Pathologic Quiz Case

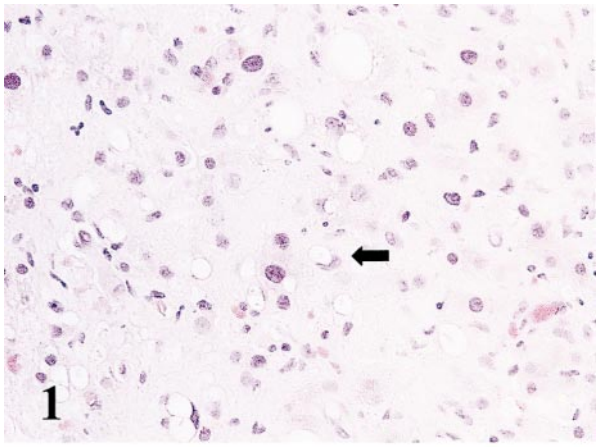
Multiple Liver and Lung Nodules

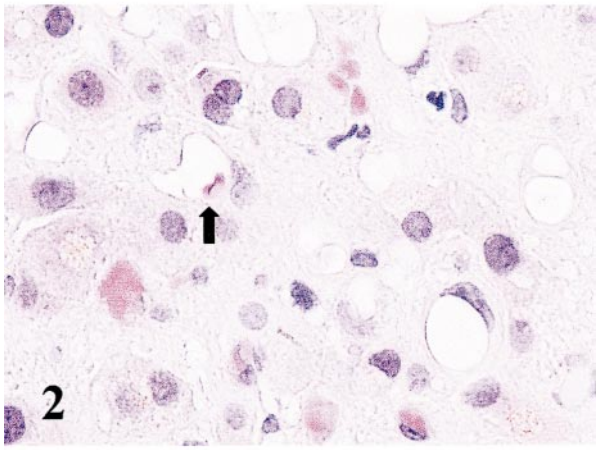
Saad Blaney, MD; Christopher Fung, MD; Carlos Garcia, MD

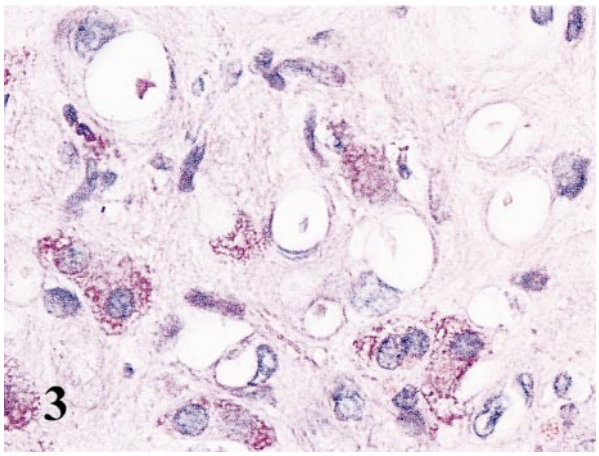
A 77-year-old man had a routine follow-up for chronic obstructive airway disease and hypertension. He had been admitted to the hospital several times within the last 5 years as a result of productive cough, dyspnea, and epistaxis. On examination, there were right upper-lobe wheezes with no accompanying rhonchi or edema. Chest X-ray and computed tomographic (CT) scan showed 2 right and 1 left lung nodules, the largest measuring 1.1 cm. The abdominal CT scan revealed multiple liver nodules in both lobes, the largest one measuring 6 cm. Under CT guidance, 3 core biopsies from the liver nodules were obtained.

The specimen consisted of 3 round yellow cores of soft tissue measuring in aggregate 1.8 × 0.2 × 0.2 cm. Microscopically, there were groups and cords of neoplastic cells located in hyalinized stroma, some of which had a myxohyaline appearance (Figure 1). Scattered clusters of tumor cells were present, with evidence of entry into vascular spaces. Tumor cells were intermediate to large and contained irregularly shaped nuclei, inconspicuous nucleoli, and variable amounts of eosinophilic cytoplasm. Some of the cells had a signet ring appearance with large intracytoplasmic vacuoles, some of which contained red blood cells (Figure 2). Most of the signet ring–like cells contained a small amount of periodic acid-Schiff (PAS)–positive material (Figure 3). No mitotic activity was seen.

What is your diagnosis?







Accepted for publication July 21, 2004.

From the Lutheran General Hospital, Park Ridge, Ill (Dr Blaney); and Mercy Hospital and Medical Center, Department of Pathology, Chicago, Ill (Drs Fung and Garcia).

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Saad Blaney, MD, Lutheran General Hospital, Department of Pathology, 5th Floor Surgical Building, 1775 Dempster St, Park Ridge, IL 60068 (e-mail: blaney208@yahoo.com).

Pathologic Diagnosis: Epithelioid Hemangioendothelioma of the Liver

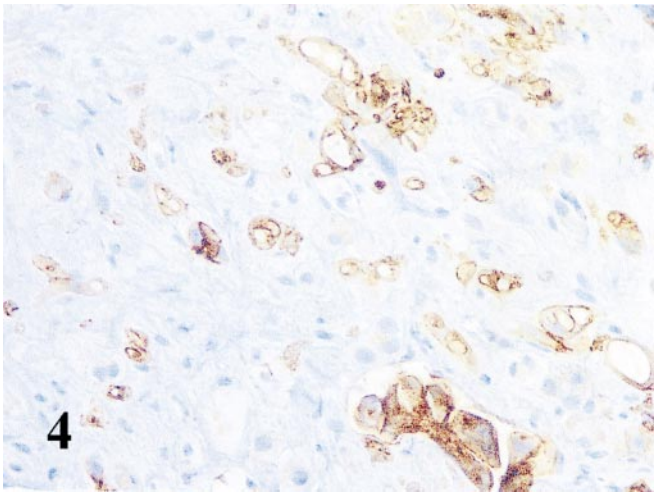
Epithelioid hemangioendothelioma (EHE) is a rare malignant tumor of endothelial origin with a distinctive microscopic appearance. Weiss and Enzinger[1] first described it in soft tissue. A similar tumor, known as intravascular bronchioloalveolar tumor, was described in the lung by Dail and Liebow in 1975.[2] This tumor can occur in the following organs as well: spleen, bone, brain, meninges, breast, heart, gastrointestinal tract, lymph nodes, and veins. The term designated tumors that exhibited behavior that was intermediate between that of hemangiomas and angiosarcomas. Other diagnostic labels for EHE have included low-grade angiosarcoma, cellular hemangioma, histiocytoid hemangioma, and angioendothelioma.

The first description of EHE as a liver primary lesion was by Ishak et al.[3] The clinical presentation of EHE of liver was nonspecific and ranged from complete absence of symptoms to hepatic failure. In the latter case, the tumor gained access to the vascular channels and slowly but relentlessly destroyed the liver. Right upper quadrant pain, epigastric discomfort, weight loss, jaundice, and weakness were other reported manifestations. Makhlouf et al[4] described metastatic disease in approximately 27% of patients with EHE of the liver, with preferential involvement of the regional lymph nodes, lung, peritoneum, and retroperitoneum. The tumor occurred more commonly in females (61%) than males (39%). The age of the patients at presentation ranged from 12 to 86 years, with a mean of 45 years. The 5-year survival rate for this tumor was 43%.

Macroscopically, 82% of the patients had multiple nodules and 18% of the patients had a solitary tumor. The majority of the lesions were rubbery-firm, white, nodular, or diffuse and usually extended to the capsule. Microscopically, the majority had an acinar pattern, with preserved portal tracts. The neoplastic cells were epithelioid, dentritic, or intermediate.

The periphery of the nodules showed the highest cellularity, with central fibromyxoid areas and occasional necrosis. Intravascular growth consisted of irregularly distributed papillary projections of tumor cells into the lumen of central or portal veins. The cells were arranges in cords, strands, small nests, or singly. Individual cells were plump, rounded, or spindled, with pale eosinophilic cytoplasm and vesicular nuclei with inconspicuous nucleoli. A variable proportion of cells typically showed striking cytoplasmic vacuolization, known as intracytoplasmic lumina (signet ring cell–like structures), within which red blood cells are occasionally seen. The dentritic cells had spindle or stellate shapes, multiple interdigitations, and a pale eosinophilic cytoplasm. The epithelioid cells infiltrated the sinusoids, terminal hepatic venules, and portal vein tributaries, causing atrophy to the hepatocytes, especially toward the centers of the nodules. Necrosis was noted in 36% of tumors, calcification in 23%, and inflammation in 86% of cases with a variety of inflammatory cells. The neoplastic cells showed strong positivity to at least one of the endothelial markers: factor VIIIR:Ag (vWF), CD34, and CD31. Tumors were commonly positive for other markers: factor XIIIa, vimentin, type IV collagen, and laminin.

Immunohistochemistry performed in the current case demonstrated strong positivity for CD34 (Figure 4), CD31, vWF, and vimentin. The tumor cells were equivocal for cytokeratins 7 and 20 and keratin (CAM 5.2) and were negative for actin, keratin (AE1/AE3), and carcinoembryonic antigen stains. Some of the tumor cells contained weakly positive PAS-diastase (PAS-D) material within intracytoplasmic lumina. Because our PAS-D control revealed weakly positive PAS-D plasma in blood vessels, we believe that the weak PAS-D–positive material in the lumen tumor cells represents plasma.



Angiosarcoma[4] tends to grow in sheets, and the tumor cells tend to be larger than those of EHE. Unlike angiosarcoma, EHE has central stromal sclerosis, hyalinization, calcification, and preservation of hepatic parenchymal architecture. Because of the epithelioid cell features (abundant eosinophilic cytoplasm, vacuolization, and intracytoplasmic lumina), these tumors may be misdiagnosed as cholangiocarcinoma or metastatic carcinoma. These are separable by their usually strong and diffuse positivity for keratin and epithelial membrane antigen, while endothelial markers are negative. Positive mucicarmine stain would favor these possibilities, and mucicarmine would be negative in the vacuoles of EHE. However, PAS-D is less helpful because it can be positive in adenocarcinoma and cholangiocarcinoma and weakly positive in the vacuoles of EHE (as seen in this case) because of the staining of the plasma in the vacuole. Epithelioid sarcomas have distinctive necrosis, eosinophilic hyaline collagen, positive staining for keratins, and epithelial membrane antigen. A caveat is that half of these sarcomas are positive for CD34 that may cause confusion with EHE. Other differential considerations include hepatocellular carcinoma (especially the fibrolamellar type), sclerosing hemangioma, spindle cell neoplasms, inflammatory pseudotumor, and bile duct adenoma.

Hepatic EHE is treated with radical hepatic resection in addition to orthotopic liver transplantation.[5] If there are identifiable metastases, no surgical treatment should be attempted. The effectiveness of chemotherapy and radiotherapy is ill defined at this time, mainly because of the rarity of these cases and lack of prospective data.

The prognosis of the disease is not affected by the spread of the tumor. Many patients live for many years without treatment; other patients may succumb to liver failure or to intraperitoneal hemorrhage. With regard to

our patient, it was difficult to determine whether the tumor started in the liver and spread to the lungs or vice versa. The patient refused chemotherapy. He is alive and in good nutritional health. Surgical excision was not attempted because of spread of the disease.

References

1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer.* 1982;50:970–981.
2. Dail DH, Liebow AA. Intravascular bronchioloalveolar tumor. *Am J Pathol.* 1975;78:6a–7a.
3. Ishak KG, Sesterhenn IA, Goodman MZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. *Hum Pathol.* 1984;15:839–852.
4. Makhlouf HR, Ishak KG, Goodman MZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. *Cancer.* 1999;85:562–582.
5. Lauffer J, Zimmermann A, Krahenbuhl L, Triller J, Baer H. Epithelioid hemangioendothelioma of the liver: a rare hepatic tumor. *Cancer.* 1996;78:2318–2327.