Rare Vascular Tumors

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Introduction

Vascular tumors are rare in both children and adults. The relative paucity of cases, diverse phenotypes, and heterogeneous clinical outcomes of these tumors has made their classification difficult. In 2013, The World Health Organization (WHO) updated the classification of soft tissue vascular tumors [1]. Pediatric tumors were not independently classified, but an intermediate category of tumors was created and subsequently further divided into locally aggressive and rarely metastasizing tumors. The International Society for the Study of Vascular Anomalies (ISSVA) created a classification system of vascular anomalies at the 1996 meeting in Rome. This schema divided vascular anomalies into tumors and malformations and provided the framework for great strides in research and treatment in the field. The classification system was expanded at the 2014 ISSVA workshop in Melbourne [2] and updated again in 2018 in Amsterdam (ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies) is available at "issva.org/classification" accessed [August 21, 2018]).

These revisions were essential to fully encompass further advances in knowledge and understanding in the field. Vascular anomalies continue to be classified as

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tumors and malformations. Vascular tumors are classified into benign, locally aggressive or borderline, and malignant entities.

Benign Tumors

Epithelioid Hemangioma

Epithelioid hemangiomas (EH) were first described by Wells and Whimster in 1969 [3]. EH is a very rare lesion and represents less than 1% of all vascular tumors. EH are benign lesions that usually occur in the skin and subcutaneous tissues. They may also occur in other regions such as bone and can often mimic malignant neoplasms [4, 5]. EH should not be confused with epithelioid hemangioendothelioma or epithelioid angiosarcoma, which are much more aggressive lesions. Clinically, EH appear as erythematous cysts or plaques and can present with local ulceration and pain. They are often mistaken for hemangiomas or pyogenic granulomas. EH may be a reactive process and have been associated with trauma, infections, or hyperestrogen states. They can involve the metaphysis and diaphysis of long bones, may be unifocal or multicentric, and may cause fracture secondary to lytic lesions [4, 6].

Histologically, EH are well-defined proliferations of capillaries surrounding a larger central vessel. The proliferation is generally due to an inflammatory infiltrate of lymphocytes. Solid portions of EH can also be present, which is atypical and may complicate the diagnosis. Tumor cells are positive for endothelial and lymphatic markers including CD31, ERG, and D2–40 and negative for cytokeratin and CAMTA1. However, lesions lack well-formed vascular channels and do not possess any cytologic atypia or mitotic activity [7]. Primary treatment of these lesions is surgical excision. Curettage and sclerotherapy have also been described. EH often recur locally, but do not have a history of distant spread and can be re-resected if necessary [5].

A recent review found that in pediatric cases there was a higher incidence of multifocal disease compared to adults (45%) and a higher recurrence rate (43% compared to 8–24% in adults) [8].

EH can present as focal or multifocal disease. When EH presents as multifocal disease, or in areas where surgical resection is not an option such as multifocal bone or hepatic lesions, medical therapy with anti-angiogenic agents may stabilize the disease and delay the destructive process. Sirolimus and interferon have both been used in patients ineligible for surgical resection with good long-term results [8]. A few patients with EH were noted to have FOS rearrangements, and targeted therapy with FOS inhibitors may bring better solutions for these patients in the near future [9].

Pyogenic Granuloma

Pyogenic granuloma (PG), also known as “lobular capillary hemangioma” is a benign reactive lesion that predominantly affects children and young adults [10]. This tumor is found between 0.5% and 1% of children typically presenting after 4 months of age. These lesions can arise spontaneously or in sites of trauma, eczema, bug bites, and burns or within capillary malformations [11]. Pyogenic granulomas

have also been associated with the use of retinoic acid compounds and contraceptives. They are characterized by erythematous vascular papules generally found on the head and neck but can also be found throughout the body.

PG can range in size from 1 millimeter to several centimeters. These lesions appear as small or large, smooth, or lobulated vascular nodules that can grow rapidly, sometimes over weeks to months, and have a tendency to bleed profusely with even minor trauma [12]. The pathophysiology of PG is not completely understood. However, it is thought to be secondary to reactive neovascularization. Microscopically, there is a proliferation of lobules of capillary vessels with fibromyxoid stroma; the surface epithelium is frequently attenuated. Ulceration and neutrophilic infiltration is often seen [13].

Some untreated lesions eventually atrophy, become fibromatous, and slowly regress. However, the vast majority of lesions require medical attention primarily because of recurrent bleeding. Localized treatment for smaller PG (less than 0.5 cm) can include cryotherapy and chemical coagulation such as silver nitrate or laser treatment [14, 15]. For lesions larger than 0.5 cm, full thickness excision to subcutaneous tissue is often required. Unfortunately, recurrences of PG are quite common. [13] Topical imiquimod may help prevent recurrence but prolonged treatment may cause irritation particularly in facial lesions [16]. There is also a report of lesion resolution in over half of patients after use of topical 1% propranolol ointment [17] Somatic activating RAS mutations have been found in Pyogenic granulomas and may lead additional therapies in the future [18].

Locally Aggressive Rare Vascular Tumors

Retiform Hemangioendothelioma

Retiform hemangioendothelioma (RH) was initially reported in 1994 by Calonje who described 15 patients with a type of low-grade angiosarcoma [19]. This tumor has been entered in the WHO reclassification as an intermediate (rarely metastasizing) vascular tumor [20]. These tumors generally have been described in young adults in the upper and lower extremities. Phenotypically they appear as a slow-growing solitary mass with a plaque-like appearance or as a subcutaneous firm nodule [21].

Pathologically, RHE involves the entire thickness of dermis and often extends into the subcutaneous tissue. Hyperchromatic hobnail endothelial cells are a common finding. Mitotic figures are rare. The vessels are elongated and arranged in a pattern which resembles the rete testis. The hobnail cells express endothelial markers including von Willebrand factor, CD31, and CD34 [22]. It is unclear whether these tumors express lymphatic endothelial markers, as conflicting reports have been found for podoplanin and other lymphatic marker expressions [23, 24]. Treatment consists of surgical excision with adequate margins and lymph node sampling (preferably by a sentinel lymph node technique). In the reported cases, local recurrence appears to be common [21]. Reports note two of 15 patients with regional lymph node metastases without any deaths due to distant disease [25]. Long-term monitoring for local recurrence is recommended.

Papillary Intralymphatic Angioendothelioma

Papillary intralymphatic angioendothelioma (PILA) also known as Dabska tumor was first described by Maria Dabska in 1969 when she reported six patients with a locally aggressive hemangioendothelioma [26]. These lesions originate within the dermis and superficial soft tissues of trunk, head and neck, or extremities. They have also been reported to arise from a pre-existing lymphatic or venolymphatic malformation and in patients with lymphedema [27]. Clinically, they appear as violaceous nodules that may be raised. They share a similar appearance to the retiform hemangioendothelioma both clinically and pathologically.

Histologically, under low power they are similar to a lymphatic malformation with large lymphatic channels and aggregates. The vessels are lined by hobnail endothelial cells which are pathognomonic of this tumor [28]. Intravascular endothelial tufts are also noted within the tumor. The endothelial cells also express von Willebrand factor, CD31, and CD34. Lymphatic markers, VEGFR3 and podoplanin, are also expressed with minimal cytologic atypia. As all tumors described showed papillary intravascular proliferation and evidence of lymphatic vessels, they were given the name PILA [29].

Wide surgical excision with lymph node sampling (using a sentinel lymph node technique) is recommended. PILA is known to spread to local regional nodes, and distant spread is uncommon [30]. However, in two cases in the original series it metastasized and caused death. Systemic chemotherapy, if required, should incorporate sarcoma-based therapies [29]. Long-term surveillance for local recurrence and distant spread is recommended.

Composite Hemangioendothelioma

Composite hemangioendothelioma (CHE) was first described in 2000 as a subset of superficial dermal and subcutaneous hemangioendothelioma tumors containing overlapping histologies: epithelioid, retiform, and spindle cell hemangioendotheliomas as well as angiosarcoma-like areas within a single tumor [31] with areas of vacuolated endothelial cells, and other vascular lesions although no lesion contains all subtypes. The definition of composite HE was redefined by the WHO in 2013 as "locally aggressive, rarely metastasizing vascular neoplasm, containing an admixture of histologically distinct components." Importantly, small biopsies of these lesions are unlikely to sample these numerous lesional components and thus may limit accuracy of diagnosis.

To date, less than 40 cases have been reported in the literature [32]. Cases have been reported from infancy to late adulthood and may be associated with other vascular anomalies including arteriovenous malformation, lymphangioma malformaitons, and lymphedema [32]. Based on reviews of the literature, most CHE lesions occur on the extremities but have also occurred in the tongue, mandibular vestibule, cheek, hypopharynx, torso, and inguinal lymph nodes. They appear reddish to bluish-purple and plaque-like to nodular ranging in size from 0.7 to 30 cm; median, 3.2 cm. Lesions are most often associated with normal laboratory findings [32–34].

Treatment with local or wide local excision without chemotherapy or radiation is typically curative. Local recurrence has been documented in 11% to 57% of cases in the literature [32, 35] with rare metastases and without tumor-related deaths. Follow-up imaging surveillance with computed tomography or magnetic resonance imaging is recommended.

Malignant Tumors

Epithelioid Hemangioendothelioma

Epithelioid Hemangioendothelioma (EHE) was first described by Weiss and Enzinger in 1982 as a tumor of intermediate malignancy that was often misdiagnosed as a carcinoma [36]. EHE generally occurs in middle-aged adult patients as a solitary mass in the deep soft tissue, viscera, or bone [37]. The WHO classifies this tumor as a variant of angiosarcoma, a locally aggressive tumor with metastatic potential. [38] The estimated prevalence of EHE is less than one in one million. The majority of patients are female with a mean age at diagnosis of 36 years of age [5]. Some epidemiologic studies have linked chronic *Bartonella* infection with development of EHE [5].

The liver appears to be the most common site of EHE presentation, followed by the lung and bone, but has been reported in numerous sites. Thirty percent of soft tissue cases are associated with metastases and when present, it is often difficult to distinguish the primary tumor from metastatic sites. Cutaneous lesions can be raised and nodular and often pigmented a red-brown color [39].

EHE is often diagnosed incidentally and symptoms are specific to the location of the lesion. Hemolytic anemia and a consumptive coagulopathy have been rarely described as presenting signs. MRI imaging for primary site is important for determining the extent of the tumor and determining surgical resectability. Patients presenting with pleural EHE may have lung nodules often within the lower portion of the lungs with hilar nodal enlargement [40]. Surveillance imaging for staging potential metastatic sites should include the liver, bone, and lung. Bony disease is noted as single or multiple lytic lesions on plain films and cross-sectional imaging. Bone metastases involving more than 50% of cortex represent a high risk of pathologic fractures. There is also some early experience using PET scanning for staging of the lesion, and F-fluorodeoxyglucose (FDG) uptake has been used as a means of assessing response [41, 42].

EHE is characterized by the t(1;3)(p36;q23–25) translocation. This translocation fuses the WWTR1 gene in 3q23–24 with the CAMTA1 in 1p36 [43]. This appears to be a unique translocation and can be very helpful for diagnosis. A fusion protein between the Yes-associated protein 1 (YAP1) gene and the transcription factor E3 (TFE3) gene has been discovered [44]. Lee et al. recently documented the co-expression for some of the patients in the series of both TFE3 and CAMTA. Lesions that were TFE3 positive were noted to be a single larger lesion and to have greater nuclear atypia and hypercellularity compared to those that were TFE3 negative [45].

Microscopically EHE are epithelioid lesions arranged in nests or cord-like patterns. Spindle cells may be present as well. Immunohistochemically, these cells express Fli-1 and CD31, and podoplanin is expressed by lymphatic endothelial cells [38]. Cellular atypia, an increased number of spindled cells, and regions of focal necrosis are thought to be associated with a more aggressive course in adults [46].

Treatment is individualized depending on the type of lesion and metastatic pattern at presentation. Aggressive surgical resection is indicated, with wide margins in soft tissue and bone. Regional lymph nodes should also be evaluated as they are the most frequent sites for metastases [21]. Metastases appear to be more common when cytologic atypia is present. Amputation should be considered particularly in lesions that have an aggressive histological appearance [47]. Liver EHE has been treated with aggressive resection and transplantation with good outcomes. For pleural EHE with multiple nodules, it is often difficult to achieve curative margins and generally requires neoadjuvant therapy prior to resection attempts [48].

Radiotherapy may have a role in localized EHE to prevent local recurrence [49]. Most cases will require adjuvant chemotherapeutic regimens. Multiple medications have been utilized including steroids, bevacizumab, paclitaxel, thalidomide, sorafenib, sunitinib [50], and sirolimus [38]. The choice of sirolimus is based on noted activation of the Ras//PI3K/PTEN /mTOR pathwath in other vascular tumors. Twenty-four patients, age 2–26 years, were evaluated in a multi-institutional case series with epithelioid hemangioendothelioma and 3 patients were treated with sirolimus achieving stable disease or partial response for more than 2.5 years [51], there are limited open clinical trials investigating the effect of targeted therapy on EHE. One includes a MEK inhibitor, trametinib, in patients > than 15 years of age with EHE and progressive disease (NCT 03148275).

Data on survival, response and reoccurence is mostly based on adult studies. The mean survival is 4.6 years ranging from 6 months to 24 years. Mortality is site dependent: 13% mortality rate for soft tissue tumors, 35% for liver tumors, and 65% for lung tumors. Overall survival (OS) is 73% at 5 years [52]. However, the OS following progressive disease is only 24% [52]. Long-term surveillance for local and distant recurrence is required for this aggressive lesion [38].

Angiosarcoma

The term “angiosarcoma” unofficially includes two entities: “hemangiosarcoma” (classic angiosarcoma) and “lymphangiosarcoma” (angiosarcoma arising from lymphatic endothelium in an area of chronic lymphedema, described first in 1948) [53]. Lymphangiosarcoma will be discussed separately and has not been acknowledged as a distinct diagnosis either by WHO or by the ICD-10 (US medical coding).

Angiosarcoma represents about 2% of soft tissue sarcomas [54], with 600 cases diagnosed in the United States per year, approximately 2 cases per million. It mostly affects elderly adults, and it has been described very rarely in children. Reports of its association to the vinyl chloride exposure [55] and previous radiation [56] have been published.

In adults, the most common location of presentation is the head and neck (sun-exposed areas) or the breast following irradiation for breast cancer, but it may arise in any location. In children, angiosarcomas may have a cutaneous localization or may develop in the deep tissue or viscera. For the cutaneous lesions, there appears to be a significant correlation with pre-existing conditions affecting the same area as the tumor [57], such as xeroderma pigmentosum [58–61] or a previous history of local radiation for another primary tumor. Even though radiotherapy is standard of care for a multitude of primary malignancies, radiation-induced angiosarcoma after irradiation of the breasts for carcinoma dominates the medical literature [62] with only sparse reports in other locations. Furthermore, it was noted that c-myc amplification is a specific marker for radiation-induced angiosarcoma of the breast [63, 64] and can be used to differentiate from other atypical vascular lesions arising after radiation for breast cancer [65].

Clinically, angiosarcomas present as a rapidly enlarging purple plaque or nodule that eventually ulcerates and may ooze serosanguinous fluid. Frequently noted are multiple satellite papules or nodules with same characteristics [66].

Ninety-six percent of adult cutaneous angiosarcomas present in the head and neck region, while in children the lower extremities seem to be more commonly affected. In adults, males are the most commonly affected, while in pediatrics, females dominate the number of cases.

Deep angiosarcomas do not appear to have a predilection for a specific location and have been described in the pericardium, the heart, the liver, the spleen, inside of pelvis, etc. Hepatic angiosarcomas will be discussed separately due to their interesting features. Histologically, angiosarcomas manifest some heterogeneity and sometimes offer significant diagnostic challenges to the pathologist. In the classical case, they are composed of racemose and arborizing vessels, exhibiting cytologic atypia with an elevated mitotic index (up to 27 mitotic figures per 10 high power fields in some publications). They may manifest endothelial stratification and while most have an epithelioid morphology (in children), some contain spindle cells.

Immunohistochemically, angiosarcoma stains positive for CD31 and CD34 (endothelial markers) and for *Ulex europaeus* and von Willebrand factor. As approximately 20% of hepatic angiosarcoma is Glut-1 positive and some of the intermediate malignant forms are still labeled as infantile hemangiomas due to this Glut-1 positivity, more studies and consensus among vascular pathology specialists are needed to identify the correct classification and best set of immunostains required for full characterization of these tumors [67].

Necrosis and hemorrhage within the tumor are very common and may affect large portions of the mass. Occasionally, angiosarcoma cells are aneuploid (especially if arising in a cutaneous area post-radiation).

The preferred imaging method is MRI with contrast of the affected area. Full metastatic evaluation including at least pulmonary CT should be obtained at initial presentation and then at reassessment time points due to its high predilection for lung metastases.

In children with hepatic hemangiomas, US with Doppler may be monitored routinely, and if the lesions do not respect the typical clinical course (proliferation, stabilization, involution at the normal age – please see chapter on infantile hemangioma for full details), MRI with contrast should be obtained.

Due to the rapid progression of angiosarcoma with local and metastatic invasion, multiple therapeutic measures are attempted. Surgical complete resection is always considered but rarely possible due to the extent of disease at diagnosis. Amputation of an extremity or complete resection of localized tumor has been described and when combined with intense systemic chemotherapy, appears to have a better outcome.

For the most cases though, after partial resection, chemotherapy with ifosfamide/doxorubicin/vincristine or gemcitabine/docetaxel has been effectively employed (see details in the hepatic angiosarcoma section). Radiotherapy has been indicated, mostly in primary cutaneous angiosarcoma, with limited efficacy.

Molecular studies of angiosarcoma tissue samples proved to have activation of PI3K/mTOR and MAPK pathways. Through mouse models of angiosarcoma exhibiting these activating mutations, it was recently shown that combined treatment with mTOR inhibitors (like sirolimus) and MEK inhibitors (like trametinib) was able to induce significant tumor regression and prevent metastases. Hopefully, in the future, similar treatment schemas may improve prognosis in patients [68].

The prognosis currently is very poor with a progression-free survival of 3–7 months, median overall survival of 14–18 months, and 5-year OS of 20–35% [54]. The numbers vary among publications, but all indicate that angiosarcoma is highly metastatic and very aggressive, with a high mortality rate. Most metastases involve the lungs and liver. Interestingly, when primary and secondary angiosarcomas were compared, the outcome was very similar despite few variations. One would think that secondary angiosarcoma (arising in an area that was previously radiated or in a patient that has received chemotherapy already for another primary malignant process) would be more aggressive, but differences were not statistically significant, making primary angiosarcoma as morbid as secondary [56].

Hepatic Angiosarcoma

Recent case reports of hepatic angiosarcoma diagnosed in early childhood and their interesting features deserve special attention [67].

Patients present most commonly between 1 and 5 years of age (with a median of 3 years). The clinical complaints include abdominal distension, abdominal pain, constipation, vomiting, fever, jaundice, or difficulty of breathing due to large abdominal volume. Frequently a history of cutaneous infantile hemangiomas during infancy with normal involution is obtained [69]. Sometimes, history includes an infantile hepatic hemangioma (IHH) treated with steroids or propranolol for a period of time prior to the diagnosis of angiosarcoma.

Multiple articles describe typical cases of childhood hepatic angiosarcoma coexisting with IHH (previously called hemangioendothelioma type I) [70, 71], and

others recapitulate malignant transformation of hemangioma toward angiosarcoma [72]. This observation differentiates the hepatic angiosarcoma presenting in childhood from adult hepatic angiosarcoma, where the coexistence of the two vascular entities (benign and malignant) was never described.

Interestingly, in patients with both cutaneous and hepatic infantile hemangiomas, only the hepatic lesions appear to progress to angiosarcoma, while the cutaneous ones respect the natural history of IH and undergo involution as expected. Also, from the considerably larger number of very aggressive, complicated IHs present in any other location than the liver, none was described to progress to angiosarcoma, suggesting the hepatic environment itself may play a role in the transformation.

Regarding the evaluation and diagnosis of a hepatic angiosarcoma, MRI with contrast by a dynamic protocol to assess filling pattern is the imaging of choice. For any new hepatic tumor, the differential diagnosis includes hepatoblastoma, mesenchymal hamartoma, hepatic hemangioma (either infantile or congenital), focal nodular hyperplasia, hepatic arteriovenous malformation, or secondary metastases. In angiosarcoma, the mass (unique or multifocal) demonstrates hyperintense T2 signal and hypointense T1 signal. It has intense diffusion restriction and heterogenous enhancement throughout suggesting intense vascularity (Fig. 7.1a, b). Intralesional hemorrhage and necrosis are common.

Patients may present with anemia and/or thrombocytopenia due to intralesional bleeding. Alpha-fetoprotein (AFP) is normal or only minimally elevated (differential diagnosis with hepatoblastoma). Liver function tests may be affected, but it is rare that the child presents in full liver failure.

Due to the critical importance of assigning the correct diagnosis, a biopsy will be almost always performed (Fig. 7.1c). This may be a complicated procedure, due to the high vascularity within the lesion and the potential risk of rupture causing intra-abdominal bleeding.

The natural history of a hepatic angiosarcoma is to metastasize quickly (especially to the lungs) Fig. 7.1d. Local invasion is also extremely common with new foci of tumor appearing in the unaffected hepatic lobe.

Whenever possible complete surgical resection of the tumor should be attempted and systemic chemotherapy initiated. Various treatment schemas have been utilized and most frequently reported including ifosfamide/doxorubicin/vincristine or gemcitabine/docetaxel [72]. The former is usually effective in soft tissue sarcomas. Six cycles of every 3-week treatments are recommended with frequent assessments.

Gemcitabine/docetaxel is also effective and it appears to be better tolerated as mostly outpatient therapy. Unfortunately, due to the very limited number of cases, there is no comparative study between the two protocols and the choice of first-line therapy is left to institutional preference.

Frequently, other anti-angiogenic agents are added to the regimen, and bevacizumab, sorafenib, sirolimus, and even propranolol have been tried with varying results. Hepatic angiosarcoma is not eligible for liver transplant in most institutions due to its highly metastatic potential even in patients with localized disease. Complete cure is rare, and chemotherapy and surgical interventions unfortunately only delay the inevitable.

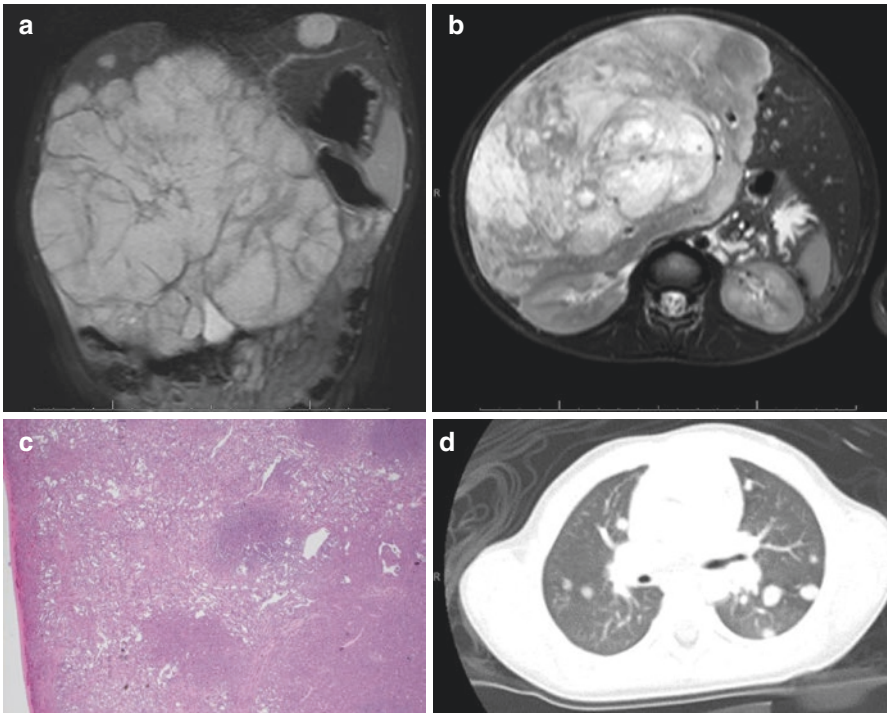

Fig. 7.1 Hepatic angiosarcoma. (**a**) 3 years old female with multifocal hepatic tumors proven to be angiosarcoma. (**b**) 3 years old male with unifocal large hepatic angiosarcoma. (**c**) H&E stain showing low-grade neoplasm alternating with solid, nodular areas highly proliferative. (**d**) Pulmonary metastases at diagnosis for patient b

Due to the above-described correlation between the IHH and the angiosarcoma, in the recently published hepatic hemangioma guidelines for diagnosis and monitoring [73], the consensus paper recommends monitoring a child with infantile liver hemangiomas until the hemangioma involution is complete.

Lymphangiosarcoma

Lymphangiosarcoma as a new entity was first described in patients with upper extremity chronic lymphedema due to breast cancer therapy [53]. The clear relationship with inadequate lymphatic drainage was confirmed by multiple case reports and small case series from the adult literature. Due to the significantly high incidence of breast cancer and resulting lymphedema, secondary lymphangiosarcoma dominates the medical literature with almost none describing primary lesions (without chronic lymphedema [74, 75] or lymphatic malformation present years prior to the malignant transformation). In the pediatric population, breast cancer is very rarely encountered, and the management of other forms of cancer almost never

results in lymphedema leaving lymphatic malformations as the major predisposing factor for lymphangiosarcoma.

The clinical presentation of a cutaneous lymphangiosarcoma closely resembles angiosarcoma with one or more reddish-purple indurated areas or nodules that develop chronic ulceration and ooze serosanguinous fluid. Pain is present and sometimes difficult to manage. When the lymphangiosarcoma does not have a cutaneous component but develops in the context of chylothorax or chylous ascites, the diagnosis is even more difficult to make and requires a high index of suspicion [76].

Lymphangiosarcoma histology resembles angiosarcoma with a dissecting growth pattern of atypical vessels lined by epithelioid cells. High mitotic index, necrosis, and hemorrhage are highly prevalent within the tumor. The immunohistochemistry may differentiate the two entities: lymphangiosarcoma is strongly positive for lymphatic markers: Prox-1 and/or podoplanin (D2-40) and less intense or completely negative for CD31 and CD34 (endothelial markers). Mouse model experiments found that constitutive activation of mTORC1 in endothelial cells may lead to the development and progression of lymphangiosarcoma through VEGF signaling [77]. Also, lymphangiosarcoma appears to have the same c-myc amplification identified in post-radiation angiosarcoma of the breast. [64]

Lymphangiosarcoma shares many features with hemangiosarcoma, including imaging characteristics, sarcoma-type attempted treatment, and poor prognosis. As majority of cases affect the extremities, complete surgical resection with amputation is commonly described. Still, due to the high metastatic potential to the liver, lungs, and bones, many cases present with metastases at diagnosis and continue to progress regardless of therapy. Chemotherapy regimens include ifosfamide/doxorubicin, gemcitabine/docetaxel, and multiple targeted anti-angiogenic drugs such sorafenib, sunitinib, bevacizumab, and the mTOR inhibitor sirolimus.

Chronic lymphedema secondary to cancer management is rare in children, but the complex lymphatic malformations where lymphedema, chylothorax, and chylous ascites are part of the condition have started to be recognized earlier especially in the multidisciplinary vascular centers. At least theoretically, if generalized lymphatic anomaly (GLA) is managed carefully from diagnosis in the pediatric years, with medical therapy (like mTOR inhibitors) to reduce the amount of effusions present, compression, and complete decongestive therapy with lymphatic massage, it is hoped that the incidence of lymphangiosarcoma will be reduced [78].

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