Epithelioid Hemangioendothelioma of the Liver: Imaging Findings with Pathologic Correlation

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Hepatic epithelioid hemangioendothelioma is a rare malignant neoplasm that has nonspecific clinical signs and symptoms and can be difficult to diagnose on the basis of biopsy results. Radiologists may suggest the diagnosis of this slowly progressive neoplasm by recognizing its characteristic radiologic features. We correlated images from CT (13), sonography (nine), and MR (six) with pathologic findings in resected whole livers (eight) and biopsy specimens (five) from 13 patients 25–58 years old. Gross pathologic examination showed a repetitive pattern of multiple solid tumor nodules, in a predominantly peripheral distribution, with coalescence as individual nodules exceeded 4 cm. Tumor nodules had a hyperemic rim. Lesions adjacent to the capsule often produced capsular retraction. These findings correlated well with imaging findings. On CT, the lesions were of low attenuation, peripherally based, and with capsular retraction or flattening in nine (69%) of 13 patients. Unenhanced CT scans showed superior conspicuity over contrast-enhanced CT scans (9/13, 69%) and showed the extent of lesions more accurately in all cases (13/13, 100%). In nine patients, lesions had a peripheral enhancement pattern of alternating attenuation values correlating with the hyperemic rim at pathologic evaluation. On sonograms, the tumors were solid and predominantly hypoechoic. On MR, tumor signal was low on T1-weighted and high on T2-weighted images, with a low-signal halo present around many of the lesions.

CT, sonographic, or MR findings of coalescent peripheral hepatic masses with capsular retraction are highly suggestive of hepatic epithelioid hemangioendothelioma.

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Hepatic epithelioid hemangioendothelioma (EHE) is a rare tumor of vascular origin that occurs almost exclusively in adults [1–6]. These tumors have a clinical course intermediate between that of benign cavernous hemangiomas and malignant angiosarcomas; most patients survive 5–10 years after diagnosis [1, 3]. Diagnosis of these tumors on clinical grounds is difficult because of their nonspecific signs and symptoms and misinterpretation of pathologic specimens [1, 3]. To date, only a few cases of hepatic EHE have been reported in the imaging literature [7–9]. In reviewing 13 cases of hepatic EHE treated at our hospital, we have detected a repetitive constellation of imaging characteristics highly suggestive of hepatic EHE. This report correlates the pathologic findings of hepatic EHE with the imaging studies.

Materials and Methods

Thirteen patients with pathologically proved hepatic EHE had imaging studies at our institution between 1985 and 1991. The patients consisted of nine men and four women (12 whites, one Hispanic) with a mean age of 39 years (range 25–58). The clinical signs and symptoms were nonspecific. Hepatomegaly and abdominal pain were the most common, but they were present in only seven patients. Liver enzymes were slightly elevated in four of 13 patients. Tests for α-fetoprotein and carcinoembryonic antigen were negative in the six

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patients tested. Eight patients underwent hepatectomy and orthotopic liver transplantation, and five had biopsies of liver lesions.

Imaging studies were usually performed within 1 month (mean, 10 days) of transplantation or biopsy. Imaging studies included CT (13), sonography (nine), and MR imaging (six). CT scans were obtained with GE 8800 (four) and 9800 (nine) scanners (General Electric, Milwaukee, WI). Scans consisted of contiguous 1-cm sections through the liver without and with administration of 150 ml of IV contrast material. (Data are not available on four of the older studies, in which drip infusions may have been used; the more recent studies were done with power injectors at 1.5 ml per second with a 40-sec delay.) Sonographic studies were performed on an Acuson scanner (Acuson Corp., Mountain View, CA) with 2.5- and 3.5-MHz transducers.

MR images were obtained in the transverse plane by using a GE 1.5-T Signa system (five cases) and a Siemens 1.0-T system (Siemens Medical Systems, Iselin, NJ) (one case). Slice thickness was 10 mm with a 2-mm gap between planes, and a 128 × 256 matrix was used. Short TR/TE (400–800/20 [TR/TE]), long TR/short TE (>1800/20–30), and long TR/TE (>1800/80–100) spin-echo images were obtained. Respiratory compensation and spatial presaturation were used to decrease motion artifacts. IV gadopentetate dimeglumine (0.1 mm/kg) was used in conjunction with short TR/TE spin-echo imaging in four patients.

All radiologic studies were retrospectively reviewed for characterization of liver parenchymal abnormalities, liver contour, liver lobe size, and splenomegaly. In 11 patients, the imaging studies were compared with pathologic reports describing examination of the resected livers, photographs of the pathologic specimens, and liver biopsy results. Investigators directly correlated radiologic images with the pathologic findings of fresh hepatectomy specimens from two patients.

Results

Pathology

Gross pathologic examination of the total hepatectomy specimens from the eight patients who had liver transplantation showed a normal red brown capsular surface with multiple subcapsular tumor nodules. Serially sectioned liver specimens showed that the EHE tumors were multiple in all patients and mostly peripheral (Fig. 1). The tumor nodules were tan white and firm, and frequently caused capsular retraction (reported in all eight patients having transplantations) (Figs. 1 and 2). Individual tumor nodules ranged from less than 1 cm to 4 cm in diameter, often with a hyperemic periphery (Figs. 1 and 2). At larger sizes, the lesions were usually confluent, producing large aggregate masses (Fig. 2). In one case, nearly the entire liver parenchyma was replaced by tumor.

Histologically, the nodules were composed of a fibrous myxoid stroma with a relatively hypocellular center. The tumor

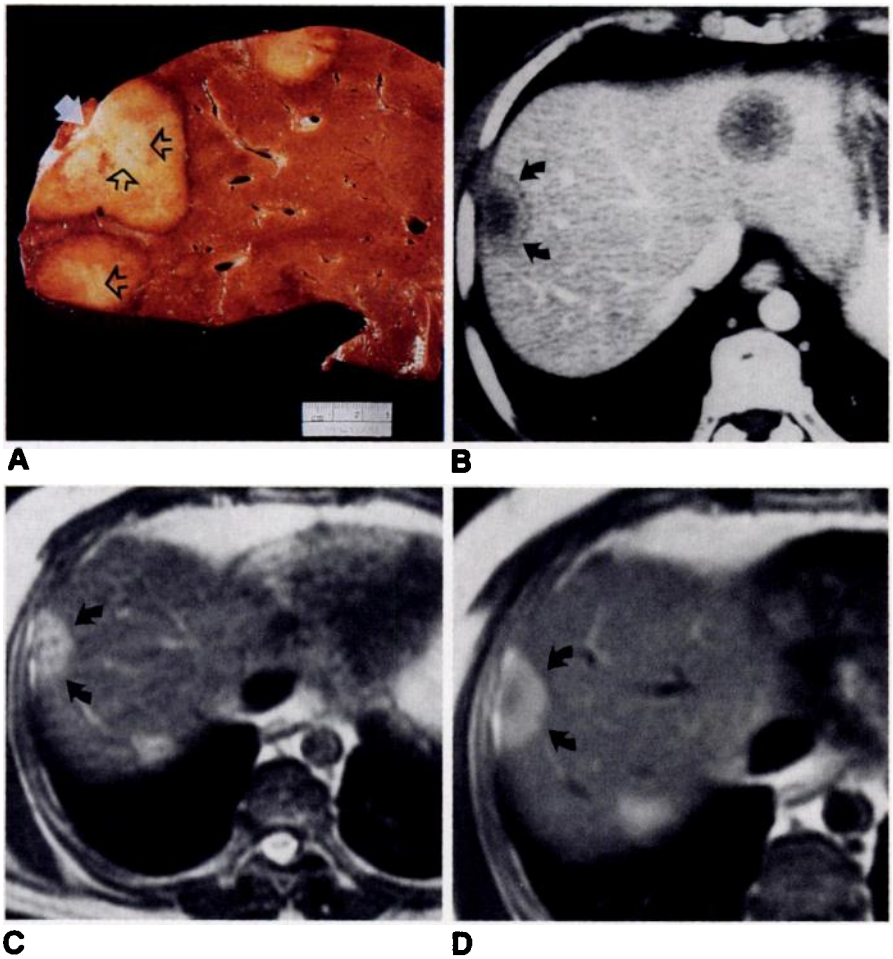

Fig. 1.—Hepatic epithelioid hemangioendothelioma with peripheral distribution of lesions and capsular retraction in a 42-year-old man.

***A*, Transverse (fresh cut) liver section through tumor nodules shows a white avascular central area (*black arrows*) surrounded by a hyperemic area. Note peripheral distribution of lesions and area of capsular retraction (*white arrow*).**

***B*, Enhanced CT scan shows tumor nodule with complex enhancement pattern consisting of a nonenhancing center, hyperemic inner rim, and low-attenuation outer halo (*arrows*).**

***C*, Long TR/TE spin-echo MR image shows high-intensity lesions, one with a thin, low-signal peripheral rim (*arrows*).**

***D*, Contrast-enhanced short TR/TE MR image shows lesion (*arrows*) with a complex enhancement pattern consisting of a hypointense (nonenhancing) central region, peripheral hyperemic zone of high signal intensity, and outermost hypointense avascular rim.**

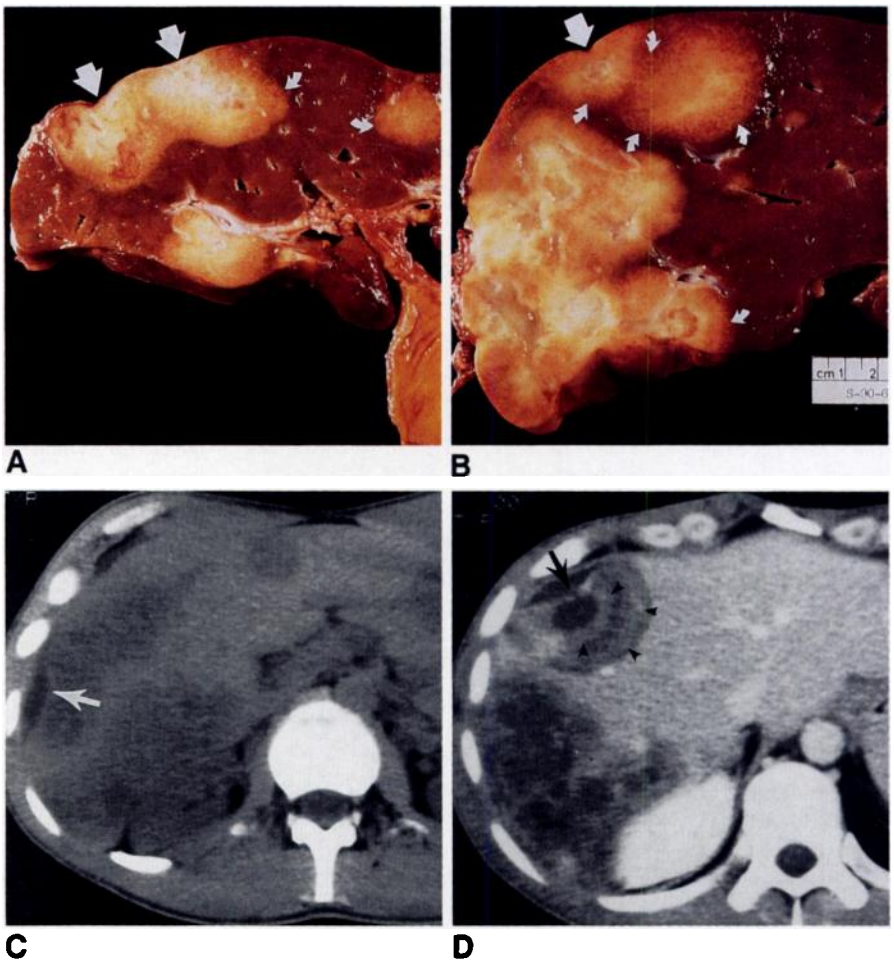

Fig. 2.—Epithelioid hemangioendothelioma of liver with coalescent tumor nodules and capsular retraction in a 29-year-old man.

***A* and *B*, Transverse (fresh cut) liver sections show peripheral distribution of confluent lesions and capsular retraction (*straight arrows*). Note also hyperemia of tumor nodule margins (*curved arrows*).**

***C*, Unenhanced CT scan at same level as *A* correlates well with liver specimen in showing peripheral confluent lesions with capsular retraction (*arrow*). A small amount of ascites is adjacent to capsular retraction.**

***D*, Enhanced CT scan at level similar to *B* correlates with liver specimen showing coalescent tumor nodules. One lesion shows capsular retraction (*arrow*) with adjacent ascites. Alternating zones of contrast enhancement (*arrowheads*) within medial segment of tumor are seen in pathologic specimen (*B*) as two confluent lesions with corresponding hyperemic zones.**

margins (periphery) showed increased cellularity with active proliferation of two cell types: dendritic and epithelioid. The epithelioid cells stained positive for factor VIII–related antigen in all 11 cases tested. At the margin of the nodules, tumor cells invaded the hepatic sinusoids, venules, and small portal vein branches, producing a narrow concentric avascular zone around the tumors.

CT

In all 13 patients, CT showed multiple liver lesions; more than 75% were peripheral and extended to the liver margin. Retraction of the liver capsule overlying tumor nodules was detected in nine patients (Figs. 1 and 2), but in less than 25% of the peripheral lesions. In no case did tumor cause a focal bulge in the liver contour. Compensatory hypertrophy of the uninvolved left lobe was seen in three patients.

Confluence of tumor nodules was seen in seven patients (Figs. 2 and 3). In all 13 patients, unenhanced CT scans showed the tumor nodules as areas of mostly homogeneous decreased attenuation compared with normal liver parenchyma. In two patients, the tumors contained calcifications (Fig. 4). Lesion conspicuity on unenhanced scans was better than or equal to that on enhanced scans in 10 of 13 cases, and the unenhanced scans were superior for showing the extent (size) of tumor involvement. In nine patients, CT with contrast material showed peripheral tumor enhancement surrounding central low attenuation. In seven of these patients, some lesions had a second, more peripheral hypodense rim that correlated with the thin avascular rim seen at pathologic examination (Figs. 1 and 2).

Sonography

Sonography showed intrahepatic lesions in eight of nine patients. Six of the eight patients had discrete, mostly peripheral, individual tumor nodules ranging in size from 2 to 4 cm. The other two patients had peripheral confluent tumor masses. The echogenicity of the tumors varied; six patients had hypoechoic masses (Fig. 3), one patient had hyperechoic masses, and one had both hypoechoic and isoechoic masses relative to liver. The hyperechoic and isoechoic masses had peripheral hypoechoic rims (Fig. 3). No correlation was found between echogenicity and the size of the tumors. The liver capsule directly overlying the tumor nodules was retracted or flattened in two patients.

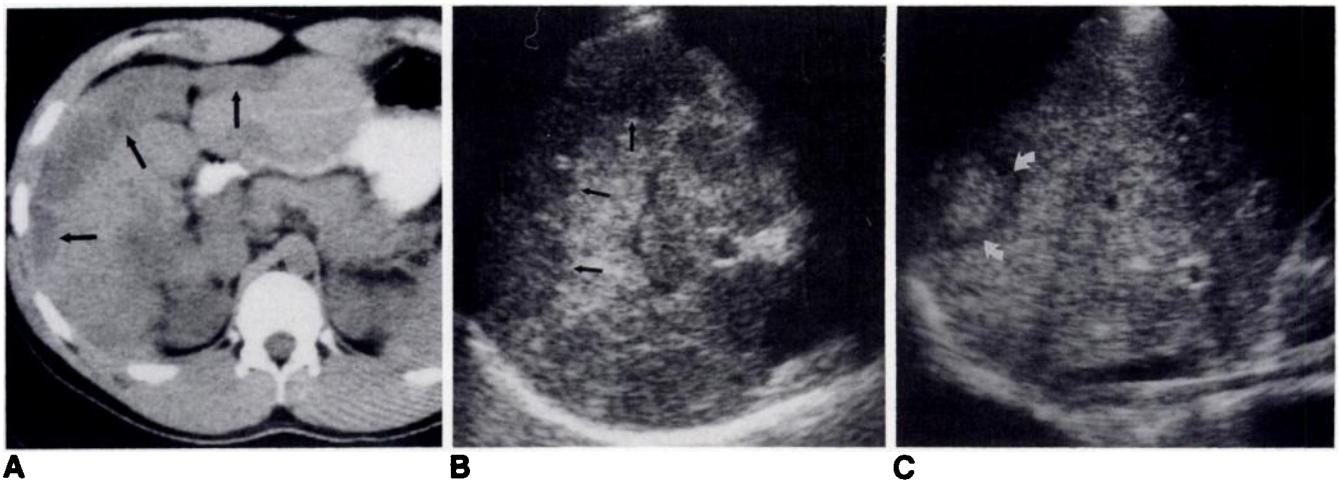

Fig. 3.—Hepatic epithelioid hemangioendothelioma with CT and sonographic correlation and different sonographic appearances in 25-year-old man.
***A*, Unenhanced CT scan shows coalescent peripheral tumor nodules (*arrows*).**
***B*, Transverse sonogram shows peripheral tumor is hypoechoic (*arrows*).**
***C*, Sagittal sonogram shows isoechoic tumor nodule with hypoechoic rim (*arrows*).**

MR Imaging

MR showed lesions in all six patients. As with CT and sonography, the lesions were multiple and located mostly in the liver periphery abutting the liver capsule. Capsular retraction or flattening, centered over the lesions, was detected in three patients.

The lesions had various signal characteristics on short TR/TE images. Three patients had low-intensity lesions, and two patients had low-intensity lesions centrally, with a thin peripheral dark rim. In one patient, the lesion had an isointense signal intensity in the center surrounded by a thin dark rim.

The long TR/TE images showed lesions of heterogeneously increased signal intensity in all six patients, five of whom also had masses with a thin peripheral dark rim (Fig. 1).

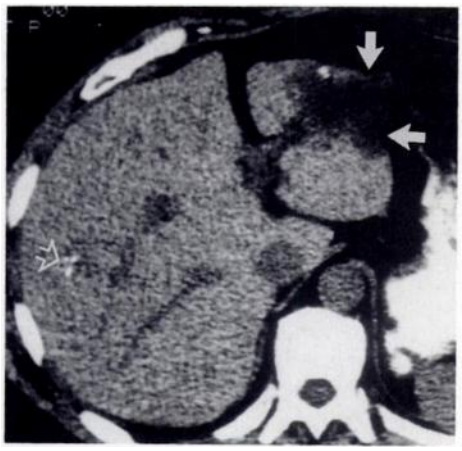

Fig. 4.—Epithelioid hemangioendothelioma of liver with tumoral calcifications and capsular retraction in a 58-year-old man. Unenhanced CT scan shows peripheral tumor nodule containing calcification and capsular retraction (*solid arrows*). Calcification is also seen in a more central liver lesion (*open arrow*).

On gadopentetate dimeglumine–enhanced short TR/TE spin-echo images, three patients had three concentric layers of alternating signal intensity. Similar to the findings on CT, lesions on MR had a hypointense central region surrounded by thick enhancement. The outer margin of the lesions showed a thin, nonenhancing hypointense rim (Fig. 1).

Discussion

The term *epithelioid hemangioendothelioma* was first coined by Weiss and Enzinger [1] in 1982 in a review of 41 patients who had similar soft-tissue tumors. The authors described a solid tumor of vascular origin that was primarily composed of epithelioid-appearing endothelial cells. Most of the tumors in their series had a clinical course between that of benign endothelial tumors (hemangiomas) and malignant angiosarcomas. Since their report, similar tumors have been detected in bone, liver, and lung [2–6]. The clinical course of hepatic EHE is identical to that of extrahepatic EHE; most patients survive 5–10 years after diagnosis [3].

EHE of the liver is usually found in young adults. The mean age of patients in this series was 39 years, and Radin et al. [8], in a review of the literature, reported a mean age of 45 years. Ishak et al. [3], in a series of 32 patients, reported that the clinical signs and symptoms and laboratory data of their patients were nonspecific. No risk factors or specific causes of hepatic EHE were identified. In several reports, cases were originally misdiagnosed as metastatic carcinoma, sclerosing hepatic carcinomas, and nonneoplastic disorders such as postnecrotic fibrosis or venoocclusive disease [3, 10, 11]. Because of the prolonged course and nonspecific clinical manifestations, the age of the patient at the time EHE is detected by biopsy or imaging studies may vary widely. More familiarity with the pathologic findings and better access to advanced imaging techniques may allow discovery of this tumor at earlier ages, as recent studies have shown [7, 8].

Furui et al. [7] and Radin et al. [8] reported on the imaging appearances of these lesions in two small series. The results of our series agree with their observations that on CT these lesions are mostly peripheral and of low attenuation, are most conspicuous on unenhanced scans, and occasionally have an enhancing peripheral rim and/or outer hyodense halo. Hypertrophy of unaffected liver regions is seen in advanced cases. Previous reports [7, 8] have shown sonographic appearances of EHE as hypodense with occasional foci of central increased echogenicity. In our series, we had similar findings; most of the lesions were hypoechoic.

The MR appearance of these tumors has been limited to one case described by Radin et al. [8]. In our series, the MR images had a distinctive appearance that in many ways correlated well with the CT appearance and the pathologic findings. The concentric alterations in signal intensity seen on short TR/TE, long TR/TE, and in particular on the contrast-enhanced spin-echo images appear to be consistent findings. Combined with the peripheral distribution and the proper clinical setting, these findings may suggest the diagnosis.

Although Furui et al. [7] described one case with "dimpling" of the margin of the liver, they concluded that these lesions generally do not alter the peritumoral hepatic contour. However, in our series, we found a much higher prevalence of liver capsular retraction centered over lesions (nine of 13 cases). This is an unusual feature of malignant lesions in the liver, as most large peripheral tumors cause a protrusion of the adjacent liver margin. Capsular retraction centered over a peripheral mass should thus be considered highly suggestive of EHE. However, lesions causing biliary obstruction can result in liver atrophy, which in some ways may simulate capsular retraction. Also, peripheral metastatic lesions treated with chemotherapy can cause an appearance similar to the retraction seen in EHE lesions, perhaps caused by a process of fibrosis similar to that seen in EHE. However, the mostly peripheral location of EHE lesions and the clinical history should allow differentiation of EHE from treated metastatic disease.

The radiologic findings seen in hepatic EHE correlate well with the pathologic findings. Macroscopically our patients with EHE had multiple, solid, firm nodules with a hyperemic periphery and dense fibrous center, similar to previously reported findings [3, 12]. Histologic findings showed that the tumor produces a fibrous myxoid stroma that is most dense in the center of the nodules, with increasing cellularity toward the periphery of the lesions. These findings account for their solid, firm consistency grossly and their hypovascular center. The actively proliferating, increased cellular periphery of the nodules accounts for the hyperemic outer portions seen on gross specimens. Tumor infiltration and occlusion of hepatic sinusoids and small vessels cause a narrow avascular zone between the tumor nodules and liver parenchyma. These findings correlate with the enhancement pattern on CT and MR, with the central portion of the nodules appearing hypodense and not enhancing to the same degree as the hyperemic periphery. The hyperemic periphery may not be hyperdense on CT; it may be isodense with normal liver parenchyma, and not detected. Thus, unenhanced CT often shows tumor conspicuity better and is more accurate in detecting tumor extent; this is in agreement with earlier reports [7, 8]. The outer, hypodense rim seen on CT and hypointense rim on MR correspond with the peripheral avascular zone, where vascular invasion is detected on pathologic examination. This may also be the reason for the halo appearance on sonography, although the peripheral hyperemic, cellular portions of the tumor may also contribute to the hypoechoic rim.

The capsular retraction or flattening seen on CT, sonography, and MR has been documented in the pathologic and surgical literature [3, 8, 12]. This retraction is most likely due to the tumor fibrous reaction, which distorts the tumor margin and adjacent liver capsule. The complete transverse imaging of CT and MR most likely explains why more cases of retraction were seen on CT and MR than on sonography. Retrospective review of sonograms also limited our ability to look for this finding, which may have been presented but not imaged.

With progression of this disease, the nodules often coalesce in the periphery of the liver. Because EHE replaces liver parenchyma slowly over years, compensatory enlargement of uninvolved portions of the liver can be seen [8, 10, 11]. This was seen in three of our patients, all of whom had extensive disease, and is a late finding in the course of the disease.

Calcification has occasionally been detected histologically, on abdominal radiographs [3], and on CT scans [7, 8]. Dense calcifications were detected on CT and sonography in two patients in our series, and is a less common finding.

REFERENCES

1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer* **1982**;50:970–981
2. Dorfman HD, Tsuneyoshi M, Bauer T. Epithelioid hemangioendothelioma of bone (abstr). *Lab Invest* **1986**;45:17
3. Ishak WG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathological study of 32 cases. *Hum Pathol* **1984**;15:839–852
4. Dail D, Liebow A. Intravascular bronchioloalveolar tumor (abstr). *Am J Pathol* **1975**;78:6a–7a
5. Dail DH, Liebow AA, Gmelich JT, et al. Intravasular bronchiolar, and alveolar tumor of the lung (IVBAT): an analysis of twenty cases of a peculiar sclerosing endothelial tumor. *Cancer* **1983**;51:452–464
6. Weldon-Linne CM, Victor TA, Christ ML. Antigenic nature of "intravascular bronchioloalveolar tumor" (letter). *Arch Pathol Lab Med* **1981**;105:628
7. Furui S, Itai Y, Ohtomo K, et al. Hepatic epithelioid hemangioendothelioma: report of five cases. *Radiology* **1989**;171:63–68
8. Radin DR, Craig JR, Colletti PM, Ralls PW, Halls JM. Hepatic epithelioid hemangioendothelioma. *Radiology* **1988**;169:145–148
9. Lee KS, Rossleigh MS, Fernandes VB, Morris JG. Scintigraphic features of malignant epithelioid hemangioendothelioma. *Clin Nucl Med* **1989**; 14:501–503
10. Clements D, Hubscher S, West R, Elias E, Macmaster P. Epithelioid hemangioendothelioma of the liver: a case report. *J Hepatol* **1986**;2: 441–449
11. Eckstein RP, Ravich RMB. Epithelioid hemangioendothelioma of the liver: report of two cases histologically mimicking venoocclusive disease. *Pathology* **1986**;18:459–462
12. Iwatsuki S, Sheahan DG, Starzl TE. The changing face of hepatic resection. *Curr Probl Surg* **1989**;5:345–348