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Management of malignant pleural effusions

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Malignant pleural effusion is a common problem in respiratory medicine and oncology and in some series accounts for up to 50% of all pleural effusions.[1 2] The median survival following diagnosis ranges from three to 12 months and is largely dependent upon the underlying malignancy. Currently, lung cancer is the most common metastatic tumour to the pleura in men and breast cancer in women. Both malignancies account for 50–65% of all malignant effusions while lymphomas, genitourinary, and gastrointestinal tumours account for a further 25%, and 7–15% of all malignant effusions have no identifiable primary.[3–5]

Malignant effusions result predominantly from obstruction and disruption of lymphatic channels by malignant cells. However, vascular endothelial growth factor (VEGF), a potent angiogenic mediator and promoter of endothelial permeability, is produced in significant amounts by diseased pleural tissue and is thought to play a part in the formation of malignant effusions and local tumour growth.[6 7]

The general approach to managing malignant effusions is determined by symptoms (dyspnoea, exercise tolerance limitation, and chest discomfort), performance status of the patient, expected survival, and response of the known primary tumour to systemic treatment. Intervention options range from observation in the case of asymptomatic effusions through simple thoracentesis to more invasive methods such as thoracoscopy, pleuroperitoneal shunting, and pleurectomy. Repeated aspiration is favoured in patients with limited survival and poor performance status and obviates lengthy hospitalisation. In the patient with reasonable survival expectancy and good performance status, every attempt should be made to prevent recurrence of the effusion. Intercostal tube drainage with instillation of a sclerosing agent, resulting in the obliteration of the pleural space, is the most widely used and cost effective method to control recurrent symptomatic malignant effusions.

Size of drainage tube

Over the last two decades several new developments have modified the method originally described by Adler and Sayek.[8] By convention, large bore intercostal tubes (size 24–32 F) have been used for drainage of malignant effusions and intrapleural administration of sclerosing agents. These large tubes are frequently associated with significant discomfort to patients and restrict mobility. Studies using small bore catheters (8–14 F) have reported similar success rates to those using large bore tubes, and small bore catheters are better tolerated and associated with less discomfort.[9–12] In the only controlled randomised study published to date, no significant difference was seen in the pleurodesis success rate but larger randomised studies are required to confirm these results.[13] A further potential advantage of the small bore catheter is in the area of ambulatory treatment of malignant effusions. Patz *et al*, using small bore catheters (10 F) and bleomycin as a sclerosing agent, achieved a modest pleurodesis success rate of 79% in outpatients.[14]

When to sclerose

Lung re-expansion remains the most important requisite for successful pleural symphysis and sclerotherapy failures usually occur when complete lung re-expansion is not

achieved. The minimum amount of pleural fluid drainage (normally taken to be less than 150 ml/day) before sclerotherapy appears to be less relevant for successful pleurodesis than confirmation of lung re-expansion radiologically.[15] The role of intrapleural fibrinolytic agents in the management of malignant effusions is in its infancy and remains controversial.[16 17]

Patient rotation and tube clamping

Rotation of the patient following intrapleural administration of a sclerosing agent is no longer thought to be critical to achieve distribution of the agent throughout the pleural space. Recent evidence using radiolabelled tetracycline revealed that the agent is dispersed throughout the pleural space within seconds in a fairly uniform fashion.[18] A subsequent clinical randomised trial found no significant difference in the success rate or duration of fluid drainage between the rotated and non-rotated patients.[19]

The practice of clamping of intercostal tubes or catheters following instillation of a sclerosing agent is to be discouraged. The reasons for this are based on the rapid dispersion of the sclerosing agent, potential complications such as tension pneumothorax in the presence of an unsuspected persistent air leak, and a lack of good evidence for its use. Removal of the intercostal tube or catheter should occur within 72 hours of sclerotherapy provided the lung remains fully expanded and there is a reduction in the rate of fluid drainage.

Sclerosing agents

The ideal sclerosing agent will have a high molecular weight, low regional and rapid systemic clearance, a steep dose/response curve, and be well tolerated with minimal side effects. Despite the evaluation of a large number of agents, no ideal sclerosing agent exists. Poor study design and disparate criteria for measuring response hamper proper comparison of these agents. The choice of a sclerosing agent is thus largely dependent on the success rate or efficacy, accessibility, safety, ease of administration, and cost.

Tetracycline was, until 1998, the most popular and widely used sclerosing agent via an intercostal tube in the UK when its production was discontinued by the manufacturer following its discontinuation in the USA in 1992.[20] Tetracycline may still be imported from Europe (Germany) at present but this supply may also cease in the near future. Tetracycline has a modest efficacy (average success rate 65%), an excellent safety profile, and it is relatively inexpensive. It is well tolerated and side effects are infrequent, mild, and transient.[21] Other tetracycline derivatives such as doxycycline and minocycline have only been evaluated in small uncontrolled trials and neither is available in the UK.[22 23]

Bleomycin is the most widely used antineoplastic agent for sclerotherapy. Its mechanism of action is predominantly as a chemical sclerosing agent similar to tetracycline and sterile talc. It is an effective sclerosant with an average success rate of 60% and has an acceptable side effect profile. However, its major limitation is the cost per treatment.[21]

Sterile talc is a trilayered magnesium silicate sheet and was first used as a sclerosing agent in 1935.[24] The modern preparation is asbestos-free and is administered either as talc poudrage at the time of thoracoscopy using an atomiser or as talc slurry via an intercostal tube. Success rates for talc poudrage and slurry range from 80% to 100%.[25–28] Earlier studies quoted higher success rates for talc poudrage than for talc slurry but Yim *et al* recently found no significant difference between the two methods with respect to success rate, duration of chest drainage, hospital stay, and complications.[29] Talc is usually well tolerated and the most common side effects reported are pleuritic chest pain and fever.

Adult respiratory distress syndrome (ARDS) or acute talc pneumonitis is a rare and occasionally fatal complication of intrapleural administration of talc. The precise mechanism leading to acute pneumonitis is unclear and has been reported with both talc poudrage and slurry.[25 30] ARDS or talc pneumonitis appears to be dose related, most cases having been associated with doses in excess of 5 g. In a recent study by York *et al* talc pneumonitis was reported in eight cases of a series of 125 patients who underwent talc slurry pleurodesis with a dose of 5 g.[31] Closer scrutiny of the study shows that five patients had radiological features consistent with ARDS and only two patients required mechanical ventilation. All eight cases received high dose corticosteroids and survived to hospital discharge.

Recent data in lower mammal studies using equivalent doses of talc per kg have shown distribution of talc particles beyond the lung to distant organs such as the kidneys and brain.[32–34] In the rat model absorption through the pleura was not dose related.[32] Distribution of talc particles and its clinical relevance in humans with diseased pleura has not yet been studied. The findings in lower mammals should be interpreted with caution as there are significant anatomical and physiological differences and all the studies were carried out in animals with normal pleura.

Forthcoming guidelines will recommend either talc slurry, tetracycline, or talc poudrage depending on local availability both of agents and thoracoscopy service.[35]

Surgical options

Pleuroperitoneal shunting is an acceptable palliative option in patients with trapped lung and large refractory malignant effusions. Insertion of the shunt is facilitated by thoracoscopy or mini-thoracotomy and is usually well tolerated.[36] Complications such as shunt occlusion, infection, and tumour seeding are not infrequent and have contributed to its low popularity. Although open pleurectomy is a very effective method of achieving pleurodesis, it has an unacceptable morbidity and mortality rate.[37] Video-assisted thoracoscopic pleurectomy appears to be a promising and much safer technique although experience is limited and it is not widely available.[38]

Video-assisted thoracoscopic surgery (VATS) and medical thoracoscopy are widely used in continental Europe and North America for both diagnostic and therapeutic purposes in malignant effusions.[39 40] Malignant effusions are the leading indication for such procedures with a high diagnostic yield of more than 90%. Their therapeutic role is well studied with pleurodesis success rates (talc poudrage) of over 90%.[28] The main indications for referral are pleural effusions of undetermined aetiology after repeated pleural fluid analysis and refractory malignant effusions unresponsive to pleurodesis via an intercostal tube.

Conclusions

There have been several advancements in the management of malignant pleural effusions over the last two decades, but further research is required. The exact mechanisms involved in the formation of malignant effusions have yet to be fully elucidated. Technical aspects such as the most appropriate intercostal tube or catheter size need to be established. Although sterile talc is the most effective sclerosing agent available at present, it is associated with a potentially life threatening—albeit rare—complication and further efforts should be made to find an alternative agent. The potential role of thoracoscopy is yet to be fully realised in both the diagnosis and treatment of malignant pleural

effusions. Only by answering some of these remaining questions will we improve the prognosis and outlook of this subgroup of patients with malignant disease.

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Obtaining tissue from the mediastinum: endoscopic ultrasound guided transoesophageal biopsy

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Endoluminal or endoscopic ultrasound (EUS) was first attempted in 1957 by Wild and Reid who placed a mechanical ultrasound transducer in the rectum.[1] It was not until 1975 that the upper gastrointestinal tract was examined when Rasmussen *et al*[2] measured the stomach wall thickness with a 6 MHz transducer passed through the biopsy channel of a gastroscope. In the 1980s, with the development of a dedicated endoscope incorporating a mechanical ultrasound transducer, EUS became important in clinical practice. Accurate local and nodal staging of oesophageal, gastric, and pancreatic tumours[3–6] and assessment of stone disease in the biliary tract[7] established EUS in the investigation of gastrointestinal disease. The accurate detection of mediastinal lymph nodes in oesophageal cancer had obvious implications for patients with lung cancer, and the role of EUS in lung cancer was first described in Japan in 1988.[8] Further work confirmed the superior accuracy of EUS in the nodal staging of lung cancer compared with computed tomographic (CT) scanning,[9] although EUS is not yet used routinely in the preoperative staging of lung cancer in the UK.

Further technical advancement led to the development of the linear EUS probe. This allows passage of a needle down the biopsy channel of the endoscope, through the wall of the gastrointestinal tract, and into adjacent structures such as lymph nodes. The orientation of the ultrasound beam, parallel rather than perpendicular to the long axis of the endoscope, allows continuous ultrasound monitoring of the needle tip. Several studies have shown that transoesophageal EUS guided fine needle aspiration (EUS-FNA) is a simple, relatively non-invasive method of obtaining tissue from various nodal stations in the mediastinum.[10–12] Only the anterior mediastinum is off limits because of air in the trachea. It is performed as a day