60} This may explain the higher number of reports of ARDS from the USA, as the common talc preparations in the USA contain predominantly 'small' (< 20 mm diameter) talc particles.⁶¹ Randomized controlled trials comparing the pulmonary and systemic inflammation after talc and tetracycline pleurodesis, and after talc pleurodesis using talc preparations of different particle sizes, have recently been completed.⁶² The results suggest that talc-induced pulmonary inflammation is a common phenomenon, although only the cases at the severe end of the spectrum are clinically apparent. Other explanations, such as the presence of contaminants (e.g. lipopolysaccharide in the talc

preparation^{63,64}), have also been suggested as the cause of talc-induced ARDS, but scientific evidence supporting these speculations is lacking.

Until results of definitive investigations become available, commercial preparations of larger talc particles should be preferred over smaller ones. In patients with pre-existing respiratory compromise, alternative pleurodesing agents should be considered. Tetracycline is also effective in treating malignant pleural effusions. In centres where parenteral tetracycline is not available, doxycycline is a reasonable alternative.^{65–68} Fever and chest pain are common side-effects.³⁸ Bleomycin is not recommended, as it is less effective yet significantly more expensive than talc or tetracycline.^{69,70}

Technical aspects of pleurodesis

Perhaps the most important advance in pleurodesis in recent years has been the use of small-bore (< 16F) catheters for ambulatory pleurodesis in suitable patients. Small-bore catheters can be inserted and subsequent pleurodesis performed on an outpatient basis, thus allowing the patient to remain active with a concomitant reduction of the inpatient costs.^{71,72} This is especially important as most patients with malignant effusions have an incurable cancer and a limited life expectancy, and every effort should be made to allow them to spend quality time outside hospital.

With an indwelling small-bore catheter (e.g. Pleur catheter), pleural fluid can be drained regularly or on an 'as required' basis, and pleurodesis can be performed via the catheters once the pleural fluid has been evacuated. Small-bore catheter drainage is more comfortable,⁷³ but as effective (success rates 70–80%) and safe^{74–76} when compared with pleurodesis using conventional large-bore chest tubes.⁷¹ However, prolonged use of indwelling catheters should be avoided if possible, as complications (e.g. infection, catheter blockage,^{71,77} and catheter tract metastases^{72,78}) can occur. The different types of small-bore catheters function on similar principles,^{71,73–75,77} but no studies have yet compared them.

It is generally believed that pleurodesis is more likely to succeed if the pleural effusion can be completely evacuated. Traditionally, instillation of pleurodesing agent is delayed until the fluid drainage is reduced to less than 150 mL/day, and this is the practice of the majority (77% in ISPP⁵) of respiratory physicians worldwide. However, pleurodesis can be equally successful if performed as soon as complete lung re-expansion is confirmed on CXR.⁷⁹ This approach is now recommended,^{33,80} as it minimizes the duration of chest tube placement and hospital stay.

Informed consent must be obtained for pleurodesis, as it is not without risk. Pain is the most common side-effect of pleurodesis; hence, narcotic analgesics and/or conscious sedation (e.g. midazolam) should be used, provided there are no contraindications. There has been little human or animal data supporting the intrapleural administration of lignocaine, although it remains a common practice.⁵ Rotation of

the patient appears unnecessary, as it did not improve the success rate of pleurodesis in studies using either tetracycline derivatives or talc slurry.^{81,82}

In patients with malignant mesothelioma, there is a considerable risk of tumour spread along the tracks of prior needle aspiration or chest tube placements.⁹ A small randomized trial has confirmed that low-grade radiotherapy (21 Gy over 3 days) of the site of pleural puncture, administered within 15 days of the pleural procedure, can prevent the development of needle track metastases,⁸³ and should be recommended for all mesothelioma patients who undergo pleurodesis.¹⁶

As mentioned, successful pleurodesis requires the induction of an acute pleural inflammatory response and subsequent pleural fibrosis.⁴⁹ In animal studies, systemic corticosteroids significantly reduced the pleural inflammation and inhibited the subsequent pleurodesis.^{84,85} While there is no human data on this subject, corticosteroid use should be reduced or discontinued temporarily before and immediately following pleurodesis, if possible. Similarly, there is cumulative evidence suggesting that the coagulation cascade plays a critical role in organ fibrosis (including pleurodesis).^{86,87} In animal studies, use of heparin can inhibit pleural fibrosis.⁸⁸ Whether, and to what extent, anticoagulants may impair successful pleurodesis in humans is not known.

Special clinical considerations

For patients whose effusion re-accumulates after an attempted chemical pleurodesis, several options are available. These include pleurodesis with a different agent,^{65,74,89} implantation of a chronic indwelling catheter or a pleuro-peritoneal shunt, serial therapeutic thoracentesis, or surgical pleurodesis with VATS.³³

Patients with limited life expectancy who are symptomatic from their pleural effusions can be treated with repeated thoracenteses or indwelling small-bore catheters.^{33,80} In very terminally ill patients, the use of narcotics and oxygen to alleviate the symptoms of dyspnoea may be more appropriate.²⁸

For patients with a trapped lung, lung re-expansion is usually not feasible. In a small number of otherwise very fit patients, thoroscopic decortication (if the lung is trapped from visceral thickening) or radiotherapy and/or endobronchial intervention (if the trapped lung arises from endobronchial obstruction) can be considered to release the trapped lung before pleurodesis. In the majority of patients, repeated thoracentesis, long-term small-bore catheter drainage or pleuro-peritoneal shunts are the more practical options. The latter can offer effective symptomatic control for patients with a trapped lung,⁹⁰ but are contraindicated if ascites is present. Potential complications of pleuro-peritoneal shunts include infection, shunt occlusion, pain,⁹⁰ and a theoretical risk of metastatic spread to the peritoneum.

In patients with a multiloculated effusion (Fig. 4), pleurodesis may fail if the pleurodesing agent cannot be freely distributed around the pleural cavity.

Isolated large locules can be drained by needle aspiration or the insertion of additional small-bore catheters under radiological guidance. Breakdown of the adhesions may be achieved by VATS or by intrapleural instillation of fibrinolytic agents (e.g. streptokinase), following which pleurodesis can be performed successfully.⁸⁹

The management of the effusion in a patient whose underlying malignancy is treatable with chemotherapy (e.g. lymphoma or small cell carcinomas) is controversial. Most physicians would favour measures to provide temporary symptomatic relief (e.g. thoracentesis) while awaiting responses to chemotherapy.⁵ If the tumour is responsive, the effusion may regress without needing pleurodesis. On the other hand, some have maintained that malignant pleural effusions should still be drained and pleurodesis performed (if there are no contraindications), as the fluid may present a site of infection during neutropenic phases of the chemotherapy courses, and some anti-neoplastic agents may accumulate in the effusion and produce delayed toxicity.⁹¹

FUTURE DIRECTIONS

The incidence of malignant pleural effusion is expected to rise in the years to come, as the life expectancy of the global population increases. Adequate control of an effusion can alleviate the patient's symptoms and significantly improve quality of life. However, current strategies for the management of malignant effusions are clearly inadequate. Present day management relies on successful obliteration of the pleural cavity, or else the patient has to be subjected to repeated invasive drainage procedures. Available pleurodesing strategies have a suboptimal success rate, frequent side-effects, and up to half of the patients are not suitable candidates (e.g. those with trapped lung).

As malignant pleural effusion represents one of the most common clinical problems involving the pleura, its better management should be made a high priority in pleural research.⁹² In the intermediate term, a search for better compounds for pleurodesis is warranted. Recent work on manipulation of cytokines (e.g. transforming growth factor beta⁹³⁻⁹⁵) to produce pleural fibrosis without inducing pleural inflammation is one step towards such a target. Transforming growth factor beta (TGFβ) is a unique cytokine with potent profibrotic as well as anti-inflammatory activities. It can significantly upregulate collagen production without stimulating IL-8 release in cultured mesothelial cells. TGFβ has been shown to consistently induce more effective pleurodesis than talc in different animal models. More importantly, unlike other existing pleurodesing agents, TGFβ did not provoke an inflammatory pleural response.⁹³⁻⁹⁵ It is therefore likely that intrapleural injection of TGFβ can produce an effective pleurodesis without eliciting pain and fever. While TGFβ has yet been used for pleurodesis in humans, it represents an encouraging attempt towards applying novel scientific knowledge to create better methods of pleurodesis.

In the longer term, the ideal management will be to 'switch off' the fluid production. This requires advances in our understanding of the pathophysiology of vascular hyperpermeability in pleural malignancies. Encouraging results are, however, emerging, especially along the lines of manipulation of vascular endothelial growth factor and its downstream pathways.¹¹

Last but not least, there have been few adequately powered clinical trials studying many of the important bedside controversies on management of malignant effusions, as highlighted in this article. The recent completion of large multicentre trials in the UK and USA on pleural sepsis and on chemotherapy for pleural mesothelioma⁹⁶ are encouraging. Such efforts should be extended to issues of malignant pleural effusions, to help establish the best strategies for clinical management and to assess the efficacy of future novel therapies.

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