Helpful Markers for Diagnosis and Prognosis: What and When

Mesothelioma Versus Carcinoma: Tempest in a Pleural Teapot?

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Key words
• malignant mesothelioma
• metastatic adenocarcinoma
• pleural biopsy
• immunohistochemistry

Objectives
At the end of this lecture attendees who paid attention will be able to,
• define diffuse pleural mesothelioma
• apply traditional and contemporary diagnostic tools to distinguish mesothelioma from its mimics
• articulate the role of pathology in predicting prognosis in patients with diffuse pleural mesothelioma

Define diffuse pleural mesothelioma
Pleural malignant mesotheliomas are serosal neoplasms derived from multipotent mesothelial cells and characterized by a diffuse pattern of growth over the pleural surface.(8) The incidence of mesothelioma in men in the USA peaked in the late 1990’s or early 2000’s although recent analysis suggests that attributable deaths may not peak until 2010.(3, 44) Death rates in Europe and Australasia may not peak until 2020.(34) Trends in incidence and death rates mirror trends in asbestos use that peaked in 1973 combined with a 20-40 year lag period in occupationally related mesotheliomas.(3) It is estimated that in North America about 90% of pleural mesotheliomas in men are asbestos related. The percentage of mesotheliomas attributable to asbestos is dramatically lower in women at about 20%.(38)

Histologically mesotheliomas are classified into three categories: epithelioid (epithelial), sarcomatoid (sarcomatous), and mixed. Epithelioid mesotheliomas are the most common, accounting for just over half of cases, and the remainder are about evenly split between sarcomatous and mixed tumors.(29) The differential diagnosis is broad and heavily dependent on the histologic type. Epithelioid mesotheliomas may be difficult to distinguish from benign mesothelial hyperplasia on one end of the spectrum, and from pleural involvement by carcinoma in obviously malignant tumors. Epithelioid hemangioendotheliomas and angiosarcomas may occasionally enter the differential diagnosis. A subset of sarcomatoid mesotheliomas may also be difficult to distinguish from benign pleural fibrosis, but when obviously malignant have a limited differential
diagnosis in the setting of diffuse pleural disease without a dominant soft tissue or parenchymal mass. Mixed tumors tend to be less problematic but are sometimes confused with either sarcomatoid carcinoma or synovial sarcoma.

**Apply traditional and contemporary diagnostic tools**

Immunohistochemistry is helpful primarily in distinguishing epithelioid mesothelioma from metastatic carcinoma. Carcinomas occasionally involve the pleura in a diffuse manner that closely mimics mesothelioma, so-called *pseudomesotheliomatous carcinoma*. (1) An ever growing list of antibodies purports variable sensitivities and specificities for distinguishing mesothelioma from adenocarcinoma as recently reviewed by Ordóñez. (33) Squamous differentiation is rare in mesothelioma and therefore metastatic squamous cell carcinoma a less common consideration for which immunostains may nonetheless be helpful. (32) A small panel of two mesothelioma associated markers (e.g. calretinin, CK5/6, WT-1, mesothelin, podoplanin), two carcinoma associated markers (e.g. MOC-31, BG-8, Ber-EP4, B72.3, CEA) and tumor specific markers as indicated (e.g. TTF-1, napsin A, ER/PR) is usually sufficient. (33, 46) Molecular studies have limited utility in the differential diagnosis of mesothelioma, with the notable exception of synovial sarcoma which can occur as a primary pleural tumor and is associated with the characteristic t(X; 18) (SYT-SSX) translocation. (45) Recently several investigators have demonstrated differences in DNA methylation profiles that may prove helpful not only in distinguishing mesothelioma from other malignant tumors such as adenocarcinoma but also in separating benign from malignant mesothelial lesions. (5, 6, 21, 42)

No single diagnostic tool outperforms routine microscopic analysis when it comes to separating benign from malignant mesothelial proliferations. Invasion into the soft tissues of the chest wall or mediastinum or into the lung is the single most important histologic finding in distinguishing mesothelioma from mesothelial hyperplasia. (7) In this context immunohistochemical stains for cytokeratins can be helpful in highlighting the presence or absence of invasion. Aside from keratin staining to assess for invasion, special stains are of limited value in any individual case although immunoreactivity for epithelial membrane antigen (EMA), desmin, p53, Bcl-2, p-170, glucose transporter (GLUT)-1, X-linked inhibitor of apoptosis protein (XIAP), and cytoplasmic and nuclear staining for β-catenin occurs more frequently in malignant mesothelial lesions. (11, 25, 37) Malignant mesotheliomas also tend to have higher proliferation rates but with sufficient overlap to limit utility in any single patient. (40) Homozygous deletion of the 9p21 locus harboring p16/CDKN2A is the most consistently observed genetic abnormality in mesothelioma and offers a molecular strategy for separating benign from malignant mesothelial lesions using a commercially available FISH assay. (4, 27) Serum biomarkers (i.e. soluble mesothelin-related peptide [SMRP], megakaryocyte potentiation factor [MPF] and osteopontin) show promise (i.e. sensitivities 73%, 34% and 47% at a specificity of 95%, respectively) but are plagued by unacceptably high false positive rates and are not yet validated for standard practice. (35)

**Role of pathology in predicting prognosis**
Mesotheliomas are lethal tumors. Prognostic factors that may impact length of progression free and overall survival include performance status, disease stage, and non-epithelioid histology (see below).(12, 19) Cytotoxic chemotherapy may extend survival. A combination of cisplatin and pemetrexed is the current recommendation for front-line therapy in patients with unresectable disease.(35, 41) Multimodality therapy in which extrapleural pneumonectomy or pneumonectomy with pleural decortication is combined with chemotherapy and radiation offers the only hope of extended survival in a highly selected subgroup of patients.(15, 16, 18, 23, 26, 36, 39, 43) In patients undergoing multimodality therapy, epithelial histology, negative margins and negative extrapleural lymph nodes are all associated with prolonged survival.(13, 17, 31, 39)

Protein expression and molecular studies may play an increasingly important role in prognosis and patient selection for aggressive therapies.(28) Expression of cyclooxygenase-2, p21 and p27 and homozygous deletion of p16/CDKN2A have been linked to shorter survivals.(2, 10, 30) A novel prediction model predicated on three ratios of expression levels for four genes using a RT-PCR technique accurately predicted overall and cancer specific survival in a large number of patients undergoing debulking surgery at a single institution.(20) Adding other pathology based prognostic variables (i.e. histology and lymph node status) to the model separated patients into low, intermediate and high risk groups with median survivals of 31.9 months, 12.9 months, and 6.9 months respectively.

Effective targeted therapies are not currently available for mesothelioma. Epidermal growth factor receptor (EGFR) expression is common in mesothelioma and is associated with an epithelioid phenotype.(14) Unfortunately trials with tyrosine kinase inhibitors have not shown the same promise demonstrated in selected lung cancer patients likely because the sensitizing mutations associated with treatment response are absent in mesothelioma.(9, 22) Overexpression of vascular endothelial growth factor (VEGF) is also common in mesothelioma but to date targeted therapies using bevacizumab in combination with other chemotherapeutic agents have not proven effective.(24) Other candidate targets in the p53, retinoblastoma protein, and Wnt pathways show promise in in vitro and animal studies using gene therapy strategies.(28)

References


