Original articles

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

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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 asbestosis 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.

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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, 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 Pneumoniosis 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 obtained. 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.

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 asbestos 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

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

Figure 1 Frequency distribution of malignant mesothelioma by age (n = 272).
Table 1 Exposure to asbestos by cases of malignant mesothelioma (n = 272)

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

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

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

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 Figure 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 duration of exposure 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...
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.

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

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Number (%)</th>
<th>Metastases (%)</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>

Figure 3 Survival curve for different subtypes of malignant mesothelioma (n = 250), p<0.05 for median survival between sarcomatous and other subtypes.

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.

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
Malignant mesothelioma in south east England

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
history is therefore still of primary importance and the di
have been optimal. A high index of suspicion classi®cation as non-exposed in our study were
in earlier series.34 This could re¯ect an im- a shorter survival with non-asbestos related
The mean latency was approximately 40 years, nor any di
distribution for age demonstrates a wide range con®rm this. Similarly, no di
erences in ®bre deposition between may occasionally be present for up to a year
ences in lymphatic question as to whether early detection ± for
improvement in dust levels, but the frequency distribution for age demonstrates a wide range of
age of onset (patients in their 30s to 90s). The mean latency was approximately 40 years, again comparable to other reports,14 as was the
least latency period at 15 years. Latency was
longer in cases of peritoneal mesothelioma as has been shown in one previous study.15
The high proportion of pleural meso-
thallemias is similar to that of most UK series, although the reverse has been documented in some
cohort studies, mainly from the USA.4
One interesting finding was the clear pred-
ominance of right sided mesotheliomas, with
a right:left ratio of 1.6:1. This has been noted in a previous review16 and described in one
previous series from Germany,17 but small case numbers have limited the certainty of such
observations. Possible explanations could in-
clude differences in ®bre deposition between the two lungs, the larger pleural surface area
of the right lung, or differences in lymphatic
Drainage.
Clinical features in our study allowed a compa-
ron between asbestos and non-asbestos re-
lated tumours. Presenting features of chest
pain, dyspnoea, and breathlessness are well
recognised,116 but did not differentiate between those with and without exposure to asbestos.
Although chest pain is commonly a presenting
feature of mesothelioma, 38% of our cases presented with pleural effusion, often accom-
panied by minor chest pain only, which suggests that mesothelioma should be con-
sidered in every case of pleural effusion.
In our study necropsies were available in a
very high proportion of cases (98%), allowing adequate histological samples and accurate
documentation of the site of the primary
tumour and of metastases. We were able to
determine histological type in 248 (91%) of
our cases, and to correlate this with clinical
behaviour. Previously, there have been con-
flicting reports regarding frequency of histo-
logical type, some ®nding a preponderance of
epithelial tumours5,18 and others showing no
difference in frequency,5,15 possibly relecting
the limited numbers reported and the variable
sampling methods employed. Our series, which
was based on necropsy cases, afforded wide
sampling of the tumour. It confims the equal
occurrence of all histological types and dem-
strates a shortening of survival with sar-
comatous cell type. No survival diference was
observed between mixed and epithelial cell
types, nor was there a diference in metastatic
potential between types.

We were particularly interested to examine
non-occupationally related mesotheliomas be-
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 diferent sex ratio (1.35:1) tends to
confrm that these were probably genuinely
non-occupational in origin. Cases were, on
average, slightly younger than the whole group,
similar to other studies,15 but not signif-
ically so. Although some previous reports have shown
a shorter survival with non-asbestos related
malignant mesothelioma,14 our study did not
confrm this. Similarly, no diferentiating features were found to sepa-
rate asbestos related from non-asbestos related
cases of mesothelioma.
Our study was not designed to evaluate treat-
ment. Although new modes of prevention and treatment are currently under development,
one major diferulty is the usual late pre-
sentation of malignant mesothelioma. In our
series 10 patients had abnormalities incident-
ally 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®ssion or chest
pain, suggesting that malignant mesothelioma
may occasionally be present for up to a year
before presentation. These ®ndings 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.

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®ndings for publication. The opinions expressed are those of
the authors and should not be taken to represent those of the
Department of Social Security.

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