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Case Report

Epithelioid angiosarcoma of the liver: report of two cases and review of the literature

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Abstract: Angiosarcoma is a malignant tumor of endothelial origin. Epithelioid angiosarcoma is a subtype of angiosarcoma, in which the malignant endothelial cells have a predominantly epithelioid appearance. So far, few cases of primary hepatic epithelioid andiosarcoma (PHEA) have been described. In this case report, we describe two rare cases of PHEA. Microscopically, the tumors were consistently composed of atypical epithelioid cells with vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm. One patient had metastatic disease and underwent palliative hepatic surgery following radiotherapy and chemotherapy, and had a postoperative survival time of 12 months, while the other patient is still alive after tumor resection. PHEA is an aggressive malignant tumor with a high rate of metastasis.

Keywords: Angiosarcoma, epithelioid angiosarcoma, metastasis, hepat

Introduction

Angiosarcoma (AS) is a rare and highly malignant soft tissue sarcoma of endothelial cell origin, which accounts for less than 1% of all soft tissue sarcomas [1]. AS may derive from the endothelia of lymphatic or blood vessels and most of them arise in the skin, breast, and soft tissues. Hepatic angiosarcomas (HAS) are much rarer and account for less than 5% of all angiosarcomas and are associated with worse survival [2]. The pathogenesis of AS is unclear, but generally considered to be associated with environmental or occupational exposure to carcinogens such as thorium dioxide, arsenic, vinyl chloride, radiation, and anabolic drugs. There is also some correlation with hemochromatosis and von Recklinghausen disease [3, 4]. However, in most cases of primary hepatic angiosarcoma, no obvious risk factor can be identified. HAS is lack of specific symptoms or signs and exhibits a spectrum of appearances in images, so pathological diagnosis is very necessary. It has a high malignancy rate with poor prognosis, and survival is typically no longer than one year [5].

Epithelioid angiosarcoma (EA) is a unique subtype of angiosarcoma, in which the malignant endothelial cells have a predominantly epithelioid appearance. EA mostly involves deep soft tissues (usually intramuscular) of the extremities. Less commonly, it arises in other sites such as thyroid gland, skin, adrenal glands, and bone [6]. Consequently, most cases of epithelioid angiosarcoma are soft tissue angiosarcomas, with a minority falling into the visceral and cutaneous categories. It generally occurs in male adults, with the highest incidence in the seventh decade. Histopathologically, expression of endothelial markers, such as CD31, CD34, FLI1, ERG, and factor VIII-RA, is characteristic of epitheloid angiosarcoma.

We report two cases of an unusual hepatic tumor, which was histopathologically diagnosed as epithelioid angiosarcoma, and review the clinicopathological characteristics and treatment modalities of EASs.

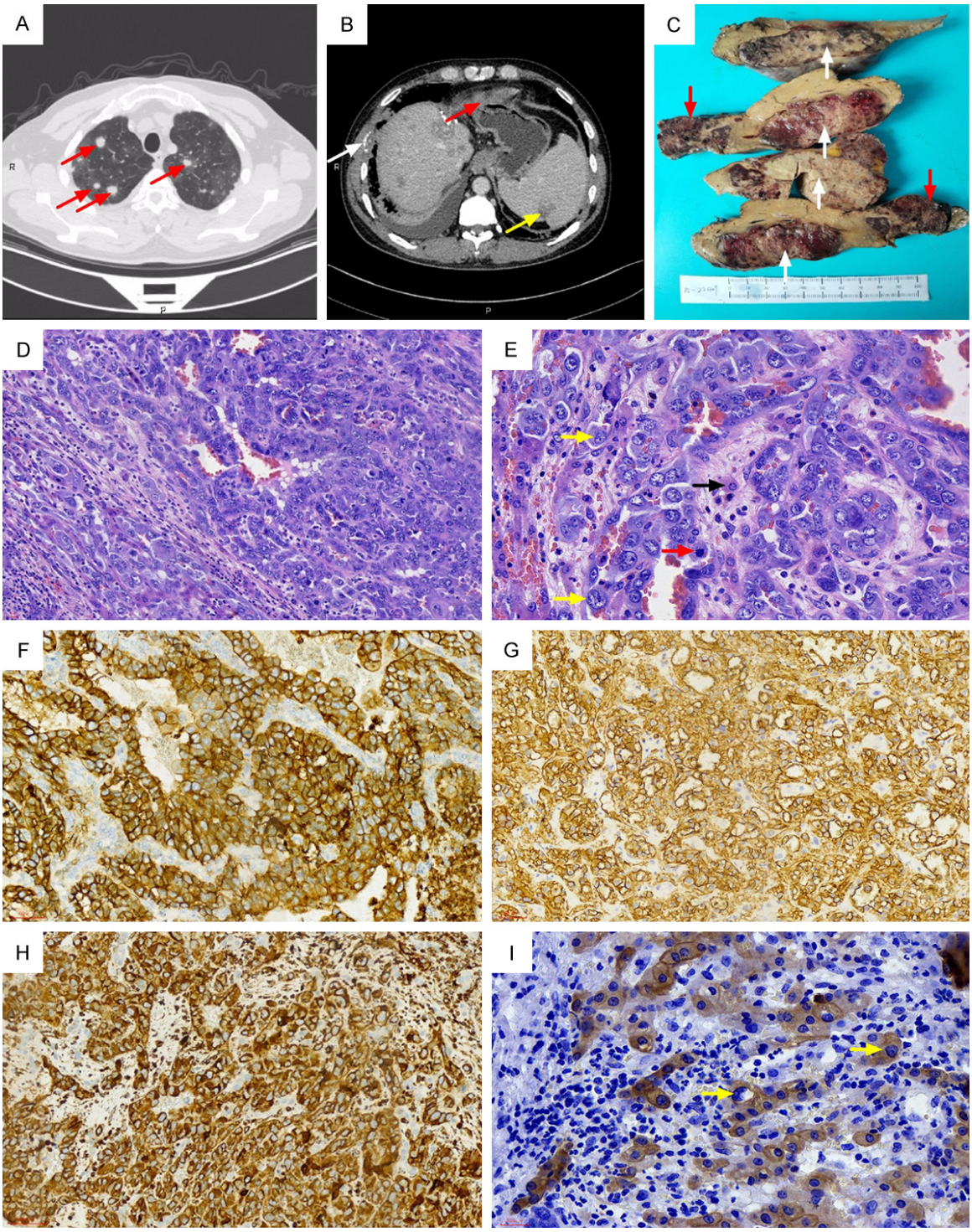

Figure 1. A: Chest CT scan showing metastatic mass lesions in lungs (red arrow). B: CT scan of abdomen revealing lytic change in 7th rib (white arrow) and mass lesions in spleen (yellow arrow) and peritoneum (red arrow). C: Cross-sectioned tumor specimen demonstrating two clearly demarcated red gray and yellow gray lesions, measuring 7 cm×5 cm×3 cm (white arrow), 5 cm×4.5 cm×3.5 cm (red arrow) each with areas of local hemorrhage and necrosis. D: HE staining of tumor showing atypical epithelioid cells and presence of vascular channels, normal hepatocytes are present (magnification, ×200). E: High power view showing tumor cells are large rounded "epithelioid" cells (yellow arrow) with abundant eosinophilic cytoplasm and relatively high pathologic mitotic figures (red arrow) and normal hepatocytes (black arrow) can be seen in the tumor (magnification, ×400). F-H: Tumor cells are strongly positive for CD31, CD34 and vimentin (magnification, ×200). I: Tumor cells are partially positive for CK, epithelioid cells are noted by yellow arrow (magnification, ×400).

Case report

Case 1

A 41-year old male was admitted to our hospital from a local clinic on December 25 in 2013. His chief complaint was intermittent upper abdominal pain for the past 1 year. The pain was exacerbated by alcohol use, but had no obvious association with food intake. During that period, he also had fatigue and weight loss without anorexia, vomiting, diarrhea, abdominal distension, or jaundice. The patient had smoked two pack of cigarettes and drank 100 ml of alcohol per day for 25 years. There was no significant history of exposure to arsenic, vinyl chloride, or Thorotrast.

Serology for hepatitis A, B and C test was negative. An ultrasound scan demonstrated hypoechoinic change in his liver. A subsequent contrast enhanced triple phase CT showed 2 mass lesions in the left liver lobe with significant liver paranchymal alteration, suggestive of a primary liver tumor. Abdominal T1-weighted magnetic resonance imaging (MRI) revealed two heterogeneous low-intensity masses, and high signal intensity was evident on T2-weighted imaging. Laboratory tests showed total bilirubin 4 mg/dL, albumin 4.3 g/dL, alkaline phosphatase 150 U/L, gamma-glutamyl transferase 90 U/L, aspartate aminotransferase 90 U/L, alanine aminotransferase 130 U/L, and lactate dehydrogenase 181 U/L. CEA 0.35 ug/L, AFP 3.32 ng/ml, CA125 17.3 U/ML, CA50 5.81 U/ML, CA199 5.2 U/ML, CA724 1.43 U/ML, CA242 1.42 U/ML, 11.91 ng/ml, CYFRA21-1 2.40 ng/ml.

The patient was put under general anesthesia and underwent hepatectomy. Left lateral liver lobe, in which two tumor masses were found, was resected during the surgery. He had an uneventful postoperative course, and was discharged 16 days after surgery. Grossly, the tumor showed a variegated appearance. Specimen cross-sectioning revealed two clearly demarcated red gray and yellow gray lesions, measuring 7 cm×5 cm×3 cm, 7 cm×4.5 cm×3.5 cm each with areas of local hemorrhage and necrosis (**Figure 1C**). No tumor emboli were found in bile duct or portal vein. Histology revealed clusters of atypical epithelioid cells with vesicular nuclei, prominent nucleoli and eosinophilic cytoplasm with increased mitotic figures, suggestive of epithelioid angiosarcoma (**Figure 1D**, **1E**). In addition to solid tumor mass, hemorrhage, and necrosis were also noted. Immunohistochemical staining was strongly and diffusely positive for CD31 (**Figure 1F**) and CD34 (**Figure 1G**) characteristic of tumor cells. Stains for SMA, vimentin (**Figure 1H**), CK (**Figure 1I**) and Ki-67 (positive rate of 40%) also showed focal positivity. CK7, CK19, CK20, villin, HSA, EGFR, AFP, Arginase-1, NapsinA, and TTF-1 were negative on immunohistochemical staining. The histopathological study confirmed the diagnosis of PHEA.

Six months later, at third time follow-up, the patient presented with chest discomfort and abdominal pain. CT imaging of Chest and abdomen revealed lytic change in 7th rib, multiple mass lesions in lungs, spleen and peritoneum (**Figure 1A**, **1B**). HEA metastases were considered, and biopsy of the metastases masses outside the liver was proposed to the patient. But he declined the biopsy after thorough discussion about risks and benefits of it. Then radiotherapy and chemotherapy with IFO + Epirubicin as first phase, Gemcitabin + Docetaxel + dexamethasone as second phase were given to him. After 12 months of tumor resection, he died from pulmonary infection.

Case 2

On March 21st in 2016, A 43 year old man presented to our hospital with complaints of weight loss and intermittent upper abdominal pain without nausea, vomiting or jaundice. He had no significant past medical history. He denied any alcohol intake or exposure to arsenic, vinyl chloride, or Thorotrast. He never used any hepatotoxic or herbal medications.

Upon examination, his abdomen was soft, nontender, nondistended. There was no hepatomegaly or any signs of juandice. Liver and renal function tests were normal. However, non-contrast enhanced computed tomography showed the presence of a 6.5 cm×4 cm×2.3 cm sized mass lesion in segment IV and V of the liver (**Figure 2A**). Several small cystic changes were also noted in right liver lobe. The tumor was slightly enhanced on subsequent contrast enhanced triple phase CT scan (**Figure 2B-D**). The remaining segments of the liver were normal, with no evidence of metastatic disease.

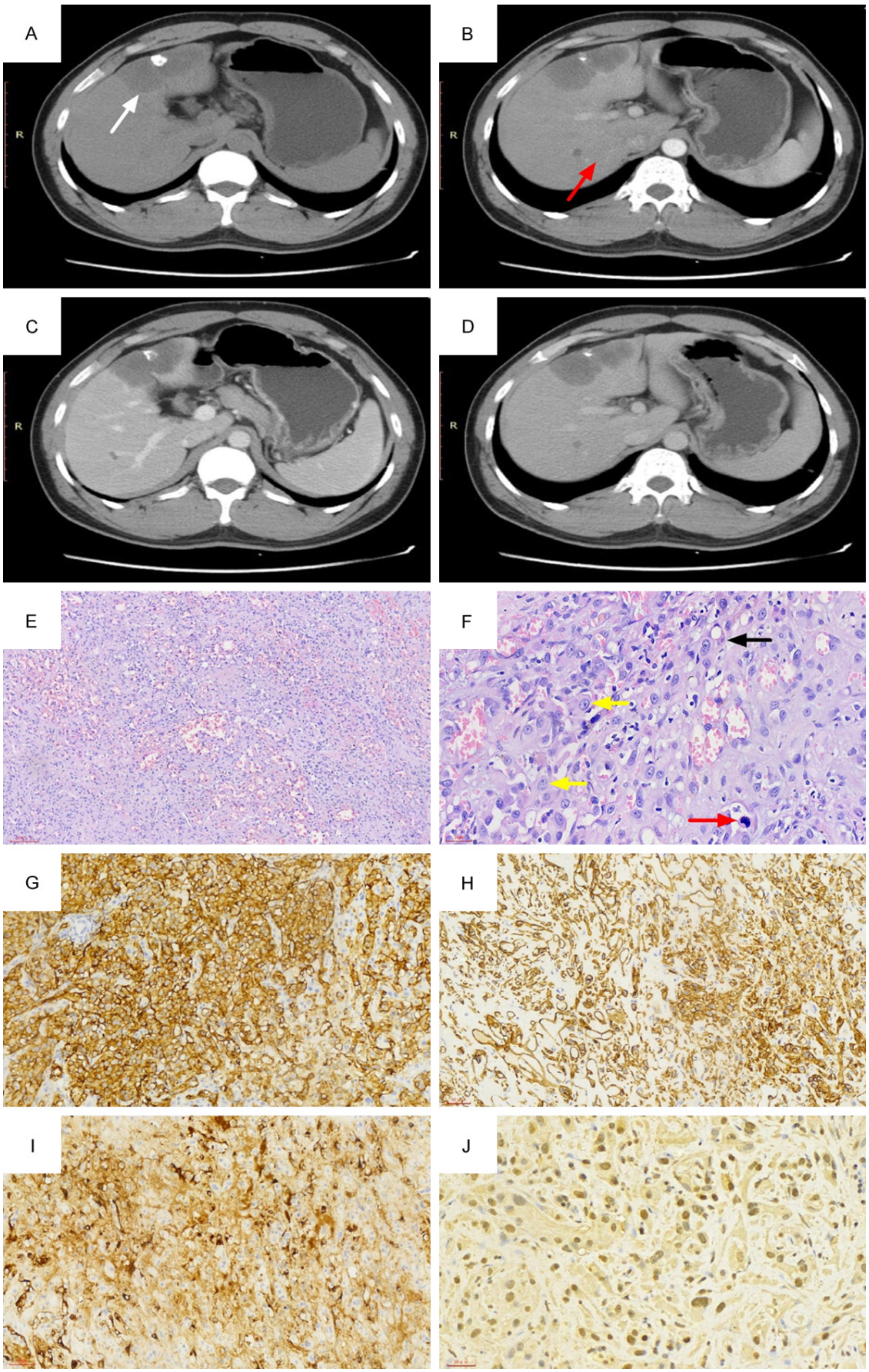
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Figure 2. (A) Non-contrast enhanced CT scan showing 6.5×4×2.3 cm sized mass lesion in segment IV and V of the liver. Small cystic change is also noted (red arrow). (B-D) Contrast enhanced triple phase CT scan, the mass lesion is slightly enhanced in arterial phase (B), portal venous phase (C) and more delayed phase (D). (E) HE staining of tumor showing epithelioid cells were arranged in sheets forming vascular channels (magnification, ×100). (F) Tumor cells consisted of large, mildly to moderately pleomorphic, round to polygonal epithelioid cells (yellow arrow), pathologic mitotic figures (red arrow) and normal hepatocytes (black arrow) can be noted (magnification, ×400). (G) Tumor cells are strongly positive for CD31, whereas hepatocytes are negative for CD31 (magnification, ×200). (H) Tumor cells are strongly positive for CD34 (magnification, ×200). (I) Tumor cells are positive for FVIII (magnification, ×200). (J) Tumor cells are partially positive for CK (magnification, ×400).

The tumor was surgically resected and sent for pathological study. Grossly, mass tumor appeared cystic with rough layers. Hemorrhagic clots can be seen inside the cyst. Microscopically, most cells are arranged in sheets, consisting of large, mildly to moderately pleomorphic, round to polygonal epithelioid cells, with central to eccentrically located nuclei containing prominent nucleoli (**Figure 2E**). Vascular channels are formed by tumor cells (**Figure 2F**). The cytoplasm of most malignant cells appeared eosinophilic, as a diagnostic feature (**Figure 2F**). Occasional cells with intracytoplasmic lumina containing erythrocytes can also be seen. On immunohistochemistry staining, tumor cells were strongly and diffusely positive for vascular endothelial markers CD31 (**Figure 2G**), CD34 (**Figure 2H**), F-VIII (**Figure 2I**) and VEGF, partially positive for vimentin, Ki67 (positive rate of 60%), CK (**Figure 2J**) and SMA, and negative for CK7, CK8, CK19, CK20, villin, Hepa-1, AFP, chromogranin and synapsin. After tumor resection, the patient was followed up on a regular basis, and neither recurrence nor metastasis of the tumor has been noted so far.

Discussion

Angiosarcoma is a rare malignant mesenchymal tumor with vascular endothelial differentiation, and is characterized by aggressive proliferation and wide distribution of tumor cells. The site of origin can be broadly categorized into cutaneous, deep soft tissue, and visceral. Classic angiosarcoma predominantly arises in the skin of sun-exposed areas like head, face, and neck. But a variety of other sites such as breast, liver, spleen, and bone were also encountered [7, 8]. EA is an unusual subtype of angiosarcoma with predominantly epithelioid morphology. It usually arises in male adults with peak incidence in seventh decade. EA most often involves deep soft tissues. The site of involvement has been correlated with the amount of lymphovascular supply and the concentration of endothelial cells [8].

Clinical manifestations of EA are not specific, and variety of clinical presentations may be encountered, due to the diversity of primary tumor sites and the highly malignant nature of the tumor. Symptoms of PHEA vary from fatigue to intermittent abdominal pain as seen in our case.

Histologically epithelioid angiosarcoma consists of large, mildly to moderately pleomorphic, round to polygonal epithelioid cells, with central to eccentrically located nuclei containing prominent nucleoli. The chromatin is peripherally marginated in the nucleus, yielding a vesicular appearance. Most malignant endothelial cells are filled with abundant eosinophilic cytoplasm, but occasional cells with intracytoplasmic lumina containing erythrocytes can usually be noted. Architecturally, most cells are arranged in sheets, but cellular islands or cords may be seen. Immunohistochemical staining is very helpful in diagnosis of EA. Common markers of endothelial cell origin such as CD31, CD34, Fli-1, Factor VIII-related antigen are often positive [9]. CD31 is the single best marker among them, particularly, if Factor VIII-related antigen is negative [10, 11]. CK, Ki67, CAM5.2, Vimentin, EMA, and FOS-B may show partial positivity to a different extent. D2-40, c-Myc, CAMTA-1, and TFE-3 staining was usually negative [12].

Epithelioid angiosarcoma may also share morphologic or histological characteristics with other benign or malignant vascular tumors such as angiomoa, angiosarcoma, hemangioblastoma, epithelioid hemangioenthelioma, undifferentiated embryonic sarcoma and Kaposi sarcoma.

Angioma, being a benign vascular tumor, is grossly characterized as a well rounded mass, and histologically demonstrates small and round to spindle-shaped tumor cells with no significant nuclear atypia. Mitotic figures are seldom seen.

Grossly, angiosarcoma shows ill-defined and diffusely infiltrative spongy nodules with hemorrhage, while microscopic analysis of the tumor shows malignant endothelial cells which grow along preexisting vascular lines. It shows solid and pseudopapillary patterns. Necrosis and hemorrhage are also present. Plump spindle cells can be found with large pleomorphic nuclei. In addition, erthrophagocytosis is less common compared to EAS (33% vs. 80%) [13]. Immunohistochemistry staining shows angiosarcoma is positive for CD31, CD34, factor VIII Weibel-Palade bodies on electron microscopy.

In hemangioblastoma, which is closely correlated with von Hippel-Lindau syndrome, tumors tend to have a complex capillary network, mainly composed of an admixed population of plump spindle cells and microvacuolated cells with eosinophilic pale or clear cytoplasm. Tumor cells may demonstrate marked nuclear pleomorphism. Mitotic activity is low (range, 0 to 2/10 HPF) with no atypia compared to EAS, and tumor cells are often positive for inhibin-α, NSE, and S-100 protein, focal SMA and EMA expression. However, ESA often negative for inhibin-α, NSE, and S-100 protein.

Epithelioid hemangioendothelioma has gross features with multiple, tan-gray, firm, circumscribed and focally confluent nodules up to 12 cm with infiltrative margins. It may show central calcification or ossification. Microscopically, the tumor exhibits a zonal pattern, with central sclerosis or hyalinization and tumor cells at the periphery in a vascular channel proliferation. Eosinophilic epithelioid tumor cells typically show vesicular nuclei with less conspicuous nucleoli. Many individual cells display intracytoplasmic lumina, containing red blood cells, although frank vascular formation is not a feature. Moreover, EHE often shows characteristic myxochondroid background, much less pronounced cytological atypia, and lower mitotic count than in EAS. Approximately 30% of EHE show significant cellular atypia, foci of necrosis, and higher mitotic activity which is associated with more aggressive behavior. Immunohistochemistry showed epithelioid hemangioendothelioma is positive for factor VIII, CD31, CD34, cytokeratin (50%) Weibel-Palade bodies, and intermediate filaments on electron microscopy [14].

Undifferentiated embryonic sarcoma (most common in school age children) is grossly well-demarcated, solitary, unencapsulated lesion. The cut surface is variegated with solid and cystic appearance, with necrosis and hemorrhage. Microscopically, pleomorphic, spindle-shaped tumor cells are embedded in an abundant mucopolysaccharide-rich myxoid matrix. If it arises in liver, dilated bile ducts and PAS-positive diastase-resistant globules will be found within the tumor cells, but tumor cells are not particularly vascular. Staining is strongly and widely positive for vimentin, focally positive for keratin, and negative for CD31 [14].

Kaposi sarcoma, an aggressive variant associated with AIDS and HHV8, is commonly seen in mucocutaneous tissues. It can also occur in deep tissues and visceral organs. Kaposi sarcoma grossly shows hemorrhagic multifocal spongy nodules ranging from 5 cm to 7 cm. Specimen taken from liver will show Lesions centered on portal tracts with poorly vasoformative spindle-cell proliferation accompanied by red blood cell extravasation and focal deposition of hemosiderin. Cytoplasmic eosinophilic hyaline globules are a typical finding in tumor cells in Kaposi sarcoma. Immunohistochemistry study demonstrates positive stain for membranous/cytoplasmic CD31 and CD34 and nuclear HHV8.

Epithelioid angiosarcoma often easily metastasizes to lymph nodes and solid organs, especially to the lungs, bone, soft tissue, and skin [15]. One patient in our case report had metastasis and survived for 12 months after diagnosis, while the other one is still alive. The literature has reported that within 2 to 3 years of diagnosis, more than 50% of patients will be dead of the disease, but 20% to 30% of people will be disease free [7, 16].

The prognosis of EA depends on the tumor site, size, stage, pleomorphism, cellularity, and mitotic activity. Other adverse prognostic indictors include bleeding, pain, proliferative index, and lesions greater than 5 cm in size (10). Even in patients with localized epithelioid angiosarcoma, multifocal involvement within the local area is very common. So recurrence rates are often high, and multidisciplinary care produces better outcomes regardless of the location of the tumor [17, 18].

Treatment modalities vary among individuals. Surgical resection of the primary tumor and radiation and chemotherapy are usually used [19]. Due to its low survival rate, in European liver transplant registry HAS is listed as an absolute contraindication to liver transplant [20]. In the elective management of unresectable primary and metastatic HAS, liver-directed transcatheter therapies are safe. Emergency embolization is an effective way for stabilizing the patient's condition and allowing more definitive treatment therapy in the future, whenever the rupture of the tumor is suspected [21]. Some earlier nine-patient centered studies showed that paclitaxel-based chemotherapeutic regimens may improve survival with a response rate of 89% and 5 months median duration of response (range, 2-13 months). The most frequent side effects of paclitaxel include neutropenia and peripheral neuropathy, which are dose-limiting [22]. Additionally, reports of complete remission after the combined use of adjuvant radiation therapy and bevacizumab, followed by surgery, have been described [23]. Most recent studies have shown that everolimus is beneficial for recurrent/metastatic EA. The most common adverse effects of everolimus are hyperglycemia asthenia and stomatitis syndrome, yet most of them are associated with dosage and can be tolerated. It is suggested that a dose of 5-10 mg/d was comparatively safe [24].

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Disclosure of conflict of interest

None.

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