J Gastrointest Canc (2012) 43:521–525
DOI 10.1007/s12029-012-9389-y

REVIEW ARTICLE

Diagnostic and Therapeutic Challenges in Hepatic Epithelioid Hemangioendothelioma

Akshitkumar M. Mistry · D. Lee Gorden · Jacob F. Busler · Alice C. Coogan · Beau S. Kelly

Published online: 29 April 2012

Abstract
Background Epithelioid hemangioendothelioma is a very rare, low-grade vascular tumor known to arise in soft tissues and visceral organs. Clinical diagnosis of hepatic epithelioid hemangioendothelioma remains a challenge, and although it is frequently managed with a liver transplant due to its multifocal nature, recurrence is a common complication.
Methods We review recent advances in the diagnosis of hepatic epithelioid hemangioendothelioma, including major genetic breakthroughs, and discuss efforts to reduce post-liver transplant recurrence of hepatic epithelioid hemangioendothelioma.

Keywords Hepatic epithelioid hemangioendothelioma · Epithelioid hemangioendothelioma · HEHE · EHE

Background

Epithelioid hemangioendothelioma (EHE), first described by Weiss and Enzinger in 1982 [1], is a rare vascular neoplasm of endothelial origin known to arise in various soft tissues and visceral organs. While classified as a malignant neoplasm by the World Health Organization [2], its clinical course is intermediate in the spectrum of vascular tumors between benign hemangiomas and malignant angiosarcomas [3–6].

The first hepatic occurrence of EHE was reported in 1984 by Ishak et al. [6]. EHE manifests in the liver typically as a primary tumor, referred as hepatic epithelioid hemangioendothelioma (HEHE) [7–9], with an incidence of less than one in a million [10]. HEHE is known to occur in individuals of all ages (reported from 3 to 86) with a peak incidence in the third and fourth decades of life and a greater frequency in women than men (3:2) [4, 5]. Although several risk factors for HEHE have been proposed, including oral contraceptives, vinyl chloride, asbestos, alcohol, thorotrast, liver trauma, hepatitis virus, alcohol, and chronic liver disease, none has been proven to increase the risk of developing HEHE [4, 11–13].

Diagnostic Challenges

Due to the rare tumor incidence and nonspecific symptoms and laboratory profiles, imaging and histopathological analysis are important in diagnosing HEHE. About half of the patients with HEHE present with right upper quadrant discomfort, hepatosplenomegaly, and/or weight loss; another 25 % are asymptomatic [4]. Increased alkaline phosphate, increased γ-glutamyl transpeptidase, and normal serum alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen 19–9 are typical lab values of patients with HEHE [4]. Fifteen percent of the HEHE patients do not even have abnormal values on common lab tests [4].

Majority (>85 %) of patients present with multifocal, bilobar lesions on radiological imaging [4]. Although lesions on ultrasound have a variable pattern of echogenicity, typical computed tomography (CT) findings include hypoattenuated lesions, which may demonstrate peripheral enhancement

A. M. Mistry (✉)
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232-0275, USA
e-mail: a.mistry@vanderbilt.edu

D. L. Gorden · B. S. Kelly
Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Vanderbilt University Medical Center, Nashville, TN 37232-0275, USA

J. F. Busler · A. C. Coogan
Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232-0275, USA

("halo" sign) in the portal venous phase after arterial contrast enhancement (Fig. 1b) and may cause "capsular retraction" if they are subcapsular (Fig. 1a) [4, 14–17]. Two patterns of HEHE are generally noted on radiological imaging: a multifocal nodular type, hypothesized to be an early stage of the disease, and a diffuse type, which is thought to be an advanced stage, where the nodules have grown and coalesced to form large confluent masses, often with associated hepatic vascular invasion and nodular transformation of the liver [13–15, 18].

Histologically, HEHE appears as nests or cords of epithelioid endothelial cells spreading within sinusoids and other vascular structures in a background that may vary from highly myxoid to hyaline (Fig. 2a) [19–21]. These cells may demonstrate intracytoplasmic lumina that sometimes contain red blood cells (Fig. 2b), and immunohistochemistry shows intense staining of these cells with CD31 (platelet endothelial cell adhesion molecule 1), CD34 (human hematopoietic progenitor cell antigen), and Factor VIII, which confirms the endothelial origin of the tumor cells (Fig. 2c–e) [4].

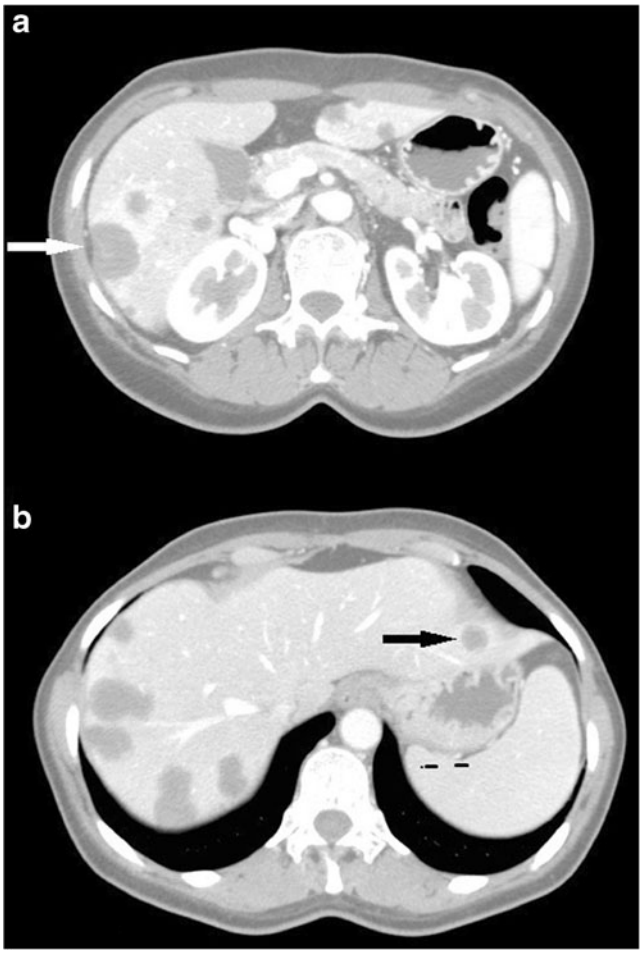

Fig. 1 Contrast-enhanced axial CT images showing hypoattenuated lesions of hepatic epithelioid hemangioendothelioma (HEHE). *Arrows* point to the unique radiological features of HEHE such as capsular retraction caused by subcapsular lesions in (**a**) and peripheral enhancement around hypoattentuated lesion in the portal venous phase after arterial contrast enhancement (the "halo" sign) in (**b**)

HEHE is highly variable in its malignant potential, with reports of patient deaths as variable as within weeks of diagnosis to living up to 27 years without treatment, and at least one reported case of spontaneous regression [4, 5, 22, 23]. This variability may reflect the difficulty in distinguishing EHE in general from other vascular tumors, likely due to the lack of specific, clinically useful, diagnostic tools. Although aggressive and atypical histologic features result in poor clinical outcome, there have been cases of EHE without atypical histological features that demonstrated metastases and poor clinical outcome [3, 24]. Furthermore, while CD31, CD34, and Factor VIII are useful markers in differentiating EHE from carcinomas in epithelial organs, they are not specific. Other vascular tumors with overlapping morphological and histological features such as angiosarcoma, angiomyolipoma, and hemangiomas also express these endothelial cell markers, hindering proper distinction from these tumors at times [25, 26].

Recent Diagnostic Advances

Two potential biochemical markers of HEHE and one genetic marker of EHE have recently been identified. It has been demonstrated that vascular endothelial growth factor (VEGF) is expressed in HEHE tumor cells with high specificity [27]. This finding is corroborated by two prior case reports that demonstrated elevated levels of serum VEGF in three patients with HEHE that significantly reduced following surgical resection of the tumor or steroid treatment [28, 29]. The role of using VEGF as a marker to gauge response to treatment, however, is still unclear. Further studies are warranted.

Podoplanin, a small mucin-like transmembrane protein that is immunoreactive to D2-40 antibody, has been recently shown to be expressed by HEHE tumor cells [26]. Detected in other cancers of squamous cells and the central nervous system, this protein has been demonstrated to be implicated in tumor cell migration and invasion [30]. Because primary vascular tumors in the liver such as angiosarcoma, angiomyolipoma, and hemangioma lack expression of podoplanin, this protein could be a useful diagnostic marker for HEHE [26].

Until recently, little was known about the genetic basis of EHE. Although there have been few cytogenetic reports of EHE demonstrating different chromosomal abnormalities [31, 32], the report by Mendlick et al. [33] first revealed an identical chromosomal translocation t(1;3)(p36.3;q25) in two EHE cases (one HEHE and a primary soft tissue EHE). Two recent follow-up studies independently identified the gene fusion product of this translocation to be WWTR1–CAMTA1, where both genes have been previously known

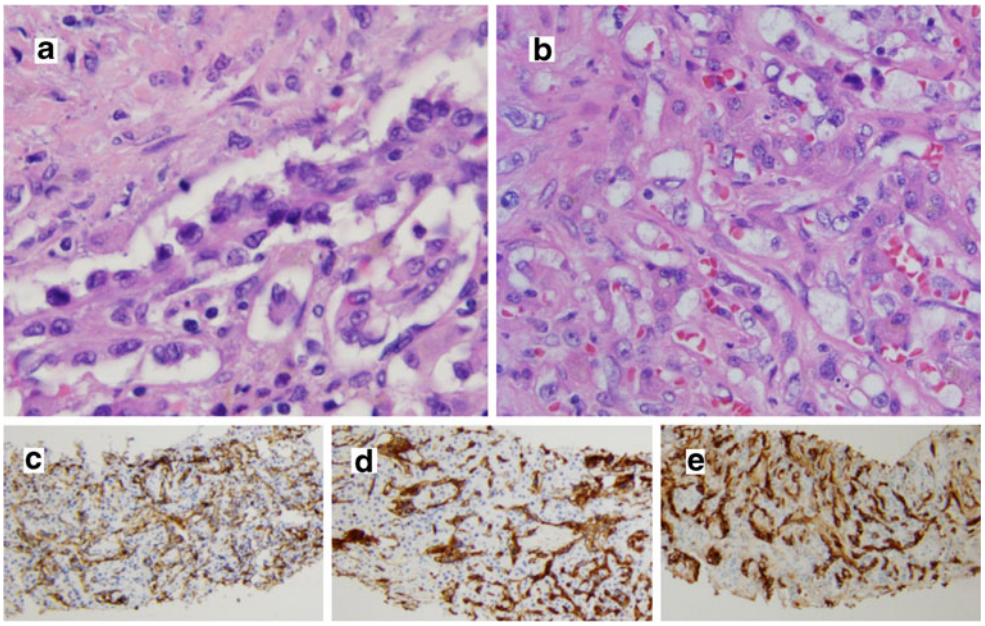

Fig. 2 Biopsy of hepatic epithelioid hemangioendothelioma lesions showing neoplastic epithelioid cells with abundant cytoplasm infiltrating sinusoids in a fibrous stroma (**a**). Note the intracytoplasmic vascular lumina that occasionally contain red blood cells (**b**). Three *insets in the bottom* show immunohistochemistry with CD31 (**c**), CD34 (**d**), and Factor VIII (**e**) characteristic of these tumor cells

to play a role in oncogenesis [34, 35]. Involvement of these genes in rearrangements was found with high sensitivity and specificity in EHE cases of various tissues (17/17 EHE cases, including 2/2 HEHE in Errani et al. [34] and 39/47, including 11/12 HEHE in Tanas et al. [35]). Moreover, surrounding normal tissues did not express the WWTR1–CAMTA1 fusion transcript [35]. This suggests that the translocation is an early somatic event that leads to EHE [35]. Other vascular neoplasms, such as hemangiomas and angiosarcomas that histologically mimic EHE, tested in these two studies (22 total in Errani et. al. [34] and 118 total in Tanas et. al. [35]), did not show rearrangement of these two genes. This suggests that EHE and epithelioid angiosarcoma are genetically distinct and argues against a biological continuum between epithelioid angiosarcoma and EHE [35]. Probing for this translocation through fluorescence in situ hybridization, as demonstrated by Woelfel et. al. [36], can serve as the specific diagnostic test of EHE that has been long sought. This discovery may also pave the way for understanding mechanisms of tumorigenesis of EHE and the development of novel therapies for this tumor.

Current Treatments

Because a majority of the patients present with extensive multifocal, bilobar disease or anatomically difficult lesions, liver transplantation (LT) is the most common and preferred treatment [4, 37–39] with 5-year survival rates ranging from 64 to 83 % [40–42]. Transcatheter arterial chemoembolization has been shown to be valuable when extrahepatic disease or comorbid conditions prohibit LT [43].

In the case of monolobar, localized disease, a complete resection of the tumor is preferred; however, palliative or incomplete resection of HEHE is discouraged as aggressive tumor recurrence has been reported [44, 45], probably due to the effects of resection-stimulated hepatotrophic growth factor release on the neoplastic cells [4, 46].

Post-transplant Recurrence of HEHE

Estimated from reports in literature, the post-liver transplant course is complicated by recurrence in approximately 30 %

Table 1 Selected studies showing the frequency and management options for recurrent HEHE [27, 38, 40–42]

Study	Year	LT (*n*)	Recurrence	Graft recurrence	Months to recurrence	Management of allograft recurrence
Emamaullee et al. [27]	2010	6	3	2	6–84	LT, IS
Nudo et al. [41]	2008	11	4	3	7–61	LT, SR, pINF
Rodriguez et al. [40]	2008	38	12	–[a]	–[a]	
Mosoia et al. [38]	2008	9	4	3	3–52	LT
Lerut et al. [42]	2007	59	14	8	6–98	CT, RT, SR with CT, RT with CT
Cumulative recurrence rate			30 %			

CT chemotherapy, *IS* immunosuppresives, *pINF* pegylated interferon, *LT* liver transplant, *SR* surgical resection, *RT* radiotherapy

[a]Data not available

of the cases (Table 1). The recurrence has an unpredictable time course and often occurs in the allograft. Similar to the development of primary HEHE, its recurrence after treatment can be subclinical. Patients may be asymptomatic with no laboratory abnormalities. Therefore, based on our experiences, we recommend routine post-liver transplant surveillance using axial CT or magnetic resonance imaging.

The mechanism of recurrence in the allograft is unclear. Recent clinical studies aimed at understanding the indications of LT in HEHE with vascular invasion or extrahepatic disease demonstrated inconsistent influence of these factors on the clinical outcome after LT [42–44]. However, in these studies, lymph node invasion did not significantly influence clinical outcome after LT.

Currently, there is no consensus regarding the management of HEHE recurrence. Second liver transplant, chemotherapy, immunosuppressives, pegylated interferon, and radiotherapy have all yielded variable results in isolation or in combination with regard to extending life span after allograft recurrence of HEHE. In light of two case reports that reported elevated levels of serum VEGF in three patients with HEHE that reduced following treatment [28, 29], Emamaullee et al. [27] investigated whether maintenance immunosuppression with sirolimus, an m-TOR inhibitor known to reduce VEGF expression and signaling [47], would be beneficial. However, sirolimus did not prevent recurrence of HEHE in two of the three patients. Although there are no reports of anti-VEGF therapy in the setting of recurrent HEHE, few recent reports have demonstrated the use of bevacizumab, an anti-VEGF antibody, in primary pulmonary EHE [48–52]. The outcomes in these reports are variable, and taking them collectively, the role of anti-VEGF therapy in the management of recurrence of EHE remains to be determined. Efficacy of anti-VEGF adjuvant therapies as well as other treatment modalities, including retransplantation, surgical resection, chemotherapy, chemoembolization, and radiotherapy, in recurrent HEHE still remains debated due to the rare incidence of HEHE, which prevents large studies for reliable conclusions.

Conflict of Interest No potential conflict of interest relevant to this article was reported.

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