Mesenchymal Neoplasms of the Liver

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KEYWORDS

• Mesenchymal hamartoma of the liver • Undifferentiated embryonal sarcoma of the liver
• Calcifying nested stromal-epithelial tumor • Anastomosing hemangioma
• Hepatic small vessel neoplasm • Epithelioid hemangioendothelioma • Hepatic angiosarcoma
• Inflammatory pseudotumor-like follicular dendritic cell sarcoma

Key points

- Mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver are related tumor types that both harbor chromosome 19q13.3/13.4 structural alterations; *TP53* alterations are common in undifferentiated embryonal sarcoma and absent in mesenchymal hamartoma.
- Calcifying nested stromal-epithelial tumor is a rare primary hepatic neoplasm that shows epithelial (but not hepatocellular) differentiation, nested architecture, and *CTNNB1* and *TERT* promoter alterations.
- Anastomosing hemangioma and hepatic small vessel neoplasm (HSVN) are rare benign vascular tumors that harbor *GNAQ*, *GNA11*, and *GNA14* mutations. HSVN shows infiltrative growth but the lack of nuclear atypia or endothelial multilayering separates it from angiosarcoma.
- Epithelioid hemangioendothelioma frequently presents with multifocal hepatic masses and harbors *WWTR1*::*CAMTA1* or, rarely, *YAP1*::*TFE3* fusion. Keratin expression is a diagnostic pitfall for misdiagnosis of carcinoma, and atypical examples can resemble angiosarcoma.
- In the liver, metastases are more common than primary malignancies; metastatic sarcomatoid carcinoma and metastatic melanoma should be considered in the differential diagnosis for sarcomatoid malignancies.

ABSTRACT

Mesenchymal neoplasms of the liver can be diagnostically challenging, particularly on core needle biopsies. Here, I discuss recent updates in neoplasms that are specific to the liver (mesenchymal hamartoma, undifferentiated embryonal sarcoma, calcifying nested stromal-epithelial tumor), vascular tumors of the liver (anastomosing hemangioma, hepatic small vessel neoplasm, epithelioid hemangioendothelioma, angiosarcoma), and other tumor types that can occur primarily in the liver (PEComa/angiomyolipoma, inflammatory pseudotumor-like follicular dendritic cell sarcoma, EBV-associated smooth muscle tumor, inflammatory myofibroblastic tumor, malignant rhabdoid tumor). Lastly, I discuss metastatic sarcomas to the liver, as well as pitfalls presented by metastatic melanoma and sarcomatoid carcinoma.

OVERVIEW

Mesenchymal neoplasms of the liver can be challenging to diagnose, in part because diagnostically helpful architectural features can be poorly represented in core needle biopsies. The rarity of primary mesenchymal neoplasms also contributes to their diagnostic challenge. Primary mesenchymal neoplasms specific to the liver include mesenchymal hamartoma of the liver (MHL), undifferentiated embryonal sarcoma of the liver (UESL), and calcifying nested stromal-epithelial tumor (CNSET). I will discuss the diagnosis of these

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tumor types, as well as recent studies that have elucidated their clinical behavior and underlying tumor biology.

The spectrum of vascular tumors includes anastomosing hemangioma (benign), hepatic small vessel neoplasm (HSVN; a benign but sometimes locally aggressive tumor), epithelioid hemangioendothelioma (EHE; a sarcoma that often has a protracted clinical course), and hepatic angiosarcoma (a definitionally high-grade, aggressive sarcoma). Despite their disparate clinical courses, these tumor types can be challenging to distinguish on core biopsies. Herein, I will discuss useful histopathologic features to distinguish these tumor types, as well as their clinical behavior and recent updates in our understanding of their pathogenesis.

Finally, I will discuss other mesenchymal tumors that can primarily involve the liver, including perivascular epithelioid cell tumor (PEComa)/angiomyolipoma, inflammatory pseudotumor-like follicular dendritic cell sarcoma (FDCS), Epstein Barr virus (EBV)-associated smooth muscle tumor, inflammatory myofibroblastic tumor (IMT), and malignant rhabdoid tumor (MRT). Because most malignant neoplasms in the liver are metastases,[1] I will also discuss metastatic melanoma and sarcomatoid carcinoma, both of which have the potential to be misdiagnosed as sarcoma.

PRIMARY MESENCHYMAL NEOPLASMS UNIQUE TO THE LIVER

Primary mesenchymal neoplasms that are specific to the liver are uncommon and include MHL, UESL, and CNSET (**Table 1**).

MESENCHYMAL HAMARTOMA AND UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER

MHL is a benign tumor type that typically occurs in patients aged younger than 2 years and is generally cured by surgical resection.[2] MHL usually presents as a solitary mass, which can sometimes be large and have a prominent cystic component.[3,4] Histologically, it is composed of an admixture of benign bile ducts and haphazardly arranged, bland spindle cells in a variably myxoid to collagenous stroma (**Fig. 1**).

MHL is characterized by recurrent alterations of chromosome 19q13.3/13.4,[5,6] including t(11;19)(q11;q13.3/13.4) involving *MALAT1* on chromosome 11.[7] These chromosomal alterations are present in the spindle cells but not the admixed bile ducts, suggesting that the latter are a nonneoplastic component of the lesion.[7] A recent case report implicated *DICER1* alterations in MHL[8]; however, the tumors in this report are unusual cystic lesions that do not seem to meet morphologic criteria for MHL and might instead represent distinctive *DICER1*-associated hepatic neoplasms.[9,10]

UESL is an aggressive malignancy that occurs in children and young adults, with a median age at presentation of around 5 to 10 years.[11] UESL tends to present as a large, sometimes painful mass. Although in initial studies UESL was associated with high mortality rate,[11] subsequent studies have shown that patients with surgically resectable disease achieve long-term disease-free survival with combined surgery/chemotherapy in most cases.[12–15] Histologically, UESL shows markedly pleomorphic neoplastic cells, some of which show spindle cell morphology. Characteristically, there are tumor giant cells that show prominent cytoplasmic hyaline globules (**Fig. 2**A). The diagnosis is based largely on morphology because UESL shows a nonspecific immunophenotype including expression of desmin and keratins in about 50% of cases each (**Fig. 2**B–C).[16] The differential diagnosis primarily includes other pleomorphic sarcomas but the rarity of pleomorphic sarcomas in young patients makes differential diagnostic considerations such as metastatic dedifferentiated liposarcoma (DDLPS) much less likely. A recent report of a rhabdoid tumor of the liver harboring t(11;19) raises the possibility that the morphologic spectrum of UESL might be wider than previously recognized, although more examples need to be studied to make this determination.[17]

There are examples of UESL *ex*-MHL, strongly suggesting that these tumor types share a common biology.[15] Consistent with this notion, UESL was found to harbor just the same chromosome 19 alterations as MHL.[7] This chromosome 19q13.3 to 13.4 locus contains chromosome 19 micro-RNA cluster (C19MC), the largest known human micro-RNA (miRNA) cluster that codes for dozens of miRNAs.[18] C19MC is primate-specific,[18] and it represents an imprinted locus, in which expression of the maternal allele is silenced while the paternal allele is expressed during placental development.[19] An alternate, unusual genetic mechanism drives another subset of MHL: "androgenetic-biparental mosaicism," in which tumor cells harbor 2 copies of the paternal allele, instead of 1 copy each of maternal and paternal alleles.[20] In this subset of cases, one allele is demethylated and expressed in the absence of a structural rearrangement, whereas the other remains methylated and silenced. C19MC expression has been implicated in

Table 1
List of primary hepatic mesenchymal neoplasms with genetic and immunohistochemical features

Neoplasm(s)	Genetic Alteration (Prevalence)	IHC Markers (Sensitivity)
MHL	19q13.3/13.4 alterations (100%)[a]	No specific markers
UESL	• 19q13.3/13.4 alterations (80%–100%) • TP53 alterations (90%) • Complex copy number alterations (100%)	• No specific markers • Keratins, desmin (50% each)
CNSET	• *CTNNB1* alterations (100%) • *TERT* promoter mutations (100%)	β-catenin (100%)
Anastomosing hemangioma HSVN	• *GNAQ* mutations • *GNA11* mutations • *GNA14* mutations	• No specific markers • Ki-67 < 10%
EHE	*WWTR1*::*CAMTA1* (90%) *YAP1*::*TFE3* (5%)	CAMTA1 (~100% for *CAMTA1* fusions) TFE3 positive, YAP1 loss (~100% for *YAP1*::*TFE3* fusion)
Primary angiosarcoma	• MAPK pathway alterations (50%) • *TP53* inactivating alterations (20%–30%) • *KDR* and/or *PLCG1* alterations (25%) • *CIC* alterations (5%–10%)[b]	p53 mutant pattern (~20–30%)
PEComa/angiomyolipoma	*TSC1*/*TSC2* alterations (90%) *TFE3* rearrangements (5%–10%)	• HMB-45/melan-A (80%–90% each) • SMA/desmin (95% positive for ≥1 marker) TFE3 (correlates with fusions)
Inflammatory pseudotumor-like follicular dendritic cell sarcoma	Not yet well defined	• CD21, CD35 (90% each) • EBV RNA ISH (100%)
EBV-associated smooth muscle neoplasm	Not yet well defined	• SMA, desmin (~100%) • EBV RNA ISH (100%)
IMT	• *ALK1* fusions (50%–60%) • *ROS1* fusions (~5%)	ALK, ROS1 (correlate with fusions)
Malignant rhabdoid tumor	*SMARCB1* inactivating alterations (~100%)	INI1 loss (~100%)
Solitary fibrous tumor	*NAB2*::*STAT6* (>95%)	STAT6, CD34 (~95% each)
Embryonal rhabdomyosarcoma	• Chromosome 11p15.5 loss of heterozygosity • Nonspecific mutations	Desmin, myogenin, myo-D1 (~100%)

Abbreviations: IHC, immunohistochemistry; SMA, smooth muscle actin; ISH, in situ hybridization.
[a] *DICER1* alterations have been reported in lesions bearing some resemblance to mesenchymal hamartoma.
[b] 30% of *CIC*-rearranged round cell sarcomas express CD31 and 50% express ERG; therefore, some reported angiosarcomas with *CIC* rearrangement might instead represent *CIC*-rearranged round cell sarcomas.

tumorigenesis of other hepatocellular neoplasms, including hepatocellular carcinoma, possibly because its miRNAs inhibit tumor suppressor genes and thus promote tumorigenesis.[21,22]

Because MHL and UESL are likely related neoplasms that harbor common C19MC alterations, studies have investigated the genetic features that might explain their disparate clinical behavior

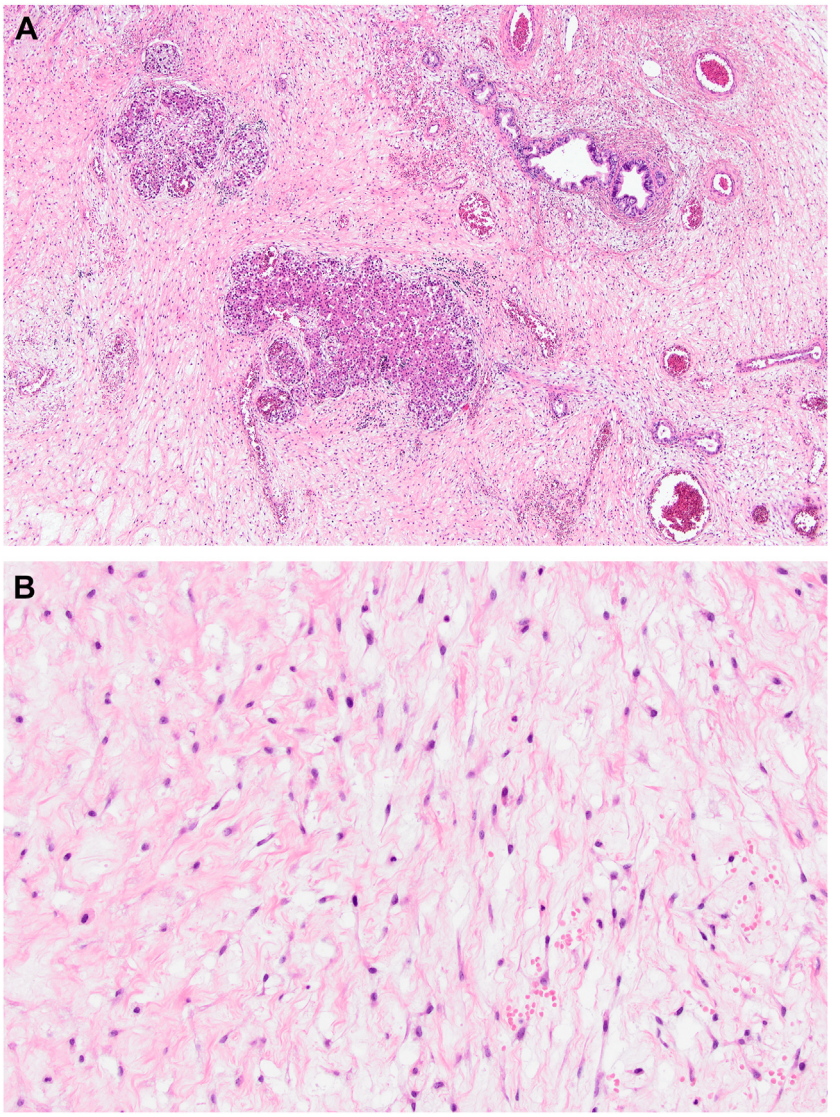

Fig. 1. MHL. (*A*) Mesenchymal hamartoma shows a proliferation of bland spindle cells, with haphazardly admixed benign bile ducts and small lobules of hepatocytes. It has been shown that the spindle cells are neoplastic, whereas the bile ducts are not. (*B*) On higher power, the spindle cells show pale eosinophilic cytoplasm and tapered nuclei. There is no cytologic atypia.

and/or progression from MHL to UESL. Published examples of UESL occurring in the setting of Li-Fraumeni syndrome implicated *TP53* alterations,[23] and additional studies demonstrated complex karyotypes in UESL.[15,24] A recent molecular genetic study of 13 UESL by Setty and colleagues systematically investigated this question; these researchers identified C19MC structural alterations in 10 of 13 tumors, *TP53* mutations/copy number loss in 12, and complex copy number alterations in all 13.[25] The authors also demonstrated C19MC miRNA overexpression in all 13 tumors. Ultimately, this study and others considered together have shown that MHL and UESL exist on a biologic spectrum, and that UESL has complex copy number alterations and *TP53* inactivation that genetically distinguish it from MHL.

CALCIFYING NESTED STROMAL-EPITHELIAL TUMOR

CNSET is a primary liver tumor that was first described in 2001,[26] and described subsequently mostly in small case series and isolated case reports. Literature surveys in 2019 identified 38 unique published examples, which occurred in young patients (median age: 14 years; range: 2–34 years), 70% of whom were female.[27,28] Some patients presented with Cushing syndrome,[29,30] and some tumors occurred in association with Beckwith-Wiedemann syndrome,[31,32] but otherwise presentations were nonspecific. Morphologically, CNSET shows nests of neoplastic epithelioid cells with palely eosinophilic cytoplasm and ovoid nuclei with small nucleoli (**Fig. 3**A–B). The nests

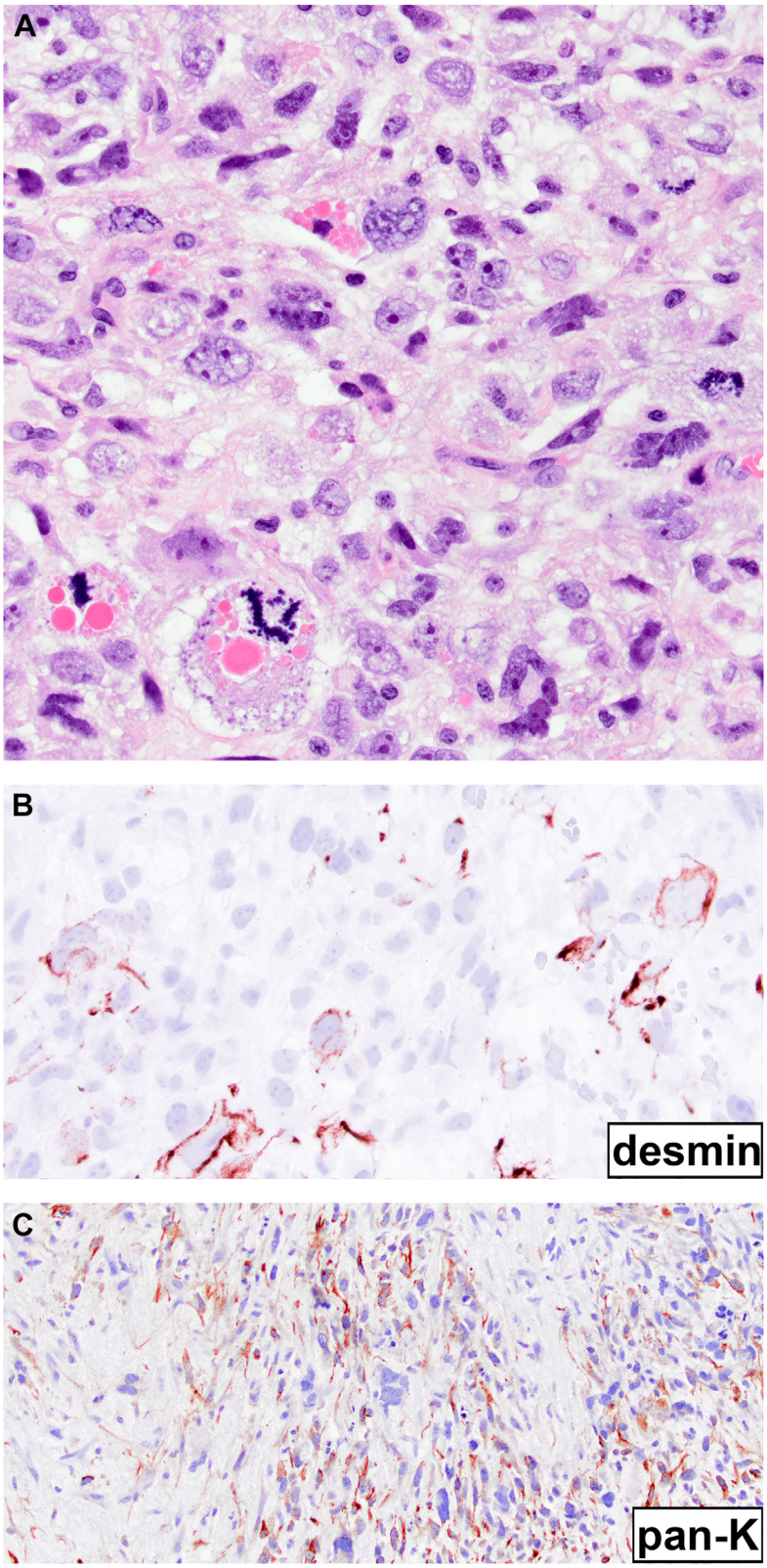

Fig. 2. UESL. (*A*) UESL is an overtly malignant, highly pleomorphic sarcoma. Neoplastic cells show intracytoplasmic hyaline globules, a characteristic feature. (*B*, *C*) IHC in UESL. UESL is essentially a morphologic diagnosis. It has a nonspecific immunophenotype; about half express desmin (*B*), and about half express keratins (*C*, pan-keratin).

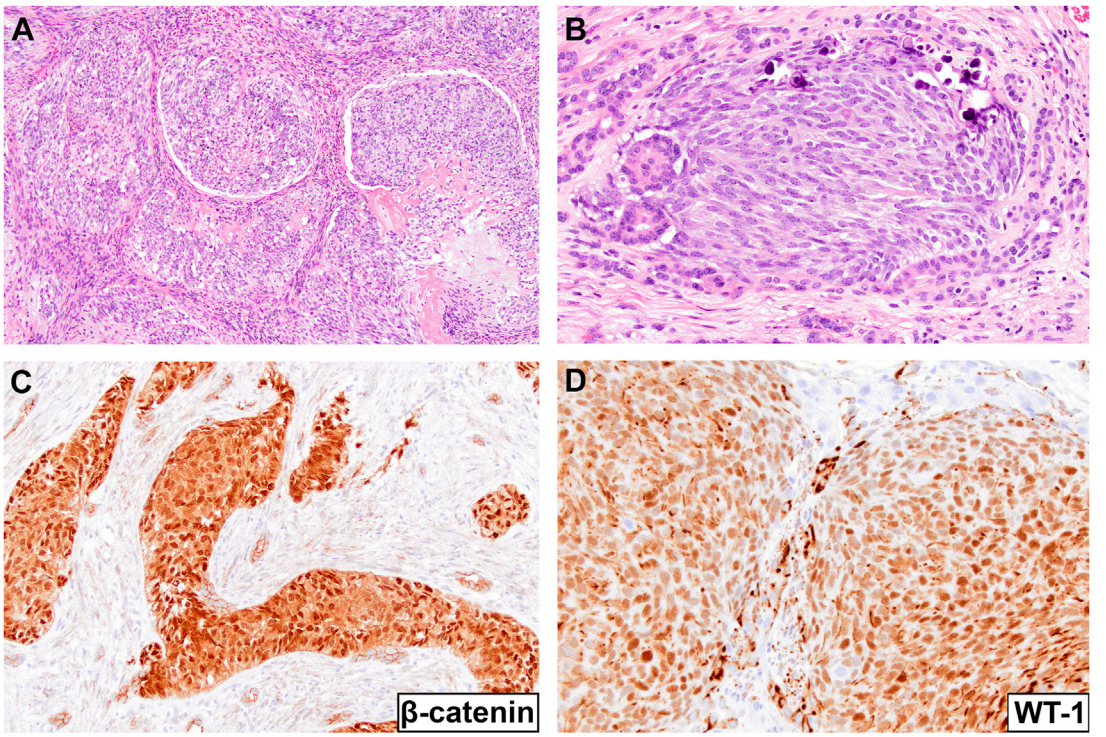

Fig. 3. CNSET. (*A*) CNSET shows nests of epithelioid neoplastic cells in a fibrotic stroma. Bone formation is present in just more than half of tumors. There are multiple foci of dense hyaline osteoid matrix in this example. (*B*) On higher power, the neoplastic cells show monomorphic ovoid nuclei with open chromatin and small, distinct nucleoli. This example shows calcifications within the tumor nest. (*C*) Nuclear β-catenin expression confirms the diagnosis of CNSET, which harbors recurrent *CTNNB1* alterations. (*D*) Nuclear WT-1 expression is also present in about 80% of CNSET. WT-1 and β-catenin expression, in conjunction with negativity for synaptophysin and chromogranin, help distinguish CNSET from metastatic well-differentiated neuroendocrine tumor.

are embedded in a characteristically abundant, spindled stroma, and there are bile ductular reactions around tumor nests in some cases. More than half of tumors show bone formation, and a minority show spindle cell morphology and/or clear cell features. Although CNSET shows epithelial differentiation, with consistent expression of keratins,[29] it lacks expression of hepatocellular or biliary proteins such as HepPar-1, arginase-1, and albumin (by in situ hybridization; ISH).[33] An initial molecular genetic study demonstrated the presence of *CTNNB1* exon 3 deletions in 2 sequenced tumors.[34] Consistent with these findings, CNSET uniformly shows nuclear expression of β-catenin, and it also shows nuclear expression of WT-1 in about 80% of cases (**Fig. 3**C–D).[27,34,35]

Until recently, there were only rare reports of metastasizing CNSET,[36,37] and only about 10% to 15% of tumors were known to have recurred locally.[27,35] A recent series with long-term follow-up demonstrated that CNSET might be more aggressive than previously thought.[33] In this series, 4 of 7 patients with follow-up developed lung metastases, and 2 of these 4 patients also developed abdominal metastases. One patient with multifocal liver tumors at presentation developed lung metastases and died of disease. Molecular genetic findings in this series confirmed the presence of *CTNNB1* alterations in all sequenced tumors, including exon 3/4 deletions and activating point mutations. Additionally, *TERT* promoter mutations were found in all sequenced tumors. Mitoses more than 5/10 high-power fields, multifocal liver tumors at presentation, and presence of *CTNNB1* deletions all were associated with a more aggressive clinical courses, although these associations need further corroboration given the small number of cases in this series.

With its nested architecture and desmoplastic-appearing stroma, CNSET presents a pitfall for the misdiagnosis of carcinoma or well-differentiated neuroendocrine tumor, especially in examples that do not show bone formation (**Table 2**). Of the primary hepatocellular neoplasms, CNSET most closely resembles hepatoblastoma, particularly the fetal subtype. Both are composed of monomorphic epithelioid cells, and both of these neoplasms express nuclear β-catenin.[38]

Table 2
Pitfalls for the misdiagnosis of carcinoma

Pitfalls for Misdiagnosis of Conventional Carcinoma			
Neoplasm	Diagnostic pitfall	Reasons for pitfall	Clues and tests to avoid pitfall
CNSET	Metastatic carcinoma	• Keratin expression • Nested architecture	• Monomorphic cytomorphology • β-catenin positivity
	Hepatoblastoma	• Keratin expression • Nested architecture	• Negativity for hepatocellular markers
	Metastatic well-differentiated neuroendocrine tumor	• Keratin expression • Nested architecture	• Negativity for neuroendocrine markers
EHE	Metastatic carcinoma	• Keratin expression • Epithelioid morphology	• Sinusoidal growth pattern • Positivity for vascular markers
Angiosarcoma	Carcinoma	• Keratin expression • Epithelioid morphology	• Sinusoidal growth pattern • Positivity for vascular markers
PEComa	Hepatocellular carcinoma	• Granular cytoplasm • Epithelioid morphology	• Unusually low mitotic activity • Keratin negativity in most cases
Malignant rhabdoid tumor	Carcinoma, hepatoblastoma	• Keratin expression • Epithelioid morphology	• Unusually young age • INI1 loss • Negativity for hepatocellular markers
DSRCT	Carcinoma	• Keratin positivity • Nested architecture • Epithelioid morphology	• Unusually young age for carcinoma • Expression of desmin
Pitfalls for misdiagnosis of sarcomatoid carcinoma			
Neoplasm	Diagnostic pitfall	Reason for pitfall	Test to avoid pitfall
Metastatic leiomyosarcoma	Metastatic sarcomatoid carcinoma	• Keratin positivity	• Desmin usually positive
Metastatic melanoma	Metastatic sarcomatoid carcinoma	• Keratin positivity (rare)	• Diffuse SOX10, S100 positivity • History of melanoma is helpful

However, hepatoblastoma does not have the dense fibrous stroma of CNSET, and it also expresses HepPar-1, arginase-1, and albumin (the latter by ISH), markers that can distinguish it from CNSET.[39,40] Another differential diagnostic consideration is hepatocellular carcinoma, which is distinguished from CNSET by the expression of HepPar-1 and arginase-1; although hepatocellular carcinoma can lose expression of these markers,[41] this loss generally occurs in poorly differentiated tumors that would not show the monomorphic appearance of CNSET. Finally, CNSET shows some morphologic overlap with metastatic well-differentiated neuroendocrine tumor, which could be a diagnostic pitfall particularly in cases of multifocal CNSET. These tumor types are easily distinguished by immunohistochemistry (IHC) because CNSET is consistently negative for chromogranin and synaptophysin while well-differentiated neuroendocrine tumors are consistently positive (see **Table 2**).

VASCULAR NEOPLASMS

Primary vascular neoplasms of the liver can be diagnostically challenging, particularly on core

needle biopsies in which architectural features are not apparent. Benign hemangiomas are the most common mesenchymal tumors of the liver, with an estimated population prevalence of 2.5%,[42] and these include sclerosed hemangioma, cavernous hemangioma, and the more recently described anastomosing hemangioma and HSVN. Of these benign hemangiomas, anastomosing hemangioma and HSVN are the only ones that present a diagnostic pitfall for the misdiagnosis of angiosarcoma. Here, I will discuss these 2 benign tumor types, along with EHE and angiosarcoma (see **Table 1**).

ANASTOMOSING HEMANGIOMA AND HEPATIC SMALL VESSEL NEOPLASM

Anastomosing hemangioma was initially described in a series of 6 tumors of the genitourinary tract,[43] and subsequently it has been described to occur in the retroperitoneum, paraspinal soft tissue, and abdominal organs including the liver.[44–46] Anastomosing hemangioma is a benign vascular tumor that shows complex, anastomosing vascular channels lined by bland endothelial cells (**Fig. 4**A). In contrast to angiosarcoma, the endothelial cells in anastomosing hemangioma are monolayered, and the tumor does not demonstrate infiltrative growth into hepatic parenchyma. Fibrin thrombi are commonly present. About half of tumors show extramedullary hematopoiesis, and about half show intracytoplasmic hyaline globules in neoplastic endothelial cells. IHC for vascular markers is useful to highlight the architecture of the lesion and to confirm the lack of endothelial multilayering (**Fig. 4**B). Anastomosing hemangioma harbors the same activating alterations that are present in other benign hemangioma types, including in *GNAQ*, *GNA11*, and *GNA14*.[47–49]

HSVN was originally described to have uncertain biologic potential,[50] but with longer clinical follow-up, it is now thought to represent a benign but sometimes locally aggressive vascular neoplasm.[51] Similar to anastomosing hemangioma, HSVN shows complex anastomosing vascular channels surfaced by a monolayer of endothelial cells that lack nuclear atypia. However, in contrast to anastomosing hemangioma, HSVN also shows infiltrative growth into adjacent hepatic parenchyma (**Fig. 4**C), which can make it challenging to distinguish from angiosarcoma. This differential diagnosis is one of the few instances in soft tissue pathology where Ki-67 IHC has diagnostic utility; in one recent series, HSVN consistently showed a Ki-67 proliferative index of less than 10%, whereas only angiosarcoma showed a higher Ki-67 proliferative index.[50] However, the converse is not true, and so a low Ki-67 does not exclude the diagnosis of angiosarcoma. Similar to anastomosing hemangioma and kaposiform hemangioendothelioma, HSVN harbors mutations in *GNAQ* and *GNA14*, and it lacks *TP53* alterations[51]; therefore, p53 IHC also has utility in distinguishing HSVN from angiosarcoma, the latter of which shows *TP53* alterations in ~20 to 30% of tumors.[52,53]

EPITHELIOID HEMANGIOENDOTHELIOMA

Although EHE was initially described as a tumor of intermediate biologic potential,[54] it is now known to be a sarcoma, the prognosis of which depends on the involved body site(s).[55–57] EHE of the liver presents with multifocal hepatic disease in about 75% of patients,[57] and it presents with involvement of extrahepatic body sites in about 40% of patients.[58,59] In long-term follow-up, most patients with hepatic EHE die of disease, with roughly 40% overall survival at 5 years of follow-up.[57,59]

There are 2 main morphologic variants of EHE, each of which has distinctive clinicopathologic features. About 90% of EHE harbor *WWTR1*::*CAMTA1* fusions.[60–62] *CAMTA1*-rearranged EHE shows mildly atypical neoplastic cells that are embedded singly and in small cords in a characteristic myxohyaline stroma (**Fig. 5**A). At its interface with background hepatic parenchyma, EHE shows a sinusoidal pattern of growth (**Fig. 5**B). EHE also shows plugging of native portal tract vessels with tumor cells, which is a helpful diagnostic clue when present. CAMTA1 IHC is highly sensitive and specific for EHE harboring *CAMTA1* fusion, with strong and diffuse nuclear expression in essentially all such cases (**Fig. 5**C).[63,64]

About 5% of EHE harbor alternate *YAP1*::*TFE3* fusions,[65] and this subtype of EHE can rarely occur in the liver.[66,67] EHE with *YAP1*::*TFE3* fusion shows distinctive morphology, with nests of epithelioid endothelial cells showing voluminous, glassy cytoplasm and frank vasoformation (**Fig. 5**D). Recent studies have shown that this subtype of EHE has a clinical course distinct from *CAMTA1*-rearranged EHE, with a higher frequency of multifocal disease and metastasis (compared with *CAMTA1*-rearranged EHE of all sites) but a significantly higher 5-year progression-free survival of 85% to 90%.[68,69] IHC directed against the C-terminus of YAP1 demonstrates the loss of expression in *YAP1*::*TFE3*-rearranged EHE (**Fig. 5**E),[70] and TFE3 IHC shows strong and diffuse nuclear expression.[65] Although it is sensitive, TFE3 IHC is somewhat nonspecific,[61,71] such that only strong and diffuse TFE3 expression in the correct morphologic context should be used to support the diagnosis

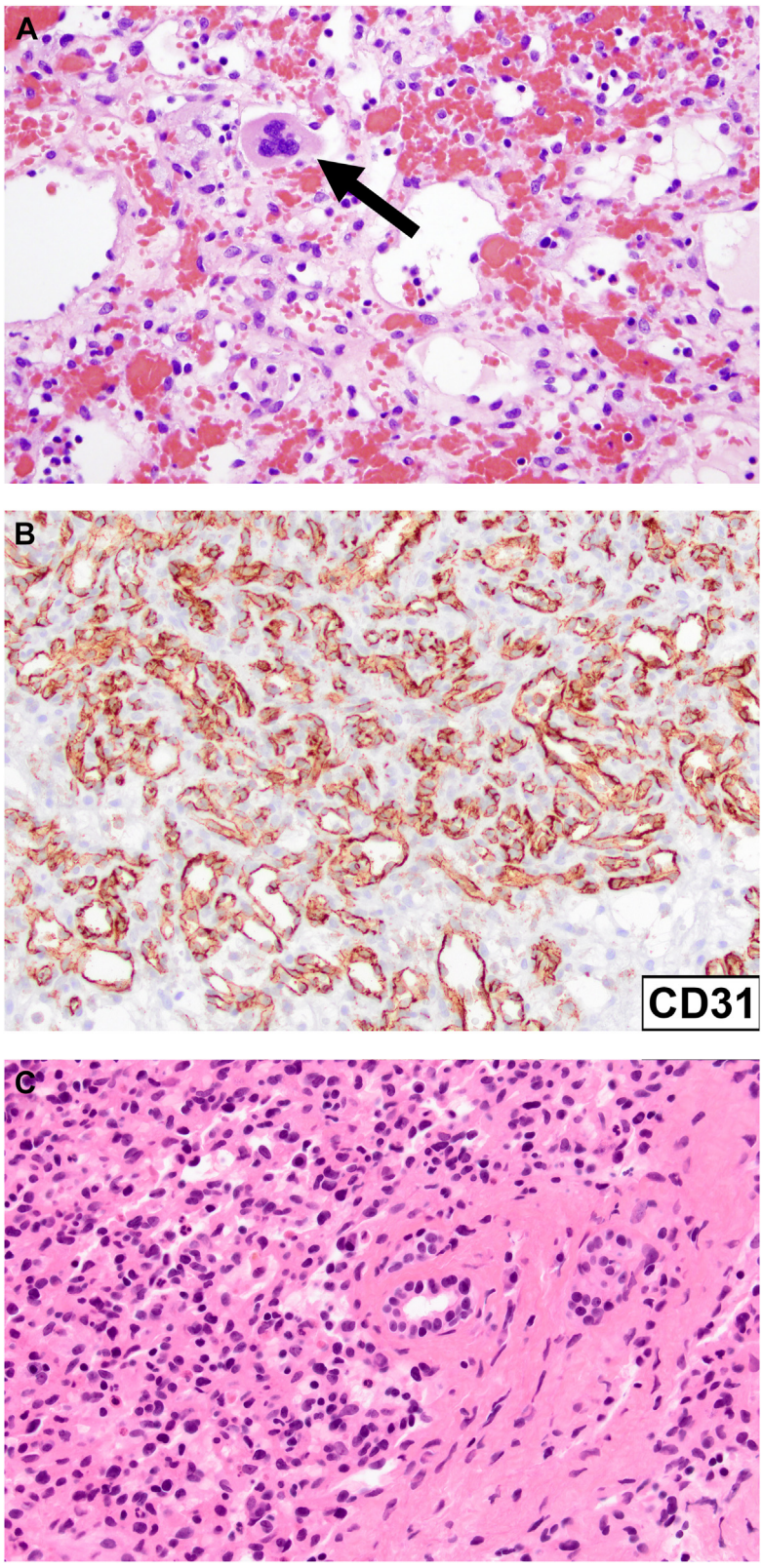

Fig. 4. Anastomosing hemangioma and HSVN. (*A*) Anastomosing hemangioma is composed of complexly anastomosing vascular channels that lack endothelial multilayering or nuclear atypia. Extramedullary hematopoiesis is a common feature, exemplified here by a megakaryocyte (*arrow*). (*B*) IHC for CD31 (shown), SMA, and/or ERG can be useful to highlight the lack of endothelial multilayering. In this hepatic anastomosing hemangioma, CD31 highlights densely packed vessels with monolayers of endothelial cells. (*C*) Although HSVN bears close resemblance to anastomosing hemangioma, it is distinguished by its infiltrative interface with adjacent hepatic parenchyma. Here, this HSVN can be seen infiltrating around a native portal tract.

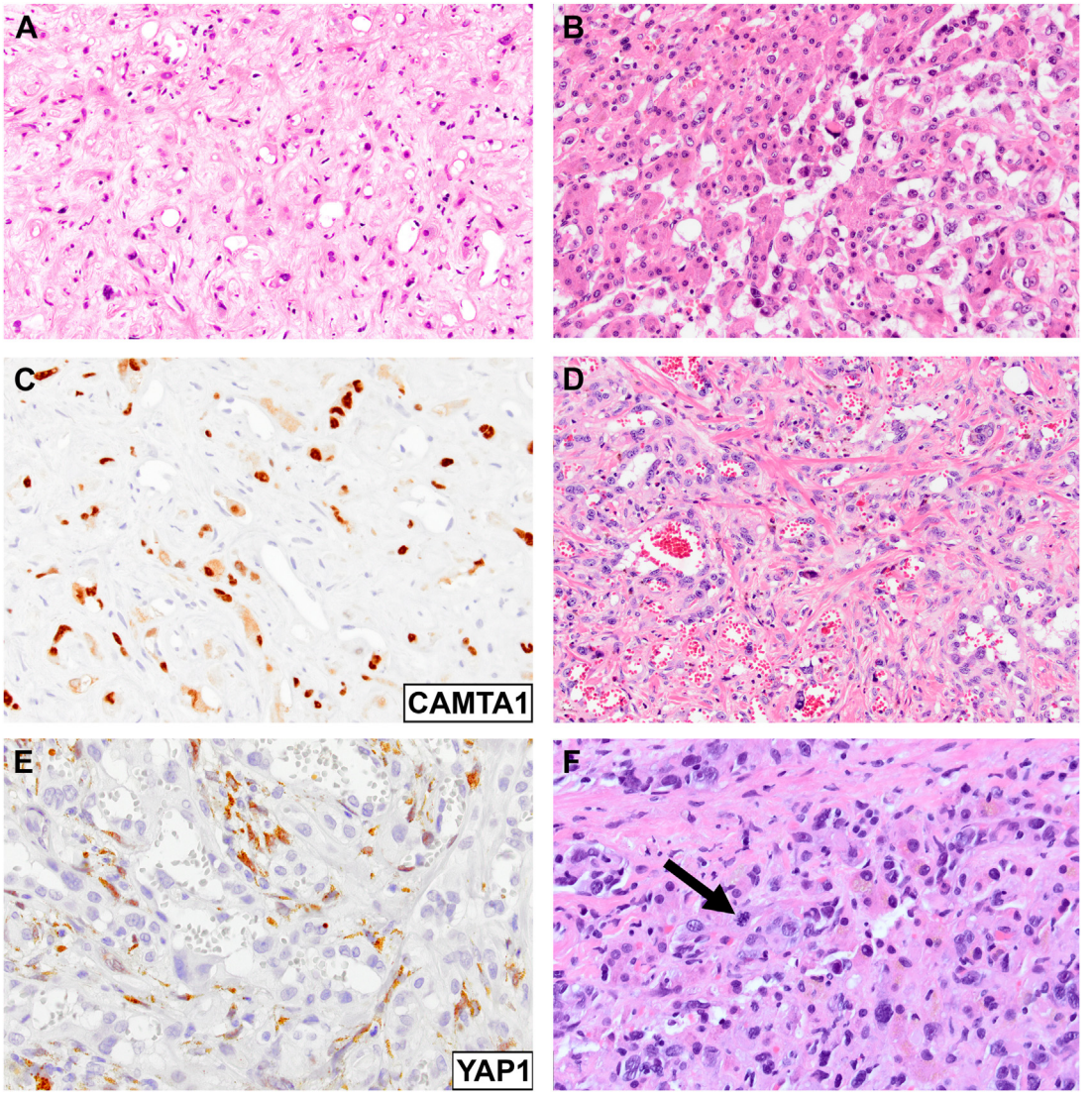

Fig. 5. EHE. (*A*) EHE with *WWTR1*::*CAMTA1* fusion shows neoplastic endothelial cells scattered singly and in cords within a characteristic myxohyaline stroma. Some cells show cytoplasmic vacuoles, a useful diagnostic feature. (*B*) At the interface between tumor and background hepatic parenchyma, EHE shows an infiltrative growth pattern along sinusoids that would be very unusual for carcinoma. (*C*) Nuclear expression of CAMTA1 by IHC is highly sensitive and specific for the diagnosis of EHE. (*D*) EHE with *YAP1*::*TFE3* fusion shows nests of epithelioid neoplastic cells with voluminous cytoplasm, round nuclei with vesicular chromatin, and prominent nucleoli. There is also frank vasoformation, in contrast to EHE with *WWTR1*::*CAMTA1* fusion. (*E*) IHC demonstrates loss of expression of the C-terminus of YAP1, consistent with *YAP1*::*TFE3* fusion. TFE3 IHC (not shown) shows strong and diffuse nuclear staining, and both stains can be used to confirm the diagnosis in the appropriate morphologic context. (*F*) Marked cytologic atypia and increased mitotic activity (*arrow*) are high-risk features associated with inferior progression-free survival.

of EHE with *YAP1*::*TFE3* fusion. Given its distinctive morphology, clinical course, and genetics, it seems likely that EHE with *YAP1*::*TFE3* fusion represents a diagnostic entity distinct from *CAMTA1*-rearranged EHE, although in the most recent WHO classification, these tumor types share a common classification.[72]

The differential diagnosis of EHE includes carcinoma (especially metastatic carcinoma in patients with multifocal liver disease) and epithelioid angiosarcoma. EHE expresses keratins in up to 60% of cases,[73] presenting a potential pitfall for the misdiagnosis of carcinoma (see **Table 2**). However, the sinusoidal growth and myxohyaline stroma of EHE

would be unusual for carcinoma, and these features should prompt consideration of a vascular neoplasm. Epithelioid angiosarcoma is another diagnostic consideration, particularly in examples of EHE with marked cytologic atypia (see later discussion). Because CAMTA1 IHC is highly specific for EHE,[64] I have a low threshold for performing CAMTA1 IHC to rule out EHE before diagnosing epithelioid angiosarcoma in the liver.

Recent studies have shown that increased mitotic activity, large tumor size, nuclear atypia, and pleural involvement are associated with decreased survival.[68,74,75] Shibayama and colleagues proposed a risk stratification model, in which tumors were stratified into low-risk, intermediate-risk, and high-risk groups based on tumor size and atypical histologic features (defined as tumor necrosis, >1 mitosis/2 mm^2, and/or marked nuclear atypia) (**Fig. 5**F).[76] In this model, low-risk, intermediate-risk, and high-risk tumors showed 5-year overall survival rates of 100%, 81.8%, and 16.9%, respectively.[76] Only 2 of 31 patients with liver involvement in this series had high-risk tumors, suggesting that high-risk liver disease is uncommon. Given that these atypical histologic features have been associated with worse prognosis in multiple studies, it is important to state their presence if they are identified.

Recent work has elucidated our understanding of the tumor biology of EHE and has pointed to potential treatment strategies. *WWTR1* encodes TAZ, and both YAP1 and TAZ are downstream effectors of the Hippo pathway that regulates cell proliferation.[77] In the protein resulting from *WWTR1*::*CAMTA1* fusion, the CAMTA1 component promotes translocation of the fusion protein into the nucleus, where the TAZ component can then serve as a transcription factor.[78] Expression of the *WWTR1*::*CAMTA1* fusion gene in a mouse model is sufficient to drive the development of EHE,[79] and the fusion proteins in both *CAMTA1*-rearranged and *YAP1*-rearranged EHE subtypes have been shown to drive oncogenic transcriptional programs.[80] These programs include the expression of connective tissue growth factor,[81] a protein that binds integrins that are thought to promote invasion and metastasis.[82,83] Integrin signaling depends on the Ras-Mitogen-activated protein kinase (MAPK) pathway,[84] and a recent in vitro study demonstrated that inhibition of this pathway with sorafenib and MAPK kinase (MEK) inhibitors decreased tumor cell colony formation.[81] These studies provide a biologic basis for recent clinical trials using the MEK inhibitor trametinib in patients with metastatic or unresectable EHE; more time is needed to determine whether this treatment is effective in preventing disease progression.

HEPATIC ANGIOSARCOMA

Hepatic angiosarcoma is a highly aggressive malignancy, with a dismal median survival of under 6 months.[85] Most hepatic angiosarcomas arise de novo, with a median age at presentation of 65 years and a slight male predominance,[86] although the age range is wide and includes children.[87] Rarely, hepatic angiosarcoma can arise due to exposure to toxins including arsenic and vinyl chloride.[88–91] Hepatic angiosarcoma shows a variety of growth patterns, and most commonly, it forms a discrete mass.[92] Less commonly, it diffusely infiltrates the liver sinusoids, a subtle growth pattern that can be hard to recognize (**Fig. 6**A–B). When hepatic angiosarcoma forms a discrete mass, it typically forms complexly anastomosing vascular channels, with cytologic atypia, endothelial multilayering, and infiltration of hepatic parenchyma (**Fig. 6**C–E). Occasional examples show spindle cell or epithelioid morphology without evident vasoformation, in which case the glassy cytoplasm is a useful diagnostic clue. It is uncommon for angiosarcoma to show prominent nuclear pleomorphism. Even morphologically low-grade appearing angiosarcomas have a high risk of distant metastasis, and so angiosarcoma is definitionally high-grade.[93] IHC demonstrates expression of CD31 and ERG in nearly all cases, whereas the sensitivity of CD34 is only ~60% to 70%.[94] CD31 IHC is particularly useful to highlight endothelial multilayering (**Fig. 6**F).

The differential diagnosis of hepatic angiosarcoma is broad and depends on the tumor morphology. Morphologically bland examples show histologic overlap with benign vascular tumors such as anastomosing hemangioma and HSVN. However, in contrast to these benign tumor types, angiosarcoma shows endothelial multilayering. There are no immunohistochemical stains that reliably distinguish angiosarcoma from these benign tumor types, although a Ki-67 proliferation index greater than 10% or a p53 mutant staining pattern would strongly favor the diagnosis of angiosarcoma in this differential.[50] The differential diagnosis also includes EHE, which can show marked cytologic atypia in some cases; CAMTA1 IHC is essentially always negative in angiosarcoma, and therefore, this marker is useful to rule out EHE with marked cytologic atypia.[63,64] Keratins are expressed in around 30% of angiosarcomas, especially ones with epithelioid morphology, presenting a potential diagnostic pitfall (see **Table 2**).[95] Diagnostic clues for angiosarcoma include the presence of glassy cytoplasm, cytoplasmic vacuoles, and infiltrative growth through hepatic sinusoids, all of which would be unusual for carcinoma. IHC for

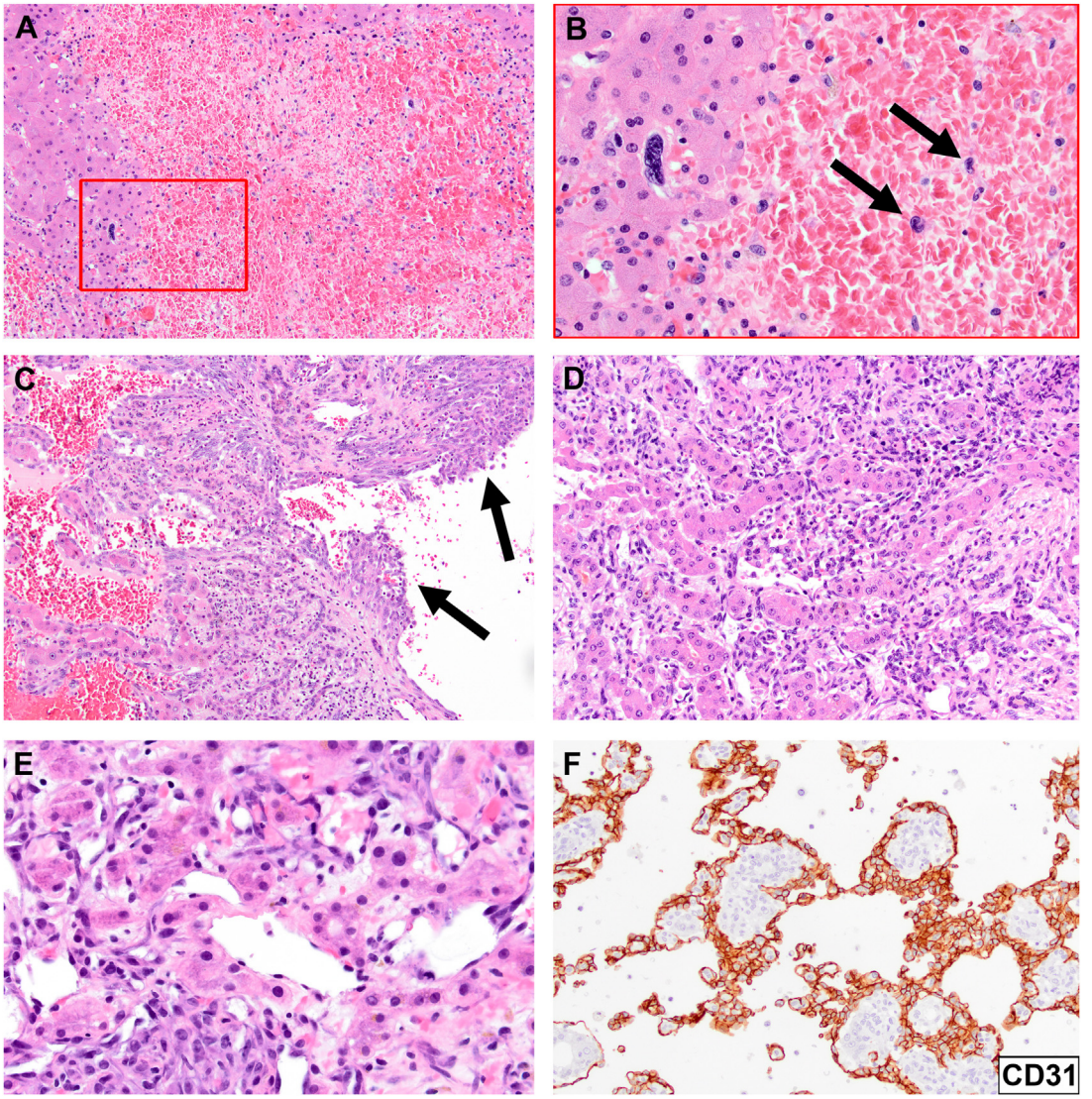

Fig. 6. Hepatic angiosarcoma. (*A*, *B*) Hepatic angiosarcoma showing hemorrhage and sinusoidal growth. (*A*) This hepatic angiosarcoma showed multiple scattered hemorrhagic foci at low power. (*B*) This higher power image of the region boxed in A shows that there are rare, atypical cells in the hemorrhage (*arrows*), as well as a markedly atypical cell infiltrating adjacent hepatic sinusoids. (*C*) This hepatic angiosarcoma shows prominent endothelial multilayering (*arrows*). (*D*, *E*) Dissecting growth through hepatic sinusoids is characteristic and provides a useful diagnostic clue. (*F*) IHC for CD31 highlights endothelial cells that are multilayered and that are wrapping around residual hepatocytes.

CD31 and ERG can resolve this differential diagnosis, with the caveat that weak ERG positivity is nonspecific and should be interpreted with caution.[96] Given the clinical implications of the diagnosis of angiosarcoma, if there is diagnostic uncertainty, then it is important to advise repeat biopsy.

The genetic features of angiosarcoma have been partially elucidated in recent studies. *MYC* amplification is characteristic of radiation-associated angiosarcoma but only present in a minor subset of primary angiosarcoma.[97,98] Instead, primary angiosarcoma shows MAPK pathway alterations in about 50% of tumors and *TP53* and/or *CDKN2A* alterations in 20% to 30%.[53] *KDR* and/or *PLCG1*, both involved in vascular endothelial growth factor signaling, are altered in about 25% of angiosarcomas, including both primary and secondary tumors.[99–101] Although angiosarcoma was originally reported to show complex copy number alterations in most cases,[102] more recent study identified this finding in only 25% of cases.[103] A small subset of angiosarcomas harbor

CIC alterations, including mutations and rearrangements[100]; these tumors show epithelioid morphology, younger than average age at presentation, and more aggressive clinical behavior.[100] However, it was shown recently that *CIC*-rearranged round cell sarcomas can express ERG in half of cases and CD31 in about a third; none of these tumors showed vasoformation, and DNA methylation profiling showed that these tumors clustered with *CIC*-rearranged round cell sarcomas and not angiosarcoma.[104] Therefore, it seems that a subset of *CIC*-rearranged round cell sarcomas likely express vascular markers and present a pitfall for misdiagnosis of epithelioid angiosarcoma.

OTHER MESENCHYMAL NEOPLASMS THAT CAN PRIMARILY OCCUR IN THE LIVER

There are several other mesenchymal neoplasms that can occur primarily in the liver, including PEComa/angiomyolipoma, inflammatory pseudotumor-like FDCS, EBV-associated smooth muscle tumor (EBV-SMT), IMT, and MRT (see **Table 1**). In this section, I will briefly survey these neoplasms, which are rare and have distinctive features that facilitate their recognition.

PERIVASCULAR EPITHELIOID CELL TUMOR/ ANGIOMYOLIPOMA

The concept of PEComa was elucidated in the 1990s, when it was determined that angiomyolipoma, pulmonary lymphangiomyomatosis, clear cell "sugar" tumor of the lung, and tumors now termed epithelioid PEComa all share ultrastructural and immunohistochemical characteristics.[105–108] We now know that both sporadic and tuberous sclerosis-associated tumors in the PEComa family harbor mammalian target of rapamycin (mTOR) pathway alterations in most cases, most commonly in *TSC1* and *TSC2*.[109,110] A minor subset of PEComas harbor *TFE3* rearrangements.[111,112]

Hepatic PEComa and angiomyolipoma both tend to occur in middle-aged adults, with a marked female predominance.[113] Angiomyolipoma shows a mixture of adipose tissue, blood vessels, and epithelioid cells (**Fig. 7**A). In PEComa, the perivascular epithelioid cells predominate, and sometimes, there are no evident adipocytes in the tumor. The neoplastic cells of PEComa show granular to clear cytoplasm and vesicular nuclei with prominent, melanocyte-like nuclei (**Fig. 7**B). Usually, smooth muscle actin (SMA) and desmin are expressed strongly but only in scattered cells, a staining pattern that would be unusual for a smooth muscle neoplasm (**Fig. 7**C). IHC also demonstrates expression of melanosomal proteins HMB-45 and/or melan-A in most tumors (**Fig. 7**D). PEComas harboring *TFE3* translocations show epithelioid morphology with prominent clear cell features, and they show nuclear expression of TFE3.[112] The morphologic differential diagnosis of epithelioid PEComa includes hepatocellular carcinoma, metastatic clear cell renal or adrenocortical carcinoma, and metastatic melanoma (see **Table 1**). IHC is useful to resolve the differential diagnosis of carcinoma; although PEComa rarely expresses keratins, it does not generally show the strong and diffuse expression seen in carcinoma.[114] Similarly, although PEComa does express melanocytic markers such as HMB-45 and melan-A, it does not express SOX10,[115] which is strongly and diffusely positive in metastatic melanoma and therefore distinguishes these tumor types.

It can be challenging to predict the behavior of PEComa based on morphologic features. In a study of PEComas of soft tissue and the gynecologic tract, worrisome features include significant mitotic activity (>1 mitoses per 50 HPF), high nuclear grade, size greater than 8 cm, and/or necrosis; tumors showing at least 2 worrisome features were considered malignant.[114] Although these criteria have not been validated in hepatic tumors, the presence of significant nuclear atypia or mitotic activity should be noted because there are rare reports of malignant PEComa of the liver giving rise to distant metastases.[116,117]

FOLLICULAR DENDRITIC CELL SARCOMA

FDCS is a rare mesenchymal neoplasm that occurs in lymph nodes, soft tissue, and viscera. Conventional FDCS occurs across a wide age range, with a peak age at presentation of around 50 years and no sex predilection. It is composed of overtly malignant-appearing, epithelioid to spindled neoplastic cells that show characteristic whorled architecture and prominent admixed lymphocytes. Conventional FDCS is exceedingly rare in the liver, with only isolated case reports in the literature.[118] In general, FDCS is an aggressive sarcoma, and up to half of patients die of disease in long-term follow-up.[119]

There is an EBV-driven variant of FDCS, termed "inflammatory pseudotumor-like FDCS" (IPL-FDCS). Although IPL-FDCS is less common than conventional FDCS in general, it has a predilection for the liver and is much more common at this body site than conventional FDCS.[120,121] IPL-DFCS has a female predominance with a median age at presentation of 45 years, and it is most common in East Asia, possibly reflecting endemic

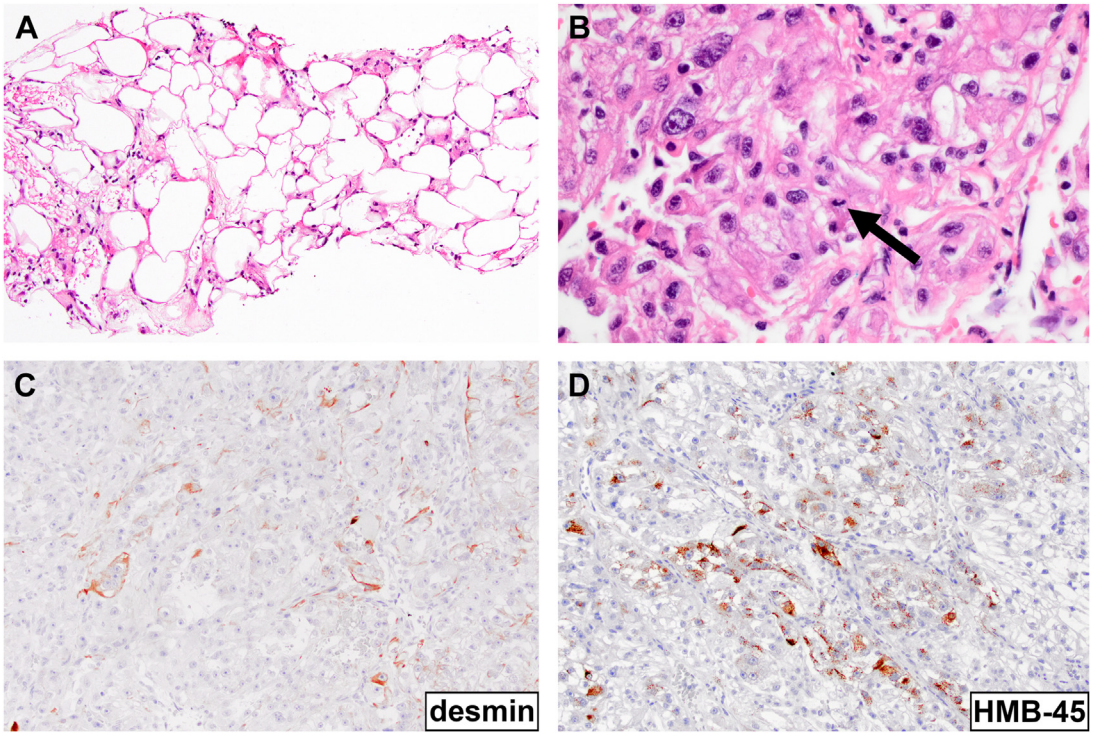

Fig. 7. PEComa/angiomyolipoma. (*A*) This angiomyolipoma of the liver is dominated by the adipocytic component and shows just scattered epithelioid neoplastic cells and small blood vessels. (*B*) This malignant PEComa of the liver shows marked nuclear atypia and mitotic activity (*arrow*). The neoplastic cells have prominent nucleoli that resemble those of malignant melanoma. Malignant PEComas of the liver are extremely rare. (*C, D*) IHC in angiomyolipoma/PEComa. (*C*). Angiomyolipoma and PEComa express SMA and desmin (shown), characteristically showing strong positivity in scattered cells. (*D*) Expression of HMB-45 (shown) and melan-A is also characteristic.

EBV infection in this region.[122] Histologically, IPL-DFCS shows the whorled architecture and lymphocytic inflammation of conventional FDCS but in contrast, it shows a more polymorphous neoplastic cell population, with less severe cytologic atypia and more fibrotic stroma (**Fig. 8**A). Similar to conventional FDCS, IPL-FDCS expresses of CD21 and CD35 in ~90% of cases each (**Fig. 8**B).[123] FDCS has also been shown to express D2-40, SSTR2A, and PD-L1 in about half of cases each, although there is no systematic study of these antibodies in IPL-FDCS.[119,124] Along with the IHC markers positive in conventional FDCS, ISH for EBV RNA can be used to confirm the diagnosis (**Fig. 8**C). EMA expression is seen in ~40% of FDCS but keratins are usually negative and help distinguish FDCS from carcinoma.[123] The differential diagnosis also includes IMT, but IMT is not as prominently whorled as IPL-FDCS, nor does it express CD21, CD35, or EBV RNA (ISH). Overall, IPL-FDCS has a better prognosis than conventional FDCS, with a roughly 30% local recurrence rate and only rare reports of metastasis to date.[122]

EPSTEIN BARR VIRUS-ASSOCIATED SMOOTH MUSCLE TUMOR

EBV-SMT is rare and occurs in severely immunosuppressed patients, generally in the setting of acquired immunodeficiency syndrome or organ transplantation.[125,126] These tumors are frequently multicentric, and the liver is a common site of involvement.[127] Microscopically, EBV-SMT has a distinctive morphology, with somewhat primitive-appearing smooth muscle cells that show brightly eosinophilic cytoplasm and distinct cell borders. Often there are admixed nodules or whorls of smaller neoplastic cells. EBV-SMT usually lacks cytologic atypia, and high mitotic activity is uncommon. IHC demonstrates the expression of smooth muscle markers, and EBV RNA ISH confirms the diagnosis. EBV-SMT is generally treated with surgery combined, if possible, with the treatment of the underlying cause of immunosuppression.[128] Patients with EBV-SMT have a mortality rate of 15% to 40%, depending on the patient population, although some of this high mortality is due to other sequelae of immunosuppression.[127,128] Patients

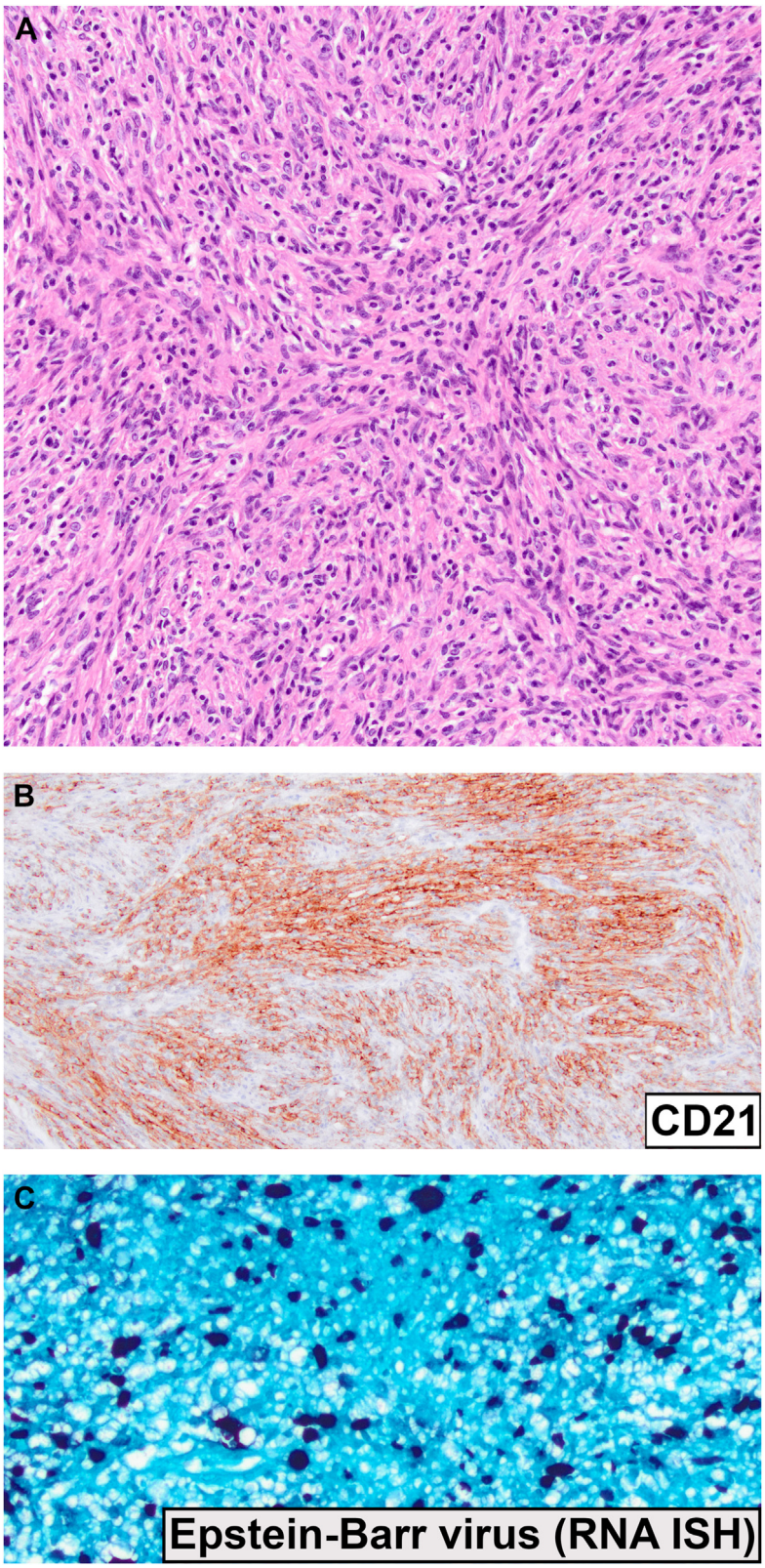

Fig. 8. IPL-FDCS. (*A*) Histologically, this IPL-FDCS of the liver shows whorls of neoplastic cells with large nuclei and prominent admixed lymphocytes. It shows somewhat more haphazard architecture and less nuclear atypia than conventional FDCS. (*B*) IHC demonstrates the expression of follicular dendritic cell markers, including CD21 (shown), CD23, and CD35; CD21 IHC highlights the whorled architecture. Follicular dendritic cells can also express desmin and keratins, presenting a potential diagnostic pitfall. (*C*) ISH for Epstein-Barr viral RNA is positive, confirming the diagnosis.

who are able to recover immune function have a very good prognosis,[128] and tumors can spontaneously resolve if the underlying immunosuppression is reversed.[129,130]

INFLAMMATORY MYOFIBROBLASTIC TUMOR

IMT is a rare mesenchymal neoplasm that commonly occurs in children and young adults, with a minority of cases occurring in older adults.[131,132] IMT is recognized to rarely occur in the liver.[133] Histologically, it is composed of fascicles of spindle cells with vesicular nuclei and prominent nucleoli. The stroma is variably myxoid to collagenous, and, characteristically, there is prominent admixed inflammation composed of plasma cells, neutrophils, and/or lymphocytes. IHC demonstrates the expression of SMA and sometimes desmin; similar to other tumors with myofibroblastic differentiation, about 15% of IMT express keratins.[134] *ALK* fusions are present in about 50% to 60% of IMT, and tumors with these fusions show strong and diffuse expression of ALK by IHC.[132] *ALK* fusions are more common in younger patients, and in older patients, the diagnosis is often based on morphology.[131] A minor subset of IMT harbor other gene fusions, including in *ROS1*.

The differential diagnosis of IMT includes inflammatory pseudotumor, metastatic leiomyosarcoma, and, possibly, sarcomatoid carcinoma. Inflammatory pseudotumors (discussed in detail in another article) show a much less organized proliferation of fibroblasts/myofibroblasts, and there is frequently an associated ductular reaction.[135] Leiomyosarcoma shows brightly eosinophilic cytoplasm and distinct cell borders, neither of which are features of IMT, and generally leiomyosarcoma shows significantly more nuclear atypia. Finally, sarcomatoid carcinoma shows more nuclear atypia and hyperchromasia than IMT.

MALIGNANT RHABDOID TUMOR

MRT is a rare, highly aggressive sarcoma of infancy and early childhood, with most patients presenting under 1 year of age. Although MRT usually occurs in the kidney or perinephric adipose tissue, rarely it can present primarily in the liver.[136,137] About 60% of patients with MRT of the liver present with metastatic disease, and 90% of patients die of disease.[138] Morphologically, MRT shows sheets of neoplastic cells with eccentric, vesicular nuclei and brightly eosinophilic cytoplasm (ie, "rhabdoid" cytomorphology). IHC demonstrates the loss of expression of integrase interactor 1 (INI1),[139] consistent with *SMARCB1* inactivation identified in essentially all cases.[140,141] About 60% of extrarenal MRT express keratins but they are consistently negative for desmin and CD34,[142] the latter of which helps distinguish MRT from proximal-type epithelioid sarcoma.[143] Keratin expression could present a diagnostic pitfall for the misdiagnosis of hepatocellular carcinoma or hepatoblastoma (see **Table 2**) but MRT can be distinguished by its rhabdoid cytomorphology, negativity for hepatocellular markers, and loss of INI1 expression.[137]

OTHER MESENCHYMAL NEOPLASMS THAT CAN OCCUR IN THE LIVER: SOLITARY FIBROUS TUMOR, LEIOMYOSARCOMA, AND EMBRYONAL RHABDOMYOSARCOMA

Other mesenchymal neoplasms that can occur primarily in the liver are exceedingly rare and include solitary fibrous tumor, primary hepatic leiomyosarcoma, and embryonal rhabdomyosarcoma (see **Table 1**). Solitary fibrous tumor shows haphazardly arranged neoplastic cells, which are ovoid to spindled in morphology. The stroma is characteristically collagenous, and there are usually admixed staghorn blood vessels. Solitary fibrous tumor is characterized by *NAB2*::*STAT6* fusions in ~95% of cases,[144,145] and IHC for STAT6 is highly sensitive and specific for the diagnosis.[146] The liver is a common site of metastasis for solitary fibrous tumor, and so this possibility should be considered, particularly in patients with a potentially spurious remote history of a "fibroma" or "meningioma."

Because metastatic leiomyosarcoma is so much more common in the liver than primary leiomyosarcoma, clinical exclusion of a primary elsewhere should be recommended. There are isolated case reports of embryonal rhabdomyosarcoma of the liver in children and adults[147]; this diagnosis can be confirmed by IHC for desmin, myo-D1, and myogenin.

SECONDARY MALIGNANCIES OF THE LIVER: PITFALLS, CHALLENGES, AND GENERAL APPROACHES TO SARCOMATOID NEOPLASMS IN THE LIVER

Metastatic neoplasms to the liver are more common than primary hepatic malignancies.[1] In particular, metastatic sarcomatoid carcinoma and metastatic melanoma can mimic sarcoma, presenting a potential diagnostic pitfall (see **Table 2**); therefore, it is important to consider a broad differential diagnosis for sarcomatoid neoplasms and to rule out sarcomatoid carcinoma

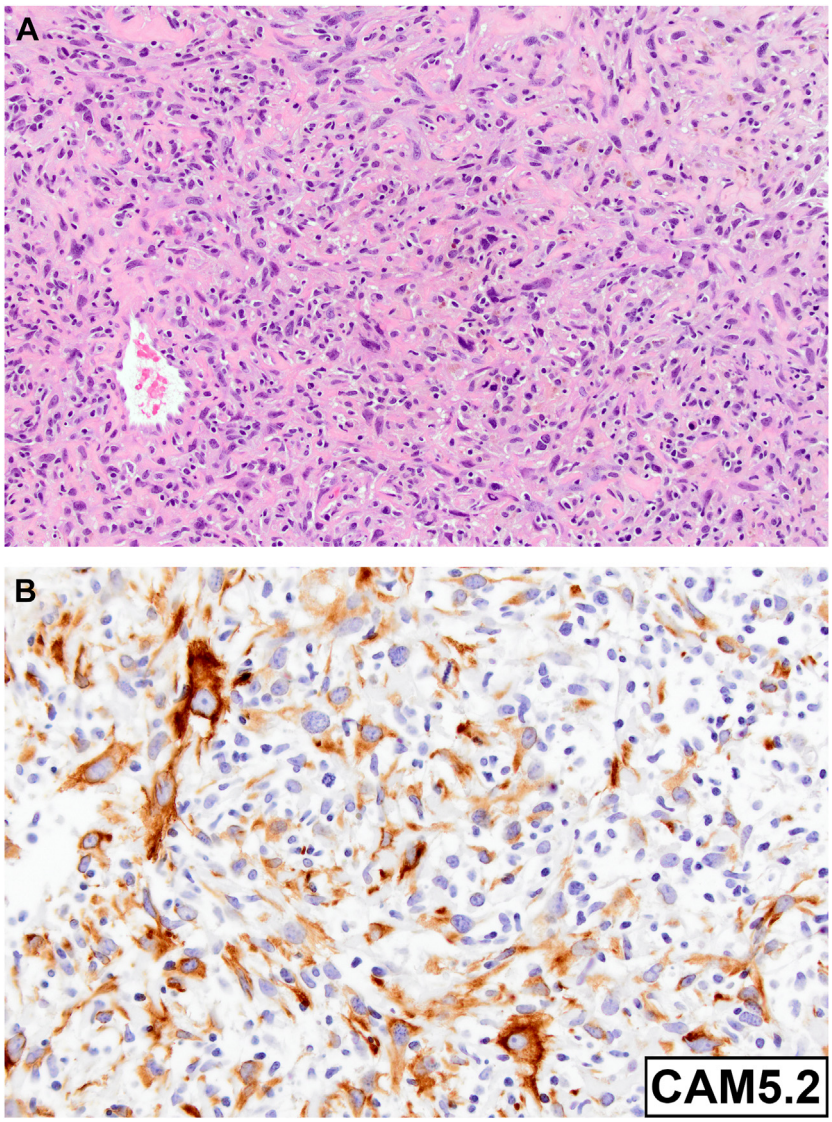

Fig. 9. Metastatic sarcomatoid carcinoma. (*A*) Sarcomatoid carcinoma usually shows mixed epithelioid and spindle cell morphology, including scattered cells with pleomorphic and hyperchromatic nuclei. Collagenous stroma is a common feature of sarcomatoid carcinoma. (*B*) CAM5.2 IHC demonstrates diffuse positivity. IHC for broad-spectrum keratins is helpful when positive but some sarcomatoid carcinomas can lose expression of keratins. A clinical history of primary carcinoma elsewhere is helpful to raise the diagnostic possibility of metastatic, keratin-negative sarcomatoid carcinoma.

and melanoma. Metastatic sarcomatoid carcinoma typically occurs in older adults and shows overtly malignant, mixed epithelioid and spindle cell morphology, with scattered cells showing hyperchromatic nuclei and nuclear pleomorphism (**Fig. 9**A). Often times patients present with widely metastatic disease, such that the primary site cannot be determined; given the dismal prognosis, with a median survival of under 1 year, determination of primary site has limited clinical utility in most cases.[148] IHC for broad-spectrum keratins can be helpful to support the diagnosis (**Fig. 9**B). Sarcomatoid carcinomas often lose the expression of transcription factors useful for determining lineage, except for sarcomatoid renal or pulmonary carcinoma that sometimes retain the expression of PAX8 or TTF-1, respectively. In general, most sarcomatoid carcinomas in the liver are metastases because primary sarcomatoid carcinoma of the liver is exceedingly uncommon.[149]

Metastatic melanoma can show predominantly spindle cell morphology and can express desmin,[150] presenting a pitfall for misdiagnosis of leiomyosarcoma (**Fig. 10**A). In most cases, melanoma shows strong and diffuse expression of both SOX10 and S-100 protein,[151] and thus these markers are very useful screens when working up a sarcomatoid neoplasm in the liver (**Fig. 10**B). The strong and diffuse expression of SOX10 and S-100 protein is also useful to distinguish melanoma from malignant peripheral nerve

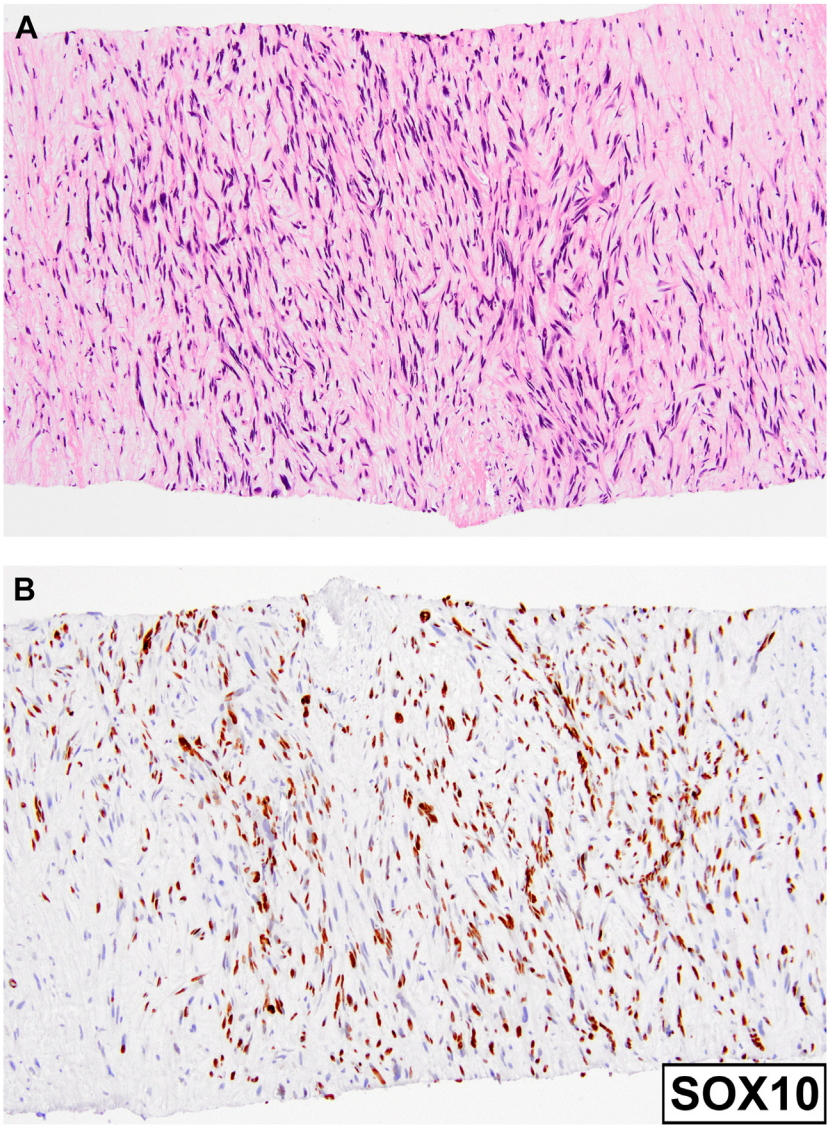

Fig. 10. Metastatic melanoma. (*A*) This metastatic melanoma is a fascicular spindle cell neoplasm with eosinophilic cytoplasm, features that raise the differential diagnosis of leiomyosarcoma. Melanoma sometimes presents with widespread metastatic disease, including liver metastases, and in about 5% of patients there is no identifiable primary tumor on subsequent clinical workup. (*B*) IHC for SOX10 (pictured) and S-100 protein demonstrates strong and diffuse expression, an extent of expression that is essentially never seen in MPNST.

sheath tumor (MPNST) because the latter never shows diffuse expression of these proteins and commonly lacks expression of both of them.[152] IHC against the trimethylated histone H3 K27 residue (H3K27me3) shows loss in ~50% of MPNST, including ~80% of high-grade examples[153]; whereas it is useful to support the diagnosis of MPNST, H3K27me3 IHC should only be used in the appropriate context because loss is also common in melanoma.[154] Melanoma can sometimes lose the expression of SOX10 and S-100 protein, in which case it is frequently misdiagnosed as a sarcoma[155]; in such cases, the clinical history of melanoma is critical, and mutation-specific antibodies for *BRAF* V600E and *NRAS* Q61R can be helpful in some cases.

Leiomyosarcoma commonly metastasizes to the liver. Morphologically, leiomyosarcoma shows fascicles of neoplastic cells with brightly eosinophilic cytoplasm, distinct cell borders, and elongated nuclei with blunt ends (**Fig 11**A). Leiomyosarcoma expresses keratins and EMA in about 40% of cases each, presenting a pitfall for the misdiagnosis of metastatic sarcomatoid carcinoma (see **Table 2**).[156] Although SMA expression is nonspecific within this differential diagnosis, IHC for desmin is helpful because desmin expression in sarcomatoid carcinoma is exceptionally rare.

Gastrointestinal stromal tumor (GIST) also frequently gives rise to liver metastases but there is nearly always a clinical history of a primary

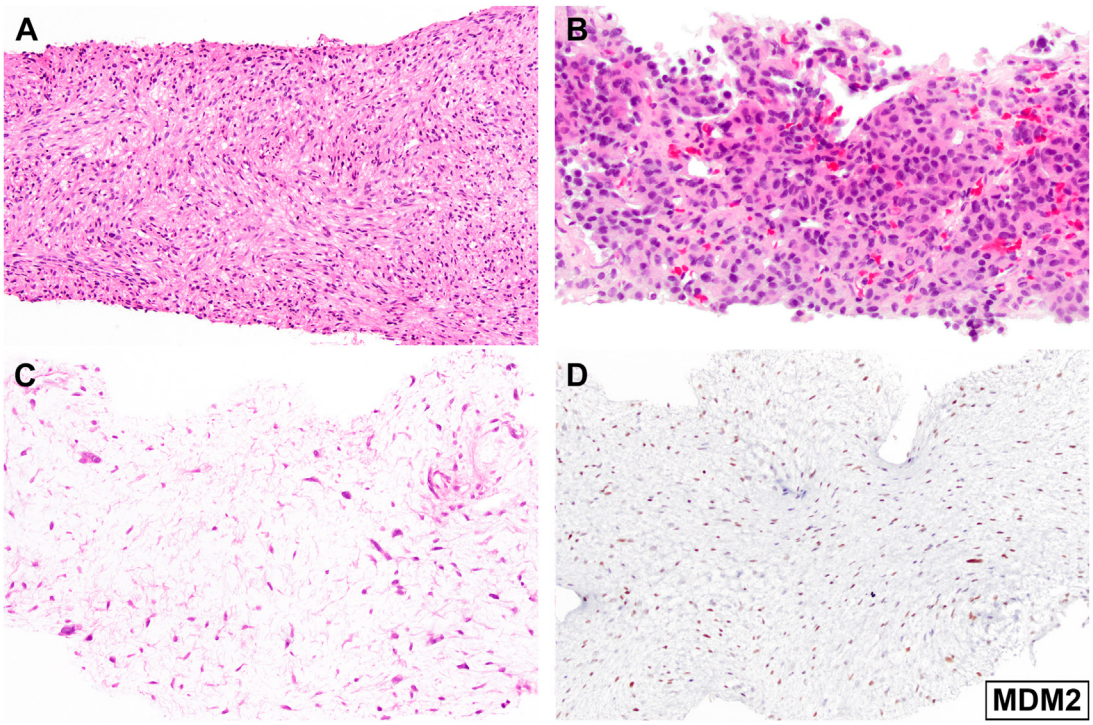

Fig. 11. Secondary sarcomas of the liver. (*A*) Metastatic leiomyosarcoma. This metastatic leiomyosarcoma shows fascicles of spindle cells with brightly eosinophilic cytoplasm and atypical nuclei. This patient had multiple liver masses but no known primary at the time of biopsy. (*B*) Metastatic GIST. This metastatic epithelioid GIST shows relatively uniform cytomorphology, a helpful diagnostic clue. It would be unusual for a patient to present with metastatic GIST in the liver without an evident mass in the luminal gastrointestinal tract. (*C, D*) DDLPS. DDLPS can present with a reported clinical history of multiple liver masses. However, re-review of the imaging generally demonstrates an associated well-differentiated component in the retroperitoneum. (*C*) Histologically DDLPS can show a wide range of morphologic patterns, which generally show at least scattered nuclear pleomorphism and/or nuclear hyperchromasia. In this example, the DDLPS is a myxoid spindle cell neoplasm, with scattered pleomorphic and hyperchromatic nuclei. (*D*) IHC for MDM2 (shown) and/or CDK4 highlights neoplastic nuclei, confirming the diagnosis of DDLPS.

tumor of the luminal gastrointestinal tract. Morphologically, GIST typically shows a monomorphic proliferation of spindled or epithelioid cells with palely eosinophilic cytoplasm and, sometimes, paranuclear cytoplasmic vacuoles (**Fig 11**B). IHC for KIT and DOG1 is helpful because only ~3% of GISTs are negative for both markers.[157]

Occasionally, DDLPS can seem clinically to be a hepatic mass or, in some cases, multiple hepatic masses. Microscopically, DDLPS shows a wide range of morphologic patterns, and most show nuclear pleomorphism (**Fig. 11**C–D). Nearly all examples of DDLPS show amplification chromosome 12q15, including *MDM2* and, in most cases, *CDK4*.[158] IHC shows expression of MDM2 and CDK4 in 85% to 95% of tumors each.[159–161] Because *STAT6* is located on chromosome 12q and coamplified in ~10% to 15% of cases, it can present a potential diagnostic pitfall for the misdiagnosis of solitary fibrous tumor.[162] Careful examination of imaging studies with an expert musculoskeletal radiologist is helpful to confirm the presence of an associated well-differentiated component. In my practice, I perform IHC for MDM2 and CDK4 in my last round of stains of pleomorphic tumors of the liver, as a screen to exclude DDLPS.

Finally, desmoplastic small round cell tumor (DSRCT) is a round cell sarcoma with *EWSR1*::*WT1* fusion that commonly presents with widely metastatic disease, including with hepatic involvement in about a third of patients.[163,164] DSRCT has a median age at presentation of around 20 to 25 years, with a striking predilection for men, and it usually shows round cell morphology with characteristic desmoplastic stroma. However, there are occasional examples with more epithelioid morphology,[165] and most DSRCT express keratins, presenting a pitfall

for the misdiagnosis of metastatic carcinoma (see **Table 2**). The most important clue to avoid this pitfall is the clinical context of a highly aggressive malignancy in a young patient. IHC can help avoid this pitfall because DSRCT expresses desmin,[164] a marker that is essentially always negative in carcinoma. The diagnosis can be confirmed by IHC directed against the C-terminus of WT-1, which is retained in the fusion protein.[166]

SUMMARY

Mesenchymal neoplasms of the liver are diagnostically challenging due to their rarity. There are multiple potential diagnostic pitfalls: sarcomas can be mistaken for carcinoma, and metastatic sarcomatoid carcinoma or melanoma can be misdiagnosed as sarcoma. Awareness of the spectrum of diagnostic possibilities and appropriate use of IHC help avoid falling into diagnostic traps.

CLINICS CARE POINTS

- Metastatic sarcomas are more common than primary hepatic sarcomas.
- Metastatic melanoma and metastatic sarcomatoid carcinoma present diagnostic pitfalls for sarcoma.
- In contrast to benign vascular tumor types, hepatic angiosarcoma demonstrates nuclear atypia and endothelial multilayering.
- Epithelioid hemangioendothelioma and hepatic angiosarcoma commonly express keratins and present a pitfall for the misdiagnosis of metastatic carcinoma.

DISCLOSURE

The author reports no conflicts of interest.

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