Innovative Therapies for Malignant Pleural Mesothelioma*

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Therapy for malignant pleural mesothelioma is in a transitional stage. Recent trials of multimodality therapy for this disease suggest that selected patient subgroups may benefit from extensive treatment. This report discusses new approaches to the treatment of malignant pleural mesothelioma. Two case reports are presented.

(CHEST 1997; 112:2698-271S)

CASE REPORTS

CASE 1

A 55-year-old man presented with increasing dyspnea. He denied any hemoptysis, described some left-sided chest aching, but otherwise had no discrete pain. He related some left-sided chest heaviness. He had a history of smoking for 20 years and had been a factory worker.

His physical examination demonstrated decreased breath sounds on the left side, but results were otherwise normal. Blood chemistry and complete blood count findings were also normal. His arterial blood gas revealed a pH of 7.38, a PCO₂ of 42 mm Hg, and a PO₂ of 79 mm Hg. Chest radiograph disclosed diffuse peripheral pleural thickening over the left hemithorax with a moderately large pleural effusion.

The patient underwent thoracentesis, which produced some straw-colored fluid. Cytologic findings were interpreted as malignant cells with some features of adenocarcinoma, although a diagnosis of malignant mesothelioma could not be eliminated. Pulmonary function tests revealed FEV₁ of 2.4 L (81% of predicted) and a FEV₁/FVC ratio of 70%. MRI revealed a chest tumor without evidence of contralateral or subdiaphragmatic extension. CT chest scan revealed diffuse pleural thickening but no evidence of a specific parenchymal mass.

A thoracoscopic biopsy was performed and revealed thick, yellow pleural fluid and pleural nodules over the entire parietal and visceral pleura. Biopsy specimens were obtained and read as consistent with malignant mesothelioma, epithelial type. Mediastinoscopy revealed large bulky nodes at levels 4L, 7, and 4R. These nodes were sampled and on permanent section revealed metastatic lymph node mesothelioma.

The patient underwent left-sided decortication and parietal pleurectomy. He was treated with postoperative radiotherapy (4,500 rad to the left hemithorax) and chemotherapy (cyclophosphamide/doxorubicin/cisplatin) and was discharged.

Approximately 1 year later, the patient presented with worsening dyspnea. He denied having weight loss, pain, productive cough, or hemoptysis. His chest radiograph was essentially stable with no remarkable change other than a mildly enlarged cardiac silhouette. His physical examination revealed fair breath sounds on the left side and good breath sounds on the right side. His heart rate was approximately 110 beats per minute, with a blood pressure of 120/70 mm Hg. His heart sounds were somewhat distant, and he had jugular venous distention approximately 2 to 3 cm above his clavicle. A cardiac echocardiogram was obtained and revealed a moderate-to-large pericardial effusion with some compression of the right atrium. The ejection fraction was 55%.

Discussion

When a pleural process, whether tumor or fluid, is identified in a symptomatic patient, the first step should be to obtain pleural fluid to evaluate dyspnea. Analysis of the fluid for lactate dehydrogenase, pH, glucose, cell count, culture, and cytology should be performed. Normal pH, glucose, and cell count rule out infectious diagnoses and support consideration of inflammatory or malignant processes. Cytologic examination will establish malignant diagnoses in over 90% of patients.

Although bronchoscopy can be helpful and may ultimately be necessary to evaluate the bronchial tree, it would not be the first step in the diagnosis of disease in this patient. An endobronchial biopsy of an obstructing tumor would not make the diagnosis of stage IIIIB (unresectable) cancer, but acquisition of malignant pleural fluid would complete not only his diagnosis but also his staging. Prior chest radiographs would be helpful in planning other aspects of treatment but would not be crucial in the patient’s immediate management. Chest CT scan would be necessary to plan treatment of either a resectable lung cancer or malignant pleural effusion but would not be the most appropriate next step. Finally, thoracoscopic biopsy would certainly be indicated if his thoracentesis were nondiagnostic but should not be done before thoracentesis is attempted.

In terms of evaluation of pleural effusion, the diagnosis of malignant mesothelioma by pleural fluid can be difficult. It is common for a diagnosis of malignant pleural effusion with adenocarcinoma to be made in error. Therefore, a repeat thoracentesis would not be useful at this point. While pleural biopsy may make the diagnosis and certainly would be a reasonable approach, it does not have the diagnostic yield of a thoracoscopic biopsy. Nonetheless, it is reasonable to perform a pleural biopsy prior to thoracoscopy. Bronchoscopy, while ultimately useful, would not be helpful in this circumstance.

Finally, determination of serum carcinoembryonic antigen level would be helpful only if the malignant cells produced this antigen. Carcinoembryonic antigen staining

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is one of the modalities that can be used to differentiate pleural effusion caused by adenocarcinoma from pleural effusion caused by malignant mesothelioma. \textsuperscript{10-12}

The staging system of Butchart and coworkers\textsuperscript{2} is most commonly cited for the staging of malignant pleural mesothelioma. In this system, stage I tumor is confined within the capsule of the parietal pleura. A stage II tumor invades the chest wall or mediastinum and has positive nodes within the chest. Stage III tumor invades through the diaphragm to the peritoneum or to the opposite pleura. Stage IV lesion has distant blood-borne metastases. The most pertinent point about this staging system is that only stage I tumors are surgically resectable.

Sugarbaker et al\textsuperscript{7} have studied the contribution of nodal status in malignant pleural mesothelioma in 52 patients who had resection (extrapleural pneumonectomy) who subsequently underwent chemotherapy (doxorubicin/cisplatin/cyclophosphamid) and radiotherapy (5,500 rad). They were able to demonstrate significant differences in survival between patients with epithelial and mixed/sarcomatous tumors and also between those who were node-negative and node-positive. Their study of 32 patients with epithelial histologic variant and trimodality therapy resulted in 1-, 2-, and 3-year survival rates of 77, 50, and 42%, respectively. Patients with mixed and sarcomatous cell disease had 1- and 2-year survival rates of 45 and 7.5%, respectively, with no patient surviving 25 months.

Similarly, positive lymph nodes were associated with poorer survival than negative nodes. Patients with epithelial histologic findings and negative mediastinal nodes had a survival rate of almost 45% at 5 years. These data indicate that epithelial tumors should be staged by mediastinoscopy prior to trimodality therapy. If the nodes are positive, consideration may be given to pleurectomy and palliative treatment only. If the nodes are negative, the patient may be a suitable candidate for aggressive therapy.

Talc pleurodesis could be performed for palliative treatment only but would unlikely give pleural symphysis due to bulky tumor. Decortication and pleurectomy would be appropriate for patients who had positive nodes or were found to have sarcomatous tumors. An extrapleural pneumonectomy with adjuvant chemoradiotherapy would be appropriate for many patients, although staging information would give a better indication of the prognosis and best modes of therapy on a case by case basis.\textsuperscript{3}

Node-positive epithelial malignant mesothelioma has an intermediate prognosis between node-negative epithelial malignant mesothelioma and sarcomatous subtypes.\textsuperscript{1-4} Therefore, for a young, healthy patient like this, either extrapleural pneumonectomy with subsequent adjuvant therapy or decortication and parietal pleurectomy would be reasonable treatment approaches. This patient underwent left-sided decortication and parietal pleurectomy with postoperative radiotherapy and chemotherapy.

At 1-year follow-up, this patient presented with a large pericardial effusion with impending cardiac compromise. He did not have tamponade, and therefore urgent, but not emergent, treatment was adequate. Digoxin, diuretics, and afterload reduction would not be appropriate in this setting; they would be appropriate for a patient with cardiac failure. Cardiocentesis would be reasonable for acute management until final treatment could be arranged. A left-sided thoracoscopic pericardial window would be difficult, if not impossible, to perform in this patient who had a previous pleurectomy, because of the dense adhesions formed between the lung and chest wall at the time of surgery. Either a subxiphoid window or a right-sided thoracoscopic pericardial window could be performed. A subxiphoid window would effectively drain the pericardial effusion, which was almost surely malignant, and would not contaminate the right side of the chest. The downside to a subxiphoid pericardial window is that the patency rate for this approach is probably less than for thoracoscopic pericardial pleural windows.\textsuperscript{13-16}

**Case 2**

A 62-year-old man presented to the hospital for repair of a right inguinal hernia. Preoperative chest radiograph revealed a mediastinal mass. A chest CT scan revealed a 3-cm mass with irregular borders in the anterior compartment, some with suggestion of invasion of the pericardium. The remainder of the chest scan was unremarkable. The patient’s ECG was also normal.

**Discussion**

The clinical aspects of this patient’s presentation suggest that the mass may be a thymoma. In that case, either needle biopsy or mediastinoscopy to make a diagnosis risks contamination of the mediastinum with cells from the biopsy. Because of the appearance of pericardial invasion and the fact that the lesion does not radiographically appear to be a lymphoma, it should be resected as a possible stage I thymoma without other prior interventions. Performing a head or bone CT scan would not be useful, because this lesion, if malignant, would be unlikely to metastasize.\textsuperscript{17-19}

**References**

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