Malignant mesothelioma: risk factors and current management

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Malignant mesothelioma is a cancer of the pleura and peritoneum often associated with asbestos exposure. Although rare its incidence is increasing, principally as a result of the long latency period of the disease. This article presents a review of mesothelioma, looking at the disease process, risk factors, causes, and current management strategies – namely surgery, chemotherapy, and radiotherapy. Some of the nursing implications are discussed along with the resources currently available to patients with mesothelioma in the UK.

While it is still a relatively rare disease, recent projections indicate that the number of men dying from mesothelioma in western Europe will almost double over the next 20 years and will account for about 250,000 deaths over the next 35 years (Peto et al, 1999). In the UK there has been a steady increase in deaths from the disease. From 1968 to 1991 the annual number of cases increased from 154 to 1,009, and this trend is predicted to continue, peaking in 2020 at 3,000 deaths (Executive Office of Population Censuses and Surveys, 1995).

The disease process

Mesothelioma principally affects the pleura and peritoneum, although in more than 90 per cent of cases the lungs are also affected. The disease can also occur in the pericardial pleura, vagina, and testes.

The pleura is the delicate serous membrane that encloses the lungs. It is composed of a single layer of flattened mesothelial cells resting on a membrane of connective tissue. It is divided into the visceral pleura, which encases the lung, dipping into the fissures between the lobes, and the parietal pleura that lines the chest wall and covers the diaphragm (Fig 1, p43).

Mesothelioma is characterised by the formation of plaques on the pleura, especially the parietal pleura, often around the diaphragm. Extension into the lungs, mediastinum, and pericardium can be seen in advanced disease. Although in general mesothelioma progresses by local invasion, 50 to 67 per cent of patients show evidence of metastatic spread on autopsy (Lee et al, 2000).

Mesothelioma differs from other forms of cancer in two ways. Firstly only very brief exposure to asbestos is enough to precipitate the disease, and secondly it can remain latent for five to 70 years. Therefore, people who have been exposed to asbestos, even if only briefly, are at risk of developing the disease at some time during their lives. Children appear to be especially susceptible and typically go on to develop the disease in their 40s and 50s, whereas people exposed after 20 years of age may not develop symptoms until their 70s (Orenstein and Schenker, 2000).

Because of its long latency period the incidence of mesothelioma is now peaking in many industrial countries. It was not until the 1970s that the hazards of asbestos exposure were really understood and protective measures implemented. The cases developing today result from asbestos exposure prior to that time (Boxes 1 and 2).

Asbestos and mesothelioma

The association between asbestos and lung cancer was first observed in 1935 (Gottschall, 2002). In the UK 80 to 90 per cent of cases of mesothelioma are linked to asbestos exposure (Attanoos and Gibbs, 1997). In these cases inhaled fibres pass through the alveoli and migrate into the pleura of the lungs where they affect the mesothelial cells, thereby causing mesothelioma.

Occasionally the disease occurs in people with no history of asbestos exposure. In these cases mineral fibre analysis of lung tissue can show levels of asbestos fibres within background reference ranges. In such cases mesothelioma may due to exposure to the following:

● Non-asbestos fibres, such as erionite, found in the
The histological type is thought to be an important factor for mesothelioma patients – with a clear survival benefit for the epithelial type. Prognostic factors such as female, early stage, epithelial histology, good performance status, age less than 70, absence of pain, and absence of weight loss need to be taken into account when planning treatment strategies (Baas, 2003).

The other important factor in determining how to treat the newly diagnosed patient is the stage of the disease. Staging systems evaluate tumour size, lymph node involvement, and the presence or absence of distant spread of the disease. A number of different staging systems have been put forward for mesothelioma but the most widely accepted is that developed by the International Mesothelioma Interest Group (IMIG). This is outlined in Table 1 (p42).

Staging of the disease, particularly assessment of the tumour size, is notoriously difficult in patients with mesothelioma. This is because mesothelioma is so diffuse that it is difficult to see where it begins and ends. It often looks like a slightly thicker area of pleura, which can only really be measured in one dimension. A team of researchers in Perth, Australia recently identified a blood test to aid in the diagnosis of mesothelioma. The test works by measuring the amount of soluble mesothelin-related proteins in the bloodstream – people with the disease have elevated levels (Robinson et al, 2003). This test has also been put forward as a potential screening tool for people who have been exposed to asbestos. However, the current treatment options for mesothelioma are so limited that there are issues about the ethics of screening. There is no point detecting a disease early if there is no adequate means of treating it.

**Treatment**

Therapies available for patients with mesothelioma are limited. Because it is such a rare malignancy there have been few well-controlled, randomised trials of appropriate therapies. Most published data is of non-randomised studies with small sample sizes. Because no curative therapy has yet been found, the current standard treatment in the UK is active symptom control.

**Presentation**

Only five to 15 per cent of cases of lung cancer are diagnosed on screening or as incidental findings (Gottschall, 2002). Most patients are only picked up once they become symptomatic. The most common presenting symptoms are dyspnoea and dull, aching chest pain. Cough, fever, malaise, and weight loss may also be present. By the time these features are apparent most patients will already have fairly advanced disease.

Mesothelioma is a notoriously difficult disease to detect and track by conventional imaging techniques and frequently a diagnosis will not be made until six to eight months after the initial symptoms have appeared (Senyigit et al, 2000). An initial chest X-ray will generally pick up diffuse pleural thickening and a pleural effusion. This will be followed by a computerised tomography scan of the chest, which will reveal specific plaques (areas of deposition of hyalinised collagen fibres) in the parietal pleura. These are sometimes described as looking like ‘table mountains’. Pleural plaques are indicative of asbestos exposure.

In general, magnetic resonance imaging does not offer any advantage over computerised tomography (CT) scanning, except in patients who may require surgery. In these patients an MRI scan can provide more detailed information about the level of tumour invasion into surrounding tissue, such as the diaphragm, which may render surgery ineffective. Positron emission tomography (PET) scanning is not thought to be helpful at this time (Eibl et al, 2003).

As well as being difficult to detect radiologically, mesothelioma is also difficult to confirm cytologically (by performing a pleural tap and looking at the cells suspended in the pleural fluid). A definitive diagnosis can only be made following a pleural biopsy.
Treatment of malignant pleural mesothelioma
can include surgery, radiotherapy and chemotherapy. However, curative surgical approaches are extremely aggressive, carrying high rates of morbidity and mortality, and are therefore only appropriate for a small number of people. Furthermore, relapse rates are high. There are two main radical surgical approaches for those few individuals with localised, resectable disease. The first is a pleurectomy, which involves resecting the affected section of pleura. The procedure has only a one to two per cent mortality rate if conducted in a specialist centre, although residual tumour is found in almost 80 per cent of patients (Hilaris et al, 1984).

An extrapleural pneumonectomy (EPP) involves the en bloc resection of the lung, the visceral and parietal pleura, and the pericardium and ipsilateral diaphragm with reconstruction of the pericardium and diaphragm. The mortality rate from this procedure has dropped from 30 per cent to five per cent but it carries a high morbidity rate with a risk of supraventricular tachycardias and post-operative pneumonia. Median survival post EPP ranges from nine to 19 months, the procedure being limited by operative deaths, residual tumour, local recurrence, and metastatic disease (Van Ruth et al, 2003).

To reduce the risk of recurrence after surgery a number of adjuvant therapies have been proposed in the hope that they might eliminate any microscopic residual disease that is missed in the operation. Some centres practise extremely aggressive combined modality therapy including surgery, radiotherapy, and chemotherapy. Although this has been shown to have better response rates than surgery alone with a median survival rate of 19 months (Sugarbaker et al, 1999), it is probable that it is only a realistic treatment option for one to two per cent of mesothelioma patients (Lee et al, 2000).

Because most patients will present with disease too advanced for an operation, surgical management has historically been limited to obtaining tissue for diagnosis or for symptom control by pleurodesis (Waller, 2003). Pleural effusion (the drainage of pleural fluid into the pleural space) is a common complication of mesothelioma. Pleurodesis involves the drainage of pleural effusions and is generally accompanied by insufflation with talc to prevent further effusion formation. The instillation of tcalc into the pleural space acts as a chemical irritant, leading to the formation of adhesions, which seal the pleural space so that no more fluid can accumulate there. This type of intervention can provide relief in up to 90 per cent of cases but unfortunately it is often short-lived (Waller, 2003).

A recent review of conservative measures for mesothelioma found survival rates to be low at around seven months, although those with an epithelial tumour survived longer (Merritt et al, 2001). Pleurodesis is not helpful in situations in which the tumour has also infiltrated the visceral pleura and the lung has collapsed.

Radiotherapy and chemotherapy

The role of radiotherapy in mesothelioma is limited because the diffuse nature of the tumour means the target area is large, resulting in unacceptable toxicity to neighbouring organs. Furthermore, although radiotherapy seems to have some effect on mesothelioma cell lines in vitro, in vivo the disease is relatively radioresistant, even at high doses. Thus the role of radiotherapy is limited to prophylaxis. Because mesothelioma has the capacity to seed down the tract of invasive surgical procedures such as thoroscopies, radiotherapy is sometimes utilised to prevent this.

Similarly, the role of chemotherapy is generally considered to be equally limited. A number of drugs have been tried over the years both individually and in combination. However, reviews of multiple studies show response rates of at best 10–30 per cent (Tomek and Manegold, 2003). Furthermore, response rates are not necessarily reflected in an increase in survival.

One of the criticisms of many of the chemotherapy studies to date is that they have not included an adequate control group. In the absence of any effective treatment for mesothelioma, many believe the control arm should be symptomatic care only. Clearly this is not an attractive option for many desperate patients who are seeking more active approaches – even if the chance of success is small. The British Thoracic Society (BTS) recently launched a large multicentre study to compare two different chemotherapy regimens, incorporating a ‘no active treatment’ arm.

The progress of the BTS study has been complicated by a new antifolate drug called pemetrexed (Alimta), which is currently undergoing trials. This drug is associated with slightly more encouraging response rates than any other chemotherapy agent to date but as yet the findings are limited to one trial, the EMPHACIS (evaluation of mesothelioma patients)

**TABLE 1. INTERNATIONAL MESOTHELIOMA INTEREST GROUP STAGING SYSTEM (ABBREVIATED)**

<table>
<thead>
<tr>
<th>TNM</th>
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<tr>
<td>T</td>
<td>Different degrees of pleural involvement from T1 = confined to ipsilateral, mediastinal diaphragmatic pleura to stage 4 involving all ipsilateral pleural surfaces combined with diffuse extension into peritoneum, mediastinal organs, contralateral pleura, internal surface or pericardium or myocardium</td>
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<tr>
<td>N</td>
<td>No lymph node involvement (NO) to contralateral mediastinal or internal mammary lymph nodes, or any supraclavicular metastases (N3)</td>
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<td>M0</td>
<td>No distant metastases and M1 = distant metastases</td>
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**References**


A more holistic approach is required that better acknowledges the impact of breathlessness have been understood from the perspective of the individual experiencing it.

Bredin et al (1999) evaluated the role of a nurse-led clinic offering non-pharmacological interventions for breathlessness. The focus was on the emotional aspects of dyspnoea and individualised coping strategies were identified to address specific patient fears. At eight weeks an assessment of these interventions was performed and it was found that they improved breathlessness, performance status and levels of depression in the treatment group compared with the control group.

While symptom control is advocated as the mainstay of therapy for mesothelioma, understandably some patients, especially the young, will elect to have active treatment despite poor data to support its efficacy. In these patients, undergoing treatment at least offers some hope, even if the odds are poor.

A small proportion of patients will require surgery, involving acute pre- and postoperative care. However, a larger proportion will be at a stage of the disease that is too advanced for an operation or will have comorbidities that render surgery inappropriate. For these people chemotherapy is the next option.

Nursing management of patients undergoing chemotherapy for mesothelioma requires skill and sensitivity. All chemotherapy, even milder regimens, involve some toxicities. Some chemotherapy regimens can be extremely toxic. Indeed, four patients in the pemetrexed study died of treatment-related toxicities (Vozelgang et al, 2002). Three of these were in the pemetrexed group, although subsequently the treatment was successfully modified to improve its safety.

Most chemotherapy schedules have the potential to lower the white blood cell count, which renders the patient at risk of life-threatening infections. Furthermore, many regimens are associated with nausea, vomiting, anorexia, and the need for frequent hospital visits and cannulations. Supporting a patient through such treatment involves providing advice and encouragement through the difficult periods, while at the same time remaining mindful of the poor prognosis of this disease and the poor evidence base for chemotherapy. Nursing care sometimes seems to perch uncomfortably between providing the patient with enough encouragement to go on while not instilling false hope.

Conclusion

The use of asbestos has been banned in the UK since 1999. Nevertheless, the legacy of asbestos exposure means that mesothelioma continues to present a clinical challenge to the medical professions. Unfortunately current therapies have failed to provide a solution and it can only be hoped that treatment for mesothelioma will from now on be conducted within the context of formal research programmes that might identify useful treatment strategies and facilitate evidence-based care.

REFERENCES


