Clinical Case of the Month

A 64-Year-Old Woman With Shortness of Breath

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CASE PRESENTATION

A 64-year-old woman with a past medical history of hypertension and diabetes mellitus presented to the emergency department complaining of shortness of breath and right-sided chest pain for one month. Her shortness of breath had gradually worsened to the point where she was feeling short of breath while at rest. She described her chest pain as sharp, worse with deep inspiration, and located near the fifth intercostal space along the midaxillary line. There was no history of chest trauma.

Review of systems revealed a dry, nonproductive cough. She denied fever, chills, leg-swelling orthopnea, paroxysmal nocturnal dyspnea, weight loss, or decreased appetite. Past surgical history was significant for a remote hysterectomy. She had a two-pack-year history of tobacco smoking but had quit 15 years prior. She occasionally drank alcohol. She was taking a thiazide diuretic, an ACE-inhibitor, aspirin, and insulin and had an allergy only to iodine. There was no history of cancer. She had remotely worked in a shipyard for two years doing primarily administrative work. Her ex-husband had worked in a shipyard for more than 20 years, and during this time, they lived in the same household.

On physical examination, she was tachypneic with respirations of 30 per minute. Oxygen saturation was 95% on room air. Her remaining vital signs were within the normal ranges. Lung examination revealed decreased breath sounds, dullness to percussion, and decreased tactile fremitus over the right mid- and lower-lung fields. Serum electrolytes, glucose, and renal- and liver-function studies were within normal limits. Her brain natriuretic peptide was 125 (Normal <100pg/mL). A plain radiograph of the chest demonstrated a large, right pleural effusion. A thoracentesis was performed, and approximately 800 milliliters of serous pleural fluid were removed, with immediate symptomatic improvement.

Pleural fluid analysis was consistent with an exudate by Light's Criteria,[1] ie, effusion total protein to serum total protein was 1.8 (>0.5), effusion lactate dehydrogenase (LDH) to serum LDH was 15.8 (>0.6), and pleural fluid LDH was 2114 (>2/3 of the upper limit of normal for serum LDH). Gram stain of the fluid was negative, as were bacterial and fungal cultures. A computed tomogram (CT) of the chest revealed a calcified pleural plaque over the right hemidiaphragm and a loculated posterior pleural effusion. Pleural-based nodules were present along the lateral and posterior chest walls. Some of the nodules appear to extend into the chest wall (Figures 1-3). A subsequent CT-guided needle biopsy was performed and sent to pathology for tissue evaluation. The patient was discharged home to await fluid cytology and biopsy results.

The fluid cytology and biopsy returned with inconclusive results, so a second biopsy was scheduled. Before it was performed, a therapeutic thoracentesis was repeated to alleviate symptoms of worsening shortness of breath. A repeat CT-guided needle biopsy was performed. The biopsy demonstrated changes consistent with a malignant epithelioid tumor, most likely a malignant mesothelioma. She was started on chemotherapy with carboplatin and pemetrexed.

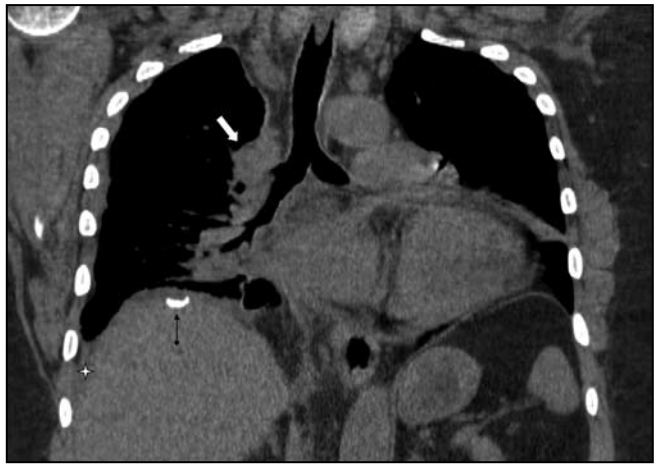

Figure 1. Coronal reconstruction of nonenhanced computed tomogram of the chest shows calcified pleural plaque with adjacent pleural thickening (thin arrow) and lobular pleural thickening with mediastinal and hilar invasion (thick arrow). Pleural fluid with mild pleural thickening extends along the lateral pleura (star). A moderate amount of pleural fluid was seen on more posterior cuts.

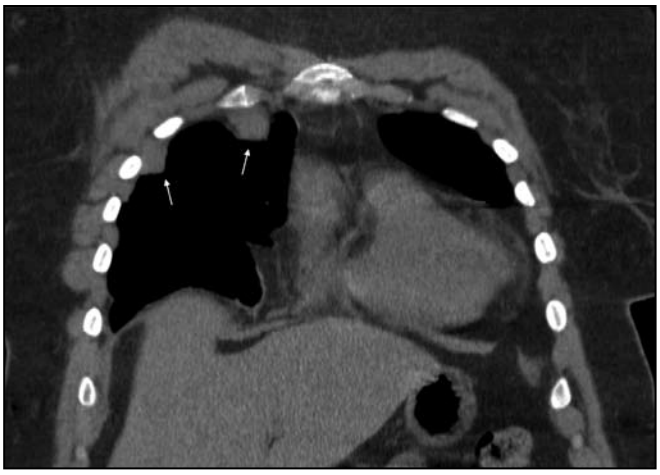

Figure 2. Coronal reconstruction of nonenhanced computed tomogram of the chest reveals two pleural masses, the lower of which demonstrates chest wall invasion (arrows).

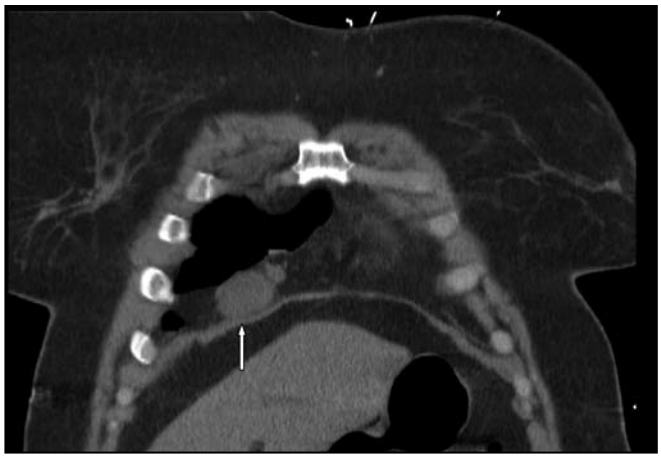

Figure 3. Coronal reconstruction of a nonenhanced computed tomogram of the chest reveals a lobular pleural-based mass (arrow).

INTRODUCTION

Malignant mesothelioma is a malignant neoplasm originating in cells from the pleural or peritoneal cavities called mesothelial cells.[2] Most cases of mesothelioma arise from the pleura and are related to a previous asbestos exposure. This exposure can be primary (directly working with asbestos-containing material) or secondary (working in the vicinity of asbestos workers or washing the clothes of family members that work at a plant).[2] Mesothelioma is not associated with smoking.

EPIDEMIOLOGY

More than three-quarters of patients with malignant mesothelioma involving the pleura are male.[3] Since the beginning of the twenty-first century, there have been 2,000 cases of mesothelioma reported per year. These numbers are increasing currently, with up to 2,200 cases a year reported in the United States.[4] A peak in cases is expected in the year 2015, after which a decline is expected in developed countries due to legislation reducing asbestos exposure in the workplace and environment. After this anticipated decline in developed countries, a further increase in cases may be observed in developing countries because of the lax regulation of asbestos mining and use of asbestos in building materials.[4]

In 1994, the Occupational Safety and Health Administration published a regulation that lowered the PEL (Permissible Exposure Limits) for occupational asbestos exposure to 0.1f/cc.[5] Asbestos-exposed workers are at increased risk for pleural plaques and parenchymal asbestosis and have a 50% chance of dying of a malignancy, compared to 18% for the general population.[4]

Mesothelioma associated with asbestos exposure has a latency period ranging from 20-40 years between first exposure and diagnosis of mesothelioma.[6] In general, this tumor is locally invasive, and death results from local extension.

CLINICAL PRESENTATION

Patients usually present in their fifth to seventh decades of life. Up to 25% of patients have symptoms for more than six months before seeking medical attention.[7] The most common symptoms are nonpleuritic chest-wall pain, cough, and dyspnea. These symptoms wax and wane but do not resolve. Other symptoms include weight loss, fatigue, night sweats, and fever.[8] On physical examination, decreased breath sounds and associated dullness to percussion in areas of marked pleural thickening and/or pleural effusion may be appreciated. Digital clubbing is uncommon. A chest-wall mass may be palpable late in the course of the disease.[8]

DIAGNOSTIC MODALITIES

Typically, a diagnosis of mesothelioma is not made for several months after symptom onset. This is especially true in areas where mesothelioma is uncommon.[3]

Imaging

If mesothelioma is suspected on initial presentation, several imaging modalities can be helpful. The initial study should be a chest radiograph. A unilateral pleural effusion may be seen, but in more advanced disease, encasement of the lung may lead to evidence of consolidation and mediastinal shift secondary to volume loss.[8] These findings may be discovered in asymptomatic patients. Radiographs may also reveal other findings, such as nodular, irregular, unilateral pleural thickening.[9] A chest CT should be done to evaluate better the pleura/chest wall and to assess for

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intrapulmonary nodules as well as mediastinal adenopathy.[7] Magnetic resonance imaging (MRI) may be superior to CT in characterizing the extent of tumor spread into bone, fissures, and diaphragm but is not routinely incorporated into clinical practice.

In addition to these anatomic imaging studies, functional imaging with fluorodeoxyglucose positron emission tomography is being increasingly employed. It is used to evaluate benign versus malignant pleural masses and to stage the extent of extrathoracic spread of disease. Fluorodeoxyglucose uptake is higher in mesothelioma than in benign pleural disease. The ultimate utility of PET scanning for initial staging of malignant mesothelioma and assessment of response to therapy is being addressed.[8]

Fluid Analysis

A thoracentesis should be done at initial presentation, a procedure which may be both therapeutic and diagnostic. Pleural fluid is typically serous and exudative. The cytologic studies will reveal a cellular fluid, containing a mixture of normal mesothelial cells, malignant mesothelial cells, lymphocytes, and polymorphonuclear leukocytes. Cytologic findings are seldom sufficient to diagnose mesothelioma.[7] Cytological studies of the pleural fluid should be done, but they provide a definitive diagnosis of mesothelioma in only 35%–50% of cases.[8]

Tissue Sampling

Tumor biopsy is necessary when there is no pleural fluid or when cytologic studies are inconclusive, usually to help distinguish this malignancy from adenocarcinoma metastatic to the pleural space.

Consequently, a tissue sample of the pleura for a definite diagnosis either by CT-guided needle biopsy or by a video-assisted thoracoscopic surgery (VATS) is pursued. VATS is reserved for patients in whom an adequate diagnostic tissue sample is not obtained with a blind or CT-guided pleura. VATS is just as effective as open thoracotomy in obtaining an adequate specimen but is less invasive.

Histopathology

The tissue sample is then analyzed and classified into three types by morphologic characteristics. The most common type is epithelioid, which also carries the best prognosis, followed by biphasic, which contains both epithelial and fibroblastic elements. The least common type is sarcomatoid mesothelioma.[10]

Despite expert pathological evaluation, a precise diagnosis of malignant mesothelioma can be very challenging. There is no immunohistochemical marker that is both sensitive and specific. The broad spectrum of morphological appearances that malignant mesothelioma can exhibit makes it one of most challenging diagnoses in surgical pathology.[11] Since it is easily mistaken histologically for adenocarcinoma, detailed immunohistochemical studies are needed to help confirm the diagnosis. Mesothelioma is characterized by staining positively for calretinin in 80% and for vimentin in 50% of cases. However, adenocarcinoma usually lacks these markers and instead stains positive for carcinoembryonic antigen (84%), CD15 (77%) and Ber-EP-4 (82%).[12]

Ultrastructural findings

When immunohistochemical and histochemical results are inconclusive, detecting characteristic ultrastructural features using electron microscopy (EM) may facilitate the diagnosis of malignant mesothelioma.[11] EM is the gold standard for the differential diagnosis of mesothelioma from other tumors affecting serosal surfaces and demonstrates long, branching microvilli compared to the short, blunt microvilli seen in adenocarcinoma. Distinguishing features may not be present in all cases, particularly in poorly differentiated tumors.[13]

Serum markers

Serum mesothelin-related protein (SMRP) can be helpful for diagnosis as it is elevated in the serum of more than 80% of patients with malignant mesothelioma. Potentially useful in following response to treatment, SMRP levels increase with the evolution of disease and decrease with regression.[3]

Staging

Although multiple different staging systems exist, that of the International Mesothelioma Interest Group has become one of the most accepted:[12]

Stage I: lymph-node-negative patients with minimal tumor confined to the parietal pleura (Ia) or with minimal visceral pleural involvement (Ib).

Stage II: lymph-node-negative patients with confluent superficial tumor on all pleural surfaces or involvement of the diaphragmatic muscle or lung parenchyma. Stages I and II are resectable.

Stage III: patients with metastases to hilar (N1) or ipsilateral mediastinal (N2) lymph nodes, or those with extension of tumor into the soft tissues or chest wall, the endothoracic fascia, mediastinal fat, or pericardium (T3 tumor). This is the most common presenting stage.

Stage IV: patients who have locally advanced tumor invading the spine or ribs, the chest wall extensively, transdiaphragmatic spread, or contralateral pleural spread. They may have contralateral or supraclavicular lymph-node involvement (N3) or distant metastases.

TREATMENT OPTIONS

The treatment options for mesothelioma depend on several parameters, including performance status, medical comorbidities, pulmonary function, stage of disease, and age of the patient. Surgical options are considered as long as the bulk of the tumor can be removed without leaving gross disease behind. If this cannot be accomplished, then supportive measures for palliation can be used.[14]

Radiation

Recently, the use of radiation therapy for the treatment of malignant mesothelioma has been discussed more in terms of multimodality therapy, prevention of localized recurrence, or palliation. The use of radiation as curative treatment is technically challenging because of all the organs that have to be included in the radiation field, with the associated toxicity to normal surrounding tissue.[14] Radiation complications include nausea, vomiting, radiation hepatitis, esophagitis, myelitis, myocarditis, and pneumonitis with further deterioration of lung function.[7]

A new type of radiotherapy called intensity-modulated radiation therapy (IMRT) has had some promising results. IMRT is a sophisticated form of three-dimensional treatment planning and delivery that allows more conformational radiation therapy to complex targets within the lung with less toxicity to the surrounding organs.

Surgery

Surgical treatment of mesothelioma is used primarily to obtain a diagnosis, for resection of early-stage disease, and for palliation of late-stage disease.[7] There are three surgical procedures that may be attempted, depending on the specific circumstance: (1) extrapleural pneumonectomy (EPP), (2) pleurectomy/decortication, or (3) pleurodesis.

EPP consists of removal of the entire parietal and visceral pleura, adjacent diaphragm, and affected lymph nodes and pericardium. It is typically reserved for patients with early-stage disease, although it may be palliative in some patients with late-stage disease.[15] While many believe that radical surgical resection may offer the only chance of cure or meaningful improvement in survival, the majority of patients presenting with mesothelioma are not candidates for radical surgical resection due to unresectable, locally advanced disease or comorbid medical illness. Surgical intervention even in the best surgical candidates is associated with high morbidity and mortality.[16]

Pleurectomy/decortication involves removal of the parietal pleura, including the portion of the pericardium, diaphragm, and mediastinum containing the tumor. It can be performed with less mortality than that associated with EPP, and in a recent review, mortality was 1.5%–2.0%.[14] This approach is feasible for patients who cannot tolerate the physiologic demand of EPP but is only palliative as complete resection of tumor is not possible.[8]

Dyspnea and discomfort secondary to pleural effusion may be quite debilitating. These symptoms can frequently be controlled with pleurodesis. The preferred approach is by VATS with infusion of tetracycline, doxycycline, bleomycin, or talc. Eighty to 100% of effusions can be controlled in this manner, and there are no differences in success rates among the agents commonly used.[8] It does not prolong survival and it is usually done in preparation for chemotherapy in patients with advanced disease.

Chemotherapy

Systemic therapy with conventional chemotherapy has been used in the management of a majority of patients in whom aggressive surgical management is not an option. Multiple single-agent or combination regimens, frequently incorporating platinums, antimetabolites, and anthracyclines, have been reported to have modest activity against malignant mesothelioma in phase I and II trials. Clinical trials have been limited by the rarity of the disease and difficulty in assessing tumor response. In general, response rates of less than 20% are reported.[8]

The combination of pemetrexed and cisplatin deserves mention since it is the current front-line regimen for this disease. The results of a phase III trial revealed that this two-drug regimen was superior to cisplatin alone, with median survival of 12 versus 9.3 months and a response rate of 41%.[17] Another phase III trial of ralitrexed and cisplatin versus cisplatin alone also revealed the benefit of combination therapy. The median survival with both drugs was 11.4 months versus 8.8 months for cisplatin alone.[18]

PROGNOSIS

The growth pattern of malignant mesothelioma is characterized by local rather than distant spread. Typically originating in one hemithorax, the disease tends to encase the lung and spread contiguously rather than metastasize to distant sites. At the time of diagnosis, most cases are

advanced to the point that curative resection is precluded, making symptomatic palliation the primary goal of therapy. The median survival is 6–8 months from diagnosis in the absence of treatment. Results with treatment are variable, but median survival of one year or more has been reported using aggressive surgical therapy, multimodality treatment, and/or palliative systemic therapy.[8] Five-year survival is less than 5%.[15] Significant prognostic indicators for a poor outcome include age older than 49 years, nonepithelial histologic type, chest pain, weight loss, elevated lactate dehydrogenase level, and poor performance status.[7]

Death most commonly occurs due to local complications such as respiratory and/or cardiac compromise, sometimes with direct myocardial invasion. Although distant/non-contiguous metastases may eventually develop, they rarely cause mortality.[8]

REFERENCES

1. Light RW. Pleural effusion. *N Engl J Med* 2002;346:1971-1977.
2. Fauci AS, Dennis LK, Braunwald E, et al. *Harrison's Principles of Internal Medicine*, 17th edition. United States: McGraw-Hill Professional; 2008:3.
3. Robinson BWS, Lake RA. Advances in malignant mesothelioma. *N Engl J Med* 2005;353:1591-1603.
4. Antman KH. Natural history and epidemiology of malignant mesothelioma. *Chest* 1993;373-376.
5. US Department of Labor. Mine safety and health administration, labor. 29 Mar. 2002. <http://www.msha.gov> (accessed 18 July, 2008).
6. Bianchi C, Bianchi T. Malignant mesothelioma: global incidence and relationship with asbestos. *Ind Health* 2007;45:379-387.
7. Hughes RS. Malignant pleural mesothelioma. *Am J Med Sci* 2005;329:29-44.
8. West H, Kelly K. Pleural malignancies and benign neoplasms of the lung. In: Hanley M, Welsh C (editors). *Current Diagnosis & Treatment in Pulmonary Medicine,* 1st edition. United States: McGraw-Hill Professional;2003:433-439.
9. McPhee SJ, Papadakis MA, Tierney LM Jr. *Current Medical Diagnosis and Treatment*. United States: McGraw-Hill Professional;2008:1-1673.
10. Sterman DH, Litzky L A, Kaiser LR, et al. Epidemiology and Pathology of Malignant Mesothelioma. *UpToDate*. <http://www.uptodate.com> (accessed 8 Aug, 2008).
11. Butnor KJ. My approach to the diagnosis of mesothelial lesions. *J Clin Pathol* 2006;59;564-574.
12. Ismail-Khan R, Robinson LA, Williams CC Jr, et al. Malignant pleural mesothelioma: a comprehensive review. *Cancer Control* 2006;13:255-263.
13. Dardick I, Jabi M, McCaughey WT, et al. Diffuse epithelial mesothelioma: a review of the ultrastructural spectrum. *Ultrastruct Pathol* 1987;11:503-533.
14. Zervos M, Bizekis C, Pass H. Malignant mesothelioma 2008. *Curr Opin Pulm Med* 2008;14;303-309.
15. Chesnutt M, Murray J, Prendergast T. Lung cancer. In: SJ McPhee, MA Papadakis, LM Tierney Jr. (editors) *Current Medical Diagnosis and Treatment 2008*. United States: McGraw-Hill Professional; 2007:1398-1404.
16. Pistolesi M, Rusthoven J. Malignant pleural mesothelioma: Update, current management, and newer therapeutic strategies. *Chest* 2004;126:1318-1329.
17. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (poststudy) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. *Ann Oncol* 2005;16:923–927.
18. Van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881–6889.

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