Malignant pleural mesothelioma at St Mary's Hospital, Portsmouth—a review of 29 fatal cases

R. N. HARRISON*  
M.B., Ch.B., M.R.C.P.  

S. C. HIBBERD  
B.M.  

J. H. DADDS  
M.B., B.S., F.R.C.P.  

St Mary's Hospital, Portsmouth

Summary
The clinical details are presented of 29 fatal cases of pleural mesothelioma in the majority of which there was a history of exposure to asbestos during dockyard work in Portsmouth. Chest pain, breathlessness and weight loss dominated the clinical picture. Analgesia and repeated pleural aspirations provided temporary relief but symptoms invariably progressed. The mean survival time was 39 weeks. Only one patient survived longer than 2 years from hospital presentation. At autopsy, extensive local spread was usual but a high proportion of patients also had metastases at distant sites.

KEY WORDS: malignant mesothelioma, asbestosis, pleural effusion.

Introduction
Although malignant mesothelioma accounts for only a fraction of deaths due to cancer, its incidence is rising. In England and Wales, the annual number of deaths from pleural mesothelioma has increased by 75% over the period 1968–1978 (Gardner, Acheson and Winter, 1982). Estimates amongst asbestos workers suggest the risk of developing mesothelioma lies between 5 and 7% (Selikoff, Hammond and Seidman, 1973) but it should probably be considered in the differential diagnosis of any insidious progressive pleural disease. Recent papers characterized a fairly uniform clinical picture produced by the disease (Roberts, 1970; Whitwell and Rawcliffe, 1971; Elmes and Simpson, 1976) and revised traditional concepts that the tumour spreads only locally and to regional lymph nodes. In the light of these studies, we have analysed clinical and autopsy details of 29 fatal cases of pleural mesothelioma seen at one hospital during a 6.5-year period.

Patients
This is a retrospective study of 29 patients (28 male and 1 female) seen at St Mary's Hospital, Portsmouth, who died of histologically proven malignant pleural mesothelioma between January 1976 and June 1982. In all cases, the diagnosis was accepted by the Pneumoconiosis Medical Panel. At death, ages ranged from 41 to 91 years with a mean of 63 years. Twenty-two patients admitted previous asbestos exposure, 27 had been in occupations where an exposure risk is recognized, 20 of them had worked at H.M. Dockyard, Portsmouth (Table 1). Chronological details of asbestos exposure were, in general, poorly recorded in the case-sheets and were not analyzed further.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dockyard workers</td>
<td></td>
</tr>
<tr>
<td>Boiler maker</td>
<td>3</td>
</tr>
<tr>
<td>Lagger</td>
<td>4</td>
</tr>
<tr>
<td>Shipwright</td>
<td>2</td>
</tr>
<tr>
<td>Labourer</td>
<td></td>
</tr>
<tr>
<td>Tool cutter</td>
<td>1</td>
</tr>
<tr>
<td>Storeman</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Builder</td>
<td>2</td>
</tr>
<tr>
<td>Electrician</td>
<td>2</td>
</tr>
<tr>
<td>Naval Engineer</td>
<td>2</td>
</tr>
<tr>
<td>Plumber</td>
<td>1</td>
</tr>
</tbody>
</table>

*The remaining 2, a waitress and a local government officer, had no history of asbestos exposure.

*Present address: Faculty of Medicine, Level D, Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.
Clinical details
The earliest symptoms were chest pain (50%), breathlessness (39%) and malaise (7%). Chest pain and breathlessness started simultaneously in one case. By their first hospital attendance, their complaints were of chest pain (79%), breathlessness (71%), cough (50%), weight loss (39%) and malaise (11%). Pain remained the sole symptom in only 14% of the patients. The pain characteristically started insidiously and was dull and persistent with exacerbations when lying on the affected side. At presentation, physical examination was negative in only one patient.

Clinical and radiological signs of a pleural effusion, confirmed by positive aspiration, were present in 20 patients at presentation. In the remainder respiratory movements, percussion note and breath sounds were usually impaired on the involved side, X-rays showed pleural thickening (Fig. 1) and pleural aspiration was unsuccessful. Symptoms in the two groups of patients were similar. One had finger clubbing, one had supraclavicular lymphadenopathy and one was pyrexial.

Investigations
There were no characteristic haematological or biochemical findings. The blood count was invariably normal at presentation, although 3 patients subsequently developed a normochromic anaemia. The initial erythrocyte sedimentation rate (ESR) ranged from 14–135 mm/hr (mean 69 mm/hr) and tended to be higher in those with pleural thickening alone (mean 87 mm/hr) compared to those with effusions (42 mm/hr). An ESR greater than 100 was seen in 6 patients at presentation.

Serial plasma electrolytes were available in 23 patients and in 9 of these plasma sodium fell below 135 mmol/litre as the disease progressed.
In those with effusions, the initial aspirate was serous in 40% and uniformly blood stained in the remainder. The fluid was invariably an exudate (mean protein concentration 45 g/litre) and in 40% of cases was described as lymphocytic. Cytology was considered diagnostic of mesothelioma in only one case.

Table 2. The success of different biopsy techniques in diagnosing pleural mesothelioma

<table>
<thead>
<tr>
<th>Type of biopsy</th>
<th>Attempted</th>
<th>Positive histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams needle</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Tru-Cut needle</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

The initial X-rays were always abnormal showing a variable pattern of irregular pleural thickening and pleural fluid. With time, the pleural shadowing progressed and characteristically was accompanied by marked ipsilateral rib crowding. Contralateral pleural plaques were identified in 25% of the patients, half of these were calcified, linear diaphragmatic calcification was seen in only one case.

Histological diagnosis
In 18 patients, histological diagnosis was made before death. The diagnostic success of the 3 techniques used is shown in Table 2. In the one case where open biopsy was inconclusive, subsequent Trucut biopsy provided the diagnosis. Abrams needle biopsy was generally attempted earlier (mean inter-

Fig. 1. Progressive pleural thickening in a 67-year-old man with no asbestos exposure. X-Rays 1 year apart.
val before death 10 months) than either thoracotomy (mean interval 5 months) or Trucut needle biopsy (mean interval 3 months).

Clinical course

The average time from hospital presentation to death was 39 weeks, with a range of 4–128 weeks. The median survival time from presentation was 28 weeks. Fig. 2 shows a life table analysis of all the patients. Six patients survived more than 1 year and one survived for 2 years. Patients with pleural effusions survived significantly longer after hospital presentation than those without fluid \( (P<0.025) \), but also presented earlier after the onset of symptoms \( (P<0.005) \). Mean survival times from the onset of symptoms were similar in those with and without pleural effusions (Table 3). Mean survival time from onset of symptoms in patients with no history of exposure to asbestos dust was 53 weeks (range 44–64 weeks).

Most patients remained comparatively well until 3 or 4 months before death. When associated with an effusion, yspnoea could be relieved by repeated aspiration but this became progressively difficult and less rewarding as the pleura thickened. A 69-year-old man presented with a right-sided bloody effusion, this was aspirated to dryness (6 litres) with complete radiological clearing at review 6 months later. A year after the original illness, he returned with a contralateral bloody effusion which persisted until his death 9 months later (Fig. 3). At autopsy, mesothelioma was found surrounding the left lung; on the right side benign pleural thickening suggested the initial effusion was ‘benign asbestos pleurisy’ (Gaensler and Kaplan, 1971). In the last weeks of life, breathlessness was the dominant and most distressing symptom. The provision of adequate pain relief was also a major problem and opiates were frequently necessary, in one case limited success was obtained with multiple posterior intercostal nerve blocks. Weight loss was marked averaging 10–25 kg from presentation to death.

One patient developed superior vena caval obstruction. One patient developed focal neurological signs from cerebral metastases. In the case of a 69-year-old man, the slow downhill course was complicated by an acute steroid-responsive neuropathy with features of the Miller-Fisher syndrome (oculomotor pareses, areflexia and ataxia). No instance of local recurrence either at needle biopsy sites or at thoracotomy scars were noted.

In all cases, treatment was conservative and symptomatic. Attempts to prevent fluid reaccumulation with local instillation of mepacrine (2 cases), bleomycin (1 case) and Corynebacterium parvum (1 case) proved unsuccessful. One patient received limited help from radiotherapy for pain relief.

Autopsy

Detailed autopsy reports were available on all but 2 cases. Characteristically, the pleural space had been

![Fig. 2. Survival curve of 29 mesothelioma patients from the time of presentation.](http://pmj.bmj.com/)

### Table 3. Mean intervals between onset of symptoms, presentation and death in 29 mesothelioma patients. A comparison of patients with and without pleural effusions (Student's t-test)

<table>
<thead>
<tr>
<th>Patients presenting:</th>
<th>with effusion (weeks)</th>
<th>without effusion (weeks)</th>
<th>( P )</th>
<th>All patients (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset 1st symptom to presentation</td>
<td>15</td>
<td>48</td>
<td>&lt;0.005</td>
<td>25</td>
</tr>
<tr>
<td>Onset 1st symptom to death</td>
<td>63.2</td>
<td>69</td>
<td>NS</td>
<td>65</td>
</tr>
<tr>
<td>Presentation to death</td>
<td>48</td>
<td>23</td>
<td>&lt;0.025</td>
<td>39</td>
</tr>
</tbody>
</table>

NS = not significant.
Malignant pleural mesothelioma

unilaterally obliterated by a dense white tumour mass 5–20 mm thick. Bilateral pleural involvement occurred in only 3 cases. Contralateral hyaline plaques were noted in a quarter of the cases.

Local spread was the rule: to underlying lung (16 cases), diaphragm (14 cases), chest wall (6 cases) and pericardium (5 cases). Intrathoracic metastatic spread was seen to hilar and mediastinal glands (7 cases) and to the opposite lung (3 cases). Tumour was confined to the thoracic cavity in only 11 of the patients. Extrathoracic spread was most common to the liver and peritoneum where involvement was almost always associated with tumour infiltration of the diaphragm. There were also isolated cases of direct tumour extension to the right adrenal, spleen, retroperitoneal space and root of the neck. Two cases without diaphragm involvement had distant metastases in the liver, peritoneum, kidney, pancreas and adrenal glands. Multiple cerebral deposits were found in one patient.

Discussion

Malignant pleural mesothelioma has been accepted as a distinct entity comparatively recently (Sano, Weiss and Gault, 1950), its link with asbestos exposure has only been appreciated since 1960 (Wagner, Sleggs and Marchand, 1960). Heavy industrial asbestos use and increased clinical suspicion have contributed to the disease's rising incidence. Unfortunately, a 20–40 year latent period between exposure and disease, combined with belated dust control, mean many new cases will arise during the remainder of this century. In England and Wales, the number of newly registered cases has risen steadily from 124 in 1972 to 248 in 1978 (Gardner, Acheson and Winter, 1982). Mesothelioma should therefore be considered whenever there is insidious pleural disease (Elmes and Simpson, 1976).

The definitive diagnosis of mesothelioma may be difficult to make during life and caution is needed, especially where there is no history of asbestos exposure. Adenocarcinoma in particular can produce diffuse metastatic pleural infiltration and may be confused with the epithelial type mesothelioma (Hasan, Nash and Kazemi, 1977). The correct diagnosis often relies heavily on the autopsy to provide adequate specimens and to exclude a primary tumour elsewhere. None of the present series was diagnosed solely on closed pleural biopsy. Cases were included only if the diagnosis from the Portsmouth pathologists was corroborated by subsequent reports from the Pneumoconiosis Medical Panel.

The age and sex distribution in the present study were similar to those in previous series. The average age at death of 63 probably reflects the latent period between exposure and the development of mesothelioma. Not surprisingly, most of the cases in Portsmouth were exposed to asbestos whilst working in the Naval Dockyard. Only 2 cases had no asbestos exposure, a similar proportion to 13 cases out of 277 reported in a larger series (Elmes and Simpson, 1976). Accurate estimates of the nature or degree of exposure could not be obtained from our records although evidence from other sources suggests that the risk of developing mesothelioma is dose-related (Parkes, 1982). The incidence of mesothelioma more than doubles if exposure is greater than 2 years. Asbestos type also influences the risk which appears to be highest with the short, small-diameter fibres of crocidolite.

The mean interval between the onset of symptoms and death was 65 weeks, almost identical to that found by Elmes and Simpson (1976). Others have suggested that patients who deny asbestos exposure fare better than those with a positive occupational history (Law, Gregor and Hodson, 1981), but our results do not support this. The presence of pleural fluid appeared not to influence survival though it may have led to earlier hospital presentation (Table 3).

There was a predominance of chest pain and dyspnœa in these cases, although other tumours, notably adenocarcinoma, can produce a very similar clinical picture. Initial investigations were often unhelpful, but as clinical suspicion for mesothelioma

FIG. 3. Chest X-Rays of a 70-year-old ex HM Dockyard worker: (a) right-sided 'benign asbestos pleurisy' April 1980; (b) normal film November 1980; (c) left effusion April 1981. Autopsy: left-sided mesothelioma.
is high in Portsmouth, the correct diagnosis was often considered early in the disease. Pleural fluid cytology and Abrams pleural biopsy both had poor yields, although results with the latter method may simply reflect operator inexperience since pleural tissue was frequently not obtained. The results with the Tru-Cut results were impressive and, contrary to conventional teaching, needle-track tumour infiltration was not a problem. The Tru-Cut needle appears to share advantages of trephine biopsy (Gellert and Steel, 1982) and should be considered as an alternative to open pleural biopsy.

The X-ray changes in this series conformed to previously described patterns (Elmes and Simpson, 1976) which are not in themselves diagnostic of mesothelioma. Others have noted the unexpectedly low incidence of radiographic pleural plaques which accompany mesothelioma. The current view is that pleural plaques are not premalignant, neither are they associated with an increased risk of malignancy. Their diagnostic value is limited to that of an index of asbestos exposure (Parkes, 1982).

The depressing clinical course was similar to that in previous series. Where appropriate, pleural aspiration relieves dyspnoea but progressive pleural infiltration makes it increasingly difficult. The proportion of cases with no fluid at presentation (30%) was similar with that of the series of Elmes and Simpson (1976). In these, the X-rays show progressive pleural shadowing associated with a 'frozen' hemithorax and increasing pain. Local attempts at pain relief were unrewarding, regular narcotic analgesics were often necessary. One patient developed neurological complications from cerebral metastases and it was uncertain whether in another, a steroid responsive neuropathy represented a paramalignant syndrome. A previous report that inappropriate anti-diuretic hormone secretion occurs in mesothelioma (Perks, Stanhope and Green, 1979) is supported by the finding that serum sodium fell below 135 mmol/l in 9 patients. However, other mechanisms may be involved especially as adrenal metastases were comparatively common (4 cases).

The autopsy results encapsulate the changing views on clinical aspects of mesothelioma. Local spread has always been acknowledged but until recently distant metastases were considered distinctly uncommon (Spencer, 1968). Intra-abdominal spread was a frequent finding, and in most instances it probably resulted from local infiltration and seeding but the occurrence of extensive metastases in the absence of diaphragmatic infiltration implicates blood-borne spread in some cases.

References


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