Malignant Mesothelioma and Central Nervous System Metastases

Report of Two Cases, Pooled Analysis, and Systematic Review

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Abstract

Rationale: The incidence and patterns of metastatic disease to the central nervous system (CNS) from malignant mesothelioma are not well characterized.

Objectives: We describe the treatment of two cases of pleural mesothelioma with CNS metastases. We also report the results of a systematic review with pooled data analysis of CNS metastases from malignant mesothelioma.

Methods: PubMed, Scopus, EMBASE, and Web of Science were searched to identify relevant published studies. Inclusion criteria for the pooled analysis were any clinical or autopsy study in which patients had a confirmed histological diagnosis of malignant mesothelioma and CNS metastasis was identified by autopsy, clinical pathological specimen, or compelling radiographic imaging. Case reports were excluded from the pooled analysis but were incorporated into the discussion. One hundred forty-one potentially relevant references were identified. Seven studies including 655 patients were included in the pooled analysis. Ninety-seven additional cases were identified and incorporated into the discussion. A systematic review of the literature is provided with pooled data analysis.

Measurements and Main Results: CNS involvement of malignant mesothelioma may occur by hematogenous spread or by local extension. Some cases may represent tumor dedifferentiation to a more aggressive histologic subtype. Surgery or stereotactic therapies may play a role for select patients; however, rapid recurrence has been reported.

Conclusions: The prognostic significance of CNS disease is not well characterized. Clinicians should consider and identify CNS involvement in patients with new or evolving neurologic symptoms because early identification may allow for palliative intervention.

Keywords: malignant mesothelioma; central nervous system; brain; spine

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Mesothelioma is a locally invasive tumor that progresses via local invasion or extension. Distant hematogenous metastasis may occur; however, metastasis to the central nervous system (CNS) has traditionally been thought to be rare. We herein present two cases of malignant mesothelioma with metastases to the brain and offer a systematic review and pooled analysis of the literature of the CNS manifestations of malignant mesothelioma.

Cases

Patient 1

A 60-year-old man was diagnosed with pleural malignant mesothelioma (malignant mesothelioma) of the epithelioid histologic subtype in June 2010. He was treated with six cycles of pemetrexed and cisplatin from July to November 2010. His disease progressed through this regimen, and he was subsequently treated with four cycles of vinorelbine from January to April 2011, three cycles of gemcitabine from May to July 2011, two cycles of paclitaxel in August 2011, and two cycles of carboplatin from October to December 2011. Despite treatment, his disease continued to progress, prompting evaluation at the National Institutes of Health in March 2012, where he was enrolled and treated as part of a phase I clinical trial.

The patient received three cycles of therapy, but restaging in July 2012 showed

disease progression. At that time his symptoms were right chest pain and mild dyspnea on exertion, which were stable. He also reported mild residual bilateral lower extremity paresthesias related to prior chemotherapy treatments. He was withdrawn from the study and subsequently treated as part of another phase I clinical trial.

In late August 2012, the patient noted weakness of his left arm and leg. He presented to a local emergency department, and MRI of the brain demonstrated three discrete enhancing masses in the right cerebral hemisphere with surrounding vasogenic edema. Figures 1A and 1B are T1-weighted axial MRI images depicting two of the masses. He underwent biopsy of the right posterior temporal lobe followed by treatment with dexamethasone and palliative whole brain radiation therapy in September 2012. Whereas the original pleural tumor biopsy revealed tubulopapillary epitheliod subtype on hematoxylin and eosin (H&E) stain (Figure 1C) with cell surface staining for mesothelin (Figure 1D), H&E staining of the right temporal brain lesion revealed a dedifferentiation to the sarcomatoid subtype (Figure 1E) with loss of cell surface staining for mesothelin (Figure 1F). The brain lesion also stained positive for calretinin and keratin-7 but was negative for CK5/6, isocitrate dehydrogenase 1, epithelial membrane antigen, glial fibrillary acidic protein, and WT-1.

The brain lesions did not respond to the systemic corticosteroid and radiation (3,500 cGy) therapies. The patient decided to forgo further therapy, pursued hospice care, and died in January 2013.

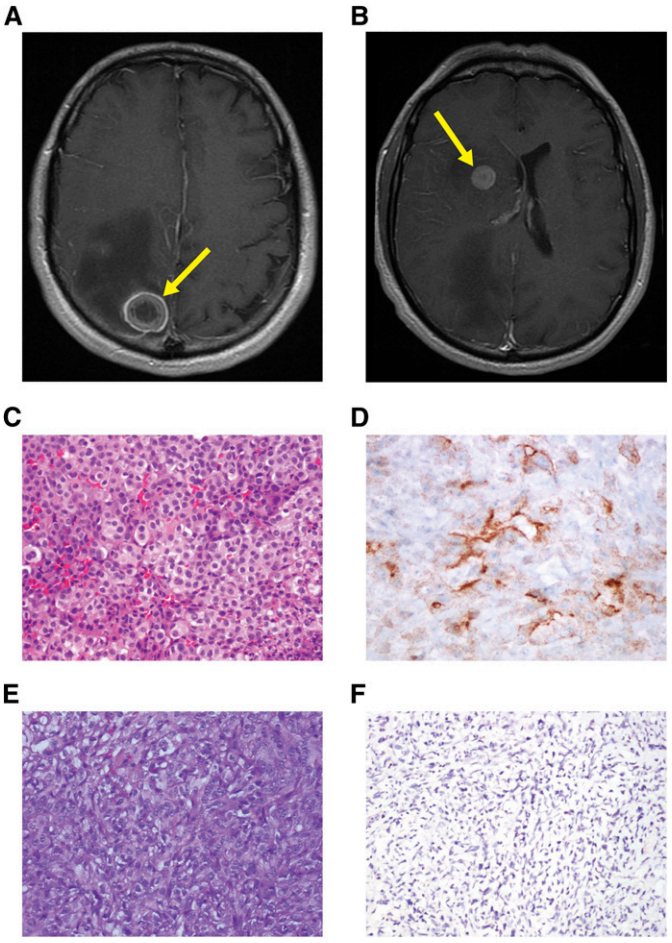

Figure 1. (*A* and *B*) T1-weighted axial MRI images depicting two of the brain metastases (*arrows*). Tissue from the original pleural tumor biopsy revealed tubulopapillary epitheliod mesothelioma on hematoxylin-and-eosin (H&E) stain (*C*) with cell surface staining for mesothelin (*D*). H&E staining of the right temporal brain lesion revealed dedifferentiation to sarcomatoid histology (*E*) with loss of cell surface staining for mesothelin (*F*).

Patient 2

A 59-year-old man was diagnosed with right-sided pleural malignant mesothelioma of epithelioid histologic subtype in September 2008. In November 2008, he commenced three cycles of pemetrexed and cisplatin; his disease progressed on this regimen, and he was referred to the National Cancer Institute in March 2009 for investigational therapy. His chief complaints were exertional dyspnea and right chest wall pain; he had no symptoms referable to CNS involvement. A protocol eligibility brain MRI demonstrated a single 3- to 4-mm enhancing lesion in the right precentral gyrus near the midline with a small amount of vasogenic edema but no mass effect (Figure 2A).

The patient underwent Stealth MRI and resection of the lesion in March 2009. Postoperative MRI showed total excision of the small tumor in the right motor strip. A repeat MRI performed 6 weeks after surgery showed a new 5-mm enhancing lesion in the left frontal white matter/superior aspect of the basal ganglia (depicted in the MRI axial FLAIR image in Figure 2B) consistent with a new metastatic lesion. H&E stain from the resection of the first brain lesion revealed findings consistent with solid epithelioid malignant mesothelioma (Figure 2C). Tumor cells stained positive for calretinin (Figure 2D), surface mesothelin (Figure 2E), keratin-8, CAM5.2, CK5/6 (focally), and WT-1 (focally) but stained negative for carcinoembryonic antigen (polyclonal and monoclonal), human mesothelial cell membrane antigen, and epithelial membrane antigen.

Methods

A systematic search was performed to capture published and unpublished studies and case reports of malignant mesothelioma involving CNS structures. PubMed, Scopus, EMBASE, and Web of Science were searched to identify relevant published studies. The search strategies were adapted to accommodate the unique searching features of each database, including database-specific MESH- and EMTREE-controlled vocabulary terms. Searches were not limited by date, language, or publication

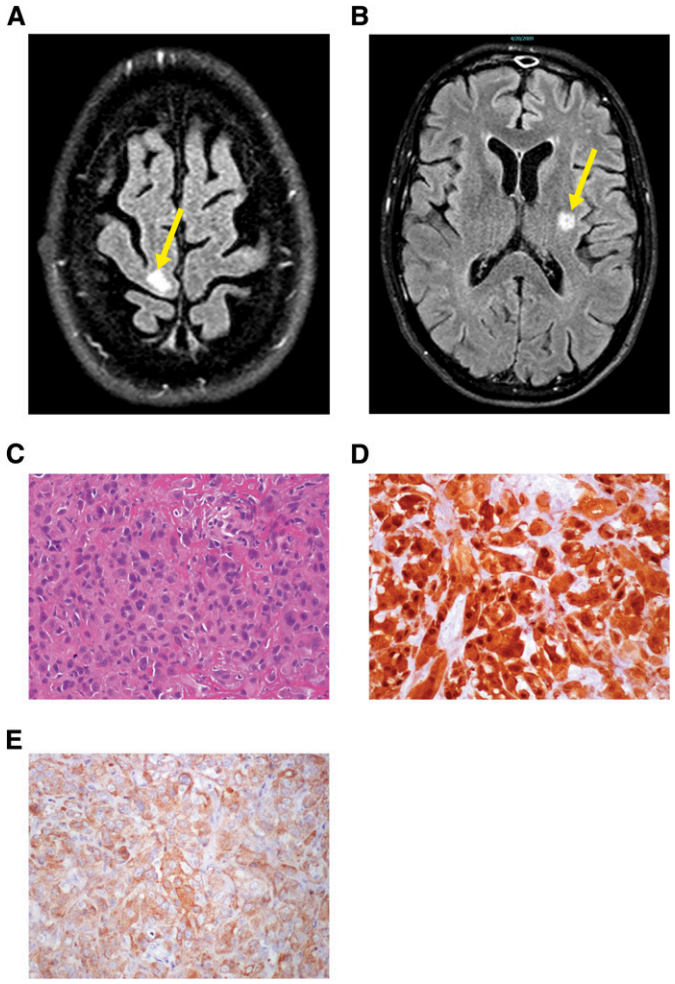

Figure 2. (*A*) MRI axial FLAIR image demonstrating a single 3- to 4-mm enhancing lesion in the right precentral gyrus near the midline (*arrow*). (*B*) MRI axial FLAIR image depicting the recurrent metastatic mesothelioma lesion (*arrow*). Hematoxylin-and-eosin stain from the resection of the first brain lesion revealed findings consistent with solid epithelioid malignant mesothelioma (*C*). Metastatic tumor cells stained positive for calretinin (*D*) and surface mesothelin (*E*).

status. The detailed search strategy is summarized in Appendix E1 in the online supplement. The cited and citing references of selected studies were also searched for additional relevant material. To minimize publication bias, relevant unpublished studies were identified by searching the Australian and New Zealand Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Cochrane Library, ClinicalTrials.gov, Current Controlled Trials, and Google.

Inclusion criteria were any clinical or autopsy study or report in which patient(s) had a confirmed histological diagnosis of malignant mesothelioma and CNS metastasis was identified by autopsy, clinical pathological specimen, or compelling radiographic imaging. Exclusion criteria for the pooled analysis were preclinical studies and case reports. Clinical and methodological diversity precluded combining these studies in a metaanalysis.

Results

The search strategy (Appendix E1) identified 141 potentially relevant references. The data from seven autopsy studies were pooled (Table 1). Of the included 655 patients, the prevalence of intracranial (brain and meningeal) metastases from malignant mesothelioma was 2.7%. In addition to the seven autopsy series and the two cases reported above, an additional 97 reported cases of malignant mesothelioma involving the CNS were identified. Each autopsy series included only persons with primary pleural malignant mesothelioma. Three series did report cases of peritoneal and intraabdominal metastases; however, no cases of intraabdominal metastases with intracranial metastases were reported (1–4). Twenty-eight cases were clinically or radiographically suspected and confirmed premortem (5–25). Forty-four cases were clinically suspected but were either not histologically confirmed (n = 26) (12, 14, 26–42) or were confirmed postmortem (n = 18) (23, 37, 43–53). An additional case was clinically suspected, but it was not specified whether histologic confirmation was pre- or postmortem (54). Additionally, 14 cases of unsuspected CNS disease were incidentally noted on autopsy (55–61).

The majority of CNS metastases identified from case reports (Table 2) resulted from pleural or pericardial disease (n = 77; 79%), with a small number from tunica vaginalis testes (n = 3; 3%). Seventeen cases were not specified. No cases of peritoneal primary disease metastasizing to the CNS were identified.

All histologic subtypes have been reported to metastasize to the CNS. Only 59 of the reported cases have specified the histologic subtype of the primary tumor, with the most common being sarcomatoid (n = 31), followed by biphasic (n = 14) and epithelioid (n = 14); 38 cases were not specified. Of the cases that reported the histologic subtype of the primary tumor (n = 59), 35 cases reported the histologic subtype of the metastatic lesion. Of the 35 cases that reported the histology on both the primary tumor and CNS metastasis, six cases displayed either less differentiated (2) or dedifferentiated (i.e., sarcomatoid; n = 4) subtypes (9, 62).

Discussion

Malignant mesothelioma is an aggressive tumor of serosal surfaces most closely linked to asbestos exposure, but ionizing radiation exposure and genetics may also be contributing risk factors (63, 64). The main determinants of prognosis for patients with malignant mesothelioma continue to be clinical factors and tumor differentiation (65). Tumor histology is the most important factor that influences patient survival, with

Table 1. Prevalence of intracranial metastases from malignant mesothelioma in autopsy studies

Reference	Patients (*n*)	Number with Brain or other Intracranial Metastases
Adams, 1986 (58)	92	2 (2%)
Finn, 2012 (67)	318	9 (3%)
Hartman, 1996 (1)	106	4 (3.8%)
Hulks, 1989 (2)	40	1 (2.5%)*
Huncharek, 1987 (3)	42	1 (2.3%)
Schlienger, 1969 (68)	25	0
Whitwell, 1971 (4)	32	1 (3%)*
Total	655	18 (2.7%)

*Metastases to meninges.

nonepithelioid histologic subtype being a negative prognostic indicator (65). Patients with sarcomatoid histology have the worst prognosis, and current therapies, such as surgery or chemotherapy, offer little benefit (66). Mesothelioma is most often a locally invasive tumor that progresses via local invasion or extension. Distant hematogenous metastasis may occur; however, CNS metastasis is thought to be rare.

The incidence of CNS metastasis from malignant mesothelioma is not known. When pooling the data from seven autopsy studies consisting of 655 patients, the prevalence of CNS (brain and meningeal) metastases from malignant mesothelioma was 2.7%; however, whether these lesions significantly alter clinical course remains unclear (1–4, 58, 67, 68). The clinical features vary depending on the CNS location involved, with the most commonly involved regions being the cerebral cortex, cerebellum, intracranial meninges, and spinal cord. Involvement of the midbrain, pons, or brainstem is less common.

Surgical resection, whole brain radiation, stereotactic spinal cord radiation, systemic corticosteroids, intrathecal or

Table 2. Role of histologic subtype in central nervous system metastasis of malignant mesothelioma

Primary Tumor Histology (n)	Primary Tumor Location (n)*	Diagnosis by Radiologic and Clinical Parameters (*n*)	Premortem Biopsy (*n*)	Postmortem Biopsy (*n*)	CNS Metastasis Histology (n)	Total Biopsy-Confirmed CNS Lesions (*n*)	CNS Histology Differed from Primary (*n*)	Reference
Epithelioid (14)	Pleural (14)	4	7	3	E (3) S (2) NS (5)	10	2	5, 8, 20, 21, 35, 41, 51, 54, 62, 70–73
Biphasic (14)	Pleural (12)	3	3	6	B (6) S (2) NS (1)	9	2	6, 7, 9, 25, 26, 44, 47, 61, 74–76
	NS (2)			2	NS (2)	2	—	1
Sarcomatoid (31)	Pleural (28)	5	10	13	S (22) NS (1)	23	—	10, 11, 16–19, 22, 24, 29, 30, 36, 43, 49, 50, 52, 53, 55, 56, 59, 60, 77–80
	Tunica Vaginalis Testes (1)	1	—	—		0	—	42
	NS (2)			2	NS (2)	2	—	1
Not specified (38)	Pleural (23)	14	—	9	NS (9)	9	—	13, 15, 23, 27, 28, 31, 34, 37–39, 45, 48, 55, 75, 81, 82
	Tunica Vaginalis Testes (2)	1	—	1	NS (1)	1	—	14
	NS (13)	1		12	NS (12)	12		57, 58, 83–85
Total	97	29	20	48	E (3) B (6) S (26) NS (33)	35	4	

Definition of abbreviations: B = biphasic; CNS = central nervous system; E = epithelioid; NS = not specified; S = sarcomatoid.
*No cases of peritoneal mesothelioma with metastasis to the CNS were identified.

systemic chemotherapy, and immunotherapy have been reported as treatment modalities with only rare cases of therapeutic response (35). Similar to case 1, the available literature suggests that 11% of cases with CNS metastases may differ histologically from the primary tumor and may even represent histologic dedifferentiation to a more aggressive histologic subtype. Unique to case 2 in this series is the fact that within 6 weeks of resection a new and larger remote metastasis was identified in the contralateral cerebral hemisphere. The recurrence of brain metastases within 5 to 7 months of surgical excision (62), or after regression in response to systemic chemotherapy, has been reported (35).

The prognosis of CNS mesothelioma is poor. It generally represents a late finding, and for cases diagnosed premortem survival is commonly on the order of weeks to months. Whereas brain metastases result from hematogenous spread, disease affecting the spinal cord most often arises from direct tumor invasion through the neural foramen. For patients who present with surgically resectable disease and good functional status, biopsy with surgical resection may be useful to secure the diagnosis. Cases of new primary CNS malignancies (e.g., glioblastoma multiforme) have been described in this patient population (69). Although less common than intrathoracic, chest wall, intraperitoneal, and abdominal wall metastasis, spread of malignant mesothelioma to the CNS may be an underappreciated yet important metastatic pattern of malignant mesothelioma.

Conclusions

Malignant mesothelioma may metastasize to the CNS via hematogenous spread or local extension. Although the overall incidence of CNS metastasis is unknown, the incidence of intracranial metastasis is nearly 3%. The absence of cases of primary peritoneal malignant mesothelioma metastasizing to the CNS may represent selection bias; nonetheless, it is intriguing and warrants formal investigation. Roughly 11% of cases may represent dedifferentiation of the primary tumor to a more aggressive histologic subtype. Surgery or stereotactic therapies may play a role in select situations; however, rapid recurrence has been reported. The prognostic significance of CNS disease is not well characterized. Clinicians should consider and seek to identify CNS involvement in patients with new or changing neurologic symptoms because early identification may allow for palliative intervention. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Hartmann CA, Schutze H. Frequency of metastases and survival in histologic subtypes of pleural mesothelioma: autopsy study of 106 cases [in German]. *Pathologe* 1992;13:259–268.
2 Hulks G, Thomas JS, Waclawski E. Malignant pleural mesothelioma in western Glasgow 1980-6. *Thorax* 1989;44:496–500.
3 Huncharek M, Muscat J. Metastases in diffuse pleural mesothelioma: influence of histological type. *Thorax* 1987;42:897–898.
4 Whitwell F, Rawcliffe RM. Diffuse malignant pleural mesothelioma and asbestos exposure. *Thorax* 1971;26:6–22.
5 Asoh Y, Nakamura M, Maeda T, Shiogai T, Ogashiwa M, Takeuchi K, Watanabe K, Tanaka U, Matsuo E. Brain metastasis from primary pericardial mesothelioma: case report [in Japanese]. *Neurol Med Chir (Tokyo)* 1990;30:884–887.
6 Wroński M, Burt M. Cerebral metastases in pleural mesothelioma: case report and review of the literature. *J Neurooncol* 1993;17:21–26.
7 Bohn U, Gonzalez JL, Martin LM, Casado A, Diaz-Rubio E, Aragoncillo P. Meningeal and brain metastases in primary malignant pericardial mesothelioma. *Ann Oncol* 1994;5:660–661.
8 Kitai R, Kabuto M, Kawano H, Uno H, Kobayashi H, Kubota T. Brain metastasis from malignant mesothelioma: case report. *Neurol Med Chir (Tokyo)* 1995;35:172–174.
9 Krishnaraj N, Leen GL, Kane P, Edge CJ, Murphy SA, Gribbin HR. Malignant mesothelioma presenting as stroke: a case report. *Eur J Cancer Care (Engl)* 2003;12:365–368.
10 Mah E, Bittar RG, Davis GA. Cerebral metastases in malignant mesothelioma: case report and literature review. *J Clin Neurosci* 2004;11:917–918.
11 Grumme T, Bingas B. Intracranial formation of metastases of diffuse pleuro-mesothelioma [in German]. *Zentralbl Neurochir* 1973;34: 41–48.
12 Brenner J, Sordillo PP, Magill GB. Malignant mesothelioma in children: report of seven cases and review of the literature. *Med Pediatr Oncol* 1981;9:367–373.
13 Hillard VH, Liu JK, Kwok A, Schmidt MH. Perineural spread of malignant mesothelioma resulting in an intradural spinal cord mass: case report. *J Neurooncol* 2007;81:185–189.
14 Mathew BS, Jyothirmayi R, Nair MK. Case report: malignant mesothelioma of tunica vaginalis testis presenting with spinal metastasis: report of two cases. *Br J Radiol* 1996;69:1067–1068.
15 Mikhael MA, Paige ML, Thayer C. Computerized tomography of malignant pleural mesothelioma with spinal canal invasion. *Comput Radiol* 1982;6:11–15.
16 Muljono A, Ng T, McMaster J, Dexter M. Choroid plexus metastases from pleural sarcomatoid mesothelioma. *Pathology* 2008;40: 530–532.
17 Okura H, Suga Y, Akiyama O, Kudo K, Tsutsumi S, Abe Y, Yasumoto Y, Ito M, Izumi H, Shiomi K. Pleural malignant mesothelioma causing cord infiltration through the nerve root: case report. *Neurol Med Chir (Tokyo)* 2009;49:167–171.
18 Payer M, von Briel T. Intradural pleural malignant mesothelioma. *Acta Neurochir (Wien)* 2007;149:1053–1056, discussion 1056.
19 Petit BM, Ruffie P, Varlet P, Ciolocca C. Meningeal metastasis of pleural mesothelioma [in French]. *Rev Mal Respir* 2001;18:661–663.
20 Soyuer I, Soyuer S, Canöz O, Coşkun S, Balkanli S. Educational case report - self-assessment: three patients with unusual metastases. *Cytopathology* 2004;15:2, 58–62.
21 Steel TR, Allibone J, Revesz T, D'Arrigo C, Crockard HA. Intradural neurotropic spread of malignant mesothelioma: case report and review of the literature. *J Neurosurg* 1998;88:122–125.
22 Richter H, Hildebrandt G, Heilbronner R. Intradural perineural spread of mesothelioma causing myelopathy by tethering of the spinal cord. *J Neurol Surg A Cent Eur Neurosurg* 2012;73:111–115.
23 Akagi S, Ozaki S, Kishimoto T. A case of splenic hemorrhage in the course of malignant mesothelioma [in Japanese]. *Nihon Kokyuki Gakkai Zasshi* 2004;42:253–256.
24 Winfree CJ, Mack WJ, Sisti MB. Solitary cerebellar metastasis of malignant pleural mesothelioma: case report. *Surg Neurol* 2004;61: 174–178, discussion 178–179.
25 Marzullo A, Scattone A, Rossi R, Cimmino A, Punzi A, Corsi F, Cavone D, Lettini T, Serio G. Malignant pleural mesothelioma presenting with symptomatic brain metastases: report of a case. *Rom J Morphol Embryol* 2013;54:649–653.
26 Huncharek M, Muscat J, Capotorto J. Pleural mesothelioma in a lift mechanic. *Br J Ind Med* 1989;46:500–501.
27 Sridhar KS, Hussein AM, Ganjei P, Thurer RJ, Raskin N, Beattie EJ. Brain metastases in malignant pleural mesothelioma: case report and review of the literature. *Am J Clin Oncol* 1989;12:222–228.
28 Murray JB, Neilly JB, Hadley D, Moran F, McKean M. Diffuse meningeal thickening associated with pleural mesothelioma. *Thorax* 1990;45: 70–71.

29 Nielsen C, Hansen IM. Sarcomatous mesothelioma of the pleura with cerebral metastases. *Med J Aust* 1990;153:625–626.
30 Davies MJ, Ahmedzai S, Arsiwala SS, Leverment JN. Intracranial metastases from malignant pleural mesothelioma. *Scand J Thorac Cardiovasc Surg* 1995;29:97–99.
31 Oksüzoğlu B, Yalçin S, Erman M, Dağdelen S. Leptomeningeal infiltration of malignant mesothelioma. *Med Oncol* 2002;19:167–169.
32 Huncharek M, Bseiso A, Hutchins L, Warner J. Presentation of malignant pleural mesothelioma with symptomatic brain metastasis: report of a case. *Tumori* 2004;90:424–427.
33 Kanbay A, Oguzulgen KI, Ozturk C, Memis L, Demircan S, Kurkcuoglu C, Akyurek N, Kurul C. Malignant pleural mesothelioma with scalp, cerebellar, and finger metastases: a rare case. *South Med J* 2007; 100:63–65.
34 Hurmuz P, Zorlu F, Cansiz C, Emri S. Malignant pleural mesothelioma with brain metastasis. *J BUON* 2009;14:123–125.
35 Colleoni M, Liessi G, Avventi C, Pancheri F, Sgarbossa G, Vicario G, Manente P. Response to chemotherapy of brain metastases from malignant pleural mesothelioma. *Tumori* 1996;82:456–458.
36 Chamberlain MC, Eaton KD, Fink JR, Tredway T. Intradural intramedullary spinal cord metastasis due to mesothelioma. *J Neurooncol* 2010;97:133–136.
37 Gijtenbeek JM, Brouwer HI, Boerman RH, Wiggenraad RG, Vecht CJ, Smitt PA. Extensive epidural cufflike growth of malignant pleural mesothelioma causing spinal cord compression. *J Thorac Cardiovasc Surg* 2002;124:200–202.
38 Jegede K, Rohatgi N, Dunwoodie E, Crosse B. Po cerebral metastases in malignant mesothelioma. *Ann Oncol* 2009;20:v26.
39 Lee AW, Nikitins I, Pozza C, Koblar SA. Pleural mesothelioma with extension into the thoracic spinal cord. *Intern Med J* 2005;35: 195–196.
40 Nakamura Y, Sato A, Takahashi S, Kanazawa T, Ito H, Maesawa C, Masuda T, Inoue H. Primary pericardial mesothelioma presenting as constrictive pericarditis. *Respiratory Medicine Extra* 2005;1:107–109.
41 Rojas JL, Alfageme I, De la Cruz I, Reyes N, Muñoz J. Radicular involvement and medullary invasion from a malignant mesothelioma. *Respiration* 2001;68:106–108.
42 Melhouf MM, Elghazi el-A, Errihani H, Sifat H, Hadadi K, Kanouni L, Mansouri H, Alhilal M, Mansouri A, Benjaafar N, Elgueddari B el-K. Paratesticular malignant mesothelioma: presentation of a case [in French]. *Ann Urol (Paris)* 1998;32:172–174.
43 Kaye JA, Wang AM, Joachim CL, Seltzer SE, Cibas E, Skarin A, Antman KH. Malignant mesothelioma with brain metastases. *Am J Med* 1986; 80:95–97.
44 Chahinian AP, Kirschner PA, Gordon RE, Szrajer L, Holland JF. Usefulness of the nude mouse model in mesothelioma based on a direct patient-xenograft comparison. *Cancer* 1991;68:558–560.
45 Lewis RA. Antemortem recognition of brain metastases in malignant mesothelioma. *Thorax* 1990;45:983–984.
46 Falconieri G, Grandi G, DiBonito L, Bonifacio-Gori D, Giarelli L. Intracranial metastases from malignant pleural mesothelioma; report of three autopsy cases and review of the literature. *Arch Pathol Lab Med* 1991;115:591–595.
47 Kawai A, Nagasaka Y, Muraki M, Fukuoka M, Satou T, Kimura M, Hashimoto S. Brain metastasis in malignant pleural mesothelioma. *Intern Med* 1997;36:591–594.
48 Kobayashi S, Ida M, Matsui O, Kuroda E, Isobe T, Matsubara F. Lipomatous change in a brain metastasis from malignant pleural mesothelioma. *Neuroradiology* 2001;43:159–161.
49 Petrovic BD, Kozic DB, Semnic RR, Prvulovic M, Djilas-Ivanovic D, Sener RN, Klem I. Leptomeningeal metastasis from malignant pleural mesothelioma. *AJNR Am J Neuroradiol* 2004;25:1223–1224.
50 Cooper D. Malignant mesothelioma invading the spinal canal. *Postgrad Med J* 1974;50:718–723.
51 de Pangher Manzini V, Chizzola A, Brollo A, Bianchi C. Diffuse neoplastic infiltration of leptomeninges by malignant pleural mesothelioma [in Italian]. *Recenti Prog Med* 1989;80:16–17.
52 Sato M, Saito T, Yamaguchi K, Sakuma H. A case of acute subdural hematoma due to dural metastasis from malignant pleural mesothelioma [in Japanese]. *No Shinkei Geka* 1994;22:247–251.
53 Wild K, Sankaran P, Nagy A, Sington J. Meningeal and brainstem infiltration by a malignant mesothelioma. *BMJ Case Rep* 2010;pii: bcr0220102755.
54 Hortobágyi T, Thomas NW, King A. 71-year-old man with multiple metastases to the brain: malignant mesothelioma with cerebellar metastasis. *Neuropathology* 2008;28:103–105.
55 Walters JL Jr, Martinez AJ. Malignant fibrous mesothelioma: metastatic to brain and liver. *Acta Neuropathol* 1975;33:173–177.
56 Schwechheimer K, Butzengeiger M. Brain metastases in malignant fibrous mesothelioma: case report and review of the literature. *Acta Neuropathol* 1983;60:301–304.
57 Brenner J, Sordillo PP, Magill GB, Golbey RB. Malignant mesothelioma of the pleura: review of 123 patients. *Cancer* 1982;49:2431–2435.
58 Adams VI, Unni KK, Muhm JR, Jett JR, Ilstrup DM, Bernatz PE. Diffuse malignant mesothelioma of pleura: diagnosis and survival in 92 cases. *Cancer* 1986;58:1540–1551.
59 Harrison RN. Sarcomatous pleural mesothelioma and cerebral metastases: case report and a review of eight cases. *Eur J Respir Dis* 1984;65:185–188.
60 Hirano H, Maeda H, Sawabata N, Okumura Y, Takeda S, Maekura R, Ito M, Maeda T, Nakane S, Uematsu K. Desmoplastic malignant mesothelioma: two cases and a literature review. *Med Electron Microsc* 2003;36:173–178.
61 Bierhoff E, Pfeifer U. Malignant mesothelioma arising from a benign mediastinal mesothelial cyst. *Gen Diagn Pathol* 1996;142:59–62.
62 Ishikawa T, Wanifuchi H, Abe K, Kato K, Watanabe A, Okada Y. Brain metastasis in malignant pleural mesothelioma presenting as intratumoral hemorrhage. *Neurol Med Chir (Tokyo)* 2010;50: 1027–1030.
63 Goodman JE, Nascarella MA, Valberg PA. Ionizing radiation: a risk factor for mesothelioma. *Cancer Causes Control* 2009;20: 1237–1254.
64 Robinson BW, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N, Winzell P, Hellstrom KE, Hellstrom I. Mesothelin-family proteins and diagnosis of mesothelioma. *Lancet* 2003;362:1612–1616.
65 Miller AC, Hassan R. Clinical and pathological features are still the best determinants of prognosis in mesothelioma. *Oncology (Williston Park)* 2012;26:1176, 1178, 1180.
66 Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. *Chest* 2009;136:888–896.
67 Finn RS, Brims FJH, Gandhi A, Olsen N, Musk AW, Maskell NA, Lee YCG. Postmortem findings of malignant pleural mesothelioma: a two-center study of 318 patients. *Chest* 2012;142:1267–1273.
68 Schlienger M, Eschwège F, Blaché R, Depierre R. Malignant pleural mesothelioma: study of 39 cases, 25 by autopsy [in French]. *Bull Cancer* 1969;56:265–308.
69 Levy A, Assouline A, Rivera S, Chargari C, Tai P. Role of conservative (palliative) care-only in the management of advanced malignant pleural mesothelioma. *Anticancer Res* 2012;32:4025–4027.
70 Zeckwar IT. Mesothelioma of the pleura. *Arch Intern Med* 1924;134: 191–205.
71 McNaughton WM, Broughton ME, Toner GC, Schwarz MA. Presentation of malignant pleural mesothelioma with cerebral metastases. *J R Soc Med* 1990;83:466–467.
72 Losi L, Cocchi R, Calbucci F, Eusebi V. Metastasis of pleural malignant mesothelioma to the brain and upper maxilla: description of 2 cases [in Italian]. *Pathologica* 2000;92:273–277.
73 Margery J, Grassin F, Le Moulec S, Ruffié P. Spinal cord compression from a malignant pleural mesothelioma [in French]. *Rev Pneumol Clin* 2005;61:112–114.
74 Cheeseman SL, Ranson MR. Cerebral metastases in malignant mesothelioma: a case report. *Eur J Cancer Care (Engl)* 1999;8: 104–106.
75 De Pangher Manzini V, Frigo A, Recchia L. Pancoast syndrome and spinal cord infiltration by malignant pleural mesothelioma: a case report in an asbestos-exposed woman. *Eur J Onc* 2003;8: 55–57.
76 Dewas S, Le Rhun E, Duhem R, Dansin E, Prevost B, Lartigau E. Solitary intramedullary metastasis from malignant pleural mesothelioma treated with CyberKnife®: a case report [in French]. *Rev Neurol (Paris)* 2011;167:185–186.

77 Schwalbe J. Zur Lehre von den primaren lungen- und brustfellgeschwülsten. *Deutsche Medicins Che Wochenschrift* 1891;17:1235–1238.
78 Satoh H, Togashi H, Ooizumi K. A case of pleural mesothelioma with brain metastasis. *J Jap Soc Int Med* 1987;76:893.
79 Okamura H, Kamei T, Mitsuno A, Hongo H, Sakuma N, Ishihara T. Localized malignant mesothelioma of the pleura. *Pathol Int* 2001;51: 654–660.
80 Mensi C, Termine L, Garberi A, Meroni S, Levi D, Balzarini L, Riboldi L. Spinal cord compression: an unusual presentation of malignant pleural mesothelioma: a case report and review of the literature. *Tumori* 2012;98:e92–e97.
81 Jänisch W, Zimmermann K. Frequency of metastases to the central nervous system of pleuramesotheliomas and lung carcinomas [in German]. *Zentralbl Neurochir* 1975;36:37–39.
82 Monzen Y. Radiotherapy for two cases of intramedullary spinal cord metastases. *Jap J Clin Rad* 2001;46:848–851.
83 Urschel HC, Paulson DL. Mesotheliomas of the pleura. *Ann Thorac Surg* 1965;1:559–574.
84 Oels HC, Harrison EG Jr, Carr DT, Bernatz PE. Diffuse malignant mesothelioma of the pleura: a review of 37 cases. *Chest* 1971;60:564–570.
85 Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of a 5-year experience, with special reference to radiotherapy. *Am J Clin Oncol* 1990;13:4–9.