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**Primary malignant vascular tumors of the liver in children: Angiosarcoma and epithelioid hemangioendothelioma**

Bannoura S *et al*. Malignant vascular tumors of the liver in children

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**Abstract**

Primary malignant vascular neoplasms of the liver, angiosarcoma and epithelioid hemangioendothelioma, are extremely rare entities in the pediatric population. International Society for the Study of Vascular Anomalies classification system is recommended for the pathologic diagnosis of hepatic vascular lesions in this age group. In this article, we highlight the clinicopathologic characteristics of hepatic angiosarcoma and epithelioid hemangioendothelioma in the pediatric population. Hepatic angiosarcoma in children shows a slight female predominance with an average age of 40 mo at diagnosis. The distinct histologic features include whorls of atypical spindled cells and eosinophilic globules, in addition to the general findings of angiosarcoma. Histologic diagnosis of pediatric hepatic angiosarcoma is not always straightforward, and the diagnostic challenges are discussed in the article. Hepatic epithelioid hemangioendothelioma also demonstrates a female predominance, but is more commonly identified in adolescents (median age at diagnosis: 12 years). Histologically, the lesion is characterized by epithelioid cells and occasional intracytoplasmic lumina with a background of fibromyxoid stroma. While *WWTR1-CAMTA1* and *YAP1-TFE3* fusions have been associated with epithelioid hemangioendothelioma, there are currently no known signature genetic alterations seen in pediatric hepatic angiosarcoma. Advancement in molecular pathology, particularly for pediatric hepatic angiosarcoma, is necessary for a better understanding of the disease biology, diagnosis, and development of targeted therapies.

**Key Words:** Pediatric; Hepatic angiosarcoma; Epithelioid hemangioendothelioma; Infantile hemangioma; Liver tumor; Molecular genetics

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**Core Tip:** Malignant hepatic vascular neoplasms are rarely encountered in the pediatric population. This review highlights the clinicopathologic characteristics of pediatric hepatic angiosarcoma and epithelioid hemangioendothelioma. They have variable clinical and radiological findings; therefore, histologic examination is the gold standard for diagnosis. Hepatic angiosarcoma in children is characterized by whorls of spindled cells and eosinophilic globules histologically. Meanwhile, epithelioid hemangioendothelioma shows epithelioid cells with intracytoplasmic lumina and a fibromyxoid background. Diagnostic challenges and molecular alterations of these entities are discussed in the article.

**INTRODUCTION**

Malignant liver tumors are rare in the pediatric population, comprising approximately 1.1% of all childhood malignancies in the United States[1]. The most common malignant hepatic tumors in children are those of epithelial origin (hepatoblastoma and hepatocellular carcinoma). Meanwhile, the less frequent malignant neoplasms of mesenchymal origin include undifferentiated embryonal sarcoma, rhabdomyosarcoma, and malignant vascular tumors[1,2]. Hepatic vascular lesions in children, both benign and malignant, may pose diagnostic challenges because of the confusing terminology and their overlapping clinical, radiologic, and pathologic features[3].

The use of previous terminology for hepatic vascular lesions in children (types 1 and 2 hemangioendothelioma) is discouraged, as these diagnostic terms have led to confusion in diagnosis and management[3]. We recommend the use of classification by the International Society for the Study of Vascular Anomalies (ISSVA) instead. This classification system was developed to allow a better understanding of the biology and genetics of vascular lesions and serves as a guide to clinicians, pathologists, and researchers[4]. For the complete list of vascular anomalies (updated in 2018), please review the ISSVA document (https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf).

Based on the biologic behavior, primary hepatic vascular tumors can be grouped into benign, borderline, and malignant lesions. Christison-Lagay *et al*[5] classify benign hepatic vascular lesions (hemangiomas) according to their clinical presentations into focal, multifocal, and diffuse hepatic hemangiomas. Histologically, focal hepatic hemangiomas are in keeping with rapidly involuting congenital hemangiomas. Meanwhile, multifocal and diffuse hepatic hemangiomas correspond to infantile hemangiomas. Kaposi sarcoma, primarily seen in immunocompromised patients, represents borderline vascular tumors of the liver. Hepatic malignant vascular lesions include angiosarcoma and epithelioid hemangioendothelioma; in this article, we will review the clinicopathologic characteristics of these two entities with a focus on the pediatric population.

**Hepatic angiosarcoma**

Angiosarcoma is a malignant vascular neoplasm that recapitulates morphological and immunohistochemical features of endothelial cells. The lesion is more commonly seen in elderly men, and usually involves the cutaneous and deep soft tissue[3]. In the pediatric population, mediastinum is a frequent site of involvement[6]. Pediatric hepatic angiosarcoma is exceptionally rare and has only been described in case reports or small case series[7]. In this age group, hepatic angiosarcoma shows a slight female predominance and the average age of presentation is 40 mo[8]. The pathogenesis of hepatic angiosarcoma in children is unclear. The association between angiosarcoma and exposure to thorotrast, vinyl chloride, androgenic and anabolic steroids, oral contraceptives, and diethylstilbestrol, as described in adults, is usually not identified in children since it requires several years of environmental exposure prior to tumor detection[8,9]. Only one case of pediatric hepatic angiosarcoma has been associated with arsenic exposure[10]. Moreover, there is no recognized syndromic or genetic association. However, pediatric hepatic angiosarcoma has been associated with different conditions, such as multiple cutaneous infantile hemangiomas[11], cutaneous mixed vascular malformations[12], and dyskeratosis congenita[13].

Children with hepatic angiosarcoma usually present with abdominal pain and distension due to rapid liver enlargement. Metastatic disease is common at diagnosis, particularly to the lungs[3,7,8]. The tumor also occasionally ruptures and leads to hemoperitoneum[2]. Other signs and symptoms include jaundice, vomiting, fever, dyspnea, and anemia[8]. The imaging features of hepatic angiosarcoma are variable and may be mistaken for benign entities such as infantile hemangioma[2]. On ultrasound, the lesion may present as solitary or multifocal, heterogeneous hypoechoic to isoechoic nodules. Computerized tomography scan often demonstrates peripheral nodular and irregular hypervascularity with arterial hemorrhage. Moreover, magnetic resonance imaging generally shows marked heterogeneity on T2-weighted images and all phases of post-contrast images, and bizarre progressive filling (instead of centripetal)[2]. Because of the nonspecific clinical and imaging findings, tissue examination remains the gold standard for the diagnosis of hepatic angiosarcoma.

Macroscopically, hepatic angiosarcoma generally demonstrates a large solitary lesion or multiple nodules, either separate or coalescing, sometimes with infiltrative borders and possibly replacing the hepatic parenchyma. The cut surface can be fleshy, cystic, and variegated with areas of hemorrhage and necrosis[8,14,15]. Histologically, pediatric hepatic angiosarcoma may be indistinguishable from adult angiosarcoma. The lesional cells may show different growth patterns: vasoformative, epithelioid/spindled, peliotic, and sinusoidal growth[16]. These cells range from eosinophilic and spindled to markedly pleomorphic with high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei, prominent nucleoli, and increased mitotic activity[8,15]. Pediatric hepatic angiosarcomas (Figure 1) usually has a characteristic component of whorls of atypical spindled cells (glomeruloid bodies) and periodic acid-Schiff-positive diastase-resistant cytoplasmic eosinophilic globules[8,9]. Intratumoral entrapment of native structures, such as hepatocytes and bile ducts, is occasionally identified. By immunohistochemistry, the neoplastic cells are positive for endothelial markers (CD31, CD34, factor VIII, FLI-1, and ERG). In addition, they are occasionally immunoreactive for podoplanin[17] and GLUT-1[18], markers for lymphatic differentiation and infantile hemangioma, respectively.

Pathologic diagnosis of pediatric hepatic angiosarcoma is not always straightforward. The lesion can have regions of small channels with bland appearing endothelium, mimicking infantile hemangioma. Potential for malignant transformation of benign vascular tumors and focal GLUT-1 positivity also make the distinction between hepatic angiosarcoma and infantile hemangioma challenging[3,7,9]. Moreover, a definitive diagnosis is sometimes difficult to render because of limited tissue or sampling. Hepatic angiosarcoma should be considered in cases of infantile hemangiomas diagnosed in patients greater than one year of age. A malignant diagnosis should also be suspected in infantile hemangiomas which are resistant to treatment, recur, or do not regress within two years of age[8,9]. Hepatic angiosarcoma showing markedly atypical cells should be distinguished from other high-grade lesions, such as undifferentiated embryonal sarcoma, rhabdomyosarcoma, and malignant rhabdoid tumor. Immunohistochemistry is usually helpful to exclude these differential diagnoses. In adults, hepatic angiosarcoma has been reported concomitantly with mesenchymal hamartoma with or without undifferentiated embryonal sarcoma component[19-21]. This association, however, has not been observed in pediatric patients. Finally, the possibility of metastatic disease should be ruled out radiologically, as secondary involvement of the liver by angiosarcoma of various primary sites (skin, spleen, and mesentery) has been reported in children[6,22-25].

Antonescu *et al*[26] reported upregulation of vascular-specific receptor tyrosine kinases in primary and radiation-induced angiosarcomas. Meanwhile, *MYC* amplification is exclusively observed in radiation-induced and chronic lymphedema-associated angiosarcomas[27]. In addition, a subset of angiosarcomas in young adults is associated with *CIC* gene abnormalities, which show an inferior outcome[28]. There are, however, no known signature molecular alterations in pediatric hepatic angiosarcoma. Marks *et al*[29] reported a novel gene fusion of *ROS1-GOPC* in hepatic angiosarcoma of a 50-year-old woman. Although the finding has not been confirmed by other studies, it has a potential clinical significance because of the established anti-cancer activity of tyrosine kinase inhibitors in tumors with *ROS1* rearrangements.

Pediatric hepatic angiosarcoma has a dismal prognosis, with a 5-year overall survival less than 30%[3]. The majority of patients succumb to disease within 12 mo after diagnosis[2]. Currently, there is no established consensus on management of pediatric hepatic angiosarcoma. Management generally depends on the extent of disease and usually involves the combination of chemotherapy, neoadjuvant or adjuvant, with surgical resection (when possible)[2,3]. Other treatment options with limited success include embolization, radiation, liver transplantation, and targeted therapy, such as mammalian target of rapamycin and vascular-specific receptor tyrosine kinase inhibitors[2,3,7].

**Hepatic epithelioid hemangioendothelioma**

Epithelioid hemangioendothelioma is an exceedingly rare tumor of vascular endothelial origin. It is more commonly seen in adult females (median age of onset is > 30 years) and has an estimated prevalence of less than 1 in 1000000[3,30-32]. In the pediatric population, it usually presents as a multifocal disease with multiorgan involvement, most frequently involving liver, lungs, bone and, soft tissue[30]. Pediatric hepatic epithelioid hemangioendothelioma shows a female predominance with a median age at diagnosis of 12 years[33]. The etiology of epithelioid hemangioendothelioma is unclear, and there are no established syndromic or genetic associations in children.

Approximately 25% of patients with hepatic epithelioid hemangioendothelioma are asymptomatic, while symptomatic patients usually show abdominal pain, weight loss, and a palpable mass[3,34]. On rare occasions, hepatic epithelioid hemangioendothelioma may present as veno-occlusive disease or Budd-Chiari syndrome[34]. Hepatic epithelioid hemangioendothelioma has characteristic radiologic findings including peripheral location of lesions, subcapsular retraction, and the “lollipop sign”. The latter represents a hepatic or portal vein tapering at the periphery of a well-defined lesion seen on computerized tomography and magnetic resonance imaging[34,35].

Macroscopic examination of hepatic epithelioid hemangioendothelioma shows firm, ill-defined, and sometimes confluent nodules with infiltrative borders[2]. The lesion usually involves both hepatic lobes with predominant peripheral or subcapsular growth pattern[34]. Histologically, the lesion is characterized by cords and nests of epithelioid cells in a variable fibromyxoid stroma (Figure 2). The lesion often appears hypocellular and deceptively bland[36]. The neoplastic cells have moderate amounts of eosinophilic cytoplasm, round nuclei, and inconspicuous nucleoli. Intracytoplasmic vacuoles/Lumina are occasionally seen. There is minimal cytologic atypia with low mitotic activity[30,34]. The neoplastic cells usually grow along vascular structures and infiltrate hepatic sinusoids, which lead to atrophy and replacement of hepatocytes. The portal tracts and hepatic venules are usually intact despite destruction of the hepatic plates. Older lesions may demonstrate sclerosis, necrosis, and/or calcification[34]. By immunohistochemistry, the neoplastic cells show expression of endothelial markers including CD31, CD34, ERG, FLI-1, factor VIII, and lymphatic marker podoplanin (D2-40). The lesional cells also demonstrate variable expression for cytokeratin and smooth muscle actin. The stroma shows variable staining with mucicarmine, para-aminosailcylic acid in early lesions, and Masson trichrome in older lesions[34]. The histologic differential diagnoses for hepatic epithelioid hemangioendothelioma include angiosarcoma, cholangiocarcinoma, metastatic carcinoma, and sclerosing hepatocellular carcinoma[34]. Important to note that these entities are mostly seen in adult patients.

Epithelioid hemangioendothelioma is associated with t (1; 3) (p36; q25) and t (11; X) (q13; p11) translocations, which correspond to *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions, respectively[37-40]. The *WWTR1-CAMTA1* translocation results in a fusion protein which allows for a TAZ-like transcriptional program and leads to oncogenesis[30]. Immunohistochemistry for CAMTA-1 and TFE3 is also useful to confirm these gene fusions[38,40]. The *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions are identified in 90% and 10% of epithelioid hemangioendothelioma cases, respectively[30].

Hepatic epithelioid hemangioendothelioma demonstrates a variable clinical course, with uncertain long-term prognosis[2]. In general, it is considered less aggressive than hepatic angiosarcoma. The presence of effusions, tumor size > 3 cm, and high mitotic index (> 3 mitoses/50 high power fields) have been associated with unfavorable outcomes[33]. Moreover, Rosenbaum *et al*[36] reported that patients with *WWTR1-CAMTA1* fusion have a less favorable outcome compared with the *YAP1-TFE3* fusion, with 5-year overall survival rates of 59% and 86%, respectively. There are currently no established standardized management protocols for the pediatric age group; surgical resection is considered the mainstay of treatment for localized disease[30,33]. In advanced disease, management is more variable, such as observation, medical therapy, and liver transplantation. Medical therapy includes standard chemotherapy and targeted agents, such as anti-vascular endothelial growth factor antibody (*e.g.,* bevacizumab) and mammalian target of rapamycin inhibitor (*e.g.,* sirolimus)[30,33].

**CONCLUSION**

Malignant hepatic vascular neoplasms in the pediatric population, including angiosarcoma and epithelioid hemangioendothelioma, are rarely encountered. Table 1 summarizes the clinicopathologic characteristics of these lesions. We recommend the use of the ISSVA classification system for the pathologic diagnosis of hepatic vascular lesions in children. Currently, there are no established management guidelines for both pediatric hepatic angiosarcoma and epithelioid hemangioendothelioma because of their rarity and heterogeneous presentations. Advancement in molecular pathology, particularly for pediatric hepatic angiosarcoma, could potentially lead to a better understanding of the disease biology, diagnosis, and development of targeted therapies.

**REFERENCES**

1 **Finegold MJ**, Egler RA, Goss JA, Guillerman RP, Karpen SJ, Krishnamurthy R, O’Mahony CA. Liver tumors: Pediatric population. *Liver Transplant* 2008; **14**:1545-1556 [DOI: 10.1002/Lt.21654]

2 **Chavhan GB**, Siddiqui I, Ingley KM, Gupta AA. Rare malignant liver tumors in children. *Pediatr Radiol* 2019; **49**: 1404-1421 [DOI: 10.1007/s00247-019-04402-8]

3 **McGuire A**, Fernandez-Pineda I, Fishman SJ, Dickie BH. Pediatric hepatic vascular tumors. *Seminars Pediatric Surg* 2020; **29**: 150970 [DOI: 10.1016/j.sempedsurg.2020.150970]

4 **Wassef M**, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, Burrows P, Frieden IJ, Garzon MC, Lopez-Gutierrez JC, Lord DJ, Mitchel S, Powell J, Prendiville J, Vikkula M; ISSVA Board and Scientific Committee. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015; **136**: e203-e214 [PMID: 26055853 DOI: 10.1542/peds.2014-3673]

5 **Christison-Lagay ER**, Burrows PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, Paltiel HJ, Klement G, Mulliken JB, Fishman SJ. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007; **42**: 62-7; discussion 67-8 [PMID: 17208542 DOI: 10.1016/j.jpedsurg.2006.09.041]

6 **Deyrup AT**, Miettinen M, North PE, Khoury JD, Tighiouart M, Spunt SL, Parham D, Weiss SW, Shehata BM. Angiosarcomas arising in the viscera and soft tissue of children and young adults: a clinicopathologic study of 15 cases. *Am J Surg Pathol* 2009; **33**: 264-269 [PMID: 18987547 DOI: 10.1097/PAS.0b013e3181875a5f]

7 **Grassia KL**, Peterman CM, Iacobas I, Margolin JF, Bien E, Padhye B, Meyers RL, Adams DM. Clinical case series of pediatric hepatic angiosarcoma. *Pediatr Blood Cancer* 2017; **64** [PMID: 28521077 DOI: 10.1002/pbc.26627]

8 **Dimashkieh HH**, Mo JQ, Wyatt-Ashmead J, Collins MH. Pediatric hepatic angiosarcoma: case report and review of the literature. *Pediatr Dev Pathol* 2004; **7**: 527-532 [PMID: 15547777 DOI: 10.1007/s10024-004-4041-x]

9 **Potanos KM**, Hodgkinson N, Fullington NM, Narla A, Albritton K, Kozakewich H, Kim HB. Long term survival in pediatric hepatic angiosarcoma (PHAS): A case report and review of the literature. *J Pedi Surg Case Rep* 2015; **3**:410-413 [DOI: 10.1016/j.epsc.2015.08.006]

10 **Falk H**, Herbert JT, Edmonds L, Heath CW Jr, Thomas LB, Popper H. Review of four cases of childhood hepatic angiosarcoma--elevated environmental arsenic exposure in one case. *Cancer* 1981; **47**: 382-391 [PMID: 7193080 DOI: 10.1002/1097-0142(19810115)47:2<382::aid-cncr2820470228>3.0.co;2-n]

11 **Nord KM**, Kandel J, Lefkowitch JH, Lobritto SJ, Morel KD, North PE, Garzon MC. Multiple cutaneous infantile hemangiomas associated with hepatic angiosarcoma: case report and review of the literature. *Pediatrics* 2006; **118**: e907-e913 [PMID: 16880251 DOI: 10.1542/peds.2006-0183]

12 **Al Dhaybi R**, Agoumi M, Powell J, Dubois J, Kokta V. Lymphangiosarcoma complicating extensive congenital mixed vascular malformations. *Lymphat Res Biol* 2010; **8**: 175-179 [PMID: 20863270 DOI: 10.1089/lrb.2009.0034]

13 **Olson TS**, Chan ES, Paessler ME, Sullivan KE, Frantz CN, Russo P, Bessler M. Liver failure due to hepatic angiosarcoma in an adolescent with dyskeratosis congenita. *J Pediatr Hematol Oncol* 2014; **36**: 312-315 [PMID: 23588325 DOI: 10.1097/MPH.0b013e318286d4d4]

14 **Awan S**, Davenport M, Portmann B, Howard ER. Angiosarcoma of the liver in children. *J Pediatr Surg* 1996; **31**: 1729-1732 [PMID: 8987004 DOI: 10.1016/s0022-3468(96)90065-2]

15 **Selby DM**, Stocker JT, Ishak KG. Angiosarcoma of the liver in childhood: a clinicopathologic and follow-up study of 10 cases. *Pediatr Pathol* 1992; **12**: 485-498 [PMID: 1409148 DOI: 10.3109/15513819209024199]

16 **Yasir S**, Torbenson MS. Angiosarcoma of the Liver: Clinicopathologic Features and Morphologic Patterns. *Am J Surg Pathol* 2019; **43**: 581-590 [PMID: 30986799 DOI: 10.1097/PAS.0000000000001228]

17 **Antonescu C**. Malignant vascular tumors--an update. *Mod Pathol* 2014; **27 Suppl 1**: S30-S38 [PMID: 24384851 DOI: 10.1038/modpathol.2013.176]

18 **North PE**, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000; **31**: 11-22 [PMID: 10665907 DOI: 10.1016/s0046-8177(00)80192-6]

19 **Kulkarni MP**, Agashe SR, Singh RV, Sulhyan KR. Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. *Indian J Pathol Microbiol* 2010; **53**: 322-324 [PMID: 20551545 DOI: 10.4103/0377-4929.64311]

20 **Li Q**, Wang J, Sun Y, Cui Y, Hao X. Hepatic angiosarcoma arising in an adult mesenchymal hamartoma. *Int Semin Surg Oncol* 2007; **4**: 3 [PMID: 17257403 DOI: 10.1186/1477-7800-4-3]

21 **Tucker SM**, Cooper K, Brownschidle S, Wilcox R. Embryonal (undifferentiated) sarcoma of the liver with peripheral angiosarcoma differentiation arising in a mesenchymal hamartoma in an adult patient. *Int J Surg Pathol* 2012; **20**: 297-300 [PMID: 22134632 DOI: 10.1177/1066896911424899]

22 **Tsao CY**, Sommer A, Hamoudi AB. Aicardi syndrome, metastatic angiosarcoma of the leg, and scalp lipoma. *Am J Med Genet* 1993; **45**: 594-596 [PMID: 8456830 DOI: 10.1002/ajmg.1320450515]

23 **Chen G**, Li M, Wu D, Tang H, Tang D. Primary splenic angiosarcoma in a 2.5-year-old boy with hepatic metastasis. *Pediatr Surg Int* 2012; **28**: 1147-1150 [PMID: 22922948 DOI: 10.1007/s00383-012-3164-9]

24 **Castro EC**, Galambos C, Shaw PH, Ranganathan S. Primary mesenteric angiosarcoma in a child with associated lymphangiectasia: a case report. *Pediatr Dev Pathol* 2008; **11**: 482-486 [PMID: 19143455 DOI: 10.2350/08-03-0438.1]

25 **Good AB**, Nascimento A, Welker KM, Arndt CA. Congenital angiosarcoma with transient response to paclitaxel. *J Pediatr Hematol Oncol* 2008; **30**: 451-453 [PMID: 18525462 DOI: 10.1097/MPH.0b013e31816916d1]

26 **Antonescu CR**, Yoshida A, Guo T, Chang NE, Zhang L, Agaram NP, Qin LX, Brennan MF, Singer S, Maki RG. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. *Cancer Res* 2009; **69**: 7175-7179 [PMID: 19723655 DOI: 10.1158/0008-5472.CAN-09-2068]

27 **Mansfield SA**, Williams RF, Iacobas I. Vascular tumors. *Seminars Pediatric Surg* 2020; **29**: 150975 [DOI: 10.1016/j.sempedsurg.2020.150975]

28 **Huang SC**, Zhang L, Sung YS, Chen CL, Kao YC, Agaram NP, Singer S, Tap WD, D'Angelo S, Antonescu CR. Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations. *Am J Surg Pathol* 2016; **40**: 645-655 [PMID: 26735859 DOI: 10.1097/PAS.0000000000000582]

29 **Marks EI**, Pamarthy S, Dizon D, Birnbaum A, Yakirevich E, Safran H, Carneiro BA. *ROS1-GOPC/FIG*: a novel gene fusion in hepatic angiosarcoma. *Oncotarget* 2019; **10**: 245-251 [PMID: 30719217 DOI: 10.18632/oncotarget.26521]

30 **Cournoyer E**, Al-Ibraheemi A, Engel E, Chaudry G, Stapleton S, Adams DM. Clinical characterization and long-term outcomes in pediatric epithelioid hemangioendothelioma. *Pediatr Blood Cancer* 2020; **67**: e28045 [PMID: 31724797 DOI: 10.1002/pbc.28045]

31 **Sardaro A**, Bardoscia L, Petruzzelli MF, Portaluri M. Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor. *Oncol Rev* 2014; **8**: 259 [PMID: 25992243 DOI: 10.4081/oncol.2014.259]

32 **Lau K**, Massad M, Pollak C, Rubin C, Yeh J, Wang J, Edelman G, Yeh J, Prasad S, Weinberg G. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. *Chest* 2011; **140**: 1312-1318 [PMID: 21546438 DOI: 10.1378/chest.11-0039]

33 **Hettmer S**, Andrieux G, Hochrein J, Kurz P, Rössler J, Lassmann S, Werner M, von Bubnoff N, Peters C, Koscielniak E, Sparber-Sauer M, Niemeyer C, Mentzel T, Busch H, Boerries M. Epithelioid hemangioendotheliomas of the liver and lung in children and adolescents. *Pediatr Blood Cancer* 2017; **64** [PMID: 28598585 DOI: 10.1002/pbc.26675]

34 **Studer LL**, Selby DM. Hepatic Epithelioid Hemangioendothelioma. *Arch Pathol Lab Med* 2018; **142**: 263-267 [PMID: 29372848 DOI: 10.5858/arpa.2016-0171-RS]

35 **Epelboym Y**, Engelkemier DR, Thomas-Chausse F, Alomari AI, Al-Ibraheemi A, Trenor CC 3rd, Adams DM, Chaudry G. Imaging findings in epithelioid hemangioendothelioma. *Clin Imaging* 2019; **58**: 59-65 [PMID: 31238187 DOI: 10.1016/j.clinimag.2019.06.002]

36 **Rosenbaum E**, Jadeja B, Xu B, Zhang L, Agaram NP, Travis W, Singer S, Tap WD, Antonescu CR. Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets. *Mod Pathol* 2020; **33**: 591-602 [PMID: 31537895 DOI: 10.1038/s41379-019-0368-8]

37 **Flucke U**, Vogels RJ, de Saint Aubain Somerhausen N, Creytens DH, Riedl RG, van Gorp JM, Milne AN, Huysentruyt CJ, Verdijk MA, van Asseldonk MM, Suurmeijer AJ, Bras J, Palmedo G, Groenen PJ, Mentzel T. Epithelioid Hemangioendothelioma: clinicopathologic, immunhistochemical, and molecular genetic analysis of 39 cases. *Diagn Pathol* 2014; **9**: 131 [PMID: 24986479 DOI: 10.1186/1746-1596-9-131]

38 **Antonescu CR**, Le Loarer F, Mosquera JM, Sboner A, Zhang L, Chen CL, Chen HW, Pathan N, Krausz T, Dickson BC, Weinreb I, Rubin MA, Hameed M, Fletcher CD. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. *Genes Chromosomes Cancer* 2013; **52**: 775-784 [PMID: 23737213 DOI: 10.1002/gcc.22073]

39 **Errani C**, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH, Antonescu CR. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer* 2011; **50**: 644-653 [PMID: 21584898 DOI: 10.1002/gcc.20886]

40 **Doyle LA**, Fletcher CD, Hornick JL. Nuclear Expression of CAMTA1 Distinguishes Epithelioid Hemangioendothelioma From Histologic Mimics. *Am J Surg Pathol* 2016; **40**: 94-102 [PMID: 26414223 DOI: 10.1097/PAS.0000000000000511]

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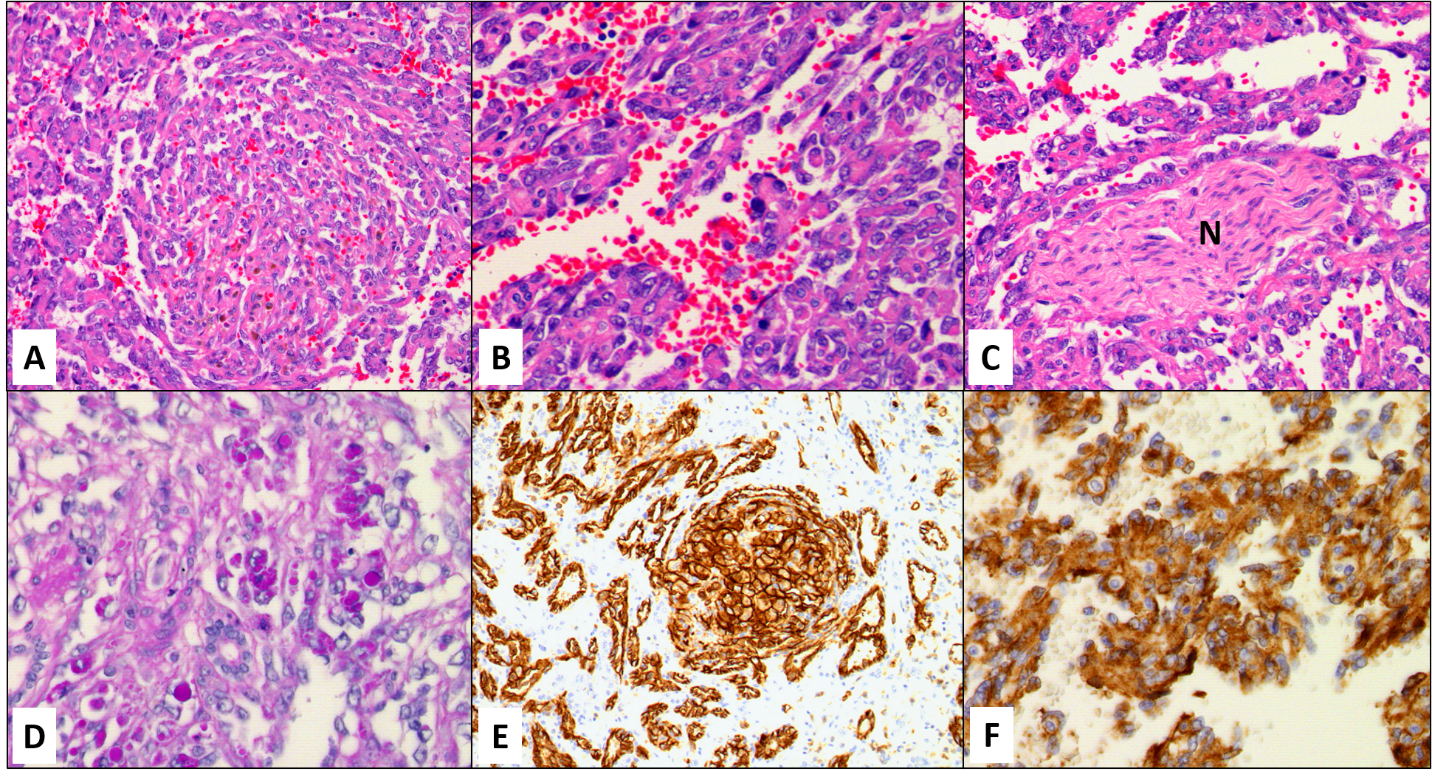
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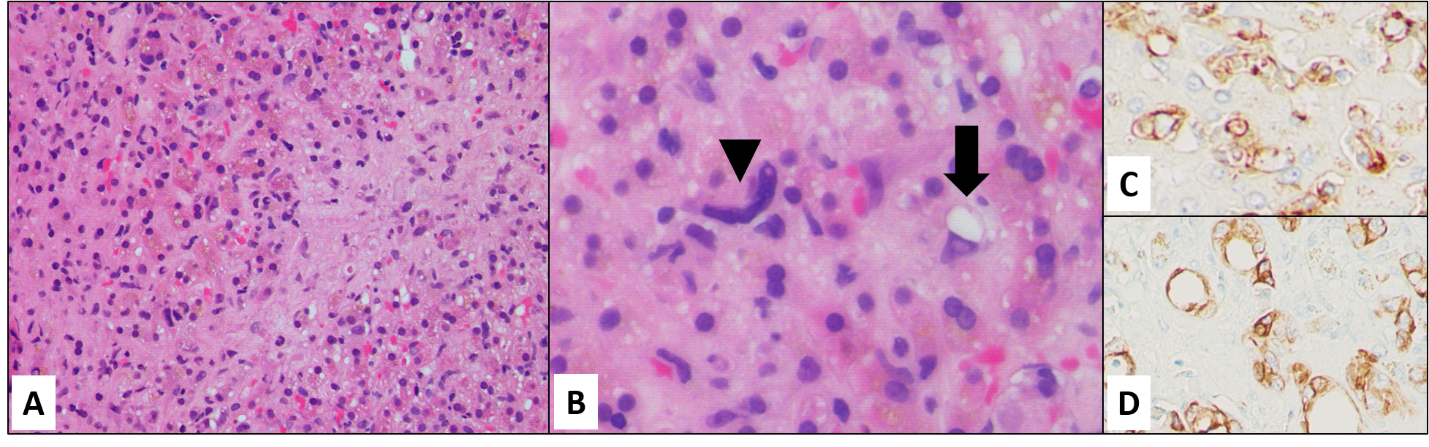
Grade E (Poor): 0

**P-Reviewer:** Wang XQ **S-Editor:** Zhang L **L-Editor:** A **P-Editor:** Wu YXJ

**Figure Legends**



**Figure 1** **Histologic findings of pediatric hepatic angiosarcoma.** A: Whorls of atypical spindled cells (Hematoxylin-eosin staining, 10 ×); B: Moderate power view of the lesional cells show moderate nuclear atypia (Hematoxylin-eosin staining, 20 ×); C: Perineural invasion is be noted in this infiltrative lesion; note the nerve bundle (N) in the center (hematoxylin-eosin staining, 10 ×); D: Periodic acid-Schiff-positive eosinophilic globules are focally identified in the lesion, usually seen in association with the whorls of atypical spindled cells/glomeruloid bodies (para-aminosailcylic acid, 10 ×); E: The lesional cells are immunoreactive for vascular markers such as CD31 (10 ×) (note the glomeruloid body in the center); F: Factor VIII (20 ×).

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**Figure 2 Pediatric hepatic epithelioid hemangioendothelioma.** A: Hypocellular epithelioid cells embedded in fibrotic stroma (right); entrapped hepatocytes with cholestasis are noted on the left (hematoxylin-eosin staining, 4 ×); B: High power view of the lesion demonstrates scattered atypical cells (arrowhead) with occasional intracytoplasmic lumen formation (arrow) (Hematoxylin-eosin staining, 20 ×); C: The neoplastic cells are immunoreactive for CD31 (20 ×); D: The neoplastic cells are immunoreactive for CK7 (20 ×).

**Table 1 Clinicopathologic characteristics of pediatric hepatic angiosarcoma and epithelioid hemangioendothelioma**

|  |  |  |
| --- | --- | --- |
|  | Angiosarcoma | Epithelioid hemangioendothelioma |
| Demographics | Female predominance; mean age at diagnosis: 40 mo | Female predominance; median age at diagnosis: 12 yr |
| Clinical presentation | Abdominal pain, and distension due to rapid liver enlargement. Lung metastasis is common | Mostly present with multiorgan involvement, most frequently involving liver, lungs, bone and soft tissue |
| Associated conditions | Cutaneous and hepatic infantile hemangiomas, cutaneous vascular malformations, dyskeratosis congenita | None reported |
| Molecular | Unknown (*ROS1-GOPC* fusion reported in an adult hepatic angiosarcoma)[29] | *WWTR1-CAMTA1* fusion (90%) *YAP1-TFE3* fusion(10%) |
| Histology | * Well-formed, anastomosing vessels to more solid areas composed of pleomorphic spindle cells. Hypercellular whorls of spindled cells (glomeruloid bodies). Intracytoplasmic eosinophilic globules (periodic acid-Schiff -positive and diastase-resistant) | * Cords and nests of epithelioid cells in a variable fibromyxoid stroma. Occasional intracytoplasmic vacuoles/lumina. Minimal cytologic atypia with low mitotic rates |
| Immunohistochemistry | CD31, CD34, factor VIII, FLI-1, ERG, occasionally podoplanin and GLUT-1 | CD31, CD34, factor VIII, FLI-1, ERG, variable podoplanin, smooth muscle actin and keratin |



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