HEMANGIOMA

Definition

Hemangioma is a benign vascular tumor composed of dilated thin-walled vessels.

Clinical Findings

Hemangiomas are the most common tumor of the adult liver, affecting approximately 5% of all livers. Hemangiomas are more common in young adult women and can enlarge during pregnancy or with estrogen therapy, although a direct causative link with estrogen therapy has been disputed. Hemangiomas are only rarely biopsied because the diagnosis is comfortably made by imaging studies in most cases. However, they can be biopsied when there are atypical imaging findings. Approximately 90% of hemangiomas are single tumors. Pain is the most common symptom, but symptoms are rare unless the tumor is greater than 4 cm.

Histologic Findings

Most hemangiomas are classified as cavernous hemangiomas and are composed of a well-circumscribed but generally unencapsulated aggregate of large caliber and thin-walled vessels. The vessels are supported by a network of fibrous stroma and are lined by flat endothelial cells without atypia or mitotic figures (Fig. 19.1, eFig. 19.1). The vessels are either empty or filled with red blood cells and may have fibrin thrombi. The centers of the lesion can be hemorrhagic or infarcted and have abundant hemosiderin-laden macrophages. In these central areas, the vessels may no longer be apparent and may be replaced by loose myxoid stroma or dense fibrosis (eFig. 19.2). In some cases, central fibrosis will coalesce into a larger central scar that can be seen grossly and on imaging studies. Calcifications may also be present in the fibrotic centers. Hemangiomas have no malignant potential, and some will entirely regress or undergo fibrosis with time.
When cavernous hemangiomas are greater than 8 cm in diameter, they are called giant cavernous hemangiomas. Their histologic findings are similar to that of smaller hemangiomas, but they are more likely (in about 40% of cases) to have an ill-defined border of vascular proliferation in the adjacent parenchyma (eFig. 19.3). This finding is called hemangiomatosis or hemangioma-like vessels and is characterized by small scattered aggregates of dilated and somewhat telangiectatic-appearing vessels that can be smaller in size than those in the main lesion.\(^1\,^2\) Similar findings can be found very focally in smaller hemangiomas also.

A rare variant of liver hemangiomas is the capillary hemangioma,\(^3\) also called a lobular hemangioma at times. Capillary hemangiomas have a modest female predominance and a wide range of reported ages. A possible predilection for Asian ethnicity has also been suggested.\(^4\) This tumor is composed of small thin-walled vessels, often growing in a lobular arrangement (Fig. 19.2). The tumors can be single or rarely multiple. The vascular lumens can be inconspicuous in some areas, leading to a more solid appearance. However, occasional larger caliber vessels can be present both at the periphery and center of the tumor. Some of the large caliber vessels can show myxoid change in their walls. Cytologically, the tumor cells are plump but without atypia or mitotic activity. Extramedullary hematopoiesis may also be present. Immunostains for vascular differentiation, such as CD34 (eFig. 19.4) or ERG can be helpful.

![Hemangioma](image_url)
Definition
Epithelioid hemangioendotheliomas (EHEs) are low-grade malignant vascular tumors composed of epithelioid and dendritic tumor cells embedded in a myxoid or hyalinized stroma.

Clinical Findings
The average age at presentation is 47 years, but the highest tumor incidence is between the ages of 30 and 40 years. There is a slight female predominance. The presenting symptoms are generally mild with vague abdominal pain, although weight loss and jaundice can also be seen. A large proportion of tumors, approximately 40%, are incidental findings.

Histologic Findings
EHEs are multifocal and involve both lobes of the liver in more than 80% of cases. The tumors range in size from subcentimeter to 14 cm. They arise in noncirrhotic livers. However, vascular spread can lead to marked atrophy and regeneration of the liver that can mimic cirrhosis. Microscopically, the tumors are generally of moderate cellularity, but the tumor cellularity can vary from marked to sparse. In all cases, the neoplastic cells are embedded in extracellular matrix. The extracellular matrix is quite distinctive and is often the first clue to the diagnosis. The extracellular matrix is often loose and amphophilic but can also have a more hyalinized and eosinophilic appearance. In general, tumor cellularity tends to be denser.
ADULT BENIGN AND MALIGNANT MESENCHYMAL TUMORS

at the periphery and sparser in the center of the tumor, which can even become densely sclerotic. The sclerotic areas can have calcifications. Some tumors may show areas of necrosis and hemorrhage.

Cytologically, the tumor cells can have an epithelioid appearance with pale eosinophilic cytoplasm (Fig. 19.3, eFig. 19.5). Cells with a dendritic appearance are also seen (the dendritic nature is further enhanced on immunostains). The epithelioid cells are eosinophilic and have moderate amounts of cytoplasm, vacuolated nuclei, and inconspicuous nucleoli. In almost all cases, especially with a large biopsy or full resection, some of the epithelioid cells will have a signet ring cell–like morphology (Fig. 19.4, eFig. 19.6), occasionally with red blood cells in the lumen. The signet ring–like cells are mucicarmine-negative. Mitotic figures tend to be absent or rare. In some cases, focal areas of better formed vessels may be present (eFig. 19.7).

EHEs typically have an infiltrative growth pattern and can grow along the sinusoids, causing atrophy or dropout of the hepatocytes. Entrapped portal tracts are common at the periphery. The portal veins and the central veins are often involved by tumor. The most common pattern of vascular involvement is fibro-obliteration of the veins, with tumor cells within a fibrotic matrix (Fig. 19.5). However, the tumor can also grow as small polypoid nodules of tumor cells within an otherwise non-obliterative vascular lumen. Hepatic arteries can also be involved, but this is less common. The tumor will involve the liver capsule in about half of cases. Most tumors will have minimal to mild inflammation. The inflammation is most commonly lymphocytic but rarely can be neutrophil-rich. In a few cases, there can be marked inflammation. Of the various histologic findings, marked tumor cellularity has the strongest predictive ability.
for aggressive behavior, but all EHEs are malignant and have the potential for aggressive behavior.

A large series of cases from the Armed Forces Institute of Pathology (AFIP) noted that a very high proportion of EHE were submitted with a wrong preliminary diagnosis. The most common misdiagnosis was cholangiocarcinoma, presumably because the tumors can have signet ring–type

FIGURE 19.4 Epithelioid hemangioendothelioma, signet ring cells. Some of the epithelioid cells have a signet ring cell morphology.

FIGURE 19.5 Epithelioid hemangioendothelioma, venous involvement. The central vein has been infiltrated and obliterated by the tumor.
cells and abundant extracellular matrix. Other common misdiagnoses were angiosarcoma and other carcinomas, including both hepatocellular carcinoma and metastatic carcinomas. Overall, the distinctive extracellular matrix and the distinctive cell types (dendritic, signet ring–like) will provide strong clues to the diagnosis in essentially all cases, a diagnosis which can then be confirmed by immunostains.

**Immunostains**

Immunostains are helpful in confirming the hematoxylin and eosin (H&E) impression. Reported rates of positivity in the largest series to date are as follows: factor VIII (99%), CD34 (94%), CD31 (86%), and factor XIIIa (100%, but only six cases were stained). Smooth muscle actin is positive in 26% and cytokeratin AE1/3 in 14%. Also of note, CD10 is positive in most EHEs, which can sometimes be confusing if the biopsy is small and the distinctive H&E findings not well represented. In general, the epithelioid areas stain better with vascular markers than the dendritic areas.

ERG is a recently reported immunostain that is a very sensitive marker for endothelial differentiation. ERG was positive in 42 out of 43 EHEs. ERG also stains about 30% to 50% of prostate cancers, a subset of meningiomas, and rare Ewing sarcomas and mesotheliomas. Blastic extramedullary myeloid tumors are also ERG-positive in most cases. However, when combined with morphology and other stains, ERG is a very useful stain for identifying vascular differentiation.

**ANGIOSARCOMA**

**Definition**

Angiosarcoma is a high-grade malignant vascular tumor that can have a variety of growth patterns.

**Clinical Findings**

Angiosarcomas of the liver can be a challenge on liver biopsy because they are rare and because they often mimic other tumors. Angiosarcomas can be primary to the liver or metastatic. Recognized risk factors for primary angiosarcomas include arsenic (found in the groundwater in some parts of the world), androgen therapy, Thorotrast, and vinyl chloride exposure. However, no cause is identified in 70% of cases. Most affected individuals are older men. The prognosis is dismal with few individuals surviving more than 6 months.

**Histologic Findings**

Angiosarcoma can be a single mass or multiple tumors. The background liver findings can show chronic inflammation or fatty change, and fibrosis can range from none to cirrhosis. Histologically, angiosarcomas can grow as clearly vascular tumors with irregular blood vessels (eFig. 19.8) or as solid
epithelioid tumors that mimic carcinomas or spindle cell tumors that mimic other sarcomas (Fig. 19.6, eFig. 19.9). An important histologic clue can be the presence of rare small slit-like spaces with red blood cells. The tumor cells typically show significant atypia and numerous mitotic figures. In some cases, the solid areas can undergo necrosis and cavitation, leaving only a rim of malignant cells surrounding a cavity filled with blood, fibrin, and necrotic debris.

As another important but subtle growth pattern, some angiosarcomas extend along the sinusoids, replacing the normal benign sinusoidal endothelial cells but leaving the hepatic plates relatively intact (Fig. 19.7, eFig. 19.10). This pattern can be diagnostically challenging on biopsy, depending on the amount of sampled tumor. A Ki-67 can be helpful in demonstrating a very high proliferate rate (eFig. 19.11). The sinusoidal growth pattern is almost always present in some part of the tumor with fully resected specimens, but the growth patterns can vary considerably on biopsy specimens. Finally, some angiosarcomas with a sinusoidal infiltrative growth pattern can cause complete or near complete loss of hepatocytes and the biopsy may show parenchymal collapse and proliferating bile ducts. The atypical endothelial cells of the angiosarcoma can be easily overlooked (Fig. 19.8, eFig. 19.12) on H&E and often require immunostain to bring them out (eFig. 19.13).

**Immunostains**

Immunostains should be used to confirm the diagnosis. Although most of the published data are from angiosarcomas in soft tissues and not specifically from angiosarcomas of the liver, the data is still informative. Endothelial differentiation can be demonstrated by immunostains for factor VIII (positive in 80% to 90% of cases), CD34 (75%), and CD31 (30%). As noted in the section on EHEs, ERG is a new and sensitive immunostain
FIGURE 19.7  **Angiosarcoma, sinusoidal pattern.** This angiosarcoma shows atypical cells growing along sinusoids, with intact hepatic plates. A Ki–67 on this case shows a very high proliferative rate (eFig. 19.11).

FIGURE 19.8  **Angiosarcoma.** This subtle angiosarcoma has led to substantial collapse of the hepatic parenchyma. Residual bile ducts can be seen. A factor 8 immunostain highlights the tumor cells (eFig. 19.13).
for vascular differentiation that can be helpful when evaluating a case for possible angiosarcoma.

Aberrant cytokeratin AE1/3 positivity can be seen in about 45% of angiosarcomas and CAM5.2 in 30% of cases, so be aware of this important diagnostic pitfall.

ANGIOMYOLIPOMA

Definition

Angiomyolipoma is a benign mesenchymal tumor composed of myoid cells, typically admixed with fat and large irregular vessels.

Clinical Findings

Most angiomyolipomas of the liver (90%) are sporadic and not part of the tuberous sclerosis complex. In most cases (90%), a single tumor is present, but rare multifocal cases have been reported. The average age is 49 years, and there is a strong female predilection. The background liver is typically nondiseased and not fibrotic. They can be diagnostically challenging, with some authors indicating that a full half of cases are initially misdiagnosed.

Histologic Findings

Angiomyolipomas are composed of admixed tumor cells showing fatty change, smooth muscle or “myoid” differentiation, and large thick-walled vessels (Fig. 19.9). The myoid component can be composed of spindle (Fig. 19.10) or epithelioid cells (Fig. 19.11). The proportion of each component can vary considerably. A subset of tumors is composed mostly

![FIGURE 19.9 Angiomyolipoma. This image shows the fat, myoid cells, and large irregular vessels. Many biopsies of angiomyolipomas will sample only some of these three elements.](image-url)
FIGURE 19.10  Angiomyolipoma, spindle growth pattern. This growth pattern can mimic metastatic gastrointestinal stromal tumors and other spindle cell tumors.

of fat. These fatty angiomyolipomas can closely mimic lipomas or liposarcomas.\textsuperscript{10,11} In fat-predominant tumors, the best place to find myoid components to help make the diagnosis are around thick-walled vessels. Other angiomyolipomas are composed mostly of spindled myoid cells and can mimic smooth muscle tumors.\textsuperscript{12} In yet another subset, the epithelioid myoid cells are predominant. This variant can closely mimic hepatocellular

FIGURE 19.11  Angiomyolipoma, epithelioid. The myoid cells in this angiomyolipoma are epithelioid and can closely mimic hepatocellular carcinoma.
carcinoma, with tumor cells showing abundant eosinophilic cytoplasm and moderate nuclear atypia. They can even have a trabecular growth pattern that closely mimics hepatocellular carcinoma. In some cases, tumor pigment can provide a clue to the diagnosis (Fig. 19.12). In other epithelioid variants, the cytoplasm will have a clear appearance and engender the differential for clear cell tumors. In fully resected specimens, at least minor components of all elements (fatty, myoid, epithelioid) are commonly seen, but in biopsy specimens, one morphologic growth pattern can predominate, so a high index of suspicion is helpful.

Other histologic findings include extramedullary hematopoiesis, which can be seen in small amounts in about half of resected specimens and is most commonly seen in cases with lots of fat. In cases with abundant fat, lipoblast-like cells with multivacuolated cytoplasm and indented nuclei can be seen. Hemorrhage, necrosis, and cholesterol clefts are present in a small proportion of cases. In rare cases, the tumors can show striking peliotic changes, often associated with hemorrhage, and can mimic a telangiectatic adenoma (Fig. 19.13). Also of note, a subset of cases can have markedly inflamed areas that closely mimic inflammatory pseudotumors of the liver. Finally, about 10% of cases may have focal areas of striking giant cell change in the myoid areas, with large, pleomorphic, and sometimes multinucleated epithelioid cells (eFig. 19.14). Cases with similar atypia in the spindle cell component have also been reported. This atypia does not indicate malignancy.

The vast majority of angiomyolipomas are benign, but rare cases can be malignant. Features that indicate malignancy include vascular invasion.
or aggressive behavior such as metastases. As noted earlier, cytologic atypia alone does not indicate malignancy. Some studies have suggested that coagulative necrosis, loss of CD117 immunostaining, marked cytologic atypia with increased mitoses, or P53 immunohistochemical positivity may be markers for more aggressive behavior, but the overall rarity of malignancy makes it difficult to develop well-defined histologic factors that predict aggressive behavior. For example, others have subsequently reported P53 positivity in epithelioid angiomyolipomas that were not overtly malignant. On the other hand, late tumor metastasis has also been reported from an angiomyolipoma that was histologically benign.

Immunostains

Angiomyolipomas are negative for cytokeratins and for hepatocyte paraffin 1 (Hep-Par1). HMB-45 is the most important positive stain, and all cases should be positive (eFig. 19.15). Of note, HMB-45 staining can be patchy, especially in fatty areas, a finding that must be taken into consideration on biopsy specimens. The myoid component will typically have strong granular cytoplasmic staining. Melan A is positive in 90% of cases. Smooth muscle actin is positive in most cases, although the literature indicates a wide range of positivity, from as low as 50% to as high as 100% of cases. In general, the spindle cell areas stain best for smooth muscle actin. CKIT (CD117) is also positive in nearly all cases, so make sure to distinguish from a metastatic gastrointestinal stromal tumor (GIST). Also of note, S100 stains are positive in most of the fatty areas and about half of the myoid areas. Angiomyolipomas are also CD68-positive (eFig. 19.16).
This can be important to know because epithelioid angiomyolipomas can sometimes mimic fibrolamellar carcinomas on small biopsies. Both can have abundant oncocytic cytoplasm and both are also CD68-positive, which can be a diagnostic pitfall. HMB-45 will be positive in angiomyolipomas but not fibrolamellar carcinomas, whereas Hep-Par1 and CK7 will be positive in fibrolamellar carcinomas but not angiomyolipomas.

**SOLITARY FIBROUS TUMOR**

**Definition**

Solitary fibrous tumor (SFT) is a benign spindle cell tumor of uncertain origin.

**Clinical Findings**

SFTs can present at a wide range of ages, but most cases occur in females older than the age of 40 years. A rare presentation of this rare tumor is hypoglycemia due to overproduction of insulin-like growth factor. Despite the term solitary in the name of the entity, rare cases can be multifocal. Most SFTs are intraparenchymal with only a small subset directly associated with the liver capsule.

**Histologic Findings**

The tumors generally show low cellularity with tumor cells embedded in a fibrous stroma (Fig. 19.14, eFig. 19.17). The stroma and cells are

![FIGURE 19.14 Solitary fibrous tumor. An SFT shows scattered small spindle cells with dense fibrosis growing in a “pattern-less pattern.”](image-url)
generally without a distinct pattern, a finding termed *patternless pattern*. Of note, some areas of SFT can become sclerosed, whereas other areas can have myxoid change. Most SFTs are benign, but approximately 10% of cases can have changes that suggest a more aggressive tumor, including increased mitoses, necrosis, and cytologic atypia. In some cases, the SFT can transform into a frank high-grade fibrosarcoma.  

A small subset of cases are multifocal within the liver and can grow around and entrap portal tracts, leading to secondary biliary cysts (Fig. 19.15). These cases also have small clusters of proliferating bile ducts at the periphery of the lesion, which may demonstrate pancreatic or hepatic metaplasia (eFig. 19.18).

**Immunostains**

The H&E impression of SFT can be confirmed by immunostains for BCL-2 (eFig. 19.19) and CD34 (eFig. 19.20). The tumors will also be vimentin-positive but should be negative for S100, desmin, CKIT (CD117), smooth muscle actin, and cytokeratins.

**SEGMENTAL ATROPHY OF THE LIVER AND NODULAR ELASTOSIS**

**Definition**

Segmental atrophy of the liver is a benign pseudotumor of the liver associated with varying degrees of parenchymal loss and replacement by elastosis and fibrosis.
Clinical Findings

These mass lesions are most commonly subcapsular and have a modest female predominance. The most common presentation is nonspecific right upper quadrant abdominal pain. They range in size from 1 to 10 cm.

Histologic Findings

The histologic findings of this pseudotumor evolve over time, and the findings in a specific case will depend on the relative age of the lesion. Early lesions demonstrate parenchymal collapse with marked bile ductular proliferation and mixed inflammation. With time, the inflammation and ductular proliferation abates and there is increasing amounts of elastosis in areas of parenchymal loss (Fig. 19.16, eFig. 19.21). Biliary cysts are also common at this stage and can sometimes dominate the histologic findings, especially if they rupture, because this can induce an intense inflammatory response. The biliary cysts appear to be retention-type cysts that develop out of entrapped bile ducts. In time, the amount of elastosis will increase and will come to dominate the histologic findings, a stage called nodular elastosis. In the nodular elastosis stage, small islands of residual and normal-appearing hepatocytes are common (Fig. 19.17). The elastosis (eFig. 19.22) will strain strongly with elastic stains, and reticulin stains will highlight abundant reticulin fibers. The elastosis often involves the liver capsule (eFig. 19.23). At high power, there will be scattered spindle cells in the matrix without atypia or mitoses (Fig. 19.18). These cells will stain with vimentin, which will also highlight dendritic

FIGURE 19.16 Segmental atrophy pseudotumor. This subcapsular mass lesion shows parenchymal collapse with mild chronic inflammation and patchy ductular proliferation. Early elastotic changes can be seen.
type extensions (eFig. 19.24). Eventually, fibrosis will increase and can ultimately lead to distinctive nodular scars (eFig. 19.25). Occasional small calcifications may be present (eFig. 19.26). Thrombosed and fibrotic vessels are commonly found (eFig. 19.27), suggesting a possible vascular injury as the etiology.

**FIGURE 19.17** Nodular elastosis. Scattered islands of residual hepatocytes are embedded in a dense extracellular matrix composed of elastic fibers and reticulin fibers.

**FIGURE 19.18** Nodular elastosis. At high power, the spindled cells within the extracellular matrix have no atypia or mitotic activity. On vimentin stain, the cells have a dendritic morphology (eFig. 19.24).
Occasionally, small foci of elastosis can be seen as isolated finding on liver biopsies and are not associated with mass lesions (eFig. 19.28). These small foci are often located in close proximity to the central vein. They are rare, and their clinical significance, if any, remains unclear.

**INFLAMMATORY PSEUDOTUMOR**

**Definition**

Inflammatory pseudotumor is a benign reactive pseudotumor composed of varying degrees of fibrosis and plasma cell–rich chronic inflammation.

**Clinical Findings**

Inflammatory pseudotumors of the liver have generated more than their fair share of the literature, with several hundred case reports. There is about a 2:1 male predominance, and the average age is 50 years. They have been linked to just about everything that can happen in the liver, from tumors to infection to chronic liver disease (especially biliary tract disease) to associations with systemic autoimmune conditions. Whether there are any morphologic differences between the different etiologic associations is not clear. Serum CA19-9 levels can be elevated. Some cases will spontaneously regress or regress on antibiotic therapy.

**Histologic Findings**

Inflammatory pseudotumors can be single lesions (approximately two-thirds of cases) or multiple lesions (approximately one-third of cases). The single lesions tend to be larger than the multifocal lesions. Overall, inflammatory pseudotumors are more common in noncirrhotic livers than in cirrhotic livers. In general, they are composed of admixed fibroblasts and inflammatory cells with varying amounts of collagen (Fig. 19.19). The collagen can be dense and have whorled appearance in some cases (eFig. 19.29). There should be no atypia in the spindle cells, and mitoses are absent to very rare. The inflammation is rich in plasma cells and T cells. B cells are generally localized to lymphoid aggregates or germinal centers. Occlusive phlebitis is commonly seen in resected specimens (Fig. 19.20) and may be sampled on biopsies. The phlebitis tends to involve medium- to large-sized portal veins and is more commonly seen in single lesions. Multifocal lesions are more commonly seen in the setting of chronic biliary tract disease.

There are many entities that can mimic an inflammatory pseudotumor, so make this diagnosis with special care. The spindled cells in inflammatory pseudotumors are vimentin-positive and often smooth muscle actin–positive. They can also show patchy cytokeratin staining. Anaplastic lymphoma kinase (ALK) staining is negative in almost all cases, with only very rare positive cases reported in the liver. When ALK is positive, the lesion is typically called an inflammatory myofibroblastic tumor, although these terms are not used consistently in the literature.
Inflammatory pseudotumors are composed of plasma cell–rich chronic inflammatory infiltrates with varying amounts of fibrosis. Many other tumors can have areas that mimic inflammatory pseudotumor so make this diagnosis carefully.

**Differential**

Several tumors can closely mimic inflammatory pseudotumors, including lymphoma and dendritic cell sarcomas. Other tumors can have areas that closely resemble inflammatory pseudotumors, including angiomyolipomas and liposarcomas. Also of note, inflammatory pseudotumors...
BIOPSY INTERPRETATION OF THE LIVER

can be rarely associated with carcinomas, including cholangiocarcinomas or other tumors that obstruct the common bile duct, with subsequent infectious cholangitis and inflammatory pseudotumor formation. Thus, after a diagnosis of an inflammatory pseudotumor is made, the patient should be further worked up for other disease processes including neoplasms and biliary tract lesions.

OTHER MESENCHYMAL TUMORS

Other rare mesenchymal tumors of the liver include lipomas, liposarcomas, and leiomyomas. In general, their histologic and immunostain findings are similar to that of tumors from other sites, so will not be discussed further here.

REFERENCES