Recurrence of Epithelioid Hemangioendothelioma during Pregnancy: Case Report and Systematic Review

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ABSTRACT

Introduction: Epithelioid hemangioendothelioma (EHE) is a family of blood vessel tumors originating in blood vessels, bone, brain, kidney, liver, and lung. EHE is more common in women, and chemotherapy, radiation, and surgery have brought few successes.

Case presentation: We present a case of a 28-year-old woman whose EHE recurred during pregnancy, suggesting hormonal involvement. We conducted a systematic review to provide analysis and interpretation of the potential significance of her disease recurring, with fatal outcome, during pregnancy.

Discussion: Very little research has explored the use of individual hormonal markers. Strongly positive expression of placenta growth factor (PlGF) and 17-beta estradiol receptors have been reported. Expression of PlGF is noteworthy in our case, in that our patient’s disease quickly and dramatically flared in the 25th week of pregnancy, near the peak in maternal PlGF production. PlGF binds to vascular endothelial growth factor-1 (VEGF-1), and PlGF may accelerate VEGF-induced angiogenesis. Taken together, these factors may explain our patient’s EHE recurrence and rapid flare-up during pregnancy. Treatment of EHE with VEGF inhibition, potentially in combination with other antiangiogenic and tumor-inhibiting therapies such as lenalidomide, thalidomide, sorafenib, and sunitinib, may also hold promise.

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a family of vascular tumors, originating in the endothelium and sharing clinical characteristics with both angiosarcoma and benign hemangioma. EHE was first identified in 1982 and is extremely rare, with an incidence rate of 0.1 per 100,000, and fewer than 200 cases ever reported in the medical literature. Because there is limited research on prognosis, a layperson registry has been established. The International Hemangioendothelioma, Epithelioid Hemangioendothelioma, and Related Vascular Disorders Support Group has tracked more than 260 patients.

The clinical presentation of EHE is quite varied; it can originate in bone, brain, kidney, liver, lung, and vascular and other soft tissues. Diagnosis is sometimes delayed owing to uncertainty about correct pathologic classification, which can significantly worsen prognosis. Little is known about prognostic factors for patients with EHE, although recent work has identified genetic alterations involving activation of the ROS1 receptor tyrosine kinase, which for other cancers has led to effective therapies working through ROS1 inhibition.

Two case series have described the prognosis of patients with hepatic EHE. In a series from China (N = 33), survival was longer in patients younger than age 47 years (hazard ratio, 7.0; p = 0.035), in those without symptoms (hazard ratio, 86.5; p = 0.001), and in those with serum cancer antigen 19-9 below 37 units/mL (hazard ratio, 5.0; p = 0.018). In a series from the United Kingdom (N = 50), patients with bilateral hepatic disease had shorter 5-year survival (51%) compared with those with unilateral disease (81%), although the study size was too small to show a significant difference (p = 0.1). There was additionally nonsignificant lower 5-year survival in metastatic (69%) compared with localized (78.3%) disease (p = 0.7). Treatment with any chemotherapy decreased 5-year survival, compared with no chemotherapy (43.6% vs 82.9%; p = 0.02).

Diagnostic approaches to EHE include computed tomography (CT), magnetic resonance imaging, and magnetic resonance imaging, and serial bone scintigraphy. (18)F-fluorodeoxyglucose-positron emission tomography with (18)F-fluorodeoxyglucose uptake has been used but is limited by lack of correlation between lesion size and maximum standardized uptake value.

Little is known about efficacy of therapy because the low incidence of EHE precludes conduct of human clinical trials. Options currently include chemotherapy, radiation, hormone therapy, thermo-ablation, and surgery, although most do not change the usually poor prognosis of a diagnosis with EHE. In patients with primary hepatic EHE, overall survival is no different following liver resection or transcatheter arterial chemoembolization (p = 0.50). Although patients with hepatic EHE have longer median survival compared with those with other hepatic vascular tumors, in these patients surgical resection does not improve survival.

Development and testing of newer therapies based on vascular endothelial growth factor (VEGF) inhibition is supported by recent studies showing positive expression of VEGF receptor in biopsied lesions. Additional case reports of success with lenalidomide, thalidomide, sorafenib (possessing both...
antiangiogenic and antiproliferative activity), and sunitinib suggest other targeted molecular therapies may also hold promise.

The current case report documents diagnosis of recurrent EHE in a pregnant woman and discusses the case in the context of a systematic review of the current literature. This report was prepared in accordance with the CARE (CAse REport) guidelines.

CASE PRESENTATION

We report a case of a 28-year-old woman originally diagnosed with EHE in 2002, at age 18 years. CT-guided biopsy of 1 of her liver lesions revealed EHE based on hematoxylin/eosin and immunohistochemical stains (Figures 1-4). Repeated CT of her chest, abdomen, and pelvis 3 months later showed progression of disease. At that time she underwent 6 cycles of carboplatin and etoposide with stabilization of disease; however, significant chest pain remained, requiring high doses of opiates. She received 1 dose of interferon, which was not tolerated. The patient was then followed up with serial CT scan showing stable disease through 2011 (Figures 5 and 6).

In 2012, the patient presented to the Emergency Department with chest pain and in acute respiratory distress. A posterior-anterior/lateral chest radiograph revealed multiple pulmonary nodules bilaterally, confirmed as “innumerable” by chest CT, along with bulky mediastinal adenopathy and multiple liver lesions consistent with metastatic disease (Figure 7).

In mid-2012, the patient presented with diffuse joint pain 6 months into her first pregnancy, and went into labor at 25 weeks. The baby was delivered and died 8 days later. The patient’s pain then continued to escalate and she developed severe cough. Repeat CT scan of her chest, abdomen, and pelvis revealed significant progression of disease, especially in the lungs and mediastinum. Biopsy of mediastinal adenopathy confirmed recurrent EHE, and the diffuse nature of disease precluded surgery.

The patient’s diffuse joint and bone pain continued to worsen, resulting in hospitalization for pain control. Bone scan was consistent with hypertrophic osteoarthropathy. During this time her respiratory status continued to worsen: chest CT revealed compression of the right upper lobe bronchus and right pleural effusion. A right-sided chest tube was inserted with drainage of a large amount of pleural fluid and palliative radiation to the mediastinal adenopathy was started. Unfortunately the patient’s respiratory status continued to decline from progressive disease as well as pneumonia. She was intubated; her condition continued to decline; she was placed on comfort measures, and she subsequently died.

Figure 1. Hematoxylin/eosin stain showing epithelioid cells with cytoplasmic vacuoles (magnification ×400).

Figure 2. Hematoxylin/eosin stain showing epithelioid cells with cytoplasmic vacuoles (magnification ×600).

Figure 3. Immunohistochemical stain positive for vascular marker CD31 (magnification ×600).

Figure 4. Immunohistochemical stain positive for vascular marker CD34 (magnification ×600).

Figure 5. Computed tomography angiography of the chest, showing stable disease in 2008.

Figure 6. Computed tomography angiography of the chest, showing stable disease in 2011.
A timeline showing progression of the case is provided in Figure 8.

**DISCUSSION**

Despite numerous publications, EHE remains a little-understood disease of poor prognosis. In the case of localized disease, prompt surgical resection appears to confer a survival advantage. Improvements in early clinical identification of suspected lesions may be accelerated by further research on the integration of tumor marker and/or hormonal testing.

In Table 1 we present results of a systematic search of treatment outcomes published since January 2011. Tumor marker expression in EHE has been reported for endothelial markers (CD31, CD34, and factor VIII-related antigen), VEGF and VEGF receptor 2, and strong expression of CD31 and vimentin. Errani et al reported that WWTR1-CAMTA1 fusion is a genetic hallmark of EHE, regardless of site of origin; they also used reverse transcription-polymerase chain reaction and gene sequencing to identify WWTR1-CAMTA1 fusion.
ascertain that in multifocal EHE, those multiple sites are monoclonal in nature, and therefore metastatic implants of the same tumor and not simultaneous occurrence of multiple neoplastic clones. Additionally, both CD31 and VEGF are overexpressed in non-small cell lung cancer, breast cancer, prostate cancer, renal cell carcinoma, mantle cell lymphoma, meningioma, pituitary adenomas, and uveal melanoma.

EHE is more common in women, and there are 3 prior case reports of its diagnosis during pregnancy, with ours being the fourth. A case report has also been published of successful management of multifocal hepatic infantile hemangioma with tamoxifen-based therapy. Tamoxifen (20 mg daily) was part of the management strategy used for our patient over a 9-day course during her acute disease recurrence.

Very little research has explored the clinical utility of individual hormonal markers in EHE. There was strongly positive expression of placenta growth factor (PIGF) in 1 case,13 positive expression of 17-beta estradiol receptors in only 1 of a series of 5 EHE patients,14 and no estrogen or progesterone receptors in another case.15 Expression of PIGF is noteworthy in our case, in that our patient’s disease quickly and dramatically flared in the

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<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Primary tumor site</th>
<th>Extent of disease</th>
<th>First-line therapy</th>
<th>Patient(s)</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Wu et al.11,12 2013</td>
<td>Vascular</td>
<td>Localized</td>
<td>Surgery</td>
<td>58-year-old woman</td>
<td>2 years, stable at time of publication</td>
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<tr>
<td>Demir et al.19,20 2013</td>
<td>Liver</td>
<td>Parenchymal lesion with metastases to lung</td>
<td>Carboplatin, pharmorubicin</td>
<td>24-year-old woman</td>
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<tr>
<td>Kiratlı et al.21,22 2013</td>
<td>Eyelid</td>
<td>Localized</td>
<td>Excisional biopsy</td>
<td>22-year-old woman</td>
<td>No recurrence at 44 months</td>
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<tr>
<td>Palföldi et al.23 2013</td>
<td>Lung</td>
<td>Metastatic to bone</td>
<td>Carboplatin, docetaxel, pharmorubicin</td>
<td>49-year-old woman</td>
<td>Stable disease 1 year after diagnosis</td>
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<tr>
<td>Yu et al.24 2013</td>
<td>Lung</td>
<td>Localized to myocardium</td>
<td>Carboplatin/etoposide, followed by surgical excision</td>
<td>39-year-old woman</td>
<td>Alive 14 months after surgery</td>
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25th week of pregnancy, near the peak in maternal PlGF production. Although in our patient’s case PlGF was not tested, we did note an abnormally low human chorionic gonadotropin level during the second trimester of pregnancy of 23 IU/mL.

A translocation involving PIGF has also been discovered in a case of EHE. Furthermore, it is known that there is binding of PIGF to VEGF receptor-1, and that PIGF may influence VEGF-induced angiogenesis, which may explain our patient’s rapid disease flare-up.

Although the scarcity of cases impedes rapid progress in histochemical characterization of EHE, a composite picture has begun to emerge that may aid researchers in its early identification, perhaps leading to earlier diagnosis and more definitive treatment. VEGF expression and hormonal receptor expression have been reported in EHE. Furthermore, there are multiple reports of successful management of this vascular cancer with antiangiogenic therapy (lenalidomide, thalidomide, and sorafenib). We therefore suggest it is possible that combination therapy of EHE with sequenced or concurrent anti-angiogenic, hormonal, and anti-VEGF agents has value as an avenue of future clinical investigation.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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How to Cite This Article


References

All Attemps at a Rational Method of Cure

The main part of the science of disease is of a purely descriptive character, a scientific interpretation of facts and a clear insight into the intimate connection subsisting between different phenomena, which may precede all attempts at a rational method of cure, having been attained in a few instances only. ... Therapeutic researchers must be regulated in the same manner as pathological. ... The more careful tracing of the progress of morbid processes, and the insight into their modes of origin and regression, enable us to determine the principles of treatment with greater clearness than formerly.

— Friedrich Theodor von Frerichs, 1819-1885, German pathologist