Malignant mesothelioma

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ABSTRACT

Seventy percent of patients with malignant mesothelioma have had exposure to asbestos fibers. Other patients without this exposure have had chronic pleural inflammation or received radiation to the thorax. Occasionally patients present with no obvious exposure history relevant to the development of malignant mesothelioma. This diagnosis needs to be in the differential diagnosis of all patients with unexplained pleural disease.

Key words: mesothelioma, asbestos, pleural disease

INTRODUCTION

Patients with malignant mesothelioma usually have had exposure to asbestos at a work site, in a building, or on clothing of a family member who works around asbestos. This diagnosis rarely occurs in patients with no relevant exposures. We review this diagnosis in a woman with no obvious exposure to asbestos or other potential causative agents.

CASE

A 54-year-old woman presented to her local emergency department with a history of dyspnea for several months and progressive dry cough for six weeks. She had non-radiating, right lower rib pain exacerbated by cough, a four-pound, unintentional weight loss, night sweats, and occasional fever. She was admitted to an outside facility for community-acquired pneumonia and treated with doxycycline with no relief. A chest x-ray done at this facility revealed a lung mass, and she was then referred to our hospital for more evaluation. A chest x-ray taken at our facility showed rightward shift of the trachea, small lung volumes in the right hemithorax, and a right basilar opacity (Figure 1). Computed tomography (CT) of the chest showed extensive right-sided pleural thickening with no pleural effusion, thickening of the fissures, loss of volume of the right lung, and several mediastinal lymph nodes (Figure 2). She underwent a thoracotomy for pleural biopsy. Pathology confirmed the diagnosis of epithelial mesothelioma (Figure 3). She had no known history of asbestos exposure. She had worked in a slaughterhouse for the past several years (the exact environmental conditions of which are unknown); she had a two-year smoking history but quit 25 years ago. She did not have any personal or family history of malignancy. She was subsequently referred to a regional cancer center for treatment.

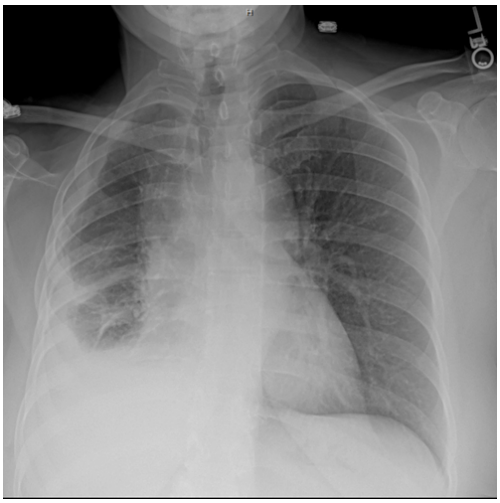

Figure 1: PA chest film shows decreased a lung volume on the right, mediastinal shift to the right, and pleural thickening in the right hemithorax.

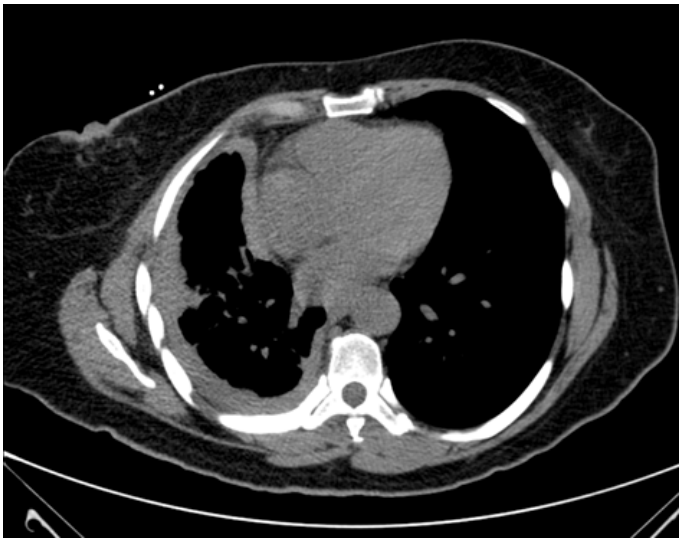

Figure 2: Computed tomography confirms extensive pleural thickening in the right chest without free fluid.

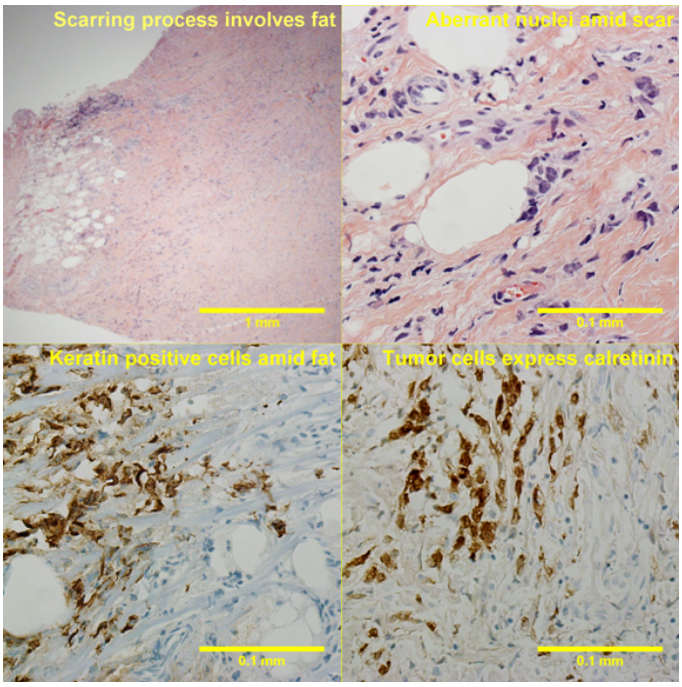

Figure 3: Histologic findings of desmoplastic mesothelioma. 4x objective top left, 40x objective in the top right, bottom left and bottom right slides. Hematoxylin and eosin stains top left and right. Immunohistochemical stains for CK AE1/AE3 (keratin) bottom left and calretinin bottom right.

Discussion

Epidemiology

Asbestos is the designation for a group of naturally occurring minerals, including chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite.[1] These fibers can be classified as serpentine or amphibole (columnar).[1] Asbestos is used commercially due to its insulating properties, tensile strength, and resistance to degradation.[1] Over 125 million people worldwide are exposed to it, and asbestos-related lung cancer has been implicated in the death of 107,000 people worldwide every year.[1] The male to female ratio in cases with malignant mesothelioma is about 3:1 with a peak incidence at 35-45 years after asbestos exposure.[2] About two thirds of cases develop between ages 50-70 years.

Several countries have banned the use of asbestos, but chrysotile is still widely used, especially in developing countries.[1] Asbestos can cause several diseases, including lung cancer, asbestosis, and mesothelioma. Mesothelioma was first linked to asbestos exposure, specifically crocidolite, by Wagner *et al* in 1960.[3] Since then, all fiber types have been associated to varying degrees with malignant mesothelioma. Approximately 70% of mesothelioma cases are associated with asbestos exposure.[4]

Crocidolite has the strongest association with malignant mesotheloma; amosite, tremolite, and actinolite are also highly associated with malignant mesothelioma.[5] Chrysotile and anthophyllite have weaker evidence supporting an association with malignant mesothelioma.[5] This is probably because chrysotile is serpentine, and anthophyllite has the largest diameter of all the amphiboles. Therefore, both are trapped more efficiently by the mucociliary surface.[5]

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DOI: 10.12746/swrccc2016.0414.188

Other possible causes of malignant mesothelioma include radiation, beryllium, erionite (a zeolite), organic chemicals, and chronic inflammation.[6] Ionizing radiation has been implicated in the development of mesothelioma in patients who have received radiation therapy directed to the chest for lymphoma, breast, lung, and other cancers. Tobacco abuse has not been shown to increase the risk of mesothelioma.

Pathology

The visceral and parietal pleura consist of a single layer of mesothelial cells with connective tissue beneath them.[7] These cells have microvilli that are covered with charged surfactant molecules which repel the opposite layer and lubricate the pleural space.[5] The mesothelial cells are also involved in absorption and phagocytosis to remove particulates from the pleural space.[7] Blood to the visceral pleura is supplied primarily by bronchial arteries with a small contribution from the pulmonary circulation. Venous drainage is into the pulmonary circulation. The surrounding systemic vessels supply blood to and from the parietal pleura.[7] The pleura minimize friction from the expansion and contraction of the lungs within the thoracic cage. Mechanical forces from the diaphragm and chest wall expansion are also minimized to protect the lung parenchyma. The pleura also have a role in protecting the lung from infection.[7]

When inhaled, asbestos fibers create direct injury that, when repaired, leads to fibrosis and plaques. Asbestos fibers may induce reactive oxygen species that cause DNA damage. Repeated cell injury followed by DNA repair and eventual mutations results in cell death or transformation to malignancy.[8] Malignant mesothelial cells may have increased interleukin-6 secretion, inducing the expression of vascular endothelial growth factor (VEGF). Patients with malignant pleural mesothelioma have higher levels of circulating VEGF than patients with nonmalignant diseases of the pleura. Decreased expression of wild type tumor suppressor genes p16, p14, and p53 has also been implicated in pathogenesis of these tumors.[9] Another signaling pathway implicated in cancer development is a chronically active Wnt pathway. Perumal *et al* have shown that secreted frizzled-related protein 4 (sFRP4) significantly reduces proliferation in a malignant mesothelioma cell line by antagonizing the Wnt pathway.[10]

Clinical presentation

Dyspnea and chest wall pain are the most common symptoms at presentation. Fever, sweats, fatigue and weight loss are not uncommon. Pleural effusion is present in more than 90% of patients with mesothelioma. However, diagnostic thoracentesis provide confirmatory cytology in only 32% of patients. Fluorescence in situ hybridization has been used to differentiate malignant from reactive mesothelial cells in effusions and has a sensitivity of 79%.[12] A thoracoscopic-guided biopsy is diagnostic in 98% of cases.

Radiology

Features of malignant mesothelioma on chest x-ray include pleural effusion, pleural thickening, lung volume reduction, hemidiaphragm elevation, intercostal space narrowing, and deviation of the mediastinum, all on the ipsilateral side.[13] Malignant mesothelioma can also present as a solid pleural density on chest x-ray.[13] Computed tomography can detect chest wall, diaphragm, and pericardium invasion; this evaluation should determine the extent of erosion of extrapleural fat planes, intercostal muscles, and bone.[13] This type of imaging is also useful to follow the pleural thickening along the lung fissures and allows evaluation of hilar and mediastinal lymph node involvement.[13] Growth of the neoplasm encases the lung and gives a rind-like appearance.[13,14] Magnetic resonance imaging is superior to CT because it allows assessment of invasion of the diaphragm, endothoracic fascia, and intercostal muscles.[7] Magnetic resonance imaging can provide better staging information for patients with a resectable tumor.[14]

Prognosis and Treatment

The TNM staging system is the most widely used staging system for malignant mesothelioma, but radiological assessment may underestimate the actual extent of the tumor. The most common stage at diagnosis is stage IV. The median survival of patients with malignant mesothelioma ranges from 9 to 17 months after diagnosis. Age over 75, male sex, bipha-

sic and sarcomatoid histology, poor European Cooperative Oncology Group performance status, lactate dehydrogenase greater than 500 UI/L, leukocytosis, and thrombocytosis are associated with worse outcomes.[15]

Radiation therapy alone has not improved survival and mainly provides palliation. The Surgery for Mesothelioma After Radiation Therapy (SMART) approach for resectable malignant pleural mesothelioma reported that preoperative radiation therapy might improve survival.[16]

Standard treatment for malignant mesothelioma includes chemotherapy with surgery (pleurectomy and pneumonectomy) and/or radiation depending on tumor invasion or may be limited to supportive care. First-line chemotherapy is pemetrexed with cisplatin.[17] However, pemetrexed/gemcitabine is the first-line chemotherapy for patients with peritoneal mesothelioma. Ranpirnase (Onconase) is a novel cytotoxic ribonuclease with a limited toxicity. It destroys transfer ribonucleic acid (tRNA); this damage causes apoptosis signals and results in the inhibition of cell proliferation.[18] Defactinib (a cancer stem cell inhibitor) received an orphan drug designation from the FDA for treatment of mesothelioma in 2013. A double-blind, placebo-controlled trial will be conducted by the manufacturer in patients with malignant pleural mesothelioma and is expected to enroll about 400 patients in 11 countries.[19] Triple modality therapy involves all 3 standard strategies, namely surgery, chemotherapy, and radiotherapy, and has a two year survival rate of 36% and a five year survival rate of 14%.

Conclusion

Our patient presented with diffuse pleural thickening in the right hemithorax. Biopsy revealed a malignant mesothelioma. This patient had no primary or secondary exposure to asbestos, and she had no other exposures or medical problems associated with the development of malignant mesothelioma. This diagnosis needs to be considered in all patients with unexplained pleural disease.

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Received: 02/13/2016
Accepted: 04/05/2016
Reviewers: Mark Sigler MD
Published electronically: 04/15/2016
Conflict of Interest Disclosures: none

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