

Malignant Pleural Mesothelioma in Parts of Japan in Relationship to Asbestos Exposure

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Abstract: Malignant pleural mesothelioma is induced by asbestos exposure. Many reports have described this situation in America and European countries, but a few have been published in Japan. In this study malignant pleural mesothelioma cases in hospitals located in an area facing the Seto Inland Sea were evaluated. A total of 106 patients were examined with 100 patients having had occupational exposure to asbestos and 6 patients without such histories of asbestos exposure. Ninety seven were male and 9 were female. Ages ranged from 41 to 87 yr with mean of 64.8 ± 5.3 yr. Thirty seven cases showed epithelial type of tumor, 25 biphasic type and 15 showed sarcomatous. The remaining 23 cases had insufficient evidence for typing the tumor. The mean survival rate for all cases was 9.2 ± 11.6 months. Fifty-one patients had occupational histories of shipyard work, 16 patients worked in asbestos cement piping, and the remainder were employed in miscellaneous jobs related asbestos exposure. The duration of asbestos exposure ranged up to 20 yr or longer with the mean of 17.2 ± 8.9 yr and the average latent period for the occurrence of malignant pleural mesothelioma was more than 31 yr with the mean of 37.0 ± 13.3 yr. Quantification of asbestos bodies in the lungs indicated a high concentration in most patients and the major types of asbestos fibers were crocidolite and amosite. Six cases appeared after exposure to chrysotile. These results indicated that ninety four percent of malignant pleural mesothelioma appeared due to the exposure to asbestos including crocidolite and amosite. The remainder may be blamed on exposure to chrysotile.

Key words: Malignant pleural mesothelioma, Asbestos exposure, Shipyard, Asbestos cement piping, Chrysotile

Introduction

Japan has been a major consumer of asbestos since the 1940's and has imported as much as 80,000 tons in 2002. Malignant pleural mesothelioma¹⁾ being a disease unique in the sense that it has a latency period of over 20 yr from the first exposure to asbestos, is not so much reported in Japan. There has been a recent increase in the number of patients with malignant mesothelioma in parts of Japan where shipyards and asbestos cement piping factories were located during and after the second World War. In most industrialized

countries which already stopped using asbestos, many reports^{2, 3)} suggest that the mortality of malignant mesothelioma would increase after a latent period of at least 15 yr or longer. We have already reported that most malignant mesothelioma cases in the Kure area facing to the Seto Inland Sea of Japan appeared due to the exposure to asbestos⁴⁻⁶⁾. The present study evokes 106 cases (100 cases of occupational exposure and 6 cases without such occupational exposure), who were examined at hospitals located in prefectures facing to the Seto Inland Sea in western Honshu, the main land of Japan. These prefectures total nearly 10 million in population with shipbuilding and asbestos cement piping work having intensified since during and after World

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War II. All 100 asbestos-exposed cases are classified by clinical features which are mentioned in the following pages.

Material and Methods

This study includes 100 cases of malignant pleural mesothelioma due to asbestos exposure and 6 cases without, diagnosed from 1980 to the end of December 1998. The cases were examined within several hospitals in prefectures facing the Seto Inland Sea. The clinical analysis for all asbestos exposed cases were broken down into the following categories. Gender, age, chief complaint, pathological type of tumor, survival time from first visit to hospital to time of death, occupational history, duration of asbestos exposure in years, lapse of time from the first exposure to the appearance of malignant pleural mesothelioma. The pathological diagnosis of malignant pleural mesothelioma was confirmed by the immunohistochemical method using the positive staining of calretinin and cytokeratine and the negative staining of CEA. In the 39 cases in which operation or autopsy were conducted, the amount of asbestos bodies and the number of fibers in the lung were determined according to the Matsuda Method⁷⁾. That is to say that pulmonary tissue was dissolved in sodium hypochlorite, then filtered in Milipore filter (5 μm) and the number of asbestos bodies was counted by lightmicroscope. Asbestos fibers were obtained by the modified Langer's method⁸⁾ and passed through a Nucleopore filter (0.25 μm) and processed using a transmission electron microscope (JEOL 100-CX). We selected a magnification of $\times 20,000$ and uncoated fibers $>0.5 \mu\text{m}$ long with parallel sides for the majority of their length and a length to width ratio of 5:1 were counted. The counting scheme included either the first 100 asbestos fibers in a completed opening or all fibers in 10 openings from each of 3 grids. Types of asbestos fibers were determined using a transmission electronmicroscope with content of metals being analyzed by an x-ray analyzer. The relative peak heights for seven elements: magnesium, silicon, calcium, sodium, manganese, iron, and aluminum were measured for each fiber^{9,10)}. Values for the relative peak-height percentage of these seven elements were plotted on a Gibbs triangular coordinate diagram. We classified fibers using a discriminate function Union Against Cancer standard analysis¹¹⁾ and major inhalation of asbestos was considered to be a main cause of malignant mesothelioma. Statistical analysis was done using student-*t* test and $p<0.05$ was determined to be significant.

Table 1. Survival period of cases classified by histological types

Histology	No. of cases	Survival time(Months)
Epithelial type	26	12.3 $\pm$ 5.7*
Biphasic type	18	7.9 $\pm$ 5.4
Sarcomatous type	10	5.5 $\pm$ 5.8*
Total	54	9.2 $\pm$ 11.6

* $p<0.05$.

Results

The 100 cases of malignant pleural mesothelioma due to occupational exposure to asbestos included 95 male and 5 female cases. Other 6 cases consisted of 2 male and 4 female. Ages ranged from 35 (the youngest) to 87 (the oldest). Five cases were younger than 51 yr of age and the remaining cases were older with a mean age of 64.8 ± 5.3 . The mean age of shipyard workers who were diagnosed with mesothelioma was 69.5 ± 9.7 yr, while the mean age of asbestos cement piping workers was 56.9 ± 6.6 yr. Asbestos cement piping workers were statistically younger than shipyard workers ($p<0.01$). The most common chief complaint reported was chest pain (67 cases), and there were 15 cases with dyspnea, as well as 9 cases with cough. In the remaining 15 cases, a chief complaint could not be ascertained. The pathological type of the tumor tissue consisted of epithelial type (37 cases), 25 cases of biphasic and 15 cases of sarcomatous type. The remaining of 23 cases had insufficient evidence for typing the tumor because tumor tissues of these 23 were obtained by needle biopsy. In examining the rate of survival, the earliest death occurred just 10 d after the first visit to the hospital. The longest period of survival was 60 months. Death occurred within 12 months for 43 cases or 72% of the group, and the mean survival rate for all cases was 9.2 ± 11.6 months. Table 1 shows the survival periods classified by histopathological type. Epithelial type tended to have significantly longer period of survival than that of the sarcomatous type ($p<0.05$). Occupational histories included 38 cases of commercial shipbuilding, 14 cases from the Japanese naval shipyard in Kure City in Hiroshima Prefecture, sixteen cases of manufacturing asbestos cement pipe and 7 cases in the construction field as listed in Table 2. The findings of asbestosis in chest x-ray examination or pathology were detected in 14 cases of asbestos cement piping workers. But, only 3 cases were confirmed in shipyard workers. The 6 non-asbestos exposure cases consisted of 4 females and 2 males. Ages ranged from 35 to 71 yr with a mean of 54.2 ± 6.8 yr. As for occupational histories, 4 cases were housekeepers with one

Table 2. Occupational histories of malignant pleural mesothelioma

Occupational history	No. of cases
Shipyards	38
Production of asbestos cement pipe	16
Japanese naval shipyard	14
Construction workers	7
Making and repairment of railroad couch	3
Automobile industry	3
Steel industry	3
Asbestos sprayer	3
Piping worker	3
Boilerman	3
Making and repairment of furnace	2
Casing	2
Guardman	1
Thermal power station	1
Environmental exposure	1
	100

case being a teacher and the other case being a farmer.

Table 3 lists the break down of duration of asbestos exposure in years. Of the cases whose full data were available, nearly half of the cases demonstrated a shorter exposure period to asbestos (under 20 yr), but others exhibited a prolonged period of more than 31 yr with mean of 17.2 ± 8.9 yr. The latent period for the occurrence of malignant pleural mesothelioma ranged from 15 yr to 72 yr. The average latency was 37.0 ± 13.3 yr. Concerning asbestos bodies found, 38 out of 39 cases exceeded 500 bodies per 5 grams of lung wet tissue. This datum is shown in Table 4. This can be classified as occupational asbestos exposure. Over a high-density exposure, 10,000 asbestos bodies per 5 grams of lung wet tissue were found in 23 cases. Cases with asbestos fibers numbering over 1 million per 1 gram of dry lung tissue totaled 38 out of 39 cases examined (Table 4). This evidence also suggests a high-density exposure rate. Actual type of asbestos determined in 39 cases were shown in Table 5. Six cases mainly consisted of chrysotile, 20 cases of crocidolite (the most carcinogenic) and 13 cases of amosite. Chrysotile was detected in 4 cases of construction workers with 2 other cases being piping workers. Furthermore, all 6 cases showed an epithelial type of tumor.

Discussion

It is well known that a malignant pleural mesothelioma is caused by exposure to asbestos⁽¹²⁾. A great majority of the male cases were primarily concerned with occupational exposure. Therefore it follows that the overwhelming

Table 3. Duration of asbestos exposure and the appearance of malignant pleural mesothelioma after the first exposure to asbestos

Duration of asbestos exposure	No. of cases
–10 yr	19
11–20	21
21–30	13
31–40	12
41–	5
	70
The appearance of malignant pleural mesothelioma after the first exposure to asbestos	
	No. of cases
–20 yr	3
21–30	16
31–40	24
41–50	21
51–	9
	73

Table 4. Numbers of asbestos bodies or fibers in the lung of cases with malignant pleural mesothelioma

No. of asbestos bodies (5 g/wet lung tissue)	No. of cases
– 500	1
501– 1,000	5
1,001– 10,000	10
10,001–50,000	12
50,001–	11
	39
No. of asbestos fibers (1 g/dry lung tissue)	No. of cases
-1×10^5	0
$1.1 \times 10^5 - 1 \times 10^6$	1
$1.1 \times 10^6 - 1 \times 10^7$	22
$1.1 \times 10^7 -$	16
	39

percentage of malignant mesothelioma cases were male from these various reports. Ninety-five of the 100 cases were male even in the data presented here, whereas 4 of the 6 non-asbestos exposure cases were female. Ninety-four percent of malignant pleural mesothelioma cases had a history of exposure to asbestos. The present study was consistent with that of Spirtas⁽¹³⁾, most of the malignant pleural mesotheliomas in the men were attributable to exposure to asbestos. In this study, we considered that the school teacher

Table 5. Kinds of asbestos fibers detected in 39 cases

No. of cases	crocidolite	amosite	chrysotile	tremolite
1, 2, 3, 4, 5	20	0	0	0
6, 7, 8	16	4	0	1
9, 10, 11, 12	15	4	0	1
13, 14, 15, 16	14	4	0	2
17, 18, 19, 20	13	7	0	0
21, 22, 23, 24	2	18	0	0
25, 26, 27	1	16	0	3
28, 29	3	15	0	2
30, 31	3	14	0	3
32, 33	1	15	0	4
34, 35	2	3	14	1
36, 37	1	1	15	3
38	2	2	14	2
39	2	3	12	3

was essentially in the non-asbestos exposure group, but, Lilienfeld¹⁴⁾ described 4 malignant mesothelioma cases of school teachers exposed to asbestos (falling from the ceiling). Therefore, we should re-examine whether all 6 cases are to be considered non-asbestos exposure or not. The survival period of this non-exposed group, was a median of 8 months. As for the histological type of this group, the epithelial type had the longest survival (12.3 months) rate and the sarcomatous type had the shortest (5.5 months), these numbers almost mirror the same data as reported by Leigh²⁾. Two cases of epithelial type survived 48 and 60 months due to operation and radiation therapy. Survival of patients with the epithelial type tumor should be considered to be prolonged via radiotherapy or operation if diagnosed in the early stages.

It is generally believed that a malignant mesothelioma appears over 20 yr after the first exposure¹⁵⁾. Although several reports^{16, 17)} on the case of malignant pleural mesothelioma demonstrate low density exposure over a prolonged period of time (more than 40 yr), our study shows a different view on the tumor since we reveal a higher density exposure but a shorter period of exposure time. Also due to the evidence of the great concentration of asbestos bodies and fibers in the lungs, our study shows that, though exposure to asbestos was for a shorter period, it resulted in a much greater intensity and high density in relationship to time exposed. Asbestosis with high-density exposure to asbestos was detected in 14 out of 16 cases among cement piping workers. Interestingly, the age of asbestos cement piping workers was younger than that of the shipyard workers (whose asbestos exposure volume seemed to be much lower). One of the reasons why asbestos cement piping workers were young, is that they exposed mainly to crocidolite. Our study showed a higher

concentration of workers sharing an occupational history of shipbuilding (commercial and/or military) and workers in actual asbestos production or asbestos spraying and jobs within the construction industry.

In Japan, recently the majority of asbestos is used in construction materials, automobile and train parts. Therefore workers in these fields are more likely to suffer malignant pleural mesothelioma than in other occupations. Using the criteria of 500 bodies of asbestos to 5 g of lung wet tissue being classified as occupational asbestos exposure as reported by Churg¹⁸⁾, 38 cases out of 39 were classified as at high risk of malignant pleural mesothelioma due to occupational exposure. In 39 of cases (39%) examined we could determine that one of three types of asbestos, crocidolite, amosite and chrysotile was the predominant factor in malignant pleural mesothelioma. Either crocidolite, amosite and chrysotile was found to be the main cause of malignant pleural mesothelioma in the present study. According to Kishizuchi's study¹⁹⁾, the 2 most dangerous asbestos types in relationship to the cause of malignant pleural mesothelioma are crocidolite and amosite²⁰⁾. Our study also confirm the third type of asbestos, chrysotile, should be considered as a cause of malignant pleural mesothelioma. Although only 6 cases of chrysotile exposure were detected, it proves that we must be aware of the danger of this particular type of asbestos as well as with crocidolite and amosite. In our 6 cases, other 2 asbestos and tremolite contaminated in chrysotile as shown in Table 5. Tremolite has been described to have a carcinogenic potential to cause malignant mesothelioma²¹⁾. The problem which chrysotile or contaminated tremolite causes malignant mesothelioma has partially been controversial. However, recently chrysotile has been reported to have a higher carcinogenic potency as a potential carcinogen as well as being a cause of malignant mesothelioma²²⁻²⁵⁾. Chrysotile shows less carcinogenicity of malignant mesothelioma than crocidolite, but has nearly equal carcinogenicity as amosite^{26, 27)}. Chrysotile has a quality to easily go out from the body and the content of asbestos in the lung does not always exhibit the real exposed dose of asbestos²⁸⁻³¹⁾. In our study, chrysotile was detected in 4 cases of construction workers. As chrysotile asbestos is widely used in Japan in a variety of applications, from construction to manufacturing, there remains a distinct possibility of increasing malignant pleural mesothelioma cases in the near future. Asbestos has not been used in shipbuilding since 1975, therefore, workers in the two industries of construction and manufacturing asbestos need to be fully examined at an earlier age as well as having more closely scheduled examinations to determine if they are in danger of contracting malignant pleural mesothelioma.

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