

Review

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Malignant pleural effusion

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Summary

Malignant pleural effusion (MPE) refers to the presence of neoplastic cells in the pleural fluid. Approximately 40 000 people per year in the UK are affected by MPE and it is associated with significant morbidity and an overall poor prognosis. Management should be prompt and care plans

should be individualized and involve a multidisciplinary team of healthcare professionals. This article reviews the pathophysiology of MPE along with available investigations and management strategies for these patients.

Introduction

Malignant pleural effusion (MPE) is defined as the presence of neoplastic cells in the pleural fluid.¹ In the setting of a known malignancy but in the absence of cytological evidence of tumour cells, a pleural effusion is termed a paramalignant effusion.² In the UK, ~40000 people per year are affected by MPE and it is estimated that up to 50% of patients with metastatic malignancy will develop a pleural effusion—either at the time of diagnosis or during the evolution of their cancer.^{1,3} The most common etiologies for MPE are lung cancer, breast cancer, lymphoma, ovarian cancer and gastric cancer, in order of decreasing frequency. These malignancies account for 80% of all MPE.^{4–6} Malignant mesothelioma is the commonest primary pleural malignancy associated with a pleural effusion. Few studies have estimated the overall proportion of pleural effusions due to mesothelioma, however 80–95% of these patients have a large pleural effusion at diagnosis.^{6,7} In ~10% of MPE the primary tumour cannot be identified despite extensive

investigation.^{8,9} The presence of an MPE portends a poor prognosis with median survival following diagnosis ranging from 3 to 12 months depending on cell type.⁶

Pathophysiology

The presence of cancer in the pleural space indicates that malignant cells have overcome the normal pleural defence mechanisms.¹⁰ Although the precise physiology of this process remains unclear, it is generally accepted that it occurs in a step-wise manner including the loss of adhesion and dislodgement of neoplastic cells from the primary tumour site; adherence and penetration of the blood vessel wall; migration through the pleura; production of autocrine growth factors and angiogenesis induction.^{10,11} The most common presenting symptom of a MPE is progressive dyspnoea and may be associated with chest pain or cough.¹² Constitutional symptoms including weight loss, malaise and anorexia are often present.^{6,12} Patients with MPE have significant symptoms, diminishing their

overall quality of life. The severity of symptoms often depends on the rate of fluid accumulation, rather than on the total quantity of fluid that might have accumulated over a prolonged time period.¹³

Investigations

A thorough history and examination should be performed on each patient and may assist in guiding further investigations.¹⁴ Particular attention should be paid to any personal or family history of malignancy or exposure to risk factors such as tobacco smoke or asbestos fibres. Clinical examination may reveal stony dullness on percussion, decreased vocal resonance and tactile fremitus along with decreased intensity of breath sounds over the affected area. The examination should also be directed to assess for a primary tumour.

Imaging techniques

The posterior–anterior (PA) chest x-ray (CXR) is a useful diagnostic tool and is abnormal in the presence of ~200 ml of pleural fluid.¹⁵ A massive pleural effusion is defined as complete or almost complete opacification of a hemithorax as visualized on the CXR.⁶ The CXR is considered the first radiologic investigation of choice for patients with a presumed MPE, however nowadays further imaging is generally indicated to assess the characteristics of the effusion in more detail.

Much interest has focused on the role of thoracic ultrasound (TUS) over the last two decades to evaluate the pleural space and aid in the safer guidance of interventions.¹⁶ It is typically performed at the bedside and allows the clinician to diagnose a variety of thoracic disorders at the point of care.¹⁷ It is a rapid, reproducible and inexpensive modality that does not expose the patient to radiation. In 2009, Qureshi *et al.* demonstrated the usefulness of TUS in differentiating malignant from benign pleural effusions with an overall sensitivity of 79% and specificity of 100%. They noted that pleural thickening >1 cm, pleural nodularity and diaphragmatic thickening >7 mm were highly suggestive of malignant disease.¹⁶ TUS may also be used as a guide for pleural procedures including thoracentesis and chest drain insertion.^{17,18} Diacon *et al.* demonstrated that puncture site selection with bedside ultrasonography increases the diagnostic yield and reduces the need for repeated attempts. This group also noted that physician experience does not predict the accuracy of puncture sites in the absence of ultrasound assistance.¹⁹ The National Patient Safety Agency in the UK has strongly advised the use of ultrasound guidance when inserting a drain and the

British Thoracic Society supported this position by issuing guidelines for pleural procedures and TUS.^{20,21} These guidelines state that TUS-assisted guidance is strongly recommended when obtaining pleural fluid for analysis. Ultrasound should be completed at the bedside immediately before the procedure rather than the 'x marks the spot' approach where imaging is completed in the radiology department prior to the patient moving back to the ward for the diagnostic procedure.¹⁵ The above recommendations have led to a change in practice and access to bedside TUS is now considered one of the cornerstones of an efficient pleural service.²² Finally, the utilization of ultrasound facilitates assessment of extrapleural findings of major clinical significance such as cervical and supraclavicular adenopathy, soft tissue lesions and liver metastases (Figure 1).¹⁶

Other imaging techniques include CT and 18F-fluorodeoxy-glucose (FDG) positron-emission tomography (PET-CT) which allow further characterization of the pleura and pleural effusion. In addition, adjacent structures can be interrogated and the primary tumour may be located.¹ Disadvantages of these modalities include radiation exposure and the poor visualization of septations within the effusion. Magnetic resonance imaging has a limited role but is superior in determining invasion of the tumour into the chest wall in the presence of an MPE.²³

Pleural aspiration

The next step in obtaining a diagnosis should be pleural fluid analysis. Prior to performing an aspiration, the physician must decide whether a diagnostic aspiration alone should be performed or combined with a therapeutic procedure for symptom relief. A 21-gauge needle and 50-ml syringe may be used for diagnostic pleural aspirations and pleural fluid should be sent for cell count, protein, lactate dehydrogenase, pH, gram stain, cytology and microbiology culture (Table 1). MPEs are generally exudates and lymphocytic predominant.¹⁵ A lower pH may be associated with a shorter mean survival and failure of chemical pleurodesis, however studies in this area are poorly powered and further research is necessary prior to the use of this index in clinical practice.^{24,25} The diagnostic yield does not increase significantly by sending more than two specimens of pleural fluid. Garcia *et al.*²⁶ reported a positive diagnosis from the first specimen in 65% patients, from the second in 27% and from the third in only an additional 5%. However in most clinical practices the yield from cytology is much lower. The optimal volume of fluid to be sent for cytological analysis has not yet been identified; however it is

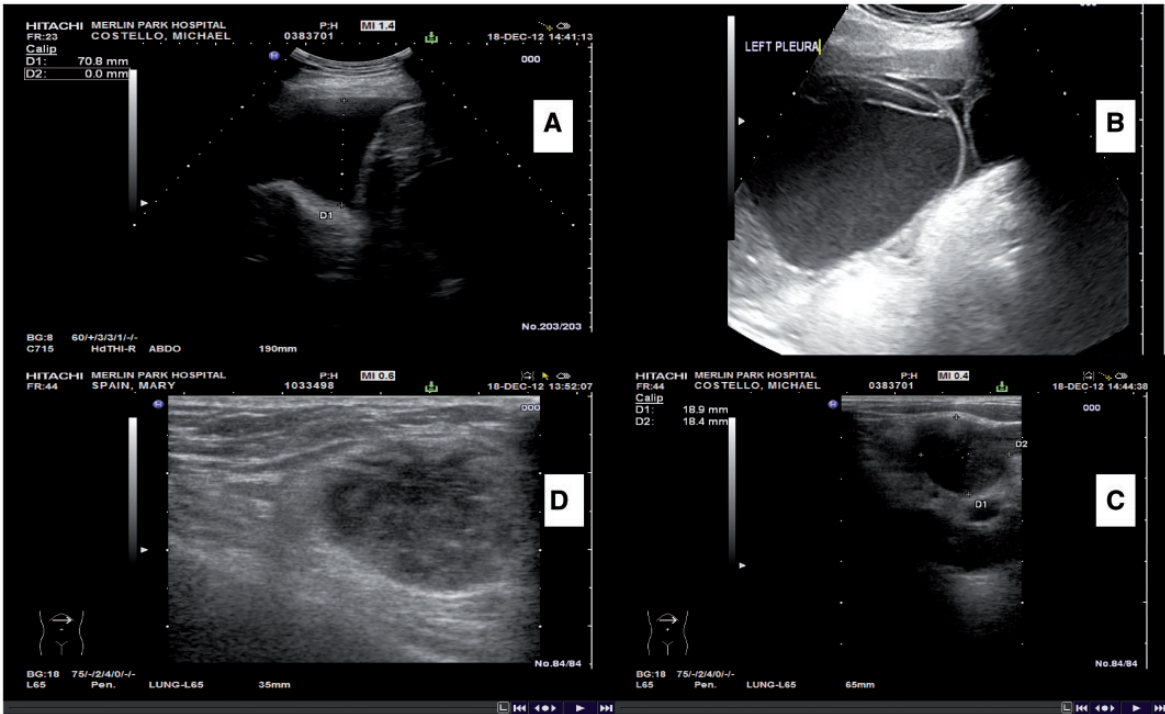


Figure 1. Clockwise from top left. (A) A simple transudative pleural effusion; (B) An MPE demonstrating an echogenic fluid with adhesions and a thickened diaphragm; (C) Pathologically enlarged cervical adenopathy; (D) A malignant skin nodule secondary to small-cell lung cancer as imaged with ultrasound.

Table 1 Routine tests of pleural fluid in the setting of suspected MPE¹⁵

Test	Information
LDH and protein	5 ml in a serum bottle with simultaneous serum sample for LDH and protein (assess if exudative effusion)
Gram stain and culture	5 ml in a sterile container. Request assessment for acid fast bacilli and tuberculosis culture if clinical suspicion high and insert a further 4 ml in anaerobic and aerobic blood culture bottles (2 ml in each) if particular concern for pleural infection.
Cytological examination and cell count	10–20 ml in a sterile container.
pH	Perform in non-purulent effusion when pleural infection is suspected. Insert 1 ml in a heparanized syringe after aspiration. The sample should be processed immediately.

LDH, lactate dehydrogenase

recommended that 20–40 ml is usually adequate for the initial analysis. It has been suggested that higher volumes can be sent at the time of second aspiration if the initial result is negative.¹⁵ This pattern of assessment can be altered by local factors such as access to medical thoracoscopy or video-assisted thoracoscopic surgery (VATS) as described below.

Pleural biopsy

In ~25% of patients, the effusion remains undiagnosed after initial pleural fluid analysis and a more

invasive approach should be adapted. The traditional method of blind, percutaneous pleural biopsy using an Abrams needle is associated with an ~50% diagnostic yield for malignancy but a high complication rate.^{15,27} This is in contrast to a CT-guided cutting-needle biopsy which allows focal areas of abnormal pleural to be targeted. It has a higher sensitivity of 87% and is now considered a superior diagnostic test to blind percutaneous biopsy.²⁷ An exception is in areas with a high incidence of tuberculosis, where blind pleural biopsy is associated with a high diagnostic yield and is likely

more cost-effective as an initial diagnostic procedure.¹⁵

Further options include either medial thoracoscopy or VATS, both of which allow direct visualization of the pleural cavity and can have both a diagnostic and therapeutic role. Medical thoracoscopy is also known as pleuroscopy and is generally performed by a respiratory physician in the endoscopy suite under minimal conscious sedation. VATS requires general anaesthesia and double-lumen tracheal intubation and is performed by thoracic surgeons in the operating theatre.²⁸ Thoracoscopy allows pleural biopsy along with therapeutic interventions including complete drainage of the pleural effusion, adhesiolysis and pleurodesis.¹ These techniques have a high diagnostic sensitivity for malignancy of ~92.6% in the case of medical thoracoscopy and 95% for VATS.¹⁵

Management

A number of factors need to be considered when planning management. These include overall expected prognosis associated with the underlying malignancy, symptoms and performance status of the patient. Care for these patients should be delivered by a multidisciplinary team incorporating interventional pulmonologist/respiratory medicine, radiology, pathology, clinical oncology, surgery, palliative medicine and associated support staff. Due to the short life expectancy of most of these patients, it is important that care is delivered in an efficient manner with minimal time delays and inconvenience to the patient. Recently specialist pleural services, often with a respiratory physician as lead, have developed in many tertiary centres. In addition, it is strongly advised that patients have access to a Lung Nurse Specialist during all stages of the diagnostic work-up and subsequent active management.

Chemotherapy and radiation therapy

The primary tumour cell type will predict responsiveness to chemotherapy or radiation in the setting of MPE. Although overall response rates are poor, lymphomas, small-cell lung cancer, germ cell tumours and cancer of the prostate, ovary and thyroid may demonstrate a reasonable response to treatment with chemotherapy.^{29,30} Radiation therapy may provide some benefit when involvement of mediastinal nodes predominates.³¹ In addition, patients with proven or suspected mesothelioma should be considered for prophylactic radiotherapy to the site of thoracoscopy, surgery or large-bore chest drain insertion.⁶

Thoracocentesis

Therapeutic thoracocentesis should be completed prior to any definitive pleural procedure to ensure that the patient benefits from removal of pleural fluid. This is suggested because symptoms such as dyspnoea may be secondary to an alternative aetiology such as trapped lung, carcinomatous lymphangitis or atelectasis by large bronchus obstruction.² Although thoracocentesis is associated with a risk of re-expansion pulmonary oedema, recent studies have demonstrated that this risk is unrelated to the amount of fluid drained and it has been suggested that no upper limit is necessary. Pleural manometry is a method by which pleural pressures can be monitored during thoracocentesis and aspiration should be discontinued once pleural pressures fall to <−20 cm water or clinically if the patient develops symptoms of dyspnea, cough or chest discomfort.^{21,32,33} Although this technique is not currently used in routine clinical practice, results from studies are promising and it may help in identifying patients at risk of re-expansion pulmonary oedema and therefore allow for greater volumes of fluid to be removed safely in selected patients.^{21,33} If symptoms improve, a definitive procedure such as pleurodesis or placement of an indwelling pleural catheter (IPC) should be considered as serial thoracocentesis is associated with patient discomfort and an associated increased risk of infection.² However, in some circumstances such as slow pleural fluid reaccumulation, where patients are unwilling or medically unable to undergo more definitive treatment, or those cases which have advanced disease with a very limited life expectancy, repeated thoracocentesis to palliate dyspnea is a viable option.

Pleurodesis

Pleurodesis involves the insertion of a sclerosing agent to induce pleural inflammation with the resulting adhesion of the visceral to the parietal pleura.² Currently available agents include bleomycin and talc. Tetracycline was a previously popular sclerosant but is no longer available in the UK for this purpose.⁶ Bleomycin, an anti-neoplastic agent has a mean success rate of 61% following a single administration and is typically instilled via a small bore chest tube.⁶ Talc, a hydrated magnesium silicate, is the most effective and least expensive agent and may be administered via a chest tube as a talc slurry or insufflated as a dry powder during the time of thoracoscopy, also known as talc poudrage.^{2,11,34} Dresler *et al.* performed a prospective, randomized controlled trial and compared thoracoscopy with talc poudrage to thoracostomy and talc slurry for

patients with documented MPE. They found both methods to be similar in efficacy; as defined as a 30-day freedom from radiological effusion recurrence in patients where lung re-expansion was >90% (insufflation 78% and slurry 71%). A *post-hoc* analysis suggested that insufflation may be better for patients with either a lung or breast primary.³⁵ Both methods of talc delivery require hospitalization and patients often experience pain and fever post-procedure.¹² Empyema is a recognized complication of pleural intervention and should be considered especially if symptoms do not resolve after a few days. Concerns regarding systemic dissemination of talc particles—leading to acute respiratory distress syndrome have been raised in previous studies; however, several clinical studies have not noted any such complications, particularly if talc preparations with large particle size (>15 µm) are used.^{36,37}

Indwelling pleural catheter

An IPC is an alternative method of controlling MPE and involves the insertion of a tunnelled small catheter into the pleural cavity which allows intermittent drainage with a vacuum bottle.² It may be considered in patients who have a limited performance status or life expectancy or in those who have trapped lung or high operative risk. IPC insertion can be performed in the outpatient setting, and may be useful for those who wish to avoid hospitalization.³⁸ In addition, it is a feasible option in patients who have failed initial talc pleurodesis. Indeed some authors now place an IPC at the time of thoracoscopy so that the pleural space can be managed effectively even if the talc pleurodesis fails.³⁹ A recent prospective study by Fysh *et al.*⁴⁰ compared MPEs treated with IPC vs. pleurodesis and concluded that patients treated with IPC required significantly fewer days in hospital and fewer additional pleural procedures with similar safety profiles and symptom control between the two groups. Similar results were reported by Davies *et al.*⁴¹ who found in a cohort of patients with malignant effusions and no previous pleurodesis, that there was no significant difference between IPC and talc pleurodesis at relieving patient-reported dyspnea. In contrast to pleurodesis, IPC requires a regular drainage schedule which may be burdensome for the patient or family members and therefore input from community support services may be additionally required.¹² In addition, cost analyses reveal that treatment with talc is less costly than IPC if the patients' life expectancy is >6 weeks.⁴² Patient choice must also be considered and each individual must balance the requirement for hospitalization in the

case of pleurodesis vs. IPC insertion in an ambulatory setting but with the associated need for ongoing drainage.

Surgery

Pleurectomy, either as an open procedure or using VATS has been described as a treatment for MPEs, however, there is not sufficient evidence to recommend this as a treatment option over pleurodesis or IPC placement.⁶

Palliation

Occasionally, due to disease severity, the patient will be unfit for any pleural-based procedures. In this instance, systemic therapies for symptom control may be necessary. When possible, this treatment should be directed by a dedicated palliative medicine team.

Conclusion

MPEs are common and indicate advanced malignancy. Given the limited life expectancy associated with this condition, swift diagnosis using high yield techniques should be prioritized. Management decisions should be taken by the multidisciplinary team on an individual patient basis but should primarily focus on symptom control by prevention of recurrent pleural effusions.

Conflict of interest: None declared.

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