

Malignant Mesothelioma: Experience at the Singapore General Hospital

K Chan,*^{MBBS, MRCP (UK), M Med (Int Med)}, K L Tan,**^{FAMS, MRCP (UK), FCCP}, H S Lee,***^{FAMS, MBBS, M Med (Occup Med)},
P Eng,****^{FAMS, MBBS, M Med (Int Med)}

Abstract

Introduction: Malignant mesothelioma is a rare occupational disease in Singapore. There have been few reports of this condition in Singapore. We aim to describe the clinical characteristics, management and outcomes in a case series of 16 patients diagnosed in a teaching hospital in Singapore. **Materials and Methods:** A chart review of all cases of malignant mesothelioma diagnosed in our institution during the period 1996 to 2001 was conducted, with particular attention to the occupational history. **Results:** There were 16 patients (15 male patients) with a median age of 61.5 (range, 46 to 78) years. Thirteen patients had malignant pleural mesothelioma (MPM) and 3 patients had mesothelioma of the peritoneum. Eleven of the patients with MPM (84.6%) presented with a pleural effusion and only 2 patients (15.4%) had chest pain. Initial pleural fluid cytology and closed pleural biopsies were negative in all patients who presented with a pleural effusion. Thoracoscopy confirmed the histologic diagnosis and allowed simultaneous talc pleurodesis in 9 patients. All patients had documented asbestos exposure, of which 14 (87.5%) were confirmed to be occupationally related. The median time from first exposure to symptoms was 33.5 (range, 16 to 53) years. The median survival was 6 months. Most of the patients (75%) received best supportive care alone. **Conclusions:** In our experience, malignant mesothelioma is an aggressive disease with a poor prognosis. It is strongly associated with asbestos exposure. Thoracoscopy is an invaluable diagnostic modality in the evaluation of a patient with occupational asbestos exposure and an undiagnosed pleural effusion.

Ann Acad Med Singapore 2003; 32:388-91

Key words: Asbestos, Occupational disease, Pleural effusion, Thoracoscopy

Introduction

Malignant mesothelioma is a rare tumour and is typically associated with asbestos exposure. In endemic areas, it has an estimated incidence as high as 66 per million for men aged 35 and above.¹ Diagnosis is often difficult and to date, no therapy has been established as curative.² Since 1968, it has become a notifiable disease in Singapore³ and patients may be eligible for Workmen's Compensation. Alternatively, they may receive financial assistance from the Ministry of Manpower.⁴ There have been few reports of this condition in Singapore.³ We aim to describe the clinical features, management and outcomes of all patients diagnosed with malignant mesothelioma in our hospital over a 5-year period (1996 to 2001).

Materials and Methods

A chart review of all patients with malignant mesothelioma diagnosed in our hospital from 1996 to 2001 was conducted. Specific information obtained included

clinical features, degree and duration of asbestos exposure, diagnostic modality employed, management and survival. In addition, detailed occupational histories were reviewed and exposure to asbestos was classified as direct or indirect. Direct occupational exposure to asbestos referred to the direct handling of asbestos, for example, applying asbestos insulation or pouring asbestos fibres in the manufacture of cement. Indirect occupational exposure referred to the circumstance of a worker in the vicinity of other workers who directly handled asbestos, for example, a clerk in an asbestos cement factory. Statistical analysis was performed using the Statistical Package for Social Sciences version 10.0.5 (SPSS Inc., Chicago, IL). Differences in median survival were compared using the Mantel-Cox log-rank test.

Results

There were 16 patients (15 male), with a median age of 61.5 (range, 46 to 78) years. Thirteen patients had malignant

* Registrar

** Consultant

*** Head and Senior Consultant

Department of Respiratory and Critical Care Medicine
Singapore General Hospital

**** Consultant

Occupational Health Department, Ministry of Manpower, Singapore

Address for Reprints: Dr Kenneth Chan, Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: gm3cpw@sgh.com.sg

pleural mesothelioma (MPM) and 3 patients had mesothelioma of the peritoneum. The clinical characteristics are summarised in Table I. Among the patients with MPM, the commonest presenting complaint was dyspnoea (84.6%). Only 15.4% of patients had chest pain. Almost all patients (84.6%) had a pleural effusion on chest radiograph. In all the patients with a pleural effusion ($n = 11$), initial thoracentesis and closed pleural biopsies (using Abram's needle) were non-diagnostic. Patient number 12 had malignant cells in the pleural fluid, but we were unable to distinguish between adenocarcinoma and mesothelioma. Histopathologic confirmation was obtained via thoracoscopy in 9 of 11 patients (81.8%) with a pleural effusion. Another patient (patient number 10) required a thoracotomy to obtain adequate tissue because of dense adhesions in the pleural space, precluding a comprehensive thoracoscopic examination. Patient number 4 defaulted follow-up after a non-diagnostic closed pleural biopsy. He eventually developed a chest wall lesion; a biopsy confirmed mesothelioma. The median time from onset of symptoms to diagnosis was 12 (range, 4 to 68) weeks.

Of the 3 patients with malignant peritoneal mesothelioma, 2 presented with abdominal pain, weight loss and peritoneal masses on computed tomography (CT). Diagnosis was established at laparotomy. The third patient presented with ascites alone, for which a laparoscopy revealed peritoneal nodules.

The relevant occupational histories of each patient are shown in Table II. All patients had documented asbestos

exposure, of which 14 (87.5%) were confirmed to be occupationally related. Seven patients (43.7%) were directly exposed. Of the 2 patients who were not confirmed to have occupationally-related asbestos exposure, 1 was a housewife (patient number 2) who was indirectly exposed to asbestos for 6 years when she washed the clothes of her son. He worked as an electrician in a company dealing with the repair of ovens, which had asbestos insulation. Interestingly, no asbestos-related disease has been detected in him thus far. The other patient (patient number 5) was a general worker in a shipyard for 28 years. Despite this, we were unable to establish a history of him either handling or being in the vicinity of asbestos containing materials. Thus, we were unable to confirm that his disease was occupationally related. The median time from first exposure to symptoms was 33.5 (range, 16 to 53) years.

All of our patients were found to have inoperable disease at diagnosis. One patient (patient number 3) underwent thoracotomy with the intention of an extrapleural pneumonectomy, but was found to have advanced disease intraoperatively. Pleurodesis was achieved utilising talc. She declined further palliative tumour-specific therapy. Three patients received palliative radiotherapy, none of whom responded. Patient 6 received gemcitabine and cisplatin, achieving stable disease for 12 months. Overall, 12 patients (75%) received best supportive care, of which 7 patients had talc pleurodesis for control of pleural effusion. All patients received care by a home palliative service or an in-patient hospice facility

TABLE I: CLINICAL FEATURES OF OUR CASE SERIES OF PATIENTS WITH MALIGNANT MESOTHELIOMA

Pt/Age/Sex	Presenting features	Onset of symptoms to diagnosis (weeks)	Histologic subtype	Diagnosis confirmed	Treatment received	Survival (mo)
Pleural mesothelioma						
1/60/M	Dyspnoea, chest pain and pleural effusion	24	Epitheloid	VATS	BSC, TP	6
2/61/M	Dyspnoea, chest pain and pleural effusion	19	Biphasic	VATS	RT, TP	20*
3/69/F	Cough, pleural mass	4	Biphasic	CT-guided biopsy	BSC	8*
4/78/M	Dyspnoea, pleural effusion	68	Biphasic	CT-guided biopsy	BSC	1
5/66/M	Dyspnoea, pleural effusion	4	Epitheloid	VATS	BSC, TP	12
6/58/M	Dyspnoea, pleural effusion, weight loss	21	Epitheloid	VATS	CTX, TP	27*
7/70/M	Dyspnoea, pleural effusion	4	Epitheloid	VATS	BSC, TP	4
8/70/M	Dyspnoea, pleural effusion, weight loss	8	Epitheloid	VATS	BSC, TP	9
9/62/M	Dyspnoea, pleural effusion	24	Epitheloid	VATS	RT, TP	12
10/59/M	Cough, weight loss, pleural mass	23	Biphasic	Thoracotomy	RT	6
11/47/M	Dyspnoea, pleural effusion	12	Epitheloid	VATS	BSC	7
12/67/M	Dyspnoea, pleural effusion, weight loss	8	Epitheloid	VATS	BSC	5
13/46/M	Dyspnoea, pleural effusion	12	Biphasic	Thoracotomy	BSC	8
Peritoneal mesothelioma						
14/57/M	Abdominal pain, peritoneal mass, weight loss	3	Epitheloid	Laparotomy	BSC	3
15/65/M	Abdominal pain, weight loss, ascites	12	Epitheloid	Laparotomy	BSC	11
16/52/M	Ascites	8	Epitheloid	Laparoscopy	BSC	2

BSC: best supportive care; CTX: chemotherapy; RT: radiotherapy; TP: talc pleurodesis; VATS: video-assisted thoracoscopic surgery

*: patients alive at time of analysis

TABLE II: EXPOSURE TO ASBESTOS IN OUR CASE SERIES OF 16 PATIENTS WITH MESOTHELIOMA

Pt	Occupation	Industry	Exposure	Duration of exposure (y)
1	Fitter	Shipyard	Indirect	7
2	General Worker	Shipyard	Indirect	2
3	Housewife	Housewife*	Indirect	6
4	Mechanic	Power station	Indirect	11
5	General worker	Shipyard	Indirect	28
6	Mixer and packer	Cement factory	Direct	7
7	General worker	Cement factory	Direct	21
8	Electrician	Shipyard	Direct	32
9	Pipe fitter	Shipyard	Direct	35
10	General worker	Shipyard	Indirect	10
11	Electrician	Power station	Indirect	16
12	Ship cleaner	Shipyard	Indirect	4
13	Sailor	Shipping	Indirect	9
14	Packer	Cement factory	Direct	4
15	General worker	Cement factory	Direct	5
16	Pipe fitter and welder	Shipyard	Direct	4

Pt: patient

* This patient was indirectly exposed to asbestos for 6 years as she washed the clothes of her son, who works as an electrician in a company dealing with the repair of ovens, which had asbestos insulation.

At the time of analysis, 3 patients were still alive. The median survival using Kaplan-Meier analysis was 6 months. There was no difference in survival between patients with epithelioid tumours and biphasic tumours (Fig. 1).

Discussion

The incidence of mesothelioma seems to be increasing in Singapore. The only previously published series of all notified cases from Singapore more than a decade ago reported 16 cases over a 17-year period,³ as compared to 16 cases from our hospital alone over a 5-year period. This is consistent with other observational studies. In Britain, the incidence of malignant mesothelioma is expected to increase from 1300 to 3000 cases per year over the next 20 years.⁵ This is mainly because of the long latent period, about 41 years⁶ between exposure and disease and the late recognition of the association between asbestos exposure and malignant mesothelioma. As Singapore's industrial period began about 30 years ago, more cases would be expected.³

All of our patients were exposed to asbestos fibres. It is extremely rare to encounter a case without asbestos exposure.⁷ Patient number 3 illustrates the need to consider non-occupational exposure to asbestos when occupational exposure is not apparent. The association between non-occupational exposure to asbestos and mesothelioma is being increasingly recognised. Schneider et al⁸ have reported a series of 5 women who developed mesothelioma from

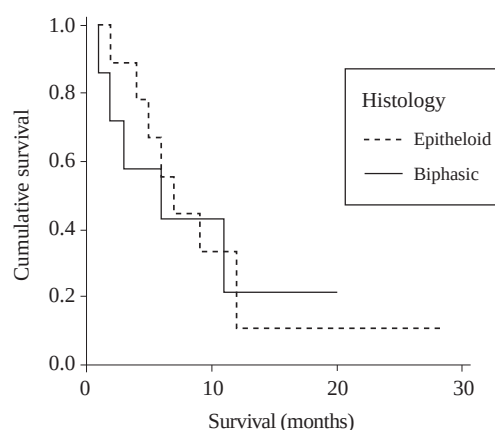


Fig. 1. Kaplan-Meier curve showing cumulative survival in our patients with 2 subtypes of mesothelioma (epithelioid and biphasic; median survival 7 versus 6 months, respectively. ($P = 0.83$ using Mantel Cox log-rank test)

cleaning the contaminated work-clothes and shoes of their husbands. In the largest case-control study examining the risk of mesothelioma associated with non-occupational asbestos exposure, domestic exposure to asbestos was associated with an odds ratio of 4.81.⁹ The study also suggested that there was a dose-response pattern in the intensity of domestic exposure.

Our experience with thoracentesis and closed pleural biopsies is similar to previously published results. The sensitivity of thoracentesis in the diagnosis of MPM is typically poor, ranging from 26% to 32%.^{10,11} Cytogenetic analysis of the pleural fluid may improve the sensitivity to 56%¹¹ but this approach remains largely investigational. The addition of a closed pleural biopsy has not improved sensitivity dramatically, only achieving a diagnosis in 30% to 38.7%.^{10,12} Thoracoscopy, however, has been shown to be highly accurate in the diagnosis of MPM. In a series of 173 patients, thoracoscopy achieved histologic diagnosis in 98% of patients.¹⁰ The procedure was well tolerated, the commonest being a fever in 14.7% of patients. Thoracoscopy also has the advantage of direct visualisation of the pleural cavity, thus improving staging and allowing pleurodesis, in patients deemed inoperable. Thoracoscopic talc poudrage affords excellent control of malignant pleural effusions, with reported success rates of up to 92.7%.¹³

Currently, malignant mesothelioma remains a uniformly fatal disease and no intervention has been shown to be curative.² No chemotherapeutic regimen has proven survival benefit, or shown to be superior to best supportive care.¹⁴ It is relatively resistant to radiotherapy and the circumferential dissemination around the hemithorax makes it difficult to deliver adequate doses without significant toxicity to the underlying structures.² Although radiotherapy has been shown to reduce pain and improve symptoms in 49% to 62% of patients,¹⁵⁻¹⁸ only 2 of our patients had chest

pain, neither of whom responded. Consequently, most of our patients (68.7%) received best supportive care only.

Because of the lack of benefit of specific anti-tumour therapy, symptom palliation is an important goal. It is recommended that all patients with malignant mesothelioma be under the care of a specialist palliative care team or a pain relief service.¹⁴

The median survival of 6 months in our series was found to be comparable to previously published results, which ranged from 5 to 14 months.^{14,19} Mesothelioma of the epitheloid sub-type confers a better prognosis.²⁰⁻²² As an example, in one study by Johansson et al,²² patients with purely epithelial mesotheliomas survived significantly longer than those with a sarcomatoid component (674 days versus 471 days; $P = 0.01$). In our study, however, we found no difference in survival between patients with the epitheloid subtype compared to the biphasic variety. This lack of difference likely reflects our small number of patients.

In our study, malignant mesothelioma is strongly associated with occupational asbestos exposure. As such, it is important that a detailed occupational history be taken for all cases of mesothelioma, starting from the very first job. Well-established industries where occupational asbestos exposure occurs include the shipyard, power stations, construction, asbestos cement factories and industries dealing with insulation. All cases of mesothelioma should be notified to the Ministry of Manpower as the patient may benefit from Workmen's compensation. Malignant mesothelioma unfortunately remains a devastating illness, with a poor prognosis and little hope for cure. A high index of suspicion is needed and early thoracoscopy may be indicated in patients presenting with a pleural effusion and exposure to asbestos.

Acknowledgements

We would like to acknowledge the following: Ms Stephanie Fook Cheong, Biostatistician, Department of Clinical Research, Singapore General Hospital for her kind assistance in statistical analyses and Dr Chuah Khoon Leong, Consultant, Department of Pathology, Singapore General Hospital for reviewing the histopathologic specimens of our patients.

REFERENCES

1. Armstrong B, Musk A, Baker J, Hunt J, Newall C, Henzell H, et al. Epidemiology of malignant mesothelioma in Western Australia. *Med J Aust* 1984; 141:86-8.
2. Lee Y C, Light R W, Musk A W. Management of malignant pleural mesothelioma: a critical review. *Curr Opin Pulm Med* 2000; 6:267-74.
3. Ho S F, Lee H P, Phoon W H. Malignant mesothelioma in Singapore. *Br J Ind Med* 1987; 44:788-9.
4. Lee H S, Phoon W S, Wang S Y T, Tan K P. Occupational respiratory diseases in Singapore. *Singapore Med J* 1996; 37:160-4.
5. Peto J, Hodgson J T, Matthews F E, Jones J R. Continuing increase in mesothelioma mortality in Britain. *Lancet* 1995; 345:535-9.
6. Yates D H, Corrin B, Stidolph P N, Browne K. Malignant mesothelioma in south east England: clinicopathologic experience of 272 cases. *Thorax* 1997; 52:507-12.
7. Hubbard R. The aetiology of mesothelioma: are risk factors other than asbestos exposure important? *Thorax* 1997; 52:496-7.
8. Schneider J, Straif K, Woitowitz H J. Pleural mesothelioma and household asbestos exposure. *Rev Environ Health* 1996; 11:65-70.
9. Magnani C, Agudo A, Gonzalez C A, Andron A, Calleja A, Chellini E, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. *Br J Cancer* 2000; 83: 104-11.
10. Boutin C, Rey F. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 1: Diagnosis. *Cancer* 1993; 72:389-93.
11. Renshaw A A, Dean B R, Antman K H, Sugarbaker D J, Cibas E S. The role of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma. *Chest* 1997; 111:106-9.
12. Whitaker D, Shilkin K B. Diagnosis of pleural malignant mesothelioma in life – a practical approach. *J Pathol* 1984; 143:147-75.
13. Cardillo G, Facciolo F, Carbone L, Regal M, Corzani F, Ricci A, et al. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. *Eur J Cardiothorac Surg* 2002; 21:302-5.
14. British Thoracic Society Standards of Care Committee. Statement of malignant mesothelioma in the United Kingdom. *Thorax* 2001; 56: 250-65.
15. Gordon W, Antman K H, Greenberger J S, Weichselbaum R R, Chaffey J T. Radiation therapy in the management of patients with mesothelioma. *Int J Radiat Oncol Biol Phys* 1982; 8:19-25.
16. Bissett D, Macbeth F R, Cram I. The role of palliative radiotherapy in malignant mesothelioma. *Clin Oncol* 1991; 3:315-7.
17. Davis S R, Tan L, Ball D L. Radiotherapy in the treatment of malignant mesothelioma of the pleura, with special reference to its use in palliation. *Australas Radiol* 1994; 38:212-4.
18. Ball D L, Cruikshank D G. The treatment of malignant mesothelioma of the pleura: a review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990; 13:4-9.
19. Ribak J, Lillis R, Suzuki Y, Penner L, Selikoff I J. Malignant mesothelioma in a cohort of asbestos insulation workers: clinical presentation, diagnosis and causes of death. *Br J Ind Med* 1988; 45:182-7.
20. Hillerdal G. Malignant mesothelioma 1982: a review of 4710 published cases. *Br J Dis Chest* 1983; 77:321-43.
21. Law M R, Gregor A, Hodson M E, Bloom H J, Turner-Warwick M. Malignant mesothelioma of the pleura: a study of 52 treated and 64 untreated patients. *Thorax* 1984; 39:255-9.
22. Johansson L, Linder C J. Aspects of histopathologic subtype as a prognostic factor in 85 pleural mesotheliomas. *Chest* 1996; 109:109-14.