Histologic Classification and Differential Diagnosis of Mesothelioma

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INTRODUCTION

Mesotheliomas are neoplasms which arise in the mesodermally derived tissues of the visceral and parietal pleura. The cells of these tissues normally differentiate into either the components of connective tissue with a predominantly fibroblastic appearance or the cuboidal and columnar mesothelial cells which resemble epithelium. Both of these types of cells can undergo a broad range of changes in reaction to a variety of noxious stimuli. The cells of a mesothelioma may closely resemble those seen in a reactive pleuritis. The cells of a mesothelial mesothelioma may closely resemble those of a carcinoma—especially a well differentiated but non-mucus secreting carcinoma of the lung, breast, kidney, or other site. Furthermore, the amount of tissue available for diagnosis is usually limited to a cytologic examination of pleural fluid, a cell block made from this material, or a small biopsy. Therefore, it is not surprising that it is extremely difficult to establish the diagnosis of mesothelioma with certainty. McCaughhey and Oldham [1] could find agreement in only 50 percent of cases among a group of experienced pathologists. For these reasons, the data concerning the incidence and epidemiology of mesothelioma are not entirely reliable. Mesothelioma is an uncommon neoplasm. McDonald et al. [2] were able to document an annual incidence of only ten cases in Canada when using stringent criteria. Carcinomas of the lung and carcinomas metastatic to the periphery of the lung and the pleura from other sites are much more common.
Epidemiology

Mesothelioma has been associated with asbestos exposure particularly during milling or industrial usage [3,4,5,6]. However, Mann and associates [7] found only three cases of mesothelioma among 54 patients dying of pulmonary asbestosis. Two of these mesotheliomas were limited to the abdomen. McDonald and his associates [8] found that only 20 percent of mesothelioma cases had a documented history of significant exposure to asbestos. The limitations of the association between asbestos exposure and mesothelioma noted above, the well established relationship between asbestos exposure combined with cigarette smoking and carcinoma of the lung [9,10,11], and the difficulty in distinguishing carcinoma from mesothelioma make it very difficult to draw conclusions about the relationship between asbestos exposure and a thoracic neoplasm in any given case. The diagnosis of mesothelioma must be based upon rather stringent criteria.

Classification

Histologically, mesotheliomas may be of a spindle or epithelial form or these may be combined in a biphasic tumor. Grossly, the tumors may be either localized or diffuse. Nearly all the biphasic or purely epithelial mesotheliomas are diffuse tumors and thereby malignant and nearly always fatal. Most of the fibrous spindle cell tumors are histologically benign and localized. A small proportion of fibrous tumors are histologically malignant. These may be either localized or diffuse.

The spindle cell mesotheliomas are not associated with asbestos exposure. There is debate in the literature as to whether or not these spindle cell tumors which form on the pleura should be characterized as mesotheliomas. The reasons for classifying the spindle cell tumors as mesotheliomas are: (1) the presence of a biphasic pattern of mesothelioma in which a spindle cell component may be quite prominent; (2) Stout and Murray's [12] and Sano et al.'s [13] report of a spindle cell mesothelioma which differentiated toward a mesothelial cell in tissue culture; (3) some ultrastructural studies, which repute to show intermediate forms between the mesothelial and spindle cell types. Kawai et al. [14], Osamura [15], Suzuki et al. [16], and Kaye and Silverberg [17] found cells with the ultrastructural features of mesothelial cells in tumors which by light microscopy appear to be spindle cell mesotheliomas. However, Wang [18], Hernandez and Fernandez [19], and Alvarez-Fernandez and Diez-Nau [20] found no epithelial or mesothelial characteristics in spindle cell mesotheliomas. It is likely that some spindle cell tumors occurring under the pleura are simply soft tissue tumors which occur at the subpleural site, and others are indeed derived from the mesothelium. It is difficult if not impossible to distinguish these two forms without electron microscopic studies.

Malignant Fibrous Mesothelioma

Malignant spindle cell mesotheliomas may be either localized or diffuse. The histologic appearance varies from that resembling a fibrosarcoma found in soft tissue to the appearance of the malignant spindle cell component seen in biphasic mesotheliomas. See Figs. 1, 2, and 3. If localized and resected the prognosis is fairly good, but any diffuse mesothelioma is essentially incurable.

Benign Fibrous Mesothelioma

These localized tumors are frequently pedunculated with the base of the pedicle on the visceral pleura, often in a fissure. The tumor may involve the periphery of the
Mesothelioma

**FIG. 1.** Malignant fibrous mesothelioma. This malignant tumor is composed of spindle and round cells which form no particular pattern. The surface mesothelium (at the top of the photomicrograph) is proliferative but not neoplastic.

Histologically, the tumors are composed of active fibroblasts which are not characterized by mitotic figures, anaplasia, or pleomorphism. The pattern has been described as a "patternless pattern." (See Fig. 4.) These lesions may reach large size but are frequently amenable to a relatively easy surgical resection. Recurrence is very unlikely [21,22] although Kerr and Nohl [23] have reported recurrence of benign fibrous mesotheliomas. Histologically malignant localized fibrous mesotheliomas recur more frequently, as reported in the series by Ratzer et al. [24] and Wanebo et al. [25]. Localized mesotheliomas are not as common as diffuse mesotheliomas.

**Biphasic Mesothelioma**

These mesotheliomas are composed of malignant spindle and mesothelial cells as those seen in the mesotheliomas which are not biphasic. The differential diagnosis of lesions such as this is from reactive mesothelium, carcinosarcoma, and metastatic synovial sarcoma. Reactive mesothelium may proliferate in such a way as to produce markedly active spindle and mesothelial cells. The distinction between a reaction and a malignant tumor is based upon the presence of a mass lesion with invasion of the adjacent tissue by cells which in general have a greater degree of nuclear pleomorphism and anaplasia than is seen in the reactive mesothelial cells. However, the distinction between tumor and reaction may be extremely difficult. The distinction between carcinosarcoma of the lung, a very unusual tumor, and mesothelioma is based upon the anatomic distribution of the lesion. Carcinosarcomas involve the lung to a marked extent while mesothelioma involves the lung to a much lesser degree. Furthermore, the most common type of carcinosarcoma is one in which the epithelial component is a squamous cell carcinoma. A biphasic carcinoma from the kidney may provide some problems in the differential diagnosis but rarely spreads diffusely over the pleura without involving the lung to a great degree. Synovial sarcoma may...
exactly mimic mesothelioma. It can only be distinguished by knowing that a peripheral lesion is present. Biphasic mesotheliomas have been associated with asbestos exposure.

**Mesothelial Mesothelioma**

The differential diagnosis of this common form of mesothelioma is extremely difficult. It must be distinguished from both reactive mesothelium and carcinoma, particularly peripheral lung cancer.

The distinction from reactive mesothelium is based upon the cytologic appearance, the presence of invasion, and the presence of a mass lesion as noted under biphasic mesothelioma.

The distinction from carcinoma is based on a number of factors. Mesotheliomas are characterized by predominantly pleural spread, although visceral and lymph node involvement may occur late in the disease, and a peculiarly varied histology. The presence of papillary, tubular, and solid patterns is frequently admixed. (See Figs. 5 and 6.) Mesothelial cells are characterized by a rather uniform cytologic appearance with little anaplasia or pleomorphism. The cells are usually large with abundant eosinophilic cytoplasm and round nuclei which have one or more nucleoli. These nucleoli may or may not be surrounded by cleared areas in the nucleus. A cell block from a pleural fluid in a patient with mesothelioma shows a relatively homogeneous

**FIG. 2.** Malignant spindle cell mesothelioma. This is a higher power view of the lesions shown in Fig. 1. The extreme vascularity of the lesion has frequently led to confusion with angiosarcoma. The spindle and clear cells which are markedly hyperchromatic and anaplastic are evident between the blood vessels.

**FIG. 3.** Malignant spindle cell mesothelioma. This mesothelioma is comprised of large numbers of extremely anaplastic fibroblast-like malignant cells.
population of cells. A cell block from a patient with metastatic carcinoma on the pleura usually shows a population of rather homogeneous reactive mesothelial cells and a second population of more pleomorphic and anaplastic cells characteristic of carcinoma.

Reactive or neoplastic mesothelial cells frequently contain hyaluronic acid. A crude assay for the presence of hyaluronic acid is obtained by staining for acid mucopolysaccharide with alcian blue. When the section is predigested with hyaluronidase, the alcianophilia is abolished. The presence of hyaluronic acid in epithelial tumor cells strongly suggests mesothelioma [26,27]. Failure to abolish the acid mucopolysaccharide staining suggests that mucus is present, indicating that the lesion is a carcinoma and not a mesothelioma. Mesotheliomas may be faintly and focally mucicarminophilic. It should be noted that both mucicarmine and acid mucopolysaccharide stains will stain ground substance in a fibrous lesion or in the desmoplastic reaction to a neoplasm. The presence of mucicarminophilia or alcianophilia is not helpful in establishing the diagnosis of mesothelioma unless it is found in an epithelial-appearing cell. Periodic-acid Schiff reagent predigested with diastase is a stain which has been recognized as reasonably specific for epithelial mucus. This stain must be negative in a mesothelioma. The problem with any or all of these stains is that frequently the epithelial (mesothelial) appearing cells in question do not stain with any of them. One is therefore left to interpret the cells from light microscopy
FIG. 6. Malignant mesothelial mesothelioma. A high-power photomicrograph of the preceding figure shows the nature of the mesothelioma cells which are present in the papillary structures. The fibrovascular core of the papillary structure is not neoplastic but is part of the host reaction to the growth of the neoplasm. The neoplastic cells are arranged along the vascular core and are seen falling off this structure into the surrounding space. The nuclei are irregular and hyperchromatic. The cytoplasm is eosinophilic and abundant.

with only the help of hematoxylin and eosin. When a large amount of tissue such as an open biopsy has been obtained, the presence of a large mass lesion and the invasion of adjacent structures is very helpful in establishing the diagnosis. However, since mesothelial mesotheliomas are almost always inoperable tumors, major surgery is usually not employed to obtain a diagnostic biopsy. The diagnosis is usually established on the basis of pleural cytology and needle or small open biopsy.

Electron microscopy may be done on very small bits of tissue from any of these three procedures and, fortunately, the ultrastructural features of mesothelial cells are distinctive. Mesothelial cells are characterized by numerous "bushy" microvilli [15,16,17,18] which are rather readily recognized in the cells of either reactive or neoplastic mesothelium obtained by either biopsy or thoracentesis. (See Fig. 7.) The cells present in a cell block made from an effusion as well as the cells in a small biopsy may be fixed in glutaraldehyde for electron microscopy.

SUMMARY

Mesotheliomas are rare tumors. Metastatic carcinomas are much more common than mesotheliomas. O'Donnell et al. found a ratio of five bronchogenic carcinomas to every mesothelioma among asbestos workers and twelve carcinomas of the lung for every pleural mesothelioma in the same group [10]. The presence of ferruginous bodies in the pulmonary tissue of a patient suspected of having a mesothelioma is not helpful in establishing the diagnosis of mesothelioma. Rosen, Melamed, and Savino [28] found asbestos fibers in the pulmonary tissue of 94 percent of adults at autopsy. Asbestos fibers are common in the urban population and asbestos exposure is associated with bronchogenic carcinoma, particularly when combined with cigarette smoking. Carcinoma of the breast and renal cell carcinoma may be extremely difficult to distinguish from either reactive mesothelium or mesothelioma by light
microscopy, although this can be done effectively with examination of the ultrastructure of the cells. Because of the rarity of well-documented cases and the inability of pathologists to consistently agree on the diagnosis of mesothelioma, it seems that all of the diagnostic tools, including electron microscopy, should be used with much greater frequency to reliably establish the true epidemiologic relationship between asbestos exposure and mesothelioma.

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