Pulmonary Adenocarcinoma Simulating Malignant Mesothelioma

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• Adenocarcinoma of the lung with pleural involvement frequently resembles pleural epithelioid mesothelioma clinically as well as macro- and microscopically. Special stains, immunohistochemical studies, and electron microscopic studies are needed to differentiate these 2 tumors. We report a case of pleural involvement by adenocarcinoma, mimicking in the hematoxylin-eosin stain an epithelioid mesothelioma, correctly identified only after immunohistochemical and electron microscopic examinations.

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There is general agreement that the microscopic characteristics of an adenocarcinoma involving the pleura and an epithelioid mesothelioma overlap in the hematoxylin-eosin–stained slide. Additional studies such as electron microscopy and immunohistochemical stains are needed for proper identification.[1] We describe a pleural tumor with "typical" features of mesothelioma in the hematoxylin-eosin stain slide that with further studies was reclassified as adenocarcinoma.

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REPORT OF A CASE

A 75-year-old male retired biology teacher with a history of hypertension, transient ischemic attack, and depression and a remote history of smoking presented with dry cough, respiratory distress, and weight loss of several months' duration. A chest radiograph showed left side pleural effusion. The patient underwent thoracentesis. Cytology of the pleural fluid was positive for malignant cells, with a differential diagnosis of epithelioid mesothelioma versus adenocarcinoma. Subsequently, the patient underwent partial pleurectomy. The pleurectomy specimen was characterized by fragments of fibrous connective tissue lined by mesothelial cells with focal papillary area. Normal mesothelium was found in continuity with hyperplastic stratified and papillary structure without invasion of the underlying fibrous connective tissue. The cells were cuboidal in the hyperplastic and papillary areas, with an increased nucleocytoplasmic ratio, round bland nuclei with low mitotic activity, and inconspicuous nucleoli (Figure 1). Thus, a diagnosis of malignant mesothelioma, epithelioid type was rendered. However, additional clinical inflammation challenged the diagnosis of epithelioid mesothelioma. The patient had a 4.4-cm perihilar mass; furthermore, the patient also had a probable brain mass (2 small enhancing lesions evaluated by magnetic resonance imaging), bony metastasis (multiple areas of increasing uptake evaluated by bone scan) and a 3-cm lesion in the right kidney (based on computed tomographic scan). All this additional clinical information favored a diagnosis of adenocarcinoma rather than malignant mesothelioma. Subsequent studies of this tumor showed that it stained positive for Leu M1, CK7, D-PAS, and alcian blue (hyaluronidase resistant) and negative for calretinin, carcinoembryonic antigen, and CK20 (Figure 2). Elec-

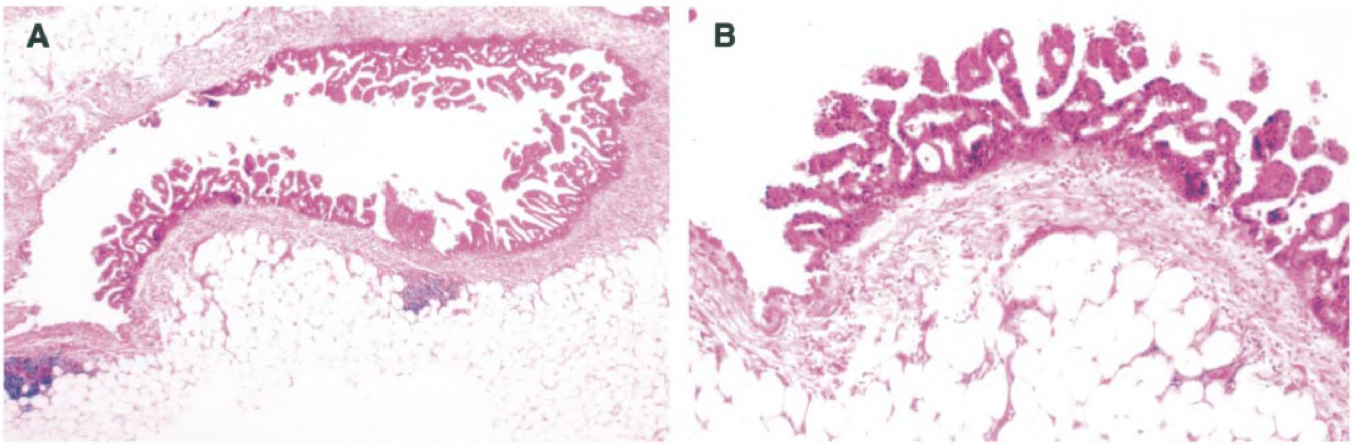

Figure 1. *A, Transition between normal mesothelium and hyperplastic stratified and papillary structures without invasion of the underlying fibrous connective tissue (hematoxylin-eosin, original magnification ×125). B, Higher magnification shows the papillary structure restricted to the pleural surface (hematoxylin-eosin, original magnification ×250).*

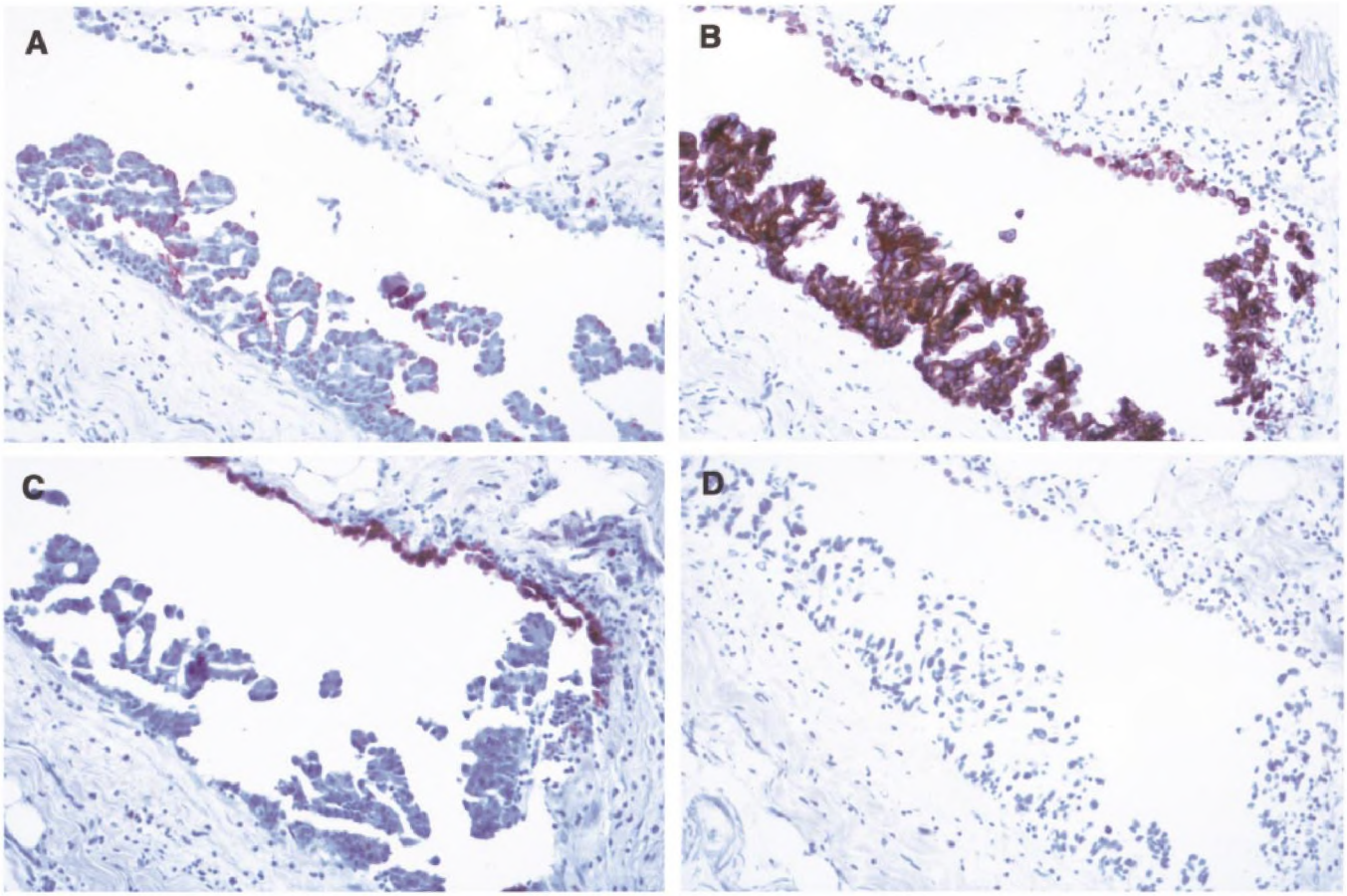

Figure 2. *Immunohistochemistry studies of the tumor cells. A, Leu M1 positive. B, CK7 positive. C, Calretinin negative. D, CK20 negative (original magnification ×200).*

Comparison of Mesothelioma and Adenocarcinoma		
Procedure	**Mesothelioma**	**Adenocarcinoma**
Special stains		
Alcian blue	+ (hyaluronidase-sensitive)	+ (hyaluronidase-resistant)
Colloidal iron	+ (hyaluronidase-sensitive)	+ (hyaluronidase-resistant)
Mucicarmine	−	+
Periodic acid–Schiff	−	+
Immunohistochemistry		
Calretinin	+	−
Cytokeratin 5/6	+	−
Thrombomodulin	+	−
HBME-1	+	−
CD44S	+	−
N-cadherin	+	−
MOC13	−	+
BG-8	−	+
Carcinoembryonic antigen	−	+
Leu-M1(CD15)	−	+
E-cadherin	−	+
Ber-EP-4	−	+
B72.3	−	+
Electron microscopy		
Microvilli	Long, slender	Short, sparse
Lumenlike structures	−	+

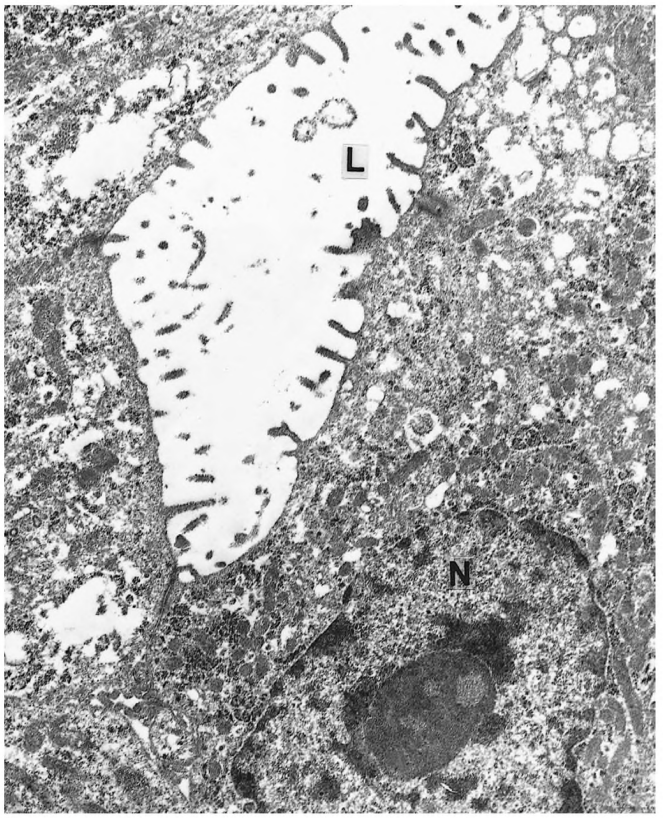

Figure 3. *Electron micrograph of the apical region of several tumor cells, which form a ductlike space with its lumen covered by short, widely spaced microvilli. L indicates lumen; N, nucleus (original magnification ×10 400).*

tron microscopic study showed tumor cells with short, widely spaced microvilli and some cells forming ductlike lumen and apical junction complex (Figure 3). All of these studies supported a diagnosis of adenocarcinoma.

COMMENT

The differential diagnosis between malignant mesothelioma of pleura and adenocarcinoma of lung with pleural involvement is problematic.[2] Their clinical features frequently overlap. They both occur in older adults, who present with chest pain, pleural effusion, and respiratory distress. Pleural thickening with a nodular mass within lung parenchyma and prominent hilar lymphadenopathy favors a diagnosis of adenocarcinoma with pleural involvement.[3]

Macroscopically, malignant mesothelioma usually presents as multiple grayish tan nodules in a diffusely thickened pleura. However, this presentation is also commonly seen in primary lung adenocarcinoma with prominent pleural involvement. Microscopically, both tumors can form papillary structures. The tumor cells in an epithelioid mesothelioma are usually more uniform, cuboidal, and less crowded than the tumor cells in adenocarcinoma, which are more pleomorphic, columnar, and crowded with nuclear molding. However, even with these guidelines, it is often difficult to differentiate malignant mesothelioma from adenocarcinoma in hematoxylin-eosin–stained slides.

Electromicroscopic studies and immunohistochemical studies, however, allow correct differentiation of mesothelioma from adenocarcinoma (Table).[4–7]

The lesion described in our case, with microscopic features typical of an epithelioid mesothelioma in the hematoxylin-eosin stain, stained negative for calretinin, was resistant to hyaluronidase in the colloidal iron stain, stained positive for Leu-M1, and had short villi and luminal and apical junctional complex on electron microscopic studies diagnostic of adenocarcinoma.

In summary, special stains, including immunohistochemical studies and electron microscopy, are essential for the differential diagnosis of malignant mesothelioma and adenocarcinoma even when "typical" features of mesothelioma are noted in hematoxylin-eosin–stained slides.

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