Cytological Diagnosis of Malignant Pleural Mesothelioma: A Cautionary Note for Lawyers in Asbestos Litigation

Edward Casmere and Joshua Lee
Law360
March 7, 2014

For a variety of reasons, lawyers in asbestos litigation are increasingly presented with fewer records and less medical evidence to evaluate malignant pleural mesothelioma claims. Frequently, the only material provided (and sometimes the only material available) is from a cytological diagnosis made from cells obtained from a pleural effusion, and not from a biopsy of the tumor itself. Diagnosing malignant pleural mesothelioma from cytology alone is extremely difficult for even the most seasoned cytopathologist, yet many participants in the tort system fail to adequately scrutinize such claims. As discussed more fully below, a definitive diagnosis of malignant pleural mesothelioma based on cytology alone is fraught with problems, and should be thoroughly investigated by attorneys on both sides of the litigation.

The human body produces nearly eight liters of pleural fluid per day. The pleural space between the visceral and parietal pleura contains approximately 10 mL of fluid at any given time, representing the balance between hydrostatic and oncotic forces in the pleural vessels and lymphatic drainage. This fluid is essential to the normal functioning of the human body. Fluid enters the pleural space from the capillaries in the parietal pleura, from interstitial spaces of the lung via the visceral pleura, or from the peritoneal cavity through small holes in the diaphragm. This fluid is removed by the lymphatic system, which has the capacity to absorb 20 times more fluid than is usually present in the pleural space. When this capacity is overwhelmed, either through excess formation or decreased lymphatic absorption, a pleural effusion develops. Pleural effusions can be caused by malignancies (whether originating in the pleura, invading the pleural space, or metastasizing to the pleura through the lymphatic system), congestive heart failure, various infections, malnutrition, pneumonia, cirrhosis, trauma, and pulmonary embolism.

Of the estimated one million pleural effusions diagnosed in the United States each year, less than 20% (approximately 175,000) are the result of a malignant process. The majority of malignant pleural effusions are caused by lung cancer (36%), breast cancer (25%) and lymphoma (10%). Out of the estimated 2,500 malignant mesothelioma cases diagnosed in the United States annually, the vast majority of which are pleural mesotheliomas, only a sub-set present with effusions. Even if every malignant mesothelioma patient in the United States presented with a pleural effusion, which they do not, malignant mesothelioma would still account for less than .5% of all pleural effusions diagnosed each year. The odds, therefore,
overwhelmingly suggest that the cause of any particular pleural effusion is something other than malignant mesothelioma.

Despite the odds against a pleural effusion being related to malignant mesothelioma, litigants often accept cytological diagnoses without question. Understanding the limitations of these diagnoses will assist attorneys for both plaintiffs and defendants in preparing and evaluating their cases.

Limitations of cytological diagnosis of malignant pleural mesothelioma include:

1. **The existence of a pleural effusion is not prima facia evidence of malignant pleural mesothelioma.** As noted above, the vast majority of pleural effusions are not related to a malignant process. The mere existence of a pleural effusion does not make it more likely that the patient has pleural mesothelioma. The statistics, in fact, suggest that the opposite is true—over 99% of pleural effusions are not related to malignant mesothelioma.

2. **Cytology provides unreliable samples.** The nature of pleural fluid limits the number of cells that can be collected and analyzed for diagnostic purposes. Cancer cells are less cohesive than benign cells and exhibit a range of changes called “anaplasia.” Cells that shed into pleural fluid can be evaluated for features of anaplasia indicative of their origin. But due to the process by which cells get to the pleural fluid, this evaluation is limited to individual or small clumps of cells. Diagnosing cancer based on the physical evaluation of individual or small clumps of cells is unreliable because it deprives the pathologist of supporting evidence including: architectural disarray, loss of orientation of one cell to another, and invasion.

   “Cytology has often been disappointing, both in identifying mesothelioma cells and in differentiating them from other tumors or from reactive mesothelial cells.” Cytology is accurately diagnostic of malignant mesothelioma in only 3 to 16% of patients. By comparison, even the limited quantity of tissue obtained through needle biopsies of the pleura increases diagnostic accuracy in all cases of malignant disease by 10 to 48%. In cases of malignant mesothelioma, needle biopsy increases diagnostic accuracy 10 to 36% over cytological diagnosis from a pleural effusion.

3. **Immunohistochemical staining of pleural effusion cytopathology can be deceptive.** Mesothelial cells are among the most undifferentiated cells in the human body. In and of itself, that fact presents significant challenges in diagnosing malignant mesothelioma. Having fewer cells to evaluate adds to the degree of difficulty.

   Pathologists use the same diagnostic immunohistochemical stains on cytology as on biopsy tissue. Immunohistochemical stains should react to cells in cytology in the same manner as they react to those types of cells in biopsy tissue. The best markers (depending on the sub-type
of mesothelioma and the differentials considered) should be the same regardless of whether the sample comes from cytology or tissue biopsy. However, the quality of cells for staining in cytology is significantly less than tissue from a biopsy.

The etiological processes that cause pleural effusions can cause normal mesothelial cells lining the pleura to react to the effusion, shed, and fall into the pleural space. Benign mesothelial cells reacting to this abuse (“benign reactive mesothelial cells”) will appear abnormal. Cytomorphologically, benign reactive mesothelial cells appear similar to malignant cells. Standard immunohistochemical stains that are sensitive and specific markers for mesothelial differentiation (e.g. Calretinin) will not distinguish between them—the mesothelial cells (whether benign reactive or malignant) will stain positive for mesothelial markers.

4. **Limited panels of immunohistochemical stains are unreliable.** Use of limited panels of immunohistochemical stains on pleural effusion cytology is not uncommon, and can result in a failure to detect the true cause of a pleural effusion. Stains selected in limited panels tend to include only two or three positive mesothelial markers and two or three negative mesothelial markers (stains such as TTF-1 or CEA that generally stain positive for lung cancer, but negative for mesothelioma).

Many cancers that metastasize to the pleura are negative for TTF-1 or CEA, but, because their pleural involvement, those tumors can stain positive for mesothelial markers. Limited panels may not detect these cancers. If pleural fluid is the only pathology available, an evaluation of the patient’s radiology and clinical course, and electron microscopy of the sample (if possible), together with results from an extensive panel of immunohistochemical stains should be conducted before accepting the diagnosis of malignant mesothelioma.

5. **Radiographic correlation of a “rind” or “peel” around the lungs in conjunction with a pleural effusion is not conclusively diagnostic of malignant pleural mesothelioma.** Parties in litigation often accept "confirmation" of a cytological diagnosis of malignant pleural mesothelioma by a finding of a “rind” on chest films. But various insults to the pleura can result in an inflammatory response with fibrin deposition resulting in a “pleural peel.” A thick fibrous peel can encase the lung and prevent expansion. A fully developed peel has three distinct layers: (1) an outer layer consisting of loosely organized vascular tissue, (2) a middle layer consisting of fibrous connective tissue that is relatively avascular and acellular, and (3) an inner layer consisting of necrotic tissue and fibrinoid masses. Radiographically, a pleural peel can resemble a “tumor rind.” Symptoms related to a thickened pleural peel also can be indistinguishable from symptoms related to malignant mesothelioma: pulmonary restriction, decreased lung volumes, reduced diffusion capacity, and lower expiratory flow rates. Without more, pleural peel or rind should not be used to confirm a cytological diagnosis of malignant pleural mesothelioma.
Published reviews by the Joint US/Canadian Mesothelioma Registry have illustrated the diagnostic problems of distinguishing between benign and malignant pleural mesothelioma. Medical articles and texts from caution against reliance on cytological diagnosis of malignant mesothelioma in varying degrees. Some take the position that the diagnosis of malignant mesothelioma “should always be based on the results obtained from an adequate biopsy (less commonly cytology, exfoliative and fine-needle aspiration) in the context of appropriate clinical, radiologic, and surgical findings.” Others note that while there is evidence that cytological recognition of an atypical mesothelial proliferation in pleural effusion may be sufficient for diagnosis, it is only when correlated with clinical background, imaging studies, and when biopsy is considered inadvisable or unnecessary.

Thus, in evaluating a malignant pleural mesothelioma claim where the diagnosis has been made solely on the basis of cytology, additional materials and medical records should be obtained and analyzed, if possible, to see if the overall clinical picture and the subsequent work-up support a malignant pleural mesothelioma diagnosis. In the absence of additional materials, cytological diagnosis of malignant pleural mesothelioma should be greeted with appropriate skepticism.

Edward Casmere and Joshua Lee are partners in Schiff Hardin’s Product Liability Group, where they represent numerous defendants in product liability, mass tort, and toxic tort cases (including alleged asbestos-related mesothelioma cases) across the United States.

---

i Northwestern Memorial Hospital, Pleural Effusions Overview, 1/23/2014 [www.nmh.org/nm/pleural-effusion-overview](http://www.nmh.org/nm/pleural-effusion-overview)


vii Id.

viii Id.

ix Id.


xi Victor Roggli, et al., Pathology of Asbestos-Associated Diseases, 2nd Ed. at 241 (2004). See also Andrew Chrug, et al., Pathology of Occupational Lung Disease, 2nd Ed. 1998, at 377. (“the commonly used criteria of malignancy, namely necrosis, cytologic atypia, and high mitotic rate, are less useful than might be presumed because many mesotheliomas appear remarkably innocuous and many reactive proliferations are cytologically quite atypical and sometimes show numerous mitoses.”); Victor Roggli, et al., Pathology of Asbestos-Associated Diseases, 2nd Ed. at 238 (2004) (“misinterpretation of reactive changes in mesothelium as malignant mesothelioma or carcinoma
constitutes a major pitfall in exfoliative cytology . . . “); Id. at 239 ("[o]n cytologic grounds alone, it may be difficult or impossible to distinguish metastatic adenocarcinoma from primary malignancies of the serosal membranes (i.e., malignant mesothelioma),” and “the cytologic distinction between mesothelioma and reactive mesothelial hyperplasia may likewise be problematic.")

