Malignant Mesenchymal Tumors

11

Lizhi Zhang

Abstract

Malignant mesenchymal tumors can either metastasize to the liver or less frequently present as primary hepatic neoplasms. Certain entities such as hepatic angiosarcoma and epithelioid hemangioendothelioma can occasionally be encountered in the routine practice of surgical pathology, whereas others discussed in this chapter are rare, some only encountered in a handful of case reports. The chapter describes the clinical and pathologic features of primary malignant mesenchymal tumors occurring in the liver, illustrates examples of them, and discusses key points in their differential diagnoses.

Keywords

Epithelioid hemangioendothelioma • Angiosarcoma • CD34 • ERG • FLI-1 • Kaposi's sarcoma • HHV-8 • Embryonal sarcoma • Mesenchymal hamartoma • Liposarcoma • Fibrosarcoma • Leiomyosarcoma • Undifferentiated pleomorphic sarcoma

11.1 Epithelioid Hemangioendothelioma

11.1.1 Definition

Epithelioid hemangioendothelioma (EH) is a distinctive low-grade malignant neoplasm composed of endothelial cells. It was first recognized in the lung and soft tissue. The first series of primary hepatic epithelioid hemangioendothelioma was reported by Ishak et al. in 1984 [1]. The epithelioid appearance of the tumor cells is frequently mistaken for metastatic carcinoma.

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11.1.2 Clinical Features

Epithelioid hemangioendothelioma is a rare primary liver tumor with an incidence of less than 0.1 per 100,000. There is a slight female predominance, with a female to male ratio of 3:2. The mean age at diagnosis is 41.7 years (range: 3–86 years) [2, 3]. The etiology of hepatic epithelioid

T. Mounajjed et al. (eds.), *Surgical Pathology of Liver Tumors*,
DOI 10.1007/978-3-319-16089-4_11,

hemangioendothelioma is unknown [3]. The most common clinical symptoms are right upper quadrant pain, hepatomegaly, and weight loss, while about 25 % of patients are asymptomatic. The majority of patients also have abnormal liver function tests; increased alkaline phosphatase and g-glutamyl transpeptidase levels are present in over two thirds of cases, and a small percentage of cases also has mildly increased transaminase and bilirubin levels. Imaging studies often do not suggest a vascular tumor. Two different types of epithelioid hemangioendothelioma with different stages have been described: (1) the nodular type, usually presenting in an early stage and (2) the diffuse type, presenting in advanced-stage disease and having hepatic vascular invasion [4].

There is no universal strategy for the treatment of epithelioid hemangioendothelioma [5]. The most common management is liver transplant [6], but other treatment options include chemoradiation therapy and liver resection [7]. Although the tumor can spread to other organs, metastasis does not appear to influence prognosis [4]. Historically, the overall 1, 3, and 5 years survival rates are 83.4 %, 55.8 %, and 41.1 %, respectively, whether or not the patients received treatment [2], but better survival rates have been described in liver transplant recipients [6]. High tumor cellularity is associated with poor outcome [3].

11.1.3 Gross Findings

Most primary epithelioid hemangioendotheliomas are multifocal, with nodule sizes ranging from a few millimeters to several centimeters [3]. The tumor nodules are white and firm, often mimicking metastatic carcinoma (Fig. 11.1). The margins of the lesions may be hyperemic, probably due to tumor cells infiltrating into the surrounding hepatic sinusoids. The tumor involves the liver capsule in about half of cases.

11.1.4 Microscopic Findings

Microscopically, epithelioid hemangioendothelioma is characterized by individual and small groups of epithelioid cells scattered in a mucopolysaccharide-rich stroma, but some tumor cells can also form capillary lumina (Fig. 11.2). The tumor cells, especially at the peripheral of the lesion, tend to grow along hepatic sinusoids, terminal hepatic veins, and portal vein branches. The underlying hepatic acinar architecture is preserved (Fig. 11.3), but the liver cell plates become gradually atrophic, and eventually disappear due to replacement by tumor. At the center of the lesion, there is typical dense, often hyalinized fibrous tissue mimicking scar tissue. The tumor produces abundant mucopolysaccharide-rich stromal matrix, but in older lesions, there is progressive fibrosis and sometimes calcifications. Intravenous growth can sometimes be in the form of solid plugs, polypoid lesions, or tuft-like projections (Fig. 11.4). The epithelioid tumor cells have abundant cytoplasm and often contain cytoplasmic vacuoles, representing intracellular vascular lumina and sometimes containing red blood cells (Fig. 11.5). The cells containing vascular lumina can mimic signet ring cells. Besides epithelioid tumor cells, "dendritic" cells can also be seen in the myxoid stroma. Those cells have spindle or irregular shapes with multiple interdigitating processes (Fig. 11.6). Irregular intracellular lumina can also be seen in these cells.

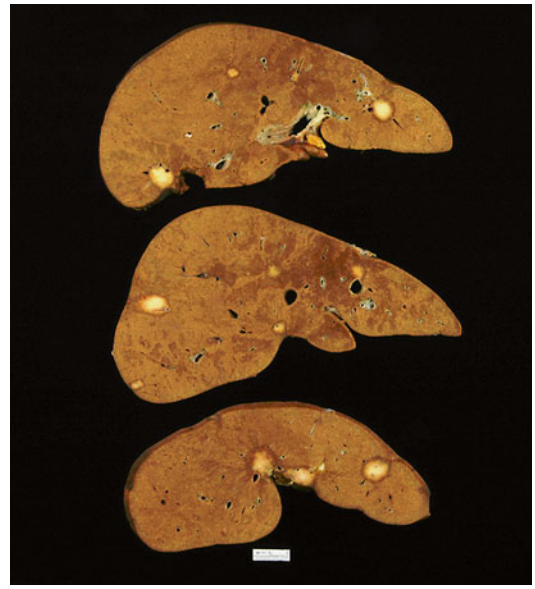

Fig. 11.1 Epithelioid hemangioendothelioma, gross. A liver explant showing multiple tumor nodules ranging from a few millimeters to several centimeters

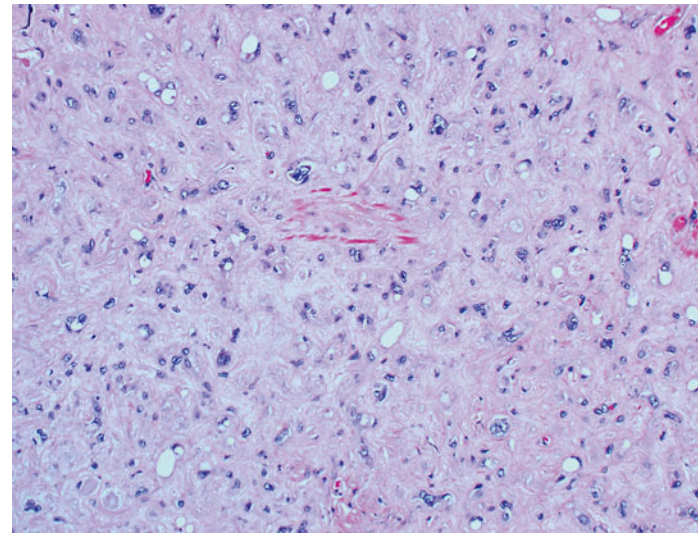

Fig. 11.2 Epithelioid hemangioendothelioma. Individual and small groups of epithelioid cells in a mucopolysaccharide-rich stroma

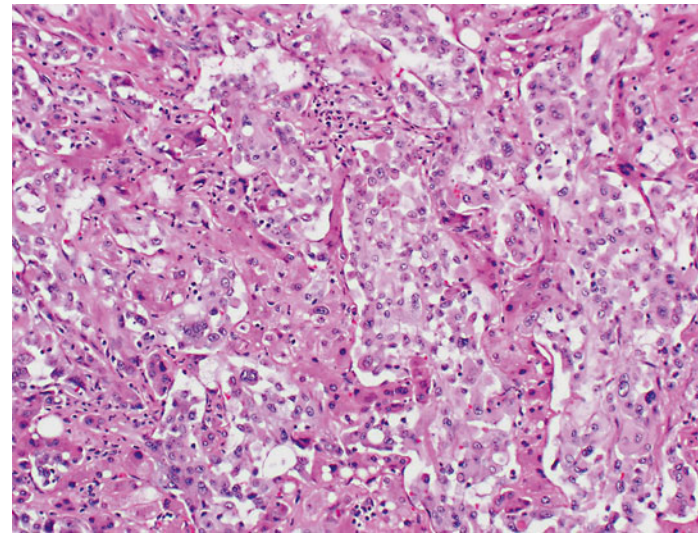

Fig. 11.3 Epithelioid hemangioendothelioma. Tumor cells grow along hepatic sinusoids but the underlying acinar architecture is preserved

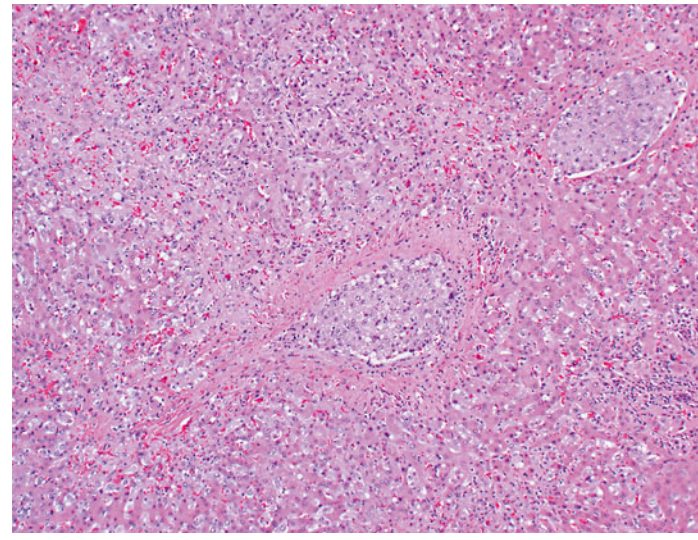

Fig. 11.4 Epithelioid hemangioendothelioma. Intravenous growth of tumor forms tumor plugs

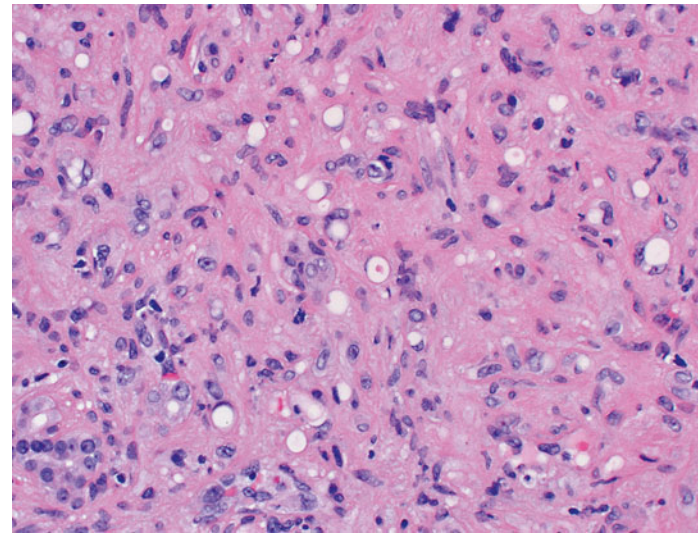

Fig. 11.5 Epithelioid hemangioendothelioma. Tumor cells with cytoplasmic vacuoles, representing intracellular vascular lumina, and containing red blood cells

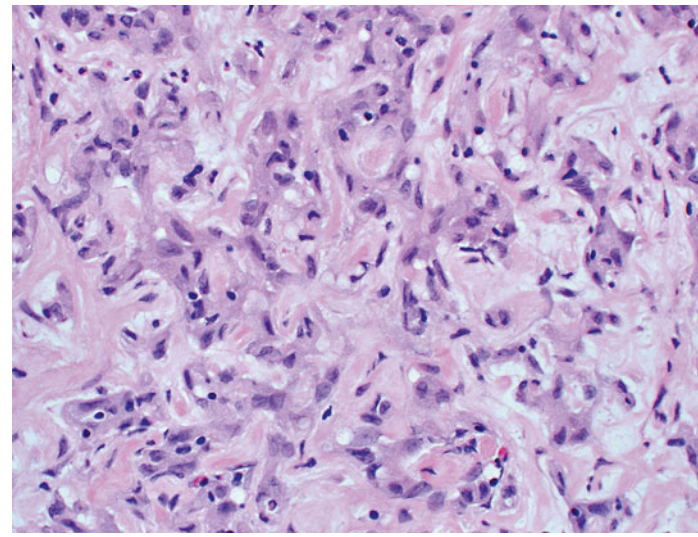

Fig. 11.6 Epithelioid hemangioendothelioma. "Dendritic" tumor cells in the myxoid stroma. Those cells have spindle or stellate shapes with multiple interdigitating processes

11.1.5 Immunohistochemical Features

Immunostains for endothelial markers, such as Factor VIII, CD34, CD31, ERG, or Fli-1, are variably positive (Fig. 11.7), with approximate rates of positive staining: VIII (99 %), CD34 (94 %), and CD31 (86 %) [3]. In many cases, the use of more than one marker is helpful to confirm the diagnosis. Overall, vascular markers stain the epithelioid areas better than the dendritic areas. ERG is also a very sensitive marker for endothelial differentiation and was positive in 42/43 of epithelioid hemangioendotheliomas [8]. However, ERG is not entirely specific and stains about 40 % of prostate adenocarcinomas as well as some meningiomas, and rare Ewing sarcomas and mesotheliomas [8, 9]. However, when ERG results are combined with morphology and with other stains, it is very helpful for identifying vascular differentiation.

Smooth muscle actin is positive in about 25 % of cases and cytokeratin AE1/3 and CK7 in 5–15 % of cases. Mucicarmine is always negative.

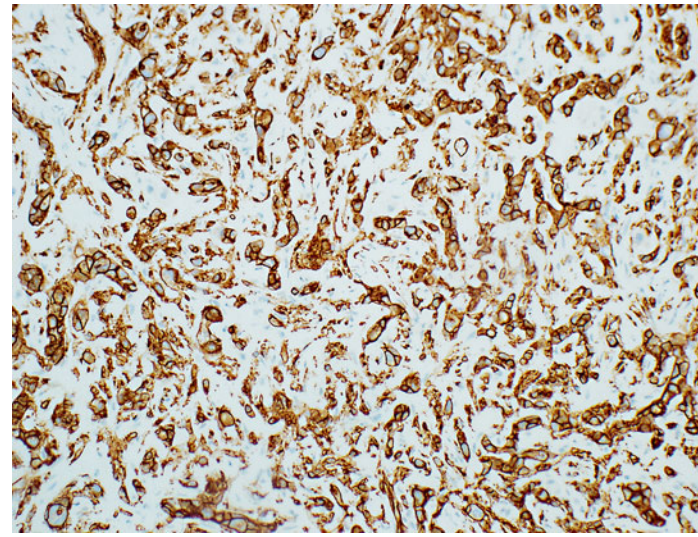

Fig. 11.7 Epithelioid hemangioendothelioma. Tumor cells express the endothelial marker CD34

Interestingly, immunostaining for CD10 is positive in most epithelioid hemangioendotheliomas [10], which can sometimes be confusing if the biopsy is small and the distinctive H&E findings not well represented.

11.1.6 Molecular Findings

Translocations appear to be important driver mutations in epithelioid hemangioendotheliomas. A translocation at t(1;3)(p36.3;q25) leads to a fusion transcript involving *WWTR1-CAMTA1* and can be detected by FISH or RT-PCR and was found in all of 17 cases in one study [11].

11.1.7 Differential Diagnosis

The differential diagnosis includes other benign and malignant vascular tumors as well as epithelial tumors. Angiosarcoma has a much more destructive growth than epithelioid hemangioendothelioma. Although the cells grow along the sinusoids, they tend to disrupt hepatocellular plates and form larger vascular channels. The cells are often spindle with more severe cytological atypia than epithelioid hemangioendothelioma. Intracellular lumina are usually not present and complex tufting into the neoplastic vascular spaces is more frequent. Metastatic adenocarcinoma or primary cholangiocarcinoma can mimic epithelioid hemangioendotheliomas, especially when the tumor has low cellularity and dense, hyalinized fibrous stroma. The epithelial cells in cholangiocarcinoma, however, often form tubules or glands and often produce mucin. Immunostains for both epithelial and endothelial markers (such as Factor VIII, CD31, CD34, ERG, and Fli-1) can separate adenocarcinoma from epithelioid hemangioendothelioma. Sometimes epithelioid hemangioendotheliomas can be mistakenly diagnosed as non-neoplastic lesions, such as parenchymal collapse, scar, cirrhosis, or veno-occlusive disease. Careful microscopic examination to identify the characteristic neoplastic epithelioid cells and "dendritic" cells in a myxoid and fibrotic background should prevent misdiagnoses.

11.2 Angiosarcoma

11.2.1 Definition

Hepatic angiosarcoma is a high-grade malignant tumor composed of endothelial cells. It is a destructive vasoformative malignant neoplasm most frequently composed of spindled cells.

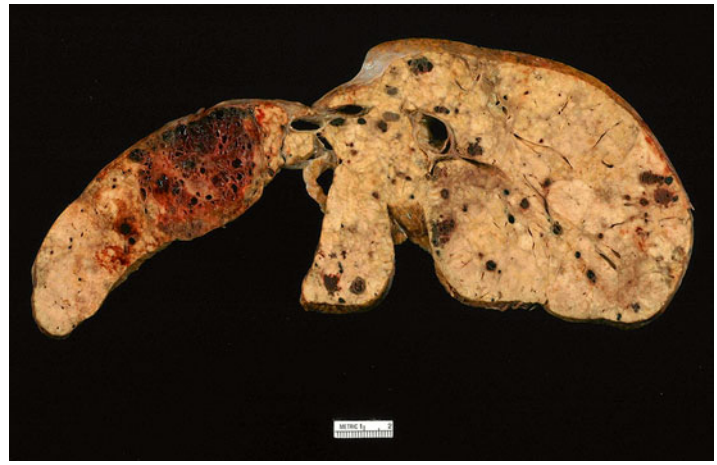

Fig. 11.8 Angiosarcoma, gross. Angiosarcoma involves entire liver with numerous gray-white and dark red masses with alternating areas of hemorrhage and blood-filled cavities with sponge appearance

11.2.2 Clinical Features

Angiosarcoma is the third most common primary liver malignancy, but it only accounts for 2–3 % of all primary liver malignancies [12, 13], with hepatocellular carcinoma and cholangiocarcinoma the most frequent. Most angiosarcomas occur in men who are older than 50 years, but it can rarely be seen in children [14]. Angiosarcoma can be associated with chronic exposure to Thorotrast, androgen steroids, vinyl chloride, arsenicals, radium, possibly copper, and with chronic idiopathic hemochromatosis [13, 15]. Many cases, however, occur in the absence of risk factors [16]. The clinical presentation of hepatic angiosarcoma is nonspecific and includes abdominal pain, weakness, and weight. Patients often have hepatomegaly, ascites, and jaundice at presentation [13]. Catastrophic intra-abdominal bleeding occurs in about one-fourth of all cases [13]. Tumors can be complicated by acute liver failure [17]. The survival of hepatic angiosarcoma is very poor [13, 17], which is attributable to its rapid progress, high recurrence rate, and resistance to traditional chemotherapy and radiotherapy. The median survival rate is 5–6 months without treatment [13]. Even after treatment, only 3 % of patients are reported to live longer than 2 years [13, 15].

11.2.3 Gross Findings

Grossly, hepatic angiosarcomas can involve the either lobe or the entire liver and can also involve the spleen. The masses are gray-white with ill-defined borders and alternating areas of hemorrhage and necrosis (Fig. 11.8). Blood-filled cavities can be seen in some areas. Thorotrast-associated tumors often have subcapsular hepatic and splenic deposits of yellow chalky material.

11.2.4 Microscopic Findings

The background liver can show chronic inflammatory disease or fatty disease and be either cirrhotic or non-cirrhotic. Histologically, angiosarcomas can have several different growth patterns. One pattern is that of a clearly vascular tumor with irregular blood vessels. A second major pattern is that of a solid epithelioid tumor that can mimic a poorly differentiated carcinoma (Fig. 11.9). A third major pattern is of a spindle cell tumor with abundant extracellular matrix that mimics other sarcomas (Fig. 11.10). In a fourth pattern, the solid areas in some angiosarcomas can undergo necrosis and cavitation, leaving a cavity filled with blood, fibrin, and necrotic debris that has only small rim of viable malignant cells. Finally, an important but subtle growth

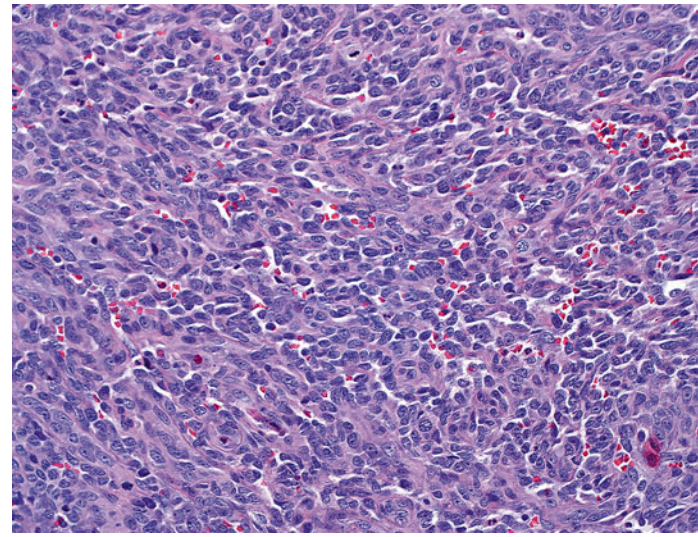

Fig. 11.9 Angiosarcoma. The tumor is growing in solids sheets, mimicking a poorly differentiated carcinoma

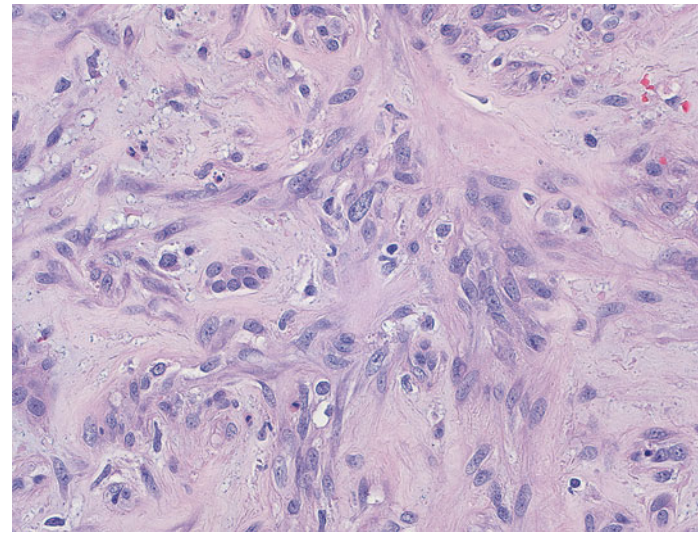

Fig. 11.10 Angiosarcoma. This tumor was submitted for consultation as a possible cholangiocarcinoma

pattern is growth along the sinusoids, replacing the normal benign sinusoidal endothelial cells but leaving the hepatic plates relatively intact (Fig. 11.11). This pattern can be very diagnostically challenging, especially on biopsy. With fully resected specimens, a sinusoidal growth pattern is almost always evident in some part of the tumor.

Microscopically, tumor cells grow along the hepatic sinusoids between the hepatocellular cords can show solid and pseudopapillary patterns (Fig. 11.12). The sinusoidal growth of tumor cells is often associated with progressive destruction of liver plates, with the eventual formation of larger vascular channels and blood cavities. The pseudopapillary pattern is mainly identified along the lining in blood-filled cavities. The tumor cells typically form irregular infiltrative and anastomosing vascular channels (Fig. 11.13) and can be spindled or epithelioid. The spindle tumor cells have poorly defined cell borders, and are usually markedly pleomorphic with hyperchromatic nuclei, but sometimes may be only mildly atypical (Fig. 11.14). The solid

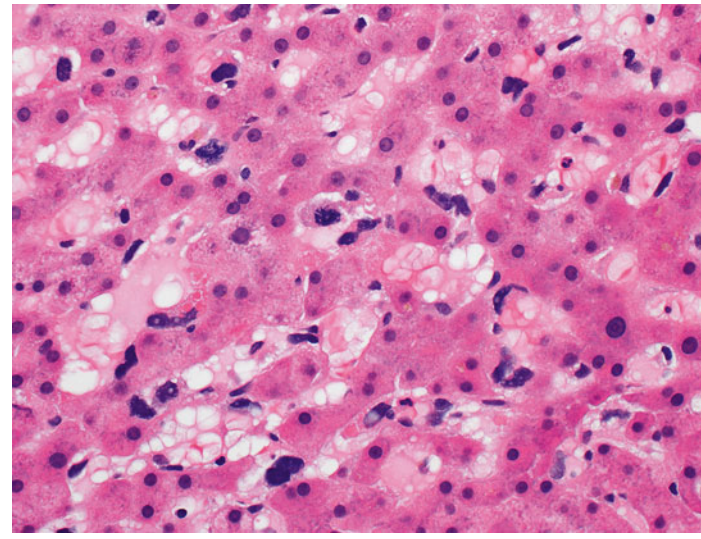

Fig. 11.11 Angiosarcoma. This subtle growth pattern can be easily missed on biopsy specimens

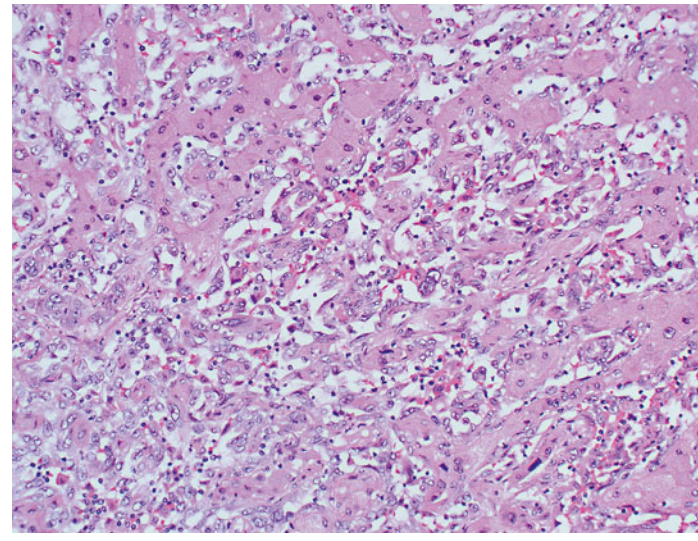

Fig. 11.12 Angiosarcoma. Tumor cells grow along hepatocellular sinusoids

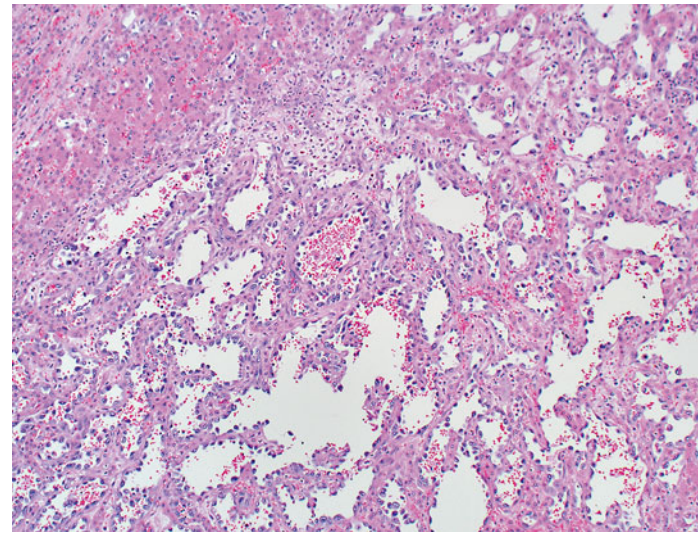

Fig. 11.13 Angiosarcoma. Tumor cells form irregular infiltrative and anastomosing vascular channels

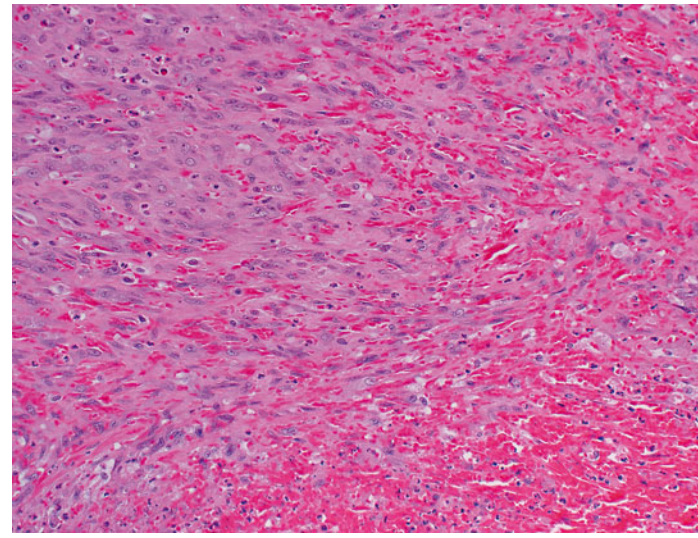

Fig. 11.14 Angiosarcoma. Spindle tumor cells have eosinophilic cytoplasm, poorly defined cell borders, and atypical hyperchromatic nuclei

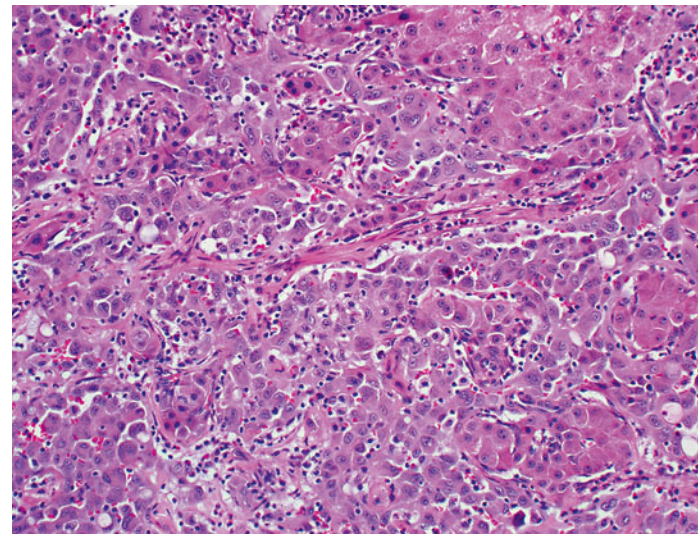

Fig. 11.15 Angiosarcoma. Epithelioid neoplastic cells grow along sinusoids with abundant cytoplasm and prominent nucleoli. No intracellular lumina are present

epithelioid pattern of growth has cells with abundant cytoplasm and prominent nucleoli that can mimic carcinoma. Intracellular lumina are not a feature of angiosarcoma (Figs. 11.9 and 11.15). Mitotic activity is easily identified. Vascular invasion of portal or hepatic vein branches leads to progressive obstruction of their lumens, which can account for the hemorrhage, infarction, and necrosis in the tumor (Fig. 11.16). Extramedullary hematopoiesis can be seen in most cases.

Hepatic angiosarcoma in children may have Kaposiform areas consisting of spindle cells, sometimes containing PAS-positive intracytoplasmic globules. Thorotrast-associated cases may have granules of Thorotrast that are brown-gray and refractile but not birefringent, either free or within macrophages. A precursor lesion consisting of endothelial hypertrophy and hyperplasia has been described in cases related to Thorotrast, vinyl chloride, and arsenic exposure [18, 19].

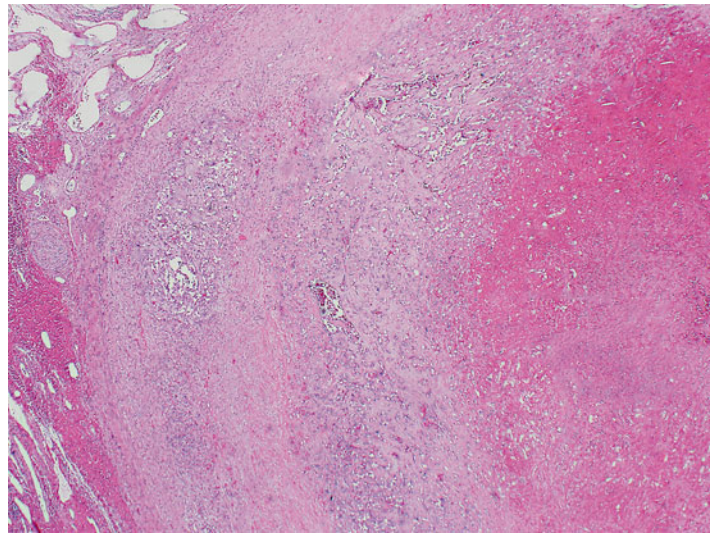

Fig. 11.16 Angiosarcoma. Vascular invasion of large portal or hepatic vein branches leading to progressive obstruction of the lumen, hemorrhage, infarction, and necrosis in the tumor

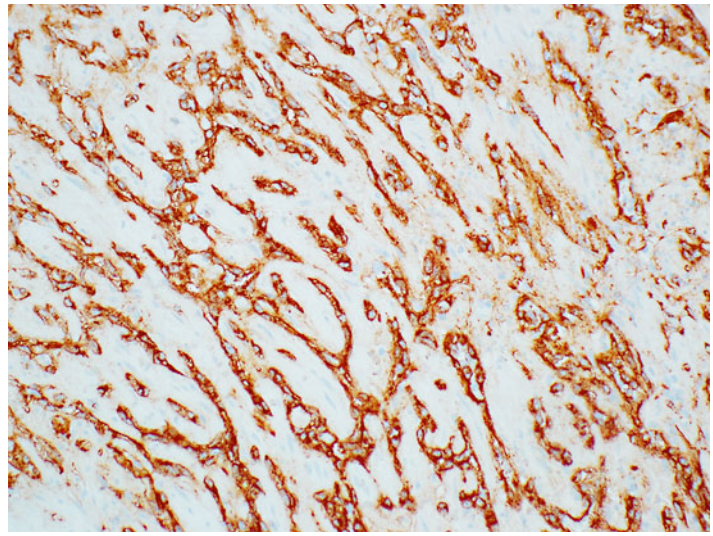

Fig. 11.17 Angiosarcoma. Tumor cells express the endothelial marker Factor VIII

11.2.5 Immunohistochemical Features

Immunostains for endothelial markers, such as Factor VIII, CD31, CD34, ERG, Fli-1, and Ulex europaeus lectin type 1, are variably positive (Figs. 11.17 and 11.18). ERG and FLI-1 are more recently available stains and are very helpful for identifying angiosarcomas. One study found 100 % of hepatic angiosarcomas are positive for ERG [20]. Overall, the frequency of positivity in angiosarcomas for the traditional markers of endothelial differentiation are as follows: 40–90 % of cases are positive for Factor VIII, 60–90 % are positive for CD34, and 30–100 % are positive for CD31 [20–23]. The wide variation in reported frequencies may in part be because these studies include angiosarcomas from different organs, but they also underscore the value of using a combination of stains for identifying an endothelial phenotype. The neoplastic cells are also positive for vimentin and can

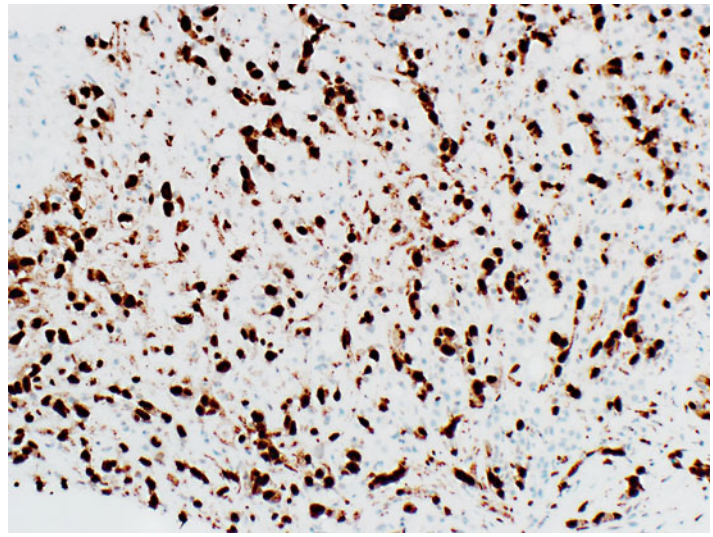

Fig. 11.18 Angiosarcoma. Tumor cells express the endothelial marker ERG

sometimes express keratin stains, which can lead to the mistaken diagnosis of carcinoma. Cytokeratin AE1/3, Cam5.2, or pan-keratin positivity can be seen in the epithelioid areas of angiosarcomas in about 30–50 % of cases [22, 23]. Rare angiosarcomas also express synaptophysin and/or chromogranin, mimicking neuroendocrine tumors [24].

11.2.6 Differential Diagnosis

Primary angiosarcoma cannot be differentiated from metastatic angiosarcoma histologically; this differentiation requires correlation with the patient's clinical findings. Epithelioid hemangioendothelioma consists of individual and small groups of epithelioid cells in a mucopolysaccharide-rich stroma, and some tumor cells have capillary lumina. The tumor cells also grow along hepatic sinusoids, but the underlying acinar architecture is predominantly preserved. In contrast, angiosarcoma often has significantly more destructive growth and more striking cytologic atypia.

Distinguishing Kaposi's sarcoma from a well-differentiated angiosarcoma can be challenging, but Kaposi's sarcoma is overall more bland cytologically and is usually centered in portal tracts, and immunoreactivity of HHV-8 in Kaposi's sarcoma is a key feature. Sinusoidal growth and formation of vascular structures can help differentiate angiosarcoma from other high-grade sarcomas (primary or metastatic) in resection specimens. In biopsy specimens, this differentiation can be difficult and usually requires immunohistochemical workup to demonstrate an endothelial phenotype. Angiosarcoma can sometimes have epithelioid morphology and express keratin stains, which can be mistaken for carcinoma. The sinusoidal growth pattern, the presence of areas of spindled cell growth, and expression of endothelial markers help sort out this differential diagnosis.

11.3 Kaposi's Sarcoma

11.3.1 Definition

Kaposi's sarcoma is a locally aggressive endothelial tumor that is uniformly associated with human herpes virus (HHV-8) infection.

11.3.2 Clinical Features

Four different forms of Kaposi's sarcoma are recognized and all can involve liver: (1) the "classic" form typically affects elderly individuals

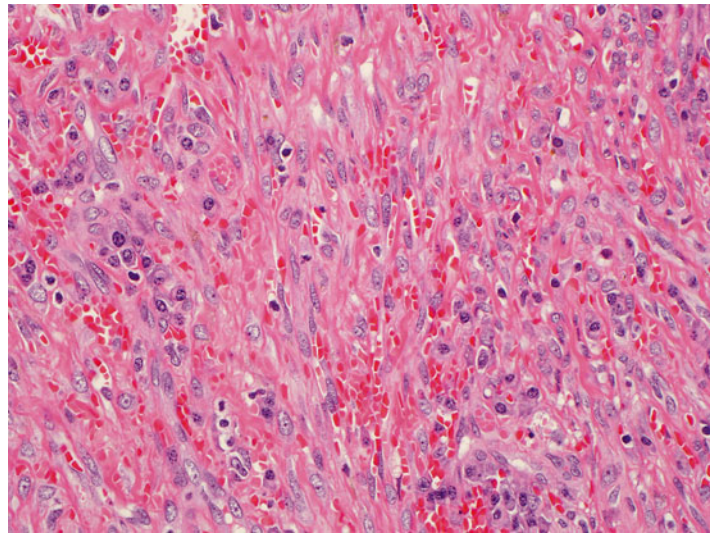

Fig. 11.19 Kaposi's sarcoma. Vascular proliferation and spindle cells with large, plump nuclei admixed with collagen fibers and extravasated red blood cells

(>60 years), mainly in the Eastern Europe and the Mediterranean region; (2) the "African endemic" form affects young adults of equatorial Africa and is characterized by localized nodular lesions; (3) the "epidemic" form of Kaposi's sarcoma occurs in patients with acquired immunodeficiency syndrome (AIDS); (4) the "iatrogenic" form is caused by immunosuppressive drugs administered after organ transplant and has aggressive behavior with a tendency to spread. Hepatic Kaposi's sarcoma is rarely detected in living patients, but autopsies show liver involvement in 35 % of patients with Kaposi's sarcoma. Abdominal computed tomography or ultrasonography with contrast agents can reveal the presence of lesions in the hepatic capsule, hilum, and large portal areas, with or without invasion of the liver parenchyma [25]. In most cases, antiretroviral therapy alone is effective in controlling this neoplastic process.

11.3.3 Gross Findings

Kaposi's sarcoma in the liver has been described as irregular, blue-black, or red-brown lesions involving large portal areas. Confluence of larger foci can resemble hemangiomas.

11.3.4 Microscopic Findings

Microscopically, Kaposi's sarcoma is usually centered in portals tracts, but the tumor can infiltrate into the adjacent liver parenchyma. The lesion consists of a vascular proliferation composed of spindle cells with large plump nuclei admixed with collagen fibers, extravasated red blood cells, and hemosiderin-laden macrophages (Figs. 11.19 and 11.20). Slit-like spaces are a common finding of Kaposi's sarcoma. PAS-positive hyaline globules, which may represent destroyed red blood cells, are frequently found in neoplastic cells.

11.3.5 Immunohistochemical Features

The neoplastic cells are positive for pan-endothelial markers including CD31, CD34, FLI-1, and ERG, but Factor VIII immunostain is usually negative. In addition, lymphatic markers such as D2–40 and podoplanin are also positive. Almost all cases display strong nuclear immunoreactivity for HHV-8 in both the spindle cells and in the cells lining the neoplastic vascular spaces, regardless their subtypes (Fig. 11.21).

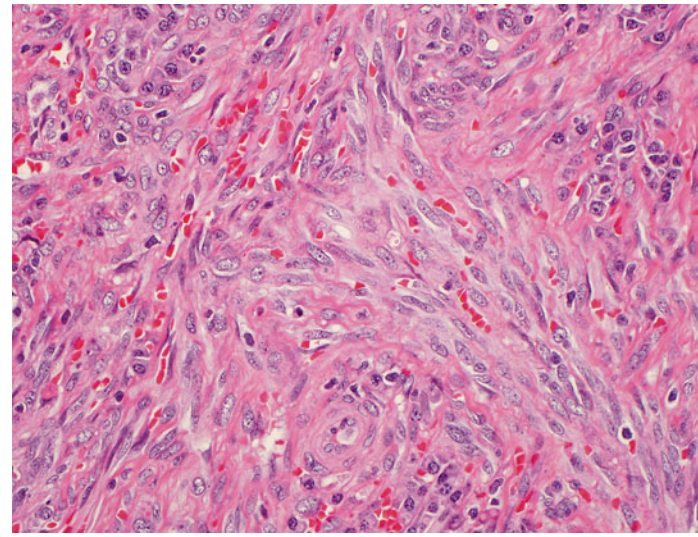

Fig. 11.20 Kaposi's sarcoma. Higher power view of the spindle cells and extravasated red blood cells

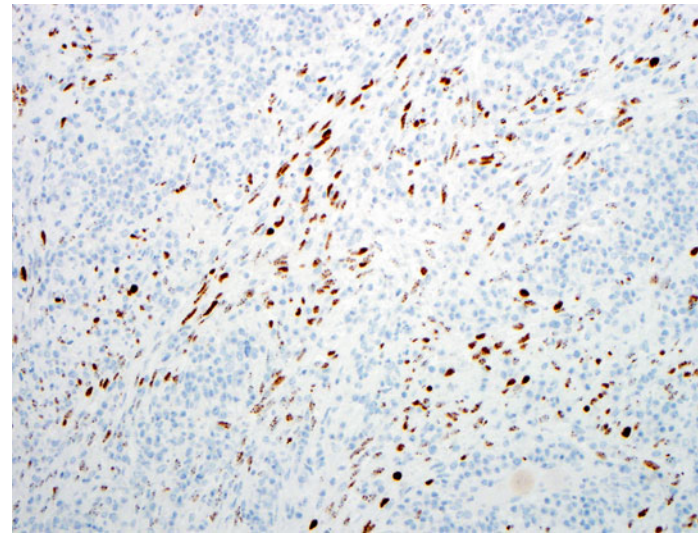

Fig. 11.21 Kaposi's sarcoma. Tumor cells express HHV-8

11.3.6 Differential Diagnosis

An accurate clinical history is very important for establishing the diagnosis. An early lesion may display only portal-based irregular, infiltrative growth of endothelial cells. In some cases, the tumor may be subtle and easy to miss. In other cases, the tumor may be obvious, but difficult to distinguish from angiosarcoma. Immunoreactivity of HHV-8 is a very helpful feature since Kaposi's sarcoma is universally positive for this antigen, whereas other vascular tumors are negative, even those from HIV-infected patients. Advanced Kaposi's sarcoma with high cellularity may also be confused with other spindle cell lesions such as metastatic GIST or fibrosarcoma. Features that distinguish Kaposi's sarcoma from these tumors include the presence of ectatic vessels and inflammatory cells at the periphery of the lesion, the presence of more curvilinear fascicles, the presence of hyaline globules, and immunoreactivity to endothelial markers and HHV-8.

11.4 Embryonal Sarcoma

11.4.1 Definition

Embryonal sarcoma is a rare primitive malignant mesenchymal neoplasm unique to liver [26]. This tumor has also been called undifferentiated sarcoma, primary sarcoma of liver, mesenchymal sarcoma, or malignant mesenchymoma, but embryonal sarcoma is the preferred term.

11.4.2 Clinical Features

Embryonal sarcoma is predominantly a disease of children and is therefore further discussed in Chap. 14. More than half the patients are between the ages of 6 and 10 years, but rare cases occur in adults [26–29]. The tumor usually grows very rapidly with areas of cystic degeneration and necrosis. The patients often present with abdominal swelling, with or without a palpable mass and pain. The diagnosis can be strongly suspected in a child with a large, rapidly growing cystic liver mass. The prognosis was very poor in the past, with a median survival of less than 1 year, but in recent years, the survival has significantly improved, with some patients living 5 or more years after combination treatments of surgery and chemotherapy [28, 30].

11.4.3 Gross Findings

Most embryonal sarcomas are located in the right lobe of the liver. They are often solitary, well demarcated, and their size range from 10 to 30 cm. The cut surface is variegated with solid, cystic, and gelatinous areas alternating with hemorrhagic and necrotic foci (Fig. 11.22) [31].

11.4.4 Microscopic Findings

Microscopically, the tumor may have a fibrous pseudocapsule separating it from the adjacent liver parenchyma. Entrapped hepatocytes and bile ducts can be identified at peripheral areas of the tumor and can be cystically dilated (Fig. 11.23). The tumor shows variable cellularity. The neoplastic cells are stellate or spindle shaped with ill-defined outlines and frequent mitotic activity (Fig. 11.24). The nuclei show marked anisonucleosis with stippled chromatin and inconspicuous nucleoli. The cells may be compactly or loosely arranged in a myxoid or fibrotic matrix, and numerous thin-walled veins

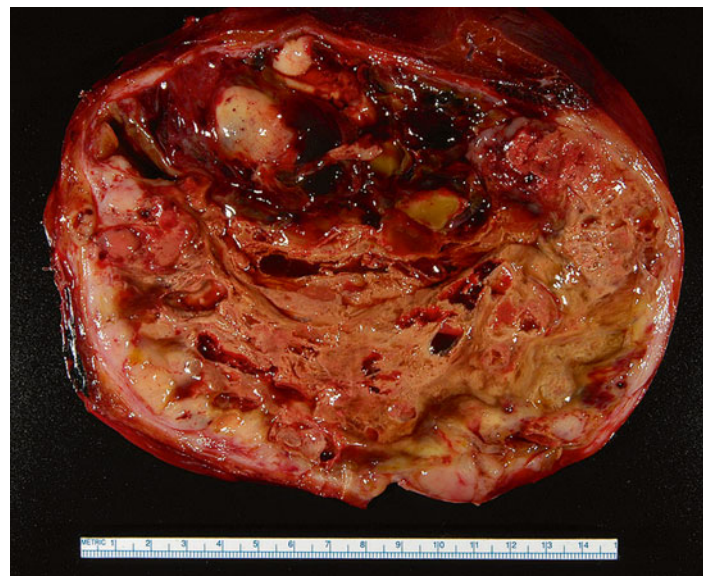

Fig. 11.22 Embryonal sarcoma, gross. A solitary, large, and well-demarcated mass. The cut surface is variegated with solid, cystic, and gelatinous areas alternating with hemorrhagic and necrotic foci

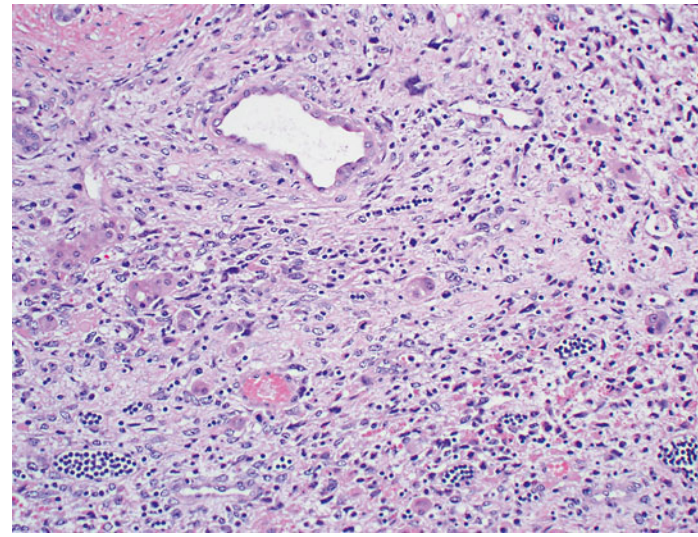

Fig. 11.23 Embryonal sarcoma. Entrapped hepatocytes and bile ducts at the periphery of the tumor, showing variable shape and cystic dilatation

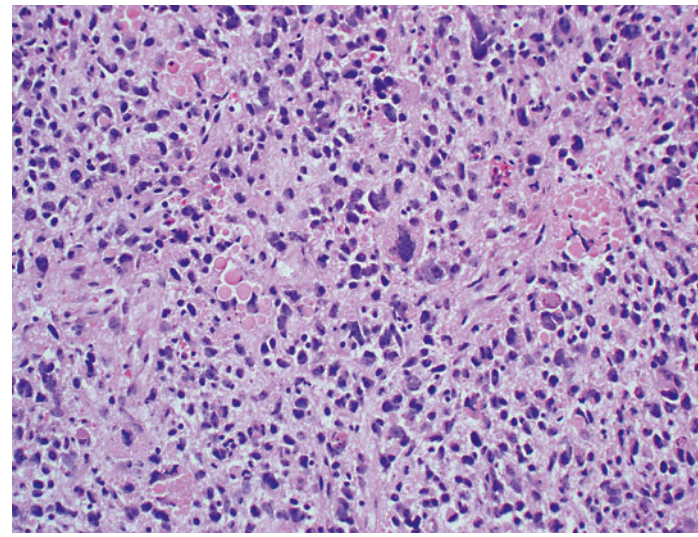

Fig. 11.24 Embryonal sarcoma. The typical tumor cells are stellate shaped with ill-defined outlines, marked anisonucleosis and frequent mitotic activity

can be often seen (Fig. 11.25). A characteristic feature is the presence of multiple, variably sized eosinophilic globules in the cytoplasm of tumor cells (Fig. 11.26). The globules are PAS positive and diastase resistant. Bizarre tumor cells and/or multinucleated giant tumor cells are often seen. Extramedullary hematopoiesis is common. Tumors in adults may have partial smooth muscle differentiation.

11.4.5 Immunohistochemical Features

The tumor cells may be positive for alpha-1 antitrypsin (Fig. 11.27), alpha-1 antichymotrypsin, CD56, and vimentin [31]. Some tumor cells can show dot-like perinuclear cytokeratin staining. Approximately 60 % of embryonal sarcomas are positive for glypican-3.

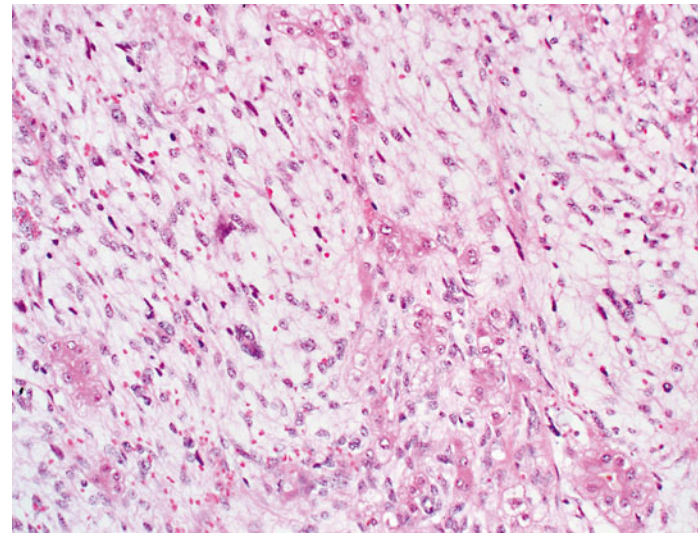

Fig. 11.25 Embryonal sarcoma. Less cellular areas with myxoid matrix

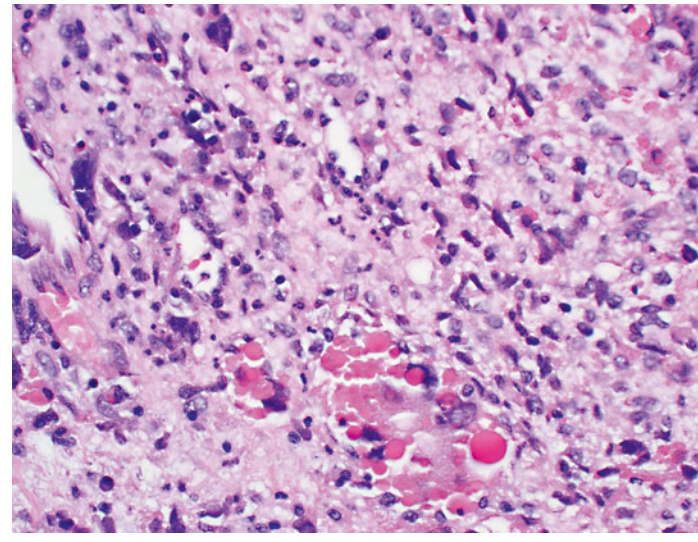

Fig. 11.26 Embryonal sarcoma. A characteristic feature is the presence of multiple variably sized eosinophilic globules

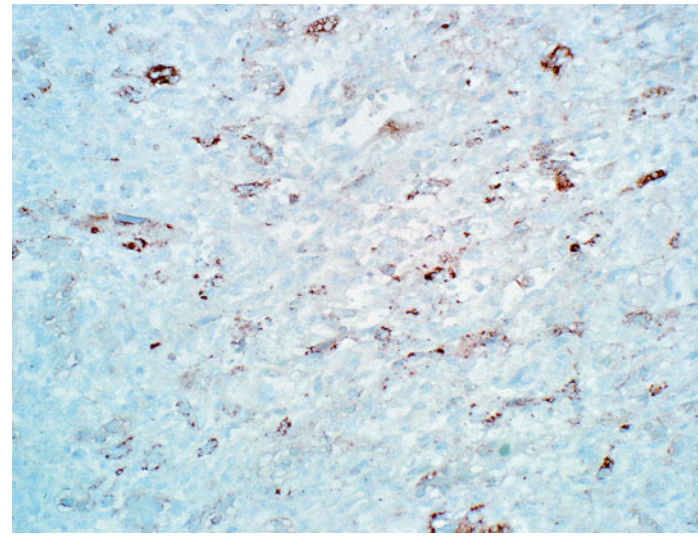

Fig. 11.27 Embryonal sarcoma. Tumor cells are weakly positive for alpha-1 antitrypsin

11.4.6 Differential Diagnosis

The main differential diagnosis is from other common mesenchymal tumors in children. Mesenchymal hamartoma usually occurs in very young children and have stromal bland cells, branching and dilated bile ducts without atypia, normal-appearing hepatocytes with retention of normal cell plate architecture, thick walled veins, variable collagen, and no giant cells. As discussed in chap. 14, mesenchymal hamartomas can be precursors to embryonal sarcoma and in some cases, areas of residual mesenchymal hamartoma can be seen embryonal sarcomas.

Embryonal rhabdomyosarcoma forms a soft polypoid mass covered by biliary-type epithelium that protrudes into the ductal lumen and shows rhabdomyoblastic differentiation with cytoplasmic cross striations. It has no diffuse anaplasia or hyaline globules and is positive for myogenin and MyoD1. In adults, the differential diagnosis is more challenging and includes fibrosarcoma and undifferentiated sarcoma, both of which lack the primitive appearance of the tumor cells in embryonal sarcoma and also lack the hyaline globules.

11.5 Liposarcoma

11.5.1 Definition

Although liposarcoma is one of the most common soft tissue malignancies, primary hepatic liposarcoma is extremely rare [32]. To date, there are only a handful of cases of primary hepatic liposarcoma reported in the literature [33]. The tumor is composed either entirely or in part of a mature adipocytic proliferation with significant variation in cell size and nuclear atypia.

11.5.2 Clinical Features

Primary hepatic liposarcoma occurs equally in men and women. The ages of the patients can range from 2 to 86 years [33]. Patients present with nonspecific symptoms including nausea, vomiting, jaundice, abdominal fullness, right upper quadrant pain, and weight loss [34]. Surgical resection with clear margins remains the mainstay of treatment. The prognosis depends on the histological subtype and the tumor grade.

11.5.3 Gross Findings

Liposarcoma is usually a large well-circumscribed lobulated mass. The cut surface is yellow to white depending on the proportions of adipose tissue, fibrotic tissue, and myxoid areas. Areas of fat necrosis are common in larger tumors.

11.5.4 Microscopic Findings

The subtypes described in soft tissue liposarcomas have all been reported in primary hepatic liposarcomas. Myxoid/round cell liposarcoma is the most common type occurring in the liver. Microscopically, the tumor is a lobulated hypocellular lesion with enhanced cellularity at the periphery. The cells are bland fusiform or round, suspended individually in a myxoid matrix. A delicate plexiform capillary vascular network is present (Fig. 11.28), resembling "chicken wire." Lipoblasts are usually easy to identify. On the other hand, when a myxoid liposarcoma dedifferentiates, the cellularity is significantly increased, and the cells become larger with a more atypical and rounded. Well-differentiated liposarcoma is composed of a relatively mature adipose tissue with significant variation in cell size and atypia. Scattered large hyperchromatic cells as well as multinucleated stromal cells are easily identified (Fig. 11.29) and are characteristic. In contrast to lipomas, liposarcomas lack capsules and have infiltrative edges (Fig. 11.30). Dedifferentiated liposarcoma is represented by the transition from a well-differentiated component to any type of non-lipogenic high-grade sarcoma. Pleomorphic and spindle cell liposarcomas are extremely rare in liver.

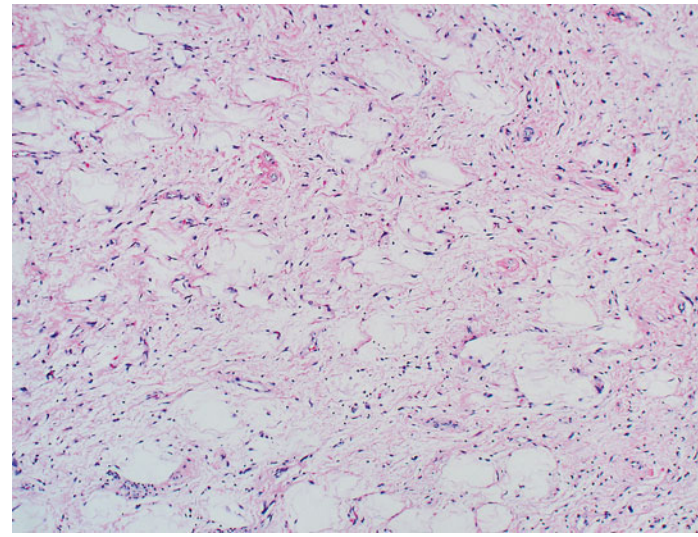

Fig. 11.28 Liposarcoma. Bland fusiform or round cells suspended individually in a myxoid matrix with a delicate capillary vascular network

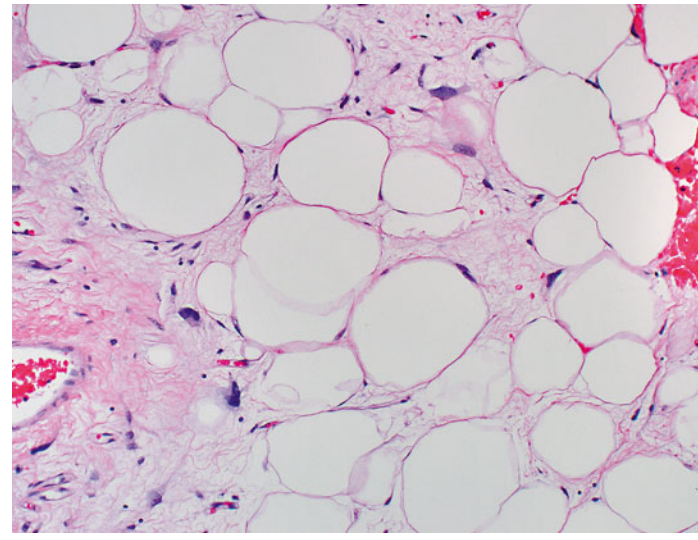

Fig. 11.29 Liposarcoma. Large hyperchromatic cells in well-differentiated liposarcoma

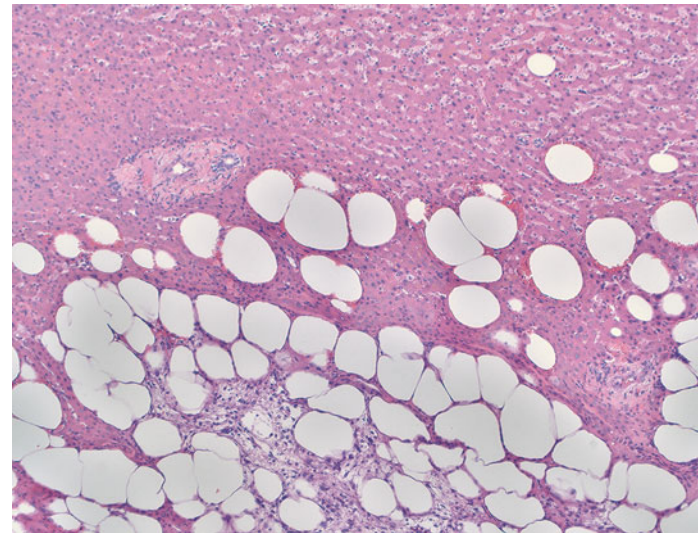

Fig. 11.30 Liposarcoma. The tumor is not encapsulated and has infiltrative borders

11.5.5 Immunohistochemical Features

Immunostains usually are not usually required for establishing a diagnosis of liposarcoma because a diagnosis based primarily on morphology. S-100 may be helpful in highlighting lipoblasts or recognizing liposarcomas with predominant round cell morphology. Immunostaining or FISH for MDM2 shows that MDM2 is amplified in the majority of liposarcomas.

11.5.6 Differential Diagnosis

Establishing a diagnosis of liposarcoma is usually not that challenging. A metastatic tumor has to be ruled out at the first. Focal fatty change of the liver may present as a mass lesion and the cells may contain a large amount of fat. However, careful examination can easily determine that the lesion is formed by fatty hepatocytes rather than adipocytes. Lipoma, another lipomatous tumor that rarely involves the liver, can be differentiated from well-differentiated liposarcomas by its capsule, lack of significant variation in cell size, atypia, and the scattered large hyperchromatic cells and multinucleated stromal cells. Immunostaining or FISH for MDM2 can be helpful to distinguish lipoma from well-differentiated liposarcoma; MDM2 is usually amplified in liposarcomas but not in lipoma. The differential diagnosis for hypercellular round cell liposarcoma or dedifferentiated liposarcoma can be difficult. Careful examination of multiple sections to identify evidence of lipogenic differentiation or lipoblasts can help to make the diagnosis.

11.6 Fibrosarcoma

11.6.1 Definition

Primary hepatic fibrosarcoma is a rare malignant tumor composed of fibroblasts with variable collagen production. This tumor may represent a malignant form or malignant transformation of solitary fibrous tumors [35].

11.6.2 Clinical Features

Primary hepatic fibrosarcoma tends to occur more often in males. Patients can range in age from 30 to 73 years (median age at diagnosis is 55 years) [36]. Patients may present with an abdominal mass with nonspecific symptoms such as abdominal pain and weight loss. The tumor is sometimes be associated with severe hypoglycemia [37, 38], secondary to insulin-like growth Factor-II secreted by the tumor. The primary treatment is surgery, but the prognosis is dismal [39].

11.6.3 Gross Findings

The tumor usually consists of a large, solitary, rounded, or lobulated mass. Small tumors may be well circumscribed with partial or complete encapsulation, but large tumors are less well defined and may grow in a diffusely invasive pattern. On cut surface, most tumors are firm and fleshy with pinkish-white to tan-yellow color and can have a whorled appearance. Focal yellowish areas representing necrosis and dark red areas representing hemorrhagic foci can be seen.

11.6.4 Microscopic Findings

The tumor typically has a rather common uniform fasciculated growth pattern consisting of fusiform or spindle cells with little variation in size and shape. The cells are arranged in curving or interlacing fascicles, forming a classical herringbone pattern (Fig. 11.31). The tumor cells have scant cytoplasm and indistinct cell borders (Fig. 11.32) and are separated by interwoven collagen fibers. In some cases, the cells are separated by thick, wire-like collagen fibers. Some tumors may have less cellular areas (Fig. 11.33) or focal myxoid areas. The fascicular or herringbone growth pattern is less distinct in high-grade fibrosarcoma. Instead, the cells are more pleomorphic, more mitotically active, and have frequent areas of necrosis and/or hemorrhage.

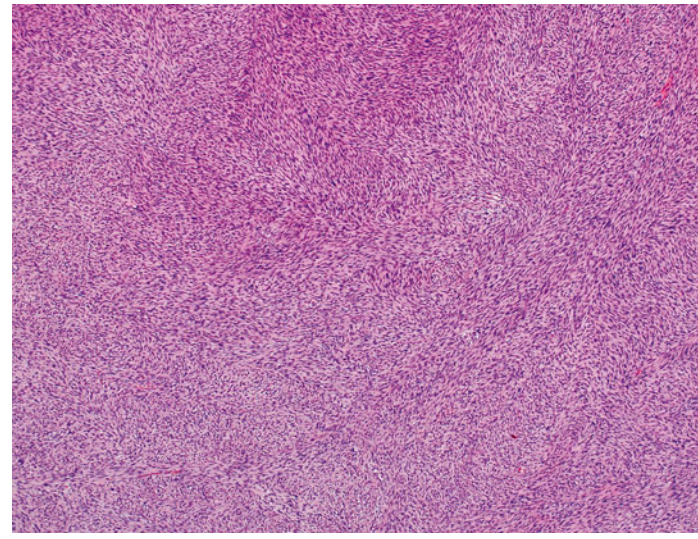

Fig. 11.31 Fibrosarcoma. Tumor cells arranged in curving or interlacing fascicles, forming a classical herringbone pattern

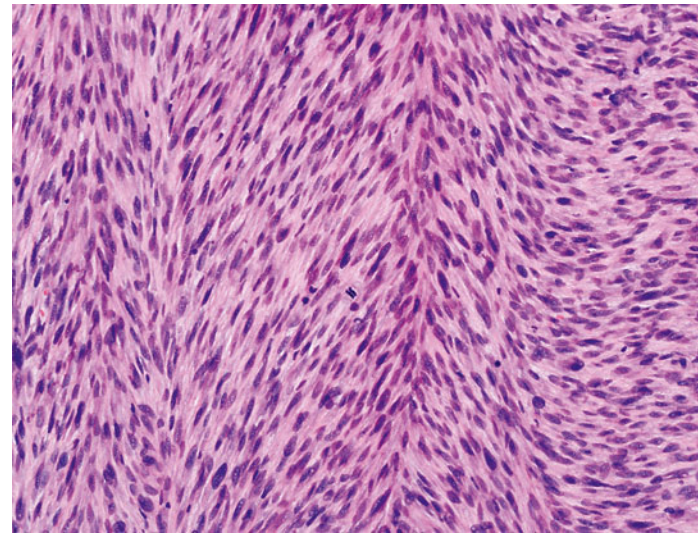

Fig. 11.32 Fibrosarcoma. Higher power examination of the same tumor seen in Fig. 11.31 shows spindled cells with scant cytoplasm, indistinct cell borders, and mitotic activity

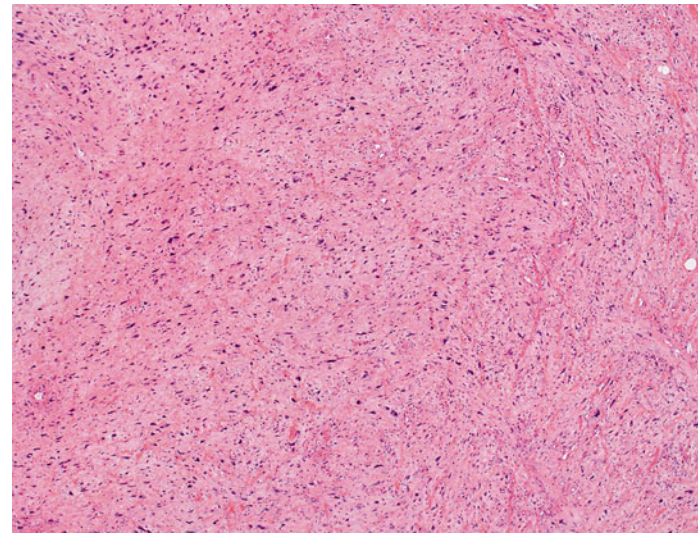

Fig. 11.33 Fibrosarcoma. Some tumors show less cellular areas

11.6.5 Immunohistochemical Features

Fibrosarcoma is positive for vimentin and negative for other lineage-specific markers such as keratin or S-100 proteins. In some cases, occasional tumor cells may be positive for smooth muscle actin or muscle-specific actin, which indicates focal myofibroblastic differentiation.

11.6.6 Differential Diagnosis

The differential diagnosis mainly includes other spindle cell tumors. In fact, some of the primary hepatic fibrosarcomas reported in the older literature likely represent malignant solitary fibrous tumors or gastrointestinal stromal tumors. Careful examination of multiple sections and ancillary studies are necessary to render a correct diagnosis. Immunohistochemical stains for specific lineage markers can separate leiomyosarcoma from fibrosarcoma (smooth muscle actin and desmin positive) and gastrointestinal stromal tumor (CD117 and DOG-1 positive). Poorly differentiated or pleomorphic fibrosarcoma can also mimic undifferentiated pleomorphic sarcoma. Microscopically, undifferentiated pleomorphic sarcoma is characterized by storiform to haphazard growth with the presence of giant cells and xanthoma-like cells. Some benign processes with reactive fibroblastic proliferation, such as inflammatory pseudotumors, usually demonstrate significant inflammatory infiltrates and less-ordered arrangement of cells, compared to fibrosarcoma. Solitary fibrous tumor lacks the herringbone pattern of fibrosarcoma and lacks the cytologic atypia and mitotic activity as well; instead solitary fibrous tumor features a "patternless" pattern of growth (see Chap. 3).

11.7 Leiomyosarcoma

11.7.1 Definition

Primary hepatic leiomyosarcoma is a rare malignant tumor that originates in smooth muscle. It usually arises in intrahepatic vascular structures, bile duct muscular wall, or ligamentum teres. Leiomyosarcoma arising from inferior vena cava is usually classified separately from primary hepatic leiomyosarcoma. Most leiomyosarcomas involving the liver are metastatic.

11.7.2 Clinical Features

Primary hepatic leiomyosarcoma occurs equally in men and women, but those arising in the inferior vena cava are more frequently seen in women. Most cases develop in adults but occasional cases have been reported in immunosuppressed children [40]; the median age of diagnosis is 58 years [41]. Tumors are often asymptomatic until they become large. Patients may present with a wide spectrum of nonspecific symptoms, such as abdominal pain, weight loss, anorexia, vomiting, jaundice, and rarely present with acute intra-abdominal bleeding secondary to tumor rupture [42]. Tumors arising in the hepatic veins can develop Budd–Chiari syndrome and usually have a worse prognosis. Complete surgical resection followed by adjuvant chemotherapy has been considered standard therapy, and a reasonable long-term survival (67 % disease-specific survival at 5 years) can be reached following complete resection [43].

11.7.3 Gross Findings

The tumor is typically solitary and often has a large size. On cut surface, most tumors are firm and fleshy with pinkish white color. Focal yellow area from necrosis and dark red area for hemorrhagic foci can also be seen (Fig. 11.34).

11.7.4 Microscopic Findings

Histologically, hepatic leiomyosarcoma shows identical features to its counterpart arising in other parts of the body. The tumor consists of bundles of elongated spindle cells intersecting at right angles (Fig. 11.35). Focal storiform, palisaded, or hemangiopericytoma-like patterns can also be present. The typical cells of leiomyosarcoma are

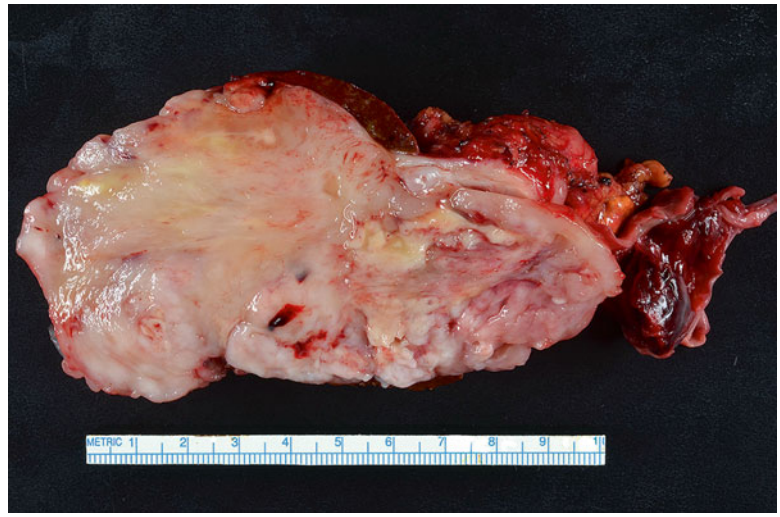

Fig. 11.34 Leiomyosarcoma, gross. A large solitary mass with fleshy, pinkish white color, and hemorrhagic foci in cut surface

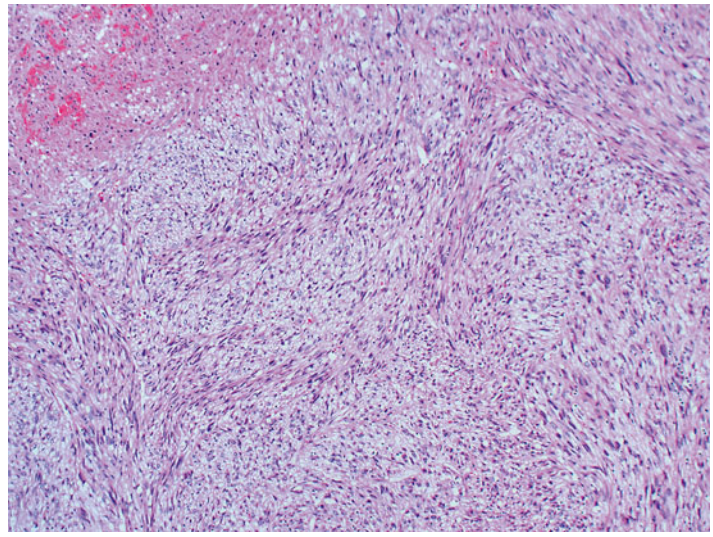

Fig. 11.35 Leiomyosarcoma. The tumor consists of intersecting bundles of elongated spindle cells at right angles

elongated with abundant eosinophilic cytoplasm. The cytoplasm may show red, hair-like longitudinal striations. The nucleus is usually centrally located and has a blunt-ended or "cigar-shaped" appearance (Fig. 11.36). In some tumor cells, a vacuole can be seen at one end of the nucleus, causing a slight nuclear indentation. Nuclear hyperchromatism and pleomorphism are notable, distinguishing leiomyosarcoma from benign smooth muscle neoplasms. Leiomyosarcoma typically shows atypia, necrosis, and increased mitotic activity (>10 mitoses in 50 high powered fields). In high-grade leiomyosarcoma, the nuclear atypical can be significant and pleomorphic area can resemble undifferentiated pleomorphic sarcoma. Multinucleated giant cells are common.

11.7.5 Immunohistochemical Features

Immunostains for smooth muscle actin (Fig. 11.37) and muscle-specific actin are positive in most leiomyosarcomas. H-caldesmon is also positive in the majority of tumors

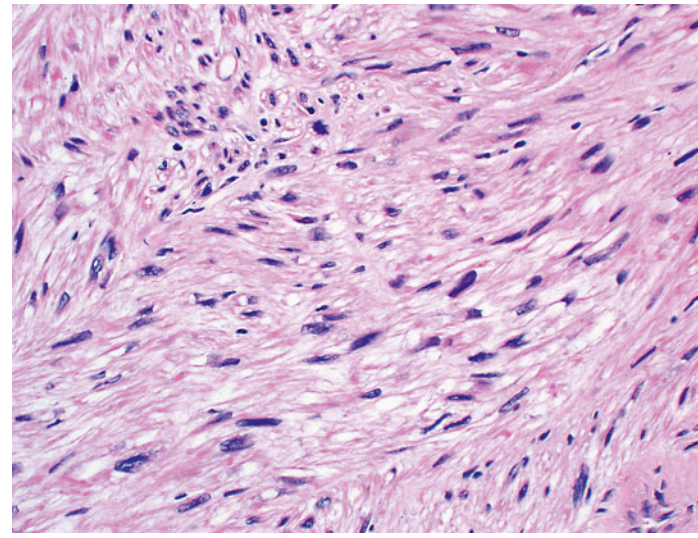

Fig. 11.36 Leiomyosarcoma. The cytoplasm of tumor cells shows red, hair-like longitudinal striations. The tumor cells also have "cigar-shaped" nuclei and mitotic activity

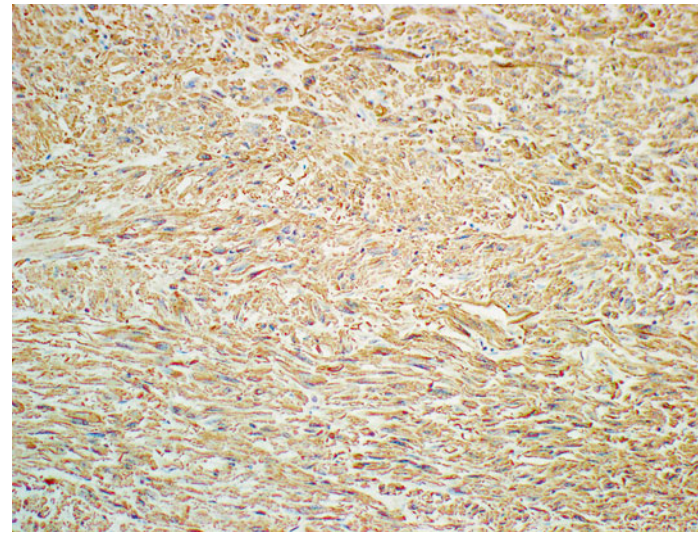

Fig. 11.37 Leiomyosarcoma. Tumor cells express smooth muscle actin

(Fig. 11.38), but desmin positivity ranges from about 50 % to nearly 100 % of tumors, depending on the study. None of these markers is absolutely specific for smooth muscle neoplasms. Therefore, a panel of several muscle markers should be applied and positivity of two of these markers is supportive of smooth muscle phenotype. Some tumors are also focally positive for EMA, CD34, keratin, and S-100 protein. CD117 is negative.

11.7.6 Differential Diagnosis

The differential diagnosis typically includes other sarcomas composed of fascicles of atypical spindle cells. First of all, metastatic leiomyosarcoma is more common than primary liver tumors, and this can only be ruled out clinically. Metastatic gastrointestinal stromal tumors can show similar morphological features to leiomyosarcoma, but immunohistochemical stains

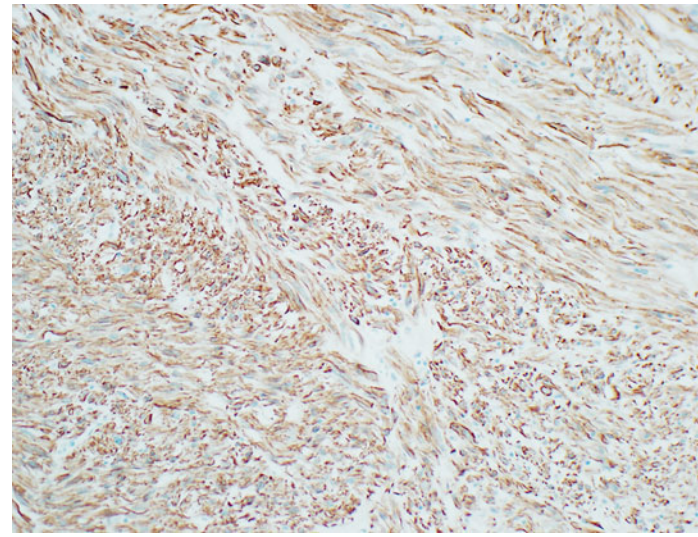

Fig. 11.38 Leiomyosarcoma. Tumor cells express H-caldesmon

for CD117 and DOG-1 can separate these two tumors. High-grade leiomyosarcoma often has pleomorphic areas that resemble undifferentiated pleomorphic sarcoma. Careful examination to find more typical smooth muscle differentiation, both by H&E sections and by immunohistochemistry, can help differentiate these two entities. Inflammatory pseudotumors are reactive myofibroblastic proliferations that can mimic leiomyosarcoma. But the spindle cells in these pseudotumors usually are more basophilic, have a less-ordered arrangement, have admixed inflammatory cells, and lack the atypia seen in leiomyosarcoma. Differentiating leiomyosarcomas from leiomyomas is accomplished morphologically; compared to the benign leiomyomas; leiomyosarcomas show atypia, necrosis, and increased mitotic activity (>10 mitoses in 50 high powered fields).

11.8 Undifferentiated Pleomorphic Sarcoma

11.8.1 Definition

Undifferentiated pleomorphic sarcoma refers to a group of high-grade sarcomas also called malignant fibrous histiocytoma and consists of frankly malignant mesenchymal cells without clear differentiation. The histogenesis and lineage of tumor cell differentiation are still unclear at this time.

11.8.2 Clinical Features

Although undifferentiated pleomorphic sarcoma is a common malignant high-grade sarcoma of soft tissue, it is an exceptionally rare primary tumor of liver. There are only a handful of case reports in the English literature [44–49]. Clinical symptoms are nonspecific. Patients can present with chest pain, right upper quadrant pain, or diffuse abdominal pain, weight loss, fever, jaundice, anorexia, malaise, and a palpable abdominal mass. Some have leukocytosis and elevated liver transaminases, alkaline phosphatase, and/or gamma-glutamyl transferase levels. Most primary hepatic undifferentiated pleomorphic sarcomas reported in the literature were treated surgically. Chemoradiation therapy usually has no effect and the prognosis is poor [48, 50, 51].

11.8.3 Gross Findings

The tumor is typically solitary, multilobulated, and fleshy, measuring 6–23.5 cm in diameter. On cut surface, most tumors are gray to white, but

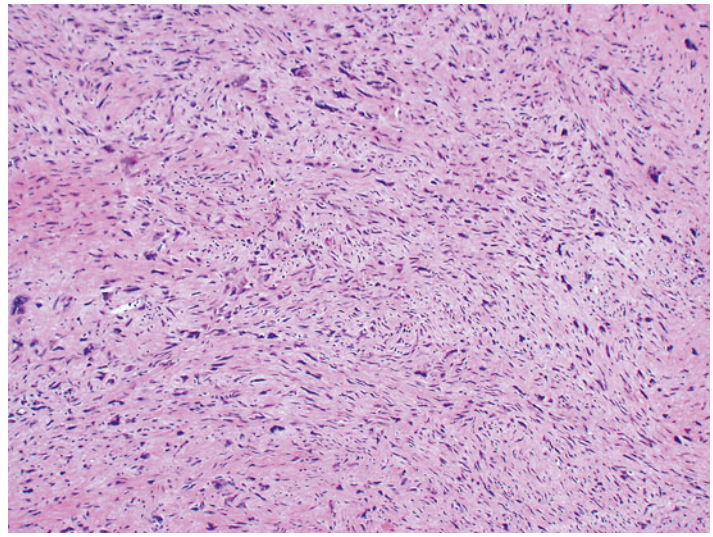

Fig. 11.39 Undifferentiated pleomorphic sarcoma. The storiform-pleomorphic variant is characterized by spindled cells arranged in short fascicles with a storiform pattern

the appearance can be heterogeneous due to the presence of various elements such as myxoid, hemorrhagic, or necrotic areas.

11.8.4 Microscopic Findings

Microscopically, the subtypes described in soft tissue undifferentiated pleomorphic sarcoma have all been reported in primary hepatic undifferentiated pleomorphic sarcomas, including storiform-pleomorphic, myxoid, giant cell, inflammatory, and angiomatoid. The storiform-pleomorphic form is the most common in the liver. It has two patterns and usually shows frequent transition between them. The storiform areas are characterized by spindle cells growing in short fascicles with a storiform pattern and arranged around slit-like vessels (Fig. 11.39). The spindle cells usually show low-grade cytological atypia. In contrast, the pleomorphic areas consist of more rounded, plumper, and pleomorphic cells, along with large numbers of giant cells that have multiple, hyperchromatic atypical nuclei. The stroma contains delicate collagen bands encircling individual cells, with variable degree of chronic inflammation. Focal myxoid change is not an uncommon feature. The myxoid type of undifferentiated pleomorphic sarcoma, on the other hand, is characterized by myxoid areas in association with areas of ordinary undifferentiated pleomorphic sarcoma, but at least half of the tumor should be myxoid in order to be designated as a "myxoid type" (Fig. 11.40). The other types of undifferentiated pleomorphic sarcoma are extremely rare in the liver [50], and the morphology is similar to their counterparts in soft tissue.

11.8.5 Immunohistochemical Features

Undifferentiated pleomorphic sarcoma does not have a specific immunophenotype. Because undifferentiated pleomorphic sarcoma is mainly a diagnosis of exclusion, immunohistochemistry is critical to exclude other malignant pleomorphic tumors, such as undifferentiated carcinomas or other high-grade sarcomas with specific cell lineages. Hence, the main role of immunohistochemistry is to provide evidence that the tumor does have a specific sarcomatous phenotype (such as smooth muscle). Although expression of CD68 has been described in undifferentiated pleomorphic sarcoma [48], this likely marks the presence of lysosomal granules rather than true histiocytic differentiation; other histiocytic markers such as Leu-s, Leu-M3, and lysozyme are negative. Undifferentiated pleomorphic sarcomas may focally express a number of intermediate filaments

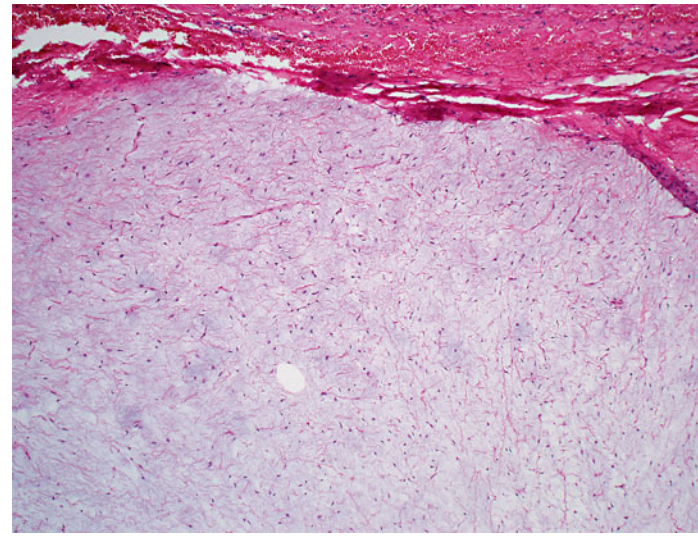

Fig. 11.40 Undifferentiated pleomorphic sarcoma. Myxoid type characterized by at least half of the tumor consisting of myxoid area containing low-grade cytologically atypical spindle cells

such as keratin or desmin, but such focal immunoreactivity alone is not sufficient to alter a diagnosis of undifferentiated pleomorphic sarcoma. On the other hand, diffuse positivity more likely reflects epithelial differentiation.

11.8.6 Differential Diagnosis

The key in the differential diagnosis is to separate undifferentiated pleomorphic sarcoma from other high-grade malignancies containing highly pleomorphic cells, such as undifferentiated carcinoma, carcinosarcoma, dedifferentiated liposarcoma, high-grade leiomyosarcoma, or a metastatic poorly differentiated malignancy such as malignant melanoma. Because the undifferentiated component of any of these neoplasms can be indistinguishable from undifferentiated pleomorphic sarcoma, careful sampling to search for more differentiated areas of the tumor is important and can unveil the lineage. The use of a targeted panel of immunohistochemical stains is also critical.

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