Benign Vascular Tumors

2

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Abstract

Benign vascular lesions in the adult liver include cavernous hemangiomas, capillary hemangiomas, anastomosing hemangiomas, and lymphangiomas. In addition, non-neoplastic lesions can mimic vascular tumors, including hereditary hemorrhagic telangiectasia and peliosis hepatis. The clinical findings, morphology, and differential of these tumors are discussed and illustrated.

Keywords

Cavernous hemangioma • Capillary hemangioma • Anastomosing hemangioma • Capillary hemangioma • Infantile hemangioma • Lymphangioma • Peliosis hepatis • Hereditary hemorrhagic telangiectasia • Angiosarcoma

2.1 Overview

The benign vascular lesions seen in the adult liver include tumors such as cavernous hemangioma and the less frequent anastomosing hemangioma and lymphangioma. Non-neoplastic lesions include hereditary hemorrhagic telangiectasia and peliosis hepatis.

The vast majority of the benign vascular tumors of the adult liver are cavernous hemangiomas, which can be readily diagnosed by imaging and histology in most cases. However, the less common tumors, such as capillary hemangiomas, anastomosing hemangioma, and infantile hemangiomas occurring in adults, are more challenging to diagnose due to their rarity and overlapping histological findings. In addition, some of these vascular tumors can have more than one growth pattern. These entities are described in detail below, but a useful tabulation of findings is shown in Table 2.1. The following general guidelines can also be useful. First, tumors are classified on the predominant pattern. For example, some cavernous hemangiomas can have focal areas, often at the tumor–liver interface, with smaller capillary-sized vessels. As another example, some anastomosing hemangiomas will have

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Table 2.1 Key findings in benign vascular tumors of the liver

Finding	Cavernous hemangioma	Infantile hemangioma	Anastomosing hemangioma	Capillary hemangioma
Predominant vessel size	Large	Intermediate to small	Small	Small
Anastomosing channels	–	–/+	+	–
Hobnail endothelial cells	–	–	+	–
Plump endothelial cells	–	–/+	–	+
Cytological atypia	–	–	+	–
Lobular pattern of growth	–	–	–	+
Glut 1 staining[a]	Anticipated to be negative	Anticipated to be positive	Anticipated to be negative	Anticipated to be negative

[a]There is very little published data. Glut 1 staining is positive in infantile hemangiomas, but has not been well-studied in adult vascular tumors; in our experience they are routinely negative

focal areas identical to typical cavernous hemangiomas. Second, the size of the vessels is a major classification break point. If the majority of the vessels are large caliber, the lesion is classified as a cavernous hemangioma. If the vessels are small caliber, then the differential includes capillary hemangioma or anastomosing hemangioma. Infantile hemangiomas tend to have vessels that are in between in size. Finally, the morphology of the cells (plump versus hobnail) and the presence or absence of anastomosing vessels will help decide on capillary versus anastomosing hemangiomas.

2.2 Cavernous Hemangioma

2.2.1 Definition

A cavernous hemangioma is a benign vascular tumor with proliferation of dilated, thin-walled vessels.

2.2.2 Clinical Features

Cavernous hemangiomas are the most common benign tumor of the liver and occur in approximately 5 % of all livers. Cavernous hemangiomas occur at all ages, but are most common in young adult women, between the ages of 30 and 50. The tumors can enlarge during pregnancy, or with use of estrogen, but the question of whether or not estrogen is a causal agent for cavernous hemangiomas is unsettled [1–3]. Cavernous hemangiomas are usually diagnosed by imaging studies and biopsies are rarely performed, unless there are atypical imaging findings.

Most patients are asymptomatic, though tumors greater than 4 cm are more likely to present with pain. One study reported that 50 % of individuals with hemangiomas presented with abdominal pain, but in most cases the pain at presentation was related to other diseases, such as irritable bowel syndrome, and not to the hemangioma [4]. Rare cases can also present with a consumptive coagulopathy, called Kasabach-Merritt syndrome [5]. A case has also been reported with high serum AFP levels, which returned to normal after resection of a cavernous hemangioma [6]. The cells producing the AFP were presumably reactive hepatocytes near the edge of the tumor.

Hemangiomas have rarely been reported in association with other liver pathology, including angiomyolipomas [7], adult polycystic liver disease [8], and Dubin-Johnson syndrome [9]. At this point, these appear to be chance co-occurrences.

2.2.3 Gross Findings

Most (approximately 90 %) of cavernous hemangiomas are single tumors, but in some cases there can be numerous tumors (diffuse hemangiomatosis) [10]. The tumors are well-circumscribed and typically non-encapsulated, with a red brown

Fig. 2.1 Cavernous hemangioma. A subcapsular, well-circumscribed, dark brown-red colored cavernous hemangioma was incidentally identified on liver explant

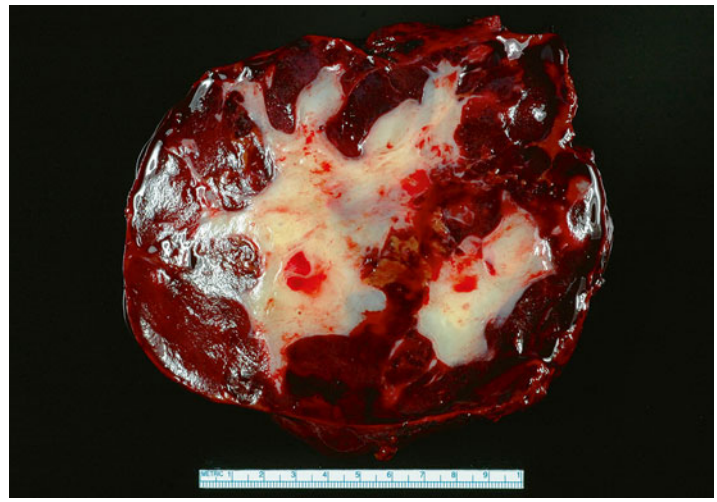

Fig. 2.2 Sclerosing cavernous hemangioma. A large cavernous hemangioma with a central whitish fibrotic area

color and honeycombed appearance. They often have a sponge-like consistency that makes them distinct from adjacent liver parenchyma (Fig. 2.1). Foci of thrombi, fibrosis, and calcification can be noted, especially in larger tumors. In some cases, the hemangioma extends from the surface as a pedunculated mass [11].

Some tumors show extensive fibrosis, in which case the vascular nature of the lesion may be less clear. In these cases, the fibrosis typically is more pronounced in the center of the tumor (Fig. 2.2) and in advanced cases, may involve the entire tumor, leading to a firm gray-white sclerotic tumor, called a sclerosed hemangioma (Fig. 2.3) [12].

2.2.4 Microscopic Findings

The tumors are composed of a proliferation of large caliber and thin-walled vessels, often filled with red blood cells, within a background of loose fibrous stroma (Fig. 2.4). The vessels are typically lined by flat endothelial cells without atypia or mitoses. Fibrin thrombi and infarction with hemorrhage and hemosiderin-laden histiocytes can also be seen within the tumor (Fig. 2.5). Cavernous hemangiomas have no malignant potential and many will regress with fibrosis over time. In some partially regressed tumors, the vascular proliferation is less apparent and large portions are replaced by myxoid or fibrous tissue, sometimes with focal

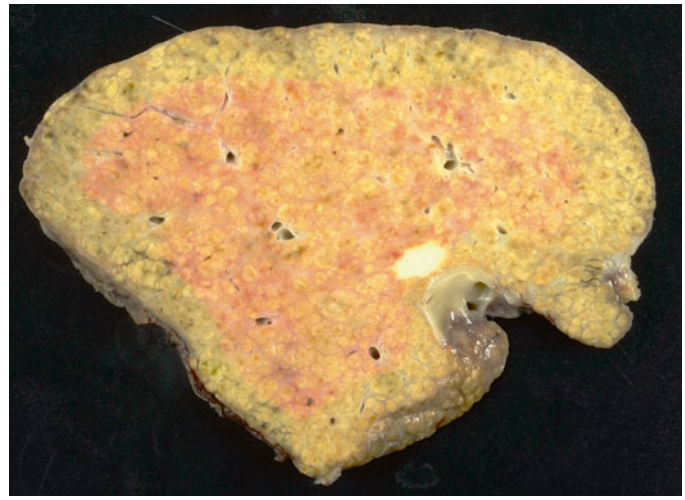

Fig. 2.3 Sclerosed cavernous hemangioma. Only a *white*, round scar remains

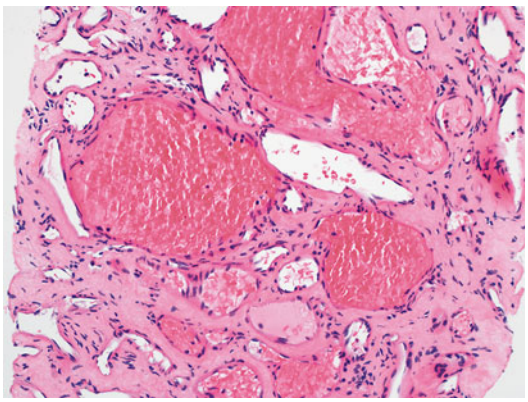

Fig. 2.4 Cavernous hemangioma. Cavernous hemangioma composed of a proliferation of thin-walled and large caliber vessels filled with red blood cells

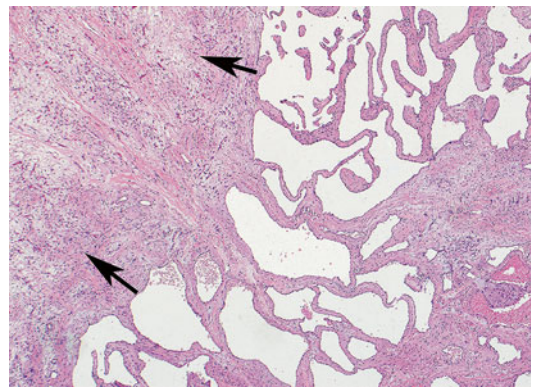

Fig. 2.6 Sclerosing cavernous hemangioma. The hemangioma is partially replaced by myxoid and fibrotic stroma (*arrows*)

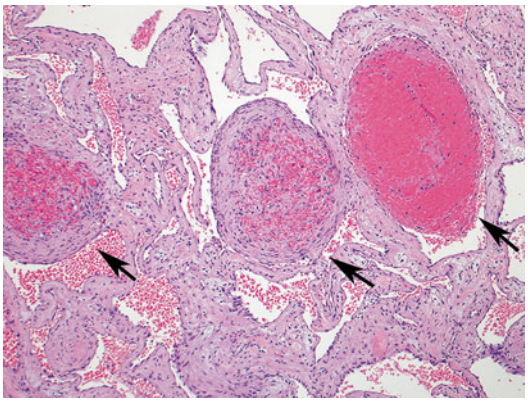

Fig. 2.5 Cavernous hemangioma. The vascular spaces are lined by a single layer of flat endothelial cells without cytological atypia. Fibrin thrombi (*arrows*) can occur within the vascular channels

calcification. In many of these cases, the fibrotic areas coalescence into a central scar (Fig. 2.6). These tumors are often referred to as sclerosing hemangiomas. In one study, there was a modest enrichment for male gender in cases of sclerosing hemangioma [12]. The fibrosis can involve the entire lesion, in which case the term sclerosed hemangioma can be used (Fig. 2.7). Sclerosed hemangiomas typically retain, at least focally, residual hemangioma vessels that allow identification of the tumor [13, 14].

Giant cavernous hemangiomas are defined somewhat variably, but common definitions include size greater than 4 cm or 5 cm [4, 15–17]. Overall, giant cavernous hemangiomas have similar histologic features to smaller cavernous

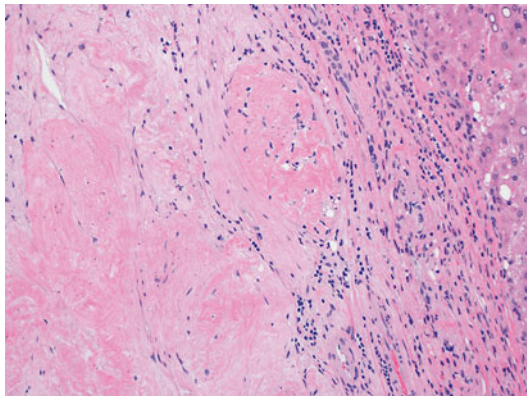

Fig. 2.7 Sclerosed hemangioma. The entire lesion is sclerotic, but vague outlines of vascular channels are apparent

hemangiomas. In approximately 40 % of cases, giant cavernous hemangiomas can have ill-defined borders, with a vascular proliferation that is composed of small aggregates of dilated, telangiectatic, and somewhat smaller-sized vessels as compared to the main tumor. This finding has been called "hemangiomatosis" (Fig. 2.8) [18, 19]. This finding is not unique to large hemangiomas and can also be focally seen at the edges of small cavernous hemangiomas.

2.2.5 Immunohistochemical Features

A variety of immunohistochemical markers can be used to confirm the presence of endothelial cell proliferation, including CD34, CD31, FLI-1, and ERG.

2.2.6 Differential Diagnosis

Lymphangioma, peliosis hepatis, and hereditary hemorrhagic telangiectasia can mimic cavernous hemangioma. In lymphangioma, the vascular proliferation contains lymph, versus red blood cells in cavernous hemangioma. In addition, lymphangiomas are positive for D2-40 by immunohistochemistry. Peliosis hepatis is characterized by cystic blood-filled spaces without endothelial lining. Hereditary hemorrhagic telangiectasia has distinct histologic features, with inter-anastomosing portal-based vessels and is discussed in more detail in a separate section below.

2.3 Capillary Hemangioma

2.3.1 Definition

A rare variant of benign hemangioma composed of capillary-sized vessels [20]. There has been some debate whether hepatic capillary hemangiomas exit as unique entities, as the "hemangiomatosis" areas at the edges of some cavernous hemangiomas can also have small caliber vessels. However, there are fully resected lesions that appear to be best classified as capillary hemangiomas.

2.3.2 Clinical Features

Capillary hemangiomas occur more commonly in middle-aged females and have been predominantly reported in East Asia [20–22].

2.3.3 Gross Findings

Capillary hemangiomas can occur as single or multiple tumors. The tumors are well-circumscribed and can be surrounded by a fibrous capsule.

2.3.4 Microscopic Findings

The tumors are composed of small caliber capillary-sized vessels and the vascular channels are lined by plump endothelial cells without atypia or mitotic activity (Fig. 2.9). The plump cells can sometimes obscure the vascular lumens, and immunostains can be helpful to confirm the vascular nature of the tumor. Foci of extramedullary hematopoiesis can also be present.

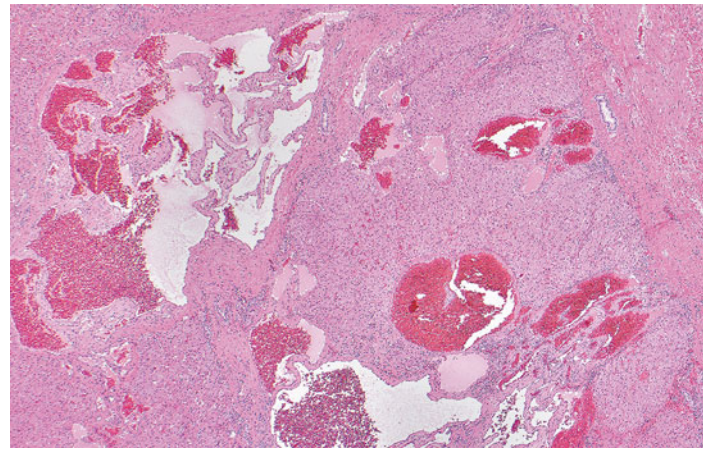

Fig. 2.8 Hemangiomatosis. A small ill-defined vascular proliferation with telangiectatic vessels is present in the liver parenchyma adjacent to a giant cavernous hemangioma

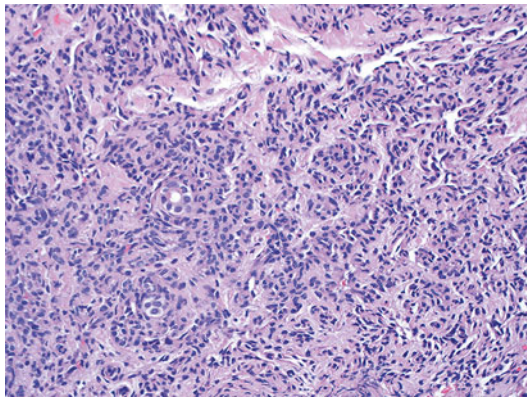

Fig. 2.9 Capillary hemangioma. The tumor is composed of capillary-sized vessels lined by plump endothelial cells. No endothelial cell atypia is present

2.4 Anastomosing Hemangioma

2.4.1 Definition

Benign hemangioma composed of a proliferation of anastomosing, capillary-sized vessels.

2.4.2 Clinical Features

Anastomosing hemangioma is a newly described variant of hemangioma and occurs primarily in the genitourinary tract and adrenal glands [23], but can also be found in the liver. Hepatic anastomosing hemangiomas have been reported to-date in adults, more commonly in women than men [24]. Most cases are incidental findings identified during workup for other processes such as malignancy, back pain, or during abdominal surgery for other causes.

2.4.3 Gross Findings

Hepatic anastomosing hemangiomas present as single tumor ranging from 2 to 6 cm in size. The tumors are grossly well-demarcated with a gray-brown color and spongy appearance.

2.4.4 Microscopic Findings

The tumor is composed of anastomosing capillary-sized vessels with mild cytological atypia and hobnail-appearing endothelial cells, with scant supporting stroma (Figs. 2.10 and 2.11). No mitotic activity is present. Vascular thrombi, extra-medullary hematopoiesis, and hyaline globules can be present. In a subset of cases, a component of more typical cavernous hemangioma can also be present.

2.4.5 Immunohistochemical Findings

The panel of immunohistochemical stains (CD34, CD31, FLI-1, and ERG) used for diagnosing cavernous hemangiomas can also be used for anastomosing hemangiomas (Fig. 2.12).

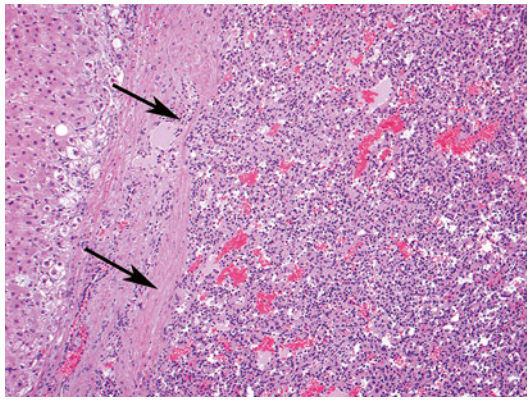

Fig. 2.10 Anastomosing hemangioma. A vascular tumor (*arrows*) with proliferation of anastomosing capillary-sized vessels

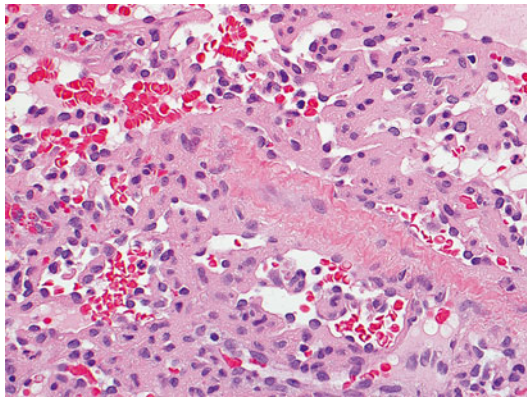

Fig. 2.11 Anastomosing hemangioma. The endothelial cells have a hobnail appearance and mild cytological atypia, but no mitotic activity

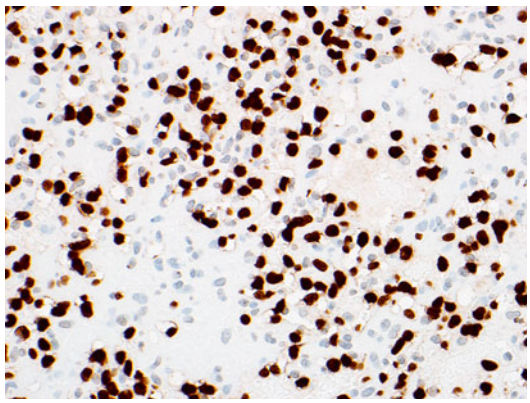

Fig. 2.12 ERG immunostain. This anastomosing hemangioma is strongly ERG-positive

2.4.6 Differential Diagnosis

The main differential diagnosis for anastomosing hemangiomas is angiosarcoma, due to the anastomosing growth pattern and the mild cytological atypia. However, the lack of marked atypia, the low proliferative rate, and the distinctive hob nail cells can assist in identifying this rare variant of hepatic hemangioma and avoid a misdiagnosis of angiosarcoma.

2.5 Infantile Hemangioma in Adults

Infantile hemangiomas are discussed in more detail in Chap. 13. The vast majority of cases occur in infants and young children, but rare cases have been reported in adults [25]. They should be diagnosed in the same way as in infants and children.

2.6 Lymphangioma

2.6.1 Definition

A benign vascular lesion composed of variable-sized spaces lined by endothelial cells and containing lymph.

2.6.2 Clinical Features

Hepatic lymphangiomas are commonly associated with systemic lymphangiomatosis, with lesions present in various organs including the spleen, skeleton, and various other organ sites. Isolated hepatic lymphangiomas are rare [26, 27]. Lymphangiomas occur in all ages, but hepatic lymphangiomas associated with systemic lymphangiomatosis typically occur in children and young adults. Clinical symptoms depend on the organ sites involved and the hepatic symptoms include hepatosplenomegaly, ascites, and liver failure.

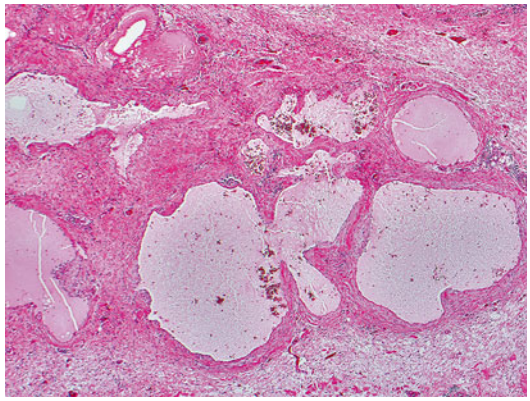

Fig. 2.13 Lymphangioma. The tumor is composed of large cystic spaces lined by endothelial cells and filled with lymph within a background of fibromyoxid stroma

2.6.3 Gross Findings

Hepatic lymphangiomas typically present as multiple variable-sized whitish, cystic lesions containing clear or chylous fluid. Single hepatic lymphangiomas can occur but are less frequent.

2.6.4 Microscopic Findings

The tumor is composed of variable-sized cystic spaces containing clear lymph fluid and lined by a single layer of endothelial cells (Fig. 2.13). The endothelial lining can show a papillary architecture in some cases.

2.6.5 Immunohistochemical Features

Immunohistochemical stains such as CD34, CD31, Factor VIII, and D2-40 can be used to highlight the proliferation of lymphatic channels.

2.6.6 Differential Diagnosis

A proliferation of lymphatic channels can be seen in mesenchymal hamartomas and has also been reported in post-traumatic injury of the bile ducts. Mesenchymal hamartoma can be distinguished from lymphangioma by the presence of other components such as bile ducts, hepatic parenchyma, and loose mesenchyme. Cavernous hemangiomas contain red blood cells, not lymph, though an occasional red blood cell may be seen in lymphangioma.

2.7 Peliosis Hepatis

2.7.1 Definition

Liver parenchyma with varied-sized cystic spaces or cavities, containing blood, but not lined by endothelial cells.

2.7.2 Clinical Features

Peliosis hepatis was initially described in patients with chronic debilitation disorders, such as cancer and tuberculosis, but most cases of peliosis hepatis encountered today are associated with anabolic steroid therapy use for hematologic diseases and malignant tumors [28, 29]. Oral contraceptives and a variety of drugs including azathioprine, tamoxifen, vitamin A, danzol, arsenic, Thorotrast, and vinyl chloride have all been associated with peliosis hepatis. Other associations include bacterial endocarditis and AIDS. Peliosis hepatis can affect all ages and both men and women. Peliosis hepatis usually has no direct clinical significance, with no effect on hepatic synthetic function or on portal blood pressure, but rarely larger lesions can rupture after trauma.

2.7.3 Gross Findings

The lesions have a dusky, purple color on cut surface and vary in size from 1 mm to several cm, with rounded cysts-like spaces. The lesions often involve large portions of the liver, but focal peliosis hepatis can also occur.

2.7.4 Microscopic Findings

The liver parenchyma is dissected by blood filled cavities. The cavities have irregular contours and

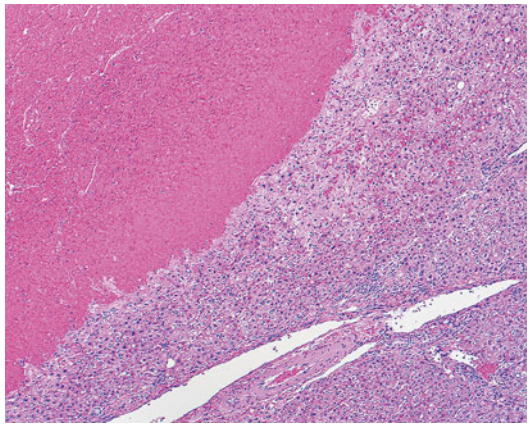

Fig. 2.14 Peliosis hepatis. Irregular contoured cavity containing red blood cells within the liver parenchyma. The cavity has no endothelial lining

are bordered by compressed hepatocytes, with no endothelial lining (Fig. 2.14). Fibrin and thrombi can be present within the cavity and communication between cavity and surrounding sinusoids can occur. The surrounding liver parenchyma retains an intact and normal sinusoidal framework by reticulum staining. In AIDS and immunocompromised patients, hepatic peliotic lesions can be caused by infection with Bartonella species, which can be identified by Warthin-Starry stain, and is also called "bacillary peliosis" [29].

2.7.5 Pathogenesis

In humans, the pathogenesis of peliosis hepatis is unknown, but most likely results from endothelial cell damage, with secondary cyst formation. In animal models, peliosis hepatis can be caused by phalloidin administration, which damages the sinusoidal walls.

2.7.6 Differential Diagnosis

Similar appearing peliotic lesions can also occur within various hepatocellular neoplasms, including hepatocellular carcinoma, hepatic adenoma, and angiosarcoma. Marked sinusoidal dilatation can sometimes mimic peliosis hepatis, but the sinusoidal dilation does not have well-defined cavity formation and it is lined by endothelial cells.

2.8 Hereditary Hemorrhagic Telangiectasia (Osler–Weber–Rendu Syndrome)

2.8.1 Definition

An autosomal dominant disorder characterized by telangiectatic vascular malformations involving a variety of organs, including the nose, oral cavity, lung, brain, gastrointestinal tract, and liver.

2.8.2 Etiology

Hereditary hemorrhagic telangiectasia is caused by abnormalities involving the TGFβ signaling pathway [30]. Three hereditary hemorrhagic telangiectasia genes have been identified. Mutations in the genes encoding Endoglin (*ENG*) and Activin A receptor type II-like 1 (*ACVRL1*) are identified in Hereditary hemorrhagic telangiectasia type 1 and Hereditary hemorrhagic telangiectasia type 2, respectively. ENG is a component of the TGFβ-bone morphogenic protein receptor complex (BMP), while ACVRL1 is a TGFβ type 1 receptor, and both work together in mediating the TGFβ signaling pathway in endothelial cells.

A third gene identified in hereditary hemorrhagic telangiectasia involves mutations in the gene *MADH4*, encoding SMAD4, and is seen in the combined hereditary hemorrhagic telangiectasia/juvenile polyposis syndrome. SMAD4 is an intracellular signaling protein involved in the TGFβ/BMP pathway. Other putative hereditary hemorrhagic telangiectasia genes have been identified on the long arm of chromosome 5 and the short arm of chromosome 7. The estimated prevalence of hereditary hemorrhagic telangiectasia is 1–20 per 100,000.

2.8.3 Clinical Features

The frequency of hepatic involvement by hereditary hemorrhagic telangiectasia ranges from 41 to 78 % by CT and ultrasound studies [31].

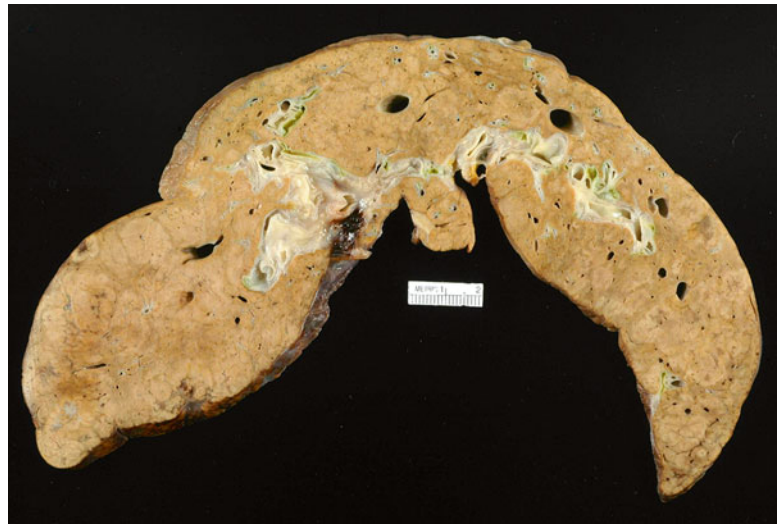

Fig. 2.15 Hereditary hemorrhagic telangiectasia. The cut surface of liver shows a nodular appearance but no cirrhosis

Only 8 % of individuals with hereditary hemorrhagic telangiectasia and hepatic involvement have symptoms. The symptoms vary widely and include abdominal pain, hepatomegaly with pulsatile liver, portal hypertension, encephalopathy, high-output heart failure due to arteriovenous shunting in the liver, and rarely biliary disease such as intrahepatic lithiasis and biliary ischemia [32]. Doppler ultrasonography, CT, MRI, and angiography can all be used to demonstrate hepatic involvement in individuals with hereditary hemorrhagic telangiectasia [33]. Only symptomatic individuals require treatment, with the treatment directed at addressing specific symptoms. Hepatic artery embolization and liver transplantation have been performed in patients not responsive to medical treatment. Interestingly, hereditary hemorrhagic telangiectasia can occasionally recur after liver transplantation [34].

2.8.4 Gross Findings

The liver capsule can show vessels with a spider-like arrangement. The cut surface of the liver is often fibrotic with a nodular appearance, but cirrhosis is rare (Fig. 2.15). Nodular transformation of the liver and focal nodular hyperplasia can also be seen in hereditary hemorrhagic telangiectasia [35, 36].

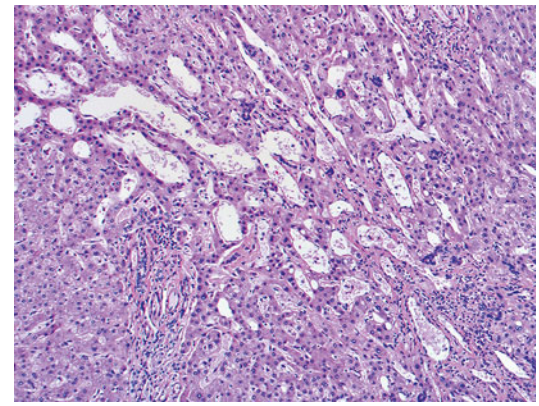

Fig. 2.16 Hereditary hemorrhagic telangiectasia. Dilated, anastomosing, and haphazardly oriented vascular channels are seen

2.8.5 Microscopic Findings

There are three distinct hepatic fibrovascular patterns described by Daly and Schiller [37]. The first pattern is composed of a haphazard, honeycomb framework of dilated sinusoidal channels with either intervening loose fibrous stroma or vessels directly within the hepatic lobules (Fig. 2.16). A second pattern consists of thick-walled, tortuous veins that are flanked by large-caliber arteries and travel randomly through the liver parenchyma, with variable amounts of fibrous tissue (Fig. 2.17). The third pattern shows

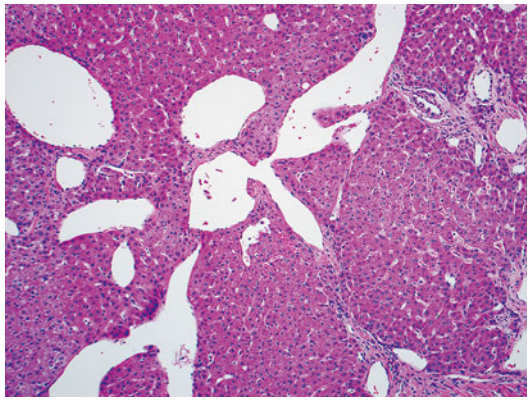

Fig. 2.17 Hereditary hemorrhagic telangiectasia. Large tortuous vein randomly travels through the liver parenchyma

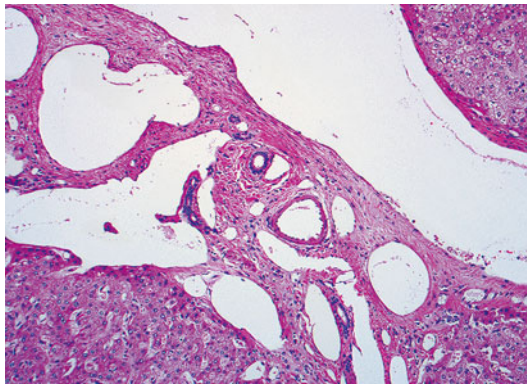

Fig. 2.18 Hereditary hemorrhagic telangiectasia. The abnormal vessels involving an enlarged fibrotic portal area

enlarged fibrotic portal tracts with multiple dilated veins, arteries, and lymphatics (Fig. 2.18). Hepatic necrosis and ischemic bile duct injury can be seen. Nodular transformation of the liver can be seen, as well as focal nodular hyperplasia. Grossly distinctive mass lesion can also occur; microscopically composed of a vascular malformation of intercommunicating thin-walled vascular network (Figs. 2.19 and 2.20) admixed with benign reactive hepatocytes.

2.8.6 Differential Diagnosis

In some cases, portal vein thrombosis can cause elevated portal pressures, with ectopic dilated portal veins extending outside the portal tracts into adjacent liver parenchyma, which can focally mimic hereditary hemorrhagic telangiectasia. However, these "herniated" portal veins lack the inter-anastomosing and haphazard arrangement of vessels seen in hereditary hemorrhagic telangiectasia. Hereditary hemorrhagic telangiectasia also typically involves other organs. Hereditary hemorrhagic telangiectasia can also present as a mass lesion on imaging studies and identification of characteristic features of fibrovascular pattern seen in hereditary hemorrhagic telangiectasia can help make the correct diagnosis.

The differential also includes an entity called "hyperplastic hepatocellular nodule with

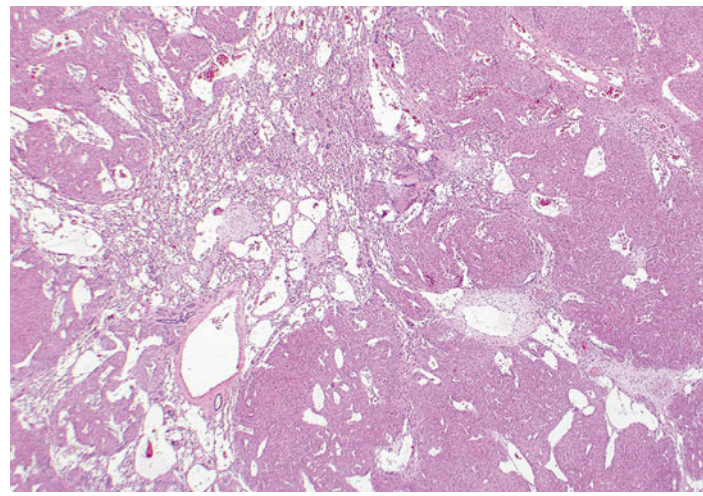

Fig. 2.19 Hereditary hemorrhagic telangiectasia. A mass lesion is formed by the abnormal vessels and nodular proliferation of hepatocytes

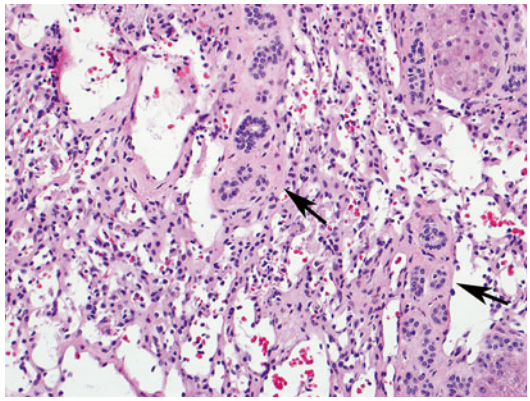

Fig. 2.20 Hereditary hemorrhagic telangiectasia. Within the center of the mass lesion, there is a proliferation of abnormal, interconnecting thin-walled vessels, intermingled with portal tracts (*arrows*)

localized hemangiomatosis" [38]. This is a mass forming lesion with focal areas that have hemangioma-like vascular proliferations involving the portal tracts, associated with a benign regenerative response in the hepatocytes. The lesion is very similar, and in some cases, indistinguishable from some of the mass-forming lesions that can be found in hereditary hemorrhagic telangiectasia. However, this entity was not reported in the setting of hereditary hemorrhagic telangiectasia and appears to be isolated lesions to the liver.

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