Treatment of Hepatic Epithelioid Hemangioendothelioma

A Single-Institution Experience With 25 Cases

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Objective: To examine treatment of hepatic epithelioid hemangioendothelioma (EHE), a rare vascular tumor with a variable course. Treatment modalities at our institution include liver resection, transplantation, and catheter-based therapies.

Design, Patients, and Main Outcome Measures: Retrospective review of 25 patients treated for hepatic EHE (1976-2007). We examined treatment modality, overall survival, complications, and clinicopathologic characteristics.

Results: Of the 25 patients treated for hepatic EHE, 17 underwent liver transplantation (LT); 4, transcatheter arterial chemoembolization (TACE); 2, resection; and 2, TACE followed by LT. Twelve patients (48%) were male. The median age at diagnosis was 38 years (range, 9 months to 72 years). Mean overall survival was 167 (95% confidence interval [CI], 123-212) months, with 172 (124-220) months in the LT group and 83 (54-112) months in the TACE group. The 2 patients in the resection group remain alive after 19 and 71 months. The 2 patients treated with TACE followed by LT died after 13 and 113 months. Extrahepatic disease was identified as a predictor of outcome. Patients with extrahepatic disease treated with TACE fared better than those treated with surgical approaches (mean survival, 83.0 [95% CI, 54.2-111.8] vs 38.8 [23.7-53.8] months; \( P = .12 \)).

Conclusions: Hepatic EHE is a rare tumor that can be treated with surgical or nonsurgical approaches. In our experience, LT is used for patients with advanced local disease, whereas TACE is the primary modality when extrahepatic disease or comorbid conditions prohibiting LT are present. To our knowledge, this is the largest single-institution experience describing the various therapeutic modalities in the treatment of hepatic EHE.

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PITHELIOID HEMANGIOENDOTHELIOMA (EHE) is a rare tumor that was first described pathologically by Weiss and Enzinger\(^1\) in 1982 in a series of 41 soft-tissue vascular tumors with behavior that was intermediate between benign hemangiomas and malignant hemangioendotheliosarcomas.

Ishak et al\(^2\) first described primary liver involvement of EHE in a multi-institutional review of 32 cases. Clinically, hepatic EHE typically presents as an incidental finding with symptoms at the time of diagnosis ranging from nonspecific to those of frank liver failure. The imaging modalities used in the diagnosis of hepatic EHE are varied, and the characteristic computed tomographic and magnetic resonance imaging findings include the presence of multiple, predominantly peripheral hepatic nodules that often become confluent. Lesions typically have a hypovascular core and a hyperemic periphery and often cause retraction of the overlying hepatic capsule\(^3\) (Figure 1). Histologically, hepatic EHE can mimic other vascular tumors of the liver such as angiosarcoma, and cases of hepatic EHE have been misdiagnosed as cholangiocarcinoma, fibrolamellar hepatocellular carcinoma, sarcoma, or mixed tumors. Positive immunohistochemical staining for factor VIII, CD34, and/or CD31 antigen on pathologic assessment represents the hallmark of diagnosis\(^4-14\) (Figure 2). Distinguishing hepatic EHE from other liver tumors is vital, because 5-year survival in hepatic EHE has been reported to be up to 55%,\(^3\) which compares favorably with that of other primary liver malignant neoplasms. To date, reports on the treatment of hepatic EHE have been limited to small

See Invited Critique at end of article
The diagnosis of hepatic EHE was based on immunohistochemical staining that was positive for factor VIII, CD34, and/or CD31. Other pathologic features, including lymph node status, mitotic features, atypia, cellularity, and angiolymphatic invasion, were also examined.

Patients were classified into 1 of the following 4 groups on the basis of treatment: LT, transcatheter arterial chemoembolization (TACE), surgical resection, and TACE preceding LT. Groups were compared for demographics, clinicopathologic characteristics, treatment-related complications, and overall survival. Survival was assessed from the time of initial treatment to the date of death. Date of death was obtained from the patients’ family or, if the patient was unavailable for follow-up, from the Social Security Death Index.

We entered and verified the data using commercially available statistical software (SPSS, version 16; SPSS Inc, Chicago, Illinois). We examined the distribution of data and calculated descriptive statistics, including frequencies, percentages, ranges, measures of variability, and central tendencies to describe the sociodemographic characteristics, treatment modalities, clinicopathologic characteristics, and treatment complications. We performed log-rank (Cox-Mantel) survival analyses using Kaplan-Meier methods to test differences in survival (in months) between patients with and without angiolymphatic invasion, lymphadenopathy, and extrahepatic disease.

Forty-two patients had a pathologic diagnosis of hepatic EHE and underwent evaluation at the University of Pittsburgh Medical Center. Twenty-five of the 42 patients were treated at our institution and thus represent the cohort of patients described in this study. The median age at the time of diagnosis was 38 years (range, 9 months to 72 years). Twelve patients (48%) were male. The diagnosis of hepatic EHE was incidental in 9 cases (36%). The most frequent symptom among patients who were symptomatic was abdominal pain in the right upper quadrant and/or epigastrium. The nonspecific symptoms with which it is associated and its rarity underscore the difficulty in making the diagnosis of hepatic EHE.

We analyzed the 4 treatment groups and found that 17 patients were treated with LT alone; 4 received TACE; 2 underwent surgical resection; and 2 received TACE followed by LT. Of the patients who received TACE as their primary treatment modality or before LT, an average of 7 cycles were administered. The initial chemotherapeutic agents administered were doxorubicin hydrochloride (5 patients) and cisplatin (1). Four of 6 patients who received TACE (67%) had more than 1 regimen of chemotherapy during the course of therapy with secondary agents including gemcitabine hydrochloride (5 patients) and cisplatin (2). All patients treated with TACE were monitored with computed tomography every 3 to 6 months during treatment, and none had local or extrahepatic progression of disease. The chemotherapeutic regimen was changed if the patient reached the maximum tolerated lifetime dose. Cardiac history, renal function, and prior chemotherapy received influenced the choice of chemotherapy.

Because of the number of censored cases (9 cases [36%]), median survival could not be calculated. The mean overall survival was 167 (95% confidence interval [CI], 123-212) months. The mean survival for the 2 largest treatment groups (TACE alone vs LT) was not sig-

**METHODS**

After institutional review board approval, a retrospective review from a prospectively established database was performed of all patients receiving treatment for hepatic EHE at the University of Pittsburgh Medical Center from 1976 through 2007. The diagnosis of hepatic EHE was based on immunohistochemical staining that was positive for factor VIII, CD34, and/or CD31. Other pathologic features, including lymph node status, mitotic features, atypia, cellularity, and angiolymphatic invasion, were also examined.
nificantly different (P = .98). Patients undergoing LT had a mean survival of 172 [95% CI, 124-220] months, whereas that of patients treated with TACE was 83 [54-112] months (P = .98). The 2 patients in the surgical resection group remained alive after 19 and 71 months, and the 2 patients treated with TACE followed by LT died after 13 and 113 months. Treatment-related complications occurred in 6 patients (24%) and were limited to the surgical groups (LT, surgical resection, and TACE followed by LT). Complications included primary graft failure (2 patients), biliary strictures requiring reoperation with anastomotic revision (2), bile leak managed conservatively (1), and incisional hernia (1). No cases of liver failure, renal failure, thrombocytopenia, or neutropenia associated with TACE occurred, and the postembolization syndrome of nausea and abdominal pain, when encountered, was effectively managed on an outpatient basis with oral antiemetics and opioids.

When we analyzed the clinicopathologic characteristics of the tumors (Table), we identified the presence of angiolymphatic invasion in 14 patients (56%). The difference in mean survival for patients in whom angiolymphatic spread was identified (148 [95% CI, 93-202] months) compared with those in whom it was absent (192 [134-251] months) was not statistically significant (log-rank test, 0.53; P = .047) (Figure 3). Six of the 21 patients whose lymph nodes were sampled at the time of surgery had pathologically positive lymph nodes. These patients experienced no difference in outcome (mean survival, 197 [95% CI, 130-266] months) compared with those whose lymph node biopsy results were negative (mean survival, 138 [100-177] months) (log-rank test, 0.86; P = .35) (Figure 4). Nine patients (36%) had radiologic evidence of extrahepatic disease extending beyond the portal nodes. The sites of extrahepatic disease included the lungs (3 patients) and the omentum, adrenal gland (superficial extension), vertebral column, chest wall, inguinal lymph node, and mediastinal lymph node (1 each). There was a statistically significant difference in the mean survival of patients who had no extrahepatic disease (202 [95% CI, 157-248] months) compared with those with extrahepatic disease (39 [37-80] months) (log-rank test, 6.19; P = .01) (Figure 5). All 4 patients in the TACE arm had extrahepatic disease; however, there was a trend toward better survival for these patients compared with the remaining 5 patients with extrahepatic disease who were treated with resection or LT (mean survival, 83.0 [95% CI, 54.2-111.8] vs 38.8 [23.7-53.8] months; P = .12).

Table. Clinicopathologic Characteristics of 25 Patients With Hepatic EHE

<table>
<thead>
<tr>
<th>EHE Characteristics</th>
<th>LT (n=17)</th>
<th>TACE (n=4)</th>
<th>Resection (n=2)</th>
<th>LT + TACE (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilobar</td>
<td>17 (100)</td>
<td>2 (50)</td>
<td>2 (100)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>4 (24)</td>
<td>2 (50)</td>
<td>2 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>6 (35)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angiolymphatic invasion</td>
<td>11 (65)</td>
<td>2 (50)</td>
<td>0</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Atypia</td>
<td>3 (18)</td>
<td>2 (50)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: EHE, epithelioid hemangioendothelioma; LT, liver transplantation; TACE, transcatheter arterial chemoembolization.

Figure 3. Kaplan-Meier survival curves for patients with vs without angiolymphatic invasion.

We herein report a series of 25 patients with hepatic EHE treated during the course of 30 years at a high-volume liver transplant and cancer center. This study, to our knowledge, represents the largest single-institution review describing the use of various approaches in the management of hepatic EHE, and as such underscores its rarity. The incidence and etiology of hepatic EHE are unknown; however, risk factors may include oral contraceptive use,13 trauma,14 exposure to vinyl chloride,15 and other occupational hazards.16 Two of the patients in the present series had used oral contraceptives, whereas 1 patient had an abdominal trauma a few months before diagnosis.

The clinical signs and symptoms of hepatic EHE are variable and range from asymptomatic to overt liver failure. Most of the patients in our series (14 patients [56%]) presented asymptotically or with vague upper abdominal symptoms. This is consistent with the largest clinicopathologic review on the subject13 in which 78.1% of the 137 patients with hepatic EHE presented with no symptoms or with only vague abdominal symptoms.

Previous descriptions of this rare tumor primarily have been case reports9,17-19 or small series of patients undergoing treatment with a single therapeutic modality.6-8,20 Considerable focus has been applied to the role of LT in the management of hepatic EHE.7,8,18-20 A recent report using data from the United Network for Organ Sharing registry for 110 patients undergoing LT for EHE during an approximately 20-year period reported a 5-year survival after LT of 64%.21 The present report is, to our knowledge, the first single-institution experience describing the results of different approaches in the treatment of hepatic EHE. Unfortunately, the small number of patients...
in our cohort makes drawing comparisons between the outcomes associated with these different approaches difficult. Furthermore, the rarity of hepatic EHE makes the prospect of prospective trials comparing different treatment modalities impractical.

None of the patients in the present study were treated with systemic chemotherapy. In other anecdotal reports, patients with hepatic EHE have responded to systemic treatments such as thalidomide, intravenous doxorubicin hydrochloride (Adriamycin), and, more recently, interferon alfa \(^{10,11,17,22}\); however, these represent single case reports that lack convincing evidence of benefit and thus are not included in our treatment armamentarium. Future studies aimed at assessing the role of systemic treatments in the management of hepatic EHE are warranted.

Well-established prognostic factors for hepatic EHE do not exist. Our series fails to identify angiolymphatic invasion or positive lymph node involvement as poor prognostic factors. However, the presence of extrahepatic disease beyond regional portal nodes is a negative predictor of outcome. Previous reports have advocated LT for hepatic EHE, even in the face of extrahepatic disease. \(^{7,8}\) Undoubtedly, the lack of proven systemic therapies and the unpredictable clinical nature of hepatic EHE entered into the clinical decisions of those authors. However, in the present report, we have found that, in the setting of extrahepatic disease, patients treated with TACE fare better and have less treatment-related morbidity than those treated with surgical approaches. The trend toward improved outcomes in this subset of patients may be attributable to the tendency of postoperative immunosuppression to cause progression of untreated, residual disease. \(^{23}\)

Given our findings, we suggest that, in the absence of metastatic disease, patients be considered candidates for LT because this is offered with curative intent. In addition, the mean survival (172 months) of patients undergoing LT for this rare tumor compares favorably with that of patients undergoing LT for other malignant neoplasms such as hepatocellular cancer. \(^{1,24}\) We have adopted a policy of TACE administration for patients with extrahepatic disease, given the presence of normal liver function and the lack of other prohibitive factors. This approach effectively palliates more advanced disease and may offer improved outcomes in this setting compared with surgical modalities. The role of preoperative TACE as an adjunct to LT is not clearly established in the present study and may warrant further investigation. Resection may be pursued in select patients in whom limited hepatic disease is present. Unfortunately, that is a clinically unusual scenario.

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Getting a Handle on Managing Rare Tumors

Few surgeons will ever encounter patients with EHE, a rare tumor. In this article, Cardinal and colleagues have summarized the current state of management for EHE and have shared their experience for treating patients with these unusual tumors. As they point out, there are no distinguishing characteristics for diagnosis, and these tumors can mimic a variety of other tumors. Careful pathologic analysis with appropriate tumor markers should be used to make the diagnosis, and appropriate imaging should be performed to evaluate for extrahepatic disease. Liver transplant is currently the most widely recommended therapy.

The present series describes a single institution’s experience managing these tumors. Although the numbers are small, the observations presented are intriguing. The authors noted a number of case reports suggesting that other forms of systemic therapies might be effective in treating these tumors, but they discounted these anecdotal and lacking convincing evidence. Based on the observations in this study, one has to question whether EHE may be responsive to a variety of treatments, and an algorithm for optimal treatment has yet to be developed. The authors proposed the possibility of preoperative TACE as an adjunct to transplant, but other therapies might also be effective and have fewer toxic effects.

In the present series, only 25 patients were reported in more than 30 years. Clearly, we need a better method for developing strategies for treating rare tumors such as EHE. Ideally, patients with these tumors should be treated at a few regional centers with both transplant and oncologic expertise. Institutions designated as regional centers should collaborate in maintaining a unique database for EHE and other rare tumors. There should be a consensus panel to develop algorithms for first-line and salvage therapies based on current available data.

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