occupational asbestos exposure. Therefore, these patients were not diagnosed as having asbestos-related lung cancer.

Regarding asbestos particles in the lung tissues of asbestos-related lung cancer patients, 61% exceeded 5000 particles per gram of dry lung tissue, but 19% had <1000 particles which corresponded to the citizen's level of exposure. These patients with pleural plaques on chest X-ray were exposed to low-density asbestos for more than 10 years. More than 5000 asbestos particles per gram of lung tissue corresponds with 25 fiber-years, and is consistent with a doubling of the lung cancer risk.[6,12] Bianchi *et al.* [11] reported that 31% of 414 necropsy cases of lung cancer exceeded 5000 particles per gram of dry lung cancer. Our data is double this data which suggests denser exposure to asbestos.

However, 11 patients without asbestosis had more than 50 000 particles and two who were construction workers with asbestosis had <5000 particles. Construction workers who ordinarily had treated chrysotile asbestos tended to have less asbestos particles in the lung than insulation or piping workers. We should examine asbestos fibers for these two patients by electron microscopy. On the other hand, the carcinogenicity and fibrogenicity of asbestos has been described as not always being correlated. Fischer suggested that 42% of asbestosis on chest radiograph had fewer asbestos particles than 25 fiber-year occupational histories.[13] Our result of asbestos particles in the lung and radiographic asbestosis corresponds with his data. Lung cancer risk was elevated in the presence of radiographic asbestosis, but occurred as a result of asbestos exposure in the absence of asbestosis. The incidence of non-small-cell lung cancer for patients with asbestosis increased, compared with asbestos-exposed patients without asbestosis.[14] Lung cancer risk increased almost linearly with cumulative dose of asbestos.[15] It is still controversial that lung cancer in the absence of asbestosis can be attributed to asbestos exposure. We should extend the number of the patients for asbestos-related lung cancer and clarify the criteria for the diagnosis of asbestos-related lung cancer without asbestosis.

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Disclosure Statement

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Clinical Study on Mesothelioma in Japan: Relevance to Occupational Asbestos Exposure

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Background *In 2003, the number of deaths due to malignant mesothelioma in Japan was 878; however, only 85 cases of mesothelioma due to asbestos exposure were authorized for compensation. The reasons for this discrepancy require evaluation.*

Method *We examined medical records, X-rays, and pathology results to evaluate mesothelioma cases in Japan between 2003 and 2005; used a questionnaire to identify occupational and environmental histories, and determined the concentration of asbestos fibers in pathology specimens.*

Results *We identified 442 definite cases of malignant mesothelioma with a median age of 68 years. There were 316 malignant mesothelioma cases with occupational asbestos exposure, 12 cases with neighborhood exposure and 5 cases with likely domestic exposure. Most (78%) of the 87 cases exceeded 1,000 asbestos particles per gram of dry lung tissue.*

Conclusion *We conclude that 79.2% of cases of mesothelioma in Japan in recent years were caused by asbestos exposure.* Am. J. Ind. Med. 53:1081–1087, 2010.

KEY WORDS: mesothelioma; pleural plaques; exposure; asbestos particles; Helsinki criteria

BACKGROUND

Until 1994, the International Classification of Diagnosis (ICD)-9 classified death due to mesothelioma and other causes of death together, and, therefore, statistics on only mesothelioma could not be obtained. After 1995, when ICD-10 was implemented and deaths due to mesothelioma were reclassified, statistics regarding incidents of death due to mesothelioma could be obtained in Japan, permitting a better understanding of this type of tumor. In 1995, the number of deaths was 500, increasing to 878 cases in 2003 and 1,050 in 2006. In Europe and America, 80% of the cases of mesothelioma are attributed to asbestos exposure; however, in Japan, only 85 cases of mesothelioma due to asbestos exposure were authorized to receive worker's compensation insurance during the 2003 fiscal year. We sought to clarify the cause of this disparity between the number of deaths and the number of compensation-authorized cases of malignant mesothelioma. There are reports [Kishimoto, 1992; Kishimoto et al., 2004] on mesothelioma and asbestos exposure from specific regions in Japan; however, there has not yet been any large-scale investigation targeting the whole nation. Accordingly, from 2003 to 2005 we conducted a 3-year nationwide study targeting 2,742 incidences of death due to mesothelioma. In addition to the relationship between asbestos exposure and mesothelioma, we investigated the diagnosis of mesothelioma in Japan.

METHODS

We reviewed all the cases in which the cause of death was diagnosed as mesothelioma based on "ICD CD46" in the demographic statistics from 2003 to 2005 and obtained

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detailed information on the clinical diagnosis, and occupational asbestos exposure for those cases.

Families that provided a letter of consent were given a questionnaire to obtain the occupational and residential histories. We also re-examined the diagnosis of mesothelioma itself based on review of medical records, radiology films, and pathology reports. We obtained cellular and pathological tissue samples and tumor tissues from the medical institutions that issued the death certificates. One radiologist and two pulmonologists re-examined the data, looking for the presence or absence of asbestos exposure based on chest images or based on the classification of pleural mesothelioma by the International Mesothelioma Interest Group (IMIG). Two pathologists reviewed the tissue and cell samples and tried to provide a definitive diagnosis.

We determined the presence or absence of asbestos exposure based on entries in the clinical records and also the family questionnaire investigation results (asbestos question sheet regarding occupational history). We investigated if the attending physician made entries regarding the occupational history in the clinical records for the incidents of death in 2004 and 2005. We define the lifetime as the time at which diagnosis was determined until the time of death.

For the cases in which excised lungs or autopsied lungs were provided by the medical institutions, we measured the number of asbestos particles in the tumor-free portion of the pulmonary tissue using the method by Kohyama [2008] at the Okayama Rosai Hospital. More specifically, the lung tissue was dehydrated at 100°C, and after accurately determining the dry weight, the tissue was dissected into small pieces and dissolved in sodium hypochlorite solution. After centrifugation at 10,000 rpm for 10 min, the supernatant was removed and the pellet was re-suspended in a new solution to total 50 ml in volume. The asbestos particles were collected on a 0.45-μm Millipore filter membrane using vacuum suction filtration and fixed with acetone on the filter membrane. The asbestos particles were counted under a phase contrast microscope and expressed as the number per gram of dry weight of lung tissue.

We used the student's test to determine the difference in the average value, and the χ^2 test to compare between two groups. Furthermore, we used the Kaplan–Meier method to compute the lifetime using the date of diagnosis as the starting point, and used the Logrank test to compare lifetimes.

RESULTS

Among the targeted 2,742 cases (878 cases in 2003, 953 in 2004, and 911 in 2005), we obtained familial consent from 956 cases (454 cases in 2003, 260 in 2004, and 242 in 2005). In the investigation of deaths in 2003, which was conducted immediately following the so-called Kubota Shock, during which the neighborhood exposure to asbestos induced more than 100 cases of mesothelioma in 2005 and public attention was focused on workplace asbestos exposure, familial consent was obtained in 51.7% of deaths. However, in 2004 and 2005, the percent decreased to 27.3% and 26.6%, respectively. From among the 956 cases in which consent was received, we obtained clinical records, medical treatment information, etc., from the medical institutions that issued the death certificates for 541 cases (56.6%), including 235 cases in 2003, 145 in 2004, and 161 in 2006 as indicated in Table I. From the information for the 541 cases provided by the medical institutions, there were 442 cases (81.7%) in which definitive diagnosis was obtained based on tissue samples. There were 49 cases (9.1%) in which only speculative clinical diagnosis was made based on data such as imaging and the concentration of hyaluronic acid in the pleural fluid, or definitive diagnosis could not be made pathologically or histologically, which were labeled as "suspected" as in Table I.

Regarding the site of mesothelioma, there were 418 cases of pleural mesothelioma (372 confirmed diagnoses and 46 suspected cases); 68 cases of peritoneal mesothelioma (65 confirmed diagnoses and three suspected cases); 3 confirmed diagnoses of pericardial mesothelioma; and 2 confirmed diagnoses of mesothelioma of the tunica vaginalis. However, 50 cases (9.2%) were determined to be diseases other than mesothelioma. In 20 of the 50 cases, lung cancer was diagnosed based on the tissue and cell samples from the autopsies carried out at the medical institutions. Furthermore, we made a comprehensive judgment considering the results from the imaging viewpoint, tissue pathology viewpoint, tumor markers, etc., and found 18 cases that were more likely lung cancer than mesothelioma and were labeled as "suspected lung cancer." Among the other 12 cases, there were 6 cases of ovarian cancer, 1 case of malignant lymphoma, 1 case of renal cancer, and other cases that were thought to be from malignant tumors such as 1 case of a solitary fibrous tumor, and 3 cases of benign asbestos pleurisy (fibrous pleurisy) that were diagnosed as mesothelioma.

TABLE I. Number of Japanese That Died of Malignant Mesothelioma From 2003 to 2005

	2003	2004	2005	Total
Population vital statistics	878	953	911	2,742
Consent from bereaved family	454	260	242	956
Information provided by hospitals	235	145	161	541
Mesothelioma	182	125	135	442
Suspected mesothelioma	26	8	15	49
Other diseases	27	12	11	50

TABLE II. Background of Patients With Mesothelioma and s/o Mesothelioma

	Confirmed mesothelioma		Suspected cases	
	Pleura	Peritoneum	Pleura	Peritoneum
No. of cases	372	65	46	3
Median age (range)	68 (38–94)	63 (16–89)	80 (54–97)	78 (59–86)
Gender				
Male	320	46	32	2
Female	52	19	14	1

Age and Gender

When comparing the background factors for the cases of mesothelioma and suspected mesothelioma, the median age for confirmed diagnosis of pleural mesothelioma was 68, and the median age for suspected mesothelioma was 80. Those cases with suspected mesothelioma were at a significantly advanced age as shown in Table II. Also, for peritoneal mesothelioma, the median age for confirmed diagnosis was 63, and 78 for suspected cases. Furthermore, there were 320 male and 52 female (6.2:1 males/females) cases of confirmed pleural mesothelioma and 32 male and 14 female (2.3:1 males/females) cases of suspected mesothelioma. On the other hand, there were 46 male and 19 female (2.2:1 males/females) confirmed cases of peritoneal mesothelioma, two male and one female case of suspected mesothelioma with there was no discernable difference in the gender groups.

Diagnostic Method

Among the 361 of 442 cases (81.7%) where the basis of diagnosis was clear, definitive diagnosis was made based on tissue analysis as indicated in Table III. The method for gathering tissue samples for the diagnosis of pleural mesothelioma cases was video-assisted thoracoscopic biopsy. This method was used for 116 cases. Cases were diagnosed based on not only video assisted thoracoscopic surgery (VATS) under general anesthesia but also with thoracoscopic surgery under local anesthesia. Subsequently, there were 106 cases of needle biopsy based diagnosis, 71 cases of thoracotomy-based diagnosis, and 11 cases where the autopsy was the first pathological diagnosis obtained.

Most cases (n = 37) of peritoneal mesothelioma were diagnosed based on laparotomy; nine cases diagnosed following laparoscopic biopsy, and four cases diagnosed based on needle biopsy. Furthermore, there were 45 cases of pleural mesothelioma and 11 cases peritoneal mesothelioma diagnosed only based on pleural fluid and ascites cell analysis. In the diagnoses based on histological analysis, there were 329 of 353 cases (93.2%) in which the presence or absence of immunostaining confirmed the diagnosis, whereas among the 56 cases of cytological examination based diagnosis less than half of the cases, 23 cases, were confirmed diagnoses (41.1%).

Tissue Type

Among the 442 cases of definitively diagnosed mesothelioma, only 305 cases (69.0%) had the cell type identified in the clinical records. There were 163 epitheliod cases (53.4%), 70 biphasic cases (23.0%), and 62 sarcomatoid cases (20.3%) [Inai, 2005].

History of Asbestos Exposure in the Workplace

There were 421 (95.2%) cases in which the presence or absence of the occupational history could be investigated based on the clinical records and the family questionnaires. Among those cases, 316 cases (75.1%) were suspected to

TABLE III. Diagnostic Procedures for Mesothelioma

	Pleura	Peritoneum	Total[a]	Immunohistochemical[b] staining
Cases	372	65	442	352/409 (86.1%)
Histological diagnosis	304	52	361	329/353 (93.2%)
Open lung and peritoneum	71	37	113	102/106 (96.2%)
Video assisted thoracoscopical biopsy	116	9	125	112/125 (89.6%)
Needle biopsy	106	4	110	105/110 (95.5%)
Autopsy	11	2	13	10/12 (83.3%)
Cytological examination	45	11	56	23/56 (41.1%)
Unknown	23	2	25	

[a]Includes a total of five cases of peritoneal and tunica vaginal mesothelioma.
[b]Denominator represents cases in which immunostaining method was employed.

have had exposure to asbestos including indirect or direct exposure as stipulated in their occupational histories. Furthermore, based on the questionnaire responses from the families, there were eight cases in which patients resided in the vicinity of the old Kubota Kanzaki factory in Amagasaki city in Japan. There were four additional cases of patients who resided in the neighborhood of an asbestos product manufacturing plant or a shipyard, totaling 12 cases of suspected neighborhood asbestos exposure. There were also five cases of occupational history in which family members were exposed to asbestos, which implied likely domestic asbestos exposure. As a result, we conclude that there were 333 cases (79.1%) of suspected asbestos exposure.

From the 188 cases of suspected occupational asbestos exposure, we identified the occupation histories of 165 cases (87.8%) based on the family questionnaires, and we concluded that the occupation histories of no more than 51 cases (27.1%) were recorded into the clinical records by the attending physician. In other words, despite the diagnosis of mesothelioma, we found that those clinicians did not obtain detailed occupational histories in many cases.

The occupational histories of the 316 cases of suspected occupational asbestos exposure are shown in Table IV. For cases in which there was the possibility of asbestos exposure in pursuing multiple occupations, the investigation selected the occupation in which the patient worked the longest. There were 69 construction workers, which makes up the largest group, 45 shipyard workers, 30 electricians, 28 steel and other manufacturing workers, 22 auto manufacturers or maintenance workers, 21 plumbers, 20 asbestos product manufacturers, and 16 wrecking crew workers and concrete product workers. There were 9 cases (27.2%) of asbestos product manufacturing workers, who were exposed to high concentrations of asbestos, among the 33 cases of peritoneal mesothelioma indicating a feature that denotes high frequency of occurrence in this occupation.

Exposure Period and Incubation Period

We investigated the exposure period, date, age, and latency period of the 316 cases of suspected occupational asbestos exposure. We examined the exposure period and incubation time for only the cases that had clinical record entries or responses by the families. The median asbestos exposure period for peritoneal mesothelioma is 20 years and the mean value is 21.7 years. For pleural mesothelioma, the median is 29 years and the mean value is 26.4 years. The latency period, which is considered to be from the first exposure to asbestos to the onset of mesothelioma, for pleural mesothelioma is a median of 41 years and an average value of 42.5 years. For peritoneum mesothelioma, the median is 41 years and the average value is 43.0 years. The median for all types of mesothelioma is 41 years, and the average value is 42.4 years. We confirmed that mesothelioma expressed itself after 40 years or more from the first exposure.

Pleura Plaque

We investigated 353 cases of the 442 cases of definitively diagnosed mesothelioma based on chest X-rays or chest CT scans, The scans were provided by the medical institutions targeting the presence of pleural plaque that was considered to be specific to asbestos exposure. We found 144 cases (40.8%) of pleural plaque. In 64 of the 144 cases (44.4%), there was calcification accompanying the pleural plaque. However, there was no statistically significant correlation found between the location of the mesothelioma and the frequency at which the pleural plaque occurred. Furthermore,

TABLE IV. Frequency of Cases Regarding Occupational Histories of Asbestos Exposure

	Pleura	Peritoneum	Pericardium	Tunica vaginalis	Total
Construction worker	65	3		1	69
Shipyard worker	40	4	1		45
Electrician	27	3			30
Steel industrial worker	25	2		1	28
Automobile manufacturer	21	1			22
Plumber	18	2	1		21
Asbestos products manufacturer	11	9			20
Wrecking crew	16				16
Cement product worker	10	1			11
Machinist	7	2			9
Warehouse worker	5	3			8
Chemical industrial worker	6		1		7
Glass maker	4				4
Others	23	3			26
Total	278	33	3	2	316

there were 316 suspected cases from the 442 cases of occupational exposure to asbestos, and among the 270 cases of the 316 cases where chest imaging was provided, 129 cases (47.8%) of pleural plaque were confirmed. In 14 of 86 cases (16.3%) in which occupational exposure to asbestos could not be confirmed, pleural plaque was confirmed. Among the 17 suspected cases of non-occupational exposure to asbestos (exposure to the neighborhood or in the home), 3 cases of pleural plaque were confirmed in which the patient was in the vicinity of the asbestos plant, a family member was working in a shipyard or engaged in plumbing as indicated in the residential history.

Asbestos Particles

We were able to measure the asbestos particles in the lungs of 40 of the pleural mesothelioma cases and 47 of the peritoneal mesothelioma cases based on the excised or autopsied lungs provided by the medical institutions. Table V shows an analysis of the number of asbestos particles and where they were found. We were able to confirm based on the Helsinki Criteria [Consensus Report, 1997], the standard for occupational exposure to asbestos, that there were 37 cases (78.7%) in which there were 1,000 particles or more of asbestos/1 g of dry lung tissue detected and 21 cases (44.7%) in which 5,000 particles or more were detected. There were a total of three unclear cases of asbestos exposure, two cases of pleural mesothelioma, and one case of peritoneal mesothelioma. Despite that pleural plaque could not be identified based on the images, the presence of more than 1,000 particles of asbestos was confirmed but these cases are thought to be mesothelioma due to asbestos exposure. Furthermore, although pleural plaque could not be confirmed, there were six cases where over 5,000 particles of asbestos were detected. We believe that we cannot make a determination on asbestos exposure based solely on the presence or absence of pleural plaque.

Asbestos Exposure and Mesothelioma

From the 442 cases in which mesothelioma was diagnosed based on pathology out of the 541 cases in this investigation, we found that there are 316 cases (71.5%) who had suspected asbestos exposure based on the occupational histories. There were 12 other cases of suspected exposure due to the neighborhood environment, and 5 cases of exposure in the home. Furthermore, another 14 cases had pleural plaques in the radiography while asbestos exposure could not be positively determined from the clinical history and the 3 other cases in which more than 1,000 asbestos particles/1 g of dry lung tissue were detected. While asbestos exposure could not be confirmed from the clinical history or pleural plaque. We determined these 17 cases also as positive asbestos exposure. Accordingly, we concluded based on these examinations that the above 350 cases (79.2%) out of the 442 cases of pathologically diagnosed mesothelioma were caused by asbestos exposure.

TABLE V. Number of Asbestos Particles

No. of asbestos particles[a]	Pleura	Peritoneum	Total
<999	10	0	10
1,000–4,999	15	1	16
>5,000	15	6	21
Total	40	7	47

[a]Per 1 g of dry lung tissue.

DISCUSSION

Among the 2,742 deaths from malignant mesothelioma based on vital statistics recorded over the 3-year period from 2003 to 2005, we targeted 956 cases in which family consent was obtained for a retrospective investigation and clarified the exposure histories of these mesothelioma cases. Among the 541 cases in which data gathering such as clinical records was possible, we confirmed the pathological diagnosis of 81.7%. We found that 372 cases originated from the pleura, 65 cases from the peritoneum, 3 cases from the pericardium, and 2 cases from the tunica vaginalis. In over 80% of the cases a definitive diagnosis was made based on histological diagnosis including immunostaining. On the other hand, in 56 cases where diagnosis was made based on cytological examination, immunocytochemical staining was positive only in 41.1% of the cases, and this brings to light the problem of diagnostic accuracy.

Currently in Japan, if mesothelioma is diagnosed the patient can receive aid through workman's compensation insurance or the asbestos health damage relief law. Although there is recognition of the improvement in diagnosis accuracy, it is clear that in the 3-year period from 2003 to 2005 the immunostaining method was not always reliable in the diagnosis of mesothelioma. In other words, in a case where diagnosis is made based only on cell examination, there may be a problem in discriminating between fibrous pleurisy (reactive mesothelial cells) [Kradin and Mark, 2006; Lyons-Boudreax et al., 2008] and lung cancer. For that reason, we found 9.2% in our examination to be diagnosed as other than mesothelioma such as lung cancer or ovarian cancer, as a result of comprehensive judgment on reviewing autopsy results, clinical records, images, etc. Because HE staining only or cell examination only was used for diagnosis in many cases, when we performed immunostaining, we were able to diagnose definitively not only lung cancer and ovarian cancer but also fibrous pleurisy (benign asbestos pleurisy). It was reported [Ordonez, 2003, 2006, 2007; Kushitani et al., 2008] that immunostaining is indispensable in a pathological

diagnosis of mesothelioma in order to distinguish pleural mesothelioma from lung cancer accompanying cancerous pleurisy, etc. Or in order to distinguish peritoneal mesothelioma from ovarian cancer accompanying cancerous pleurisy, etc. Furthermore, a definitive diagnosis could not be made based on the pathology in 9.1%. The reasons that a definitive diagnosis could not be reached were that the disease advanced rapidly and a detailed examination could not be performed, or although the attending physician recommended tests to diagnose suspected cases of mesothelioma, because the patient was of advanced age either the patient or the family requested not to have invasive tests done. Taking these conditions into consideration, pressing for improvement in the diagnostic accuracy in the diagnosis of mesothelioma is a paramount problem.

Among the 541 cases in this investigation, 442 cases were diagnosed with mesothelioma based on pathology and, among those cases, 71.5% were suspected to be exposed to asbestos based on the occupational history. The types of occupation that were common were construction work, working in a shipyard, electricians, steel products, and other manufacturing work. From 1950 and later, we understand that asbestos was used in these types of occupations, and asbestos was imported into Japan in large quantities for these types of work. We identified that these occupations frequently appear in high-risk groups. Seventeen other cases of non-occupational exposure to asbestos were suspected (12 cases suspected based on residential histories, and 5 cases were thought to be exposure in the home). On the other hand, 40.8% of cases with pleural plaque were confirmed from the 353 cases where the medical institutions provided chest images. Furthermore, among the 47 cases in which the asbestos particles were found in the lungs, 78.7% were found to have more than 1,000 particles/1 g of dry weight lung tissue. There were a total of 79.2% that had occupational or residential histories indicating asbestos exposure, images indicating the existence of pleural plaque, or measurements of the asbestos particles in the lungs and any of these would imply asbestos exposure. Based on the analysis done on these various types of data, 79.2% of the 442 cases were found to have asbestos exposure as the cause of mesothelioma. Furthermore, by examining the origin of the mesothelioma based on the occupations, the cases in which the occupational histories indicated asbestos product manufacturing work, where the patient would be exposed to high concentrations of asbestos, had high levels of asbestos particles in the lungs and were characteristic of the peritoneal mesothelioma cases, which comprise a large number of the cases.

Since 1950 the amount of asbestos used in Japan increased and reached its peak in 1974 at 350,000 tons. After that a trend appeared that showed a decrease in asbestos use until its ban in September 2006. For that reason, compared to Australia, England, and Belgium the amount used and the period of usage are high [Kohyama and Hoshino, 2008]. However, the frequency of occurrence of mesothelioma in the three countries was 30/1,000,000 people, and in Japan the occurrence rate was 7/1,000,000 people [Bianchi and Bianchi, 2007] but currently it is 9/1,000,000 people. Based on the current investigation, if we consider that in Japan the incubation period from the first time the patient was exposed to asbestos to the occurrence of mesothelioma is 43 years, based on the report by Murayama et al. [2006], we must expect two- to threefold the number of new patients in Japan. However, despite having a history of asbestos exposure, in no more than 27.1% of the cases was the occupational history entered in the clinical records. The importance and the repercussions of obtaining and recording the occupational history must be instilled in the clinicians who examine patients of asbestos-related diseases.

CONCLUSIONS

Among 442 cases of definite malignant mesothelioma, between 2003 and 2005, in Japan, 316 cases were exposed to occupational asbestos exposure; 12 cases had neighborhood exposure; and 5 cases had domestic exposure. We conclude that 79% of Japanese mesothelioma cases have been caused by asbestos exposure in recent years.

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ORIGINAL PAPER

Clinical investigation of malignant mesothelioma in Japan

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Abstract
Purpose The asbestos-related problems caused much social concern; however, no large-scale study was conducted about clinical features of MM in Japan. Patients with MM who have a history of occupational asbestos exposure (AE) are provided worker's compensation in Japan. However, only about 10% of MM cases were actually claimed and compensated. So there is still controversy over the association between MM and AE. The aim of this study is to investigate the clinical features of MM. We also aimed to clarify the association between MM and occupational AE in Japan.
Methods We examined the clinical features of MM cases. Clinical information was obtained including gender, age, site of origin, pathological subtype, radiological findings, and treatment outcome. To investigate the association between MM and AE, investigators interviewed all patients regarding work and residential history.
Results Between January 2005 and December 2007, 105 cases (median age: 63 years, range 35–80, male/female: 88/17) were diagnosed with MM in the Rosai Hospital group and related facilities. Among them, 94(89.5%) cases originated in the pleura, 7(6.7%) in the peritoneum, 2(1.9%) in the pericardium, and 1(0.9%) in the tunica vaginalis testis. There were 69(65.7%) epithelioid, 19(18.1%) biphasic, 16(15.2%) sarcomatoid, and 1 unclassified pathological subtypes of MM. A favorable survival rate was indicated in the patient group of MPM that underwent surgery compared to others, though it was not statistically significant ($P = 0.1743$). The occupational AE was indicated in 89 cases (84.8%). Three patients had no history of occupational AE, but lived with someone who was in an occupation that handled asbestos. There were two patients in which AE was indicated in their life environment. Altogether, AE was indicated in 93(88.6%) patients.
Conclusions This study stresses the urgent need for physicians to acknowledge the association between MM and AE, and to inquire thoroughly regarding AE to the patients with MM.

Keywords Pleura · Peritoneum · Pericardium · Pemetrexed

Dr. K. Yamazaki passed away in 2008.

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Introduction

Malignant mesothelioma (MM) is an aggressive tumor that develops from the mesothelial cell of the pleura, peritoneum, pericardium, or testicular tunica vaginalis. A newspaper article published in June 2005 reported that 5

residents who lived near a now-closed asbestos cement pipe plant in Amagasaki, Japan, developed pleural mesothelioma (Ohshima 2005). The asbestos-related problems that this article raised caused much social concern; however, no large-scale study was conducted about clinical features of MM in Japan. One of the most important issues is the association of MM and asbestos exposure (AE). An association between MM and AE has been well-known worldwide since the 1950s (Magnani et al. 2000; Newhouse and Thompson 1965; Rees et al. 1999). There is so far one report that demonstrated association between AE and MM in western parts of Japan (Kishimoto et al. 2004). Patients who have a history of occupational AE and developed MM are provided worker's compensation in Japan. However, among 2,641 cases who died of MM between 2002 and 2004, only 287 cases claimed the compensation and 269(10.2%) was actually compensated (Ministry of Health, Labor, and Welfare of Japan, http://www.mhlw.go.jp/houdou/2006/05/h0530-1.html). As a result, there is still controversy over the association between MM and AE in Japan.

Based on these statistics, we hypothesized that there would be more MM cases in which patients and/or physicians were unaware of occupational AE. One of the reasons for the uncertainty might be the long latency of the disease after AE and that the work history of each patient has not been fully investigated. In such cases, retrospective investigation of medical records after the death is often unsuccessful in clarifying occupational AE.

The Rosai Hospital group, specialized facilities established to treat occupational illnesses, conducted this study to investigate the clinical features of MM in Japan. These features include the site of origin, pathological subtype, radiological findings, and treatment outcome. Especially, we aimed to clarify the association between MM and occupational AE in Japan. For this purpose, all the patients were interviewed regarding their entire work history and living environment since their youth at the diagnosis of MM.

Materials and methods

Enrolled patients were those who were diagnosed MM and in treatment between January 2005 and December 2007. The essential aim of this study was to make face-to-face interview to the patients to clarify the history of AE, so the patients diagnosed before 2004 and were in treatment in 2005 were also included. Clinical information was obtained from each facility by survey sheet including gender, age, site of origin, pathological subtype, and treatment outcome. The radiological images and pathological specimens were sent to Okayama Rosai Hospital for review of the diagnosis and analyses.

The clinical stage of malignant pleural mesothelioma (MPM) was determined according to International Mesothelioma Study Group (IMIG) criteria (Rusch 1996) based on the staging procedure including computed tomographic (CT) scans of the chest and abdomen, magnetic resonance images of the brain, and Technetium-99 m hydroxymethylene diphosphonate bone scans. Characteristic radiological findings that indicated AE were assessed concerning the presence of pleural fluid, asbestosis, rounded atelectasis, and pleural plaque based on chest X-ray and CT. Survival data were determined from the day of diagnosis to the day of death or last follow-up, and analyzed based on the Kaplan-Meyer method using SPSS 11.0 software (SPSS, Inc., Chicago, IL).

To investigate the association between the occurrence of MM and AE, all the patients were interviewed regarding their work history and that of the family members, and residential history, since their youth, which may suggest environmental exposure to asbestos.

Results

Patient characteristics

Between January 2005 and December 2007, 105 cases (median age: 63 years, range 35–80, male/female: 88/17) were diagnosed with MM in 31 Rosai Hospitals and related facilities. Among them, 94(89.5%) cases originated in the pleura, 7(6.7%) in the peritoneum, 2(1.9%) in the pericardium, and 1(0.9%) in the tunica vaginalis testis. There was one case in which the origin, whether the pleura or pericardium, was undetermined. There were 69(65.7%) epithelioid, 19(18.1%) biphasic, 16(15.2%) sarcomatoid, and 1 unclassified pathological subtypes of MM. According to the IMIG staging system, there were 19 Stage I, 8 Stage II, 34 Stage III, and 29 Stage IV patients with MPM. The characteristics of the patients are summarized in Table 1.

Diagnostic procedure

Fifty-five patients were diagnosed based on video-assisted thoracoscopic biopsy under either general or local anesthesia or laparoscopy. Twenty-eight patients were diagnosed based on open-chest biopsy. Percutaneous needle biopsy was performed in 18 patients for diagnosis. Three patients were diagnosed based on cytological examination of pleural fluid. A patient with mesothelioma in the tunica vaginalis testis was diagnosed after the tumor resection.

Table 1 Patient characteristics

Age	
Median (range)	63(35–80)
Gender	
M/F	88/17
Site of origin	
Pleura	94
Peritoneum	7
Pericardium	2
Tunica vaginalis testis	1
Undetermined	1
Subtypes	
Epithelioid	69
Biphasic	19
Sarcomatoid	16
Unclassified	1

Radiological findings

Radiological findings were available in 103 cases. Pleural effusion was documented in 74(71.8%) cases, pleural plaque in 42(40.8%) cases, and asbestosis was not found. In the case of MPM, radiological findings were available in 88 cases. Among them, pleural effusion was documented in 69(78.4%) cases, pleural plaque in 35(39.8%) cases.

Treatment outcome

Among 94 patients with MPM, 36 patients underwent surgery as the principal treatment modality. Adjuvant chemotherapy was delivered in 12 cases and radiotherapy was added in 7 of these 36 cases. Six patients had multimodality treatment comprising surgery, radiotherapy, and systemic chemotherapy. Systemic chemotherapy was delivered in 49 patients as the initial treatment. Major chemotherapy regimens are as follows; Cisplatin + pemetrexed were administered in 18 cases, vinorelbine + gemcitabine were administered in 12 cases, and cisplatin + gemcitabine were administered in 6 cases.

Survival analysis was performed with patients with MPM diagnosed between 2005 and 2007. The median overall survival time (MST) of the patients was 13.2 months (95% confidential interval: 11.23–15.17). Overall survival according to the clinical stage is shown in Fig. 1a. A favorable survival rate is indicated in the earlier stages (I and II) where the MST is 17.9 months (95% C.I. 9.07–26.66) rather than in the advanced stages (III and IV) where the MST is 12.8 months (95% C.I. 10.34–15.19) ($P = 0.0707$). A favorable survival rate is indicated in the patient group that underwent surgery with the MST of 15.1 months (95% C.I. 10.23–20.04) compared to the other groups with the MST of 12.7 months (95% C.I. 8.95–16.45) ($P = 0.1743$) (Fig. 1b), though these were not statistically significant.

Patients with malignant peritoneal mesothelioma were treated with platinum-based chemotherapy combined with pemetrexed (3 cases) or paclitaxel (one case). Two cases with malignant pericardial mesothelioma were treated with platinum-based chemotherapy combined with pemetrexed. Surgical resection was performed on the MM patient with tunica vaginalis testis.

Asbestos exposure

The occupational history was obtained from all the patients and occupational AE was indicated in 89 cases (84.8%), including 23 cases in the shipbuilding industry, 16 in the construction industry, 9 in plumbing, 8 in

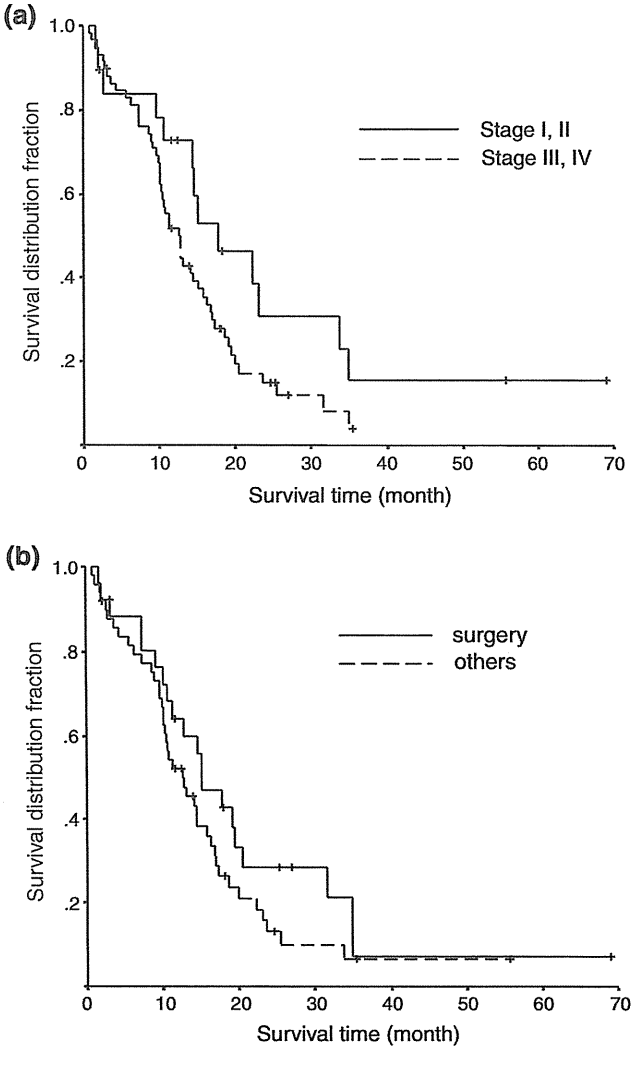

Fig. 1 Overall survival curve of patients with malignant pleural mesothelioma according to clinical stage (**a**) and treatment (**b**)

Table 2 Occupational history related to asbestos exposure

Shipbuilding	23
Construction	16
Plumbing	9
Electric work	8
Manufacturing	7
Asbestos products industry	5
Automobile manufacture	5
Steel production	3
Pottery and porcelain	3
Fiber product	2
Coating industry	2
Warehouse management	2
Chemical works	1
Cement manufacture	1
Metallic manufacture	1
Other asbestos-handling work	1
Total	89

Table 3 Patients characteristics of patients without asbestos exposure

Age	Gender	Site of origin	Subtype	Occupation
40	F[#]	Pleura	Sarcomatoid	Designer
43	M[§]	Pleura	Sarcomatoid	Bank staff
44	M	Pleura	Biphasic	Medical doctor
47	F	Pericardium	Biphasic	Office worker
48	F	Peritneum	Epithelioid	Homemaker
50	F	Pleura	Epithelioid	Homemaker
56	F	Pleura	Epithelioid	Homemaker
61	F	Pericardium	Epithelioid	Office worker
62	M	Pleura	Epithelioid	Utility worker
63	M	Pleura	Epithelioid	Cook
63	M	Pleura	Sarcomatoid	School teacher
64	F	Pleura	Epithelioid	Office worker

[#] female, [§] male

electrical work, and 7 in the manufacturing industry as shown in Table 2. Three patients had no history of occupational AE, but lived with someone who was in an occupation that handled asbestos. There were two patients in which AE was indicated in their life environment, i.e., living in a neighborhood near an asbestos products factory. The remaining 12 of the 105 patients had no history of occupational or environmental AE. The characteristics of these 12 patients were summarized in Table 3. As a result, AE was indicated in 93(88.6%) patients. The median time of AE was 29(1–60) years and the median time between the first AE and development of MM was 41(4–60) years.

Discussion

The clinical features of the 108 MM cases were investigated. This is the first nationwide study in Japan to clarify the characteristics and treatment outcome of MM cases.

MM is diagnostically challenging. Significant numbers of patients with MM demonstrate pleural effusion at the initial presentation, but there are many other diseases or conditions that demonstrate pleural effusion. In our cohort, pleural effusion was documented in 70(77.8%) of the cases with MPM. However, Aleman et al. reported that MPM accounted for only 6.7% of cases with malignant pleural effusion (Aleman et al. 2007). In patients demonstrating pleural fluid and/or diffuse pleural thickening, MPM could be one of the causes, especially if the patient has a history of AE, or some characteristic radiological findings indicating AE such as pleural plaque. However, the frequency of radiological findings indicating AE was very low. In our cohort, pleural plaque was found in 41% of the cases with MPM, and asbestosis was not found. MM should be kept in mind in the case of pleural effusion, even when characteristic radiological findings that suggest AE are not found.

Definite pathological diagnosis of MM should be based on immunohistochemical reactivity to some markers such as calretinin and thrombomodulin, in addition to the usual hematoxylin-eosin staining (Kushitani et al. 2008). Recently, Takeshima et al. reported that the diagnosis of MM was suspicious in approximately 15% cases who died of "MM" in Japan (Takeshima et al. 2009). In our cohort, 101 (96.2%) cases were diagnosed based on the materials obtained through procedures such as thoracoscopy or percutaneous biopsy. We are convinced that the diagnoses in our cases based on central review of pathological examination containing immunohistological analysis.

Concerning the treatment strategy, surgical resection such as extrapleural pneumonectomy (EPP) was performed in cases at an earlier stage (Stage I or II) with good performance status. The overall survival rate was relatively favorable in the group that underwent surgery with the MST of 20.0 months. A few patients received postoperative adjuvant chemotherapy and/or radiotherapy. Trimodality therapy, consisting of EPP, systemic chemotherapy, and adjuvant hemithoracic radiotherapy, has been reported to offer long-term survival in selected patients with MPM (Sugarbaker et al. 1999). The comparison of the survivals after treatment needs to be evaluated carefully, because these results are containing patient selection bias. An extrapleural pneumonectomy has been indicated in selected patients with earlier stage and better performance status. Further studies as prospective clinical trials are warranted to evaluate the feasibility and effectiveness of these combined modalities. For patients with advanced disease,

systemic chemotherapy was administered. As a chemotherapy regimen, a combination of cisplatin and pemetrexed, gemcitabine, or vinorelbine was mainly administered. Recently, pemetrexed, a multi-targeted antifolate, has demonstrated modest activity against MPM in combination with cisplatin (Vogelzang et al. 2003) or carboplatin (Castagneto et al. 2008). Since the approval of pemetrexed by the Ministry of Health, Labour and Welfare in Japan in 2006, the combination of cisplatin and pemetrexed has been considered as the standard regimen against MM. However, the treatment outcome is still unsatisfactory with an MST of only about one year. In addition, there are many aged patients with MM with some concomitant medical problems. Novel approaches are needed that incorporate new chemotherapeutic or molecular-targeted therapies.

Another principal objective of this study was to clarify the association between MM and AE. For this purpose, the patients were interviewed concerning their work and residential histories. As a result, occupational AE was revealed in more than 80% of the cases. This was reported in other countries (Wagner et al. 1960), but this is the first report to describe the detailed proportion of AE in MM in Japan. These include cases in which occupational AE was not described in the clinical record, but was revealed based on the interviews. The median duration of AE was 29 years and the median time of latency between AE and development of MM was about 40 years. The industrial use of asbestos was banned in Japan in 2006, but the number of incidences of MM is anticipated to continue to increase for the next few decades due to past usage of asbestos (Robinson and Lake 2005). This study stresses the urgent need for physicians to acknowledge the association between MM and AE, and to inquire thoroughly regarding AE in their work history and living environment since their youth.

In conclusion, the clinical features of Japanese MM cases were investigated. A strong association with occupational AE was demonstrated.

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Conflict of interest statement We declare that we have no conflict of interest.

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Malignant Pericardial Mesothelioma with Response to Chemotherapy

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Key Words: Asbestos, Calretinin, Pemetrexed, Irinotecan.

(*J Thorac Oncol.* 2009;4: 1440–1441)

Malignant pericardial mesothelioma (MPerM) is an extremely rare and lethal cardiac tumor.[1] The prognosis is poor, and treatments such as surgery and radiotherapy have not demonstrated an impact on disease progression. We report a case of MPerM with response to chemotherapy.

CASE REPORT

A 61-year-old woman was referred to our hospital because of dyspnea on exertion. A computed tomography (CT) scan of the chest showed diffuse thickening of the pericardium (Figures 1*A*, *B*). The presence of fluid in the right pleural cavity was apparent, but tumor formation was not found on the pleura or the lung. Cardiac ultrasonography showed impaired left ventricular wall motion and dilatation of the inferior vena cava with loss of respiratory fluctuation. Cytologic examination of the pleural fluid was negative (class II). An open-chest, pericardial biopsy was performed without pleural inspection or biopsy. Microscopic examination of the specimen showed proliferation of mesothelial cells with nuclear atypicality consistent with malignant mesothelioma (Figure 2*A*). Immunohistochemical analyses revealed that the cells were calretinin positive, epithelial membrane antigen positive, and carcinoembryonic antigen negative (Figures 2*B–D*). These findings confirmed the diagnosis of malignant mesothelioma. Systemic chemotherapy consisting of carboplatin (AUC = 5, day 1) and pemetrexed (500 mg/m^2, day 1) was initiated, and regression of the pericardial thickening was exhibited after the second course (Figure 1*C*). The dyspnea on exertion was relieved. Six cycles of the chemotherapy were given; however, 6 months later, pleural fluid accumulated in the left cavity and mesothelioma cells were detected in the fluid. As salvage chemotherapy, irinotecan hydrochloride (60 mg/m^2, days 1, 8, and 15) was administered. A CT scanning of the chest after the second course showed regression of the pericardial tumor and decrease in the amount of pleural fluid. Two months later, the patient died of disease progression, 18 months after the diagnosis. Autopsy was not allowed.

DISCUSSION

MPerM is a rare tumor, which has a reported incidence of 0.0022% in an autopsy series of 500,000 case studies.[2] A clinical sign is constrictive pericarditis. Cardiac ultrasonography may reveal an effusion or myocardial mass. A CT scanning of the chest may also show pericardial effusion, thickening of the pericardium, or pericardial mass formation.[1] However, these findings are nonspecific. In the current case, the CT scanning showed diffuse thickening of the pericardium, indicating constrictive pericarditis, but no tumor formation. MPerM should be noted as one cause of unexplained constrictive pericarditis.

The prognosis for MPerM is poor, and the clinical course is progressive. No clinical trial has yet been conducted and standard treatment has not yet been established. Recently, pemetrexed, a multitargeted antifolate, has demonstrated modest activity against malignant pleural mesothelioma in combination with cisplatin[3] or carboplatin.[4] Irinotecan was also reported to demonstrate a modest activity against pleural mesothelioma in a clinical trial.[5] There is no previous report that these regimens were applied to MPerM, so the current case might be the first report that these regimens have shown clinical activity against MPerM.

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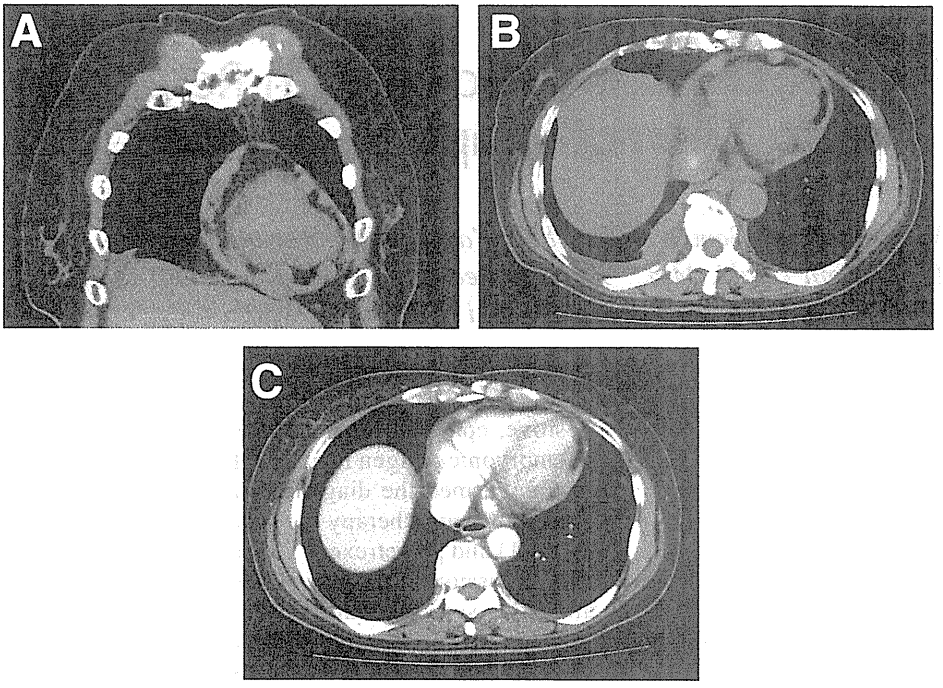

FIGURE 1. CT scan of the chest at the time of diagnosis showing diffuse thickening of the pericardium; (*A*) sagittal and (*B*) horizontal views. After administration of chemotherapy consisting of carboplatin and pemetrexed, (*C*) regression of the pericardial thickening was exhibited.

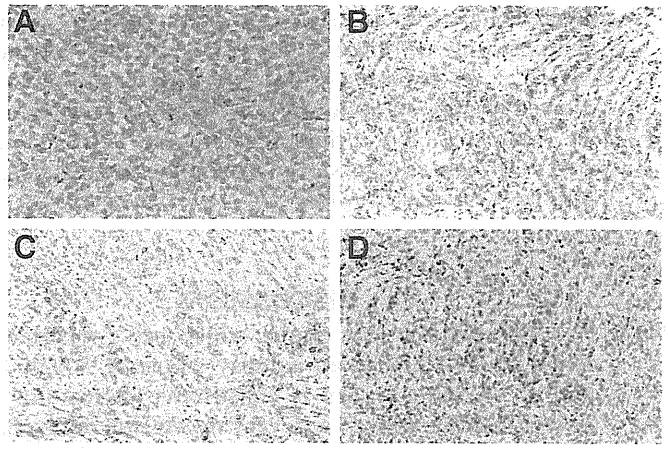

FIGURE 2. *A*, Microscopic examination of the biopsy specimen showed proliferation of mesothelial cells with nuclear atypicality consistent with malignant mesothelioma (hematoxylin-eosin, 40×). *B*, Immunohistochemical analysis revealed positive expression of calretinin (20×), (*C*) epithelial membrane antigen (20×), and (*D*) negative expression of CEA (20×).

In conclusion, MPerM is an extremely rare neoplasm. A combination chemotherapy consisting of carboplatin and pemetrexed or irinotecan monotherapy would be a favorable treatment option against MPerM.

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Accuracy of pathological diagnosis of mesothelioma cases in Japan: Clinicopathological analysis of 382 cases

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ABSTRACT

Incidences of mesothelioma are on the rise in Japan. However, the accurate frequency of mesothelioma occurrence is still unknown. The aim of this study is to clarify the accuracy of pathological diagnosis of mesothelioma. Among the 2742 mesothelioma death cases extracted from the document "Vital Statistics of Japan" for 2003–2005, pathological materials were obtained for 382 cases. After these materials were reviewed and immunohistochemical analyses were conducted, mesothelioma was diagnosed by discussions based on clinical and radiological information. Sixty-five cases (17.0%) were categorized as "definitely not/unlikely" mesotheliomas, and 273 cases (71.5%) were categorized as "probable/definite" mesotheliomas. The percentage of "probable/definite" pleural and peritoneal mesothelioma cases in males was 74.3% and 87.5%, respectively, and that of pleural cases in females was 59.2%; however, the percentage of "probable/definite" peritoneal cases in females was only 22.2%. These results suggest that the diagnostic accuracy of mesothelioma is relatively low in females and in cases of peritoneal and sarcomatoid subtype mesotheliomas; furthermore, approximately 15% of cases of deaths due to mesothelioma in Japan are diagnostically suspicious.

1. Introduction

Mesothelioma is a malignant tumor originating from the mesothelial cells of the pleura, peritoneum, pericardium, and testicular tunica vaginalis. The occurrence of this tumor is associated with occupational and environmental asbestos exposure [1–5]. The frequency of mesothelioma occurrence is on the rise in Japan. The data obtained from the "Vital Statistics of Japan" indicated that there were 500 cases of death due to mesothelioma in 1995, 710 cases in 2000, and 911 cases in 2005. Many of the deaths were due to past usage of asbestos, especially after the 1950s [3,4]. An epidemiological study estimated that there would be approximately 100,000 deaths in Japan due to pleural mesothelioma in the next 40 years, and the peak incidence of mesothelioma would occur during the period 2030–2034 [6]. Therefore, there is an urgent need for accurate diagnosis and treatment of patients suffering from mesothelioma. However, the accurate frequency of mesothelioma occurrence is still unknown because different diagnostic methods and criteria are used in different medical institutes, and no nationwide mesothelioma registry systems have been established in Japan thus far.

Currently, it is recommended that definite mesothelioma diagnosis be possible by histological or cytological analyses by immunohistochemistry using the currently available antibodies [7,8]. However, thus far, these procedures have not been carried out appropriately either in Japan or other countries. In Japan, during the period 2003–2005, a total of 2742 deaths due to mesothelioma were reported in the document "Vital Statistics of Japan," which has been published by the Ministry of Health, Labor and Welfare. However, precise clinicopathological analyses with regard to the accuracy of the diagnosis in these cases have not yet been conducted.

The aim of this study is to review past death cases diagnosed with "mesothelioma" and clarify the accuracy of their pathological diagnosis. In addition, to improve diagnostic accuracy, critical pathological diagnostic problems have been analyzed.

2. Materials and methods

2.1. Patient selection

From the "Vital Statistics of Japan" document for the period 2003–2005, we extracted 2742 deaths that occurred due to

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mesothelioma. In addition, we examined the death certificate files of each of these patients at the Ministry of Health, Labor and Welfare, Japan, after obtaining permission from the Minister for Internal Affairs and Communications, Japan. After examination, we requested all the medical institutes in which mesothelioma cases were reported during this period to submit materials for pathological diagnosis. The materials, including histological and cytological specimens, immunohistochemical slides, unstained slides, paraffin blocks, and formalin-fixed tumor tissues, were obtained for 382 cases (13.9%) from 297 medical institutes with the permission of the families of the deceased and medical institutes. The details of materials obtained are as follows: 46 cytological slides (CS), 21 histology slides stained with hematoxylin and eosin (H&E; SHE), 7 CS and SHE, and 308 CS and/or SHE with immunohistochemistry, including the 237 cases that were analyzed by immunohistochemistry in our department.

The planning of this study was approved by the ethical committee at Okayama Rosai Hospital, Japan.

2.2. Pathological evaluation

After the materials (H&E-stained tissue slides or Papanicolaou or Giemsa stained cytology slides and H&E and immunohistochemically stained tissue slides) were reviewed, immunohistochemical analyses were conducted in cases with unstained slides, paraffin blocks, or formalin-fixed tumor tissues; the analyses were based on the morphology and location of the tumor. Immunohistochemical staining was performed using the Histofine Simple Stain MAX-PO (MULTI) kit (Nichirei, Tokyo, Japan).

Due to limitations with regard to the unstained slides, antibodies against the following markers were initially selected: calretinin (Polyclonal, Zymed, San Francisco, CA, USA), D2-40 (clone D2-40, Nichirei BioScience, Tokyo, Japan), cytokeratin marker (CAM5.2; clone 2A4, Becton-Dickinson, Franklin Lake, NJ, USA), pancytokeratin (clone AE1/AE3, DAKO, Glostrup, Denmark), carcinoembryonic antigen (CEA; clone COL-1, Nichirei), thyroid transcription factor-1 (TTF-1; clone 8G7G3/1, DAKO), and desmin (clone D33, DAKO) when epithelioid or biphasic mesothelioma was suspected [9–11]. Calretinin, D2-40, CAM5.2 (clone 2A4, Becton-Dickinson, Franklin Lake, NJ, USA), pancytokeratin (clone AE1/AE3, DAKO), CEA, and desmin, were selected for the diagnosis of sarcomatoid or desmoplastic mesothelioma [12–15]. Additionally, Wilms tumor gene (WT1; clone 6F-H2, DAKO), thromomodulin (clone 1009, DAKO), epithelial membrane antigen (EMA; clone E29, DAKO), CA19-9 (clone NS19-9, TFB, Tokyo, Japan), epithelial antigen (clone Ber-EP4, DAKO), epithelial-related antigen (clone MOC-31, DAKO), myf-3 (clone 3A11, Novocastra, Newcastle upon Tyne, UK), CD34 (clone QBEnd/10, Novocastra), CD45R (clone 2B11 + PD7/26, DAKO), CD3 (clone PC3/188A, DAKO), CD20 (clone L26, DAKO), and estrogen receptor (ER; clone 1D5, DAKO) were used as appropriate. Antigen retrieval was performed in an autoclave. On the basis of the number of tumor cells observed following immmunohistochemical staining, the tumors were scored using the following semiquantitative system: 0, no or trace staining; score 1+, <5% tumor cells; score 2+, 6–50% tumor cells; score 3+, >51% tumor cells. The definition of a "positive case" in this study is a case with a score of more than 1+. Additional immunohistochemistry of the cytological specimens was not conducted in this study.

2.3. Clinicopathological analysis and categorization of each case

After the independent diagnosis of each case by pathologists (Y.T., K.I., and V.J.A.) according to WHO criteria [16] and clinical analysis by 4 physicians (T.K., K.G., K.A., and N.F.) and 1 radiologist (K.K.), a clinico-pathological discussion was initiated to confirm the final diagnosis. The cases with questionable and/or atypical mesothelioma findings were especially discussed.

For mesothelioma analysis, each case was categorized into either of the 4 subcategories: "inadequate/insufficient" (undetermined due to insufficient materials and information), "definitely not/unlikely" (definitely not mesothelioma and/or unlikely mesothelioma), "possible" (possible mesothelioma), "probable/definite" (probable mesothelioma and/or definite mesothelioma). This conservative category system was used in this study because of the heterogeneous nature of the available diagnostic materials and methods, and because there was, incomplete information and insufficient or inadequate materials for pathological diagnosis that prevented final and certified diagnosis.

2.4. Statistical analysis

A statistical analysis was performed by the Mann–Whitney's *U*-test for the detection of differences in the distribution in each category by various factors. In this analysis, the cases in the "inadequate/insufficient" category were excluded.

3. Results

3.1. Distribution of the 382 "clinical" mesothelioma cases into the diagnostic categories

The distribution of cases in the diagnostic categories "inadequate/insufficiency," "definitely not/unlikely," "probable," and "probable/definite" categories was 19 (5.0%), 65 (17.0%), 26 (6.8%), and 272 (71.2%), respectively. Among the 272 in the "probable/definite" category, 214 cases (78.7%) were considered as "definite" mesothelioma cases.

3.2. Proportion of cases in each diagnostic category depending on primary tumor sites and gender

By analysis of the primary tumor site, a relatively higher rate of "probably/definite" pleural mesothelioma cases were observed (72.0%) as compared to peritoneal cases (64.0%). On the other hand, a relatively higher rate of "definitely not/unlikely" peritoneal mesothelioma cases was noted (32.0%) compared with the pleural cases (14.8%).

Out of 7 other primary site cases, 6 cases (87.5%), including 4 pericardial cases, 1 testicular tunica vaginalis case, and 2 cases with unknown primary sites, belonged to the "probably/definite" category.

The proportion of cases in each diagnostic category based on the primary tumor site (pleura and peritoneum) and gender is shown in Table 1. A relatively high rate of "probable/definite" pleural mesothelioma was observed among the males (74.3%) and females (59.2%). Further, a high rate of "probable/definite" peritoneal mesothelioma was noted among the males (87.5%) but there were only 4 cases (22.2%) among the females. In conclusion, a relatively high rate of diagnostically suspicious cases was noted in the case of females and in the case of peritoneal mesothelioma.

3.3. Summary of the immunohistochemical profiles of various lesions in each category

A summary of the immunohistochemical results obtained with the markers calretinin, D2-40, cytokeratin (CAM5.2 and/or AE1/AE3), CEA, and TTF-1 in 308 cases analyzed in each category are provided in Table 2.

Table 1
Proportions of cases in each diagnostic category depending on primary tumor sites[a] and gender.

Category	Pleura[b]		Peritoneum[c]	
	Male No. of cases (%)	Female No. of cases (%)	Male No. of cases (%)	Female No. of cases (%)
Inadequate/insufficiency	12 (4.3)	7 (14.3)	0 (0)	0 (0)
Definitely not/unlikely	37 (13.4)	11 (22.4)	3 (9.4)	13 (72.2)
Possible	22 (8.0)	2 (4.1)	1 (3.1)	1 (5.6)
Probable/definite	205 (74.3)	29 (59.2)	28 (87.5)	4 (22.2)
Total	276 (100)	49 (100)	32 (100)	18 (100)

[a] Excluding 4 pericardial cases, 1 testicular tunica vaginalis case and 2 unknown primary site cases.
[b] $p = 0.40$ by Mann–Whitney's *U*-test (between male and female pleural cases).
[c] $p < 0.0001$ by Mann–Whitney's *U*-test (between male and female peritoneal cases).

Table 2
Summary of the immunohistochemical profiles of various lesions in each category.

Pathological diagnosis	Markers					
	Calretinin *n* (%)	D2-40 *n* (%)	Cytokeratin[a] *n* (%)	CEA *n* (%)	TTF1 *n* (%)	Desmin *n* (%)
"Definitely not/unlikely" mesothelioma[b]						
Pulmonary adenocarcinoma	1/8 (12.5)	0/5 (0)	3/4 (75)	5/8 (62.5)	6/8 (75.0)	1/2 (50)
Pulmonary sarcomatoid carcinoma	6/7 (85.7)	3/6 (50.0)	5/6 (83.3)	2/3 (66.7)	0/1 (0)	0/4 (0)
Fibrous pleuritis	4/8 (50)	2/4 (50)	3/4 (75)	ND[c]	ND	4/4 (100)
Serous adenocarcinoma, peritoneum	0/3 (0)	0/3 (0)	3/3 (100)	2/5 (40)	ND	ND
Sarcoma, NOS	1/4 (25)	2/4 (50.0)	1/4 (25)	ND	ND	0/3 (0)
"Possible" mesothelioma						
Epitheliod or biphasic	2/4 (50)	2/4 (50.0)	3/4 (75.0)	0/7 (0)	0/3 (0)	0/1 (0)
Sarcomatoid	3/3 (100)	2/3 (66.7)	2/3 (66.7)	0/3 (0)	0/1 (0)	0/2 (50)
"Probable/definite" mesothelioma						
Epithelioid	132/137 (96.4)	81/84 (96.4)	48/50 (96.0)	3/118 (2.5)	0/43 (0)	7/72 (9.7)
Biphasic	27/30 (90)	15/18 (83.3)	22/22 (100)	0/25 (0)	0/10 (0)	2/17 (11.8)
Sarcomatoid	33/43 (76.7)	15/21 (71.4)	35/35 (100)	0/13 (0)	0/4 (0)	3/31 (9.7)
Desmoplastic	4/4 (100)	2/2 (100)	4/4 (100)	0/1 (0)	ND	0/4 (0)

[a] Including CAM5.2 or AE1/AE3 positivity.
[b] Predominant final diagnoses are indicated.
[c] Not done.

In brief, each of the "probable/definite" mesothelioma and pulmonary sarcomatoid carcinoma subtypes showed a high calretinin positivity (more than 50%). Further, D2-40 positivity in the "possible" and "probable/definite" mesothelioma cases was greater than 50%. In addition, the cases of pulmonary sarcomatoid carcinoma, fibrous pleuritis and sarcoma, NOS were 50% positive. CEA positivity in the case of pulmonary adenocarcinoma, pulmonary sarcomatoid carcinomas, and serous papillary adenocarcinomas invading the peritoneum in females was relatively high (62.5%, 66.7%, and 40%, respectively); however, only 3 "probable/definite" category cases (2.5%) tested positive. Only 6 pulmonary adenocarcinoma cases tested positive for TTF-1.

3.4. Relationship between pathological diagnostic methods and proportion of cases in each diagnostic category

To evaluate the efficiency of the various pathological diagnostic methods for mesothelioma, the proportion of cases in each category were differentiated according to the 4 types of pathological specimens (i.e., only cytology slides with Papanicolaou (Pap) stain (CS), only histological slides with H&E stain (SHE), both CS and SHE, and CS or SHE with immunohistochemistry) (Table 3). The result revealed a higher percentage of cases in the "probable/definite" category for cases with immunohistochemistry than for those without immunohistochemistry.

Table 3
Relationship between pathological diagnostic methods and proportion of cases in each diagnostic category.

Category	Methods			
	CS[a] No. of cases (%)	SHE[b] No. of cases (%)	Both CS and SHE No. of cases (%)	CS and/or SHE with IH[c,d] No. of cases (%)
Inadequate/insufficiency	6 (13.0)	2 (9.5)	1 (14.3)	10 (3.2)
Definitely not/unlikely	14 (30.4)	3 (14.3)	1 (14.3)	47 (15.2)
Possible	8 (17.4)	6 (28.6)	1 (14.3)	11 (3.6)
Probable/definite	18 (39.2)	10 (47.6)	4 (57.1)	240 (78.0)
Total	46 (100)	21 (100)	7 (100)	308 (100)

[a] CS: cytology specimen with Papanicolaou stain.
[b] SHE: histological slides with H&E stain.
[c] IH: immunohistochemistry.
[d] $p < 0.0001$ by Mann–Whitney's *U*-test (difference in category proportion by the presence of immunohistochemistry).

Table 4
Correct diagnosis of cases in "definitely not/unlikely" category.

Site	Correct diagnosis	No. of case
Male		
Pleura	Pulmonary adenocarcinoma	14
	Pulmonary sarcomatoid carcinoma	6
	Non-small cell lung carcinoma	1
	Pulmonary carcinosarcoma	1
	Fibrous pleuritis	8
	Sarcoma, NOS	2
	Metastatic renal cell carcinoma	1
	Thymic carcinoma	1
	Malignant lymphoma	1
	Solitary fibrous tumor	1
	Reactive mesothelial hyperplasia	1
Peritoneum	Adenocarcinoma	1
	Renal cell carcinoma	1
	Reactive mesothelial hyperplasia	1
	Total	40
Female		
Pleura	Pulmonary adenocarcinoma	3
	Pulmonary sarcomatoid carcinoma	3
	Non-small cell lung carcinoma	2
	Fibrous pleuritis	1
	Malignant lymphoma	1
	Solitary fibrous tumor	1
	Reactive mesothelial hyperplasia	1
Peritoneum	Serous adenocarcinoma	6
	Adenocarcinoma, NOS	2
	Carcinosarcoma	2
	Sarcoma, NOS	2
	Rhabdomyosarcoma	1
	Total	25

3.5. Correct diagnosis of cases in "definitely not/unlikely" category

Pathological diagnoses of the cases in the "definitely not/unlikely" category are summarized in Table 4. Among the pleural cases in males, pulmonary adenocarcinoma (14 cases), pulmonary sarcomatoid carcinoma (6 cases), and fibrous pleuritis (8 cases) were dominant. Among the pleural cases in females, there were a majority of pulmonary adenocarcinomas (3 cases) and pulmonary sarcomatoid carcinomas (3 cases) similar to the result in the case of the males. Among the peritoneal cases in females, serous adenocarcinomas (6 cases) from the female genital tract were prominent.

Representative cases placed in the "definitely not/unlikely" category are shown in Figs. 1–3.

4. Discussion

The present study involved a clinicopathological analysis of cases where death occurred due to clinical mesothelioma, as per the files from the "Vital Statistics of Japan" for the period 2003–2005. Although a limited amount of information was available for all cases and there was a certain amount of bias depending on the cooperating institutes and submitted materials, we attempted to identify some characteristic problems in the diagnosis of mesothelioma in Japan. Consequently, we decided to consider 65 cases belonging to "definitely not/unlikely" category, and therefore, we assumed that approximately 15% of mesothelioma deaths were diagnostically suspicious, especially in females with peritoneal and sarcomatoid subtype mesothelioma. All the medical institutes from which pathological materials were collected did not provide the slides stained with the recently recommended immunohistochemical panel, and our department could not perform immunohistochemistry with a uniform antibody panel owing to the limitation of submitted materials. Therefore, the error score (i.e., approximately 15%) estimated in this study might be higher than the "actual" error score. However, such comprehensive data concerning the accuracy of mesothelioma diagnosis has not been previously reported in Japan. It is ideal to analyze the autopsy materials to precisely and definitely diagnose clinical "mesothelioma" patients. However, there are limitations to conducting an autopsy in all cases and reevaluating all materials submitted for pathological diagnosis in each medical institute. Therefore, we used the conservative category system, i.e., "inadequate/insufficient", "definitely not/unlikely", "possible", and "probable/definite".

There are many diseases that must be differentiated from mesothelioma. Epithelioid mesothelioma must be differentiated from pulmonary adenocarcinoma, metastatic adenocarcinoma, peritoneal serous adenocarcinoma, ovarian adenocarcinoma, and reactive mesothelial hyperplasia. Sarcomatoid mesothelioma should be differentiated from pulmonary sarcomatoid carcinoma, true sarcoma arising in the chest wall and parietal pleura, pulmonary primary sarcoma, and various types of intraabdominal sarcomas. The biphasic type must be differentiated from pulmonary biphasic pulmonary blastoma, carcinosarcoma, synovial sarcoma, and carcinosarcoma of the female genital tract (ovary and uterus). The desmoplastic type must be differentiated from fibrous or organizing pleuritis [7,8]. It must be understood that mesothelioma has clinical and pathological heterogeneities and that relatively rare tumors may pose diagnostic difficulties. As expected, the above-mentioned diseases were responsible for mesothelioma death cases, as indicated in Table 4.

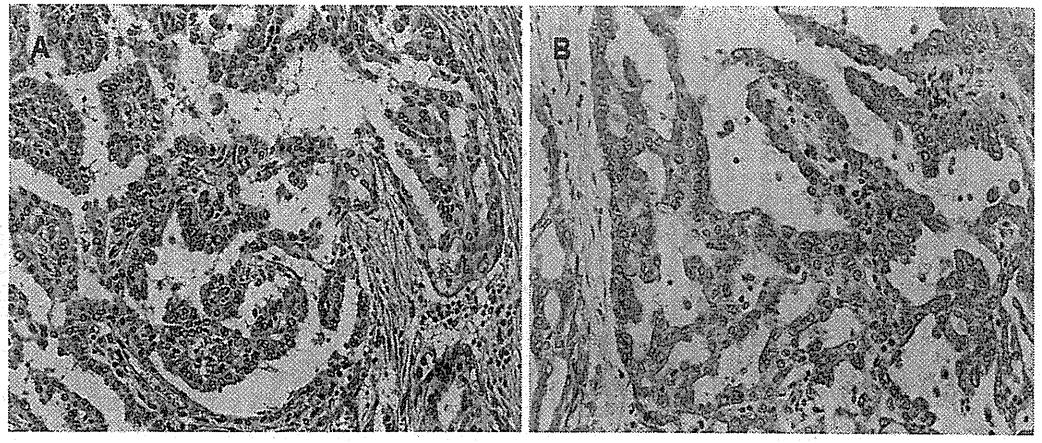

Fig. 1. Pulmonary adenocarcinoma invading the parietal pleura (69-year-old male). (A) Atypical epithelial cells showed a papillary invasive growth pattern (H&E, ×200). (B) Immunohistochemically, the tumor cells were positive for CEA (immunostaining, ×200).

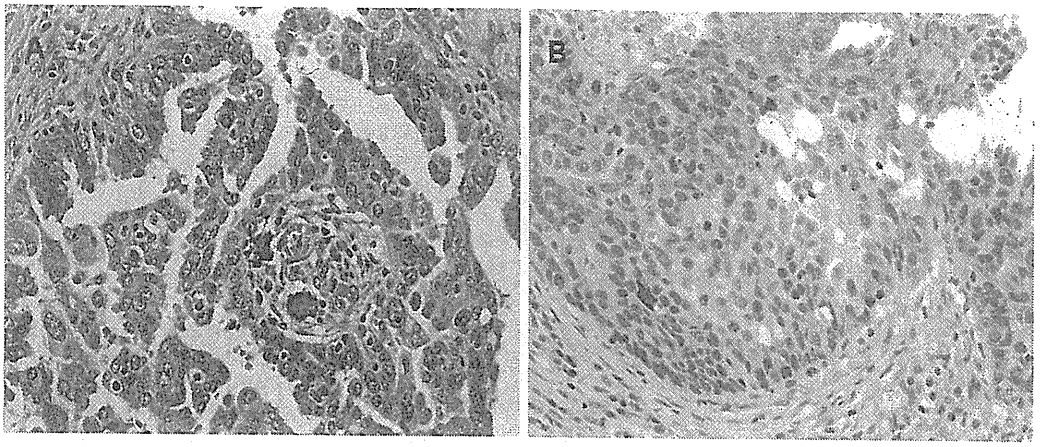

Fig. 2. Serous papillary adenocarcinoma invading the peritoneum (55-year-old female). (A) Atypical epithelial cells show a complex papillary growth pattern with psammoma bodies (H&E, ×200). (B) Tumor cells tested positive for the estrogen receptor (immunostaining, ×200).

Recently, many mesothelial and non-mesothelial markers have been developed to differentiate mesothelioma from other malignant tumors and benign lesions [9–11,13]. Immunoshistochemical analysis is absolutely necessary for the accurate diagnosis of mesothelioma. Therefore, we discussed the differential diagnosis of mesothelioma from pulmonary adenocarcinoma, pulmonary sarcomatoid carcinoma, fibrous pleuritis, and ovarian serous carcinomas, which are the predominant disorders as mentioned in Table 4, especially with regard to the utility of immunohistochemistry using the antibody panel.

In this study, 17 pulmonary adenocarcinomas were misdiagnosed as mesotheliomas (4.5% of 382 cases). Differentiation between epithelioid mesothelioma and pulmonary adenocarcinoma is sometimes difficult. This is because some pleural mesotheliomas invade the pulmonary parenchyma and exhibit lepedic growth [7]. Sometimes pulmonary adenocarcinomas may grow along the visceral and/or parietal pleura, mimicking the growth of malignant pleural mesothelioma; this growth is detected clinically and/or radiologically and it is called "pseudomesotheliomatous adenocarcinoma" [17,18]. Over the last 10 years, many immunohistochemical markers for differentiating between epithelioid mesothelioma and pulmonary adenocarcinoma have been developed [10,19–24]. Ordonez [22,23] stated that calretinin and CK5/6 (or WT1) were positive markers and CEA and MOC-31 (or B72.3, Ber-Ep4, or BG-8) were negative markers. We demonstrated that the combination of CEA, calretinin, and WT1 or thrombomodulin was the best antibody panel for differential diagnosis [10]. Recently, D2-40 or podoplanin was reported to be useful for distinguishing mesothelioma from pulmonary adenocarcinoma [25]. On the basis of these facts, we selected the antibody panel from among calretinin, D2-40, CAM5.2, CEA, TTF-1, and desmin for differential diagnosis. The application of these antibodies will contribute to increase the diagnostic accuracy of epithelioid mesothelioma.

Differentiation between sarcomatoid mesothelioma and pulmonary sarcomatoid carcinoma is still very difficult if no adequate clinical and pathological information is available. The higher number of pulmonary sarcomatoid carcinomas in the "definitely not/unlikely" category may be reflective of the difficulties in the diagnosis of sarcomatoid mesothelioma (Table 4). Pulmonary sarcomatoid carcinoma is described as a poorly differentiated non-small cell lung carcinoma containing a component of sarcoma or sarcoma-like differentiation [7]. At present, no sensitive or specific markers for differentiation of these tumors are available; thus, it is very important to obtain precise clinical and gross pathological findings (i.e., main location of tumor, presence of intrapulmonary nodule, presence of adenocarcinoma or squamous cell carcinoma foci, etc.). However, the primary site must be determined by examination of the surgically resected tumor and/or autopsy materials. Histologically, therefore, the development of new markers for differential diagnosis is necessary. Kushitani et al. [10] indicated that no significant differences exist between tumors in the expression of calretinin, WT1, AE1/AE3, CAM5.2, and EMA. Recently, Hinterberger et al. [14] stated that calretinin and D2-40 immunostaining in the case of sarcomatoid mesothelioma will improve the diagnos-

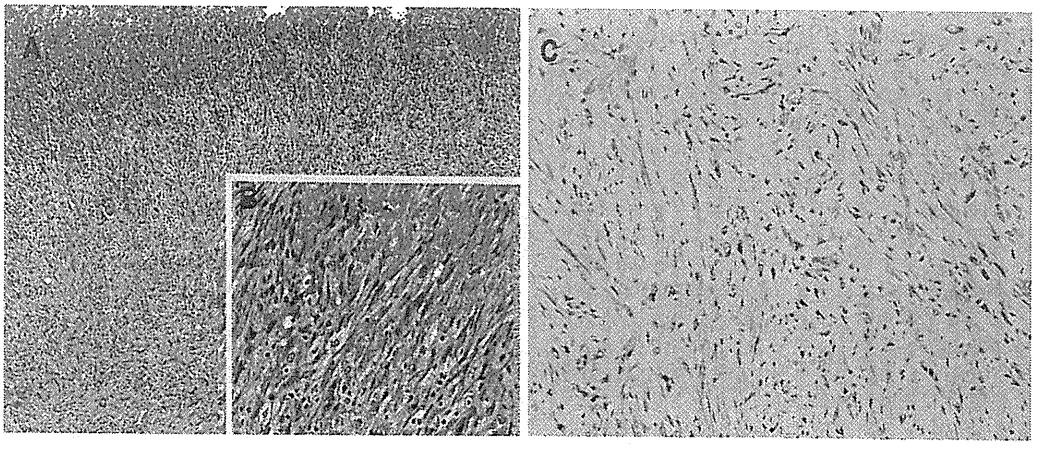

Fig. 3. Fibrous/organizing pleuritis (73-year-old male). (A, B) Spindle-shaped cells proliferating in a "zonation" fashion. The surface of this lesion is composed of fibrin, immature spindle cells, and capillaries (H&E, A: ×40, B: ×200). (C) Some spindle cells tested positive for desmin (immunostaning, ×200).