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Combination capecitabine and bevacizumab in the treatment of metastatic hepatic epithelioid hemangioendothelioma

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***Abstract*:** Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, often misdiagnosed vascular neoplasm with clinical behaviors that range from indolent to highly aggressive. Even when the appropriate diagnosis is achieved, the best treatment for HEHE has not been defined or standardized, further complicating the care of these patients. We present a diagnostically challenging case of HEHE where we utilized capecitabine and bevacizumab as another novel treatment option.

Keywords: metastatic, heptatic, epithelioid, hemangioendothelioma, capecitabine, bevacizumab

Introduction

First described in 1982, epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm of endothelial origin known to arise in various soft tissue and visceral organs. Common sites of disease include liver, lungs, lymph nodes, peritoneum and bones [Mistry *et al.* 2012]. The estimated incidence of hepatic epithelioid hemangioendothelioma (HEHE) is less than one in one million [Mehrabi *et al.* 2006]. The clinical course of HEHE can vary between benign hemangiomas to malignant angiosarcomas, thus rendering prognosis unpredictable. Mostly afflicting people in the third or fourth decade of life, there is no known etiology for HEHE. Cases reported in the literature have posited a causal relationship between use of oral contraceptives, liver disease, liver trauma, asbestos, vinyl chloride or thorotrast [Mistry *et al.* 2012; Mehrabi *et al.* 2006].

Diagnosing HEHE is challenging given the rarity of the disease and lack of clinically useful diagnostic tools. Misdiagnosis is common, occurring in up to 80% of cases [Mehrabi *et al.* 2006]. Up to 25% of patients are asymptomatic, and 15% have normal laboratory values including normal tumor markers at time of diagnosis [Mistry *et al.* 2012]. Imaging, including computerized tomography (CT) and magnetic resonance imaging (MRI), is also nonspecific [Mistry *et al.* 2012; Mehrabi *et al.* 2006; Amin *et al.* 2011]. A majority of patients presents with multifocal, bilobar hepatic lesions with peripheral enhancement ('halo' sign) and capsular retraction [Mistry *et al.* 2012; Mehrabi *et al.* 2006; Amin *et al.* 2011]. Definitive diagnosis requires histopathologic examination. HEHE appears in nest or cords of epithelioid endothelial cells that are positive for CD31, CD34 and factor VIII on immunohistochemistry [Mistry *et al.* 2012; Mehrabi *et al.* 2006]. Furthermore, vascular endothelial growth factor (VEGF) has been found to be overexpressed in HEHE [Emamaullee *et al.* 2010]. Importantly, podoplanin, a small mucin-like transmembrane protein involved in cell migration and invasion, is expressed in HEHE, distinguishing HEHE from other primary vascular tumors such as angiosarcoma or hemangiomas, which lack podoplanin expression [Mistry *et al.* 2012;Wicki and Christifori, 2007]. In 63% of cases, chromosomal translocation t(1;3)(p36.3;q25) causing gene fusion product WWTR1-CAMTA1 has been identified, which plays a role in oncogenesis [Mistry *et al.* 2012; Woelfel *et al.* 2011; Errani *et al.* 2011].

There is no consensus on standard of care or treatment strategies. Treatment experiences reported in the literature are limited to case reports or retrospective case series from single institutions [Mehrabi *et al.* 2006; Rodriguez *et al.* 2008; Cardinal *et al.* 2009]. The rarity of HEHE precludes prospective studies to elucidate optimal management. Treatment approaches vary, but

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include liver resection, liver transplantation, radioembolization/chemoembolization, radiotherapy, chemotherapy, combined-modality therapy and observation. In the proper candidate, liver transplant has 5-year survival rates ranging from 43 to 83%. Cumulative recurrence rate following liver transplant is about 30%, including recurrence in the allograft [Mistry *et al.* 2012; Mehrabi *et al.* 2006; Rodriquez *et al.* 2008; Cardinal *et al.* 2009]. In addition, extrahepatic HEHE at presentation can range from 37 to 48% [Mehrabi *et al.* 2006; Grotz *et al.* 2010; Thomas *et al.* 2014]. The presence of extrahepatic disease does not significantly affect overall survival (OS) after liver transplantation [Grotz *et al.* 2010].

When treated with chemotherapy/radiotherapy alone, 5-year OS is estimated to be about 30% [Mehrabi *et al.* 2006]. Multiple single agent and combination regimens have been used (Table 1). However, there are no case reports in the literature regarding the use of capecitabine in combination with bevacizumab in the treatment of metastatic HEHE. We present a case of metastatic HEHE currently being treated with capecitabine and bevacizumab.

Case presentation

A 56-year-old woman presented in 2007 with worsening wheezing and a dry cough for approximately 10 months. Her past medical history included diabetes mellitus type II, allergic rhinitis and a 38-pack year history of tobacco use. A CT scan of the chest, abdomen and pelvis found multiple bilateral subcentimeter pulmonary nodules and multiple rim enhancing liver masses with liver capsular retraction (Figure 1a-c).

A core biopsy of a liver lesion revealed immunohistochemistry (IHC) positivity for cytokeratin 8+18, cytokeratin 7, cytokeratin 20 and carcinoembrionic antigen (CEA). Thyroid transcription factor 1 (TTF-1) and estrogen receptor (ER)/progesterone receptor (PR) were negative. Additionally, trichrome staining revealed fibrosis, favoring breast, lung or upper gastrointestinal malignancy. A subsequent positron emission tomography (PET) scan reported no abnormal uptake in the liver lesions.

Given her history, symptoms and pathology, she was treated with carboplatin and gemcitabine. CT imaging after two cycles reported stable liver lesions. The pulmonary nodules were not well visualized. Given minimal response, she then received two cycles of carboplatin and paclitaxel; subsequent imaging showed stable liver disease. Given stability, she opted for a treatment break which lasted 14 weeks. Restaging imaging revealed enlarged liver lesions. Her initial core liver biopsy was re-reviewed at another institution and the consensus was that her liver findings were the result of a bile duct carcinoma. This information prompted a change in regimen to single-agent oral capecitabine. She remained on capecitabine for 1 year with stable disease demonstrated with repeat serial imaging.

After a 4-month treatment break, subsequent restaging imaging revealed enlarging liver lesions. Another biopsy of a liver lesion was performed. IHC was positive for cytokeratins 7 and 8+18, consistent with adenocarcinoma. Results of molecular profiling of the liver lesion biopsy suggested hepatocholangioma. She was treated with sorafenib for 6 months at which point, she elected to stop given adverse side effects and stable disease demonstrated on imaging. After 4 years of observation, capecitabine was reinitiated after she complained of right upper quadrant pain and imaging revealed enlarging liver lesions. Another liver lesion biopsy was performed, which confirmed HEHE. IHC was positive for CD31 and CD34.

Bevacizumab was added to capecitabine given available data showing benefit [Grotz *et al.* 2010; O'Grady, 2000; Lazarus *et al.* 2011; Gaur *et al.* 2012; Salech *et al.* 2010; Agulnik *et al.* 2013]. After 6 months of treatment, the patient continued to show response to treatment (Figure 2a–c) as well as remaining asymptomatic. She is currently being evaluated for liver transplantation.

Discussion

Early therapeutic options other than surgery have not been clearly defined or agreed upon for HEHE. Despite poorer survival outcomes with the use of chemotherapy alone, numerous regimens have been used with varying results [Mistry *et al.* 2012; Mehrabi *et al.* 2006; Thomas *et al.* 2014]. Neoadjuvant biotherapy, specifically interferon-α, for HEHE prior to liver transplant has been described; however, there is no standard neoadjuvant chemotherapy regimen known prior to surgery. There were two cases where patients were free of disease at follow up following orthotropic liver transplant after progressing with chemotherapy or embolization [Thomas *et al.* 2014]. Additionally, there have been limited case reports using adjuvant

Table 1. Various chemotherapeutics used in the treatment of epithelioid hemangioendothelioma and their outcomes.

Reference	Sites of disease	Age (years)	No. patient	Chemotherapy	Dose	Outcome	Duration of follow up
Belmont *et al.* [2008]	Lung	41	1	Carboplatin, paclitaxel, docetaxel, bevacizumab	15 mg/kg, every 21 days (bevacizumab)	Partial Response	13 months
Kim *et al.* [2010]	Lung, liver, bone	44	1	Carboplatin, paclitaxel, bevacizumab	15 mg/kg, every 21 days (bevacizumab)	Progression	Not available
Mizota *et al.* [2011]	Lung, liver	59	1	Carboplatin, paclitaxel, bevacizumab	15mg/kg, every 21 days (bevacizumab)	Progression	3 month
Lazarus *et al.* [2011]	Lung	42	1	Paclitaxel, bevacizumab	Unknown	Progression	1–2 months
Lazarus *et al.* [2011]	Lung	42	1	Carboplatin, etoposide, bevacizumab	Unknown	Progression	2–3 months
Salech *et al.* [2010]	Lung, liver	40	1	Thalidomide	300 mg daily	Partial response	109 months
Raphael *et al.* [2010]	Lung, liver	53	1	Thalidomide	400 mg daily	Stable disease	84 months
Kassam and Mandel [2008]	Lung, liver	13	1	Thalidomide	400 mg twice daily	Progressive disease	Not available
Bolke *et al.* [2006]	Liver, bone	47	1	Thalidomide	Unknown	Progressive disease/death	Not available
Mascarenhas *et al.* [2005]	Lung, liver	52	1	Thalidomide	Unknown	Partial response	Not available
Sumrall *et al.* [2010]	Brain, bone, liver, lung	31	1	Lenalidomide	25 mg daily for 21/28 days	Stable disease	48 months
Schilling *et al.* [2009]	Lung, liver, spleen	33	1	Lenalidomide	30 mg daily for 21/28 days	Stable disease	6 months
Radzikowska *et al.* [2008]	Lung	62	1	Interferon α-2a	3 million units, 3 times/week	Stable disease	3 months
Saleiro et al. [2008]	Lung	39	1	Interferon α-2a	Unknown	Progressive disease	9 months
Calabro *et al.* [2007]	Lung, liver, spleen	53	1	Interferon α-2a	Unknown	Stable disease	Not available
Kayler *et al.* [2002]	Liver, spleen, uterus, peritoneum	21	1	Interferon α-2a	3 million units daily	Partial response	4 months

(Continued)

Table 1. (Continued)

Reference	Sites of disease	Age (years)	No. patient	Chemotherapy	Dose	Outcome	Duration of follow up
Hassan *et al.* [2005]	Thyroid	73	1	Interferon α	3 million units, 5 times/week	Progressive disease	2 months
Marsh Rde *et al.* [2005]	Breast, lung, liver	57	1	Interferon α	3 million units, 5 days/week for 1 year	Complete response	84 months
Al-Shraim *et al.* [2005]	Lung, skin	51	1	Interferon α	7 million units, 3 times/week	Progressive disease	2 months
Agulnik *et al.* [2013]	Unknown	Unknown	1	Bevacizumab	15 mg/kg, every 21 days	Partial response	Not available
Agulnik *et al.* [2013]	Unknown	Unknown	1	Bevacizumab	15 mg/kg, every 21 days	Stable disease	Not available
Agulnik *et al.* [2013]	Unknown	Unknown	1	Bevacizumab	15 mg/kg, every 21 days	Progression	Not available
Lakkis *et al.* [2013]	Lung, liver, spleen	58	1	Cyclophosphamide	50 mg daily, continuous	Progression	6 months
Lakkis *et al.* [2013]	Lung, liver, bone	40	1	Cyclophosphamide	50 mg daily, continuous	Partial response	24 months
Kelly and O'Neil [2005]	Liver, bone	52	1	Liposomal doxorubicin	45 mg/m^2, every 21 days	Partial response	22 months
Grenader *et al.* [2011]	Lung, liver	32	1	Liposomal doxorubicin	20 mg/m^2, every 21 days	Partial response	7 months
Pintoffl *et al.* [2009]	Lung, liver, bone	32	1	Gemcitabine	1000 mg/m^2, days 1, 8, and 15, every 28 days	Stable disease	72 months
Sangro *et al.* [2012]	Lung, liver	22	1	Sorafinib	200 mg every 36 hours	Partial response	6 months
Trautmann *et al.* [2011]	Bone	19	1	Bevacizumab	7.5 mg/m^2 every 21 days	Stable disease	16 months
Coppo *et al.* [2004]	Bone	70	1	Pamidronate	90 mg, twice monthly	Complete response	72 months

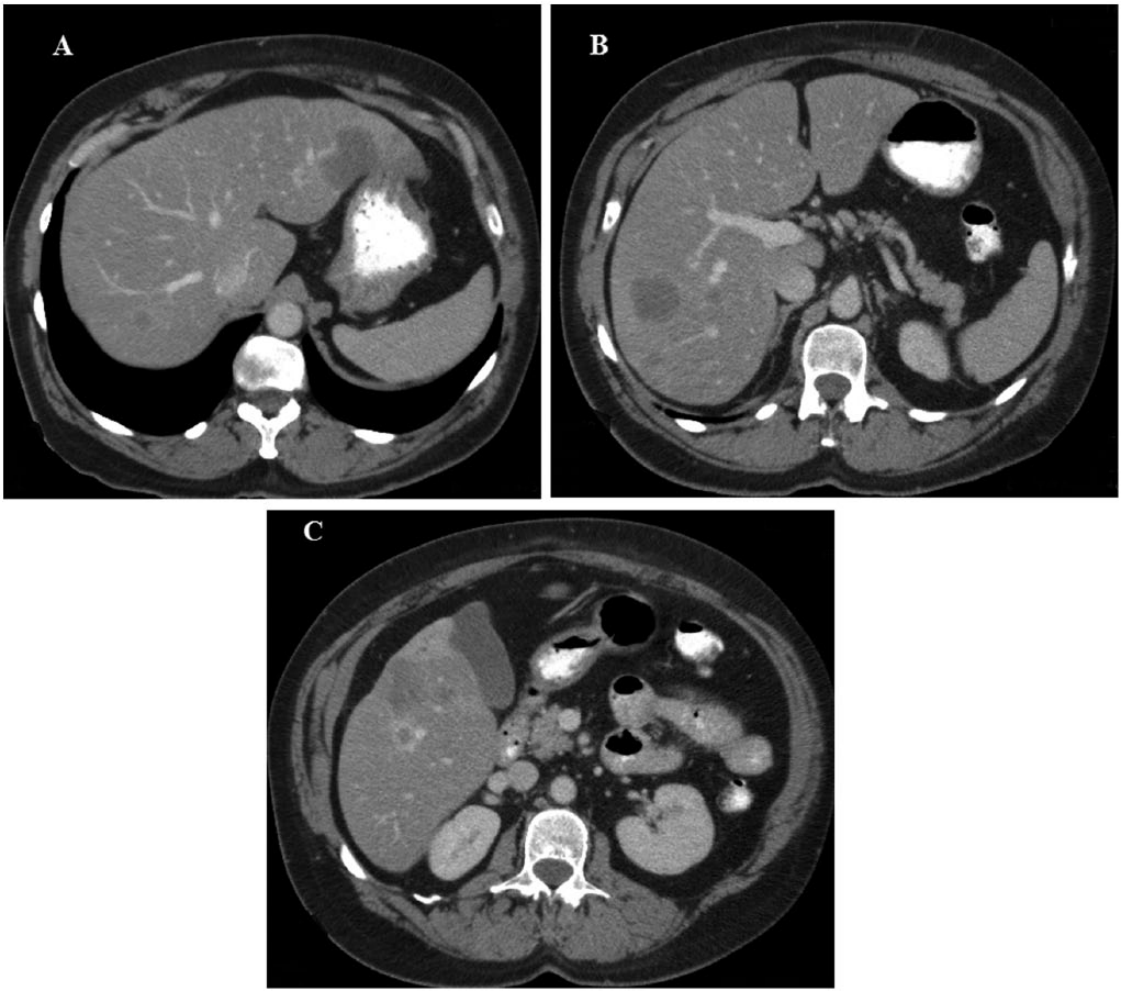

Figure 1. Contrast enhanced axial computerized tomography images showing multiple attenuated lesions of hepatic epithelioid hemangioendothelioma. There are multiple lesions with varying size (A–C), the largest was 4.6 cm (A). Some lesions are rim enhancing and there is evidence of capsular retraction (C).

chemotherapy with interferon-α with mixed results [Mehrabi *et al.* 2006; Makhlouf *et al.* 1999]. Our case report describes the use of capecitabine and bevacizumab, which may prove to be a treatment option other than surgery, especially in situations when surgical resection is impossible. Furthermore, combination capecitabine and bevacizumab has the potential to be a reasonable neoadjuvant option, with the aim of converting patients to resection candidates.

Although capecitabine was utilized in this case before the accurate diagnosis was made, there is evidence to support the use of 5-fluorouracil based therapy in patients with HEHE. Hepatic intra-arterial 5-fluorouracil was used successfully in HEHE to prolong survival [Makhlouf *et al.* 1999; Holley and Cuschieri, 1989; Lauffer *et al.* 1996]. The use of systemic 5-fluorouracil in combination with other chemotherapy was also attempted in a patient with HEHE who was initially diagnosed with cholangiocarcinoma, thus making 5-fluorouracil an option for systemic therapy [Mehrabi *et al.* 2006; O'Grady, 2000].

Given VEGF expression in HEHE, there is the rationale to use anti-VEGF agents such as bevacizumab either alone or in combination with other chemotherapy in the treatment of pulmonary and metastatic EHE. In particular, bevacizumab has been used with carboplatin, paclitaxel, docetaxel and/or etoposide [Grotz *et al.* 2010; O'Grady, 2000; Lazarus *et al.* 2011; Gaur *et al.* 2012]. Most commonly, bevacizumab is used in combination with paclitaxel. Regardless of the chemotherapy bevacizumab is

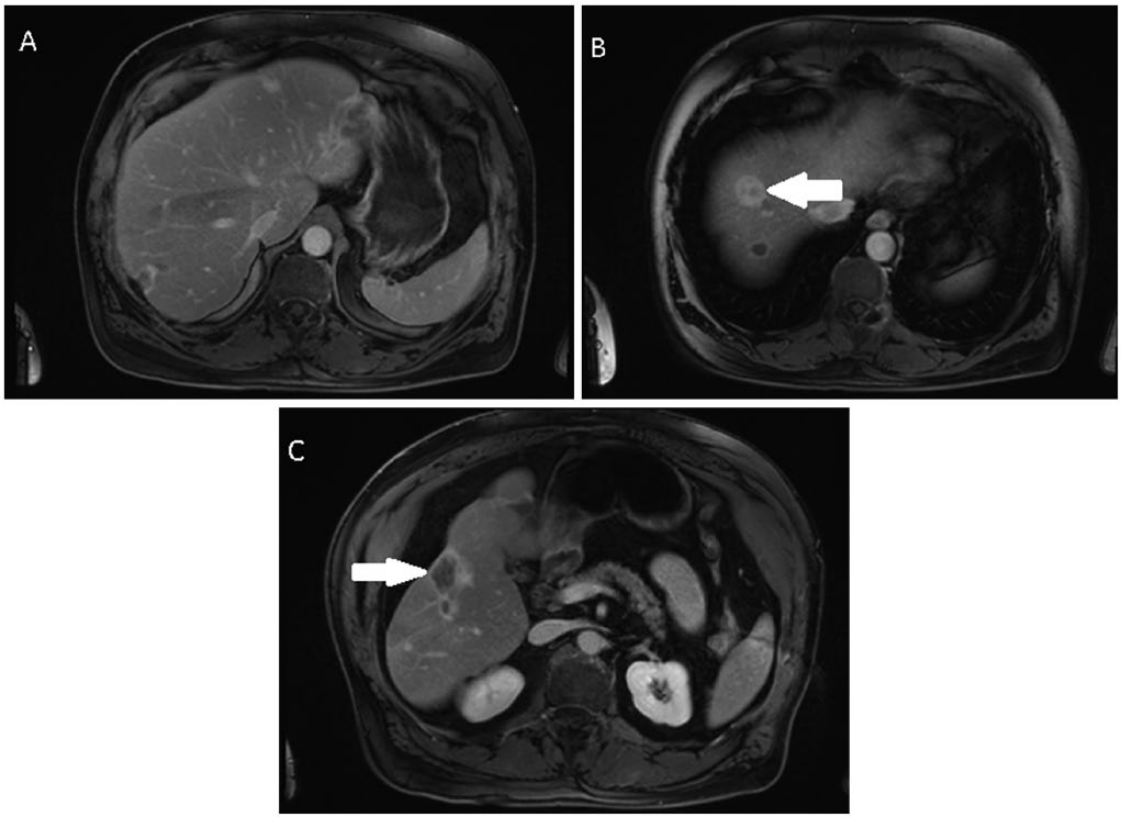

Figure 2. Contrast enhanced axial magnetic resonance imaging (MRI) images while on capecitabine and bevacizumab. The initial hepatic lesion seen in Figure 1a is no longer visible (A). Index lesion at the junction of segment IV/VII (arrow) measures 2.6 cm × 2.2 cm (B). The index coalescent lesions seen in segments V/VI (arrow) measure approximately 5.3 cm × 3.4 cm (C).

paired with, progression-free survival (PFS) and OS varies from months to years [Grotz *et al*. 2010; Lazarus *et al*. 2011; Gaur *et al*. 2012; Salech *et al*. 2010]. A single-arm, multicenter, phase II trial utilizing single agent bevacizumab for unresectable EHE reported PFS and OS of 39 weeks and 143 weeks, respectively, when bevacizumab was given at 15 mg/kg every 3 weeks [Agulnik *et al*. 2013].

Other therapies reported include combination or single-agent regimens of the following: interferon-α, sunitinib, sorafenib, thalidomide, lenalidomide, vinorelbine, dacarbazine, cisplatin, ifosfamide, etoposide, docetaxel, paclitaxel, nab-paclitaxel, liposomal doxorubicin, gemcitabine, pamidronate, cyclophosphamide and nonsteroidal anti-inflammatory drugs [Cardinal *et al*. 2009; Gaur *et al*. 2012; Sangro *et al*. 2012; Raphael *et al*. 2010; Sumrall *et al*. 2010; Schilling *et al*. 2009; Sharif *et al*. 2004; Marquez-Medina *et al*. 2004; Belmont *et al*. 2008; Cronin and Arenberg, 2004; Schattenberg *et al*. 2008; Grenader *et al*. 2011; Kelly and O'Neil, 2005; Pintoffl *et al*. 2009; Coppo *et al*. 2004; Lakkis *et al*. 2013] (see Table 1).

Capecitabine and bevacizumab have not been previously described to treat HEHE. This proved to be an effective, tolerable regimen for a patient with metastatic hepatic hemangioendothelioma. Although liver transplantation or resection may present the best options for improved survival, clinicians should consider the use of capecitabine with bevacizumab in the treatment of HEHE, especially in those awaiting liver transplantation or nonsurgical candidates.

Conflict of interest statement

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