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ORIGINAL PAPER

Clinical investigation of malignant mesothelioma in Japan

Nobukazu Fujimoto · Keisuke Aoe · Kenichi Gemba · Katsuya Kato · Koichi Yamazaki · Takumi Kishimoto

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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.

N. Fujimoto (✉) · K. Gemba · T. Kishimoto
Department of Respiratory Medicine, Okayama Rosai Hospital, 1-10-25 Chikkomidorimachi, Minamiku, Okayama 7028055, Japan
e-mail: nfuji@okayamaH.rofuku.go.jp

K. Aoe
Department of Medical Oncology, National Hospital Organization Yamaguchi-Ube Medical Center, 685 Higashikiwa, Ube 7550241, Japan

K. Kato
Department of Radiology, Okayama University School of Medicine, 2-5-1 Shikatacho, Kitaku, Okayama 7008558, Japan

K. Yamazaki
Department of Internal Medicine, Hokkaido University School of Medicine, Kita 14, Nishi 5, Kitaku, Sapporo 0608648, Japan

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

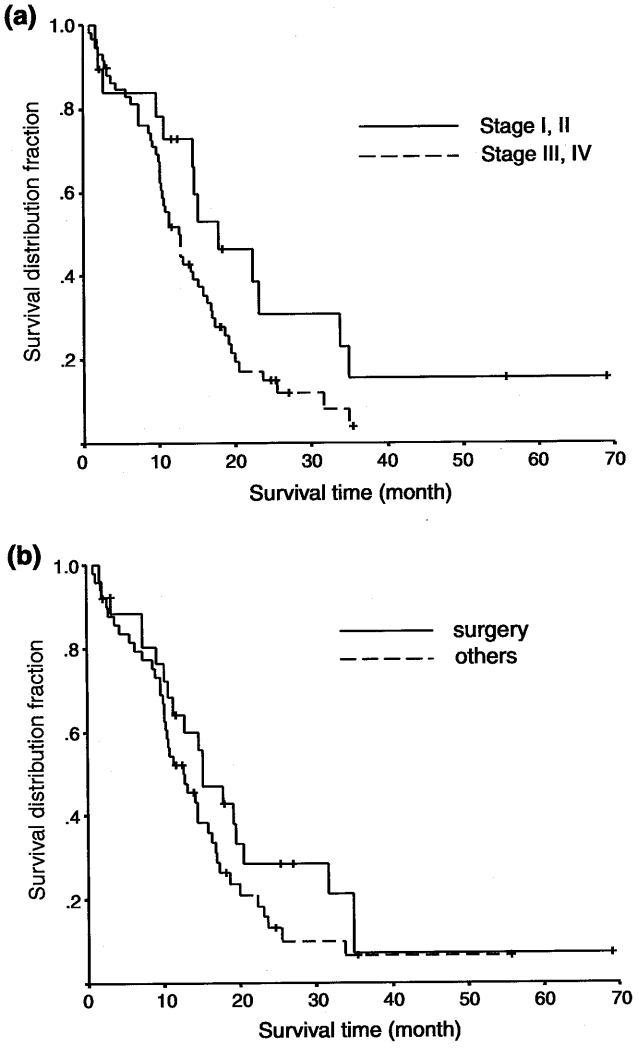

Fig. 1 Overall survival curve of patients with malignant pleural mesothelioma according to clinical stage (**a**) and treatment (**b**)

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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