Malignant mesothelioma in south east England: clinicopathological experience of 272 cases

D H Yates, B Corrin, P N Stidolph, K Browne

Abstract

Background – Malignant mesothelioma is a rare pleural tumour associated with asbestos exposure. The proportion of malignant mesothelioma unrelated to asbestos exposure, and any differentiating features between exposed and unexposed cases, are not well described. This study describes occupational, clinical, and pathological features in a large cohort of cases of malignant mesothelioma from south east England.

Methods – All 272 cases from this region were studied, either in life or after death when necropsy examination suggested malignant mesothelioma. Detailed information was gathered regarding the occupational history, clinical course, and mode of death. Necropsies were performed in 98% of cases. Lung tissue was examined histologically to confirm the diagnosis, subtype of tumour, presence or absence of asbestososis and asbestos bodies.

Results – Exposure to asbestos was documented in 87% of cases, while in the remainder, no asbestos exposure was found nor were asbestos bodies seen; 94.5% were pleural, 5.1% peritoneal, and 0.4% pericardial. Right sided tumours were more common than left sided tumours (ratio 1.6:1). Patients usually presented with breathlessness and chest pain, but 33% presented with pleural effusion in the absence of chest pain. The mean (SD) time from first exposure to asbestos to symptoms was 40 (12) years with a median (interquartile range (IQR)) survival of 14 (12.5) months. The median (IQR) survival time in sarcomatous, epithelial, and mixed cell type malignant mesothelioma was 9.4 (10) months, 12.5 (18) months, and 11 (14) months, respectively, and was significantly greater in cases detected by chance. Clinical features were similar in asbestos related and non-asbestos related malignant mesothelioma.

Conclusions – In south east England most cases of malignant mesothelioma are associated with asbestos exposure. Clinical features do not differentiate between asbestos related and non-asbestos related disease.

(Thorax 1997;52:507–512)

Keywords: mesothelioma, asbestos, pleural tumour.

Malignant mesothelioma is an uncommon tumour usually attributable to asbestos exposure, which is rising in incidence in the UK. Clinical and pathological features of malignant mesothelioma have been previously well described. In many published series, however, numbers are small and complete clinical, occupational, and pathological details have been difficult to obtain. The proportion of tumours not related to asbestos, survival with different tumour subtypes, and features of non-asbestos related tumours are also uncertain. This report provides complete documentation of 272 cases where mesothelioma was the cause of death within a defined geographical area in the south east of England for the calendar year 1987.

In the UK a system of compensation for occupational lung disease has existed since 1931, and a regional network of Pneumoconiosis Panels (now called Medical Boarding Centres (MBCs)) assesses live and posthumous claims. The London MBC area covers all of the industrial south east.

In England all deaths suspected of being due to industrial disease must be reported to the coroner and a necropsy performed. Until April 1988 it was mandatory for coroners to refer all cases of malignant mesothelioma to MBCs for special examination of the lungs. A report by specialist physicians as to cause of death and presence or absence of an occupational lung disease was then made to the coroner.

Although only cases where there was any suspicion of industrial causation were legally required to be reported to the coroner, in practice – because of compensation issues – almost all cases diagnosed as malignant mesothelioma were referred. It is, however, possible that a small number of cases remained unreported because of the extreme improbability of any asbestos exposure. Clinical information was supplemented by verification of occupational exposure to asbestos, as government offices carefully verified potential asbestos exposure. This system resulted in the gathering of complete information on all cases of malignant mesothelioma in the region, but ended in 1988 with the abolition of industrial death benefit.

1987 was therefore the last year of complete registration of all cases of malignant mesothelioma in which any suspicion of asbestos causation had arisen.

Methods

CASE GATHERING

All deaths from malignant mesothelioma occurring in 1987 were studied. These included
patients examined in life for industrial disablement benefit or on appeal, those where such a diagnosis had been considered in life or discovered after death, and those confirmed at necropsy.

OCCUPATIONAL HISTORY
Occupational histories were obtained from multiple sources. Where a claim had been made for benefit, a detailed employment history was available. Where no claim had been made, occupational details were obtained from widows, hospital case notes, and coroners’ reports from inquests. In each such case the available employment history was examined by experienced occupational respiratory physicians, and further details regarding each and any employment which might have entailed contact with asbestos were obtained. Those employments involving contact with asbestos in the south east region had been previously documented by the MBC over a period of 30 years by the collation of results from periodic asbestos examinations in asbestos manufacturing and other industries and by claims for asbestos related diseases. These records were consulted where no history of asbestos exposure was observed. In addition, employment records were searched. Occupational details were verified by local government officers who confirmed contact with asbestos from previous employers, work mates, and relatives by obtaining written confirmation that the person had worked in the relevant employment, and the dates of such employment.

Cases were categorised into four groups on the basis of occupational history and histological findings: (1) definitely exposed, (2) probably exposed, (3) non-occupationally exposed, and (4) non-exposed. Thus, a case where few occupational details were available but asbestos bodies were easily seen on histological examination of necropsy material was classified as asbestos exposed. Where no asbestos bodies were seen but the decedent had worked in an occupation where asbestos exposure was likely, the case was classified as probably asbestos exposed. Probable exposure was also recorded when the decedent had worked in a less likely but recognised industry with no or very few asbestos bodies seen. Non-occupational exposure included a history of exposure outside the workplace. Non-exposure was only accepted where no asbestos bodies were seen and the complete occupational history indicated that exposure to asbestos was unlikely. These criteria resulted in a case being more likely to be classified as asbestos exposed than otherwise.

CLINICAL FEATURES
Clinical features were identified from regular examinations made by the MBC in life, hospital records, chest radiographs, coroners’ inquests, and necropsy records.

HISTOPATHOLOGICAL EXAMINATION
Lungs were examined macroscopically and three blocks were taken of both the tumour and the uninvolved lung. Histological examination was performed by one of the authors (BC) without knowledge of the occupational history. When only a glandular pattern was evident, haematoxylin and eosin staining was supplemented by diastase periodic acid Schiff and alcian blue staining with hyaluronidase control for mucous substances and by immunocytochemistry for carcinoembryonic antigen.

To identify asbestos bodies three unstained sections of the contralateral lung, 30 µm thick, were scrutinised in their entirety. Asbestos bodies were documented as absent, occasional, scanty, easily found, or numerous and asbestosis was diagnosed only when interstitial fibrosis was accompanied by numerous asbestos bodies. In two cases where the histological findings were doubtful the clinical and radiological features were considered carefully before inclusion in the series.

ANALYSIS OF DATA
Differences in proportions within groups were examined by χ² tests and differences in age were examined by unpaired two-sided Student’s t tests. All calculations were performed with a Dell PC and the NCSS statistical software program. Results are reported as mean (SD) and survival data as medians with interquartile ranges. Significance levels were taken at p<0.05.

Results
AGE, SEX DISTRIBUTION, AND SMOKING HABITS
From a total of 285 cases referred, 272 (252 men) were accepted as being malignant mesothelioma. The mean (SD) age at death was 65.2 (9.5) years, ranging from 39 to 92 years (Fig 1), with no difference between men (65 (10) years) and women (66 (9.6) years).

The median survival from time of symptom onset was 14 (12.5) months (range 0–91 months) with survival of women not significantly different from that of the men. Most patients survived less than nine months and survival beyond 40 months was very rare (4%). Survival was significantly shorter in peritoneal
Table 1 Exposure to asbestos by cases of malignant mesothelioma (n = 272)

<table>
<thead>
<tr>
<th>Occupational exposure</th>
<th>Number of cases</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>212</td>
<td>(77.9)</td>
</tr>
<tr>
<td>Probable</td>
<td>24</td>
<td>(8.8)</td>
</tr>
<tr>
<td>Possible non-occupational</td>
<td>4</td>
<td>(1.5)</td>
</tr>
<tr>
<td>No exposure</td>
<td>30</td>
<td>(11)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>272</td>
<td>(100)</td>
</tr>
</tbody>
</table>

Table 2 Occupational exposure to asbestos by cases of malignant mesothelioma (n = 272)

<table>
<thead>
<tr>
<th>Certain or probable occupational exposure:</th>
<th>Number of cases</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipbuilding and repair</td>
<td>42</td>
<td>(15.4)</td>
</tr>
<tr>
<td>Boiler, pipe and heating</td>
<td>40</td>
<td>(14.7)</td>
</tr>
<tr>
<td>Carpenters</td>
<td>30</td>
<td>(11.0)</td>
</tr>
<tr>
<td>Electricians</td>
<td>27</td>
<td>(9.9)</td>
</tr>
<tr>
<td>Construction and demolition</td>
<td>23</td>
<td>(8.5)</td>
</tr>
<tr>
<td>Asbestos manufacturing and sales</td>
<td>14</td>
<td>(5.1)</td>
</tr>
<tr>
<td>Insulation work, laggers</td>
<td>13</td>
<td>(4.8)</td>
</tr>
<tr>
<td>Electricity generation</td>
<td>11</td>
<td>(4.0)</td>
</tr>
<tr>
<td>Steamers and dockers</td>
<td>6</td>
<td>(2.2)</td>
</tr>
<tr>
<td>Railway coach construction</td>
<td>6</td>
<td>(2.2)</td>
</tr>
<tr>
<td>Laboratory and research</td>
<td>7</td>
<td>(2.6)</td>
</tr>
<tr>
<td>Navy seamen</td>
<td>3</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Possible non-occupational exposure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative of occupationally exposed worker</td>
<td>2</td>
<td>(0.7)</td>
</tr>
<tr>
<td>(one husband, one father)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut asbestos board for home refit</td>
<td>1</td>
<td>(0.4)</td>
</tr>
<tr>
<td>Lived near an asbestos factory</td>
<td>1</td>
<td>(0.4)</td>
</tr>
<tr>
<td>No-exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office and school</td>
<td>8</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Housework and domestic cleaning</td>
<td>4</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Mail sorting and delivery</td>
<td>2</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Factory and craft work</td>
<td>12</td>
<td>(4.4)</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>272</td>
<td>(100)</td>
</tr>
</tbody>
</table>

Figure 2 Frequency distribution of malignant mesothelioma by latency (n = 168 where dates of occupational exposure to asbestos had been verified).}

mesotheliomas (7 (4) months). Smoking habits were not analysed because smoking is not a risk factor for mesothelioma.6

OCCUPATIONAL EXPOSURE TO ASBESTOS

Occupational details were obtained in all but two cases. In 10 cases, although asbestos exposure was denied or could not be identified, numerous asbestos bodies were seen and these were classified as asbestos exposed.

Occupational exposure to asbestos was noted in 86.8% of cases (212 certain and 24 probable exposures; table 1). There were 30 cases where no history of asbestos exposure could be elicited, and no asbestos bodies were identified. Four cases (two relatives of asbestos workers, one who cut asbestos board during kitchen alterations at his home, and one living near an asbestos factory) were accepted by the coroner as having possible non-occupational exposure although no asbestos bodies were identified (table 2). No definite categorisation could be made in two cases due to insufficient information.

There were 168 cases (61.8%) where the dates of first exposure had been fully verified – that is, exact date of first exposure had been verified from objective records such as employment records rather than by recall of dates by patients, relatives or colleagues. The mean (SD) latency (defined as interval from first exposure to death) for all cases was 41.4 (11.7) years (range 15–67). Latency was longer in the peritoneal cases at 46.7 (11.3) years (p<0.05). The frequency distribution for latency is shown in fig 2. Reliable information on duration of exposure was available in 166 cases (61%). It was not possible to identify asbestos type, but mixed exposure was usual in the UK. The mean duration of exposure for the whole group was 19 (13) years, ranging from three months to 53 years. Duration of exposure for peritoneal cases was not significantly different from that of pleural cases (17.3 (14) versus 19 (13) years), although the reliability of these figures is questionable as information on exposure duration was available in only nine peritoneal cases. In 34 cases there was no history of occupational exposure to asbestos and no asbestos bodies were identified.

SITE OF TUMOUR

The site of the tumour was determined from clinical, radiographic, and necropsy data. When pleural tumours were bilateral, the site was classified according to the side of first onset of symptoms or first radiographic abnormality. Similarly, where there were both peritoneal and pleural tumours, the primary site was judged from the presenting clinical features.

Pleural tumours occurred in 257 cases with a right sided predominance (157 right sided, 99 left sided; ratio 1.6:1). In one case the original side of the pleural tumour could not be determined. Peritoneal tumours occurred in 14 cases (5.1%), with one pericardial malignant mesothelioma.

PATHOLOGY

Necropsies were conducted in 267 cases (98.1%) and mesothelioma was confirmed histologically in 265 (97.4%). In two cases the histological findings were equivocal despite special staining but the diagnosis was accepted on clinical and radiological grounds. In the remaining five cases histological confirmation was obtained from stored biopsy material.

Metastases (defined as secondary spread to the other lung, the peritoneum or more distant) were present in 150 cases (55.1%). Asbestosis
was more common in peritoneal than in pleural cases, although numbers were small – five (35.7%) versus 10 (3.9%), respectively (p<0.01). Asbestos bodies were present in 125 cases (46%), plaques were found either at necropsy or radiologically in 78 (28.7%).

Classification of malignant mesothelioma into histological subtypes is shown in Table 3. Although necropsies had been performed on 267 cases, histological subtyping was only available in 250 cases due to technical factors such as insufficient tissue or poor state of preservation. There were 83 sarcomatous mesotheliomas, 81 epithelial, 84 mixed, and two where the histological pattern could not be determined. A mixed pattern was diagnosed whenever both sarcomatous and epithelial components were evident, no matter how small the minor component. The mean survival time for epithelial cases was 16.2 (13) months, 14.7 (13.5) for mixed type and 10.1 (7.5) for sarcomatous cases, the latter being significantly shorter (p<0.05; fig 3). The median (interquartile range) survival times for epithelial, mixed and sarcomatous types were 12.5 (18) months, 11 (14) months, and 9.4 (10) months, respectively. When histological type was compared with frequency of metastasis no significant difference was seen between histological subtypes.

Table 3 Survival and metastases according to cell type (n=250)

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Number (%)</th>
<th>Metastases n (%)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>81 (32)</td>
<td>50 (62)</td>
<td>16.2 (13)</td>
</tr>
<tr>
<td>Mixed</td>
<td>84 (34)</td>
<td>48 (57)</td>
<td>14.7 (13.5)</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>83 (33)</td>
<td>43 (52)</td>
<td>10.1 (7.5)</td>
</tr>
<tr>
<td>Unable to type</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The continuing increase in death rate from malignant mesothelioma among workers exposed to asbestos implies that this rare tumour will become increasingly common.1 Our study reports the largest number of cases of malignant mesothelioma from the UK since 1976,3 and clarifies the clinical and occupational features which may prove useful for the early diagnosis of this tumour. The system of routine referral of every suspected asbestos related death to MBCs which was in operation in 1987 should have diminished the occupational selection bias which usually occurs in reports from pneumoconiosis units, although such a bias cannot be discounted. The high availability of necropsy tissue allowed verification of the diagnosis on histological grounds, and occupational histories were obtained from a wide variety of sources and carefully screened for possible exposure by a number of methods.

Clinical Features

Most patients presented with chest pain and breathlessness. Other features included lassitude, weight loss, night sweats, pneumothorax, and a chest wall mass. Pleural effusion accompanied by breathlessness but without pain were the presenting features in 90 cases (33%). Chest pain initially unaccompanied by pleural effusion was present in 104 cases (38%). Fifty five cases (20%) presented with other symptoms including peritoneal malignant mesotheliomas (abdominal discomfort, swelling and ascites), those who were picked up incidentally (n=10), and those who presented with a chest wall mass (n=11). In 23 cases the presenting symptoms were unknown.

The mean (SD) survival time in those presenting with an effusion was no different in those with a pleural effusion (15 (11) months) and those with chest pain (13 (9) months). In 10 cases the diagnosis had been reached after a routine chest radiograph for some other reason; none of these had any chest symptoms. Their median survival was significantly longer at 21 (4) months (p<0.05). In these, a pleural abnormality was followed by an effusion in six cases and chest pain was a later development, on average about 12 months after the effusion.

Mesotheliomas with no occupational exposure

Thirty four cases with no occupational exposure were identified. In these the male to female ratio was 1.35:1, significantly different from that of the group as a whole (12.6:1). This confirms the findings of Hirsch et al,7 Peto et al,8 and Law et al9 in their reports of non-asbestos related cases. The mean age at death was lower than in those with asbestos related mesotheliomas (63.0 (10.2) years versus 65.4 years), and their survival time was shorter than in the main group (13 (12) months), but these differences were not statistically significant. There were 33 pleural mesotheliomas (20 right sided) and one peritoneal.

Although no asbestos exposure had been recalled in life and no asbestos bodies were seen at necropsy, the occupations of six patients could possibly have entailed some exposure. If these were removed from the series, however, the mean age and survival were not significantly changed.

Figure 3 Survival curve for different subtypes of malignant mesothelioma (n=250). p=0.05 for median survival between sarcomatous and other subtypes.
Malignant mesothelioma in south east England

Malignant mesothelioma is usually a disease of late middle age and the mean age seen in similar to other studies, 78 but not significantly mesothelioma. non-occupational in origin. Cases were, on have been optimal. A high index of suspicion classification as non-exposed in our study were in earlier series.34 This could reflect an im-

The mean latency was approximately 40 years, nor any di-

in a previous review16 and described in one survival in these patients was longer than in
differences in registry as non-exposed from non-asbestos related cause these have been reported to have a different survival in previous studies.7-9 Criteria for classification as non-exposed in our study were more rigid than for cases of exposure to asbestos and the different sex ratio (1.35:1) tends to con-

Our study was not designed to evaluate treat-
ment. Although new modes of prevention and treatment are currently under development, one major difficulty is the usual late pre-
sentation of malignant mesothelioma. In our series 10 patients had abnormalities incidentally discovered during routine chest radio-

graphs for investigation of other diseases. The survival in these patients was longer than in the group as a whole, and a small pleural abnormality preceded either effusion or chest pain, suggesting that malignant mesothelioma may occasionally be present for up to a year before presentation. These findings raise the question as to whether early detection – for example, by screening of high risk groups – could alter disease outcome in the future by appropriate treatment of limited disease.

We thank Kate O’Dwyer for her valuable help in the preparation of this manuscript and Owen Eggington, Chief Medical Officer, Department of Social Security, for permission to submit our

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Thorax 1997 52: 507-512
doi: 10.1136/thx.52.6.507

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