JAOA CASE REPORT

Malignant Mesothelioma: A Case Presentation and Review

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Diffuse malignant mesothelioma is the most common primary tumor involving the pleura. Unfortunately, it also poses the most difficulty for physicians to diagnose and treat. Latency from the time of initial asbestos exposure, clinical features of chest pain and dyspnea, and radiographic findings of pleural effusion or pleural thickening are the characteristic features. Pathologic verification remains challenging. The primary distinctions to be made are between reactive and neoplastic mesothelial processes and between malignant mesothelioma and metastatic adenocarcinoma. Adequate tissue sampling is important to help diagnose malignant mesothelioma. This article describes a rare subtype of mesothelioma and illustrates the difficulty in establishing the diagnosis. Also included is a discussion of the clinical features, diagnostic dilemmas, and unsatisfactory outcome associated with this disease.

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Malignant mesotheliomas arise from mesothelial cells lining the visceral cavities. Patients with this malignancy generally do not have a complete response; malignant mesotheliomas pose both a diagnostic and a treatment challenge. The extremely long latency from time of initial asbestos exposure to tumor development and the lack of effective modes of therapy are barriers to eradicating the disease. Diagnosis requires recognition of patients at risk and knowledge of the typical clinical features of the disease. Effective treatment is limited for most patients with malignant mesotheliomas. Without treatment, the median survival time is between 4 and 13 months. Patients in whom the disease is detected early have a survival benefit from a multimodality therapeutic approach. A variety of new treatment modalities is available, but few patients have a complete response.

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Report of Case

A 76-year-old man was seen for evaluation of abnormal findings on a chest x-ray film revealing pleura-based densities. He had a medical history of Hodgkin disease dating back to 1961, at which time he had received a 6-week course of radiation therapy. He had mild aortic stenosis and hypertension.

Three months before the current evaluation, this patient began to have dyspnea, fatigue, cough, and wheezing. His dyspnea was initially associated with vigorous exertion, but within a few months, it occurred with mild exertion. In addition, he had rib pain on the lower right side and anorexia along with a 25-pound weight loss. He had no fever, hemoptysis, or leg edema.

The patient's daily medications included hydrocodone for pain plus a β-blocker, aspirin, and triamterene. He had no known allergies. His social history was notable for smoking one pack of cigarettes per day for 45 years. He had worked as a sales technician for an aluminum manufacturing company and was unaware of having been exposed to asbestos. He denied doing vehicular brake work or engaging in any activity that might have put him at risk for asbestos exposure. He had no family history of lung disease.

On physical examination, the patient appeared chronically ill but in no acute distress. His systolic blood pressure was 125 mm Hg and diastolic blood pressure, 80 mm Hg; pulse rate, 90/min and regular; and respirations, 22/min. The findings from the head, eyes, ears, nose, and throat examination were unremarkable. His sinuses were nontender and his neck, supple. His trachea was midline, and he had restricted chest wall movement on the right side. He had decreased breath sounds and dullness to percussion at the base of the right lung. Cardiac rhythm was regular, with an aortic stenosis systolic murmur noted. Examination of the extremities revealed no clubbing, cyanosis, or lower leg edema.

Baseline spirometry revealed a forced vital capacity (FVC) of 1500 mL (41% of predicted), forced expiratory volume in 1 second (FEV_1) of 1180 mL (49% of predicted), and FEV_1/FVC of 78%, findings that are consistent with a restrictive ventilatory process.

Chest x-ray film revealed an apparent pleural effusion on the right side (*Figure 1*); however, thoracentesis failed to



Figure 1. *Posteroanterior radiograph shows a large right-sided pleura-based confluence.*

obtain pleural fluid. A chest computed tomography (CT) scan was ordered and revealed a nodular pleura-based mass on the right side (*Figure 2*).

The patient then underwent an open thoracoscopy with visualization of the pleural space and a pleural biopsy (*Figure 3*). The biopsy revealed a malignant spindle-shaped cell neoplasm with mixed hypercellular and hypocellular areas that had collagenized foci. Nuclear atypia and mitotic figures were prominent, and a patchy lymphocytic infiltrate was present. The tumor was diffusely positive only for vimentin immunohistochemical stain. Tumor cells were negative for other immunohistochemical stains, including cytokeratin cocktail (high- and low-molecular-weight cytokeratin), calretinin, S100 stain, CD34, and cytokeratin 5/6. Outside pathologic consultation was required.

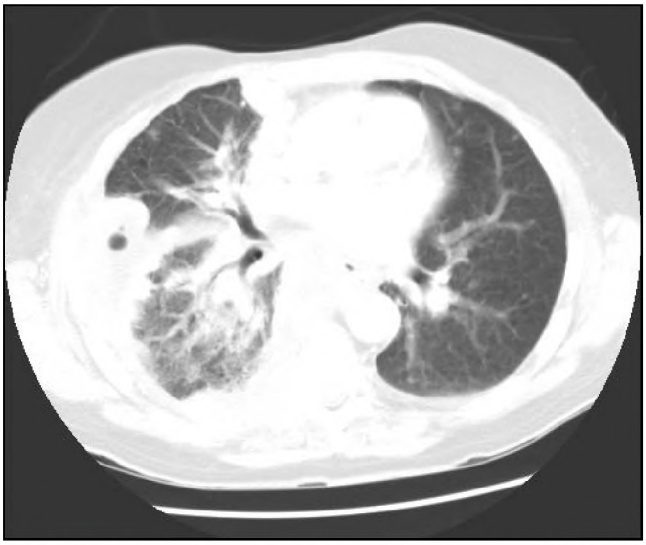


Figure 2. *Computed tomography scan of the chest reveals a nodular pleura-based mass without pleural effusion surrounding the right lung.*

The consultant's opinion was that in concert with a high clinical suspicion of mesothelioma, these patterns were consistent with a mixture of the desmoplastic and lymphohistiocytoid variants of sarcomatoid mesothelioma. It is hypothesized that the tumor was undifferentiated to the degree of losing expression of calretinin and cytokeratin, two usual components of mesothelial cells.

The patient was referred to the thoracic surgical and oncology division. Because of the advanced stage of his disease and the aggressive nature of this variant of malignant mesothelioma, his clinical course rapidly deteriorated and he died 3 months after diagnosis. He had not received surgical or chemotherapeutic treatment.

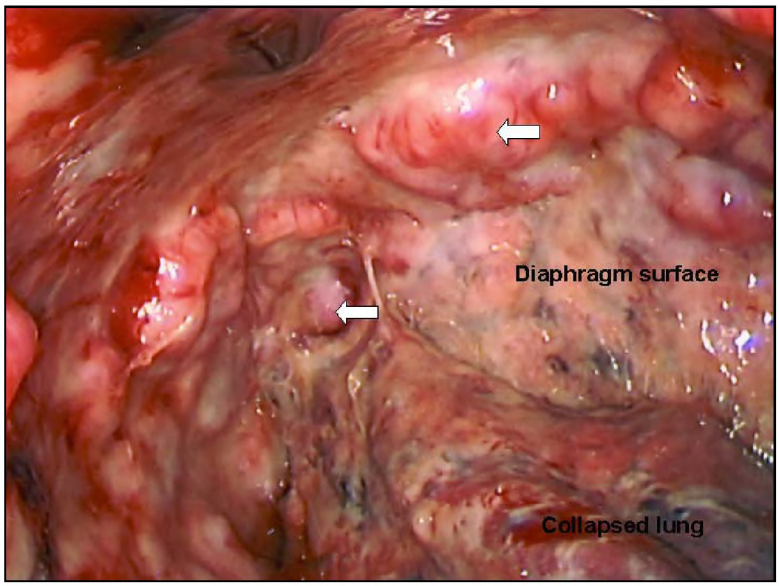


Figure 3. *Biopsy specimen taken by means of video-assisted thoracoscopy shows internal view of the thorax with irregular nodular-appearing pleura (arrows). The lung is collapsed, and the tumor encases the entire right pleural space.*

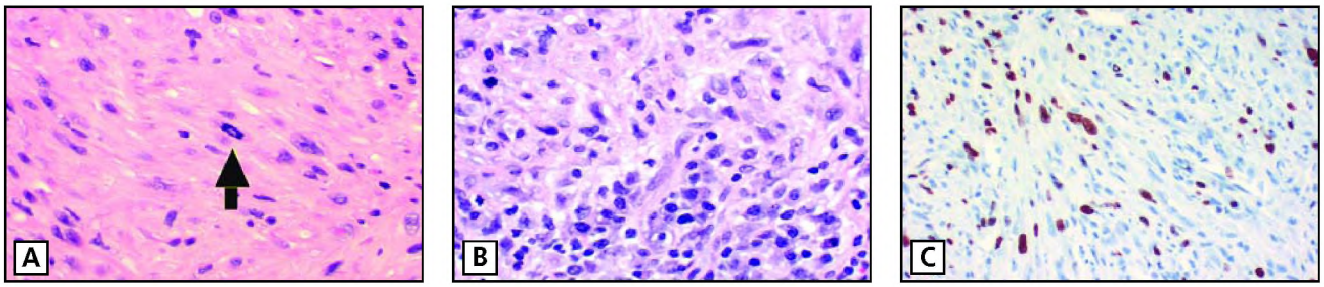


Figure 4. A: *Desmoplastic, hypocellular pattern in sarcomatoid mesothelioma. Mitotic figures can be seen in this neoplasm and in reactive processes (arrow) (hematoxylin-eosin, original magnification ×400).* **B:** *Hypercellular field with lymphocytes and plasma cells (lower half) corresponding to the lymphohistiocytoid pattern of sarcomatoid mesothelioma (hematoxylin-eosin, original magnification ×400).* **C:** *The nuclear proliferation marker MIB-1 monoclonal antibody to the Ki-67 nuclear proliferation antigen MIB-1/Ki-67 shows nuclear positivity in about 20% of tumor cells. (Ki-67 immunostain, original magnification ×200).*

Discussion

Diffuse malignant mesothelioma is a once-rare primary neoplasm of the mesothelial tissues of the pleura, peritoneum, pericardium, and tunica vaginalis testis. Currently, approximately 3000 cases are reported annually in the United States, and approximately 80% of these lesions occur in individuals who have been exposed to asbestos.[1] The incidence of malignant mesothelioma is increasing because of the long latency period (≥30 years) from asbestos use and exposure before the 1960s.[2]

The earliest description of primary pleural malignancy was reported before 1900, and several reports suggesting causal effects from asbestos were published in the first half of the 20th century.[3] Several factors contributed to the delay in establishing mesothelioma as an asbestos-induced malignancy, including the limited workplace epidemiologic data and the misclassification of most reported cases as other tumors. Additional reasons for the delay in establishing an association between asbestos exposure and mesothelioma include the difficulty in determining the etiologic features and, at that time, the lack of specific tumor markers.

Diffuse malignant mesothelioma needs to be distinguished from the less-common focal benign mesothelioma. These pleural tumors, which are not related to asbestos exposure, have a favorable prognosis and often do not recur after surgical resection.[4,5]

Etiology and Clinical Presentation

Most diffuse malignant mesotheliomas arise in workers with direct occupational exposure to asbestos. *Asbestos* is the commercial name for a hydrated magnesium silicate fiber. There are two main families of asbestos fiber, the serpentine (chrysotile) and the amphibole (eg, crocidolite, amosite, and tremolite) forms. Serpentine fibers are curly, whereas amphibole fibers are needlelike. Considerable debate exists about differences in fibrogenicity and carcinogenic properties.[6]

The clinical presentation and manifestations of malignant mesothelioma can be insidious. Despite the varying clinical presentations, the disease process is usually advanced at the time of diagnosis. When first seeking medical attention, most patients have aching pleuritic chest pain that is usually severe enough to require opioids.[7] Dyspnea, cough, fatigue, and weight loss occur in up to 50% of patients.[8] As many as 25% of patients have symptoms for 6 months or more before seeking medical attention.[9] The mean age at presentation is 60 years because of the long latency period between occupational asbestos exposure and the development of the tumor. Rarely, malignant mesothelioma occurs in patients younger than 20 years.[10] The ratio of men to women is 5:1.[11]

Findings at physical examination depend partly on whether the mesothelioma is an epithelial or a sarcomatous-type tumor. Epithelial and mixed-type tumors are associated with small pleural effusions or no free fluid. The most typical findings at physical examination are dullness to percussion and decreased breath sounds. Digital clubbing may also be present. As the disease progresses, there may be marked unilateral contraction of the affected side of the chest wall with narrowed interspaces, a mass in the chest wall, or both.[12] Mesotheliomas have been known to grow along aspiration sites of a previous thoracentesis, thoracotomy, or thoracoscopy.[13] It is uncommon for patients to have associated ascites or peritoneal involvement from a pleural primary tumor. Distal metastasis is common in patients with sarcomatous tumors.[13]

The findings of the laboratory workup of patients with mesothelioma usually are nonspecific and include hypogammaglobinemia, eosinophilia, and anemia.[14] The most common abnormality is thrombocytosis (platelet counts of $400\times10^9/\mu L$), which is seen in as many as 90% of patients, with about 15% of patients having counts greater than $1000\times10^9/\mu L$.[8]

Radiologic Features

The findings of the chest x-ray film at presentation are rarely normal in patients with malignant mesothelioma.[15,16] Seventy-five percent of initial chest x-ray films of patients with malignant mesothelioma reveal pleural effusion, with 60% of the effusions on the right side.[17] Effusions usually are large and

occupy more than 50% of the hemithorax. Pleural plaques with varied radiographic features may be evident in both the affected and the contralateral lung. The most common radiographic feature is diffuse irregular pleural thickening with or without an associated pleural effusion. Initially, in patients with malignant mesothelioma, an effusion alone or a pleura-based mass can be detected.[11] As the disease progresses, pleural effusion and diffuse pleural thickening increase. The involved hemithorax may eventually result in multilobulated thickening with contraction and fixation of the chest wall. As the lung becomes encased by the tumor, the mediastinum shifts as the result of volume loss.[18]

Chest CT is helpful in increasing the clinical suspicion of a malignant pleural process and is particularly valuable in assessing the extent of disease.[15,19] Computed tomography scans of 50 patients with malignant mesothelioma revealed pleural thickening in 46 (92%), thickening of the pleural surfaces of the interlobar fissures in 43 (86%), pleural effusion in 37 (74%), pleural calcifications in 10 (20%), and invasion of the chest wall in only 9 (18%).[15] When the diaphragm is affected, CT scans show a clear fat plane between the inferior diaphragmatic surface and the adjacent abdominal organs as well as a smooth inferior diaphragmatic contour, usually called the "split pleura sign."[18]

Some physicians also use magnetic resonance imaging for staging and preoperative evaluation because its resolution sometimes permits determination of the extent of disease,[18] a benefit not all radiologic studies provide.

^{18}F-fluorodeoxyglucose positron emission tomography shows promise as a tool for differentiating benign from malignant disease, as well as being an adjunct for staging.[20]

Histologic Diagnosis

Clinical evaluation of a patient with pleural effusion and pleural thickening includes thoracentesis and pleural biopsy if the patient can undergo these procedures. However, a diagnosis of mesothelioma is possible in less than a third of cases by closed pleural biopsy or thoracentesis.[21]

Combined histochemical and immunohistochemical staining techniques with electron microscopic analysis of pleural fluid cell blocks are often needed to confirm diagnosis. Despite the small size of the tissue sample, pleural biopsy may still aid in the diagnosis and improves the patient's chance of a timely diagnosis.[21] Patients with negative diagnostic studies often undergo an open pleural biopsy. Video-assisted thorascopy is becoming the diagnostic method of choice.[22]

The varied histologic appearance of malignant mesothelioma, which includes the epithelial, sarcomatoid (fibrous), and biphasic (mixed) patterns, provides a diagnostic challenge. Because a large proportion of these tumors arise within the pleura, it is often difficult to differentiate between a sarcomatoid component and reactive pleural fibrosis. Similarly, distinguishing metastatic adenocarcinoma to the pleura from the epithelial pattern of malignant mesothelioma can be challenging. Initially, it is often difficult to distinguish between a reactive mesothelial process and a neoplastic mesothelial lesion. Often, identifying mesothelioma versus another malignant process can be almost impossible if only a small amount of tissue is available, making a repeated biopsy necessary. The cytologic smears of needle biopsies and sections from cell blocks of pleural fluid can establish the diagnosis of malignancy, but they usually cannot distinguish between a metastatic adenocarcinoma and a mesothelioma.[23] Thus, the diagnostic acumen of one or a group of pathologists familiar with the appropriate use of ancillary studies is essential to making an accurate diagnosis. A consulting pathologist assisted in confirming the diagnosis of malignant mesothelioma in the patient described here.

Sarcomatoid mesothelioma generally has a less favorable prognosis than its epithelioid and biphasic counterparts.[24] The lesion in the patient described contains cellular and paucicellular regions. The paucicellular desmoplastic areas are difficult to distinguish from reactive fibrosis (*Figure 4A*). In the cellular areas, an inflammatory infiltrate can be seen in a reactive process, but in the patient described, it is consistent with the lymphohistiocytoid variant (*Figure 4B*). Mitotic figures are often seen in malignant mesothelioma (*Figure 4C*), but they are not specific to malignant mesothelioma as they may also be seen in such processes as reactive pleural fibrosis, reactive mesothelial hyperplasia, nodular fasciitis, or inflammatory pseudotumor.

Histochemical, immunohistochemical, and electron microscopy are three techniques that aid in the diagnosis of malignant mesothelioma.[25] Histochemical stains identify adenocarcinoma by finding mucin-containing cells. No specific immunohistochemical marker has been found for mesothelioma, so a battery of immunohistochemical stains is used to differentiate mesothelioma from other neoplasms, especially adenocarcinoma.

Markers for Mesothelioma

Currently, the two most sensitive markers for mesothelioma in our laboratory are used concurrently: calretinin, a calcium-binding protein, and cytokeratin 5/6, intermediate-weight keratins 5 and 6. In addition to these two markers, thrombomodulin and mesothelin are useful.[26] The nuclear antigen TTF-1 (thyroid transcription factor) may be used to identify lung adenocarcinoma in immunohistochemistry studies. A cytokeratin cocktail (mixture of low- and high-molecular-weight keratins) immunostain was of limited value in the case described because both mesothelial cells and entrapped submesothelial fibroblasts can be positive for this stain. Some authors have found that expression of Ki-67, a nuclear antigen that is present in proliferating cells, when an MIB-1 immunostain is used, has prognostic significance.[24,27] One study found that in patients with greater than 30% MIB-1–positive cells, the 50% survival time was only about 3 months, whereas in patients with less than 30% MIB-1–positive cells, the 50% sur-

vival time was about 11 months.[24] The patient described in our report had approximately 20% positivity to MIB-1 immunostain in hypercellular areas (*Figure 6*), portending a short survival time.

The sarcomatoid variant of malignant mesothelioma may be less amenable to diagnosis using immunohistochemistry than the epithelioid variant.[28,29] The current patient's stained section of malignant mesothelioma was negative for calretinin and cytokeratin 5/6. It has been suggested that some malignant mesotheliomas, including possibly this patient's, become undifferentiated and lose keratin and calretinin expression.[30]

Electron microscopy may be diagnostic in individual malignant mesotheliomas but is usually not done if clinical history, radiologic findings, morphology, and results of immunohistochemical staining are consistent with the diagnosis.[31] In distinguishing malignant mesothelioma from adenocarcinoma, characteristic long, opulent microvilli containing glycocalyceal bodies and secretory granules within and on the surface of tumor cells are in contrast to the shorter, less frequently seen microvilli in adenocarcinomas. Unfortunately, not all specimens are saved by glutaraldehyde fixation for electron microscopy and the study of formalin-fixed tissue by microscopy yields less satisfactory images.

In this case, as in all lung and pleura-based lesions, it is important to correlate histologic findings with radiologic findings. The presence of an intraparenchymal lung nodule in addition to a pleural nodule may more strongly suggest a lung carcinoma that has metastasized to the pleura than it does a malignant mesothelioma.

Treatment and Prognosis

The medical treatment modalities and surgical procedures for malignant mesothelioma are beyond the scope of this article, but treatment options are well documented in many comprehensive reviews.[7,32,33] However, to date, no randomized trial has demonstrated a group survival benefit for any mode of therapy or combination of therapeutic modalities over palliative care. Nevertheless, multimodality approaches can be considered for the treatment of patients with malignant mesothelioma. Given the limitations of standard therapeutic options, patients should be considered for referral to clinical research centers that have an interest in this disease.

Most patients with pleural mesothelioma, whether treated or untreated, will die of complications of local disease. Increasing bulk of the tumor, jeopardized lung function, and respiratory compromise are progressive. Respiratory failure is the major cause of mortality despite the fact that as many as 82% of patients have distant metastases at the time of autopsy.[34] Frequent sites of metastases are the liver, adrenal gland, kidney, and contralateral lung. Intracranial metastases have been reported but are rare.[35]

The International Union Against Cancer proposed a tumor node metastasis (TNM) staging system that evolved into the presently described International Mesothelioma Interest Group (IMIG) staging system.[36] The IMIG staging system is the only system that has been validated in two large surgical series of mesothelioma.[37] Grondin and Sugarbaker[38,39] proposed the alternative, but complementary, Brigham staging system based on tumor size, resectability, and nodal status.

Good surgical reviews exist. Operative intervention in mesothelioma are categorized as: (1) primary effusion control, (2) cytoreduction before multimodal therapy, or (3) delivery and monitoring of innovative modes of intrapleural therapy. All modalities, especially extrapleural pneumonectomy, carry short- and long-term risks. Arrhythmias requiring medical management are the most common postsurgical complication. Recurrence is common at the extrapleural incision site, and the long-term survival is disappointing, with a median survival range of 9 to 17 months.[40]

New studies are looking at the angiographic mechanisms that are active in mesothelioma. One study demonstrated increased vessel density as well as vascular endothelial growth factor (VEGF) and its receptors and newer novel antiangiogenic compounds that inhibit thymidine kinase activity of the VEGF receptors.[33] Molecular chemotherapy for mesothelioma is under study and shows promise. This novel therapy uses gene therapy by transfection of the herpes simplex thymidine kinase gene to a tumor by infecting it within an adenovirus construct. This construct is then instilled into the pleural space of patients.[41]

Comment

Malignant mesothelioma can be difficult to diagnose and is nearly untreatable. Asbestos exposure remains a major factor in the pathogenesis of this malignancy. Diagnosis requires recognition of patients at risk and knowledge of the clinical features of the disease.

Adequate tissue sampling is important to permit accurate diagnosis. The management of mesotheliomas continues to be investigated with novel therapeutic and treatment options. Despite these changes, however, no standard or effective treatment for patients with malignant mesothelioma exists. Patients who have early disease when they first see a physician may derive a survival benefit from a multimodality therapeutic approach. However, despite the availability of several diagnostic and therapeutic options, most patients with malignant mesothelioma will rapidly die of the disease.

References

1. Roggli VL. Malignant mesothelioma and duration of asbestos exposure: correlation with tissue mineral fibre content. *Ann Occup Hyg*. 1995;39:363-374.

2. Britton M. The epidemiology of mesothelioma [review]. *Semin Oncol*. 2002;29:18-25.

3. Baas P, Schouwink H, Zoetmulder FA. Malignant pleural mesothelioma. *Ann Oncol*. 1998;9:139-149.

4. Antman KH, Corson JM. Benign and malignant pleural mesothelioma. *Clin Chest Med*. 1985;6:127-140.

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5. Janssen JP, Wagenaar SS, van den Bosch JM, Vanderschueren RG, Planteydt HT. Benign localized mesothelioma of the pleura. *Histopathology*. 1985;9:309-313.

6. Cullen MR. Controversies in asbestos-related lung cancer. *Occup Med*. 1987;2:259-272.

7. Ruffie P, Lehmann M, Galateau-Salle F, Lagrange JL, Pairon JC for the French National Federation of Cancer. Malignant mesothelioma. *Br J Cancer*. May 2001;84(suppl 2):49-50.

8. Rusch VW. Clinical features and current treatment of diffuse malignant pleural mesothelioma. *Lung Cancer*. 1995;12(suppl 2):S127-S146.

9. Chahinian AP, Pajak TF, Holland JF, Norton L, Ambinder RM, Mandel EM. Diffuse malignant mesothelioma. Prospective evaluation of 69 patients. *Ann Intern Med*. 1982;96(6 pt 1):746-755.

10. Anand A. Prognostic factors of malignant mesothelioma of the pleura [letter]. *Cancer*. 1994;73:755.

11. Antman KH, Blum RH, Greenberger JS, Flowerdew G, Skarin AT, Canellos GP. Multimodality therapy for malignant mesothelioma based on a study of natural history. *Am J Med*. 1980;68:356-362.

12. Dorward AJ, Stack BH. Diffuse malignant pleural mesothelioma in Glasgow. *Br J Dis Chest*. 1981;75:397-402.

13. Law MR, Gregor A, Husband JE, Kerr IH. Computed tomography in the assessment of malignant mesothelioma of the pleura. *Clin Radiol*. 1982;33:67-70.

14. Hillerdal G. Malignant mesothelioma 1982: review of 4710 published cases. *Br J Dis Chest*. 1983;77:321-343.

15. Kawashima A, Libshitz HI. Malignant pleural mesothelioma: CT manifestations in 50 cases. *AJR Am J Roentgenol*. 1990;155:965-969.

16. Gottehrer A, Taryle DA, Reed CE, Sahn SA. Pleural fluid analysis in malignant mesothelioma. Prognostic implications. *Chest*. 1991;100:1003-1006.

17. Hillerdal G. Pleural malignancies including mesothelioma. *Curr Opin Pulm Med*. 1995;1:339-343.

18. Patz EF Jr, Shaffer K, Piwnica-Worms DR, Jochelson M, Sarin M, Sugarbaker RD, et al. Malignant pleural mesothelioma: value of CT and MR imaging in predicting resectability. *AJR Am J Roentgenol*. 1992;159:961-966.

19. Rusch VW, Godwin JD, Shuman WP. The role of computed tomography scanning in the initial assessment and the follow-up of malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 1988;96:171-177.

20. Benard F, Sterman D, Smith RJ, Kaiser LR, Albelda SM, Alavi A. Prognostic value of FDG PET imaging in malignant pleural mesothelioma. *J Nucl Med*. 1999;40:1241-1245.

21. Herbert A, Gallagher PJ. Pleural biopsy in the diagnosis of malignant mesothelioma. *Thorax*. 1982;37:816-821.

22. van Gelder T, Hoogsteden HC, Vandenbroucke JP, van der Kwast TH, Planteydt HT. The influence of the diagnostic technique on the histopathological diagnosis in malignant mesothelioma. *Virchows Arch A Pathol Anat Histopathol*. 1991;418:315-317.

23. Dejmek A. Methods to improve the diagnostic accuracy of malignant mesothelioma. *Respir Med*. 1996;90:191-199.

24. Beer TW, Buchanan R, Matthews AW, Stradling R, Pullinger N, Pethybridge RJ. Prognosis in malignant mesothelioma related to MIB 1 proliferation index and histological subtype. *Hum Pathol*. 1998;29:246-251.

25. Amin AM, Mason C, Rowe P. Diffuse malignant mesothelioma of the peritoneum following abdominal radiotherapy. *Eur J Surg Oncol*. 2001;27:214-215.

26. Miettinen M, Limon J, Niezabitowski A, Lasota J. Calretinin and other mesothelioma markers in synovial sarcoma: analysis of antigenic similarities and differences with malignant mesothelioma. *Am J Surg Pathol*. 2001;25:610-617.

27. Bianchi C, Brollo A, Ramani L, Bianchi T, GiarelliL. Asbestos exposure in malignant mesothelioma of the pleura: a survey of 557 cases. *Ind Health*. 2001;39:161-167.

28. Attanoos RL, Gibbs AR. Pathology of malignant mesothelioma. *Histopathology*. 1997;30:403-418.

29. Attanoos RL, Webb R, Dojcinov SD, Gibbs AR. Malignant epithelioid mesothelioma: anti-mesothelial marker expression correlates with histological pattern. *Histopathology*. 2001;39:584-588.

30. Suster S, Moran CA. Applications and limitations of immunohistochemistry in the diagnosis of malignant mesothelioma. *Adv Anat Pathol*. 2006;13:316-329.

31. Poulain L, Sichel F, Crouet H, Bureau F, Gauduchon P, Gignoux M, et al. Potentiation of cisplatin and carboplatin cytotoxicity by amphotericin B in different human ovarian carcinoma and malignant peritoneal mesothelioma cells. *Cancer Chemother Pharmacol*. 1997;40:385-390.

32. van Ruth S, Baas P, Zoetmulder FA. Surgical treatment of malignant pleural mesothelioma: a review. *Chest*. 2003;123:551-561. Available at: http://www.chestjournal.org/cgi/reprint/123/2/551. Accessed January 5, 2007.

33. Kindler HL. Malignant pleural mesothelioma. *Curr Treat Options Oncol*. 2000;1:313-326.

34. Huncharek M, Muscat J. Metastases in diffuse pleural mesothelioma: influence of histological type. *Thorax*. 1987;42:897-898.

35. 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.

36. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. *Chest*. 1995;108:1122-1128. Available at: http://www.chestjournal.org/cgi/reprint/108/4/1122. Accessed January 5, 2007.

37. Conlon KC, Rusch VW, Gillern S. Laparoscopy: an important tool in the staging of malignant pleural mesothelioma. *Ann Surg Oncol*. 1996;3:489-494.

38. Grondin SC, Sugarbaker DJ. Pleuropneumonectomy in the treatment of malignant pleural mesothelioma. *Chest*. 1999;116(6 suppl):450S-454S. Available at: http://www.chestjournal.org/cgi/reprint/116/suppl_3/450S. Accessed January 5, 2007.

39. Grondin SC, Sugarbaker DJ. Malignant mesothelioma of the pleural space. *Oncology (Huntingt)*. 1999;13:919-926.

40. Pass HI, Kranda K, Temeck BK, Feuerstein I, Steinberg SM. Surgically debulked malignant pleural mesothelioma: results and prognostic factors. *Ann Surg Oncol*. 1997;4:215-222.

41. Benard J. At the front line of malignant melanoma, great maneuvers: to cut the road to Bc12 and "attack with chemotherapy"[in French]. *Bull Cancer*. 1998;85:520-521.