Vascular tumors of the mediastinum

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Abstract: Vascular tumors represent only a sliver of all tumors affecting the mediastinum, but they pose diagnostic challenges due to significant overlap among entities, ever-evolving classification schemes, and the exquisite rarity of some of the entities not only in the mediastinum but in pathology practice as a whole. Most of the vascular tumors are better known to the practice of soft tissue pathology, from which some of the knowledge of clinical behavior can be extrapolated. For example, the stratification of epithelioid hemangioendothelioma (EHE) into two biologically separate categories has effectively translated from the somatic soft tissues to the thorax. For other entities, the effective validation of soft tissue parameters is hindered by the small numbers of reported mediastinal cases. Many of the treatment modalities have also transferred over, with the key differences resting on the difficulty in achieving complete surgical resection for mediastinal tumors as opposed to those in the somatic soft tissues. Accordingly, systemic drug therapies have emerged as attractive options for some of the mediastinal vascular tumors, such as kaposiform hemangioendothelioma (KHE) and Kaposi sarcoma (KS). The categories presented herein mirror the classification scheme set forth by the 5th Edition WHO Classification of Soft Tissue and Bone Tumors. This review focuses on the biologically aggressive vascular neoplasms while limiting discussion of the benign entities to relevant comparisons in the differential diagnoses. While distinguishing among the benign entities has academic importance, in practice, the stakes are far higher for diagnosing the biologically aggressive tumors given their marked heterogeneity in clinical outcomes. Practical advice for problem areas in pathology will be reviewed alongside tumor pathobiology, including the latest in molecular diagnostics.

Keywords: Angiosarcoma; vasoformative; hemangioendothelioma; Kaposi

Intermediate (locally aggressive)

Kaposiform hemangioendothelioma (KHE)

Clinical features

Originally described as a deep-seated tumor of infants, as reflected in its archaic name *kaposiform infantile hemangioendothelioma*, this lesion is now known to affect a range of ages and a variety of sites (1). In a cohort of 146 patients with KHE, the vast majority were diagnosed within their first year of life, and half of the cases involved the extremities (2). Adults tend to suffer worse outcomes (3). The mediastinum, including the heart, is a known site of origin (4-7). Morbidity stems from complications of: (I) locally aggressive tumor growth, resulting in compression of vital structures, and/or (II) platelet trapping within the vascular channels of the tumor, leading to consumptive coagulopathy, a condition known as the eponymous Kasabach-Merritt phenomenon. During the
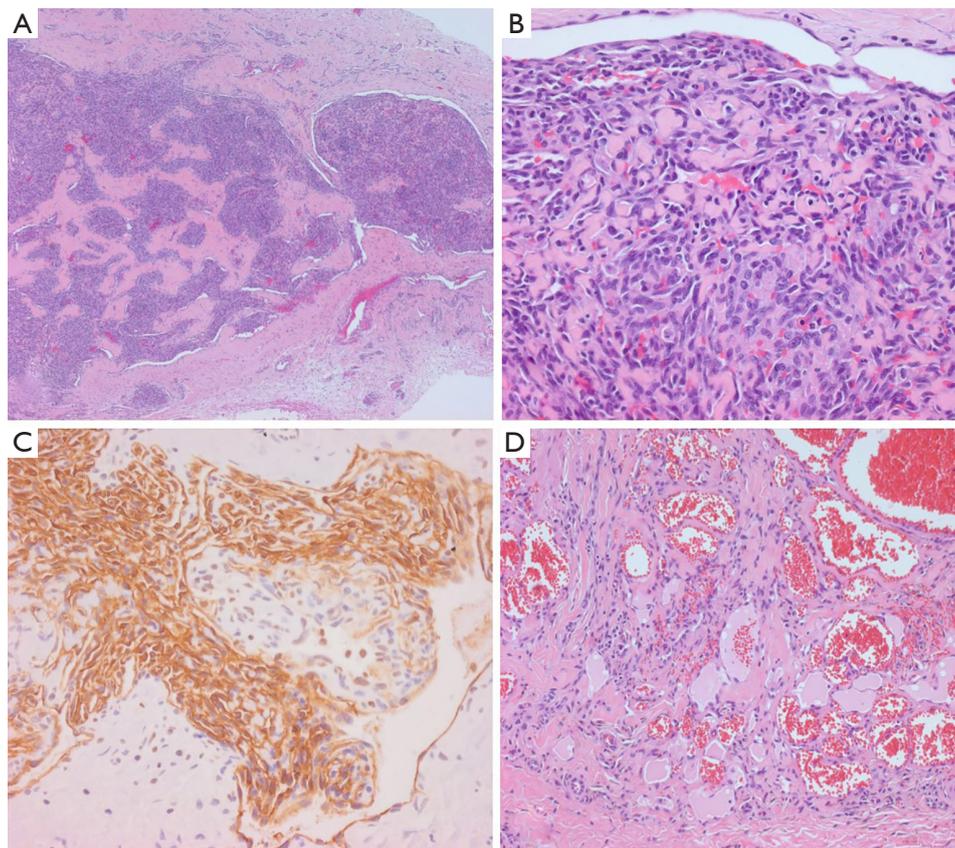
Figure 1 Kaposiform hemangioendothelioma (KHE). (A) The tumor exhibits a lobular yet infiltrative silhouette [hematoxylin and eosin stain (H&E), ×5]. (B) Slit-like vascular spaces are admixed with spindled and rounded cells (H&E stain, ×20). (C) In addition to endothelial markers, lymphatic markers also highlight a portion of the lesional cells (IHC D2-40, ×20). (D) A preceding lymphovascular malformation was observed years before the KHE diagnosis in this patient (H&E stain, ×10).

active phase of the Kasabach-Merritt phenomenon, the size of the tumor mass increases as clotting progresses, further compressing vital structures. Consensus guidelines for treatment are emerging (8), with increasing evidence for the efficacy of mTOR inhibitor sirolimus (6,9).

Pathologic features

Low-power examination reveals an infiltrative yet lobular proliferation of cellular nodules composed of well formed capillaries admixed with short fascicles of spindle cells with slit-like vascular channels (*Figure 1*). Crescentic lymphatic channels reside at the periphery of nodules. Extravasated RBCs, intraluminal thrombi, and hemosiderin deposits can also be observed (9,10).

Ancillary studies

Focal expression of lymphatic markers (D2-40, PROX1, and

VEGFR3), and more extensively, vascular markers (CD31, CD34, ERG), is observed in the spindled endothelial cells of KHE (*Figure 1C*) (9). There is no expression of human herpesvirus 8 (HHV8). Based on limited molecular data, there is some evidence of a translocation between chromosomes 13 and 16, while other cases exhibit an activating mutation of *GNA14* (a paralogue of *GNAQ*) (9).

Differential diagnosis

Morphologic resemblance to Kaposi sarcoma (KS) is obvious from the name of the tumor. However, the consistently lobular growth pattern of KHE is not a feature of KS, and HHV8 expression is absent in KHE. Infantile (juvenile) hemangioma may enter the differential diagnosis owing to a lobulated tumor border together with densely packed vascular nodules (*Figure 2*), but these tumors spontaneously involute, are not associated with the
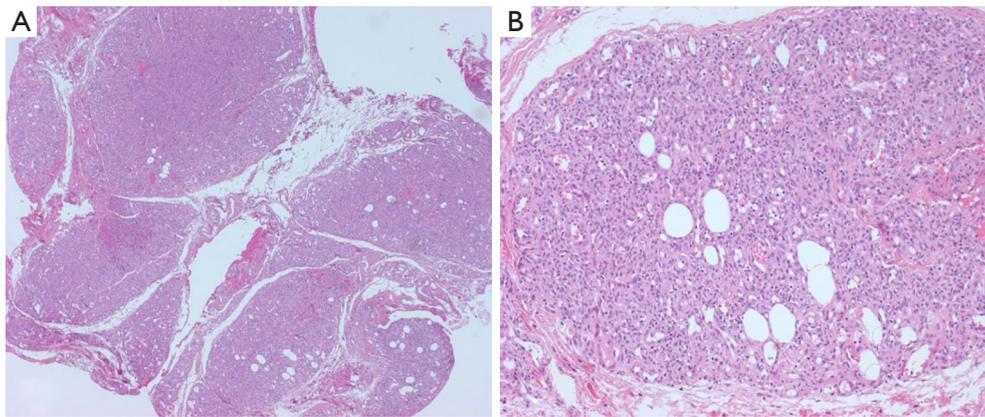
Figure 2 Infantile (juvenile) hemangioma, characterized by a lobulated tumor border and densely packed vascular nodules. These tumors express GLUT-1 by immunohistochemistry. (A, H&E stain, ×5; B, H&E stain, ×10).
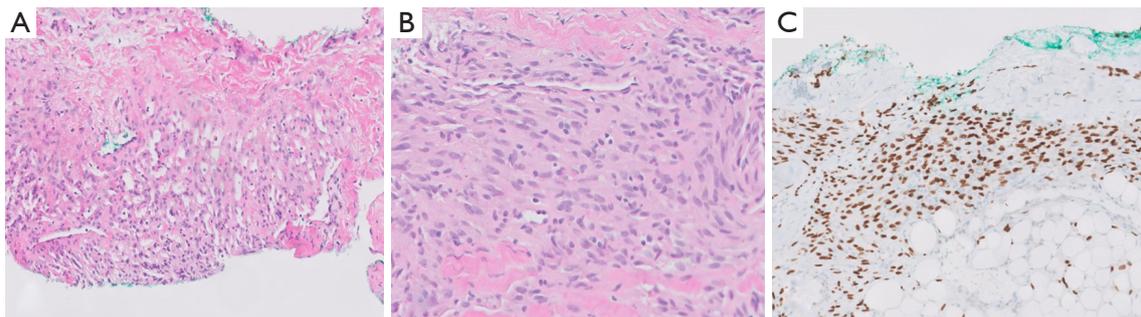

Figure 3 Kaposiform lymphangiomatosis, from a 12-year-old girl with multifocal involvement (neck, thorax/mediastinum, abdomen, pelvis, spine, and femur). The patient continues to experience thrombocytopenia, but her disease is overall well controlled with sirolimus therapy. (A) Poorly defined collections of tumor cells compared to the cellular nodules of KHE (H&E stain, ×20). (B) Slit-like vascular spaces and spindled cells resemble KHE (H&E stain, ×40). (C) Immunohistochemistry for PROX1, a lymphatic marker, highlights the tumor cells (IHC PROX1, ×40). KHE, kaposiform hemangioendothelioma.

Kasabach-Merritt phenomenon, and express GLUT-1 by immunohistochemistry (11).

Kaposiform lymphangiomatosis (KLA) is a recently introduced term for a lymphatic anomaly which overlaps substantially with KHE and may in fact represent a clinicopathologic variant of KHE rather than a disease *sui generis*. To further confuse the picture, the terms "generalized lymphatic anomaly and Gorham-Stout disease" have entered into this mix of lymphatic anomalies (12,13). For convenience, one can regard these as clinical variants of histologically similar lymphatic pathologies. A few subtle differences can be identified between KHE and KLA: (I) multifocality within the mediastinum and lung is more characteristic of KLA, (II) histologically, KLA exhibits more dispersed and poorly defined collections of

tumor cells (*Figure 3*), and (III) both KLA and KHE have increased activity in RAS/PI3K/mTOR signaling pathways, but somatic activating NRAS variants have been found in KLA but not KHE (14).

Intermediate (rarely metastasizing)

Retiform hemangioendothelioma

Cases of retiform hemangioendothelioma involving mediastinal structures are few and far between; therefore, only a brief description follows. This tumor most commonly involves superficial tissue planes. A mediastinal case presented as pleural nodules in a patient with dry cough, dyspnea, and pleural effusion (15).

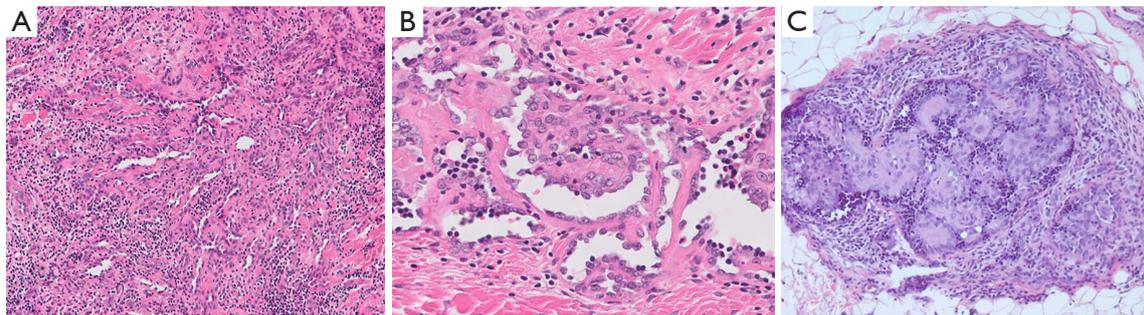Histologic examination discloses arborizing vascular

Figure 4 Retiform hemangioendothelioma. (A) Ill-defined, arborizing vascular channels (H&E stain, ×20). (B) Hobnail endothelial cells line the channels. Note the intravascular papillae and the background lymphocytes (H&E stain, ×40). (C) For comparison: papillary intralymphatic angioendothelioma (Dabska tumor) showing intravascular papillae with hyaline cores (H&E stain, ×10).

channels recapitulating the structure of the rete testis (*Figure 4*). The vascular channels are lined by hobnail endothelial cells. Numerous lymphocytes permeate the channels and the stroma. Intravascular papillae with hyaline cores may be seen, creating overlap with papillary intralymphatic angioendothelioma (Dabska tumor) (*Figure 4C*). Endothelial cells express vascular markers and lymphatic marker PROX1, but they only rarely express D2-40 (16).

Papillary intralymphatic angioendothelioma (Dabska tumor)

Reports of this tumor in the mediastinum were not found, but since cases have been reported in intra-abdominal sites and even within the bone (17), the thorax could theoretically be involved. The key to diagnosing this tumor lies in recognizing the distinctive hobnail, "match-stick"-like appearance of the endothelial cells lining the lymphatic channels and covering the papillary hyaline cores. Immunohistochemistry shows immunoreactivity for the lymphatic markers (D2-40, PROX1, and VEGFR3). There is significant overlap with retiform hemangioendothelioma (discussed above).

Composite hemangioendothelioma

By definition, this tumor exhibits at least two morphologically distinct vascular components (18). A lone report describes mediastinal involvement (19). Akin to retiform hemangioendothelioma, this tumor most commonly involves superficial tissue planes. There is an association with Maffucci syndrome and Kasabach-Merritt phenomenon (20), though the latter is most closely linked to KHE. These tumors usually behave in a low-grade manner, with potential for local recurrence but minimal potential for distant metastasis and death (20,21). While the combination of retiform hemangioendothelioma and epithelioid hemangioendothelioma (EHE) is most common, many other benign and malignant components can be observed, ranging from hemangioma to angiosarcoma-like areas (18). Rarely, there are areas with a neuroendocrine appearance which show synaptophysin immunoreactivity; this may portend a worse prognosis. Molecular studies have uncovered novel *PTBP1-MAML2* and *EPC1-PHC2* gene fusions in two cases (22). Despite the rarity of these neuroendocrine cases, the 5th Edition WHO Classification formally recognizes them as a subtype of composite hemangioendothelioma (18).

Kaposi sarcoma (KS)

Clinical features

Typically a tumor of mucocutaneous and visceral sites, KS can affect any body site, the mediastinum being no exception. Lymph nodes are frequently involved (23). KS manifests as one of several clinical subtypes: (I) classic (indolent), (II) endemic (African), (III) AIDS-associated, and (IV) iatrogenic (18). Cardiac KS has been found across all clinical subdivisions, based on autopsy findings between the 1950s through the 1980s. The epicardium seems to be more frequently affected than the myocardium or endocardium (23). KS can also involve the thoracic duct and adjacent mediastinal structures, manifesting as chylothorax. The thoracic duct can serve as either a site of origin or a target of metastasis for KS (23,24). Doxorubicin is frequently the first-line therapy for systemic or extensive KS, but newer targeted therapies are showing promise in clinical trials (25).

Pathologic features

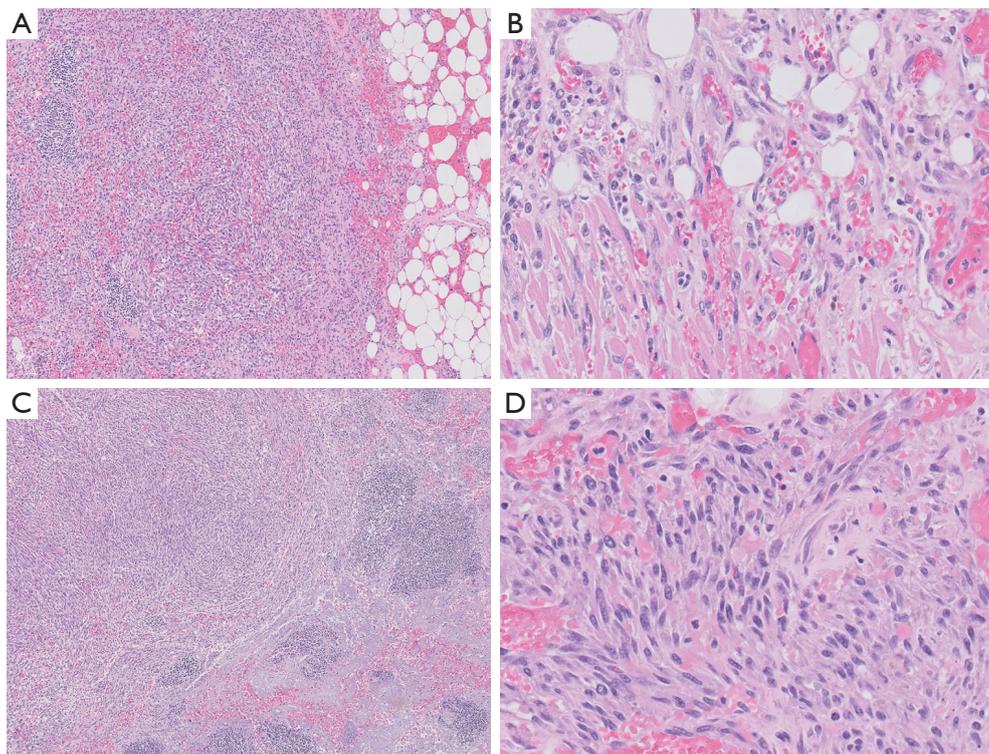Characteristic features include relatively monotonous-

Figure 5 Kaposi sarcoma. (A) Kaposi sarcoma infiltrating the subepicardial adipose tissue in a 40-year-old HIV-positive heart transplant patient (H&E stain, ×5). (B) Permeation of cardiac muscle fibers (H&E stain, ×40). (C,D) Mediastinal lymph node involvement in the same patient (C, H&E stain, ×5; D, H&E stain, ×40).

appearing spindle cells, increased numbers of slit-like vascular channels, hemorrhage, hemosiderin deposition, and hyaline globules (*Figure 5*). If identified, the so-called "promontory sign" is a helpful feature, consisting of small vessels protruding into the lumen of a larger vessel. Chronic inflammation, including plasma cells, is a secondary feature. Many of the morphologic variants of KS presented in the cutaneous literature are not relevant to the mediastinum; however, brief mention will be made of the hemangioma-like, lymphangioma-like, and anaplastic variants (25,26). The hemangioma-like and lymphangioma-like patterns exhibit typical KS sarcoma in at least part of the lesion. Anaplastic KS is a pauci-vascular spindle cell proliferation with a greater degree of nuclear atypia, increased mitotic activity (5 to 20 mitoses per 10 high-power fields), and occasional necrosis. These features have been associated with aggressive behavior (27,28).

Ancillary studies
Tumor cells express vascular and lymphatic markers (29). Since HHV8 underlies KS tumorigenesis, HHV8 immunohistochemistry serves as the diagnostic key (*Figure 6*). Expression of the HHV8 virus produces the latency-associated nuclear antigen (LANA), which binds to retinoblastoma protein and p53, affecting cell proliferation and apoptosis (30). Comparative genomic hybridization studies have demonstrated 11q13 involvement, including *FGF3/4* target genes. *KRAS* and *TP53* aberrations have also been reported (18).

Differential diagnosis
Diagnosing lymphangioma/hemangioma-like KS requires a careful search to identify any areas of typical KS to trigger HHV8 immunohistochemistry. Distinction of anaplastic KS from angiosarcoma can be problematic, especially in spindle cell examples. The differential diagnosis with KHE was discussed above.

Pseudomyogenic hemangioendothelioma

Clinical features
An example of this relatively recently characterized tumor

has been reported to involve the mediastinum; specifically, thoracic vertebrae with extension into the pleural cavity (31). A far more common presentation is a young man with multifocal involvement of tissue planes of the lower limb (cutaneous/subcutaneous > intramuscular > bone), or less commonly the trunk, upper limbs, or head and neck (18). Biological behavior is considered intermediate owing to frequent recurrences but low rates of distant metastasis (32).

Pathologic features

Microscopic examination reveals loose fascicles and sheets of plump spindled to polygonal cells with deep eosinophilic cytoplasm, resembling rhabdomyoblasts (*Figure 7*). Neutrophils are often present (*Figure 7C*). Nuclear pleomorphism tends to be limited, and mitotic activity is low (1 per 10 HPF on average). Vascular invasion
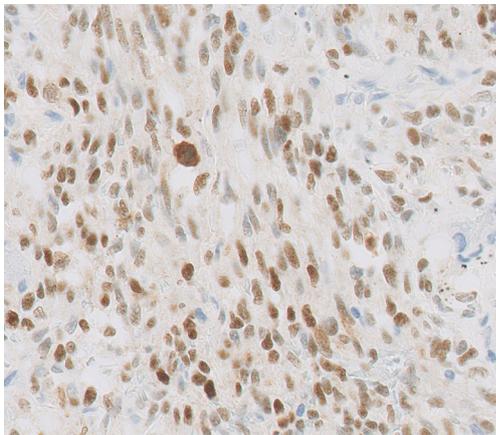

Figure 6 Kaposi sarcoma. HHV8 immunohistochemistry reveals strong nuclear reactivity (IHC HHV8, ×40). HHV8, human herpesvirus 8.

and necrosis are infrequent features (32).

Ancilllary studies

Immunohistochemistry of the tumor reveals partial expression of both epithelial and vascular markers, characterized by immunoreactivity for AE1/AE3, ERG, and FLI1, but only variable Cam5.2 and CD31, and no expression of CD34 or MNF116 (32,33). The tumor is designated as *pseudo*myogenic because it lacks expression of myogenic marker desmin (and only variably expresses SMA) despite the myogenic/rhabdoid appearances. Strong and diffuse expression of FOSB by immunohistochemistry is effective in distinguishing pseudomyogenic hemangioendothelioma from morphologic simulants. FOSB immunoreactivity reflects a *SERPINE1-FOSB* (or *ACTB-FOSB*) gene fusion that has been identified as a consistent genetic alteration in these tumors (22,34,35). The fusion type has no bearing on clinical behavior, but the *ACTB-FOSB* variant has a greater tendency to present as a solitary lesion (36).

Differential diagnosis

The predominantly myoid-appearing spindle cell morphology, expression of ERG/FLI1, lack of EMA, CD34, and PAN-K expression, and intact INI-1 sets this tumor apart from epithelioid sarcoma, with which it is closely intertwined due to its original designation as "epithelioid sarcoma-like hemangioendothelioma" (32). Other spindle cell tumors that may enter the differential, such as sarcomatoid carcinoma and rhabdomyosarcoma, exhibit overt features of malignancy. Vascular tumors would only be considered upon observing FLI1/ERG immunoreactivity, as vasoformation is lacking by H&E examination. However,
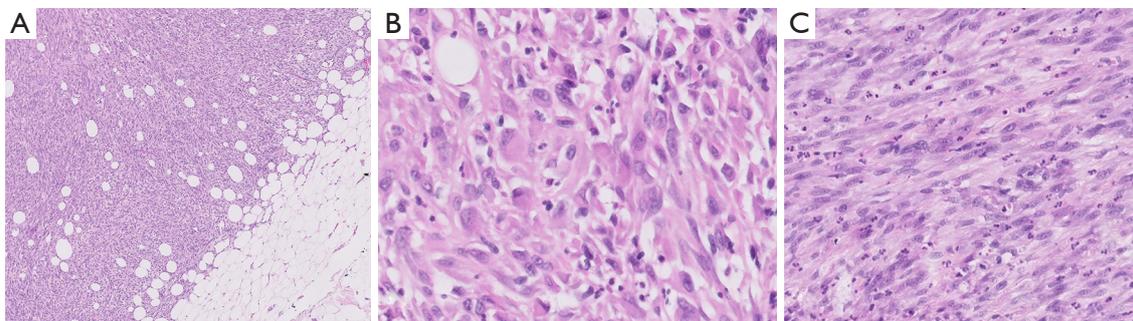

Figure 7 Pseudomyogenic hemangioendothelioma. (A) The tumor exhibits an infiltrative interface with the native adipose tissue (H&E stain, ×5). (B) Rhabdomyoblast-like cells with eccentric nuclei and abundant, dense, eosinophilic to amphophilic cytoplasm, mimicking myogenic tumors (H&E stain, ×40). (C) Neutrophils are scattered throughout the tumor in some cases (H&E stain, ×20).
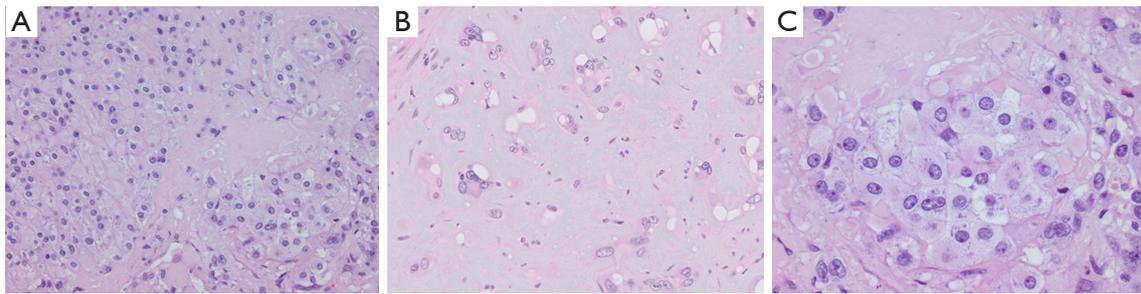
Figure 8 Classic epithelioid hemangioendothelioma. (A) Tumor cells are epithelioid with round nuclei, small nucleoli, and moderate amphophilic cytoplasm (H&E stain, ×20). (B) Myxochondroid (basophilic) matrix and tumor cells with intracytoplasmic vacuoles imparting a signet-like appearance ("blister cells") (H&E stain, ×40). (C) Hyaline (eosinophilic) matrix is seen at the periphery of this collection of epithelioid cells (H&E stain, ×40).

no other vascular tumor exhibits the unique constellation of morphologic and immunophenotypic traits of pseudomyogenic hemangioendothelioma.

Malignant

Epithelioid hemangioendothelioma (EHE)

Clinical features

EHE is a malignant vascular tumor composed of epithelioid endothelial cells in a myxohyaline matrix. Most commonly, it occurs in the somatic soft tissues, lung, and liver, but the tumor can arise from any body site. Adults are affected far more often than children. Superficial lesions are usually solitary, while visceral and bone tumors are frequently multiple, representing local metastatic spread (18). Mediastinal cases of EHE have earned a special place in the literature (37,38). Frequently, the tumor involves or originates from the superior vena cava or the innominate vein (39). For mediastinal cases, the size of the tumor is recorded in place of TNM staging (18). Several factors come into play for prognosticating these tumors: (I) anatomic site (lung and bone tumors behave worse than soft tissue ones), (II) select gross and microscopic tumor characteristics (tumor size and mitotic activity), and (III) molecular fusion type (discussed below). Pleural involvement portends an aggressive clinical course, with only 22% of patients surviving to 5 years, compared to a >70% overall survival rate (40).

Pathologic features

Angiocentric tumors expand the vessel wall, obliterate the lumen, and spread centrifugally into surrounding tissues (18). An infiltrative border is characteristic. The tumor consists of epithelioid (and sometimes fusiform) cells arranged as cords or nests within a hyaline (eosinophilic) to myxochondroid (basophilic) matrix (*Figure 8*). Primitive vasoformation manifests as intracytoplasmic vacuoles, which occasionally contain erythrocytes. Cells have round nuclei, inconspicuous nucleoli, intracytoplasmic vacuoles, and moderate amounts of eosinophilic cytoplasm. Cytologic atypia, mitotic activity, and necrosis are unusual (*Figure 9*), and their presence has been correlated with more aggressive behavior by some authors (40). However, Deyrup *et al.* have reported that cytologic atypia and tumor necrosis were *not* significant, but that >3 mitotic figures/50 high power fields and tumor size >3.0 cm correlated with unfavorable clinical outcomes (41).

Ancillary studies

Tumor cells express vascular markers (*Figure 10*) and occasionally epithelial markers; in fact, 29% of EHE show keratin expression (37). Molecular analysis reveals a *CAMTA1-WWTR1* gene fusion in most cases (~90%), while a subset exhibits *YAP1-TFE3* gene fusions (42). Alternative *WWTR1* partners, *MAML2* and *ACTL6A*, have been found to have a predilection for cardiac involvement (43). The *YAP1-TFE3* subset bears several noteworthy differences relative to the *CAMTA1-WWTR1* group: (I) more favorable outcomes (the 5-year survival being 86%, versus 59% for cases with *CAMTA1-WWTR1* fusions) (40), (II) occurrence in a younger age group (44), (III) more solid growth, greater vasoformation, and brightly eosinophilic cytoplasm (45). These cases also exhibit nuclear TFE3 immunolabeling (*Figure 10C*) (44), albeit with imperfect specificity. CAMTA1 immunohistochemistry (*Figure 11*) is a useful surrogate for molecular testing (46).
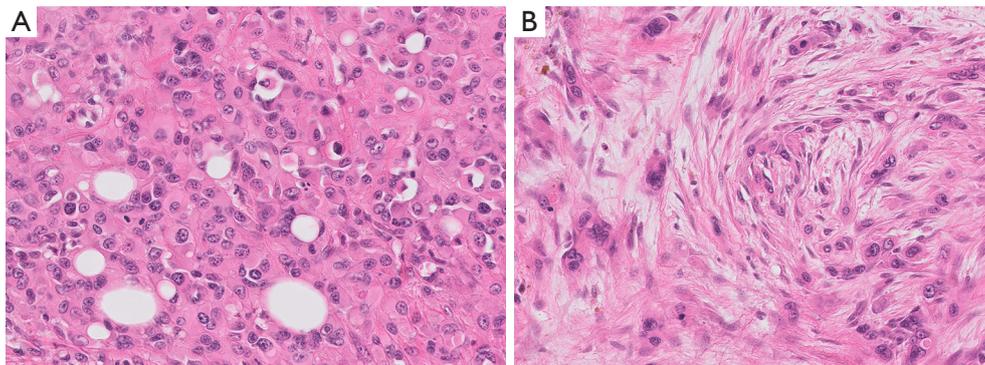
Figure 9 Epithelioid hemangioendothelioma with atypical features. (A) Infiltration of fat at the tumor border in a case with some cytologic pleomorphism (H&E stain, ×20). (B) Focal spindling and notable nuclear pleomorphism (H&E stain, ×40).
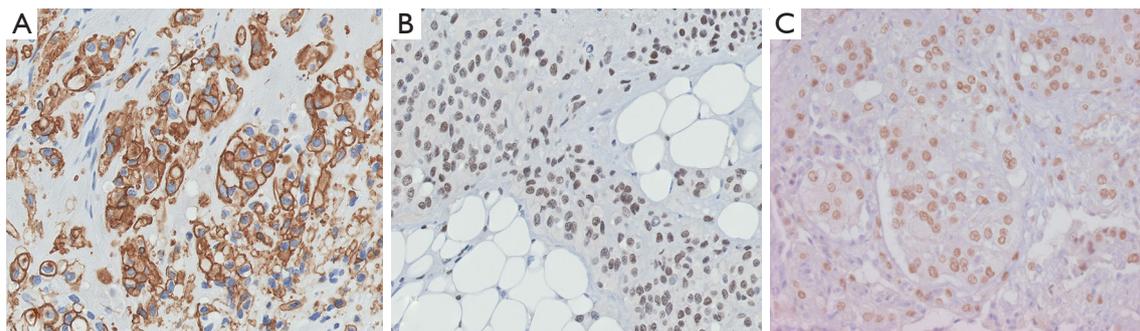

Figure 10 Epithelioid hemangioendothelioma immunohistochemistry. (A) CD34 expression of tumor cells (CD31, ERG were also positive) (IHC CD34, ×40). (B) FLI1, another vascular marker, highlights the nuclei of tumor cells (IHC FLI1, ×20). (C) TFE3 immunohistochemistry in a case with a *YAP1-TFE3* gene fusion (IHC TFE3, ×20).

Differential diagnosis

In the mediastinum, where serous membranes abound, mesothelioma is a legitimate contender for the diagnosis of any malignant epithelioid neoplasm. The combination of any vasoformation, strong expression of vimentin (*Figure 12*), minimal cytokeratin expression, and expression of two or more endothelial markers clinches the diagnosis of EHE over mesothelioma (47). WT1 immunohistochemistry shows nuclear labeling of mesothelioma, while cytoplasmic labeling is seen in vascular tumors. Cytologically atypical cases of EHE are distinguished from epithelioid angiosarcoma based on the presence of distinctive extracellular matrix, intracytoplasmic vacuoles, and nuclear cytoplasmic inclusions (37). Clear-cut vasoformation with hemorrhage and formation of blood lakes should steer away from the diagnosis of EHE. Overall, angiosarcoma exhibits greater pleomorphism, mitotic activity, and frequent necrosis. On limited biopsy samples, when the distinction is difficult, molecular studies can provide a solution. However, some literature indicates that all epithelioid vascular tumors of the pleura should be considered highly malignant regardless of EHE-like histologic features (48). This opinion is consistent with the results of recent studies showing poor outcomes in cases with pleural involvement (mentioned above). For cases arising from veins, consideration may be given to intravascular epithelioid hemangioma, but these tumors exhibit lobular/multilobular growth rather than the infiltrative cords and strands of tumor cells seen in EHE (49).

Angiosarcoma

Clinical features

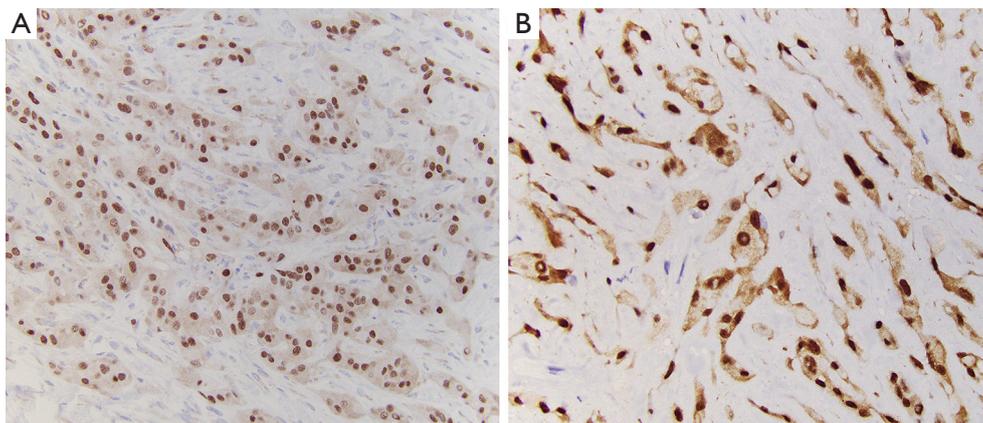Angiosarcomas are biologically aggressive malignancies with

Figure 11 CAMTA1 immunohistochemistry. Epithelioid hemangioendothelioma with the *WWTR1-CAMTA1* fusion exhibits strong, diffuse nuclear expression of CAMTA1, which is a surrogate for this fusion. Images courtesy of C. D. M. Fletcher, Brigham and Women's Hospital. (A, IHC CAMTA1; ×20; B, IHC CAMTA1; ×40).
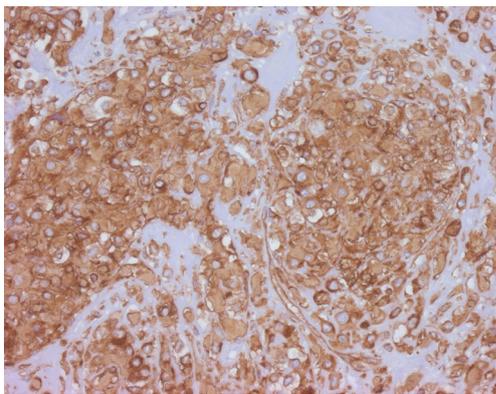

Figure 12 Epithelioid hemangioendothelioma, vimentin expression. The strong and diffuse expression of vimentin helps to distinguish EHE from carcinoma and mesothelioma (note that mesothelioma can have focal/moderate expression). IHC vimentin, ×20. EHE, epithelioid hemangioendothelioma.

high rates of mortality. More than half of patients die within a year of diagnosis (45). Most cases arise in the skin, followed by the deep soft tissues, breast, bone, and viscera. The mediastinum is a frequent site of involvement in children, who are only very rarely affected by angiosarcoma (18). Within the mediastinum, the anterior compartment is most often involved (50). The heart, great vessels, esophagus, and the thymus have all been documented as sites of origin (50-53). Angiosarcomas can arise secondarily within other tumors of the mediastinum, some examples including primary germ cell tumors (54,55) and schwannomas (56). Tumors are treated by resection, with or without chemotherapy (50,51,57).

Some literature studies suggest a survival advantage for patients treated with the combination of surgery and radiation (58).

Pathologic features

Tumor morphology can span a broad spectrum, ranging from strikingly low-grade appearances simulating hemangiomas to high-grade undifferentiated sarcomas (*Figure 13*). Vasoformation manifests as large cavernous spaces, irregular anastomosing channels, capillary-like proliferations, and slit-like channels lined by hyperchromatic endothelial cells. Vasoformation can be obscured when neoplastic cells grow in sheet-like, solid patterns. In areas of solid growth, tumor cells can be spindled or epithelioid. Some cases are entirely epithelioid (so-called epithelioid angiosarcoma). Essentially all cases exhibit hemorrhage, hemosiderin deposition, and multilayering of endothelial cells. Minor features include papillary projections resembling endothelial hyperplasia, pleomorphic tumor giant cells, fibrous or myxoid tumor stroma, and dissection into fat or other structures (50). Necrosis is often present, and mitotic activity appears to correlate with the degree of tumor differentiation (50). Foamy cell angiosarcoma is an extraordinarily rare and unusual variant of angiosarcoma which presents major diagnostic challenges and requires ancillary studies for diagnosis (*Figure 14*) (59).

Ancillary studies

Angiosarcomas express both vascular and lymphatic markers (29). Expression of at least two vascular markers
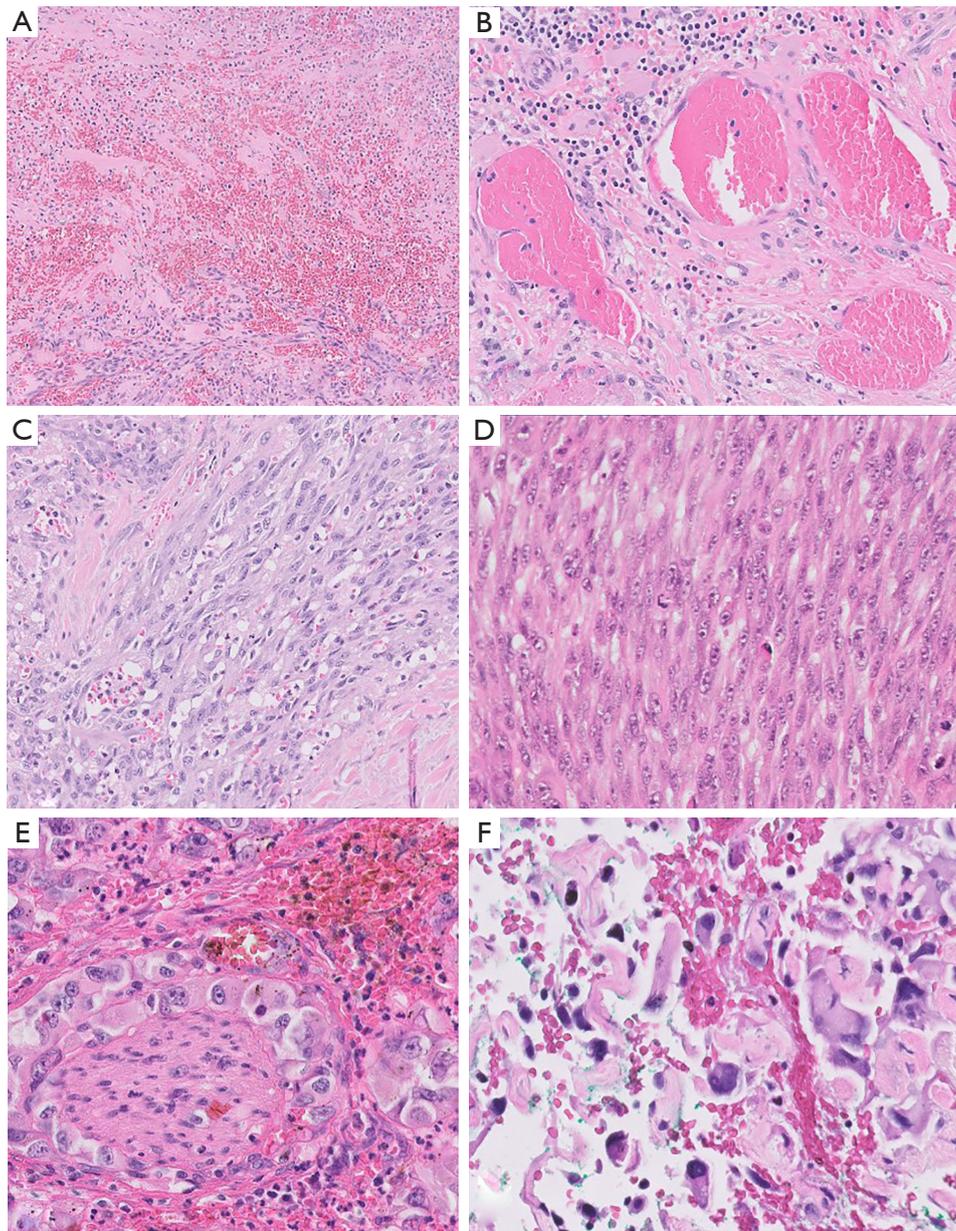
Figure 13 Angiosarcoma. (A) Typical hemorrhagic appearance (H&E stain, ×10). (B) Ectatic, blood-filled channels mimicking hemangioma (H&E stain, ×20). (C) Higher-grade appearance with subtle anastomosing vascular channels (H&E stain, ×20). (D) Spindled phenotype, with solid growth and minimal vasoformation (H&E stain, ×20). (E) Epithelioid phenotype (epithelioid angiosarcoma), with hemorrhage and perineural invasion (H&E stain, ×20). (F) Pleomorphic cytomorphology, with hemorrhage (H&E stain, ×40).

is recommended to underpin the diagnosis (*Figure 14*). Epithelioid cases exhibit some cytokeratin expression in about a quarter of cases, most commonly pankeratin, CK7, CAM5.2 , or CK18 (37). MYC protein expression is most consistently observed among radiation-induced angiosarcomas of the breast, but there is limited utility of this marker at other anatomic sites (60). A positive result is more diagnostically useful than a negative one. MYC protein overexpression reflects *MYC* gene amplification, a consistent finding among post-irradiation angiosarcomas (less commonly *FLT4* amplification, *PTPBR* mutation, and *PLCH1* mutation). Primary angiosarcomas tend to
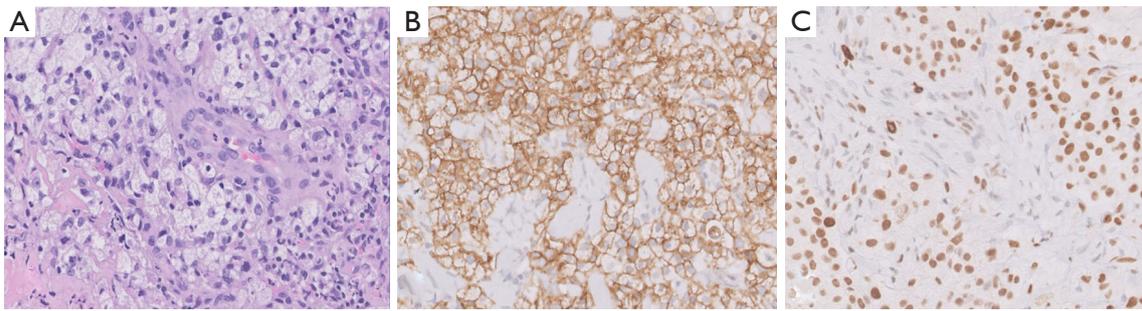
Figure 14 A rare variant of angiosarcoma with immunohistochemistry. (A) The foamy-cell appearance of this unusual angiosarcoma engenders a broad differential diagnosis and therefore requires immunohistochemistry (H&E stain, ×40). (B) CD34 immunohistochemistry shows a membranous pattern of expression (CD31 was also positive) (IHC CD34, ×40). (C) ERG immunohistochemistry shows diffuse nuclear expression (IHC ERG, ×40).
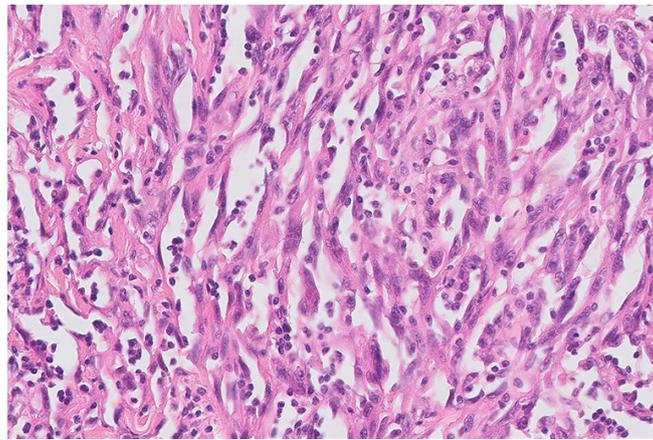

Figure 15 Spindle cell melanoma with pseudovascular spaces mimicking angiosarcoma (H&E stain, ×40).

exhibit complex karyotypes with occasional *KDR* or *CIC* mutations (22).

Differential diagnosis

Cases with epithelioid cytomorphology mimic carcinoma, an issue that can be further confounded by cytokeratin expression. Moreover, an epithelioid malignancy in the mediastinum is statistically far more likely to represent carcinoma than any mesenchymal neoplasm (61). Therefore, any evidence of vasoformation or a hemorrhagic background should trigger a panel of vascular markers. Distinction from mesothelioma would follow the same approach as discussed above for EHE. One potential pitfall is that D2-40 expression is seen in both mesothelioma and angiosarcoma. Spindled morphologic variants overlap with other sarcomas, but the typical immunohistochemical workup for sarcoma includes at least one vascular marker, which would indicate a vascular lineage. Spindle cell melanoma can exhibit pseudovascular spaces mimicking angiosarcoma (*Figure 15*), again requiring immunohistochemistry to nail down tumor origin. As mentioned above, some cases of EHE can pose a diagnostic dilemma, but the specialized matrix is the key to EHE. Molecular studies can be employed as an objective means to discriminate between the two.

Anastomosing hemangioma, which also occasionally occurs in the mediastinum, can simulate well-differentiated angiosarcoma (*Figure 16*) owing to its non-lobular, anastomosing growth pattern and mild nuclear atypia. Moreover, it may focally infiltrate into the surrounding soft tissue or viscera. However, anastomosing hemangioma lacks the diffusely infiltrative growth and other malignant features of angiosarcoma. Further diagnostic clues to anastomosing hemangioma include intralesional mature adipose tissue, small thrombi, and extramedullary hematopoiesis. The
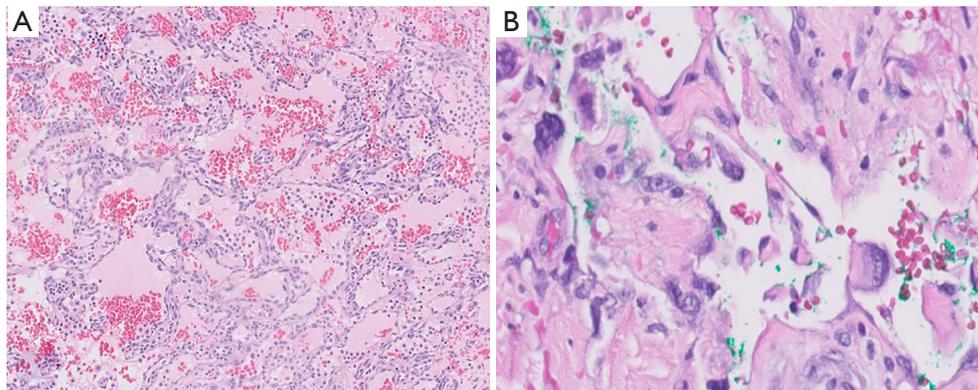
Figure 16 Angiosarcoma simulating anastomosing hemangioma. (A) The anastomosing channels in this angiosarcoma mimic the appearance of anastomosing hemangioma (H&E stain, ×10). (B) The channels are lined by endothelial cells with a degree of atypia that exceeds what is acceptable for anastomosing hemangioma (H&E stain, ×40).

finding of a *GNAQ* mutation would also support a diagnosis of anastomosing hemangioma (62,63).

Footnote

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