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Long term survival in pediatric hepatic angiosarcoma (PHAS): A case report and review of the literature

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Kristina M. Potanos [a], Nicole Hodgkinson [a], Nora M. Fullington [a], Anupama Narla [b], Karen Albritton [c], Harry Kozakewich [d], Heung Bae Kim [a,*]

[a] Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[b] Division of Pediatric Hematology/Oncology, Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA, USA
[c] Department of Oncology, Cook Children's Medical Center, University of North Texas Health Science Center, Fort Worth, TX, USA
[d] Department of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Pediatric hepatic angiosarcoma (PHAS) is extremely rare, with only five reported tumor-free survivors. Aggressive surgical resection and chemotherapy have been the management in all documented survivors of this disease, however no specific treatment guidelines are established. We present a case of PHAS with the longest reported tumor-free survival at over six years off therapy.

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1. Case report

A previously healthy three-year-old girl presented with right-sided abdominal pain and general malaise. Her past history was unremarkable and there were no known environmental exposures. Physical exam demonstrated tachypnea and hepatomegaly and ultrasound revealed a hepatic mass. Contrast computed tomography (CT) scan confirmed a heterogeneous mass measuring $13.8 \times 12.8 \times 14.1$ cm, involving nearly the entire right lobe with effacement of the renal vein and IVC adjacent to the mass (Fig. 1). There was no evidence of metastatic disease. Laboratory values, including alpha feto-protein, were within normal limits. Due to the proximity of the mass to the portal vein, it was initially considered unresectable, and she underwent ultrasound-guided biopsy of the mass with port placement for expected neo-adjuvant chemotherapy. The biopsies demonstrated an endothelial neoplasm consistent with PHAS. The histopathologic features were similar to those encountered in the resection specimen described below. With no proven chemotherapy for PHAS, treatment with Paclitaxel and Bevacizumab was initiated with informed consent based on use in the adult angiosarcoma population. The first course consisted of Paclitaxel alone to monitor tolerance, as there were no pediatric trials combining the agents. Paclitaxel was tolerated, but because the mass had remained radiographically stable in the week following diagnosis, complete resection was recognized as the best chance for survival. Three weeks after presentation, the patient underwent right hepatic tri-segmentectomy. Intraoperative frozen sections demonstrated a close margin anterior to the portal vein plate necessitating additional resection to the extent deemed safe. Final pathology demonstrated viable tumor over a 1 cm area at this margin. The patient was discharged home postoperatively without complication.

Chemotherapy began ten weeks postoperatively, after pathologic confirmation of the diagnosis and a restaging CT scan. The six-month course included six 28-day cycles of Paclitaxel 50 mg/m^2 (days 1,4,8,11,15 and 18), and Bevacizumab 10 mg/m^2 IV (days 1 and 15). Serial CT and magnetic resonance imaging (MRI) throughout chemotherapy treatment did not yield evidence of tumor recurrence. Following chemotherapy, she was monitored with serial MRI every three months for two years and then alternating ultrasound or MRI every three months to date. Most recently, over six years off therapy, there is no evidence of tumor recurrence.

1.1. Pathology

A $15 \times 11 \times 10$ cm circumscribed, non-encapsulated mass extended to the resection margin superior to the portal vein. The

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* Corresponding author. Department of Surgery, Fegan 3, 300 Longwood Avenue, Boston, MA 02115, USA. Tel.: +1 617 355 8544; fax: +1 617 730 0316.
E-mail address: heung.kim@childrens.harvard.edu (H.B. Kim).

Fig. 1. Contrast CT scan at presentation demonstrating a large heterogeneous mass involving most of the right hepatic lobe.

mass was soft and pink-tan with several areas of necrosis and hemorrhage up to 3 cm in diameter (Fig. 2A). Histopathologically, most of the tumor demonstrated short fascicles of spindled endothelial cells (EC) with peripheral strands of biliary epithelium unrelated to portal tracts (Fig. 2B). Atypical ECs were spindled (kaposiform) with lightly eosinophilic cytoplasm and enlarged nuclei with coarsened chromatin and small nucleoli. The lumens were inconspicuous (Fig. 2C). Other areas showed expanses of solid aggregates of ECs with more pleomorphic vesicular nuclei, larger nucleoli, and apoptosis (Fig. 2D and E). Another pattern was anastomotic widened channels with papillations and endothelial redundancy (Fig. 2F). Occasional ECs contained eosinophilic cytoplasmic inclusions staining positive with the periodic acid-Schiff stain. Infrequent vascular invasion was limited to small veins. Peripherally, layered spindled ECs replaced normal sinusoids (Fig. 2G). Several sections showed a few small foci with small channels with flattened bland endothelium (Fig. 2H). Occasional mitoses were observed but a precise mitotic count was difficult to ascertain because of apoptosis. The proliferation marker, MIB-1, showed an index of up to 25% in the EC population within "hot spots." Immunostaining showed lesional EC throughout the tumor were positive for CD31, CD34, LYVE-1, and Glut-1 and negative for D2-40 and Prox-1. Cytogenetic analysis of mitotic cells from 7 to 10 day cultures of tumor samples revealed a normal karyotype.

2. Discussion

PHAS is a rare pediatric hepatic vascular tumor, with fewer than 50 reported cases. It occurs twice as often in girls, and the reported age at diagnosis is two months to fifteen years [1]. To date, there are only five reported cases of disease-free survival in PHAS [2–6].

Although environmental exposures have been linked to adult hepatic angiosarcoma, only one case of PHAS has been potentially linked to arsenic exposure [7], as these chemicals require several years of exposure prior to tumor detection [8]. Associated signs and symptoms include jaundice, abdominal pain, vomiting, fever, tachypnea, and dyspnea, and those related to lung, bone, lymphatic, adrenal, or renal metastases [4]. Accurate diagnosis requires biopsy because clear, reliable, distinguishing radiographic features between PHAS and benign tumors are not always present [9]. While PHAS may be histopathologically indistinguishable from adult hepatic angiosarcoma, it usually has a characteristic component of hypercellular fascicles and whorls of atypical spindled endothelial cells and cytoplasmic eosinophilic globules [3,10,11]. However, a diagnosis of PHAS is almost always challenging because PHAS can have regions of small channels with bland or only minimally atypical endothelium [3,12] thereby mimicking hepatic infantile hemangioma (solitary, multifocal or diffuse types according to the Hepatic Tumor Registry Classification) [13,14], or reactive vasculature around another tumor; thus limited sampling of a lesion may be inconclusive or misleading (personal observation, HK). Furthermore, some hepatic hemangiomas, particularly of the multifocal or diffuse type, have papillation with endothelial redundancy or pleomorphism that may be extremely difficult to distinguish from PHAS (personal observation, HK). Many pathologists diagnose atypical hepatic vascular tumors that don't reach the level of an obvious angiosarcoma as infantile hemangioendothelioma type 2 as described by Dehner and Ishak [15]. As opposed to their histopathologically benign-appearing infantile hemangioendothelioma type 1 category, category type 2 is more aggressive-appearing with branching vascular structures, irregular budding and tortuous vascular spaces lined by larger and more hyperchromatic and pleomorphic endothelial cells. Some observors have chosen to regard infantile hemangioendothelioma type 2 as angiosarcoma [10]. In our experience, in infants who have died with extensive multifocal or diffuse hepatic hemangioma (probably equivalent to infantile hemangioendothelioma type 2 on the aggressive end of the spectrum), there has usually been a lesser degree of pleomorphism and mitotic activity and the solid spindled areas (often called kaposiform), if present, were small and widely dispersed as compared to PHAS. Nevertheless, the distinction between hepatic hemangiomas particularly of the multifocal or diffuse types, infantile hemangioendothelioma type 2, and PHAS can be difficult if not impossible on needle biopsies and sometimes even at autopsy because of overlapping features and because the criteria cited above are subjective to some degree. Additionally, there may be a reluctance on the part of the pathologist to make an outright diagnosis of malignancy because of therapeutic implications, particularly hepatic transplantation in some cases. It should also be emphasized that a vascular lesion encountered during infancy but failing to regress within two years of age or a vascular lesion discovered after the age of two should be viewed with extreme suspicion because of the possibility of it being a PHAS.

PHAS often presents as a large tumor, making resection difficult [3]. Although the literature is limited, it appears that aggressive surgical resection offers the best chance for survival. Limited reports on liver transplantation for PHAS have had mixed results, but have resulted in survival for some patients [5,6,9]. In our patient, liver transplantation was considered both preoperatively and after return of the microscopic positive margin after resection. However, given the certainty of the diagnosis by biopsy and the overall poor prognosis of PHAS, it was decided to proceed with an attempt at resection since we believed we could achieve a total gross resection with an extended right hepatectomy.

The average documented survival for PHAS is less than 16 months [9]. The five tumor-free survivors described in the literature
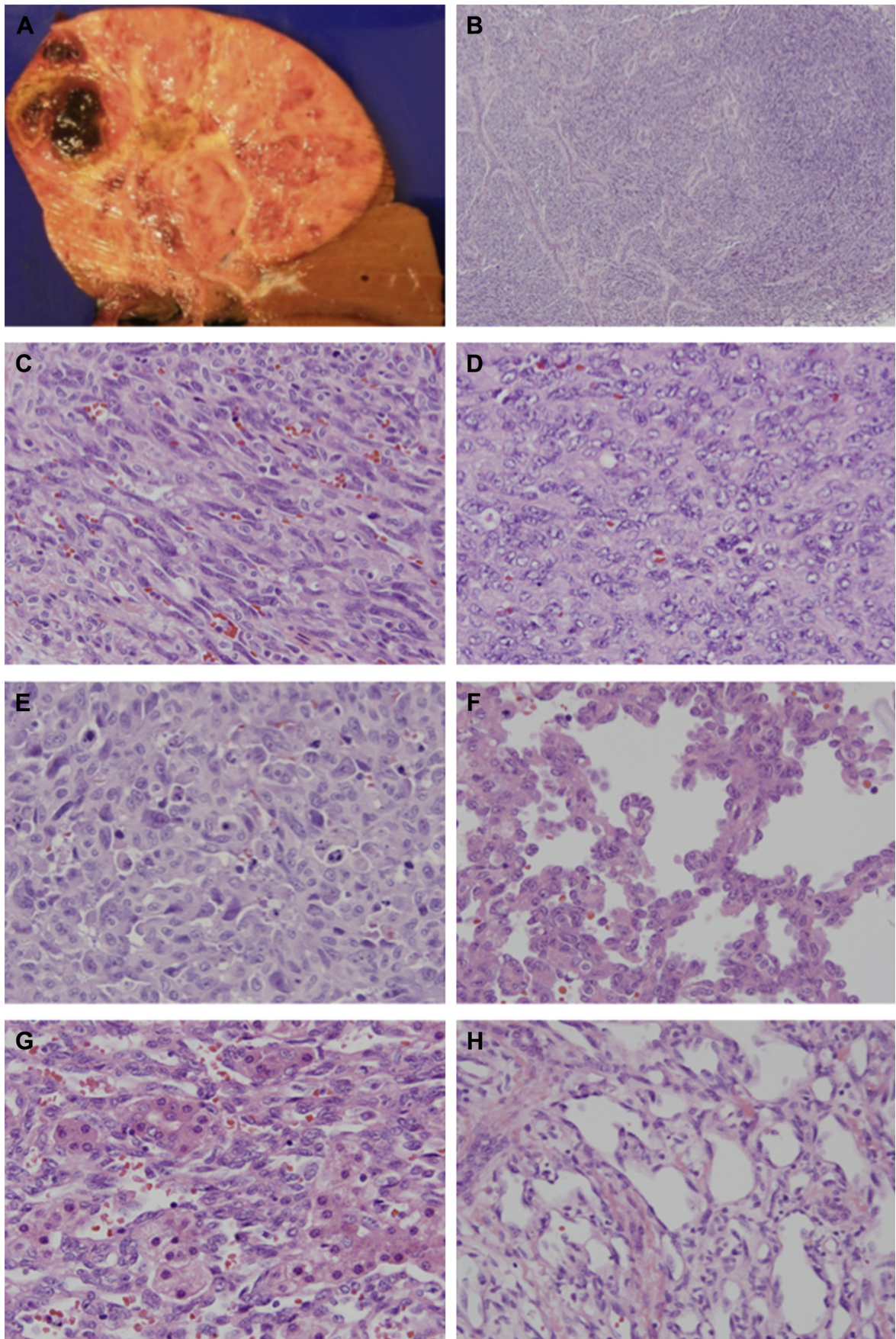
Fig. 2. Gross specimen with tumor and necrotic foci (A). Histopathology: tumor nodules (B); "spindled kaposiform" endothelial cells (EC's) (C); enlarged nuclei and prominent nucleoli (D); pleomorphic ECs with apoptosis (E); rounded, crowded ECs (F); EC layers separate hepatocyte cords (G). (H) demonstrates small channels, flattened endothelium and bland nuclei. EC = endothelial cell.

all underwent resection in combination with chemotherapy; however, there are no agreed upon treatment guidelines. This is the first report of chemotherapy with Paclitaxel and Bevacizumab for PHAS. A variety of regimens reported in PHAS management have been based on protocols for sarcoma treatment. These have not proven to be efficacious and are known to have numerous side effects. Anecdotal experience, however, does exist to support the use of taxanes in adult angiosarcomas [16,17]. The use of vascular endothelial growth factor (VEGF) inhibitors has been explored in patients with sarcomas and was especially compelling in the treatment of angiosarcoma given the high rate of VEGF expression in these tumors [18]. In adults, a Phase III study of Paclitaxel/Bevacizumab in metastatic breast cancer and a Phase II study comparing Bevacizumab plus Carboplatin and Paclitaxel with Carboplatin and Paclitaxel alone demonstrated the potential advantage of this combination in refractory solid tumors [19,20]. Furthermore, Phase I studies of each individual drug in children showed that both drugs were relatively well tolerated, with toxicity almost exclusively limited to myelosuppression. We therefore decided to use the combination of Paclitaxel/Bevacizumab in this patient with PHAS, and utilize traditional sarcoma-based therapy for disease progression and/or unacceptable toxicity from the novel regimen. The patient tolerated the chemotherapy extremely well with no acute toxicities. Six years off therapy, she has no evidence of disease recurrence and has had no evidence of complications of treatment such as growth disturbance, cardiac toxicity or developmental issues.

3. Conclusion

In summary, aggressive surgical resection should be performed in patients with PHAS to optimize outcome. Post-operative adjuvant chemotherapy using Paclitaxel and Bevacizumab should be considered for patients even after complete gross resection given the historically poor outcomes in patients with PHAS. If this chemotherapy regimen proves to be efficacious in PHAS, more aggressive modes of liver resection including liver transplantation may be entertained in the future.

Conflict of interest statement

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. To the best of our knowledge no conflicts of interest, financial or other, exists.

References

[1] Geramizadeh B, Safari A, Bahador A, Nikeghbalian S, Salahi H, Kazemi K, et al. Hepatic angiosarcoma of childhood: a case report and review of the literature. J Pediatr Surg 2011;46:E9–11.
[2] Kirchner SG, Heller RM, Kasselberg AG, Greene HL. Infantile hepatic hemangioendothelioma with subsequent malignant degeneration. Pediatr Radiol 1981;11(1):42–5.
[3] Selby DM, Stocker JT, Ishak KG. Angiosarcoma of the liver in childhood: a clinopathologic and follow-up study of 10 cases. Pediatr Pathol 1992;12(4):485–98.
[4] Gunawardena S, Trautwein L, Finegold M, Ogden A. Hepatic angiosarcoma in a child: successful therapy with surgery and adjuvant chemotherapy. Med Pediatr Oncol 1997;28(2):139–43.
[5] Walsh R, Harrington J, Beneck D, Ozkaynak MF. Congenital infantile hepatic hemangioendothelioma type II treated with orthotopic liver transplantation. J Pediatr Hematol Oncol 2004;26(2):121–3.
[6] Nord KM, Kandel J, Lefkowitch JH, Lobritto SJ, Morel KD, North PE, et al. Multiple cutaneous infantile hemangiomas associated with hepatic angiosarcoma: case report and review of the literature. Pediatrics 2006;118(3):e907–913.
[7] Awan S, Devenport M, Portmann B, Howard ER. Angiosarcoma of the liver in children. J Pediatr Surg 1996;31(12):1729–32.
[8] Noronha R, Gonzalez-Crussi F. Hepatic angiosarcoma in childhood. Am J Surg Pathol 1984;8(11):863–71.
[9] Dimashkieh H, Mo J, Wyatt-Ashmead J, Collins M. Pediatric hepatic angiosarcoma: case report and review of the literature. Pediatr Dev Pathol 2004; 7(5):527–32.
[10] Ishak KG, Goodman ZD, Stocker JT. Malignant mesenchymal tumors. Tumors of the liver and intrahepatic bile ducts, third series, fascicle 31. Washington DC: American Registry of Pathology; 2001. p. 301–6.
[11] Selby DM, Stocker JT, Waclawiw MA, Hitchcock CL, Ishak KG. Infantile hemangioendothelioma of the liver. Hepatology 1994;20(1):39–45.
[12] Dehner LP. The challenges of vasoformative tumors of the liver in children. Pediatr Dev Pathol 2004;7(5):A5–7.
[13] Hsi Dickie B, Fishman SJ, Azizkhan RG. Hepatic vascular tumors. Semin Pediatr Surg 2014;23(4):168–72.
[14] Rialon KL, Murillo R, Fevurly RD, Kulungowski AM, Christison-Lagay ER, Zurakowski D, et al. Risk factors for mortality in patients with multifocal and diffuse hepatic hemangiomas. J Pediatr Surg 2015;50(5):837–41.
[15] Dehner LP, Ishak KG. Vascular tumors of the liver in infants and children. A study of 30 cases and review of the literature. Arch Pathol 1971;92: 101–10.
[16] Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 1999; 86(10):2034–7.
[17] Schlemmer M, Reichardt P, Verweij J, Hartmann JT, Judson I, Thyss A, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer 2008;44(16):2433–6.
[18] D'Adamo DR, Anderson SE, Albritton KA, Yamada J, Riedel E, Scheu K, et al. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. J Clin Oncol 2005;23(28):7135–42.
[19] Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357(26):2666–76.
[20] Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22(11):2184–91.