Editorial

Hepatic epithelioid hemangioendothelioma: pitfalls in the treatment of a rare liver malignancy

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Hepatic epithelioid hemangioendothelioma (HEHE) is a member of a group of rare liver neoplasms with vascular lineage that are collectively known as primary hepatic vascular malignancies (PHVM) and account for less than 1% of liver tumors (1). The other PHVM are angiosarcoma (AS) and hemangiopericytoma, with AS being the most prevalent of the three, followed by HEHE, while hemangiopericytoma is exceedingly rare (2). Surgery, in the form of resection or transplantation, remains the only curative-intent treatment option for patients with PHVM, as there are no established effective systemic therapies.

These uncommon tumors can pose several challenges to the clinician, beginning with establishing the correct diagnosis. HEHE is more common in middle-aged women, but as the accompanying article to this editorial highlights, it can also afflict women in much younger age (3). Clinically, HEHE is most often asymptomatic as it develops in the normal liver in the absence of cirrhosis. When symptoms occur, right upper quadrant pain is the most common complaint (4). In the accompanying case-report, the patient originally experienced abdominal pain and bloating for three years, followed eventually by unintentional weight loss. Radiographically, HEHE typically manifests as multifocal, coalescent hepatic nodules in the liver periphery, with associated capsular retraction. Peripheral arterial ring enhancement and target appearance on portal venous phase are commonly seen on computed tomography (CT). Similarly, multilayered target appearance is typically seen on magnetic resonance imaging (MRI) sequences (5,6). HEHE can sometimes display a distinct "lollipop" appearance on cross-sectional imaging, whereas a large vessel occluded by tumor is the "stick" and the tumor is the "head" of lollipop (7). Nevertheless, in the majority of patients, imaging alone will not be pathognomonic for the diagnosis of HEHE, as it can be particularly challenging to distinguish HEHE from AS based on radiographic appearance (8). In fact, Wilson *et al.* found that up to 30% of patients with AS were initially thought to harbor a less aggressive PHVM based on imaging alone (9).

Given the limitations of imaging, tissue sampling, either percutaneously or via a surgical biopsy, is often necessary to establish the diagnosis of HEHE. It is paramount to correctly identify the histologic subtype of PHVM, as each entity portends different prognosis. On the one hand HEHE can be an indolent tumor with favorable outcomes following surgical treatment, while AS and hemangiopericytoma tend to be aggressive malignancies with associated poor outcomes despite surgical intervention (2,10,11). Percutaneous biopsy for PHVM has historically been considered unsafe due to risk of bleeding, but a contemporary series from Korea demonstrated that it is a safe approach with a low incidence of clinically significant post-procedure bleeding (3 out of 33 patients) that was managed with either transfusion or embolization, without the need for urgent surgical intervention (12). Therefore, it remains at the discretion of the clinician to choose the

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best approach to biopsy. Once tissue is obtained, HEHE displays several distinctive histologic features that can lead to its diagnosis. On microscopy, it is often centered around a feeding vessel and has a dense, fibrotic, or myxoid stromal matrix. The tumor cells are epithelioid, have occasional intracytoplasmic lumens containing red blood cells, but do not form actual vessels. The neoplasm can invade sinusoids and larger vessels (13). Furthermore, molecular studies are indispensable in solidifying the diagnosis of HEHE, as most tumors harbor either the CAMTA1-WWTR1 or the YAP1-TFE3 fusions, which can be detected by immunohistochemistry, fluorescence in situ hybridization (FISH) or reverse transcriptase-polymerase chain reaction (RT-PCR) (13,14). Experienced liver pathologist involvement is crucial in these investigations and there should be no hesitation to seek a second opinion, if needed, given the critical nature of establishing the correct diagnosis of an uncommon tumor. Failing to do so can have dire consequences for the patient, as described in the accompanying case report, where a three-year delay in diagnosis of HEHE occurred as two tumor biopsies were read as negative and no specialized immunohistochemistry stains were performed.

Once the diagnosis of HEHE is established, staging work-up should be performed including cross-sectional imaging of the abdomen and chest. Additionally, the grade of the tumor should be determined by expert review of the sampled tumor. Treatment options should then be discussed by a multidisciplinary team to include liver radiologists, pathologists, hepatic and transplant surgeons. In general, surgery, in the form of resection or transplantation, is the mainstay of cure for patients with HEHE, but it remains unclear which patients derive the most benefit from these interventions. A recent review of the National Cancer Database (NCDB) identified tumor grade, tumor size, presence of metastasis and presence of involved surgical margins to be associated with worse survival (10). Therefore, it would appear that patients with low-grade, small size tumors, without metastasis, who undergo a margins negative resection benefit the most from surgical intervention. However, Lai *et al.* in a study of 149 transplant recipients with HEHE found that the presence of extrahepatic metastasis was not a contraindication for liver transplantation, as outcomes remained acceptable (15). Making the determination of whether liver resection or transplantation is the best approach for a specific patient can be challenging. A retrospective review of 30 patients by Grotz *et al.* suggested that liver resection, when feasible and able to obtain negative surgical margins, can lead to equivalent outcomes as liver transplantation (16). However, a more recent review of 334 HEHE patients in the NCDB by Kaltenmeier *et al.* found that liver transplantation was associated with longer survival (17). Paradoxically though, no intervention was associated with better survival than liver resection in their cohort, which suggests that there was clinical bias in which patients were offered surgery, and therefore therapeutic recommendations based on retrospective reviews of large cancer registries should be interpreted with caution. Finally, a small series of four patients by Na *et al.* suggested that living donor liver transplantation can be an option for patients with HEHE without macrovascular invasion or metastasis (18).

The accompanying case-report by Ribeiro *et al.* (3) highlights several "real-world" challenges that clinicians must be mindful of when dealing with uncommon liver neoplasms, such as HEHE, which do not always fit their textbook descriptions. First of all, although HEHE typically afflicts middle-aged women, in this case the patient was a female in her teenage years, therefore clinicians should not rely on demographics alone to rule-out certain liver neoplasms. Second of all, it is paramount to refer patients with atypical liver imaging or biopsy findings to centers with hepatobiliary expertise, as in this case abnormal MRI and liver biopsy findings were not correctly interpreted as malignant for several years. Thirdly, although HEHE has been largely described in the literature as an indolent tumor with median survival of upwards of 10 years, it appears that it can progress more rapidly in certain patients, as demonstrated by this case report, which again underscores the need for prompt diagnosis. Furthermore, there are no prospective studies to guide the management of HEHE patients, and it remains unclear which patients benefit most from resection versus liver transplantation. In general though, existing studies suggest that low-grade, smaller size tumors, without distant metastasis derive the most benefit from surgery (10). Finally, there are unfortunately no effective system therapies for patients with advanced disease, as exemplified by the accompanying case report, where sorafenib was administered without benefit. Although some studies have suggested that the mTOR inhibitor, sirolimus, may be effective against HEHE, more research is needed in this field (19).

In conclusion, HEHE is a rare PHVM that can pose significant diagnostic and management challenges. Patients with HEHE are best managed in a multidisciplinary fashion in centers with hepatobiliary expertise. There

are distinct genetic alterations that can help diagnose HEHE. For patients with localized disease liver resection or transplantation remains the mainstay of cure. Although HEHE oftentimes follows an indolent course with prolonged survival, a subset of patients can exhibit rapid progression and metastasis.

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