Practical Interpretation of Liver Biopsy, Volume 2

Edited by
Xiuli Liu
Jinping Lai
Nirag Jhala

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PREFACE

Our understanding of liver diseases has expanded in the last several decades as a result of advances in epidemiology, virology, immunology, and molecular biology. New revolutionary therapeutic agents such as anti-viral agents for hepatitis B and hepatitis C provide a cure for such patients. Recent clinical trials for non-alcoholic steatohepatitis reveal promising results. Liver pathology interpretation has played an essential role in all these aspects of *Hepatology* by providing information on the severity and stage of liver diseases and by pinpointing the etiology in some cases and narrowing down differential diagnoses in many other cases.

The spectrum of liver diseases undergoes dynamic changes. Liver pathology practice seems a daunting task for many pathologists including general pathologists, junior gastrointestinal and liver pathologists, in part, due to the complexity of anatomy, sophistication of biochemicals and metabolic functions, and multi-faceted clinical presentations of many liver diseases. In many cases, a liver biopsy only represents a snapshot of the liver disease and does not allow a pathologist to get a whole picture regarding the clinical course and reversibility of disease. A long-term clinical and histological follow-up provides the most meaningful liver pathology education in many cases. However, this type of information is difficult to acquire during our pathology residency and even liver pathology fellowship.

In this book, we include many common liver diseases with a brief clinical presentation, laboratory findings, and histological features. We also include histologic findings corresponding to treatment responses in some entities where specific therapies exist, notably, anti-viral agents in hepatitis B and C and removal of iron and copper in hereditary hemochromatosis and Wilson's disease. For metabolic liver diseases and hereditary diseases, we also emphasize the tissue allocation, biochemical analyses, ultrastructural examination, and genetic analyses.

This book reflects our struggling and thriving journey as liver pathologists. We intend to pass what we have learned from our combined 150+ years liver pathology practice to the readers of this book; we hope this book will help them generate an accurate histologic interpretation of the liver biopsies

during their practice. In addition, we would like to dedicate this book to all patients who have given us the privilege to review their liver biopsies, to learn, to share, and to teach.

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CHAPTER TWENTY

NON-NEOPLASTIC NODULES OF THE LIVER

L. WALDEN BROWNE, PHD, MD

Abstract

A liver biopsy is commonly used to diagnose liver mass lesion(s). However, not all liver mass lesions are neoplastic diseases. In many instances, the liver biopsy from the mass lesion may reveal a reactive process. A pathologist's knowledge and high vigilance of these non-neoplastic mass-forming entities help direct clinical treatment and management of these lesions. The accurate diagnosis of such entities is best achieved through a multidisciplinary approach. This chapter discusses the most common benign/reactive processes which may present as a mass lesion in the liver, with an emphasis on focal nodular hyperplasia, nodular regenerative hyperplasia, inflammatory processes (inflammatory pseudotumor, hepatic pseudolymphoma, follicular cholangitis), extramedullary hematopoiesis, focal fatty nodule, and segmental atrophy of the liver.

Keywords: Liver mass; Focal nodular hyperplasia; Nodular regenerative hyperplasia; Focal fatty nodule; IgG4-sclerosing cholangitis; Inflammatory pseudotumor; Extramedullary hematopoiesis; Segmental atrophy; Nodular elastosis.

Introduction

Imaging studies are commonly performed to investigate patients with abdominal pain or symptoms of the upper gastrointestinal tract. Thus, liver lesions/masses are increasingly identified. While some entities such as focal nodular hyperplasia have specific characteristics on imaging studies, some of the lesions can be deemed indeterminate by imaging and subjected to biopsy for a definite diagnosis. A liver pathologist should use a systemic approach to identify the non-neoplastic changes in the biopsy which

potentially account for the radiographically evident lesion/mass. A pathologist's knowledge and high vigilance of these non-neoplastic mass-forming entities help direct clinical treatment and management of these lesions. The accurate diagnosis of such entities is best achieved through a multidisciplinary approach. This chapter discusses the most common benign/reactive processes which may present as a mass lesion in the liver with an emphasis on focal nodular hyperplasia, nodular regenerative hyperplasia, inflammatory processes (inflammatory pseudotumor, hepatic pseudolymphoma, follicular cholangitis), extramedullary hematopoiesis, focal fatty nodule, and segmental atrophy of the liver. It also mentions rare conditions such as hepatic endometriosis, adrenal rest tumor, and intrahepatic splenic tissue.

1. Focal nodular hyperplasia

A. Definition

Non-neoplastic mass formed by hyperplastic hepatocytes in response to multifactorial localized vascular flow abnormalities in the liver.[1,2]

B. Clinical features and physical examination

Focal nodular hyperplasia (FNH) is most commonly detected in young women as an incidental imaging finding and is most often asymptomatic. There is no known association with oral contraceptive use.[3] FNH much less commonly occurs in men and children.[4,5] Rare large lesions can impinge on adjacent organs and/or cause abdominal pain. FNH may occasionally regress.[6]

C. Laboratory tests

Not pathologically relevant.

D. Imaging studies

The majority (90%) of cases of FNH can be diagnosed with imaging. Contrast-enhanced ultrasonography (US) is associated with a spoke-wheel sign in FNH.[7] T1-weighted magnetic resonance imaging (MRI) and T2-weighted MRI also have strongly suggestive enhancement characteristics for the main nodular tissue and the central scar.[8,9]

E. Macroscopic and histological abnormalities

Macroscopically, FNH frequently consists of a lobulated, non-encapsulated pale or tan firm mass that can range in size from a few millimeters to greater than 10 cm. The nodular zones of the mass are separated by a radiating, stellate pattern of fibrous strands, although some cases of FNH lack a central scar.[10]

Microscopically, FNH consists of bland-appearing hepatocytes arranged in slightly irregular hepatocyte trabeculae of 1-2 cells-thick. The nodules are associated with arterioles unaccompanied by native bile ducts. The areas of fibrosis frequently contain large, irregularly-shaped arterioles that on cross section have an asymmetric appearance. Lymphocytes and ductular reaction are frequently seen at the edges of the fibrous areas, and cholate stasis is sometimes noted in the adjacent hepatocytes. The absence of portal areas across broad areas of the liver parenchyma is sometimes the first clue of the presence of the lesion in small biopsies, although it is important to remember that needle core biopsies sometimes represent only partial penetrative sampling of FNH with adjacent normal liver also frequently sampled. Microscopic features of FNH are shown in **Figs. 20.1, 20.2, 20.3, 20.4, and 20.5.**

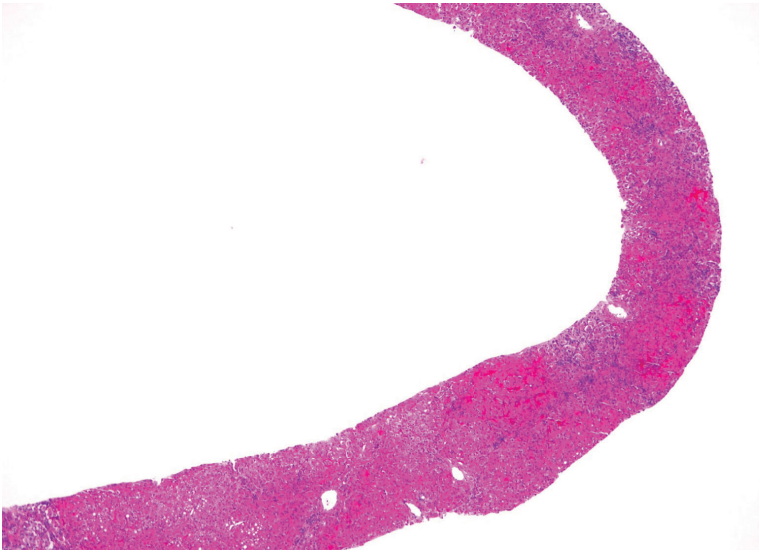

Fig 20.1 Features of focal nodular hyperplasia. Biopsy reveals benign liver parenchyma with nodular regeneration and fibrosis. Low power view.

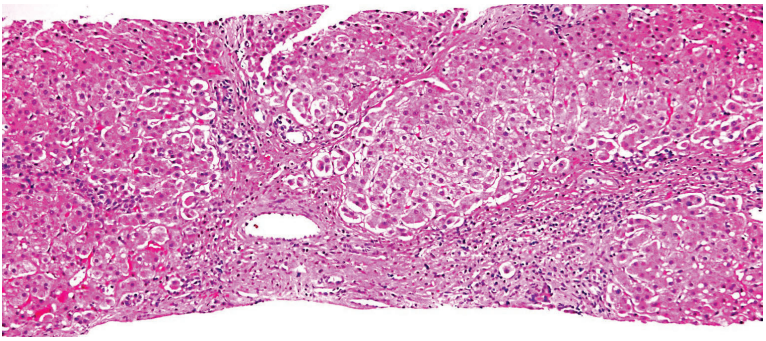

Fig 20.2 Features of focal nodular hyperplasia. Broad fibrous bands dissecting hepatocyte nodules. Intermediate power view.

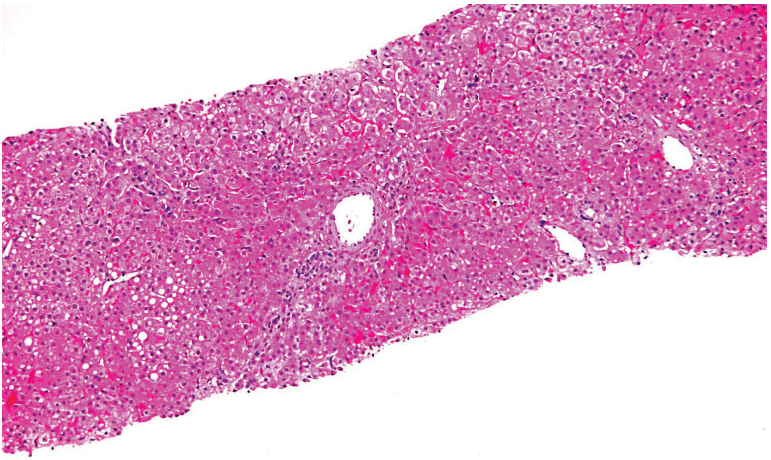

Fig 20.3 Features of focal nodular hyperplasia. Abnormal and thickened arterioles in the central scar.

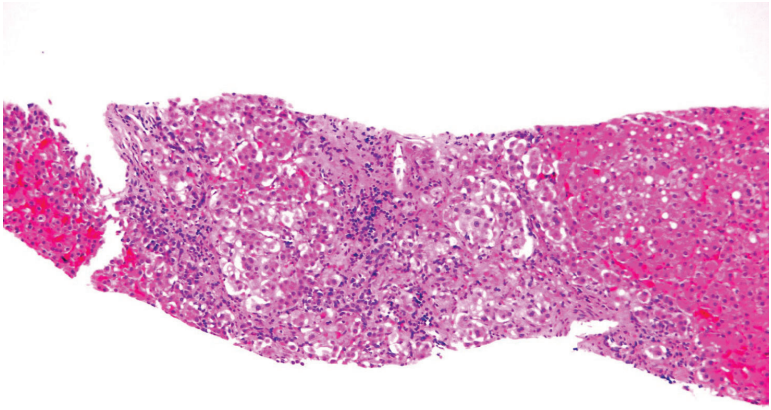

Fig 20.4 Features of focal nodular hyperplasia. Ductular reaction and cholate stasis manifested by enlarged and pale peri-septal hepatocytes are present.

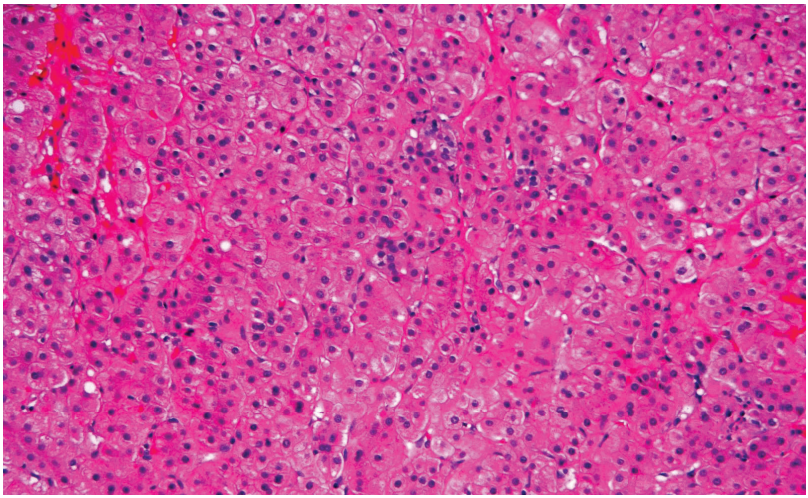

Fig 20.5 Hepatocyte proliferation with rosette formation in the hepatocyte nodules in focal nodular hyperplasia.

F. Special histochemical stains and immunohistochemistry

Reticulin staining typically highlights intact reticulin fibers surrounding narrow hepatocyte trabeculae of 1-2 cells-thick that shows some irregularity in their overall distribution. Trichrome staining highlights the fibrosis. CD34 immunostaining frequently highlights aberrant arterialization of the sinusoidal spaces, and this stain is sometimes useful in mapping out the areas of lesional tissue in fragmented needle biopsy cores for comparison with other stains. However, aberrant CD34 immunolabeling is not a specific finding, since it is also associated with many hepatocellular neoplasms. Glutamine synthetase immunostaining frequently shows a map-like pattern of strong immunolabeling in FNH (**Fig. 20.6**), and when present in small biopsies, this feature is extremely useful in establishing the diagnosis of FNH. Immunostaining with C-reactive protein and serum amyloid A is either absent or very patchy and light in FNH. Immunostaining with liver fatty acid binding protein (LFABP) is intact, although of technical note, this immunostaining in many hands shows very light positivity in most liver tissue. Beta-catenin immunostaining does not show aberrant nuclear staining in FNH.

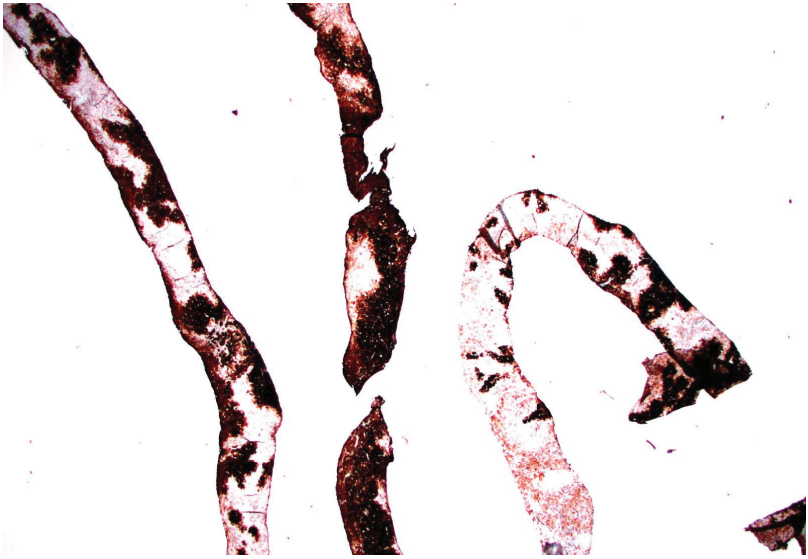

Fig 20.6 Map-like immunoreactivity of glutamine synthetase in lesional hepatocytes in focal nodular hyperplasia (immunohistochemical stain).

G. Differential diagnosis

Inflammatory hepatocellular (hepatic) adenomas (**Figs. 20.7, 20.8, 20.9 and 20.10**) pose the most challenging diagnostic difficulty but they show strong diffuse immunolabeling with serum amyloid A and/or C reactive protein. Fatty change is more commonly seen in hepatocellular adenomas than in FNH, but there is considerable morphologic overlap between FNH and adenomas.[11,12] Therefore, ancillary studies are important in categorizing these lesions. Atypical beta-catenin-activated hepatocellular adenomas show strong diffuse immunostaining with glutamine synthetase and aberrant nuclear immunostaining with beta-catenin. Steatotic/hepatic nuclear factor 1-homeobox-A (HNF1A)-inactivated hepatocellular adenomas show loss of immunolabeling with LFABP.

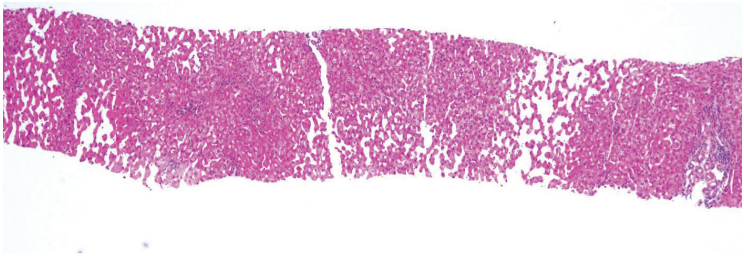

Fig 20.7 Features of inflammatory hepatocellular adenoma. Biopsy of liver mass reveals nodular regeneration and sinusoidal dilatation (telangiectasia). Low power view.

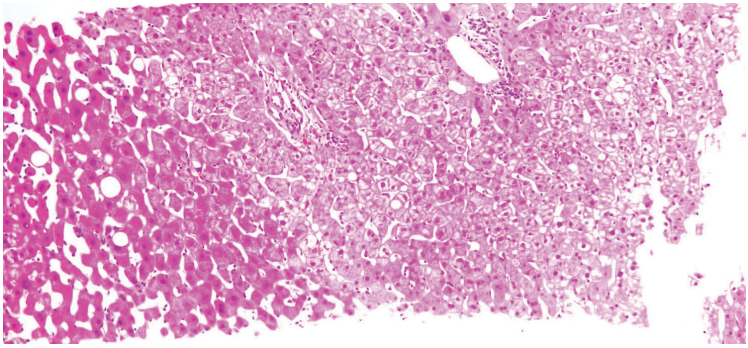

Fig 20.8 Features of inflammatory hepatocellular adenoma. Interface between portal tract-containing background liver (left) and lesional tissue with angiectasia. Intermediate power view.

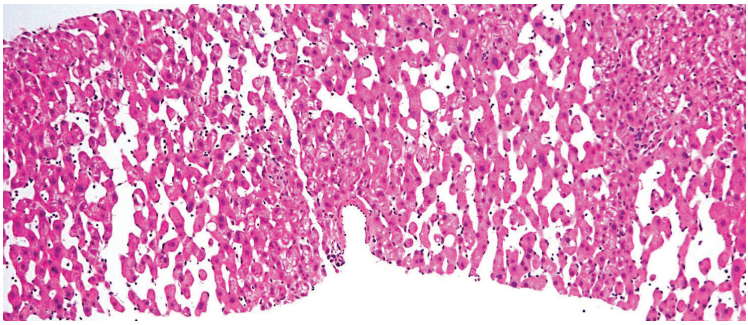

Fig 20.9 Sinusoidal dilatation in the lesional tissue in inflammatory hepatocellular adenoma.

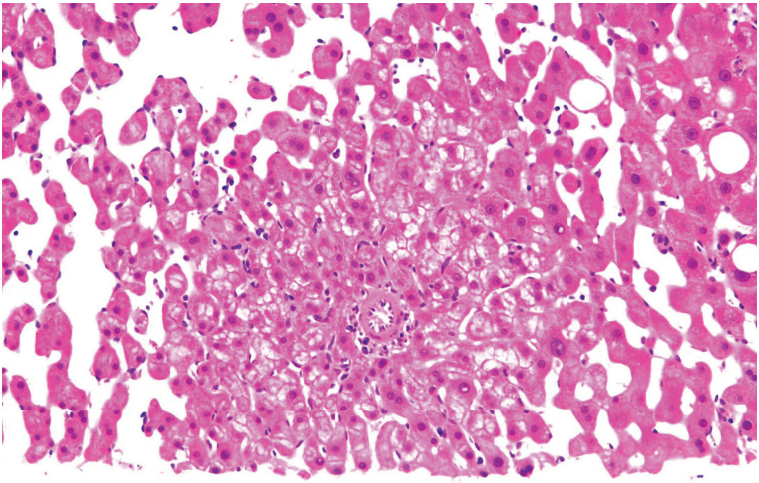

Fig 20.10 Isolated arteriole in the lesional tissue is a common finding in inflammatory hepatocellular adenoma.

Hepatocellular carcinoma (HCC) generally shows loss of reticulin staining and aberrantly-wide hepatocellular trabeculae of 3 or greater-cells-thick. HCC sometimes also shows aberrant nuclear immunolabeling with beta-catenin. Strong immunolabeling with glypican-3 when present supports a diagnosis of HCC, but since the differential diagnosis is most commonly with well-differentiated HCC, which is frequently negative for glypican-3, glypican-3 may be of limited utility in this context. The fibrosis on a small biopsy of FNH could raise the possibility of cirrhosis in a histologic

preliminary differential diagnosis. Radiologic and clinical correlation is important in this context. Cirrhosis would not show a map-like pattern of immunolabeling with glutamine synthetase. Cytokeratin 7 (CK7) immunostaining highlights ductular reaction in both FNH and cirrhosis, but to the extent that CK7 highlights native bile ducts, it could prove useful in excluding a diagnosis of FNH.

2. Nodular regenerative hyperplasia

A. Definition

Nodular regenerative hyperplasia (NRH) is a benign nonspecific reactive process that is characterized by noncirrhotic regenerative and hyperplastic nodules that alternate with parenchymal atrophy, and which most commonly diffusely involves the liver.[13]

B. Clinical features and physical examination

NRH occurs in both men and woman and at all ages, although it is more common in older individuals. NRH is thought to represent a nonspecific response to vascular injury in the liver that involves small portal veins and hepatic arteries. Patients frequently have portal hypertension. The clinical features and/or symptoms indirectly seen with NRH can be associated with a broad array of diseases that cause the vascular injury that precipitates NRH. These diseases include several hematologic disorders, autoimmune disorders, renal diseases, prothrombotic states, medications, and a growing list of other conditions. NRH is often secondarily associated with other liver disorders, including masses, primary biliary cholangitis, primary sclerosing cholangitis, hepatic vascular disorders, hepatoportal sclerosis, Budd-Chiari syndrome, liver transplantation-related changes, and hereditary hemorrhagic telangiectasia.

C. Laboratory tests

Patients with NRH may have no abnormal serologic liver testing results, although some patients have an elevated alkaline phosphatase (ALP) level or gamma glutamyl transferase (GGT) level.[14,15]

D. Imaging studies

Radiologically, NRH may present as multiple nodules, large masses, or a radiologically normal liver, the latter because the nodules measure less than 0.5 cm in diameter.[16] NRH is among the constellation of liver lesions that radiologically mimic cirrhosis.[17]

E. Macroscopic and histological abnormalities

Macroscopically, NRH diffusely involves the entire liver as numerous small nodules that range in size from 1-3 mm generally, and which can cause surface nodularity that mimics cirrhosis.

Microscopically, at low power, NRH has a nodular appearance without evidence of fibrosis (**Figs. 20. 11 and 20.12**). At higher power, the nodularity is revealed as alternating areas of atrophic hepatocytes and enlarged regenerative hepatocytes that are nevertheless contained within trabeculae that are 1-2 cells-thick. The regenerative nodules contain central portal areas and peripheral central zones.

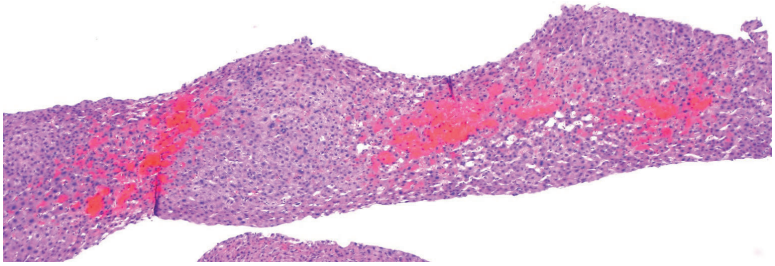

Fig 20.11 Nodular regenerative hyperplasia. Biopsy of the liver shows centrilobular hemorrhage and sinusoidal dilatation alternating with nodular regeneration

Fig 20.12 Trichrome stain does not reveal fibrosis. This case of nodular regenerative hyperplasia is secondary to Budd-Chiari syndrome.

F. Special histochemical stains and immunohistochemistry

A reticulin stain is the most useful ancillary test in the diagnosis of NRH, since it will highlight the alternating areas of compressed atrophic hepatocyte trabeculae and regenerative hypertrophic hepatocyte trabeculae. The trichrome stain will also confirm the absence of significant fibrosis, since absent significant fibrosis is a definitional requirement of NRH. Immunohistochemical staining generally is not necessary except in a subset of cases where it is necessary to exclude other entities in the differential diagnosis.

G. Differential diagnosis

Cirrhosis is the entity that needs to be excluded most frequently in the diagnosis of NRH, especially since biopsies are often obtained to rule out cirrhosis. The trichrome stain, which will show an absence of significant fibrosis, is a most useful ancillary study in this respect, although the reticulin stain will also confirm the absence of fibrosis in NRH. If a mass is suspected clinically, then further immunohistochemical stains to exclude hepatocellular adenomas might be warranted. NRH will not show strong diffuse immunolabeling with serum amyloid A or C-reactive protein, as would be expected with inflammatory hepatocellular adenoma. NRH will

show a patchy reactive pattern of immunolabeling with glutamine synthetase, but the strong map-like pattern of immunolabeling that is characteristic of focal nodular hyperplasia will be absent. The presence of intervening portal areas, along with a reticulin stain showing narrow hepatocyte trabeculae, generally suffices to exclude a diagnosis of hepatocellular carcinoma. Since NRH can be secondarily associated with other liver tumors, it is important to examine carefully all components of small liver biopsies that sometimes only capture a minute portion of the neoplasm at the tips or edges of the biopsy cores. Furthermore, if the radiologic impression is that of a true mass, a comment indicating that NRH-like changes can be seen sometimes adjacent to an unsampled mass, and that another biopsy may be considered, might prove to be an important suggestion to the clinicians.

3. Inflammatory pseudotumors

A. Definition

Inflammatory pseudotumors include lymphoplasmacytic-type inflammatory pseudotumor and fibrohistiocytic-type inflammatory pseudotumor.[18] Inflammatory myofibroblastic tumors are now thought to be neoplastic in nature and have been separated out from the pseudotumor category.

Lymphoplasmacytic-type inflammatory pseudotumor represents a liver manifestation of immunoglobulin subclass G4 (IgG4)-related disease and is characterized as a hepatic mass with a preponderance of IgG4-positive plasma cells, and which is associated with fibrosis and obliterative phlebitis. Patients mostly have elevated serum IgG4.

Fibrohistiocytic-type inflammatory pseudotumor is characterized as a mass with foci of suppurative and xanthogranulomatous inflammation, a lymphoplasmacytic inflammatory infiltrate, and a minority population or absence of IgG4-positive plasma cells.

B. Clinical features and physical examination

Lymphoplasmacytic-type inflammatory pseudotumors frequently form a mass along the biliary tree, and with liver masses, the clinical concern is most frequently for a perihilar cholangiocarcinoma. However, lymphoplasmacytic-type inflammatory pseudotumors generally respond well to steroids, so the pathologic identification may prove to be crucial in avoiding unnecessary surgery. The majority of patients with lymphoplasmacytic-type inflammatory

pseudotumors have IgG4-related disease in other organs, although in about 8% of cases the liver may be the primary manifestation.[19] Most cases arise in the sixth decade or later, and there is a male predominance. In contrast, fibrohistiocytic-type pseudolymphomas occur in both men and woman, and most nodules are located in the peripheral liver parenchyma.

C. Laboratory tests

The majority (80%) of patients with lymphoplasmacytic-type inflammatory pseudotumors have elevated serum IgG4, although elevated IgG4 is not completely specific.[20] Other serological abnormalities include immunoglobulin G (IgG) elevations (60%), antinuclear antibodies (40%), and rheumatoid factor (20%).[21]

D. Imaging studies

As noted above, since lymphoplasmacytic-type inflammatory pseudotumors of the liver often form a mass in the perihilar region, they radiologically mimic cholangiocarcinoma. Fibrohistiocytic-type inflammatory pseudotumors more commonly present as masses in the peripheral liver.[18]

E. Macroscopic and histological abnormalities

Macroscopically, lymphoplasmacytic-type inflammatory pseudotumors present as an unencapsulated but circumscribed mass in the biliary tree with a firm tan-white cut surface. Microscopically, lymphoplasmacytic-type inflammatory pseudotumors show a predominantly periportal distribution of lymphocytes and IgG4-positive plasma cells, which is associated with a storiform pattern of fibrosis and obliterative phlebitis. Refer to **Chapter 7** for detailed discussion.

Macroscopically, fibrohistiocytic-type inflammatory pseudotumors are characterized by an irregularly shaped mass or masses, which sometimes have foci of necrosis. Microscopically, fibrohistiocytic-type inflammatory pseudotumors are comprised of a mixed inflammatory infiltrate that includes histiocytes and neutrophils in a background of fibrosis (**Figs. 20.13, 20.14, 20.15, 20.16, 20.17, and 20.18**).

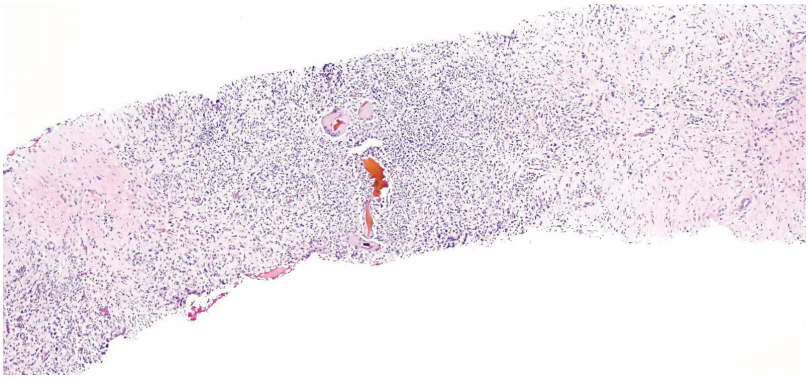

Fig 20.13 Fibrohistiocytic-type inflammatory pseudotumor. The biopsy from a liver mass shows fibrosis and inflammation with extravasated bile with giant cell response. Low power view.

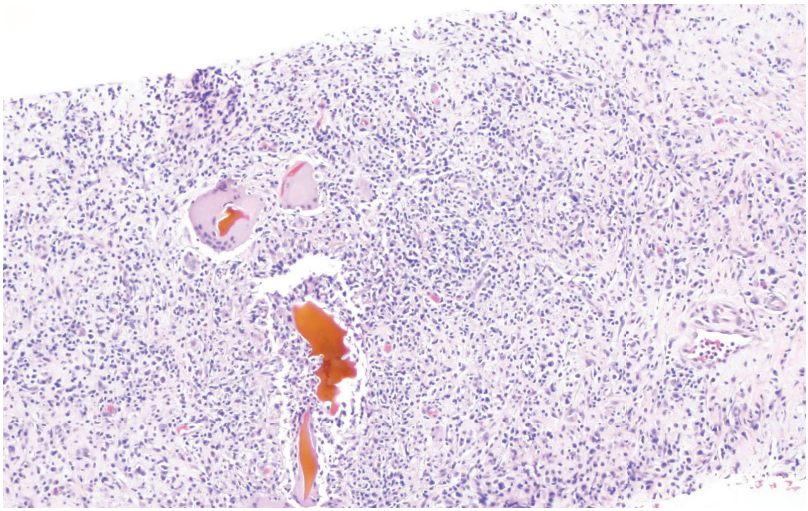

Fig 20.14 Fibrohistiocytic-type inflammatory pseudotumor. The biopsy from a liver mass shows fibrosis and inflammation with extravasated bile with giant cell response. Intermediate power view.

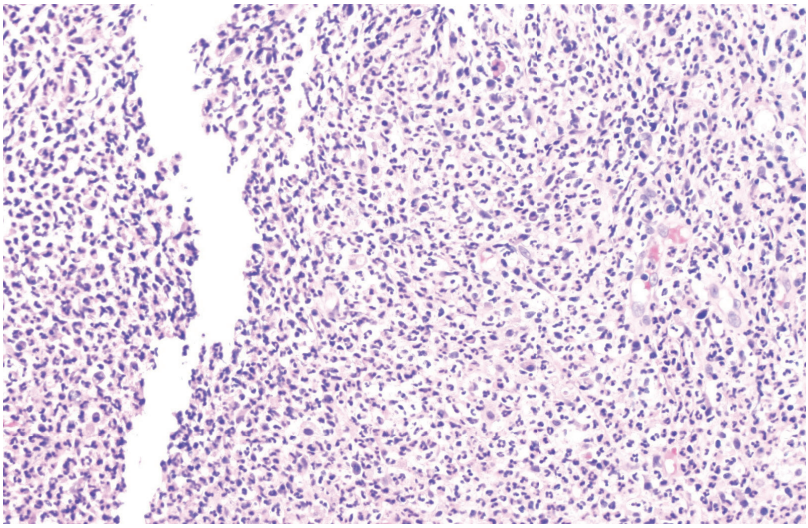

Fig 20.15 Fibrohistiocytic-type inflammatory pseudotumor. There is mixed mononuclear and neutrophilic inflammation.

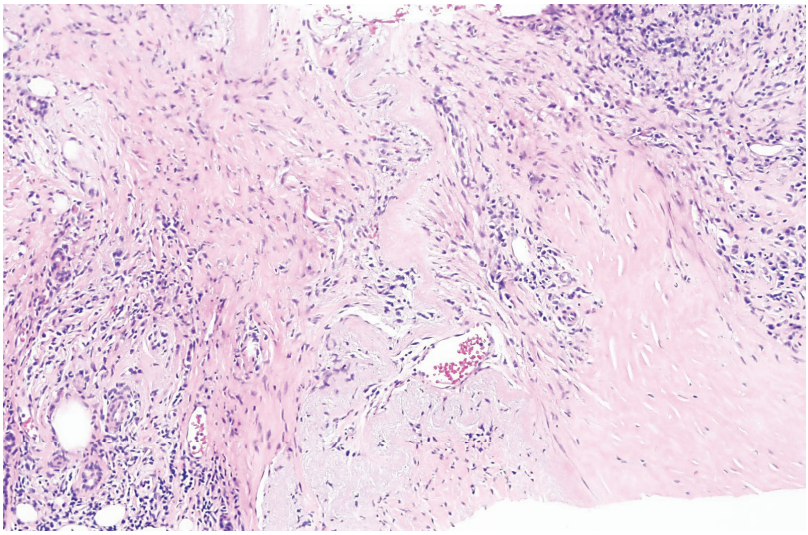

Fig 20.16 Fibrohistiocytic-type inflammatory pseudotumor. In the center of the lesion, there is fibrosis and elastosis, but less inflammation.

Fig 20.17 Inflammatory pseudotumor. The inflammatory infiltrate is primarily composed of CD3 positive T cells (immunostain).

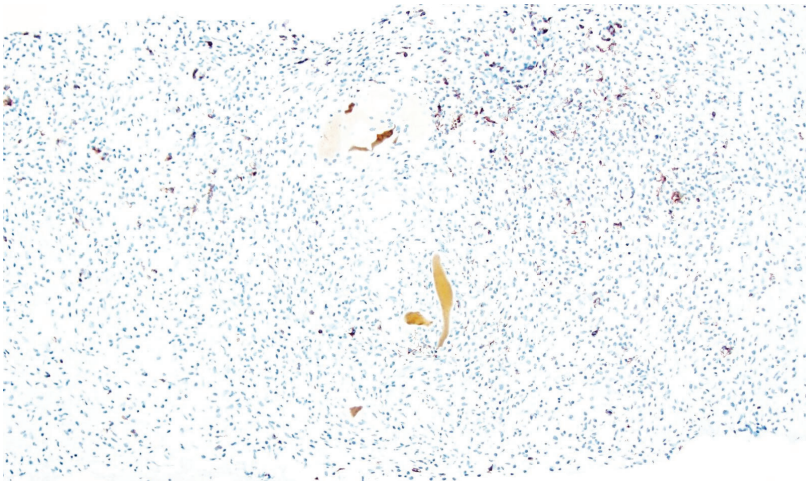

Fig 20.18 Inflammatory pseudotumor. Only few CD20 positive B cells are present (immunostain).

F. Special histochemical stains and immunohistochemistry

The plasma cells in lymphoplasmacytic-type inflammatory pseudotumors by definition show an increase of IgG4-positive plasma cells defined as greater than 50 per high-power field or IgG4-positive plasma cells representing greater than 40% of the total number of IgG-positive plasma cells.[22] In contrast, fibrohistiocytic-type inflammatory pseudotumors do not have a preponderance of IgG4-positive plasma cells. Kappa and lambda immunostains or in situ hybridization will indicate the polyclonal nature of the plasma cells. CD68 and CD163 immunostains highlight the histiocytes in fibrohistiocytic-type inflammatory pseudotumors, but these immunostains generally are not required for a diagnosis.

G. Differential diagnosis

Perihilar cholangiocarcinoma is the most important entity to exclude in the differential diagnosis for lymphoplasmacytic-type inflammatory pseudotumors. The biliary epithelium in lymphoplasmacytic-type inflammatory pseudotumors may show some reactive changes, but the degree of cytologic and architectural atypia associated with cholangiocarcinoma will not be present. Furthermore, cholangiocarcinoma would not be expected to be associated with an aberrantly increased ratio of IgG4-positive plasma cells. On small biopsy material, if a clear-cut increase of IgG4-positive plasma cells is not appreciated, caution should be used in rendering the final diagnosis, since unsampled cholangiocarcinomas can sometimes be associated with secondary fibroinflammatory changes sampled on small biopsy material that could provide a false sense of complacency. This pitfall is true for fibrohistiocytic-type inflammatory pseudotumors, as well, so correlation with the clinical and radiologic findings is crucial to determine whether the targeted lesion was adequately sampled and not just adjacent fibroinflammatory changes. Positive microbiology cultures of a fibrohistiocytic-type inflammatory pseudotumor would add further evidence against a neoplasm.

Inflammatory myofibroblastic tumors, which are now considered true neoplasms, are often associated with positive immunohistochemical staining or fluorescence *in situ* hybridization (FISH) for ALK-1 or ROS-1.[23]

4. Hepatic pseudolymphoma

A. Definition

Hepatic pseudolymphoma is also known as reactive lymphoid hyperplasia of the liver and represents a benign, idiopathic, nodule-forming reactive lymphocytic lesion. By definition, neoplastic lymphoproliferative processes have been ruled out.[24]

B. Clinical features and physical examination

Most cases of hepatic pseudolymphoma are identified incidentally with imaging in adults, with the majority occurring in women.[25] A subset of hepatic pseudolymphoma cases occurs in patients with chronic liver disease, extrahepatic autoimmune disorders, or a history of malignancy.[25-27]

C. Laboratory tests

No pathologically relevant positive testing. Negative testing that would otherwise be associated with lymphoproliferative processes would be consistent with a diagnosis of pseudolymphoma.

D. Imaging studies

Pseudolymphoma is typically identified incidentally with imaging. 80% of patients have a single nodule and 20% have multiple nodules identified with imaging.[25,26,28]

E. Histological abnormalities

Hepatic pseudolymphoma is characterized microscopically by nodular aggregates of mature-appearing lymphocytes and reactive-appearing lymphoid follicles. The lymphocytes may be associated with fibrosis and surround, but generally do not infiltrate, the usual liver components such as native bile ducts.

F. Histochemical stain and immunohistochemistry

By definition, neoplastic lymphoproliferative processes must be excluded in order to establish a diagnosis of hepatic pseudolymphoma. Hepatic pseudolymphomas should demonstrate an admixture of numerous CD3-

positive T cells and lesser numbers of CD20-positive B cells, a low proliferation index with Ki-67, few or absent IgG4-positive plasma cells, and a polytypic pattern of immunostaining with kappa and lambda.

G. Differential diagnosis

Mucosa-associated lymphoid tissue (MALT) lymphoma is the neoplastic lymphoproliferative process that most closely resembles hepatic pseudolymphoma morphologically. In MALT lymphoma, the lymphocytes are cytologically monotonous and infrequently infiltrate and injure the biliary epithelium. MALT lymphoma is predominantly comprised of B cells with a light chain restriction. Challenging cases can be sent to specialized laboratories for immunoglobulin gene rearrangement studies.[29]

5. Follicular cholangitis

A. Definition

Follicular cholangitis is an under recognized mass-forming lesion that generally involves the large bile ducts or hilum, and which is characterized by aggregates of polyclonal lymphocytes and reactive lymphoid follicles.[30,31]

B. Clinical features and physical examination

Most patients with follicular cholangitis present with jaundice, and the presence of a hilar mass may raise clinical concern for a diagnosis of cholangiocarcinoma.

C. Laboratory tests

No pathologically relevant serologic abnormalities.

D. Imaging studies

Imaging studies reveal bile duct strictures or a hilar mass. The strictures could raise the possibility of primary sclerosing cholangitis (PSC) in the radiologic differential diagnosis, and the hilar mass could raise the radiologic possibility of cholangiocarcinoma.[32]

E. Macroscopic and histological abnormalities

Macroscopically, follicular cholangitis is characterized by a white firm poorly defined nodule surrounding large bile ducts, the latter of which remain intact. Microscopically, follicular cholangitis is characterized by a periductal lymphocytosis associated with reactive lymphoid follicles and fibrosis. The lymphocytes are mature-appearing and are comprised of an admixture of T cells and B cells. The lymphoid follicles are well circumscribed, rimmed by a mantle zone, and contain germinal center with mitotic figures and associated tingible-body macrophages.[31]

F. Histochemical stain and immunohistochemistry

The lymphocytes in the inflammatory infiltrate and the lymphoid follicles show a reactive phenotype. The lymphocytes are comprised of CD3-positive T cells and CD20-positive B cells, which are polyclonal by kappa and lambda immunostaining or in situ hybridization. Occasional eosinophils may be present, although neutrophils are not prominent. The plasma cells that are present do not show an increase in the IgG4 to IgG ratio by immunohistochemistry.

G. Differential diagnosis

PSC shows bile duct loss and injury, which differs from follicular cholangitis, the latter in which the bile ducts remain intact. Cholangiocarcinoma will be excluded by the absence of malignant epithelium in follicular cholangitis.[33] IgG4-related disease / inflammatory pseudotumor involving the hilum is excluded by the absence of a relative increase of IgG4-positive plasma cells in the total population of IgG-positive plasma cells.

6. Extramedullary hematopoiesis

A. Definition

Extramedullary hematopoiesis (EMH) in the liver can form a nodule or mass mimicking a neoplasm.[34,35] EMH has also been associated with massive hepatic necrosis.[36] Hepatic EMH is characterized by the presence of erythroid and myeloid precursors and megakaryocytes in the liver.

B. Clinical features and physical examination

Most adult cases of EMH occur in the setting of bone marrow diseases such as chronic myeloproliferative disorders, anaplastic anemia, or other bone marrow space occupying lesions such as metastases.

C. Laboratory tests

Patients with extra medullary hematopoiesis may have complete blood count (CBC) abnormalities associated with the bone marrow defects in hematopoiesis.

D. Imaging studies

Patients with hepatic EMH often have hepatomegaly, and as noted above, it occasionally forms a nodule or mass identified by imaging.

E. Histological abnormalities

Extramedullary hematopoiesis is comprised microscopically of erythroid and myeloid precursors and megakaryocytes that typically are located in the sinusoidal spaces, although they may also form scattered aggregates (**Figs. 20.19, 20.20**).

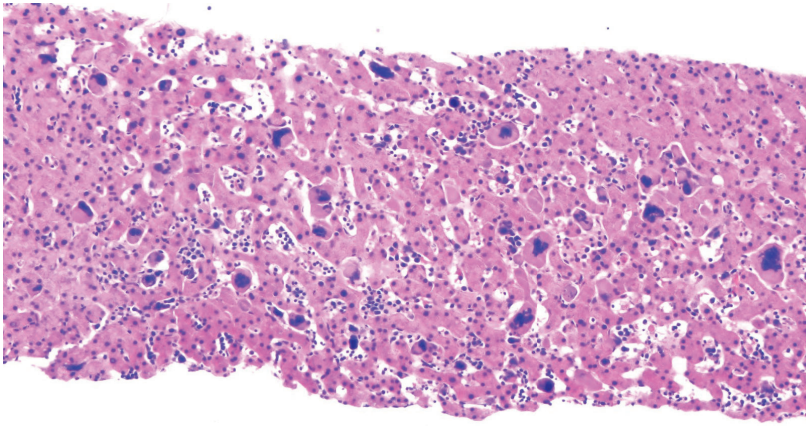

Fig 20.19 Extramedullary hematopoiesis is comprised microscopically of erythroid and myeloid precursors and megakaryocytes that typically are located in the sinusoidal spaces. Low power view.

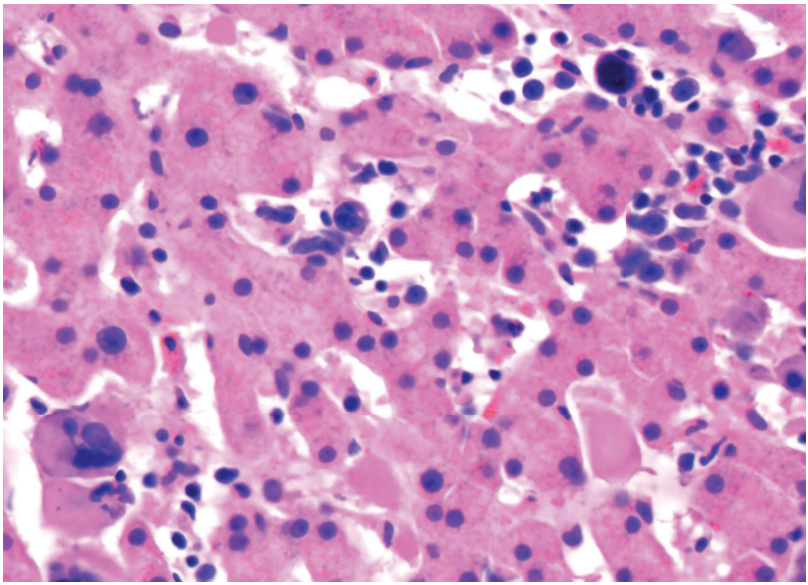

Fig 20.20 Extramedullary hematopoiesis is comprised microscopically of erythroid and myeloid precursors and megakaryocytes that typically are located in the sinusoidal spaces. High power view.

F. Special histochemical stain and immunohistochemistry

While not generally necessary to establish a diagnosis, the components of EMH can be immunolabeled in order to delineate an admixture of cell types. For instance, CD61 highlights megakaryocytes. Granulocytes can be highlighted with myeloperoxidase (**Fig. 20.21**). Erythroid precursors can be highlighted with glycophorin (**Fig. 20.22)**. If a lymphoproliferative process is in the differential diagnosis, further immunohistochemistry staining may be appropriate.

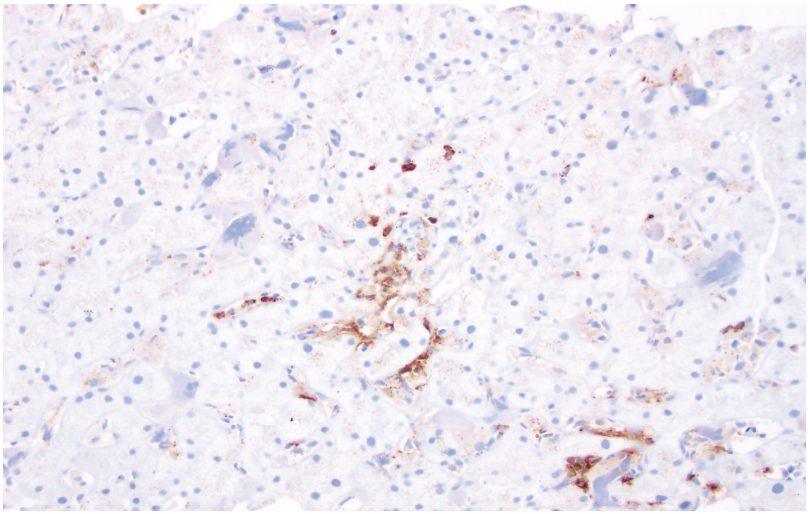

Fig 20.21 Granulocytes in extramedullary hematopoiesis are highlighted with myeloperoxidase (Immunostain).

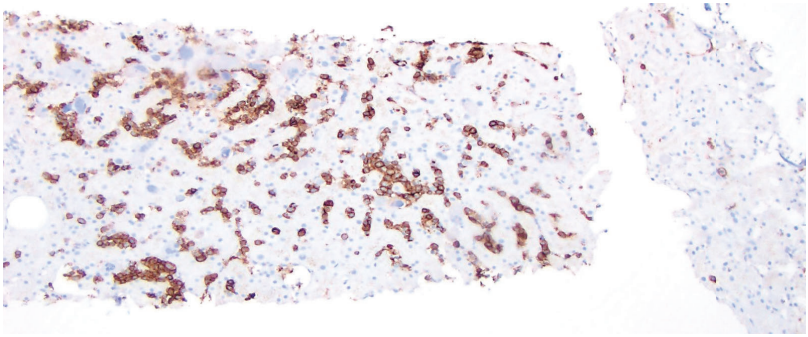

Fig 20.22 Erythroid precursors in extramedullary hematopoiesis are highlighted with glycophorin (Immunostain).

G. Differential diagnosis

The diagnosis of EMH is usually straightforward with routine histology, but lymphoproliferative disorders could enter into the differential diagnosis. EMH is sometimes seen in association with neoplasms, including embryonal sarcoma, mesenchymal hamartoma of the liver, and hepatic infantile hemangiomas.[37]

7. Focal fatty nodule

A. Definition

Focal fatty nodule of the liver is characterized by a benign nodule of hepatocytes with fatty change in a background of liver parenchyma with no significant steatosis.[38]

B. Clinical features and physical examination

Most cases of focal fatty nodules are incidental findings. Focal fatty nodules range in size up to 12 cm and is generally located in the subcapsular area of the liver. Large nodules have been associated with traumatic rupture.[39] Focal fatty nodules are thought to be associated with the same conditions associated with fatty liver disease and steatohepatitis, including obesity.[38] Focal fatty nodules have been reported both in adults and children, but are most common in adult women.[38,40]

C. Laboratory tests

No pathologically relevant serologic testing.

D. Imaging studies

Focal fatty nodules can generally be recognized with computed tomography (CT) imaging, although by ultrasonography they can be mistaken for hepatic neoplasms.[41]

E. Macroscopic and histological abnormalities

Macroscopically, focal fatty nodules are mostly located in the subcapsular areas of the liver parenchyma and on cut section have a yellow-tan nodular appearance. Microscopically, the nodules are comprised of closely approximated hepatocytes with large-droplet fatty cell change (**Figs 20.23 and 20.24**).

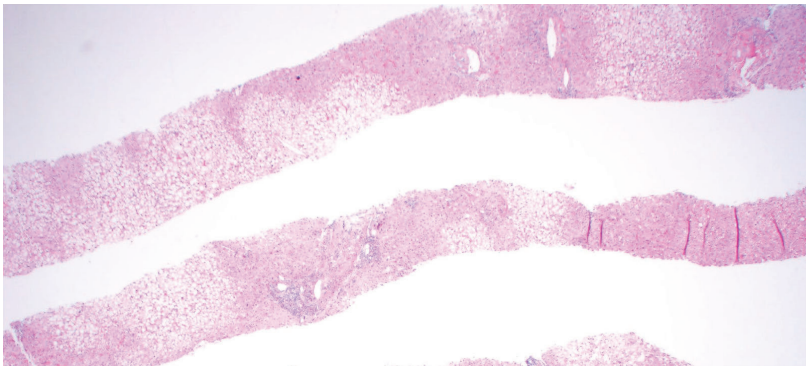

Fig 20.23 Biopsy from a liver mass shows extensive steatosis with normal distribution of portal tracts and central veins. Low power view.

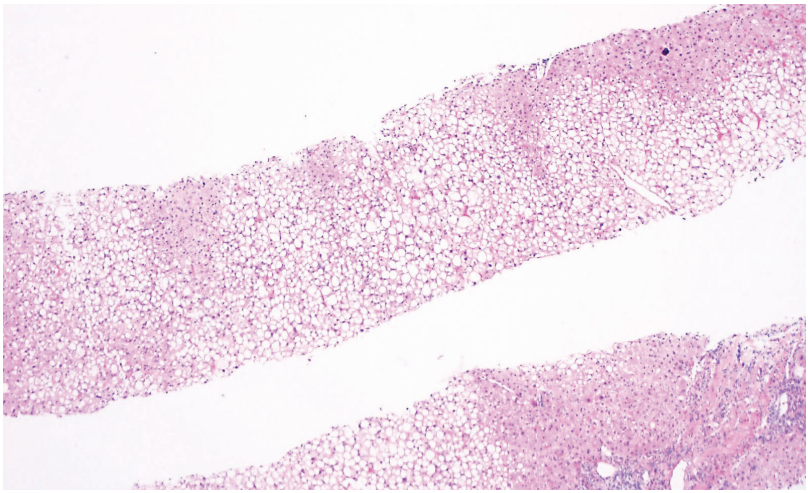

Fig 20.24 Biopsy from a liver mass shows extensive steatosis with normal distribution of portal tracts and central veins. Intermediate power.

F. Special histochemical stain and immunohistochemistry

The diagnosis is usually straightforward with routine H&E histology. If an angiomyolipoma with a prominent adipocytic component enters into the differential diagnosis, angiomyolipomas are typically positive for HMB-45 (**Figs. 20.25, 20.26, 20.27, and 20.28**), whereas the fatty change in focal fatty nodules is not.

G. Differential diagnosis

In rare cases, as noted above, an angiomyolipoma (HMB-45-positive) with a prominent adipocyte component might enter into the differential diagnosis.

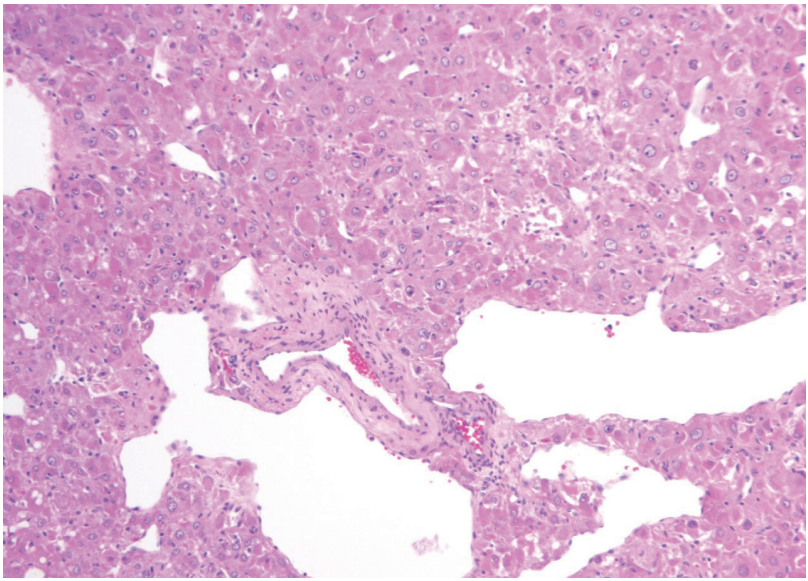

Fig 20.25 Angiomyolipoma of liver can mimic hepatocellular neoplasm in this fat poor area. The tumor consists of sheet of epithelioid epithelial cells with eosinophilic and granular cytoplasm. An isolated arteriole is noted.

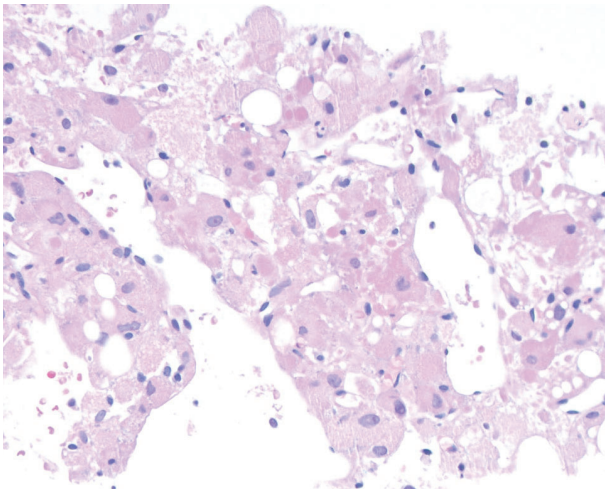

Fig 20.26 Other areas of this angiomyolipoma contain admixed of fat and epithelial cells with eosinophilic and granular cytoplasm.

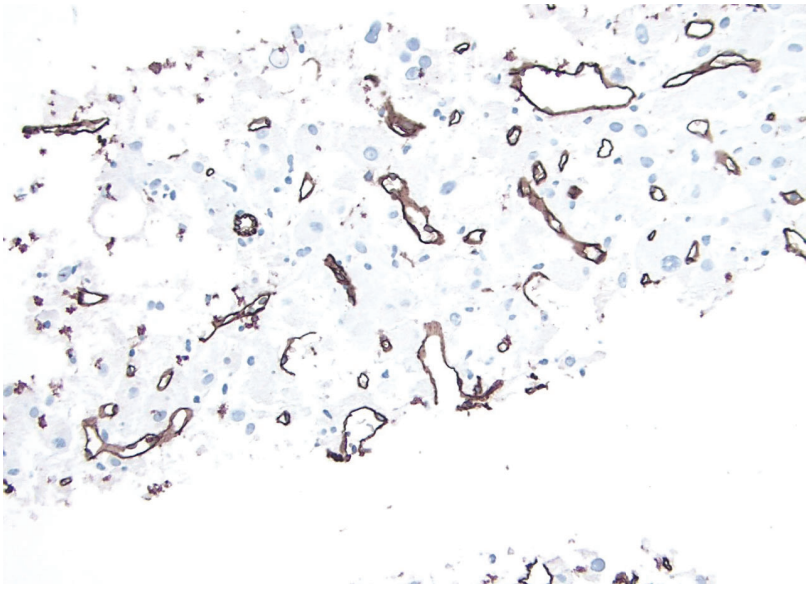

Fig 20.27 Immunostain for CD34 highlight diffuse “capillarization of sinusoids” in angiomyolipoma, mimicking sinusoidal changes in a hepatocellular neoplasm (Immunostain).

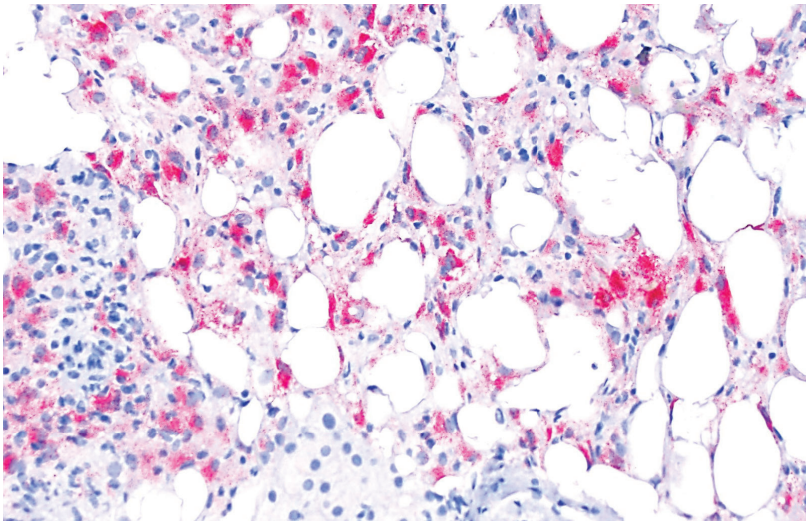

Fig 20.28 Immunoreactivity for HMB45 confirms the diagnosis of angiomyolipoma (Immunostain, red chromogen).

8. Hepatic syphilis presenting as a pseudotumor

A. Definition

Syphilis can present in the liver as a pseudotumor. Syphilis is caused by the spirochete *Treponema pallidum*, which is most commonly sexually transmitted. During the secondary stage, syphilis presents in the liver as syphilitic hepatitis, and during the tertiary stage, as gummas.

B. Clinical features and physical examination

The majority of recent cases of syphilis are reported in men who have sex with men.[42] Typically, although uncommonly, mass lesions of syphilis present during the tertiary stage of syphilis as gummas. Gummatous hepatic syphilis has long been recognized.[43] In 1946, the first cases were reported of gummatous hepatic syphilis being treated successfully with penicillin.[44] Recent cases reported in human immunodeficiency virus (HIV)-positive homosexual men were clinically suspected to have malignant neoplasms in the liver.[42]

C. Laboratory tests

Patients who are clinically suspected to have syphilis should have serologic Rapid Plasma Reagin (RPR) testing or an alternative performed. Elevated ALP levels can be observed in cases of hepatic syphilis.

D. Imaging studies

Hepatic gummas may be visible on CT imaging as low-attenuation lesions with slight peripheral enhancement and rare calcifications. Gummas may be single or multiple. This appearance may be confused with metastatic cancer or an abscess.[45]

E. Macroscopic and histological abnormalities

Macroscopically, hepatic gummas present as irregular firm tan-white nodules that may be associated with calcifications.[46] Gummas may be associated with abscesses. Microscopically, the gummas show fibrosis with mixed inflammation, generally with numerous plasma cells. Furthermore, gummas are characterized as tuberculoid giant cell granulomata with amorphous necrotic centers.

F. Special histochemical stain and immunohistochemistry

Since the H&E histologic findings are not pathognomonic, it is often the clinical history that suggests the possibility of a syphilitic gumma in the differential diagnosis, although a high index of suspicion may be warranted in the absence of other clear etiologies. Immunohistochemistry staining for *Treponema pallidum* is extremely useful in this context, although it is important to confirm the presence of spirochete morphology in the positively stained microorganisms. The latter is also true for Warthin-Starry Silver staining.

G. Differential diagnosis

Other inflammatory pseudotumors, such as IgG4-related disease / lymphoplasmacytic-type inflammatory pseudotumor or fibrohistiocytic-type inflammatory pseudotumor, enter into the differential diagnosis but would be expected to be negative for *Treponema pallidum* microorganisms. IgG4-positive plasma cells would not be expected to be disproportionally increased in gummas.

9. Endometriosis/endometrioma

A. Definition

Endometriosis is characterized in general as endometrial glands and stroma located in organs outside of the uterine endometrium and myometrium. It occurs in 10-15% of women of reproductive age, although it can also occur in postmenopausal women.[47] In the liver, it can present as a nodule or cyst.[48-50]

B. Clinical features and physical examination

Hepatic endometriosis and endometriomas present in women of reproductive age, and rarely in postmenopausal women. Approximately three quarters of women with endometriosis report abdominopelvic pain, dysmenorrhea, or heavy menstrual bleeding.[51] Endometriosis of the liver is most commonly identified with imaging.

C. Laboratory tests

Not pathologically relevant.

D. Imaging studies

The imaging features of hepatic endometriosis vary and depend on the extent, the age of the patient and normal hormonal fluctuations of the menstrual cycle. There are no MRI, CT, or US characteristics that are exclusively specific to hepatic endometriosis. However, common imaging features include well defined lobulated cystic lesions with solid components and septations. The imaging features may suggest the possibility of a metastatic neoplasm.[52]

E. Macroscopic and histological abnormalities

Hepatic endometriosis most commonly presents as cysts associated with hemorrhage, although it may be present as an ill-defined nodule. Microscopically, once the possibility of endometriosis is considered in the differential diagnosis, the diagnosis is relatively straightforward. Endometriosis is characterized by bland-appearing endometrial glands with surrounding endometriotic stroma and hemorrhage, and two of these features are generally sufficient to establish the diagnosis.

F. Special histochemical stain and immunohistochemistry

The endometrial epithelium and stroma are both positive for estrogen receptor (ER), the epithelium is positive for keratins including CK7, and the stroma is positive for CD10.

G. Differential diagnosis

Endometriotic cysts of the liver may mimic mucinous cystic neoplasms of the liver.[50] A history of endometriosis elsewhere in the patient is useful when available, especially if this is encountered at the time of a frozen section. Immunohistochemistry staining for ER will be positive in the endometrial cells and negative in the epithelial cells of mucinous cystic neoplasms. Immunostaining for CD10 will be positive in the stromal cells of endometriotic cysts and negative in the ovarian-like stroma of mucinous cystic neoplasms, the latter of which will be positive for inhibin.

10. Segmental atrophy of the liver presenting as a pseudotumor

A. Definition

Segmental atrophy of the liver is characterized by collapse of the liver parenchyma, and it can lead to the development of a pseudotumor. It undergoes various stages, which include parenchymal collapse, nodular elastosis, and nodular fibrosis.[53]

B. Clinical features and physical examination

Segmental atrophy of the liver presenting as a pseudotumor occurs in a wide range of patients with a slight female predominance. Patients may present with right upper quadrant abdominal pain or ascites. Segmental atrophy may be identified incidentally within imaging.[53]

C. Laboratory tests

Not pathologically relevant.

D. Imaging studies

Segmental atrophy may be identified incidentally with imaging and raise the specter of a neoplasm.[54]

E. Macroscopic and histological abnormalities

Macroscopically, segmental atrophy presenting as a pseudotumor has ill-defined borders and a firm white cut surface. Microscopically, the lesions characterize progressing through stages, which include parenchymal collapse, elastosis, and fibrosis (**Figs. 20.29, 20.30, 20.31, 20.32, 20.33, and 20.34**). The lesion is associated with abnormally thick-walled arteries and veins, some of which may be thrombosed. Early lesions show collapsed hepatic parenchyma with ductular reaction and chronic inflammation. Subsequently, the ductular reaction and chronic inflammation regress and there is an emergence of retention-like biliary cysts, and elastosis becomes more prominent. Finally, the pseudotumor progresses to a densely fibrotic nodule.[53]

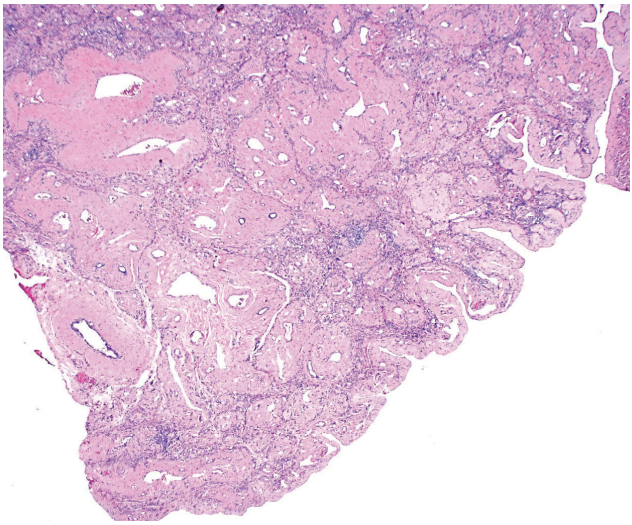

Fig 20.29 Segmental atrophy is characterized by parenchymal collapse, elastosis, and fibrosis primarily in the subcapsular region. Low power view.

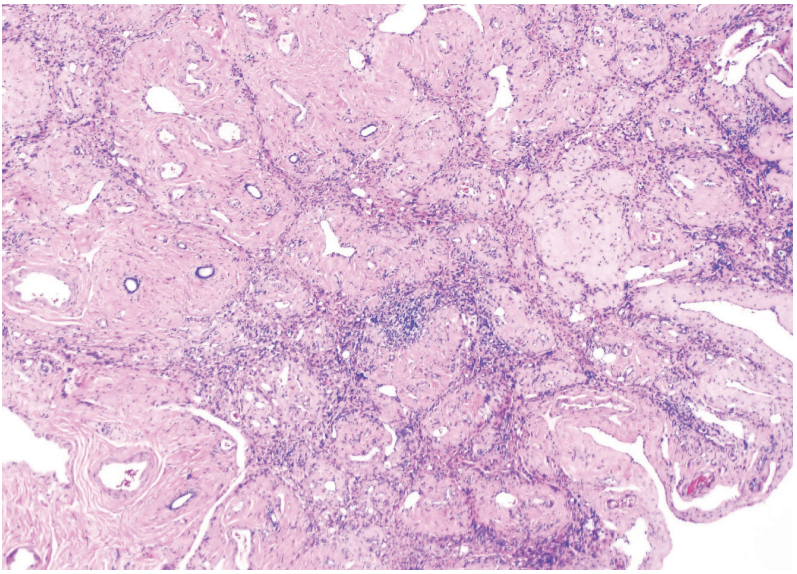

Fig 20.30 Segmental atrophy is characterized by parenchymal collapse, elastosis, and fibrosis primarily in the subcapsular region. Intermediate power view.

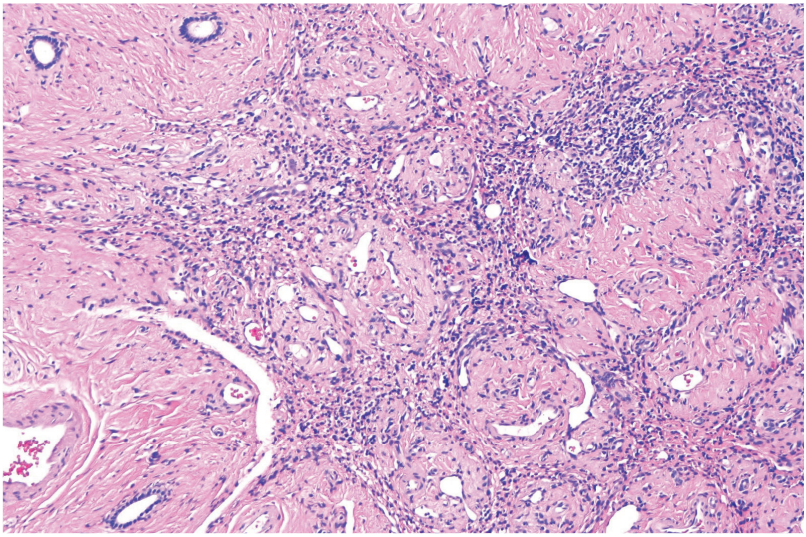

Fig 20.31 Early lesions of segmental atrophy show collapsed hepatic parenchyma with ductular reaction and chronic inflammation. Intermediate power view.

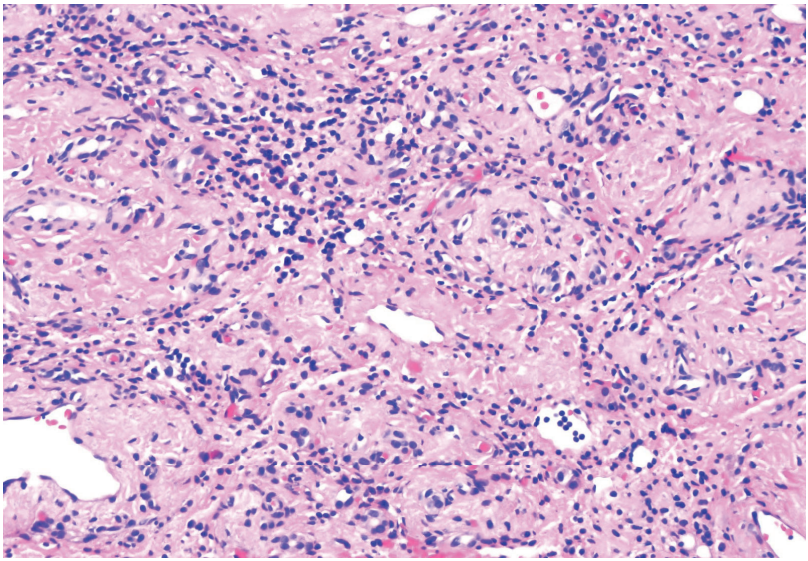

Fig 20.32 Early lesions of segmental atrophy show collapsed hepatic parenchyma with ductular reaction and chronic inflammation. High power view.

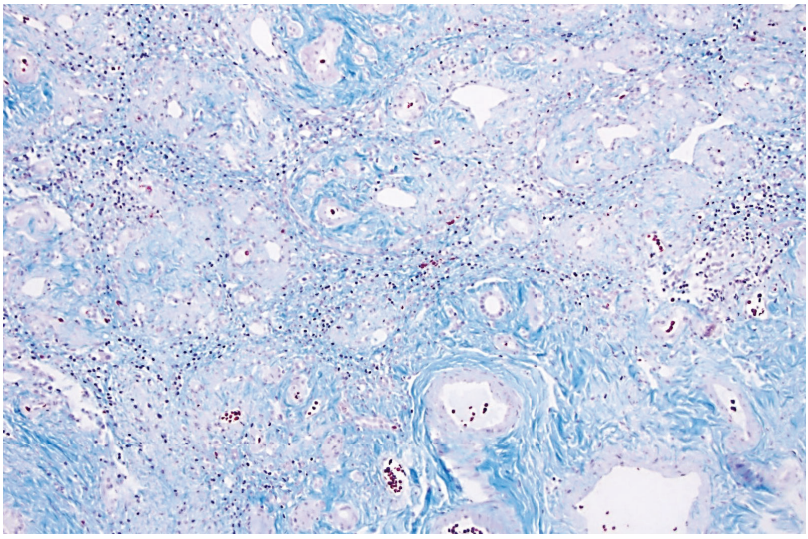

Fig 20.33 Fibrosis becomes more prominent in late stage of segmental atrophy (Trichrome stain).

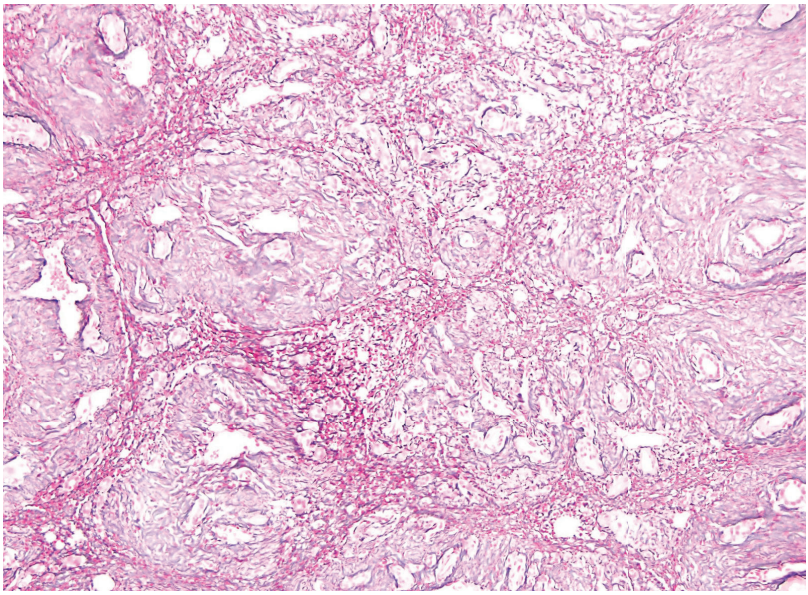

Fig 20.34 Elastosis becomes more prominent in late stage of segmental atrophy (Elastin stain).

F. Special histochemical stain and immunohistochemistry

Generally not indicated.

G. Differential diagnosis

The dense elastosis can suggest a diagnosis of amyloidosis, the latter of which can be excluded with a Congo red stain. Segmental atrophy of the liver most likely represents one manifestation of the atrophy-hypertrophy complex, although the atrophy-hypertrophy complex generally involves the entire liver lobe, whereas segmental atrophy of the liver is -- as its name suggests -- focal and segmental and is generally a subcapsular nodule.[53] Regardless, the importance of recognizing segmental atrophy of the liver resides in recognizing that is a benign mimic of neoplasia.

11. Pseudolipoma of Glisson capsule/hepatic pseudolipoma

A. Definition

Pseudolipoma of Glisson capsule is a rare benign entity that is thought to arise from a detached piece of pericolonic fat that undergoes degenerative changes, develops a fibrous capsule, and becomes lodged between the superior surface of the liver and the diaphragm.[55]

B. Clinical features and physical examination

Pseudolipoma of Glisson capsule is rare but most commonly encountered in men after the fifth decade of life.

C. Laboratory tests

Not pathologically relevant.

D. Imaging studies

On CT, a pseudolipoma of Glisson capsule appears as a well-circumscribed nodule on the liver surface with a center of fat or soft-tissue attenuation. On MRI, it appears as fat signal intensity on all the MRI sequences.[56]

E. Macroscopic and histological abnormalities

Macroscopically, pseudolipoma of Glisson capsule is seen as a nodule that is embedded on the surface of the right aspect of the liver and attached to the Glisson capsule. It generally has a fibrous capsule surrounding a mineralized and rough cut surface. Microscopically, there is a hyalinized capsule surrounding necrotic adipocytes.

F. Special histochemical stain and immunohistochemistry

Generally not useful.

G. Differential diagnosis

The differential diagnosis macroscopically includes a metastatic neoplasm, which can be readily ruled out microscopically.

12. Adrenal rest tumor

A. Definition

Adrenal rest tumors are tumors of adrenocortical cells that rarely occur in the liver, which are thought to arise from adrenal rest, and which are not contiguous with the adrenal gland.

B. Clinical features and physical examination

Adrenal rest tumors may be nonfunctional and incidentally identified, or functional and produce Cushing syndrome.

C. Laboratory tests

Adrenal rest tumors sometimes produce corticosteroids resulting in Cushing syndrome.[63,64]

D. Imaging studies

Hepatic adrenal rest tumors may show the following radiologic features: a solitary hepatic mass containing distinct components of fat and soft tissue attenuation; a round, well demarcated mass of the right posterior hepatic lobe in the subcapsular region; independent original adrenal glands, vascular supply of the tumor mainly by the hepatic artery.[65]

E. Macroscopic and histological abnormalities

Macroscopically, adrenal rest tumors are circumscribed yellow-brown nodules. They range in size from 2.5 to 18 cm in diameter.[65] Microscopically, the tumors are comprised of polygonal cells with oval nuclei and finely granular cytoplasm arranged in cords.

F. Special histochemical stain and immunohistochemistry

Adrenal rest tumors are positive for inhibin and Melan-A, in contrast to hepatocytes. One potential differential diagnosis is metastatic adrenal cortical carcinoma, however, abdominal imaging of the adrenal glands would be helpful.

G. Differential diagnosis

Adrenal rest tumors morphologically resemble hepatocellular neoplasms. Adrenal rest tumors are negative for HepPar-1 by immunohistochemistry, whereas well-differentiated hepatocellular proliferations are generally positive for HepPar-1.

13. Intrahepatic splenic tissue

A. Definition

Intrahepatic splenic tissue is benign ectopic spleen in the liver that most commonly occurs after splenectomy or trauma.[66]

B. Clinical features and physical examination

Intrahepatic splenic tissue may be an incidental finding, but it also may mimic a neoplasm.[66-68]

C. Laboratory tests

Not pathologically relevant.

D. Imaging studies

MRI of intrahepatic splenic tissue is mainly hypointense on T1- and hyperintense on T2-weighted images.[69,70]

E. Histological abnormalities

Microscopically, intrahepatic splenic tissue resembles native splenic tissue with red pulp and white pulp separated by a marginal zone.

F. Special histochemical stain and immunohistochemistry

Generally not indicated. Splenic tissue will be negative for hepatocyte marker such as HepPar-1.

G. Differential diagnosis

Microscopically, the diagnosis of intrahepatic splenic tissue is straightforward, once the possibility is considered. In cases where clinicians suspect metastatic tumor in a patient who already carries a diagnosis of malignancy elsewhere in the body, confirmatory and exclusionary immunostains may be considered to be reassuring.

References

1. Wanless IR, Mawdsley C, Adams R. On the pathogenesis of focal nodular hyperplasia of the liver. Hepatology 1985;5:1194-1200.
2. Wanless IR, Albrecht S, Bilbao J, Frei JV, Heathcote EJ, Roberts EA, Chiasson D. Multiple focal nodular hyperplasia of the liver associated with vascular malformations of various organs and neoplasia of the brain: a new syndrome. Mod Pathol. 1989;2:456-462.
3. Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118:560-564.
4. Luciani A, Kobeiter H, Maison P, Cherqui D, Zafrani ES, Dhumeaux D, Mathieu D. Focal nodular hyperplasia of the liver in men: is presentation the same in men and women? Gut 2002;50:877-880.
5. Bouyn CI, Leclere J, Raimondo G, le Pointe HD, Couanet D, Valteau-Couanet D, Hartmann O. Hepatic focal nodular hyperplasia in children previously treated for a solid tumor: incidence, risk factors, and outcome. Cancer 2003;97:3107-3113.
6. Mamone G, Caruso S, Cortis K, Miraglia R. Complete spontaneous regression of giant focal nodular hyperplasia of the liver: Magnetic resonance imaging evaluation with hepatobiliary contrast media. World J Gastroenterol. 2016;22:10461-10464.
7. Yen YH, Wang JH, Lu SN, Chen TY, Changchien CS, Chen CH, Hung CH, Lee CM. Contrast-enhanced ultrasonographic spoke-wheel sign in hepatic focal nodular hyperplasia. Eur J Radiol. 2006;60:439-444.
8. Grazioli L, Bondioni MP, Haradome H, Motosugi U, Tinti R, Frittoli B, Gambarini S, Donato F, Colagrande S. Hepatocellular adenoma and focal nodular hyperplasia: value of gadoxetic acid–enhanced MR imaging in differential diagnosis. Radiology 2012;262:520-529.
9. Burns PN, Wilson SR. Focal liver masses: enhancement patterns on contrast-enhanced images—concordance of US scans with CT scans and MR images. Radiology 2007;242:162-174.

10. Sempoux C, Balabaud C, Bioulac-Sage P. Pictures of focal nodular hyperplasia and hepatocellular adenomas. World J Hepatol. 2014;6:580-595.
11. Shafizadeh N, Kakar S. Diagnosis of well-differentiated hepatocellular lesions: role of immunohistochemistry and other ancillary techniques. Ad Anat Pathol. 2011;18:438-445.
12. Joseph NM, Ferrell LD, Jain D, Torbenson MS, Wu TT, Yeh MM, Kakar S. Diagnostic utility and limitations of glutamine synthetase and serum amyloid-associated protein immunohistochemistry in the distinction of focal nodular hyperplasia and inflammatory hepatocellular adenoma. Mod Pathol. 2014;27:62-72.
13. Steiner PE. Nodular regenerative hyperplasia of the liver. Am J Pathol. 1959;35:943-953.
14. Morris JM, Oien KA, McMahon M, Forrest EH, Morris J, Stanley AJ, Campbell S. Nodular regenerative hyperplasia of the liver: survival and associated features in a UK case series. Eur J Gastroenterol Hepatol. 2010;22:1001-1005.
15. Reshamwala PA, Kleiner DE, Heller T. Nodular regenerative hyperplasia: not all nodules are created equal. Hepatology 2006;44:7-14.
16. Dachman AH, Ros PR, Goodman ZD, Olmsted WW, Ishak KG. Nodular regenerative hyperplasia of the liver: clinical and radiologic observations. AJR Am J Roentgenol. 1987;148:717-722.
17. Jha P, Poder L, Wang ZJ, Westphalen AC, Yeh BM, Coakley FV. Radiologic mimics of cirrhosis. AJR Am J Roentgenol. 2010;194:993-999.
18. Zen Y, Fujii T, Sato Y, Masuda S, Nakanuma Y. Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Mod Pathol. 2007;20:884-894.
19. Coffin CM, Humphrey PA, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor: a clinical and pathological survey. Semin Diagn Pathol. 1998;15:85-101.
20. Zen Y, Kawakami H, Kim JH. IgG4-related sclerosing cholangitis: all we need to know. J Gastroenterol. 2016;51:295-312.
21. Okazaki K, Uchida K, Fukui T. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. J Gastroenterol. 2008;43:409-418.
22. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181-1192.
23. Antonescu CR, Suurmeijer AJ, Zhang L, Sung YS, Jungbluth AA, Travis WD, Al-Ahmadie H, Fletcher CD, Alaggio R. Molecular

characterization of inflammatory myofibroblastic tumors with frequent ALK and ROS1 fusions and rare novel RET gene rearrangement. Am J Surg Pathol. 2015;39:957-967.
24. Sharifi S, Murphy M, Loda M, Pinkus GS, Khettry U. Nodular lymphoid lesion of the liver: an immune-mediated disorder mimicking low-grade malignant lymphoma. Am J Surg Pathol. 1999;23:302-308.
25. Okada T, Mibayashi H, Hasatani K, Hayashi Y, Tsuji S, Kaneko Y, Yoshimitsu M, Tani T, Zen Y, Yamagishi M. Pseudolymphoma of the liver associated with primary biliary cirrhosis: a case report and review of literature. World J Gastroenterol. 2009;15:4587.
26. Zen Y, Fujii T, Nakanuma Y. Hepatic pseudolymphoma: a clinicopathological study of five cases and review of the literature. Mod Pathol. 2010;23:244-250.
27. Hayashi M, Yonetani N, Hirokawa F, Asakuma M, Miyaji K, Takeshita A, Yamamoto K, Haga H, Takubo T, Tanigawa N. An operative case of hepatic pseudolymphoma difficult to differentiate from primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. World J Surg Oncol. 2011;9:3. doi: 10.1186/1477-7819-9-3.
28. Zhou Y, Wang X, Xu C, Zhou G, Zeng M, Xu P. Hepatic pseudolymphoma: imaging features on dynamic contrast-enhanced MRI and diffusion-weighted imaging. Abdom Radiol. 2018;43:2288-2294.
29. Lu C, He Q, Zhu W, Fu C, Zhou J, Tao Y, Liu S, Xiao D. The value of detecting immunoglobulin gene rearrangements in the diagnosis of B-cell lymphoma. Oncotarget. 2017;8:77009-77019.
30. Aoki T, Kubota K, Oka T, Hasegawa K, Hirai I, Makuuchi M. Follicular cholangitis: another cause of benign biliary stricture. Hepatogastroenterology 2003;50:639-642.
31. Zen Y, Ishikawa A, Ogiso S, Heaton N, Portmann B. Follicular cholangitis and pancreatitis–clinicopathological features and differential diagnosis of an under-recognized entity. Histopathology 2012;60:261-269.
32. Lee JY, Lim JH, Lim HK. Follicular cholangitis mimicking hilar cholangiocarcinoma. Abdom Imaging 2005;30:744-747.
33. Fujita T, Kojima M, Kato Y, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Clinical and histopathological study of “follicular cholangitis”: sclerosing cholangitis with prominent lymphocytic infiltration masquerading as hilar cholangiocarcinoma. Hepatol Res. 2010;40:1239-1247.

34. Wiener MD, Halvorsen Jr RA, Vollmer RT, Foster WL, Roberts Jr L. Focal intrahepatic extramedullary hematopoiesis mimicking neoplasm. AJR Am J Roentgenol. 1987;149:1171-1172.
35. Kwak HS, Lee JM. CT findings of extramedullary hematopoiesis in the thorax, liver and kidneys, in a patient with idiopathic myelofibrosis. J Korean Med Sci. 2000;15:460-462.
36. Craig CE, Quaglia A, Dhillon AP. Extramedullary haematopoiesis in massive hepatic necrosis. Histopathology 2004;45:518-525.
37. WHO classification of tumors at editorial board. *WHO classification of tumors: Digestive system tumors*. 5th ed. (IARC: Lyon, France 2019).
38. Brawer MK, Austin GE, Lewin KJ. Focal fatty change of the liver, a hitherto poorly recognized entity. Gastroenterology 1980;78:247-252.
39. Marmorale C, Romiti M, Bearzi I, Giovagnoni A, Landi E. Traumatic rupture of nodular focal fatty infiltration of the liver: case report. Ann Ital Chir. 2003;74:217-221.
40. Grove A, Vyberg B, Vyberg M. Focal fatty change of the liver. A review and a case associated with continuous ambulatory peritoneal dialysis. Virchows Arch A Pathol Anat Histopathol. 1991;419:69-75.
41. Wang SS, Chiang JH, Tsai YT, Lee SD, Lin HC, Chou YH, Lee FY, Wang JS, Lo KJ. Focal hepatic fatty infiltration as a cause of pseudotumors: ultrasonographic patterns and clinical differentiation. J Clin Ultrasound 1990;18:401-409.
42. Hagen CE, Kamionek M, McKinsey DS, Misdraji J. Syphilis presenting as inflammatory tumors of the liver in HIV-positive homosexual men. Am J Surg Pathol. 2014;38:1636-1643.
43. Rolleston H, McNee JW. Diseases of the Liver. Gall-bladder and Bile-ducts, London. 1929.
44. Tucker HA, Dexter DD. Treatment of gummatous hepatic syphilis with penicillin: report of two cases. Arch Intern Med. 1946;78:313-322.
45. Gaslightwala I, Khara HS, Diehl DL. Syphilitic gummas mistaken for liver metastases. Clin Gastroenterol Hepatol. 2014;12:e109-110.
46. Alergant CD. Gumma of liver with calcification. AMA Arch Intern Med. 1956;98:340-343.
47. Clement P, Stall J, Young R. Atlas of Gynecologic Surgical Pathology. 4th Edition (London: Elsevier 2019).
48. Finkel L, Marchevsky A, Cohen B. Endometrial cyst of the liver. Am J Gastroenterol. 1986;81:576-578.
49. Rivkine E, Jakubowicz D, Marciano L, Polliand C, Poncelet C, Ziol M, Barrat C. Hepatic endometrioma: a case report and review of the literature: report of a case. Surg Today 2013;43:1188-1193.

50. Hsu M, Terris B, Wu TT, Zen Y, Eng HL, Huang WT, Yeh MM. Endometrial cysts within the liver: a rare entity and its differential diagnosis with mucinous cystic neoplasms of the liver. Hum Pathol. 2014;45:761-767.
51. Ballard KD, Seaman HE, De Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case–control study—Part 1. BJOG. 2008;115:1382-1391.
52. Asran M, Rashid A, Szklaruk J. Hepatic endometriosis mimicking metastatic disease: a case report and review of the literature. J Radiol Case Rep. 2010;4:26-31.
53. Singhi AD, Maklouf HR, Mehrotra AK, Goodman ZD, Drebber U, Dienes HP, Torbenson M. Segmental atrophy of the liver: a distinctive pseudotumor of the liver with variable histologic appearances. Am J Surg Pathol. 2011;35:364-371.
54. Spolverato G, Anders R, Kamel I, Pawlik TW. Segmental atrophy of the liver: an uncommon and often underrecognized pseudotumor. Dig Dis Sci. 2014;59:3122-3125.
55. Quinn AM, Guzman-Hartman G. Pseudolipoma of Glisson capsule. Arch Path Lab Med. 2003;127:503-504.
56. Shin NY, Kim MJ, Chung JJ, Chung YE, Choi JY, Park YN. The differential imaging features of fat-containing tumors in the peritoneal cavity and retroperitoneum: the radiologic-pathologic correlation. Korean J Radiol. 2010;11:333-345.
57. Chui AK, Lo KW, Choi PC, Sung MC. Primary hepatic pregnancy. ANZ J Surg. 2001;71:260-261.
58. Kirby NG. Primary hepatic pregnancy. Br Med J. 1969;1:296.
59. Børlum KG, Blom R. Primary hepatic pregnancy. Int J Gynaecol Obstet. 1988;27:427-429.
60. Yadav R, Raghunandan C, Agarwal S, Dhingra S, Chowdhary S. Primary hepatic pregnancy. J Emerg Trauma Shock 2012;5:367-369.
61. Brouard KJ, Howard BR, Dyer RA. Hepatic pregnancy suspected at term and successful delivery of a live neonate with placental attachment to the right lobe of the liver. Obstet Gynecol. 2015;126:207-210.
62. Harris GJ, Al-Jurf AS, Yuh WT, Abu-Yousef MM. Intrahepatic pregnancy: A unique opportunity for evaluation with sonography, computed tomography, and magnetic resonance imaging. JAMA 1989;261:902-904.
63. Wallace EZ, Leonidas JR, Stanek AE, Avramides A. Endocrine studies in a patient with functioning adrenal rest tumor of the liver. Am J Med. 1981;70:1122-1126.

64. Contreras P, Altieri E, Liberman C, Gac Jr AL, Rojas A, Ibarra A, Ravanal M, Serón-Ferré M. Adrenal Rest Tumor of the Liver Causing Cushing's Syndrome: Treatment withKetoconazole preceding an Apparent Surgical Cure. J Clin Endocrinol Metab. 1985;60:21-28.
65. Tajima T, Funakoshi A, Ikeda Y, Hachitanda Y, Yamaguchi M, Yokota M, Yabuuchi H, Satoh T, Koga M. Nonfunctioning adrenal rest tumor of the liver: radiologic appearance. J Comput Assist Tomogr. 2001;25:98-101.
66. Davidson LA, Reid IN. Intrahepatic splenic tissue. Journal of clinical pathology. 1997;50(6):532-533.
67. Lacerda MA, Ludwig J, Ward EM. Intrahepatic spleen presenting as a mass lesion. Am J Gastroenterol. 1993;88:2116-2117.
68. Yoshimitsu K, Aibe H, Nobe T, Ezaki T, Tomoda H, Hayashi I, Koga M. Intrahepatic splenosis mimicking a liver tumor. Abdominal imaging. 1993;18:156-158.
69. Setiawan H, Harrell RS, Perret RS. Ectopic spleen. A sonographic diagnosis. Pediatric radiology. 1982;12:152-153.
70. De Vuysere S, Van Steenbergen W, Aerts R, Van Hauwaert H, Van Beckevoort D, Van Hoe L. Intrahepatic splenosis: imaging features. Abdominal imaging. 2000;25:187-189.

CHAPTER TWENTY-ONE

NON-NEOPLASTIC CYSTIC LESIONS OF THE LIVER

MENAKA RAJU, MD

Abstract

Liver biopsy is commonly used to diagnose liver mass lesion(s) including cystic lesions. Hepatic cystic lesion have a broad differential diagnoses. Although some hepatic cystic lesions have characteristic and diagnostic radiographic features, some of them are deemed indeterminate and biopsy is commonly performed to diagnose those lesions. Many hepatic cysts are non-neoplastic. Pathologist's knowledge and high vigilance of these non-neoplastic hepatic cysts help direct clinical treatment and management of these lesions. The accurate diagnosis of such entities is best achieved by a multidisciplinary approach. This chapter discusses the most common benign/reactive hepatic cysts.

Keywords: Solitary hepatic cyst; Polycystic liver disease; von Meyenburg complex; Cystic hepatic mesenchymal hamartoma; Ciliated hepatic foregut cyst; Echinococcal cyst; Hepatic abscess; Solitary necrotic nodule; Peliosis hepatis.

Introduction

Cystic lesions of the hepatobiliary tree represent a broad spectrum of entities, ranging from benign developmental cysts (simple cyst, hamartomas) to potentially malignant (cystadenoma) or overtly malignant lesions (cystadenocarcinoma).[1,2] Depending on their location, these lesions can be also classified as extrahepatic and intrahepatic. In this chapter we will touch base on the non-neoplastic cystic lesions of liver, some of which will be elaborately discussed elsewhere in this book including **Chapter 22**.

1. Solitary hepatic cyst

A. CLINICAL PRESENTATION: Solitary hepatic cyst or simple hepatic cyst has a prevalence ranging from 2.5% to 18%.[3] The incidence of this cyst is larger in adults older than 50 years, with female to male ratio of 1.5:1. The prevalence is around 18% in adult population.[4] Asuquo *et al*. observed a F:M ratio of 1.5:1 in asymptomatic and 9:1 in symptomatic or complicated simple cysts, indicating role of female hormones.[5]

PATHOGENESIS: Majority of simple cysts are congenital and are believed to arise due to aberrant bile duct development, secondary to defects in chromosome 16. The latter forms microhamartoma, which separates out from the draining biliary tree and forms a cyst in later life, due to accumulation of clear yellow fluid. However, the content can be mucoid, bloody, or purulent.[6-8]

B. CLINICAL FEATURES AND PHYSICAL EXAMINATION: Simple hepatic cysts are usually single, although rarely as many as ten cysts may be found. Usually the surrounding liver is normal. Majority of these cysts are small, but can grow to over 30 cm in selected cases.[9]. Clinically evident cysts are distinctly uncommon; however, a careful search at autopsy will reveal small cysts as a relatively frequent incidental finding. In a small fraction of patients, symptoms, such as abdominal pain, early satiety, nausea and vomiting, arise as a result of a mass effect.[10] Physical examination may reveal a palpable abdominal mass or hepatomegaly.[6] Complications such as rupture, torsion, intracystic hemorrhage and bacterial permeation may be seen[11-13]. Rarely an adenocarcinoma may develop in simple cysts, although squamous carcinoma and adenosquamous carcinoma have also been reported.[14-17]

C. LABORATORY TESTS: In most patients, liver function tests are within the normal range, but a minority of patients have elevated serum gamma-glutamyl-transferase (GGT)[18]. Several studies have also shown that serum and cyst fluid levels of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9) may be elevated.[19] CA 19-9 is expressed in the inner epithelial lining of a simple cyst and leads to increased cyst fluid and serum CA 19-9 levels.[2]

D. IMAGING STUDIES: The ultrasonography (USG) and computed tomography (CT) scan are highly sensitive in picking up these cysts. Simple cysts are thin-walled, and show a homogenous low-density interior.[20] The largest reported simple cyst in literature contained 17 liters of fluid.[21]

Asymptomatic single liver cysts, even when large, do not require treatment or surveillance.[22]

E. PATHOLOGICAL FEATURES: Histologically, they are lined by a single layer of cuboidal to columnar epithelium that resembles biliary epithelium (**Figs. 21.1, 21.2, 21.3, and 21.4**). The epithelium may be attenuated, denuded, or exhibit squamous metaplasia. Surrounding the epithelial layer a thin wall of mature fibrous tissue is seen, which may contain bile ducts and large blood vessels, with a peripheral zone of compressed hepatic parenchyma.[1]

F. HISTOCHEMICAL STAIN AND IMMUNOHISTOCHEMSITRY: The lining epithelial cells are immunoreactive for cytokeratin (CK): CK8, CK18, CK7, and CK19 reflecting their cell lineage.

G. DIFFERENTIAL DIAGNOSIS: Cysts in a polycystic liver disease, parasitic cysts, Caroli's disease, congenital hepatic fibrosis (CHF), and liver abscesses.

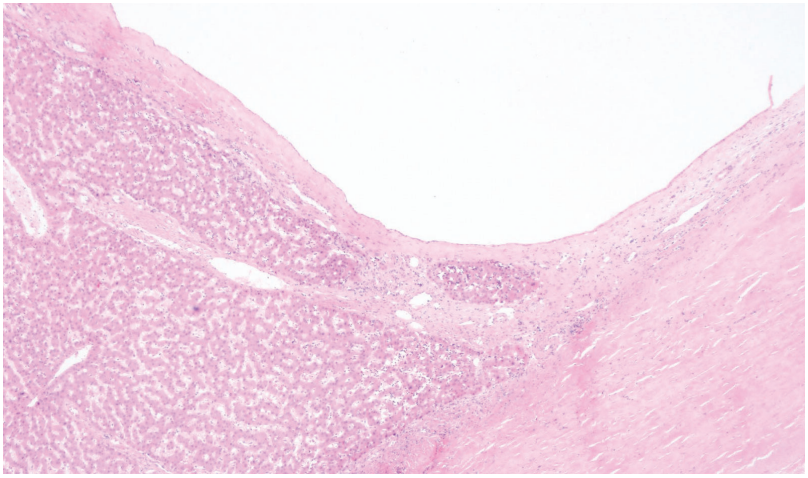

Fig. 21.1 Solitary hepatic cyst or simple hepatic cyst includes fibrous wall lined by a single layer of epithelium.

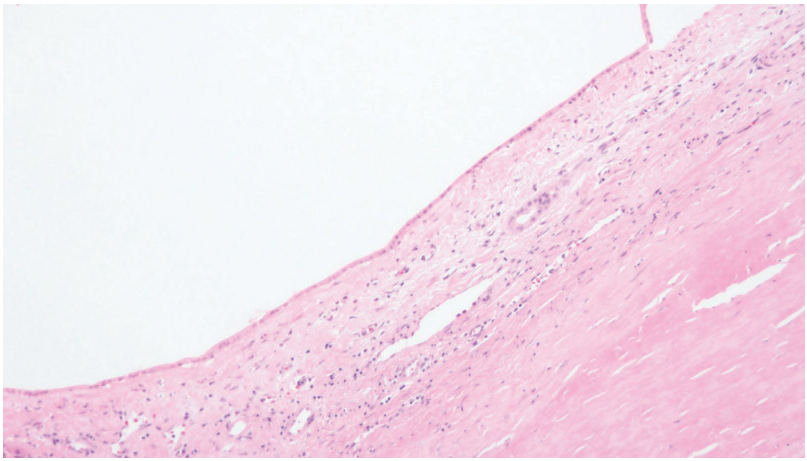

Fig 21.2 The epithelial lining in this solitary hepatic cyst or simple hepatic cyst is cuboidal.

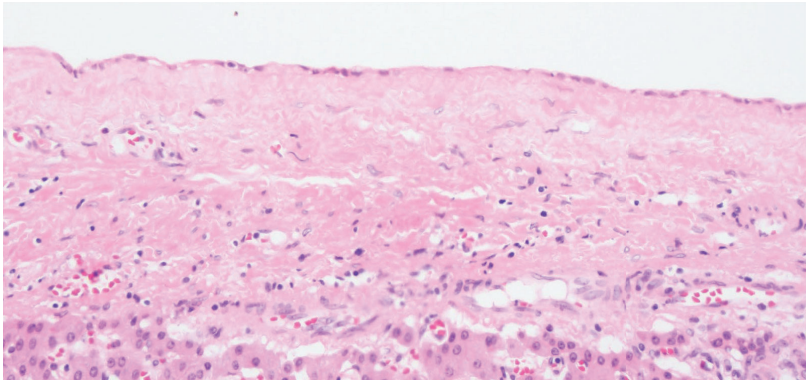

Fig 21.3 The epithelial lining in this solitary hepatic cyst or simple hepatic cyst is attenuated.

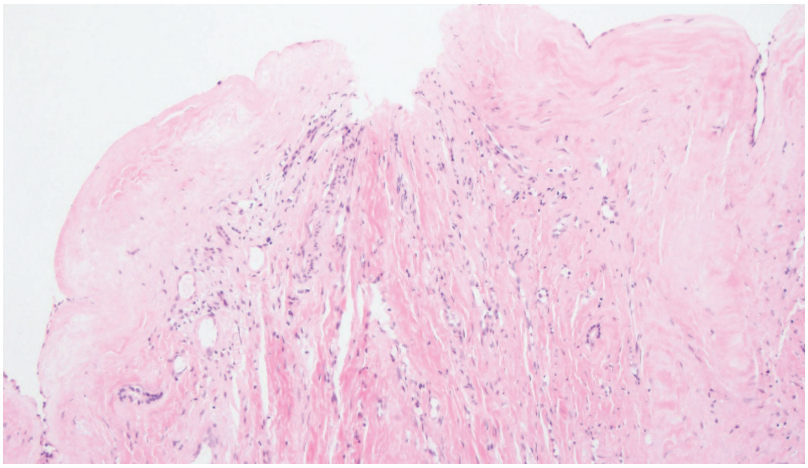

Fig 21.4 The epithelial lining in this solitary hepatic cyst or simple hepatic cyst is denuded.

2. Cysts in polycystic liver disease

A. CLINICAL PRESENTATION: Polycystic liver disease (PCLD) is part of a fibropolycystic liver disease characterized by multiple simple hepatic cysts. It is defined by the presence of 20 or more cysts in the liver parenchyma. It is an autosomal-dominant condition that can be associated with autosomal-dominant polycystic kidney disease (ADPKD), which is found in 50% of these patients. Polycystic liver disease is a rare condition with a slight predominance of females. Its prevalence is estimated to be 1:158,000 population.[2,23-25] Prevalence of PCLD is likely to be underestimated as most patients are asymptomatic.

80% of patients have no genetic mutations; however, 20% of cases have mutation in the short arm of chromosome 19.[2] Mutation of *PRKCSH* and *SEC63* genes are associated with defects in the function of the proteins hepatocystin and Sec63, respectively, and are responsible for 33%–50% of these cases. However, exact mechanism is not yet known.[24]

B. PHYSICAL EXAMINATION: PCLD is predominantly discovered during the fourth or fifth decade of life and is more common and more symptomatic in women[26-28]. Female sex, exogenous estrogen, and multiple pregnancies are risk factors for cyst progression. While the majority are asymptomatic, 3% patients can have abdominal symptoms. Massive

hepatomegaly can cause abdominal distension, pain, early satiety, gastroesophageal reflux, and extreme malnutrition.[1] A minority of patients present with acute complications, typically occur in large cysts, due to cyst rupture, hemorrhage, infection and compression of adjacent vital structures (inferior vena cava – IVC, portal vein, and biliary tree)[29]. The screening of these conditions is not recommended unless there is a clinical suspicion or indication for transplantation. Liver transplantation is the only curative treatment. Patients with PCLD have a slight predisposition towards developing cholangiocarcinoma.[30,31]

C. LABORATORY TESTS: Even with the marked growth of cysts, liver function tests are usually normal except for a mild elevation in alkaline phosphatase (ALP) or GGT[26]. Tumor marker, CA 19.9 is elevated in 45% of cases due to secretion by biliary epithelium.[1,32]

D. IMAGING STUDIES: The most common methods of diagnosis of PCLD are ultrasound and CT due to their widespread availability.[33,34] Although USG and CT scan can detect these cysts, magnetic resonance imaging (MRI) is most sensitive.[35,36] The diagnosis is considered when >20 isolated cysts are seen in the liver.

E. PATHOLOGICAL FEATURES: Macroscopically, an enlarged liver shows multiple unilocular variably sized cysts. The cysts do not communicate with biliary tree. Histologically, multiple diffuse cystic lesions with features indistinguishable from solitary hepatic cysts are seen, except for their larger numbers and association with changes in the surrounding liver (**Figs. 21.5, 21.6, and 21.7**). Typically, von Meyenburg complexes are present in up to 40% cases.

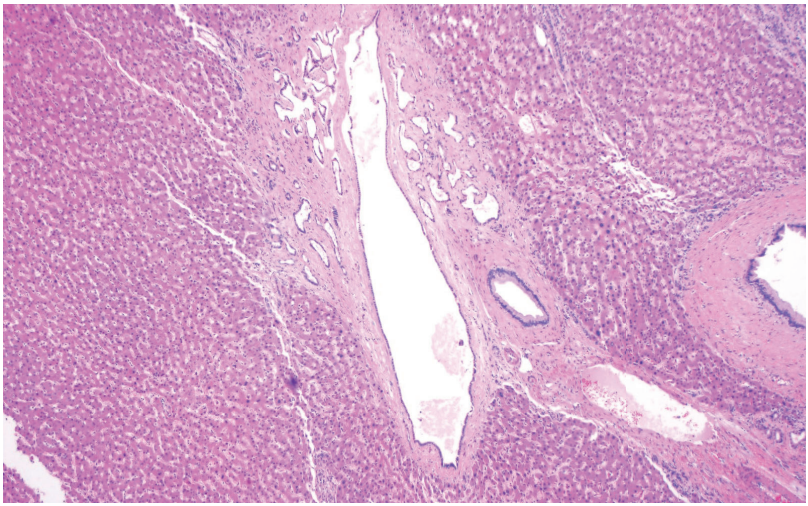

Fig 21.5 Polycystic liver disease shows multiple diffuse variably sized cystic lesions with features indistinguishable from solitary hepatic cysts.

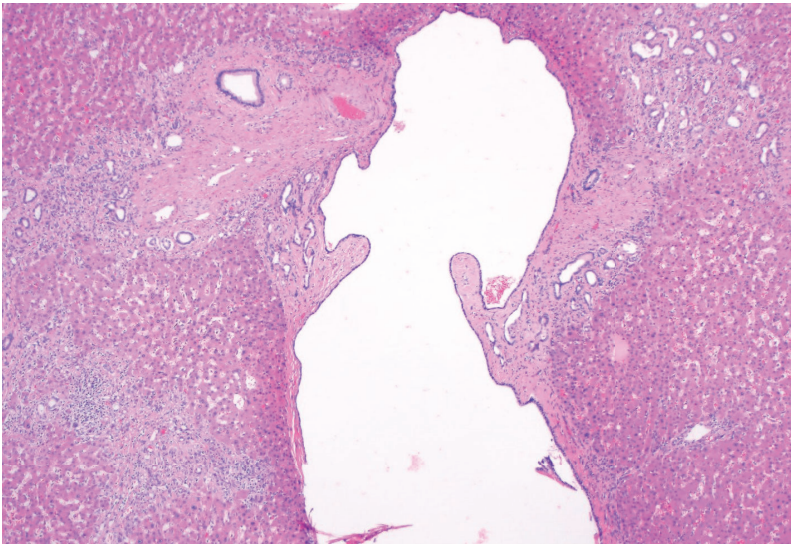

Fig 21.6 The cysts in polycystic liver disease are often associated with nearby von Meyenburg complexes.

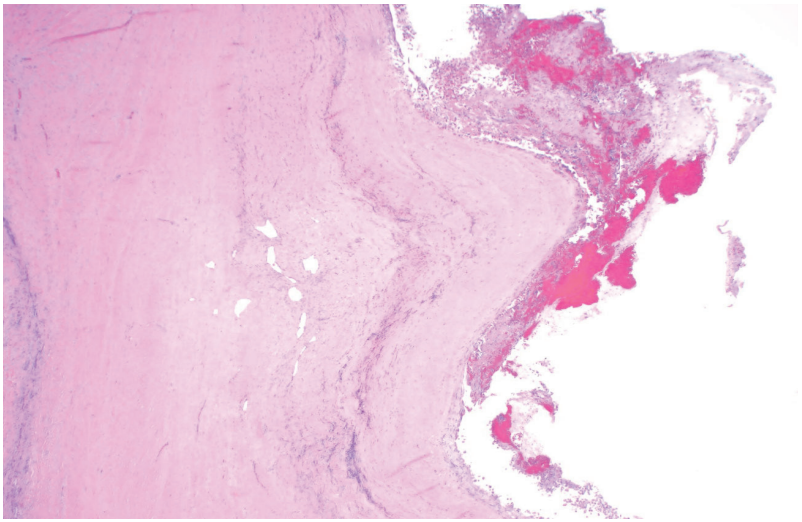

Fig 21.7 The large cyst in polycystic liver disease may show denudation and hemorrhage and with thickened fibrous wall.

F. HISTOCHEMICAL STAIN AND IMMUNOHISTOCHEMSITRY: The lining epithelial cells are immunoreactive for CK8, CK18, CK7, and CK19 reflecting their cell lineage.

G. DIFFERENTIAL DIAGNOSIS: parasitic cysts, Caroli's disease, congenital hepatic fibrosis, and liver abscesses.

3. Von Meyenburg complexes (biliary microhamartoma)

A. CLINICAL PRESENTATION: Biliary hamartomas, also known as von Meyenburg complexes (VMC), are benign congenital lesions thought to arise as a developmental anomaly caused by ductal plate malformation. They may occur in an otherwise normal liver or in association with a variety of fibropolycystic liver diseases including Caroli's disease, congenital hepatic fibrosis and autosomal dominant polycystic disease.[37,38]

B. PHYSICAL EXAMINATION: They are asymptomatic and are almost always discovered incidentally in laparoscopic procedures or in autopsies with a prevalence ranging from 0.7% to 2.8%. They are usually small (up to several mm in diameter), multiple, firm and white, mimicking metastatic seedling on the surface of the liver and are thus sampled for intraoperative consultation. VMCs do not cause symptoms or abnormalities in liver tests,

but rarely they can present as episodes of recurring cholangitis or with infectious complications.

C. LABORATORY TESTS: With the recent advent of noninvasive imaging modalities (ultrasound, CT and MRI), they can now be diagnosed in non-surgical clinical practice. In this setting, VMCs should be differentiated from Caroli's disease and metastatic disease. On ultrasound, VMCs are shown as multiple hyper- or hypoechoic areas with comet tail echoes. The CT appearance of VMCs consists of multiple, irregular, small, low attenuated areas, that do not normally enhance on contrast injection. MRI of the liver and magnetic resonance cholangiopancreatography (MRCP) are superior to ultrasound and CT in diagnosing these lesions, showing multiple irregularly delineated hyper-intense cystic nodules, not communicating with the biliary tree.[39] Liver biopsy is not contraindicated and should be performed if diagnosis is in doubt, especially in oncology patients.[40,41] They usually show no remarkable change on long term follow up imaging.[42-45]

D. PATHOLOGICAL FEATURES: On gross examination, bile duct hamartomas are small, ranging from 2 to 5 mm in diameter. They are usually multifocal, gray to white in color and irregular in shape.

On microscopic examination, bile duct hamartomas are often located within and at edge of portal tracts and are not connected to normal biliary tree (**Figs. 21.8 and 21.9**). They are composed of variably dilated small to medium sized bile ducts surrounded by dense fibrous stroma. The ducts are lined by cuboidal to flattened epithelium. There is essentially no atypia or mitotic activity noted. Ducts may contain eosinophilic proteinaceous debris or inspissated bile. Varying degrees of dilatation may lead to cyst formation. Malignant transformation of these lesions has been described, particularly to cholangiocarcinoma (**Figs. 21.10 and 21.11**), thus leading to the recommendation for periodical follow-up of these patients. Notably, molecular evidence for the neoplastic potential of VMCs has been recently reported.[37,46,47]

E. HISTOCHEMICAL STAIN AND IMMUNOHISTOCHEMSITRY: The lining epithelium is immunoreactive for CK7, CK8, CK18 and CK19, reflecting a lineage of biliary cell origin.[48]

F. DIFFERENTIAL DIAGNOSIS: Peribiliary gland hamartoma (bile duct adenoma), ductular reaction, metastatic adenocarcinoma.

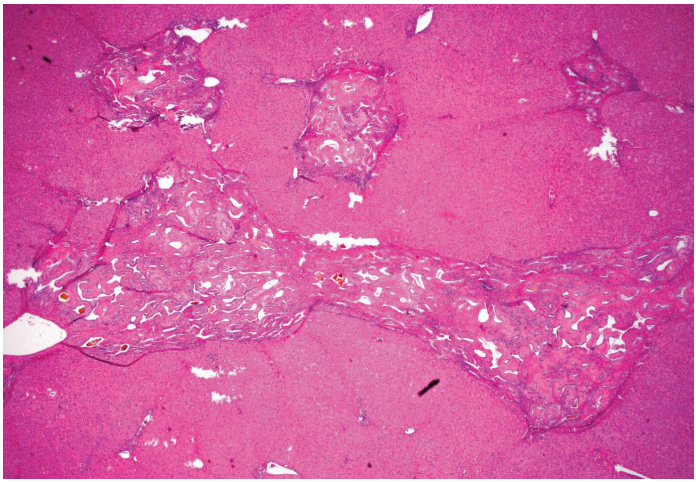

Fig 21.8 von Meyenburg complex is composed of small, irregularly shaped glands lined by cuboidal cells in a fibrous stroma. These glands are not connected to the normal biliary tree.

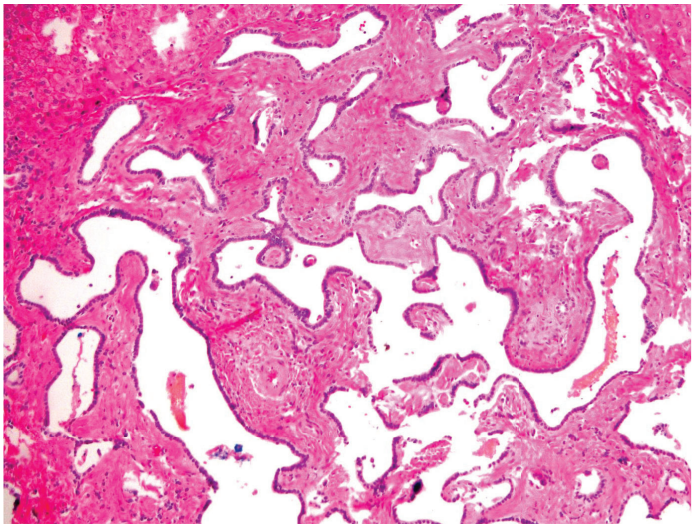

Fig 21.9 The glands in this von Meyenburg complex are more dilated and irregular.

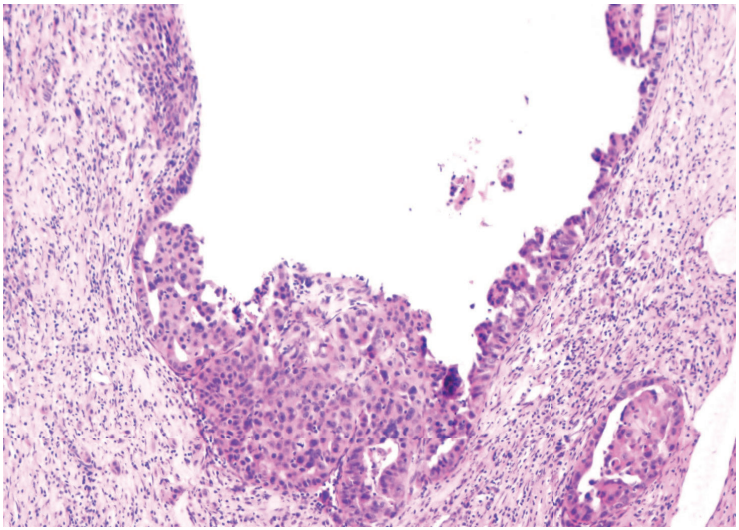

Fig 21.10 There is high-grade dysplasia in the lining epithelium of the glands of von Meyenburg complex.

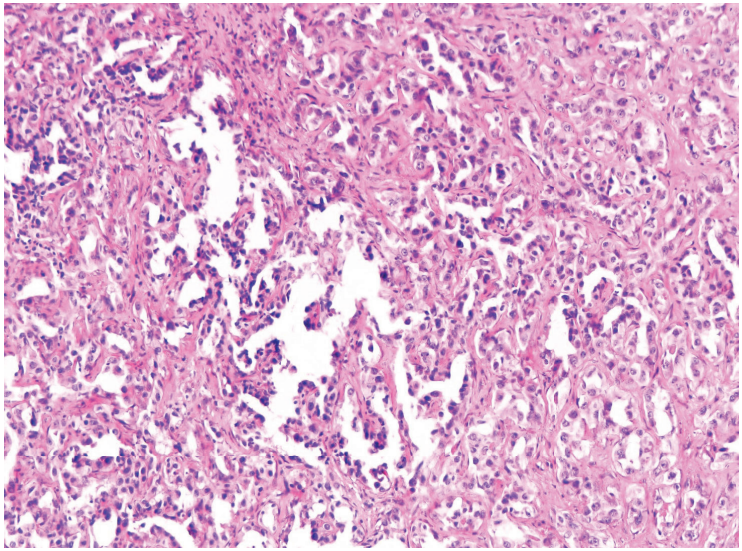

Fig 21.11 Invasive cholangiocarcinoma arising from von Meyenburg complex with high-grade dysplasia.

Key points to pathologists:

- Benign dilated ductal structures in hyalinized stroma next to portal tracts
- Lined by flat epithelium that lacks atypia
- May contain bile and are microcystic
- Multiple widely scattered VMCs raise the possibility of associated fibropolycystic disease.

4. Cystic hepatic mesenchymal hamartoma (cHMH)

cHMH is a rare, benign and commonly multicystic developmental tumor of loose connective tissue with occasional risk of malignancy. It is a hamartomatous growth of mesenchymal tissue around the portal tracts and appears as a congenital, localized, abnormality of the ductal plate development, due to interstitial deletion near chromosome 19q13.4.[49-51] Characteristically, this mesenchymal lesion undergoes cystic degeneration and enlarges due to accumulation of cyst fluid.[52,53]

It represents about 18%–29% of all primary hepatic tumors.[54] cHMH is the second most common benign hepatic tumor in childhood and accounts for approximately 5% of pediatric liver tumors. Approximately 85% of the affected children present before 3 years of age. Less than 5% of the cases occur after the age of 5 years. They are rarely seen in adults. The tumor is slightly more common in boys in pediatric cases and shows female predominance in adult cases. Association with polycystic kidney disease, congenital hepatic fibrosis and biliary hamartoma have been reported.

A. CLINICAL PRESENTATION: The typical presentation is one of asymptomatic, rapid abdominal distention with a palpable mass on physical examination. The rapid expansion of the tumor is believed to be due to degeneration of the mesenchyme and fluid accumulation. Other uncommon associated symptoms are vomiting, fever, constipation, diarrhea, and weight loss. cHMH is sometimes associated with placental anomalies including vascular thrombosis and mesenchymal stem villous hyperplasia. Treatment consists of surgical resection and they have excellent prognosis after complete excision. Occasional spontaneous regression without treatment has been reported. Although rare, malignant transformation to embryonal sarcoma (malignant mesenchymoma) has been reported.[55,56]

B. PHYSICAL EXAMINATION: While the smaller cysts are nontender and asymptomatic, larger masses present with painless abdominal mass and complications including ascites, jaundice, and even congestive heart failure can occur. Occasionally, the mass will expand rapidly, most likely because of rapid accumulation of fluid within cystic spaces.

C. LABORATORY TESTS: No specific panel of laboratory tests is characteristic of cHMH. Laboratory studies often reveal normal liver function tests and various tumor markers, including β-human chorionic gonadotropin, α-fetoprotein, and vanillylmandelic acid, are usually negative.[55] Abdominal ultrasound demonstrate either a multicystic or solid lesion, which are usually hypodense and hypovascular. Although not required for diagnosis, CT and MRI are useful for surgical planning. Even intrauterine, cHMHs have been documented in several reports, which can be detected prenatally by ultrasound and MR.[55,57]

D. PATHOLOGICAL FEATURES: Macroscopically, size of these lesions can vary greatly in size, from a few centimeters up to 30 cm. The tumors may bulge from the surface of the liver or can be pedunculated (in up to 20% of cases and is usually attached to inferior surface of liver). Seventy five percent occur on the right side, fewer occur on the left, and rarely both lobes are involved. The masses are well demarcated, but do not show a capsule. The cut surface usually shows few to multiple cystic spaces, which do not communicate with the biliary tract. The size of the cyst ranges from a few millimeters to 15 cm. Larger cysts have a gray to tan lining and contain clear to yellow fluid or gelatinous material. The surrounding tissue is commonly yellow tan to brown.[54,55,57]

Microscopically, the tumor consists of a mixture of varying components of mesenchymal cells, bile ducts, hepatocytes, blood vessels and cystic spaces. The tumor lacks normal portal tracts and shows irregular tumor border without true capsule. The cystic spaces have a lymphangioma-like appearance but are devoid of lining epithelium. They likely represent cystic degeneration of loose primitive mesenchyme. The mesenchymal component is typically myxoid and tend to form loose sheath around the distorted bile ducts or vessels. The myxoid mesenchyme is hypocellular and composed of spindled or stellate fibroblasts and myofibroblasts. These cells lack nuclear pleomorphism, mitotic activity or necrosis. Branching bile ducts similar to malformed ductal plates are usually present throughout and are surrounded by loose mesenchyme or dense collagen. Neutrophil infiltration may be seen in these ducts. Hepatocytes may be present in single cords or in large groups, especially at the periphery of the mass. These hepatocytes are cytologically

normal appearing but may show reactive changes. Numerous arteries, veins and capillaries are seen throughout the lesion, however thick-walled vessels may be prominent at periphery of tumor. There may be scattered infiltrates of lymphocytes and plasma cells. Foci of extramedullary hematopoiesis may be seen.[55,57,58]

E. HISTOCHEMICAL STAIN AND IMMUNOHISTOCHEMSITRY: The mesenchyme is positive for vimentin, smooth muscle actin and desmin. Bile ducts are positive for cytokeratins 7 and 19. Hepatocytes are positive for Heppar1. Some cases of cHMH show a balanced translocation involving some breakpoint on chromosome 19, as seen in undifferentiated embryonal sarcoma.[58,59]

F. DIFFERENTIAL DIAGNOSIS: The differential diagnoses include: bile duct adenoma, cystadenoma, bile duct hamartoma, infantile hemangioma, infantile hemangioendothelioma, embryonal sarcoma, and mixed epithelial-mesenchymal hepatoblastoma.[57]

5. Ciliated hepatic foregut cyst (CHFC)

Ciliated hepatic foregut cysts (CHFCs) are benign lesions that have been described in most gastrointestinal organs, including the liver. They form where the foregut extends during the embryonic period, and are extremely rare.[60-63]

A. CLINICAL PRESENTATION: The mean age of patients with CHFC was 48+/-12 years. The male/female ratio was 1.1:1. Most cases are asymptomatic and incidentally found during abdominal imaging studies, however patients may present with epigastric or right upper quadrant pain. Imaging characteristics include: predominance in segment IV, small size, and subcapsular location. Two thirds are hypoechoic on USG, hypodense on CT, and highly hyperintense on T2-weighted images on MRI.[60,63,64]

B. PATHOLOGICAL FEATURES: The ciliated foregut cysts are often small (measuring less than 4 cm), unilocular, subcapsular, and located in segment IV of the left lobe of the liver. They are frequently discovered incidentally and are usually benign. CHFCs typically consist of four layers: (1) an inner layer of ciliated, pseudostratified columnar epithelium; (2) loose lamina propria; (3) a smooth muscle band, ranging from one to three layers in thickness; and (4) an outer fibrous capsule.[60,61] While the inner epithelial lining is most commonly ciliated and pseudostratified, rare cases with squamous metaplasia, and/or gastric metaplasia have been reported.

Surgical resection is generally the preferred method of treatment given the potential, albeit rare, malignant transformation reported. Interestingly, all of the malignant cases reported have shown squamous differentiation.[60,65,66]

C. DIFFERENTIAL DIAGNOSIS: Differential diagnosis includes solitary hepatic cysts, hepatobiliary cystadenomas and echinococcal cysts. The lining epithelium of all these other cystic lesions are not ciliated, a distinctive feature found in ciliated foregut cysts.[61]

6. Echinococcal (hydatic) cyst

Echinococcal cyst (EC) or hydatid disease is a parasitic infection caused by *Echinococcus sp*. *E. granulosus* produces unilocular cystic lesions, while *E. multilocularis* and *E. vogelii* produce multilocular alveolar cysts. Echinococcosis is widely distributed worldwide. Dogs and sheep serve as definitive and intermediate hosts for *E. granulosus*, whereas foxes and rodents serve as definitive and intermediate hosts for *E. multilocularis*. People are only incidentally infected when they ingest tapeworm eggs.[2]

A. PATHOGENESIS: Tapeworm attaches to the small intestinal mucosa in the definitive hosts, usually dogs. Humans are accidentally infected by exposure to contaminated feces. The ingested parasitic eggs hatch in the small intestine. The resulting larvae travel through the portal vein into the liver, lungs, and other tissues, and the larvae develop into hydatid cysts. The liver is the most common site for cystic lesions (52-77%) seen in hydatid disease, followed by lung (10-40%), brain, and other viscera. The cyst is slow growing (about 1 mm diameter per month in liver) and exists subclinically for several years.[2,67]

B. CLINICAL FEATURES: Diagnosis is made in part by clinical history with attention paid to patient's residence, place of origin and occupation to identify high-risk patients. Hydatid cysts can go undetected for many years due to the slow growth and development of cysts and the response of the host's immune system.[68] Symptoms are usually due to space – occupying repression or displacement of vital host tissue. Depending on the size and location, cysts can eventually exert pressure on nearby structures, producing abdominal discomfort and pain. Compression of bile ducts causing obstruction can manifest as obstructive jaundice, abdominal pain, anorexia, and pruritus. Rarely they can compress portal vein and cause portal hypertension. Cyst fluid is highly antigenic and hence rupture of a hydatid cyst may cause fever, pruritus, eosinophilia, or fatal anaphylaxis.[69]

C. LABORATORY TEST: Diagnosis of echinococcal cyst involves both serological evaluation and imaging modalities. Serologic tests are associated with a high incidence of false-negative and false-positive results. Most commonly used serological methods are latex agglutination, hemagglutination and enzyme-linked immunosorbent assay (ELISA).

D. IMAGING STUDIES: USG and CT are the first choices of imaging in the diagnosis of EC, with the specificity of USG in the range of 90%. CT is helpful for confirming the diagnosis and can reveal calcified cystic walls, daughter cysts, and exogenous cysts, as well as for evaluating the cyst volume and density. Four different radiographic appearances have been described on imaging: simple cyst with no internal architecture, cyst with daughter cysts and a matrix, calcified cyst, and complicated cyst. CT and MRI have very high specificity and sensitivity in the detection and differential diagnosis of hepatic cysts and extracapsular (satellite) cysts. Accurate diagnosis of ECs is essential because the mortality of these lesions is slightly higher than for simple cysts, estimated at 2-5%.[2,70,71]

E. PATHOLOGICAL FEATURES: Liver biopsy should not be used in the diagnosis of liver cysts suspicious for echinococcosis due to the risk of leakage of antigens that may lead to anaphylactic shock. Fine needle aspiration fluid can be spun down and searched for protoscolices or hooklets. Fine needle aspiration is reported to be a safe procedure, however arguments about this issue persists.[72-74] *E. granulosus* cysts are usually single unilocular, spherical and ranges upto 35 cm in diameter and have a fibrous rim. Whereas *E. multilocularis* liver lesions are multilocular and are necrotic with no fibrous rim.

The viable cyst of *E. granulosus* hydatid cyst has three layers: (*a*) the outer peripheral layer, composed of modified host cells that form a dense and fibrous protective zone (**Fig. 21.12**); (*b*) the middle laminated membrane, which is acellular and allows the passage of nutrients (**Fig. 21.13**) and can be highlighted by Grocott's methenamine silver (GMS) stain (**Fig. 21.14**); and (*c*) the inner germinal layer, where the scolices (the larval stage of the parasite) and the laminated membrane are produced (**Fig. 21.15**). Protoscolices represent incipient heads of adult tapeworms and are ovoid and contain 2 circles of hooklets and a sucker (**Fig. 21.6**).[72]

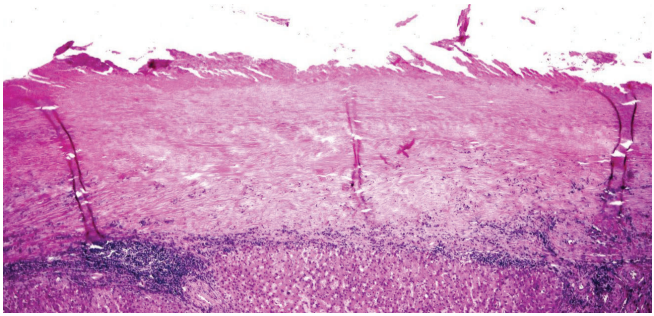

Fig 21.12 The outer peripheral layer of hydatid cyst is composed of modified host cells forming a dense and fibrous protective zone.

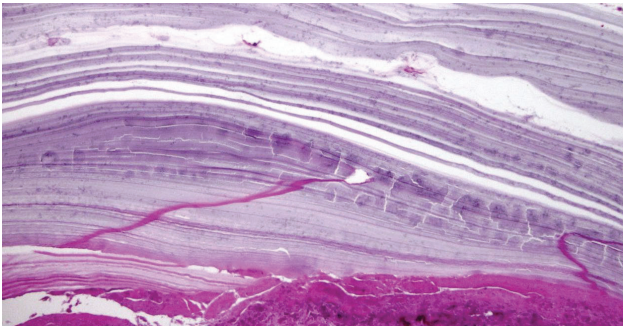

Fig 21.13 The middle laminated layer of hydatid cyst is composed of acellular membrane.

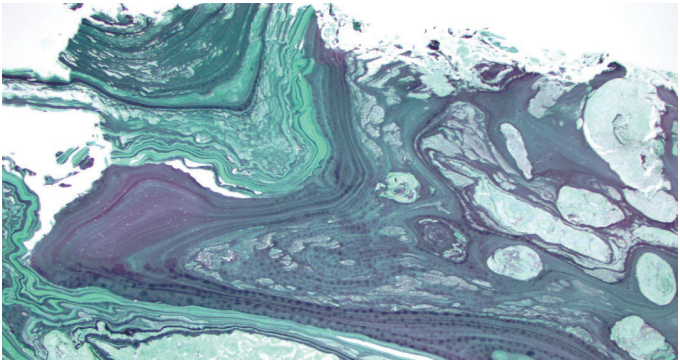

Fig 21.14 GMS stain highlights the laminated middle layer of hydatid cyst.

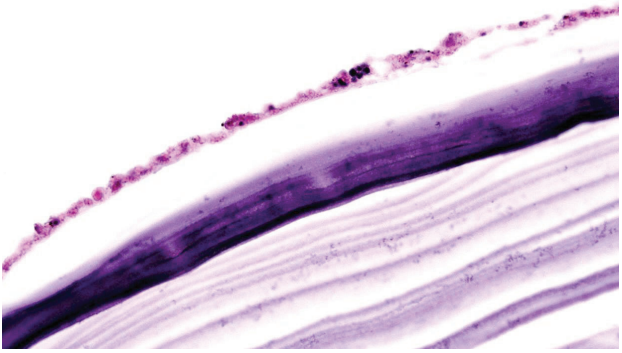

Fig 21.15 The inner layer of hydatic cyst is where the scolices are produced.

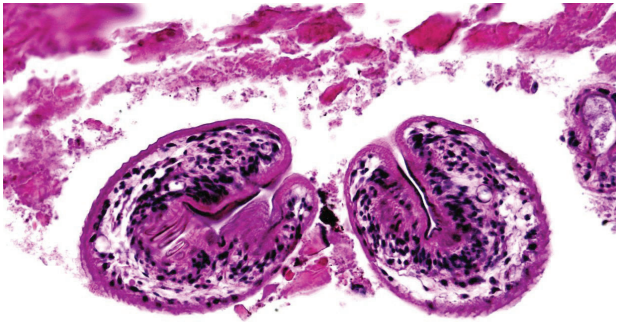

Fig 21.16 Protoscolices represent incipient heads of adult tapeworms and are ovoid and contain 2 circles of hooklets and a sucker.

Cyst fluid is clear or pale yellow, has a neutral pH, and contains sodium chloride, proteins, glucose, ions, lipids, and polysaccharides. The fluid is antigenic and may also contain scolices and hooklets. When vesicles rupture within the cyst, scolices pass into the cyst fluid and form a white sediment known as hydatid sand. Rupture of the cyst leads to multifocal new cyst formation (daughter cysts), which may present exophytic growth, biliary communication and peritoneal seeding. Daughter cyst may also be produced by protoscolices being released from germinal center.[75]

E. multilocularis and *E. vogelii* produce multilocular alveolar cysts (1 to 10 mm in diameter) and grow in an exogenous proliferation with cysts progressively invading the host tissue by peripheral extension of the process originating in the germinal center. The larva causes invasive and destructive changes in the infected liver, mimicking malignant neoplasm on imaging studies. As the lesion heals, it invariably becomes calcified. Host reaction to the growing intact hydatid cysts may only present granulation tissue and fibrotic wall. Only when the larva dies or the cyst ruptures does the inflammation become more evident with abundant eosinophils along with giant cell granuloma.[76,77]

F. HISTOCHEMICAL STAIN AND IMMUNOHISTOCHEMSITRY: Hooklets (**Fig. 21.17**) are partially acid-fast on Ziehl-Neelsen stain, stain with GMS and are birefringent.

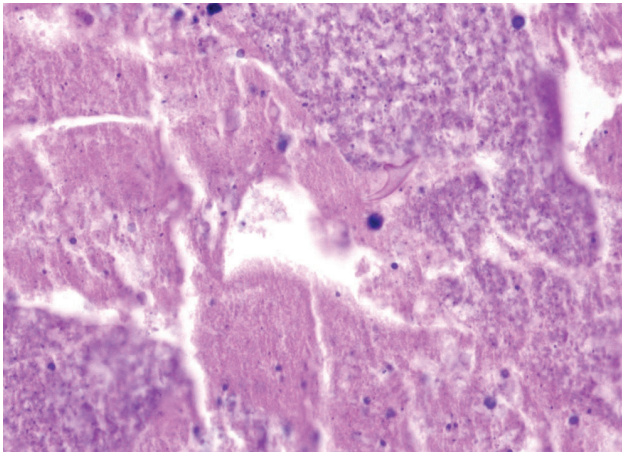

Fig 21.17 Sometime, the cyst undergoes degeneration and the hooklet is the only evidence of echinococcal infection.

G. DIFFERENTIAL DIAGNOSIS: Differential diagnoses are broad and include amebic abscess, pyogenic abscess, and non-infectious processes such as fibropolycystic liver disease. Presence of protoscolices distinguishes *Echinococcus*.

H. TREATMENT: The treatment of hepatic hydatid disease, including surgery (open or laparoscopic), percutaneous treatments [*e.g.*, puncture aspiration injection re-aspiration (PAIR) method] and chemotherapy, is indicated to reduce symptoms and prevent complications. PAIR is the

treatment of choice for EC, as a recent review showed that PAIR resulted in parasitological clearance (*i.e.*, negative serodiagnostic tests) in 95.8% of cases.[2,9,78,79]

7. Hepatic abscess (HA)

Hepatic abscess (HA) is defined as an encapsulated collection of suppurative material within the liver parenchyma, which may be infected by bacterial, fungal, and/or parasitic micro-organisms.[80] The most common type is the pyogenic abscesses (incidence: 2.3 cases/100,000 people/year). Fungi, such as candida and aspergillus are found in 15% cases and amebic abscess, accounts for only 3%–9% of all cases of liver abscess in developing countries.[81] In a majority of cases there is no clear etiology and are classified as cryptogenic.[82,83]

Pyogenic abscesses are usually polymicrobial, however the most commonly implicated organisms are E.coli, Klebsiella, Streptococcus, Staphylococcus, and anaerobes. Most amoebic infections are caused by Entamoeba histolytica. Males are more frequently affected than females. Age plays a factor in the type of abscess one develops. People aged 40-60 years are more vulnerable to developing liver abscess that does not result from trauma.[81] Risk factors predisposing patients to HA range from diabetes mellitus (DM), cirrhosis, general immune-compromised state, use of proton pump inhibitor (PPI) medications, gender, and age. DM is a predisposing factor for HA that is well documented in the literature. Studies have found DM as a concomitant disease in 29.3%–44.3% of patients with HA. Diabetic patients are also more likely to present with multiple abscesses.[84-86]

Liver abscess usually develop from an intraabdominal infection disseminated from the portal vein or from an injury to the liver. Historically, hepatic abscess is usually associated with acute appendicitis or intraabdominal infections. Currently, the most common route of infection is the biliary tree, responsible for 30%–50% of cases of HA.[87,88] The right lobe is more commonly affected due the fact that the right lobe portal blood flow is supplied predominantly by the superior mesenteric vein, whereas the left lobe portal blood flow is supplied by the splenic vein.[1]

A. CLINICAL PRESENTATION: The diagnosis of HA can be a challenge, as signs and symptoms may vary. Usual symptoms of HA include fever, jaundice, abdominal pain, nausea, vomiting, and weight loss. On physical exam, a patient can have hepatomegaly with an enlarged mass and jaundice.

Complications include rupture and spread of infection into the thoracic cavity or even formation of hepatobronchial fistulae.[89,90]

B. IMAGING STUDIES: Both USG and CT scan are reliable in the diagnosis and follow-up of the liver abscesses. The USG or CT is followed by needle aspiration under guidance to identify the exact causative organism which is essential for diagnostic as well as therapeutic purposes. Stains and cultures should be obtained from direct aspirate. The positivity rate of bacterial culture in aspirate and blood is only 50%.[91] Culture of peripheral blood may not correlate with pus culture results. Drainage of the abscess and antibiotic/anti-parasitic treatment are the cornerstone of treatments. Now with modern therapy available, liver abscesses have a much better prognosis.[83,86]

C. PATHOLOGICAL FEATURES: On gross examination, pyogenic abscesses present as single or multiple cavities (occurs in 25-45% of cases), filled with foul-smelling, creamy yellow, necrotic material which may have a fibrous capsule.

Microscopic examination reveals collection of abundant neutrophils admixed with bile and fibrin (**Fig. 21. 18**). Adjacent hepatocytes appear reactive and surrounding fibrosis may be variable. Histochemical stains (tissue gram stain, fungal silver stain, acid-fast stain and steiner stain) should be performed to identify organisms including fungal organisms (**Fig. 21.19**). In addition, aerobic/anaerobic culture of abscess content are required to determine the causative organisms.

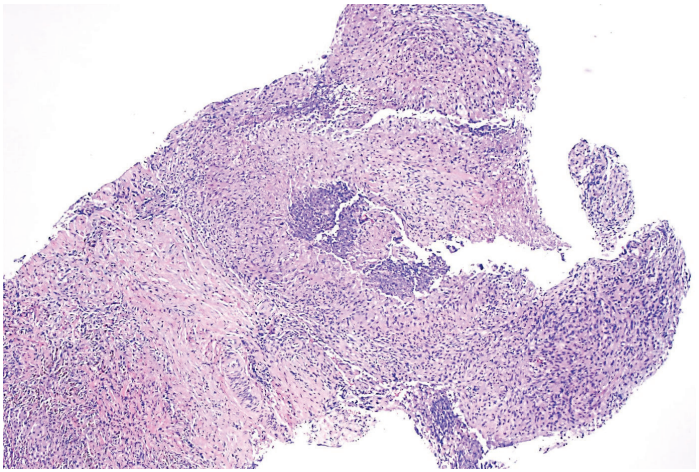

Fig 21.18. Hepatic abscess is characterized by collection of abundant neutrophils, necrosis, admixed with fibrin. Adjacent liver parenchyma shows dropout, old hemorrhage, reactive hepatocytes, and fibrosis.

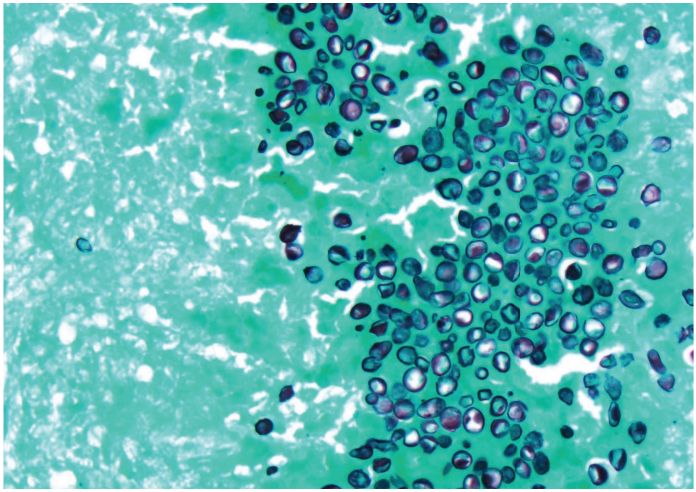

Fig 21.19 GMS stain reveals organisms with morphology consistent with candida species in the center of the hepatic abscess.

The abscess in amebiasis contains grossly chocolate-colored fluid that resembles anchovy paste, which corresponds to the necrotic contents. The liver involvement in amebiasis consists of central necrotic material with abundant nuclear debris and few intact inflammatory cells. Mononuclear cells are present at advancing edge, which will eventually develop into fibrosis and granulation tissue. Trophozoites, characterized by foamy cytoplasm, round and eccentric nuclei, are most often present at advancing edge and mimic macrophages. Hence, fine-needle aspiration cytology (FNAC) from the center of the abscess does not yield any trophozoites, and only in 15% cases, FNAC can contribute in diagnosis. The peripheral abscess wall if sampled may yield amoebic trophozoites, as they commonly invade the surrounding hepatocytes.[1,92,93] Hepatic cat scratch disease can present as hepatic abscesses in the presence or absence of lymphadenopathy[94] Biopsy may show stellate microabscesses (**Fig. 21.20**) and steiner stain may reveal coccobacillary organism *Bartonella henselae*, singly (**Fig. 21.21**) or in small clumps. In some cases, clinical history of close contact with cats, skin test, serology test, and molecular test might be helpful in confirming the diagnosis[95]

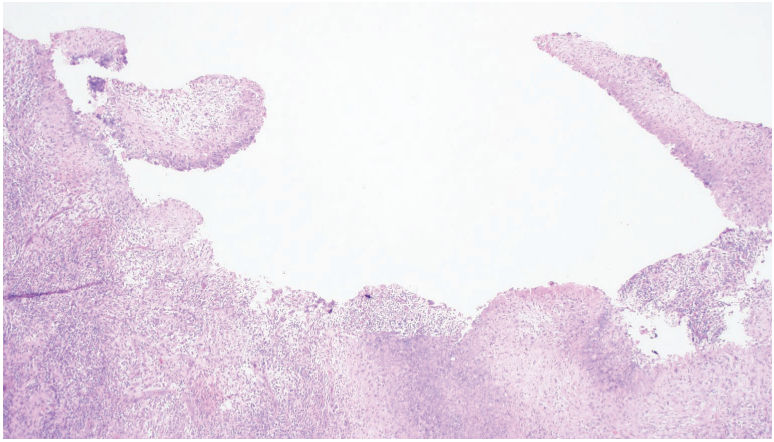

Fig 21.20 Hepatic cat scratch disease in this case presents as an abscess.

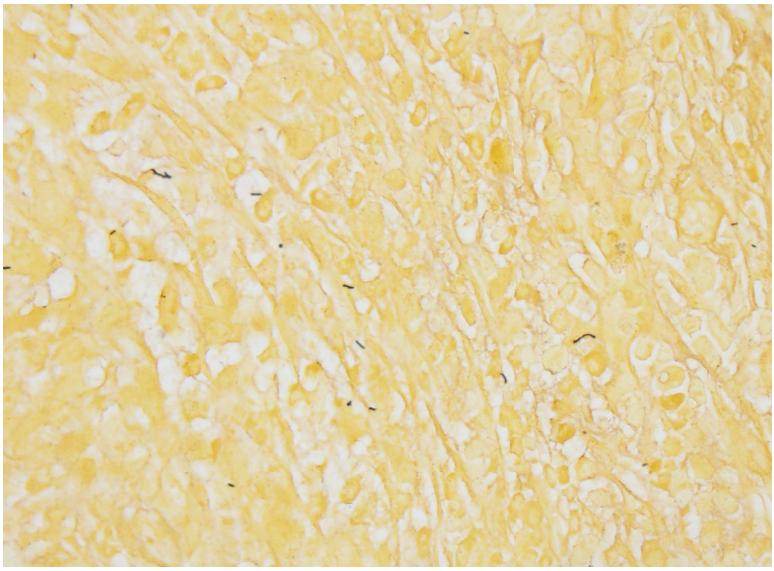

Fig 21.21 Steiner silver stain reveals the presence of *Bartonella henselae* in hepatic cat scratch disease (the same case as depicted in Fig 21.20).

D. DIFFERENTIAL DIAGNOSIS: Liver abscess manifests with right upper quadrant pain, fever, and hepatitis. Therefore many liver and non-liver ailments are in its clinical differential diagnosis. Abscess is a histologic pattern and does not provide etiology. Culture, special stains for organisms, and molecular tests for infectious agents are essential for the differential diagnoses as the treatment is quite different for different etiologies.

8. Miscellaneous non-neoplastic cystic lesions

A. ***Intrahepatic pseudocyst*** is an infrequent condition that may occur in the setting of pancreatitis, usually as a complication of acute alcoholic pancreatitis.[96] An intrahepatic pseudocyst may require prompt percutaneous or endoscopic drainage or surgical resection if it is large or symptomatic to prevent complications.[97]

B. ***Biloma*** is defined as large intra- or extra-hepatic bile collection outside the biliary tree with a well-demarcated capsule. They generally caused by injury to biliary tree due to trauma or surgery[98]. However, there are few reported cases of spontaneous biloma in the literature.[99] The most frequent cause of spontaneous biloma is choledocholithiasis.

They are often found in peri-hepatic tissues related spatially to the gallbladder or larger hepatic ducts. Large collections of bile often occur after injury to a large duct wall or gallbladder that results in rupture or ischemic damage or severe infections of biliary tree. The lesion consists of bilious debris admixed with and surrounded by inflammatory cells and macrophages, which often have a xanthomatous appearance. An exuberant fibrous connective tissue reaction may occur at the periphery of lesion and impart an encapsulated appearance. Most patients with bilomas are treated with nonoperative management.[98,100] Infected biloma requires surgical intervention such as percutaneous drainage.[22,101]

C. ***Solitary necrotic nodule (SNN) of the liver*** is an unusual benign lesion that is often an incidental finding on abdominal imaging, intraoperative examination, or post mortem. Most reported cases of solitary necrotic nodule have been in males, and over three quarters of these lesions have occurred in the right lobe of the liver, particularly under the superficial capsule. SNNs are usually single, but can also be multiple. The mean diameter of SNN is 2.3 cm. The etiology of SNN is still unclear. Several pathogenetic hypotheses of SNN are suggested: evolution of hepatic hemangioma; lesion of traumatic etiology; and sequelae of previous infection such as parasite.

SNN shares characteristic histologic findings: central necrotic zone of amorphous, eosinophilic debris rimmed by a hyalinized fibrotic capsule containing elastic fibers. The central necrotic areas occasionally contain dystrophic calcification, cholesterol clefts, foam cells, and shadows of degenerated cells. The peripheral fibrotic portion reveals varying amount of elastic fibers, varying numbers of small arteries and veins, and mononuclear inflammatory cells. Histologic findings may vary depending on the etiology of the SNN. The presence of feeding vessel and remnant hemangiomatous vascular structures and prominent sclerosis suggests an involution of hemangioma. In case of parasitic origin, degenerated larva can be seen in the necrotic center.[102,103]

The ultrasound appearance of SNN is usually of a "target" lesion with a hyperechoic center, while on CT scan they appear as non-enhancing hypodense lesions that are typical of metastatic adenocarcinoma or peripheral cholangiocarcinoma. The finding of necrotic cellular material on biopsy and the hard and "gritty" nature of the nodules, further enforces the impression of malignancy. Currently, permanent histological examination of SNNs is the only accurate method of diagnosis. However, SNNs are usually of a bilobed or lobulated shape that is unusual for malignant liver

lesions, and they often lie in close proximity to hepatic inflow structures. SNN should be suspected in liver lesions with this configuration, location, and on a biopsy showing a large amount of necrosis.[104]

D. ***Hepatic endometriosis/endometriotic cysts*** can rarely occur in the liver and they are discussed in **Chapter 20**.

E. ***Peliosis hepatis*** is a rare vascular condition of the liver characterized by the presence of cystic blood-filled cavities. It was first reported in 1861 by Wagner and was named by Schoelank in 1916.[105] The pathogenesis remains unclear but is thought to involve hepatocellular necrosis, destruction of the reticulin framework, and sinusoidal endothelium.[105] The clinical course of peliosis hepatis is variable from being asymptomatic, a slowly progressive disease, or fatal with massive hemorrhage.[106] Some of the cases are associated with human immunodeficiency virus (HIV) infection, *Bartonella* infection, or use of certain drugs such as oral contraceptives and androgenic-anabolic steroids.[105]

Radiographically, differential diagnosis of peliosis hepatis includes multiple abscesses, adenoma, focal nodular hyperplasia, hemangiomatosis, or liver metastases. A percutaneous needle biopsy can confirm the diagnosis but it carries risk of hemorrhage. Microscopically, peliosis hepatis shows round or oval intralobular blood filled cavities that are randomly distributed between areas of normal hepatic parenchyma (**Figs. 21.22 and 21.23**). The cavities may communicate with sinusoids that are sometimes dilated.

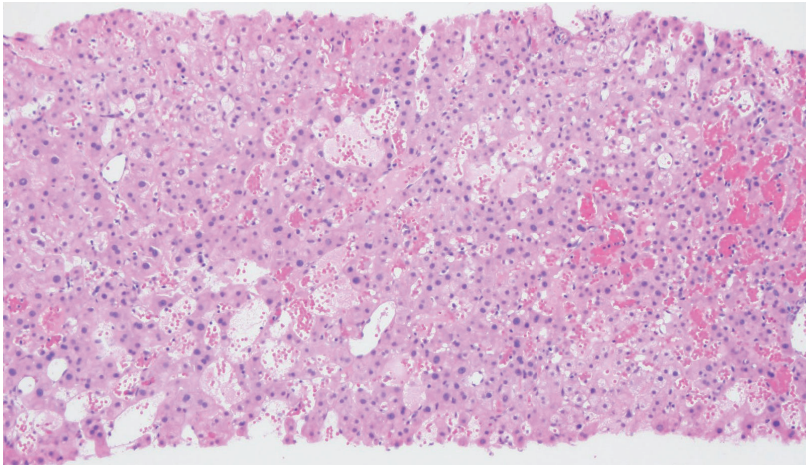

Fig 21.22 Biopsy from a liver lesion showing round or oval intralobular blood filled cavities, features of peliosis hepatis.

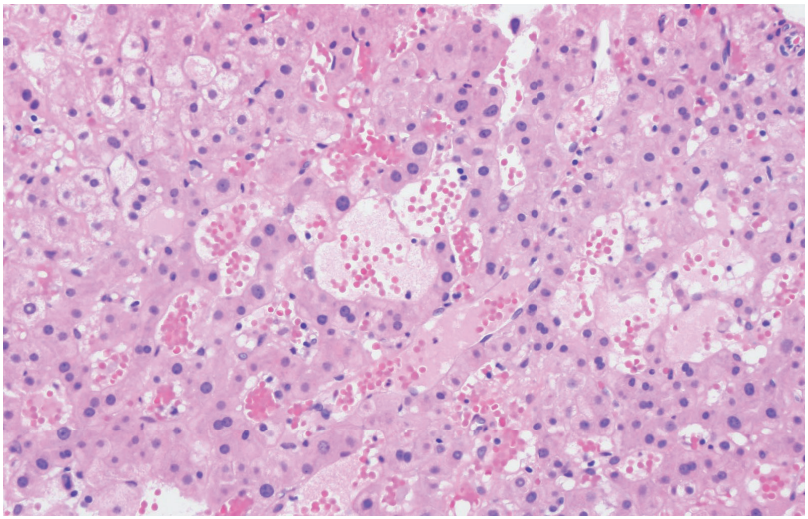

Fig 21.23 Some of the blood filled cavities are void of endothelial cells in peliosis hepatis.

References

1. Das P, Sharma P, Nakra T, et al. Spectrum of hepatobiliary cystic lesions: A 7-year experience at a tertiary care referral center in North India and review of literature. Indian J Pathol Microbiol. 2017;60:487-500.
2. Rawla P, Sunkara T, Muralidharan P, Paj JP. An updated review of cystic hepatic lesions. Clin Exp Hepatol. 2019;5:22-29.
3. Gaines PA, Sampson MA. The prevalence and characterization of simple hepatic cysts by ultrasound examination. Br J Radiol. 1989;62:335-337.
4. Carrim ZI, Murchison JT. The prevalence of simple renal and hepatic cysts detected by spiral computed tomography. Clin Radiol. 2003;58:626-629.
5. Asuquo M, Nwagbara V, Agbor C, Otobo F, Omotoso A. Giant simple hepatic cyst: a case report and review of relevant literature. Afr Health Sci. 2015;15:293-298.
6. Cowles RA, Mulholland MW. Solitary hepatic cysts. J Am Coll Surg. 2000;191:311-321.
7. Caremani M, Vincenti A, Benci A, Sassoli S, Tacconi D. Ecographic epidemiology of non-parasitic hepatic cysts. J Clin Ultrasound. 1993;21:115-118.
8. Katkhouda N, Mavor E. Laparoscopic management of benign liver disease. Surg Clin North Am. 2000;80:1203-1211.
9. Lantinga MA, Gevers TJ, Drenth JP. Evaluation of hepatic cystic lesions. World J Gastroenterol. 2013;19:3543-3554.
10. Bahirwani R. Reddy KR. Review article: the evaluation of solitary liver masses. Aliment Pharmacol Ther. 2008;28:953-965.
11. Hanazaki K, Wakabayashi M, Mori H, et al. Hemorrhage into a simple liver cyst: diagnostic implications of a recent case. J Gastroenterol. 1997;32:848-851.
12. Salemis NS, Georgoulis E, Gourgiotis S, Tsohataridis E. Spontaneous rupture of a giant non parasitic hepatic cyst presenting as an acute surgical abdomen. Ann Hepatol. 2007;6:190-193.
13. Byrne WJ, Fonkalsrud EW. Congenital solitary nonparasitic cyst of the liver: a rare cause of rapidly enlarging abdominal mass in infancy. J Pediatr Surg. 1982;17:316-317.
14. Azizah N, Paradinas FJ. Cholangiocarcinoma coexisting with developmental liver cysts: a distinct entity different from liver cystadenocarcinoma. Histopathology 1980;4:391-400.

15. Gresham GA, Rue LW 3rd. Squamous cell carcinoma of the liver. Hum Pathol. 1985;16:413-416.
16. Hayashi I, Tomoda H, Tanimoto M, et al. Mucoepidermoid carcinoma arising from a preexisting cyst of the liver. J Surg Oncol. 1987;36:122-125.
17. Pliskin A, Cualing H, Stenger RJ. Primary squamous cell carcinoma originating in congenital cysts of the liver. Report of a case and review of the literature. Arch Pathol Lab Med. 1992;116:105-107.
18. Waanders E, van Keimpema L, Brouwer JT, et al. Carbohydrate antigen 19-9 is extremely elevated in polycystic liver disease. Liver Int. 2009;29:1389-1395.
19. Choi HK, Lee JK, Lee KH, et al. Differential diagnosis for intrahepatic biliary cystadenoma and hepatic simple cyst: significance of cystic fluid analysis and radiologic findings. J Clin Gastroenterol. 2010;44:289-293.
20. Seo JK, Kim SH, Lee SH, et al. Appropriate diagnosis of biliary cystic tumors: comparison with atypical hepatic simple cysts. Eur J Gastroenterol Hepatol. 2010;22:989-996.
21. Haap M, Seeger A, Haas CS. Giant solitary hepatic cyst. Liver Int. 2008;28:840.
22. Macedo FI. Current management of noninfectious hepatic cystic lesions: A review of the literature. World J Hepatol. 2013;5:462-469.
23. Gevers TJ, Drenth JP. Diagnosis and management of polycystic liver disease. Nat Rev Gastroenterol Hepatol. 2013;10:101-108.
24. Veigel MC, Frescott-Focht J, Rodriguez MG, et al. Fibropolycystic liver disease in children. Pediatr Radiol. 2009;39:317-27; quiz 420-421.
25. Everson GT, Taylor MR, Doctor RB, Polycystic disease of the liver. Hepatology 2004;40:774-782.
26. Van Keimpema L, De Koning DB, Van Hoek B, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. Liver Int. 2011;31:92-98.
27. Torres, V.E. and P.C. Harris, Autosomal dominant polycystic kidney disease: the last 3 years. Kidney Int. 2009;76:149-168.
28. Alvaro D, Mancino MG, Onori P, et at. Estrogens and the pathophysiology of the biliary tree. World J Gastroenterol. 2006;12:3537-3545.
29. Gevers TJ, Inthout J, Caroli A, et al. Young women with polycystic liver disease respond best to somatostatin analogues: a pooled analysis of individual patient data. Gastroenterology 2013;145:357-365.e1-2.

30. Grünfeld JP, Albouze G, Jungers P, et al. Liver changes and complications in adult polycystic kidney disease. Adv Nephrol Necker Hosp. 1985;14:1-20.
31. Niv Y, Turani C, Kahan E, Fraser GM. Association between pancreatic cystadenocarcinoma, malignant liver cysts, and polycystic disease of the kidney. Gastroenterology 1997;112:2104-2107.
32. Caroli J. Diseases of the intrahepatic biliary tree. Clin Gastroenterol. 1973;2:147-161.
33. Belibi FA and Edelstein CL, Unified ultrasonographic diagnostic criteria for polycystic kidney disease. J Am Soc Nephrol. 2009;20:6-8.
34. Nicolau C, Torra R, Badenas C, et al. Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis. Radiology 1999;213:273-276.
35. Turkbey B, Ocak I, Daryanani K, et al. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (ARPKD/CHF). Pediatr Radiol. 2009;39:100-111.
36. Akhan O, Karaosmanoglu AD, Ergen B. Imaging findings in congenital hepatic fibrosis. Eur J Radiol, 2007;61:18-24.
37. Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme "ductal plate malformation". Hepatology 1992;16:1069-1083.
38. Karhunen PJ. Adult polycystic liver disease and biliary microhamartomas (von Meyenburg's complexes). Acta Pathol Microbiol Immunol Scand A. 1986;94:397-400.
39. Mortele B, Mortele K, Seynaeve P, et al. Hepatic bile duct hamartomas (von Meyenburg Complexes): MR and MR cholangiography findings. J Comput Assist Tomogr. 2002;26:438-443.
40. Eisenberg D, Hurwitz L, Yu AC. CT and sonography of multiple bile-duct hamartomas simulating malignant liver disease (case report). AJR Am J Roentgenol. 1986;147:279-80.
41. Davidoff S, Kim S, Friedman B. Von Meyenburg complexes (bile duct hamartomas). Clin Gastroenterol Hepatol. 2006;4:xxvi.
42. Luo TY, Itai Y, Eguchi N, et al. Von Meyenburg complexes of the liver: imaging findings. J Comput Assist Tomogr. 1998;22:372-378.
43. Guo Y, Jain D, Weinreb J, Von Meyenburg Complex: Current Concepts and Imaging Misconceptions. J Comput Assist Tomogr. 2019;43:846-851.
44. Sinakos E, Papalavrentios L, Chourmouzi D, et al. The clinical presentation of Von Meyenburg complexes. Hippokratia 2011;15:170-173.

45. Zheng RQ, Zhang B, Kudo M, Onda H, Inoue T. Imaging findings of biliary hamartomas. World J Gastroenterol. 2005;11:6354-6359.
46. Jain D, Sarode VR, Abdul-Karim FW, Homer R, Robert ME. Evidence for the neoplastic transformation of Von-Meyenburg complexes. Am J Surg Pathol. 2000;24:1131-1139.
47. Jain D, Ahrens W, Finkelstein S. Molecular evidence for the neoplastic potential of hepatic Von-Meyenburg complexes. Appl Immunohistochem Mol Morphol. 2010;18:166-171.
48. Hornick JL, Lauwers GY, Odze RD, Immunohistochemistry can help distinguish metastatic pancreatic adenocarcinomas from bile duct adenomas and hamartomas of the liver. Am J Surg Pathol. 2005;29:381-389.
49. Rakheja D, Margraf LR, Tomlinson GE, Schneider NR. Hepatic mesenchymal hamartoma with translocation involving chromosome band 19q13.4: a recurrent abnormality. Cancer Genet Cytogenet. 2004;153:60-63.
50. Chung EM, Cube R, Lewis RB, Conran RM. From the archives of the AFIP: Pediatric liver masses: radiologic-pathologic correlation part 1. Benign tumors. Radiographics. 2010;30:801-826.
51. Stocker JT, Ishak KG, Mesenchymal hamartoma of the liver: report of 30 cases and review of the literature. Pediatr Pathol. 1983;1:245-267.
52. Wada M, Ohashi E, Jin H, et al. Mesenchymal hamartoma of the liver: report of an adult case and review of the literature. Intern Med. 1992;31:1370-1375.
53. Yen JB, Kong MS, Lin JN. Hepatic mesenchymal hamartoma. J Paediatr Child Health 2003;39:632-634.
54. DeMaioribus CA, Lally KP, Sim K, Isaacs H, Mahour GH. Mesenchymal hamartoma of the liver. A 35-year review. Arch Surg. 1990;125:598-600.
55. Siddiqui MA, McKenna BJ. Hepatic mesenchymal hamartoma: a short review. Arch Pathol Lab Med. 2006;130:1567-1569.
56. Ramanujam TM, Ramesh JC, Goh DW, et al. Malignant transformation of mesenchymal hamartoma of the liver: case report and review of the literature. J Pediatr Surg. 1999;34:1684-1686.
57. Stringer MD, Alizai NK. Mesenchymal hamartoma of the liver: a systematic review. J Pediatr Surg. 2005;40:1681-1690.
58. Sugito K, Kawashima H, Uekusa S, Inoue M, Ikeda T, Kusafuka T. Mesenchymal hamartoma of the liver originating in the caudate lobe with t(11;19)(q13;q13.4): report of a case. Surg Today 2010;40:83-87.

59. Lauwers GY, Grant LD, Donnelly WH, et al. Hepatic undifferentiated (embryonal) sarcoma arising in a mesenchymal hamartoma. Am J Surg Pathol. 1997;21:1248-1254.
60. Bishop KC, Perrino CM, Ruzinova MB, Brunt EM. Ciliated hepatic foregut cyst: a report of 6 cases and a review of the English literature. Diagn Pathol. 2015;10:81.
61. Vick DJ, Goodman ZD, Deavers MT, Cain J, Ishak KG. Ciliated hepatic foregut cyst: a study of six cases and review of the literature. Am J Surg Pathol. 1999;23:671-677.
62. Dockerty MB, Gray HK, Henson SW Jr. Benign tumors of the liver. III. Solitary cysts. Surg Gynecol Obstet. 1956;103:607-612.
63. Ansari-Gilani K, Modaresi Esfeh J. Ciliated hepatic foregut cyst: report of three cases and review of imaging features. Gastroenterol Rep (Oxf). 2017;5:75-78.
64. Sharma S, Dean AG, Corn A, et al. Ciliated hepatic foregut cyst: an increasingly diagnosed condition. Hepatobiliary Pancreat Dis Int. 2008;7:581-589.
65. Kaplan KJ, Escobar M, Alonzo M, Berlin JW. Ciliated hepatic foregut cyst: report of a case on fine-needle aspiration. Diagn Cytopathol. 2007;35:245-249.
66. De J, Rossman L, Kott MM, Deavers MT. Cytologic diagnosis of ciliated hepatic foregut cyst. Diagn Cytopathol. 2006;34:846-849.
67. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev. 2004;17:107-135.
68. Zhang W, Ross AG, McManus DP. Mechanisms of immunity in hydatid disease: implications for vaccine development. J Immunol. 2008;181:6679-6685.
69. Siracusano A, Teggi A, Ortona E. Human cystic echinococcosis: old problems and new perspectives. Interdiscip Perspect Infect Dis. 2009;2009:474368.
70. Sayek I, Tirnaksiz MB, Dogan R. Cystic hydatid disease: current trends in diagnosis and management. Surg Today 2004;34:987-996.
71. Marrero JA, Ahn K, Rajender Reddy K. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014;109:1328-1347; quiz 1348.
72. Chrieki M. Echinococcosis--an emerging parasite in the immigrant population. Am Fam Physician 2002;66:817-820.
73. Gottstein B. Molecular and immunological diagnosis of echinococcosis. Clin Microbiol Rev. 1992;5:248-261.

74. Saenz-Santamaria J, Moreno-Casado J, Nunez C. Role of fine-needle biopsy in the diagnosis of hydatid cyst. Diagn Cytopathol. 1995;13:229-232.
75. Pedrosa I, Saiz A, Arrazola J, Ferreiros J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complications. Radiographics 2000;20:795-817.
76. Ozkok A, Gul E, Okumus G, et al. Disseminated alveolar echinococcosis mimicking a metastatic malignancy. Intern Med. 2008;47:1495-1497.
77. Czermak BV, Akhan O, Hiemetzberger R, et al. Echinococcosis of the liver. Abdom Imaging. 2008;33:133-43.
78. Brunetti E, Junghanss T, Update on cystic hydatid disease. Curr Opin Infect Dis. 2009; 22:497-502.
79. Smego RA Jr, Sebanego P. Treatment options for hepatic cystic echinococcosis. Int J Infect Dis. 2005;9:69-76.
80. Serraino C, Elia C, Bracco C, et al. Characteristics and management of pyogenic liver abscess: A European experience. Medicine (Baltimore) 2018;97:e0628.
81. Akhondi H, Sabih DE. Liver Abscess, in StatPearls. 2019, StatPearls Publishing LLC.: Treasure Island (FL).
82. Malik AA, Bari SU, Rouf KA, Wani KA. Pyogenic liver abscess: Changing patterns in approach. World J Gastrointest Surg. 2010;2:395-401.
83. Huang CJ, Pitt HA, Lipsett PA, et al. Pyogenic hepatic abscess. Changing trends over 42 years. Ann Surg. 1996;223:600-607; discussion 607-609.
84. Lee KT, Wong SR, Sheen PC. Pyogenic liver abscess: an audit of 10 years' experience and analysis of risk factors. Dig Surg. 2001;18:459-465; discussion 465-466.
85. Tian LT, Yao K, Zhang XY, et al. Liver abscesses in adult patients with and without diabetes mellitus: an analysis of the clinical characteristics, features of the causative pathogens, outcomes and predictors of fatality: a report based on a large population, retrospective study in China. Clin Microbiol Infect. 2012;18:E314-330.
86. Mavilia MG, Molina M, Wu GY. The Evolving Nature of Hepatic Abscess: A Review. J Clin Transl Hepatol. 2016;4:158-168.
87. Kumar D, Ramanathan S, Al Faki A, Nepal P. Faecolith migrating from the appendix to produce liver abscess after subhepatic laparoscopic appendectomy. Trop Doct. 2015;45:241-244.
88. Matthews JB, Gertsch P, Baer HU, Blumgart LH. Hepatic abscess after biliary tract procedures. Surg Gynecol Obstet. 1990;170:469-475.

89. Hernandez JL Ramos C. Pyogenic hepatic abscess: clues for diagnosis in the emergency room. Clin Microbiol Infect. 2001;7:567-570.
90. Chandok N. Polycystic liver disease: a clinical review. Ann Hepatol. 2012;11:819-826.
91. Lodhi S, Sarwari AR, Muzammil M, Salam A, Smego RA. Features distinguishing amoebic from pyogenic liver abscess: a review of 577 adult cases. Trop Med Int Health 2004;9:718-723.
92. Ruiz-Hernandez JJ, Leon-Mazorra M, Conde-Martel A, et al. Pyogenic liver abscesses: mortality-related factors. Eur J Gastroenterol Hepatol. 2007;19:853-858.
93. Rahimian J, Wilson T, Oram V, Holzman RS. Pyogenic liver abscess: recent trends in etiology and mortality. Clin Infect Dis. 2004;39:1654-1659.
94. Delbeke D, Sandler MP, Shaff MI, Miller SF. Cat-scratch disease: report of a case with liver lesions and no lymphadenopathy. J Nucl Med. 1988;29:1454-1456.
95. Baptista MA, Lo DS, Hein N, et al. Cat-scratch disease presenting as multiple hepatic lesions: case report and literature review. Autops Case Rep. 2014;4:43-48.
96. Scappaticci F, Markowitz SK. Intrahepatic pseudocyst complicating acute pancreatitis: imaging findings. AJR Am J Roentgenol. 1995;165:873-874.
97. Edmonds PJ, Arroyo JP, Morales A, Brown RM, Ely EW. Intrahepatic Pancreatic Pseudocyst: a rare complication of pancreatitis. J Gastrointestin Liver Dis. 2017;26:222.
98. Vazquez JL, Thorsen MK, Dodds WJ, Quiroz FA, Martinez ML, Lawson TL, Stewart ET, Foley WD: Evaluation and treatment of intraabdominal bilomas. AJR Am J Roentgenol. 1985;144: 933-938.
99. Akhtar MA, Bandyopadhyay D, Montgomery HD, Mahomed A: Spontaneous idiopathic subcapsular biloma. J Hepatobiliary Pancreat Surg. 2007;14:579-581.
100. Tamura N, Ishihara S, Kuriyama A, Watanabe S, Suzuki K. Long-term follow-up after non-operative management of biloma due to blunt liver injury. World J Surg. 2015;39:179-183.
101. Bas G, Okan I, Sahin M, Eryilmaz R, Isik A. Spontaneous biloma managed with endoscopic retrograde cholangiopancreatography and percutaneous drainage: a case report.J Med Case Rep. 2011;5:3. doi: 10.1186/1752-1947-5-3.
102. Tsui WM, Yuen RW, Chow LT, Tse CC. Solitary necrotic nodule of the liver: parasitic origin? J Clin Pathol. 1992;45:975-978.

103.Noh SJ, Jachin S, Moon WS, et al. Solitary necrotic nodule of the liver. Clin Mol Hepatol. 2012;18:235-238.
104.Koea J, Taylor G, Miller M, Rodgers M, McCall J. Solitary necrotic nodule of the liver: a riddle that is difficult to answer. J Gastrointest Surg. 2003;7:627-630.
105.Zucchetti BM, Shimada A, Siqueira LT. Peliosis hepatis simulates liver metastases. J Glob Oncol. 2018;4:JGO.2016.008839.
106.Biswas S, Cogna S, Patel P. A fatal case of intra-abdominal hemorrhage following diagnostic blind percutaneous liver biopsy in a patient with peliosis hepatis. Gastroenterol Res. 2017;10:318-321.

Chapter Twenty-Two

Neoplastic Tumors of Liver

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Abstract

Broadly speaking, primary tumors of the liver arise from a limited number of non-neoplastic constituents which include hepatocytes, biliary epithelium, and vascular structures. While these narrow origins might suggest a relatively restricted set of pathologic entities, a diverse array of tumor types result from these humble roots necessitating a thorough understanding by surgical pathologists. However, while liver masses are not uncommon in the general population, this relative incidence is not typically reflected in the number of cases encountered in a conventional surgical pathology practice. This dichotomy has a number of causes with the primary reason being that many liver lesions are amenable to definitive characterization by radiographic features, circumventing the need for histologic assessment. Therefore there is a consistent need for educational resources in the area of liver tumors and hopefully this volume provides some guidance.

Keywords: Liver cancer; Liver tumor; Hepatocellular carcinoma; Hepatocellular adenoma; Hepatoblastoma; Cholangiocarcinoma; Hemangioma; Focal nodular hyperplasia.

1. Vascular tumors

A. Hemangioma

a. Clinical features: Hepatic hemangiomas represent the most common liver tumor with a prevalence of 2.5% based on imaging investigations and higher estimates based on autopsy studies.[1] Like many of the benign liver lesions, hemangiomas are much more frequently appreciated in women than men. Given this epidemiological finding it is not surprising that some studies have suggested that hormones such as estrogen play a role in their development.[2] While considered to have no predilection for malignant transformation, these vascular tumors can rarely pose a threat to patients in the form of spontaneous rupture, a phenomenon that occurs in approximately 0.5% of individuals and is most often associated with tumors measuring 4 cm or greater.[1] Hemangiomas are typically solitary lesions and are most often encountered on imaging studies performed for unrelated reasons. Biopsies of such lesions are not frequently encountered as the radiographic findings by multiple modalities are relatively diagnostic.

b. Pathologic features: Hepatic hemangiomas are composed of proliferations of inconspicuous appearing vessels lined by flattened endothelial cells (**Fig. 22.1**). These vessels are often accompanied by a homogenous appearing stroma which is typically devoid of normal hepatocellular constituents. The exception to this would be at the periphery of a lesion where it may interdigitate with the surrounding parenchyma.[3] Complicating biopsy interpretation is the propensity for hemangiomas to partially involute which may incite a fibrotic or myxoid stromal response, with or without calcifications. Identifying residual vascular structures may be challenging in these cases and the use of endothelial markers such as CD31, CD34, or ERG may be helpful (**Figs. 22.2 and 22.3)**. While a vast majority of these adult tumors are of the cavernous type, lesions composed of smaller and occasionally inconspicuous vessels can also occur and have been termed capillary hemangiomas. These vascular lesions are typically smaller than those of the cavernous type and are of little clinical consequence once recognized. However, they may present with atypical imaging findings leading to pathologic assessment by biopsy.

Other described variants include sclerosing hemangiomas and anastomosing hemangiomas.[4,5] Sclerosing hemangiomas may radiographically mimic malignancies such as cholangiocarcinoma, hepatocellular carcinoma, metastatic tumors, or organized abscesses.[4] These tumors represent an involutional form of cavernous hemangiomas and consist of variably sized

vessels associated with a thickened myxoid to fibrotic stroma.[4,6] Anastomosing hemangiomas, which are more commonly encountered in the genitourinary tract, consist of anastomosing capillary-sized vessels with endothelial cells demonstrating a hobnail appearance which may be accompanied by mild cytologic atypia. These tumors may be difficult to distinguish from well differentiated angiosarcomas, particularly on biopsy.[5] In these situations, a biopsy interpretation of atypical vascular proliferation may be warranted.

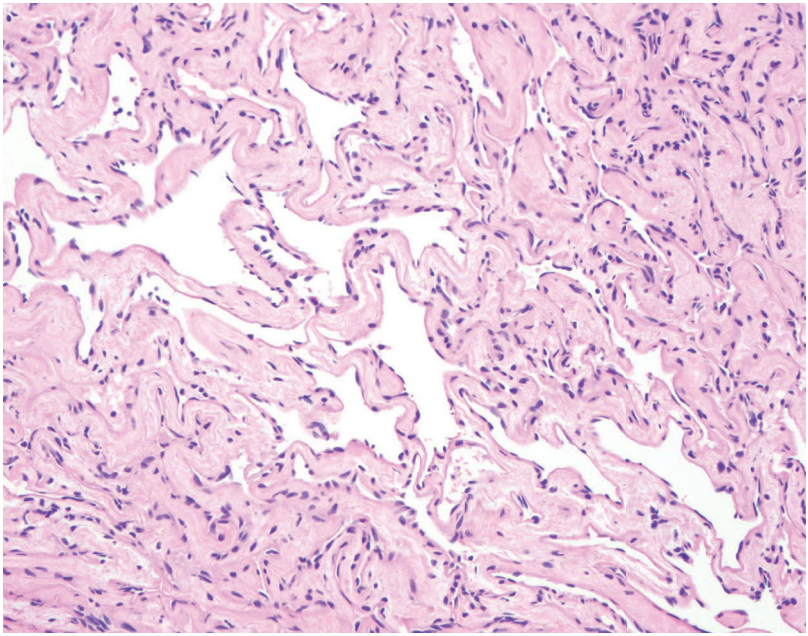

Fig 22.1 Liver hemangioma with delicate vascular lumens lined by bland endothelial cells associated with a paucicellular stroma.

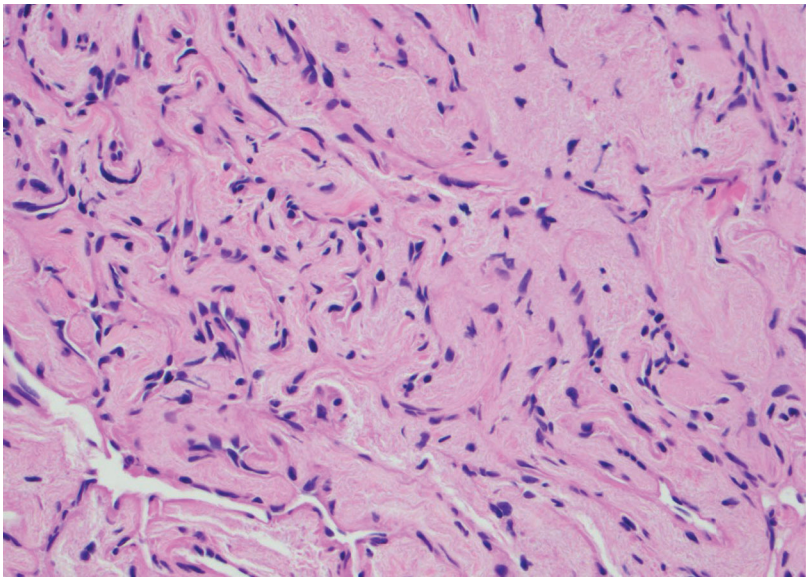

Fig 22.2 Liver hemangioma with markedly compressed slit like channels.

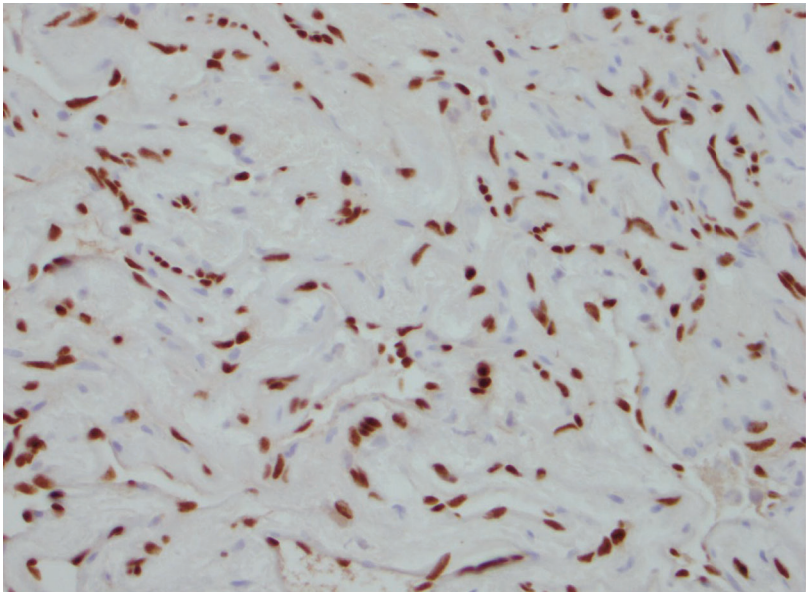

Fig 22.3 Immunohistochemistry for ERG highlights the vascular nature of the lesion depicted in Fig. 22.2.

B. Epithelioid hemangioendothelioma

a. Clinical features: Epithelioid hemangioendothelioma are rare tumors of vascular origin that may arise in various sites within the body including soft tissues and visceral organs such as the liver. Other common areas of involvement include the lungs and bones.[7] These tumors, which are now all considered to be malignant, typically afflict young adults during the fourth decade of life and are slightly more common in women with an estimated male to female ratio of 2:3.[8] The vast majority of hepatic hemangioendothelioma present as incidental findings on imaging, however, liver involvement is usually extensive and multifocal involvement of both hepatic lobes is frequently encountered. Patients typically lack any evidence of background liver disease and no convincing predisposing factors have been noted. As the efficacy of systemic therapy appears to be lacking, the mainstay of treatment is resection with up to 45% of patients ultimately undergoing liver transplant for disease control.[8] While they all possess some degree of propensity to progress, hemangioendothelioma are considered to be of somewhat lower malignant potential than angiosarcomas with 1 year and 5 year survival rates of 83.4% and 41.1% respectively.[8]

b. Pathologic features: Recognition of hepatic hemangioendothelioma, particularly on biopsy, can be quite challenging and up to 75% of cases may be initially mischaracterized pathologically.[9] Key histologic features include epithelioid cells with somewhat modest eosinophilic cytoplasm, which is typically pale in character, embedded in a loose myxoid matrix. Intratumoral cellularity can be quite variable and the background stroma may become hyalinized, particularly within the center of lesions. Cellular atypia is typically lacking as is appreciable mitotic activity. The vacuolated cytoplasm of tumor cells may impart a signet ring cell-like morphology or at times appear to contain red blood cells giving the appearance of intracytoplasmic lumina (**Fig. 22.4**). This vacuolization is reported to occur in all cases and may be a prominent feature of some tumors.[9]

These tumors may demonstrate a number of peculiar growth patterns which may be appreciated on biopsy. Lesional cells have a propensity to infiltrate and subsequently obliterate the lumens of vascular structures, a finding which is most frequently appreciated in hepatic veins. Additionally, just as in hepatic angiosarcomas, tumors cells frequently extend beyond the main portion of the tumor by colonizing the adjacent sinusoids.[10] This phenomenon is particularly important to recognize in cases in which biopsies may be inadvertently obtained from liver parenchyma outside of the radiographic lesion.

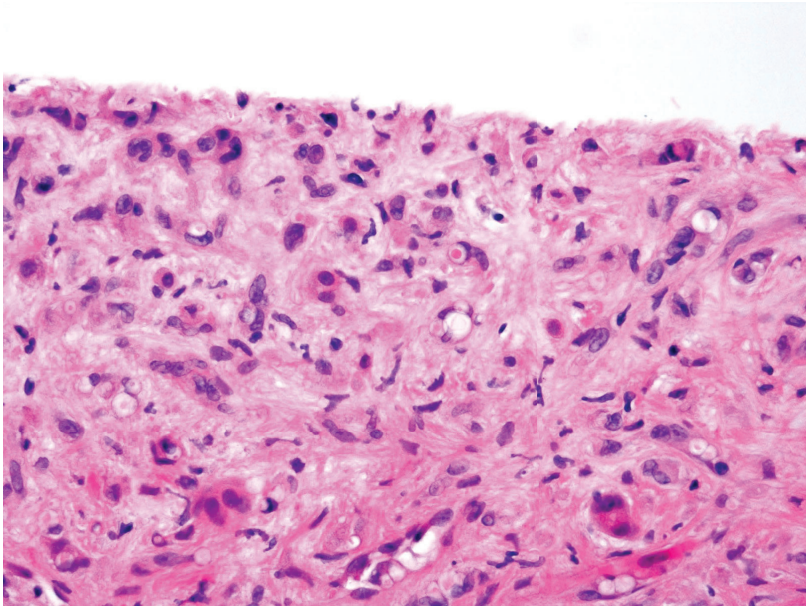

Fig 22.4 Epithelioid hemangioendothelioma demonstrating vacuolated epithelioid cells haphazardly embedded in a myxoid stroma with occasional apparent intracytoplasmic red blood cells.

Given its propensity to mimic other liver-based tumors, particularly intrahepatic cholangiocarcinomas, epithelioid hemangioendothelioma thankfully have a rather distinct immunohistochemical profile. The vast majority of cases express markers of vascular differentiation including ERG, CD34, and CD31 (**Figs. 22.5 and 22.6**). Care should be taken however in interpreting expression in the correct population of cells as background vascular structures in other tumors will also express these markers. Also, a minor proportion of hemangioendotheliomas have been known to demonstrate reactivity for cytokeratins such as CAM5.2, so expression of these epithelial markers should not exclude these lesions from the differential. Importantly, it has now been recognized that a majority of hemangioendotheliomas harbor a *CAMTA1-WWTR1* fusion and detection of CAMTA1 overexpression by immunohistochemistry has shown promise as an additional diagnostic tool, particularly if angiosarcoma is in the differential.[11]

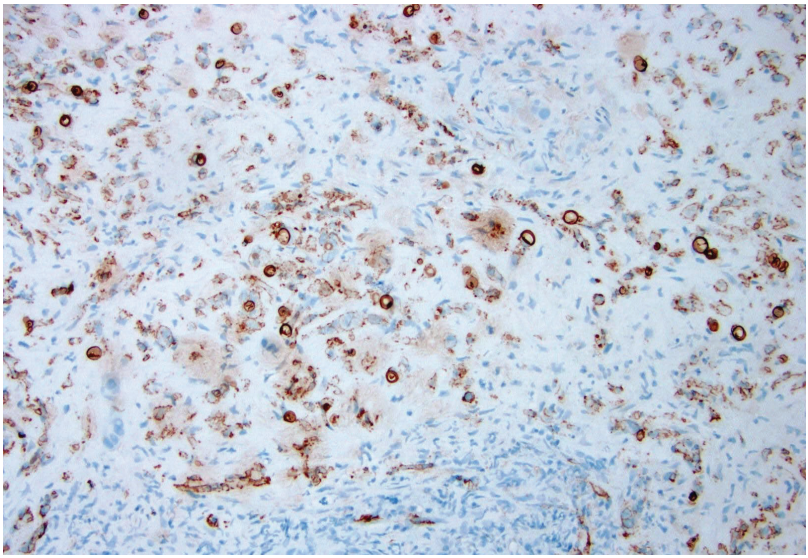

Fig 22.5 Immunoreactivity for CD34 in epithelioid hemangioendothelioma.

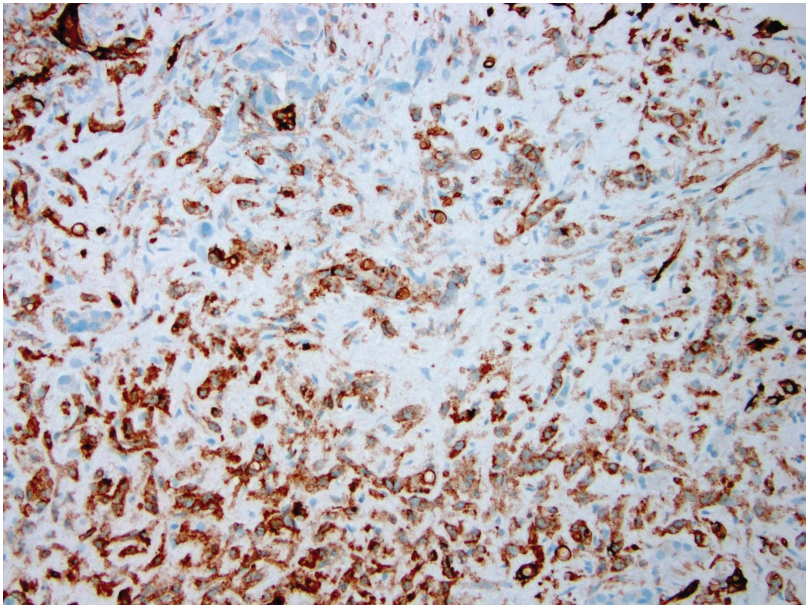

Fig 22.6 Strong immunoreactivity for CD31 in epithelioid hemangioendothelioma.

C. Angiosarcoma

a. Clinical features: While angiosarcoma is the most common sarcoma to arise in the adult liver, these malignant mesenchymal tumors remain quite rare, representing approximately 2% of all primary liver tumors with 0.5-2.5 cases for every 10,000,000 people.[12, 13] Affecting men more often than women, it has been estimated that up to 25% of hepatic angiosarcomas are associated with carcinogen exposure including most prominently occupational exposure to vinyl chloride and the radioactive contrast agent Thorotrast, the latter of which was used in the United States up until the 1950s. Presenting symptoms are typically non-specific and tumors are often multifocal at the time of presentation. Imaging studies including contrast-enhanced CT typically reveal multifocal large hepatic masses with heterogeneous enhancement indicative of tumor necrosis and hemorrhage.[14] In cases associated with Thorotrast exposure, residual contrast agent may be appreciated.[15] Angiosarcomas of the liver carry a poor prognosis and the mainstay of treatment remains complete surgical resection if feasible. As the radiographic findings associated with hepatic angiosarcomas are relatively nonspecific, demonstrating overlapping features with other liver tumors such as intrahepatic cholangiocarcinomas, biopsies are often necessary to establish a diagnosis. While complications such as severe hemorrhage have been reported, these instances are relatively uncommon.[16, 17]

b. Pathologic features: In its most straightforward form, hepatic angiosarcomas may be recognized on biopsy as proliferations of irregular blood vessels lined by notably atypical endothelial cells (**Figs. 22.7, 22.8, 22.9**). Mitoses are not infrequently encountered as are areas of hemorrhage and necrosis. Occasionally, the neoplastic cells may be quite compact imparting a solid appearance to the tumor with only focal evidence of vasoformative elements. Additionally, tumor cells may demonstrate a spectrum of morphologies from spindled to more epithelioid.[18] While more conventional foci may be appreciated on resection specimens, a low threshold for evaluating for vascular markers by immunohistochemistry should be considered in biopsy specimens of atypical liver malignancies (**Figs. 22.10, 22.11, and 22.12**). Angiosarcomas of the liver also have a tendency to extend through adjacent sinusoidal spaces, occasionally contributing to parenchymal collapse, where recognition of their presence may be more difficult (**Figs. 22.13 and 22.14**). In rare cases, these tumors may also mimic sinusoidal obstruction syndrome/venoocclusive disease (**Fig. 22.15**), a scenario in which careful correlation with clinical and radiographic studies is crucial.[19]

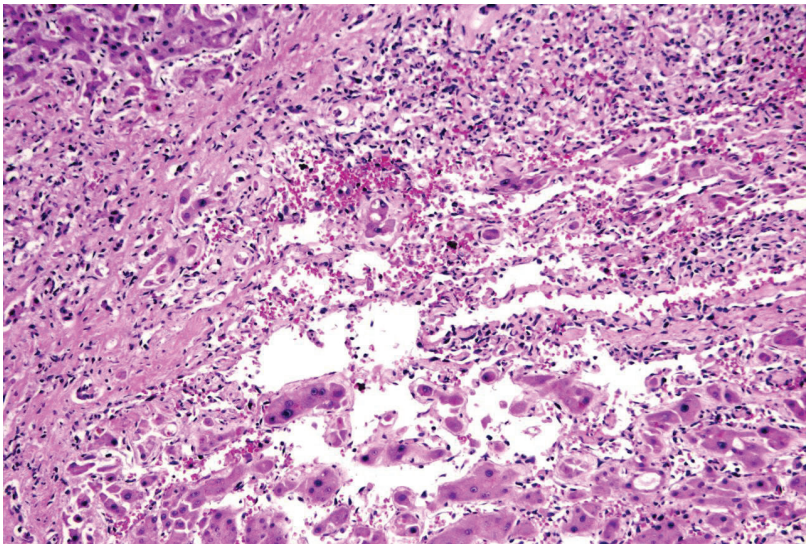

Fig 22.7 Hepatic angiosarcomas may be recognized on biopsy as proliferations of irregular blood vessels lined by notably atypical endothelial cells.

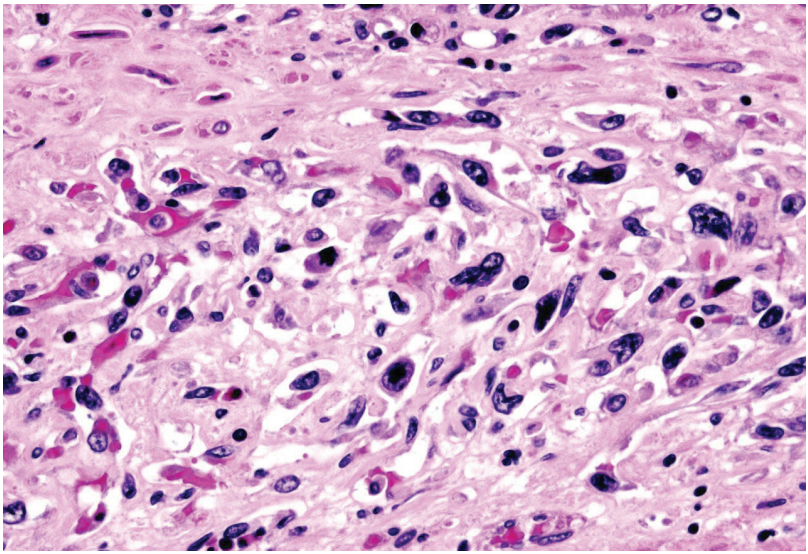

Fig 22.8 High power magnification shows notably atypical and hyperchromatic endothelial cells in hepatic angiosarcoma.

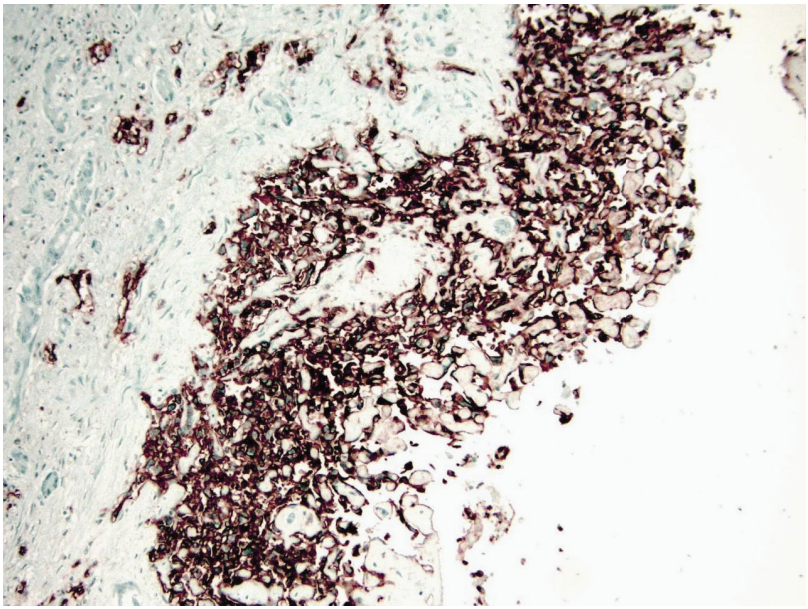

Fig 22.9 Immunoreactivity of CD31 in hepatic angiosarcoma.

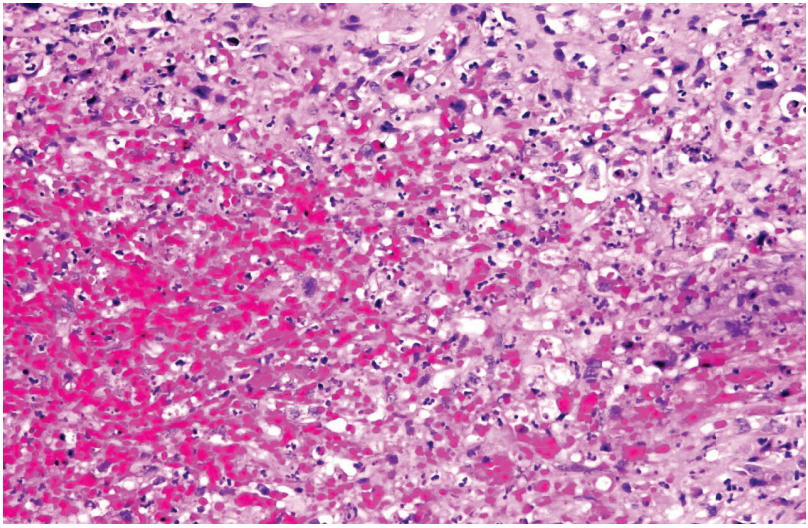

Fig 22.10 Hemorrhage and parenchyma collapse at the periphery of hepatic angiosarcoma.

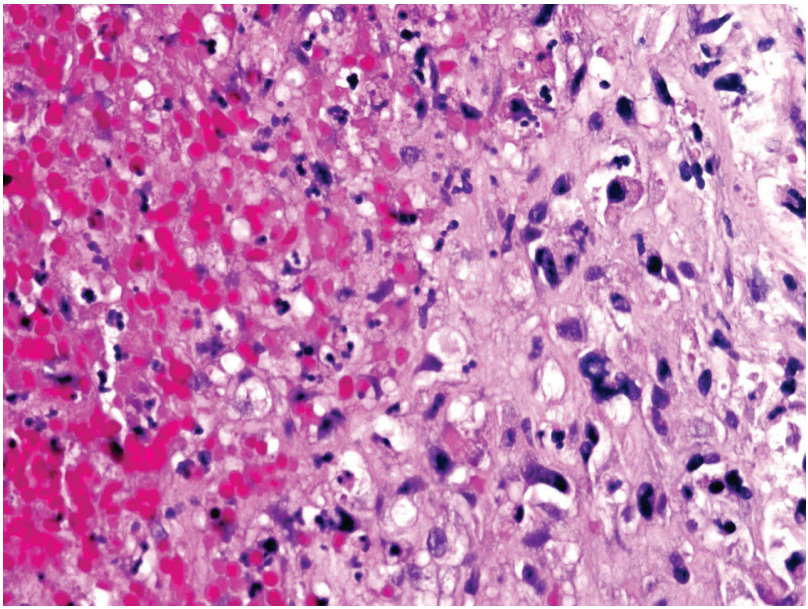

Fig 22.11 Atypical and hyperchromatic endothelial cells are present at the periphery of a hemorrhagic lesion which is confirmed to be an angiosarcoma by immunohistochemistry for CD31 (fig. 22.12, below).

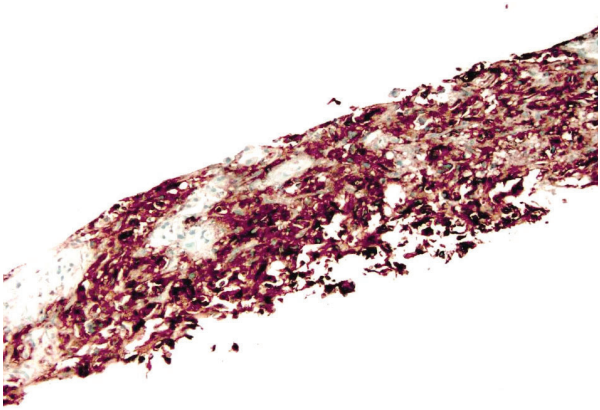

Fig 22.12 Immunohistochemistry for CD31 confirms an endothelial origin for these highly atypical cells at the periphery of a hemorrhagic lesion as depicted in fig. 22.11 (above).

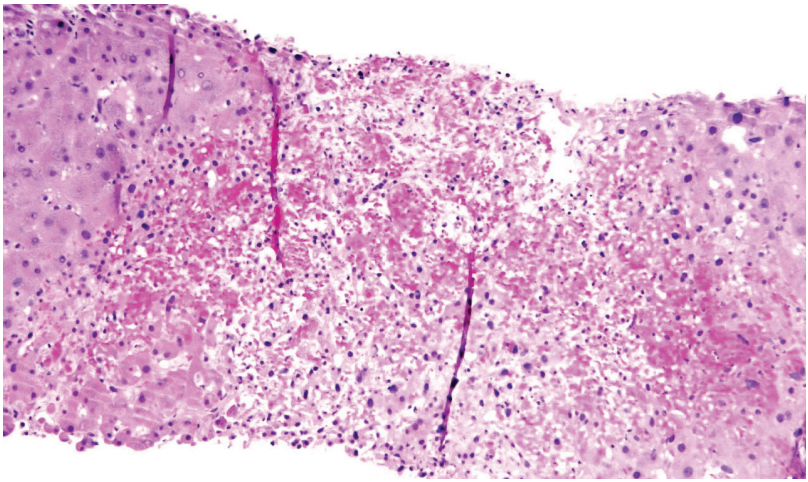

Fig 22.13 Angiosarcomas of the liver also have a tendency to extend through adjacent sinusoidal spaces, occasionally contributing to parenchymal collapse, where recognition of their presence may be more difficult.

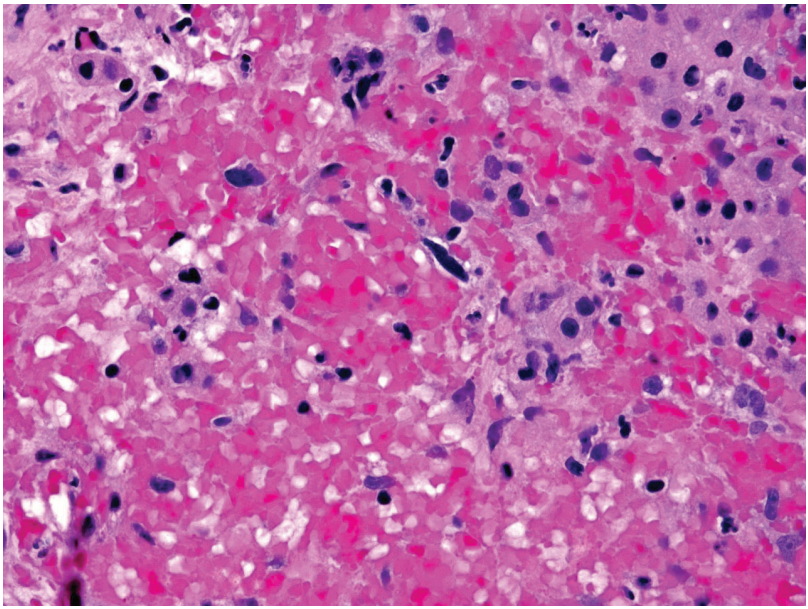

Fig 22.14 High power view of the parenchymal collapse may reveal atypical and hyperchromatic cells.

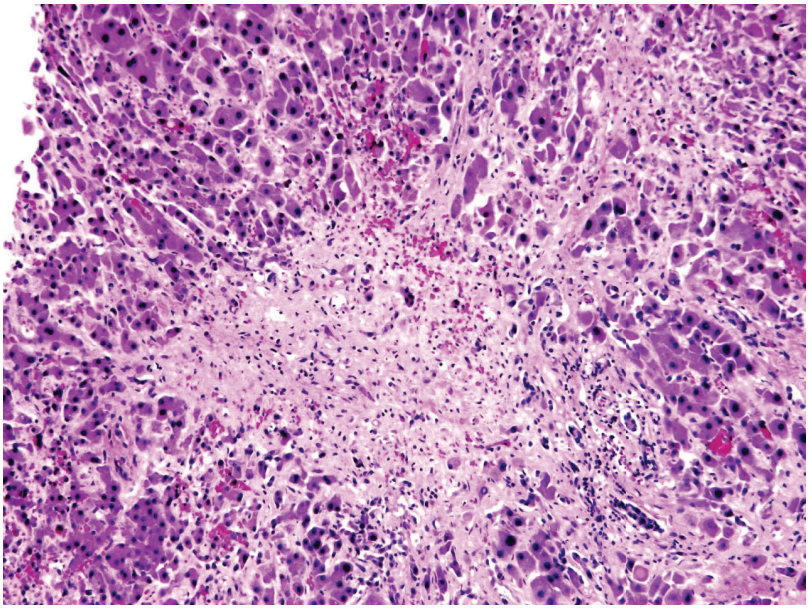

Fig 22.15 In this case, angiosarcoma obliterates the central vein mimicking sinusoidal obstruction syndrome/venoocclusive disease.

Beyond immunohistochemical studies for vascular markers, ancillary testing for hepatic angiosarcomas is not routinely utilized. However, elevated Ki67 proliferation indices (above 10%) and expression of p53 or c-Myc have been associated with these tumors.[20, 21] While not specific, mutations in *KRAS* have been identified in a subset of hepatic angiosarcomas arising in the sporadic setting as well as those associated with vinyl chloride or Thorotrast exposure.[22, 23]

2. Hepatocellular tumors

A. Focal nodular hyperplasia

a. Clinical features: Although once thought to represent a true neoplasm, focal nodular hyperplasia is now understood to be a reactive polyclonal phenomenon associated with a preceding vascular anomaly.[24] These tumors typically occur in young adults and have a striking female predilection. Although once believed to be associated with the use of oral contraceptives, this link remains controversial. While some have suggested that the use of

oral contraceptives may simply increase the size of preexisting lesions, this influence has also been questioned.[25] Lesions are largely asymptomatic and are most frequently encountered as incidental findings on radiographic studies performed for unrelated reasons. With a reported prevalence of up to 3%, focal nodular hyperplasias are one of the most commonly encountered benign liver tumors, second only to liver hemangiomas.[26] The background liver is typically unremarkable although similar lesions have been described in the setting of cirrhosis with these tumors being referred to as "focal nodular hyperplasia-like nodules".[27] Utilizing magnetic resonance imaging, the radiographic methodology of choice for these tumors, focal nodular hyperplasias often present with a vascular hyperintense central scar. This finding in the appropriate clinical context may be virtually radiographically diagnostic of these tumors.

b. Pathologic features: On resection specimen, the diagnosis of focal nodular hyperplasia is relatively straightforward given the characteristic presence of a well-formed central scar in most cases. The matter is somewhat more complicated on biopsy as a direct gross assessment is not possible. Given this limitation, reliance on the corresponding radiographic impression is crucial in this setting. Histologically, these lesions are composed of nodules of bland appearing hepatocytes separated by variously sized bands of dense fibrosis. These bands often contain muscular arteries and are accompanied by a notable ductular proliferation (**Fig. 22.16**). These structures also typically demonstrate some degree of lymphocytic infiltration. While a relatively unique histology among primary liver tumors, these features can easily be misinterpreted as representing cirrhotic liver if the pathologist is not made aware that a biopsy was obtained from a mass forming lesion.

Perhaps the single best ancillary tool in the biopsy diagnosis of focal nodular hyperplasia is glutamine synthetase immunohistochemistry. In normal liver, expression of this enzyme, which plays a role in nitrogen metabolism, is largely restricted to perivenular hepatocytes. In contrast, in focal nodular hyperplasia this protein can be appreciated in large haphazard groups of hepatocytes leaving still other areas completely devoid of reactivity. This pattern of expression has been referred to as "map-like" in the past given its geographic configuration (**Fig. 22.17**). Use of this immunohistochemical study has been shown to increase the diagnostic yield of these lesions by as much as 60%.[28]

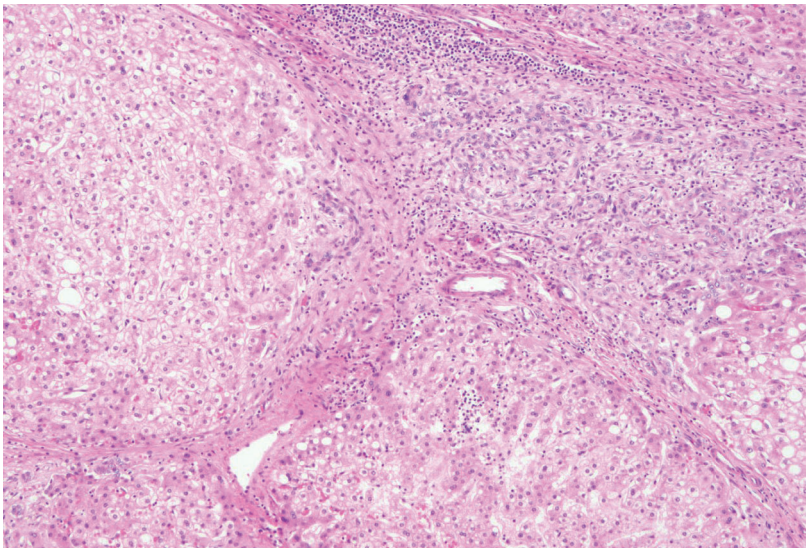

Fig 22.16 Focal nodular hyperplasia with discrete aggregates of hepatocytes enveloped in fibrosis and prominent arteries accompanied by a ductular proliferation.

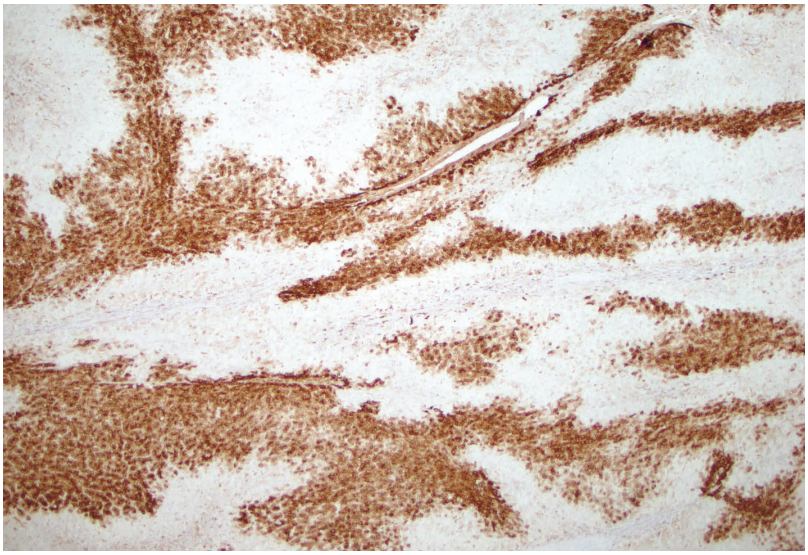

Fig 22.17 “Map-like” pattern of reactivity for glutamine synthetase in focal nodular hyperplasia.

B. Hepatocellular adenoma

a. Clinical features: Of the well characterized benign neoplasms of the liver, hepatocellular adenomas (HCAs) are the most infrequently encountered. These tumors classically develop in women of child bearing age and are strongly associated with the use of oral contraceptives. HCA can occur outside this setting however and tumors associated with obesity and metabolic syndrome, even in men, are being increasingly recognized.[29] Other well described risk factors include anabolic steroid use and heritable conditions such as familial adenomatous polyposis, glycogen storage diseases, and β-thalassemia.[30, 31] While considered to be benign lesions, HCAs do harbor a small risk of malignant transformation which is most commonly associated with those harboring β-catenin activating mutations. Additionally, adenomas do have a propensity to hemorrhage, particularly when they are larger than 5 cm, which can lead to significant complications.[32]

b. Pathologic features: Biopsy assessment of potential HCAs is challenging. In addition to the histologic findings enumerated below, it is just as imperative to assess the clinical presentation of the patient. As noted above, these tumors most frequently occur in female patients of childbearing age. A definitive biopsy diagnosis outside this setting should only be made with extreme caution. The same restraint should be exercised in those individuals known to have a history of background liver disease.

HCAs are characterized by several different molecular subtypes which include *HNF1A*-inactivated (H-HCA), β-catenin activated (b-HCA), inflammatory (I-HCA), and combined β-catenin-inflammatory (b-I-HCA).[33] An additional group has also been recently recognized termed sonic hedgehog HCAs.[34] All of these subtypes share some histologic features including being composed of benign appearing hepatocytes arranged in plates no thicker than 1-2 cells. Minimal if any nuclear atypia should be present and mitotic activity, particularly on biopsy specimens, should not be readily apparent. Biopsies of HCAs typically appear as though they consist of non-neoplastic liver parenchyma at low power. At higher magnification, recognition of unpaired arteries will disclose their neoplastic nature. These basic characteristics can also be seen in well-differentiated hepatocellular carcinoma so attention to the clinical setting and recognition of atypical features such as thickened plates, nuclear atypia, mitotic activity, or frequent rosette formation is imperative.

Built on this basic histologic framework, the various subtypes of HCA also demonstrate individualistic microscopic features. H-HCA are typically composed of clear hepatocytes with diffuse steatosis **(Fig. 22.18)**. Beyond these histologic features, these adenomas will also exhibit a loss of liver fatty-acid binding protein (LFABP) by immunohistochemistry. b-HCA may demonstrate mild evidence of cytologic or architectural atypia, including foci of rosette formation. I-HCAs will display sinusoidal dilation accompanied by pseudoportal tracts containing inflammatory cell infiltrates and proliferating ductules **(Fig. 22.19)**. These tumors exhibit diffuse reactivity for C-reactive protein (CRP) and serum amyloid A (SAA) by immunohistochemistry.

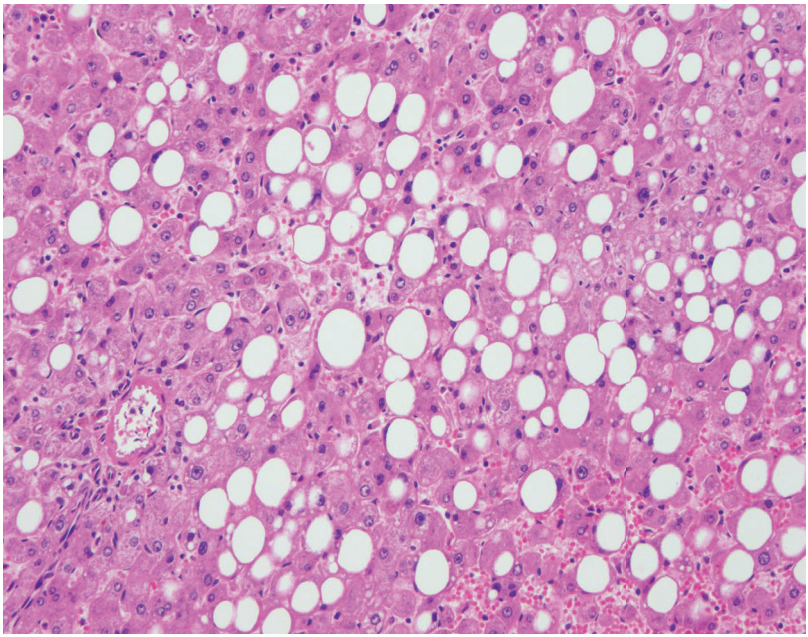

Fig 22.18 *HNF1A*-inactivated (steatotic) hepatocellular adenoma (H-HCA) exhibiting largely unremarkable hepatocyte plates with prominent steatosis and unaccompanied artery.

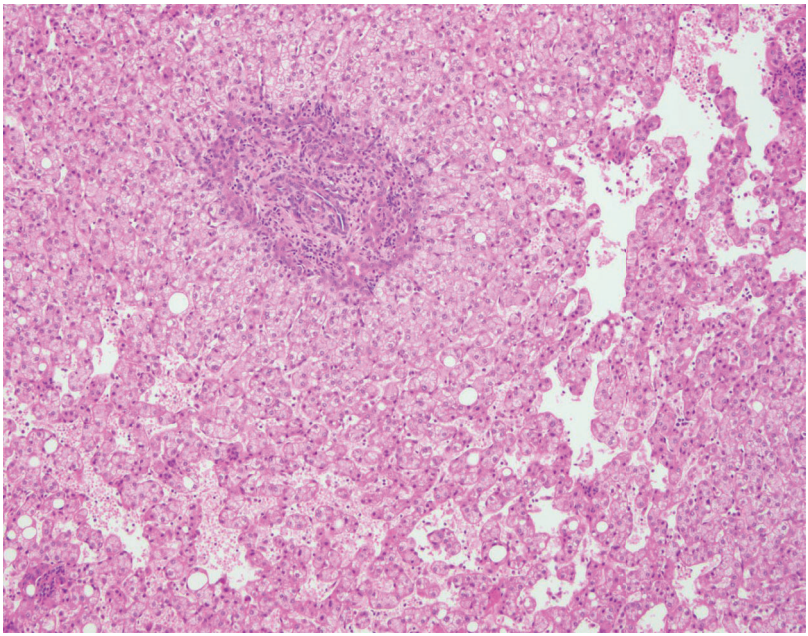

Figure 22.19 Inflammatory hepatocellular adenoma (I-HCA) with prominent artery ringed by proliferating ductules and associated inflammation, simulating a portal tract. Sinusoidal dilation is also prominent in this case.

Recognition of these subtypes on biopsy specimens may be clinically relevant as b-HCAs have a higher propensity for malignant transformation and in some centers tumors less than 5 cm may be treated initially with observation if they are thought to be of low risk.[35] In addition, the recently recognized group of HCAs with alterations in the sonic hedgehog pathway are known to have a propensity to hemorrhage, even at a small size. The most useful immunohistochemical study in the delineation of the former group is glutamine synthetase (GS) which is upregulated in b-HCAs. Those with the highest risk of malignant transformation, adenomas with mutations in exon 3 of *CTNNB1*, will demonstrate strong diffuse reactivity for this marker **(Figs. 22.20A and 22.20B)** while other subtypes of adenoma lack this expression.[36] GS staining can be graded as diffuse positive (moderate to strong cytoplasmic staining in >50% of tumor cells) or negative (perivascular staining, patchy parenchymal or absent/weak staining).[37] Of note, immunohistochemistry for β-catenin can also be performed but significant nuclear reactivity may be focal (**Fig. 22.20C**) or occasionally negative, particularly in biopsy specimens. Cases with any nuclear β-catenin

staining or diffuse positive GS staining are considered β-catenin activated.[37-39]

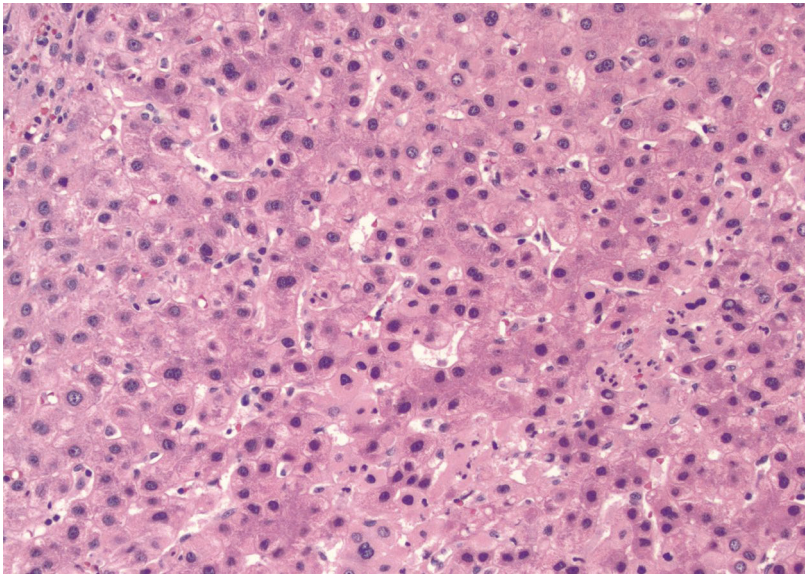

Fig 22.20A Proliferation of benign hepatocytes in a β-catenin activated hepatocellular adenoma (b-HCA). Courtesy of Dr. Xuchen Zhang, Yale University.

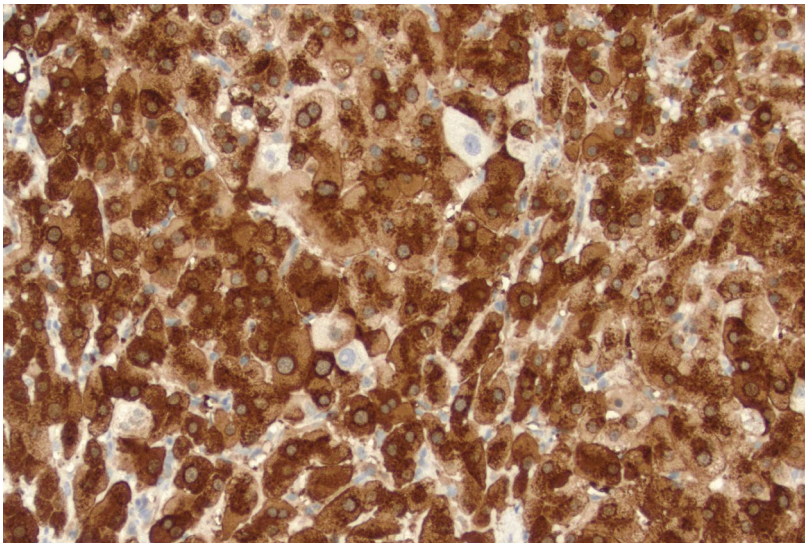

Fig 22.20B Immunohistochemistry for glutamine synthetase reveals strong and diffuse immunoreactivity in this adenoma depicted in fig. 22.20A. This staining pattern serves as a surrogate marker for alterations in exon 3 of *CTNNB1*. Courtesy of Dr. Xuchen Zhang, Yale University.

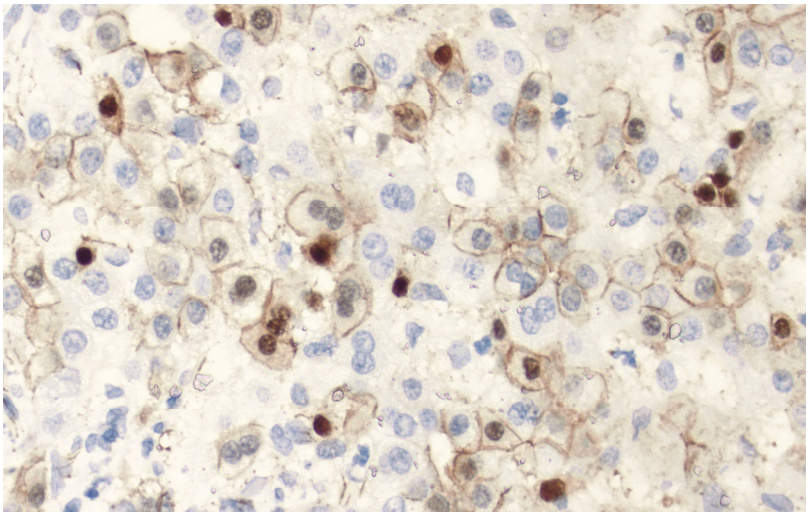

Fig 22.20C Nuclear immunoreactivity of β-catenin in b-HCA as depicted in figs. 22.20A and 22.20B. Of note, the number of β-catenin positive nuclei can be variable and can be very few in some cases. Courtesy of Dr. Xuchen Zhang, Yale University.

An abundance of immunohistochemical studies can now be used to subclassify HCA [**Table 22.1**].

Table 22.1: Immunohistochemical studies used to subclassify HCA.

	H-HCA	b-HCA	b-I-HCA	I-HCA without β-catenin activation	Untypable HCA
LFABP	Loss	Intact	Intact	Intact	Intact
β-catenin	Membranous	Any nuclear	Any nuclear	Membranous	Membranous
GS	<50%	>50%	>50%	<50%	<50%
SAA	Not diffuse	Not diffuse	Diffuse (>50%)	Diffuse (>50%)	Not diffuse

Note: H-HCA, *HNF1A*-inactivated hepatocellular adenoma; b-HCA, β-catenin activated hepatocellular adenoma; b-I-HCA, combined β-catenin activated-inflammatory hepatocellular adenoma; I-HCA, inflammatory hepatocellular adenoma; LFABP, liver fatty-acid binding protein; SAA, serum amyloid A; GS, glutamine synthetase.

C. Atypical hepatocellular neoplasm/Well-differentiated hepatocellular neoplasm of uncertain malignant potential

HCA may occur in patients with atypical clinical features such as women of particularly young or old age (<15 years or >50 years), male patients of any age, or patients using anabolic steroids. [37] In some cases, the hepatocellular lesion may demonstrate overlapping morphologic features of typical HCA and hepatocellular carcinoma or uncharacteristic findings such as areas of reticulin loss and foci with atypical morphology (<5% of the tumor).[37] The atypical features include nuclear crowding (small cell change), pseudogland formation, and/or nuclear atypia, or pigmentation.[37, 40] Studies have shown that such lesions with overlapping features often harbor cytogenetic alterations similar to well differentiated hepatocellular carcinomas.[37] Thus several terms such as atypical hepatocellular neoplasm (AHN) and well differentiated hepatocellular neoplasm of uncertain malignant potential (HUMP) have been proposed in the past to embody the uncertain natural history of these tumors that cannot be confidently classified as either HCA or carcinoma [**Table 22.2**].[41] It should be stressed however that these diagnoses should only serve as interim statements to guide clinical management rather than a definitive diagnostic category.[40] Follow-up data regarding such tumors is limited, but adverse outcomes such as recurrence or metastasis was observed at a rate of about 5%.[37]

Table 22.2: Histologic features of HCA, HUMP, and HCC.

	FNH	HCA	HUMP	HCC
Central scar/thick fibrous bands	Present	Absent	Absent	Absent
Ductular reaction	Present	Absent[a]	Absent	Absent
Portal tract	Absent	Absent[b]	Absent	Absent[c]
Similarity to normal or background hepatocyte	Yes	Yes	Most part	Different
Small cell change	No	No	Focal (<5% of tumor)	Variable
Pseudo-gland formation	No	No	Focal (<5% of tumor)	Variable
Nuclear atypia	No to mild	No to mild	Focal (<5% of tumor)	Obvious

Liver cell plate	≤2 cell thickness	≤2 cell thickness	≤2 cell thickness	Often thickened to ≥3 cell thickness
Reticulin fiber	Intact	Intact	Intact or focal loss (<5% of tumor)	Diffuse loss in many cases
Mitoses	Absent	Absent	Absent	Absent/present
Abnormal mitotic figures	Absent	Absent	Absent	Absent/present
Isolated arteriole	None or rare	Present	Present	Often present
Tumor necrosis	None	None (except for coagulative necrosis)[d]	None (except for coagulative necrosis)[d]	Absent/present
Invasion into nearby parenchyma	No	No	No	In some cases
CD34 in capillaries	Focal	Focal/diffuse	Focal/diffuse	Diffuse
GS staining	MAP like	Variable	Variable	Variable
Glypican 3	Neg	Neg	Neg	Variable

Note: [a]may be present in inflammatory HCA; [b]pseudoportal tract may be present in inflammatory HCA; [c]Portal tract may be incorporated into the periphery of HCC; [d]Necrosis similar to infarct, usually seen in large lesion or after embolization therapy for hemorrhage.

Key points to pathologists when encountering a liver mass/lesion biopsy with well differentiated hepatocytes:

- Identify lesional tissue from nearby non-lesional liver tissue
- Determine lesional tissue as hepatocellular or non-hepatocellular
- Determine lesional tissue as benign versus malignant
- For benign hepatocellular lesion, determine focal nodular hyperplasia versus neoplastic/clonal
- Use a minimal panel of stains (reticulin, immunostains for LFABP, GS, β-catenin, SAA) to further characterize benign hepatocellular lesion

D. Hepatocellular carcinoma

a. Clinical features: The incidence of hepatocellular carcinoma is increasing globally and malignant liver tumors now represent the second leading cause

of cancer related mortality worldwide.[42] In the United States the incidence of hepatocellular carcinoma has tripled over the past 30 years where it has become the fastest rising cause of cancer-related deaths.[43] Generally speaking, these tumors most often arise in patients with chronic liver disease and demonstrate a male predominance, with a male to female incidence of approximately 3.5:1.[44] While viral hepatitis is the largest contributing factor to the development of hepatocellular carcinoma worldwide, non-alcoholic fatty liver disease is emerging as a frequent contributing factor.[45,46] Hereditary diseases affecting the liver (genetic hemochromatosis, alpha 1 antitrypsin deficiency, glycogen storage disease, and hereditary tyrosinemia) and exogenous hepatocarinogenic substances are also risk factors for hepatocellular carcinoma.

Patients with hepatocellular carcinoma can present with clinical symptoms related to the tumor or the underlying liver disease such as right upper quadrant abdominal pain, weight loss, or decompensation of cirrhosis. Common signs are hepatosplenomegaly, jaundice and ascites. Symptomatic hepatocellular carcinomas are of advanced stage and carry a poor prognosis. Asymptomatic tumors are usually found in patients during surveillance by imaging studies such as ultrasound, contrast-enhanced computed tomography (CT), and/or magnetic resonance imaging (MRI).

Radiographically, hepatocellular carcinomas often demonstrate hyperenhancement with early washout on CT or MRI performed with contrast. In high-risk patients with lesions greater than 1 cm, these features alone are considered as diagnostic for hepatocellular carcinoma.[47] Due to the specificity of these imaging techniques, biopsies of presumed hepatocellular carcinomas may not be obtained and the patient may be treated without a tissue diagnosis. When similar findings are noted in low-risk patients, or atypical features are noted radiographically in high-risk patients, a biopsy may then be considered to guide subsequent management/treatment. Additionally, with the slowly emerging momentum for targeted therapies, biopsies of suspected hepatocellular carcinomas may increase in the future so as to assess the lesions for potential oncologic targets.[48]

b. Pathologic features: HCCs have several growth patterns: single nodule, a predominant mass with several nearby smaller satellite nodules, a diffuse growth pattern resembling cirrhosis (cirrhotomimetic), and multiple distinct nodules. The tumors vary in color, from green, yellow, to light tan, depending upon the degree of their bile and fat components.

By default, HCCs are primary liver cancers showing hepatocellular differentiation by morphology and/or immunohistochemistry. These tumors lose normal architectural structures such as portal tracts and can be accompanied by a reduction or loss of the normal reticulin framework. Corresponding to the arterial phase enhancement, HCCs often show increased arterialization with isolated/aberrant arterioles in the parenchyma and sinusoidal capillarization. Cytologic atypia may vary depending upon the differentiation of the tumor. Hepatocytes in HCCs often demonstrate 4 growth patterns (**Figs. 22.21, 22.22, 22.23, and 22.24**): trabecular, solid (compact), pseudoglandular (pseudoacinar), and macrotrabecular pattern (defined as trabeculae ≥ 6 cells thick). These patterns often co-exist in 50% of resected HCCs with the trabecular pattern being the most common.

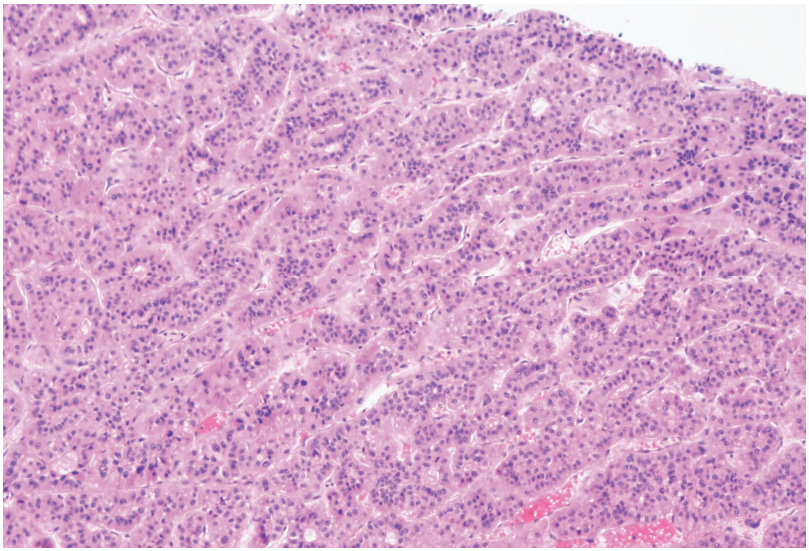

Fig 22.21 Basic growth pattern of hepatocellular carcinoma: trabecular pattern. A minor component of pseudoglandular pattern is also present.

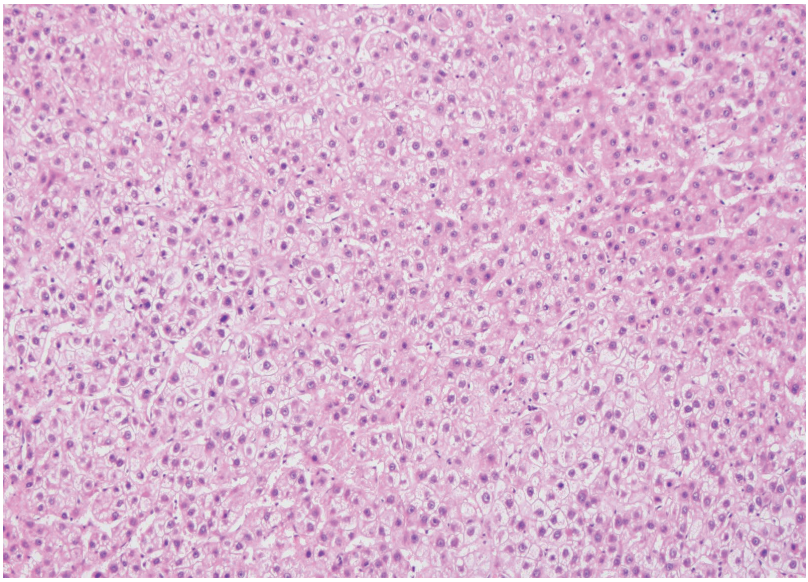

Fig 22.22 Basic growth pattern of hepatocellular carcinoma: solid pattern.

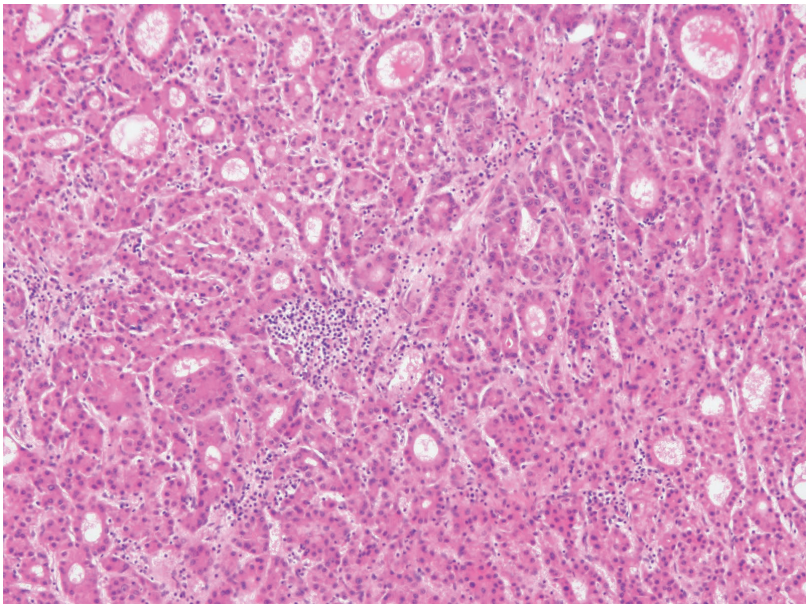

Fig 22.23 Basic growth pattern of hepatocellular carcinoma: pseudoglandular pattern.

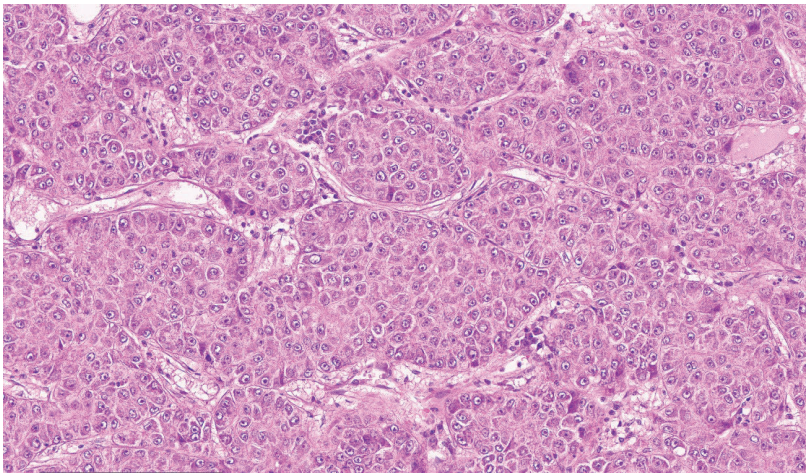

Fig 22.24 Basic growth pattern of hepatocellular carcinoma: macrotrabecular pattern.

Cellular changes such as bile, fat, glycogen (clear cell change), and lipofuscin may be seen. In addition, several inclusions such as hyaline bodies, Mallory hyalines, and pale bodies have been observed in HCCs.

Although histologic patterns in HCCs are not reported in surgical pathology reports, tumor grade is often assessed and reported. Based on the degree of differentiation on H&E staining, using the morphology of normal hepatocytes as a reference, HCCs are often graded as well differentiated, moderately differentiated, or poorly differentiated [**Table 22.3**]. Tumor grade on biopsy material appears to correlate well with the grade on the respective resection specimen.[49] Tumor grade is prognostic after curative resection or liver transplantation.[50-52] The worst grade tends to drive the prognosis.[53]

Table 22.3: Criteria for grading hepatocellular carcinoma.

	Low power	High power
Well differentiated	Resembling normal hepatocyte or hepatocellular adenoma; low nuclear/cytoplasmic (N/C) ratio	Abundant and eosinophilic to moderate and basophilic cytoplasm Minimal to mild nuclear atypia
Moderately differentiated	Obviously malignant but with morphology of hepatocellular differentiation; high N/C ratio	Abundant and eosinophilic to moderate and basophilic cytoplasm Moderate nuclear atypia (nucleomegaly, variation, nuclear membrane irregularity, and nucleolus)
Poorly differentiated	Obviously malignant and morphology of hepatocellular differentiation not apparent; marked high N/C ratio	Moderate to scant basophilic cytoplasm Marked nuclear pleomorphism

c. Hepatocellular carcinoma subtypes

Several HCC subtypes are recognized and some of them are included in the current WHO Classification of Digestive System Tumours published in 2019.

i. Steatohepatitic HCC

Salomao et al (2010) first recognized steatohepatitic HCC in explant livers with chronic HCV infection and noted that it shared many of the morphological features of steatohepatitis, such as large droplet steatosis, ballooning malignant hepatocytes, Mallory-Denk bodies and pericellular fibrosis (**Figs. 22. 25, 22.26, 22.27 and 22.28**).[54] A potential link between nonalcoholic fatty liver disease (NAFLD) and steatohepatitic HCC has been proposed and the tumorigenesis may involve the activation of the IL-

6/JAK/STAT pathway.[55, 56] Diagnosis of steatohepatitic HCC is challenging, especially in biopsy material. Major differential diagnoses include steatohepatitis, steatohepatitic focal nodular hyperplasia, and focal steatosis.[56] Useful features for diagnosing steatohepatitic HCC include lack of portal tracts, presence of isolated arterioles, mitotic figures, and loss of reticulin fiber (**Figs. 22.25, 22.26, 22.29, and 22.30**). Other useful findings include sinusoidal capillarization on immunostain for CD34 (**Fig. 22.31**), diffuse glutamine synthetase staining, glypican-3 immunoreactivity, and nuclear β-catenin staining. Reticulin stain is felt to be less useful in this setting as reticulin fiber loss can be seen in benign fatty liver.[57]

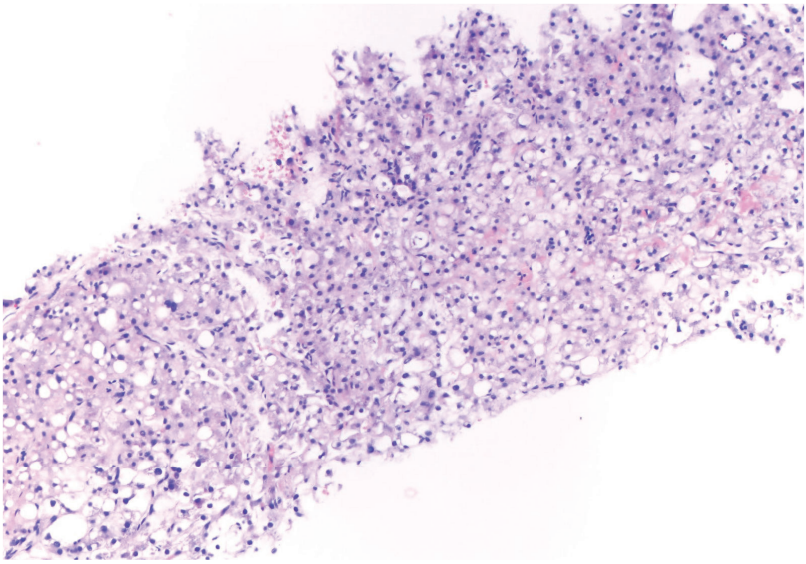

Fig 22.25 Biopsy from a liver mass reveals steatotic hepatocytes with mild atypia. Of note, there is a lack of portal tracts. Intermediate power view.

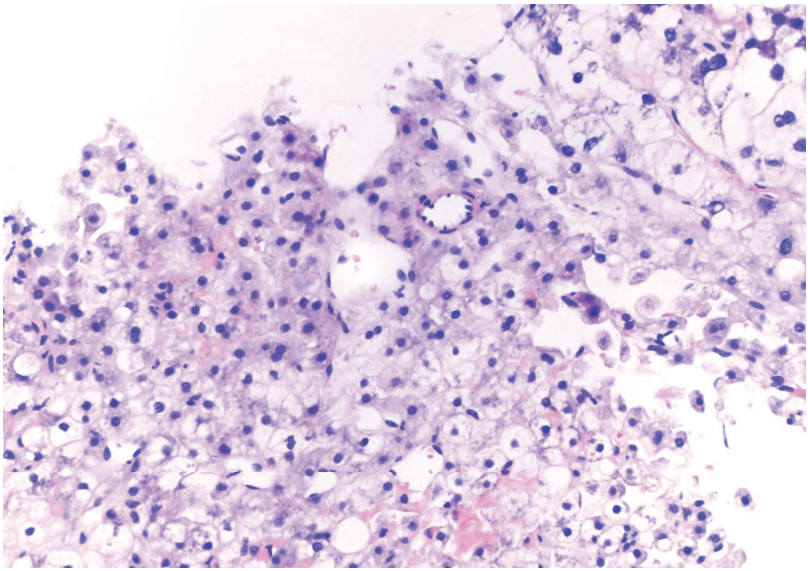

Fig 22.26 High power view reveals the presence of isolated arterioles in the lobule and ballooned hepatocytes in addition to steatosis.

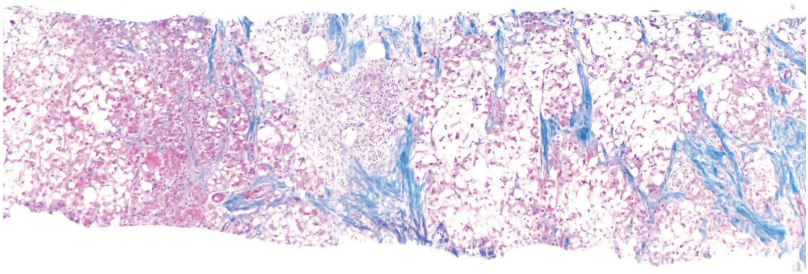

Fig 22.27 Low power view reveals extensive perisinusoidal “chicken wire” type fibrosis. Low power view. Trichrome stain.

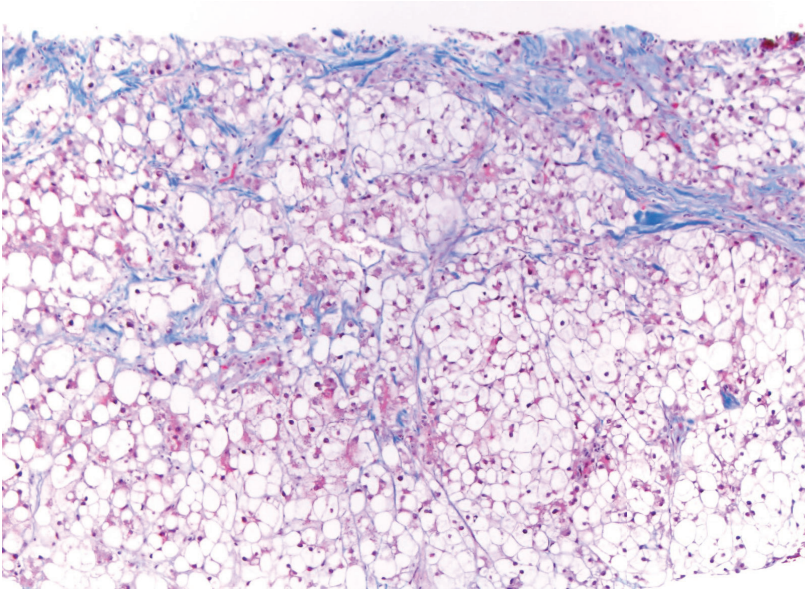

Fig 22.28 High power view reveals perisinusoidal fibrosis. Trichrome stain.

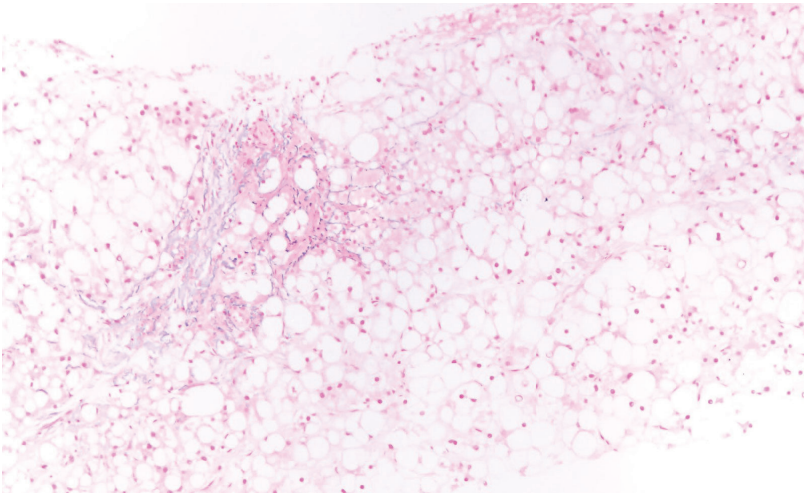

Fig 22.29 Loss of reticulin fiber is noted in the lesion. Reticulin stain.

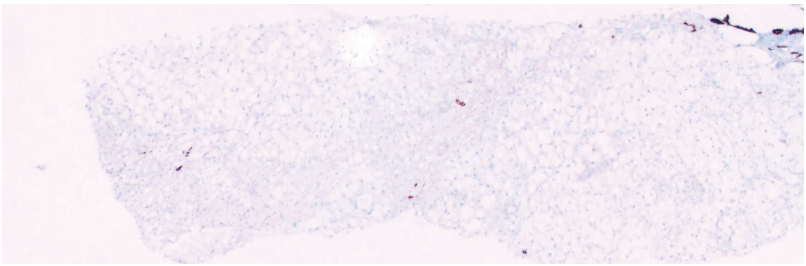

Fig 22.30 Lack of portal tracts in this steatotic liver lesion is confirmed by immunochemistry for cytokeratin 7.

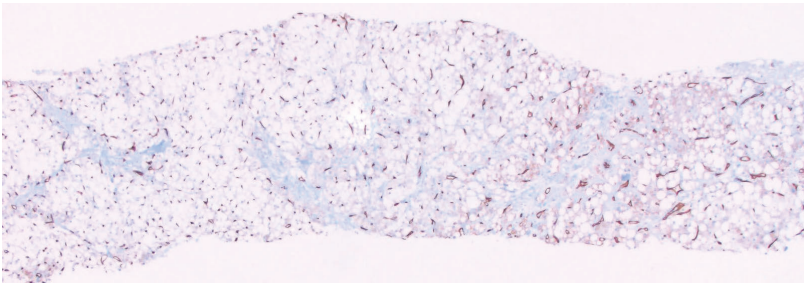

Fig 22.31 Presence of capillarization of sinusoids, as demonstrated by diffuse immunoreactivity for CD34, is helpful in diagnosing the steatohepatitic variant of hepatocellular carcinoma.

ii. Clear cell HCC

Clear cell HCC is defined as a HCC with at least 50% of clear cells **(Fig. 22.32)**, with these tumors accounting for 7.3% - 12.5% of all liver cancers.[58] The clear tumor cells contain abundant intracellular glycogen and a variable degree of fat vacuoles, with a reduction in the number and size of organelles.[59] Clear cell HCC may show atypical enhancement due to fewer intratumoral arteries. These tumors appear to be associated with a better prognosis.[60, 61] Due to the clear cell morphology, the differential diagnosis includes metastatic clear cell renal cell carcinoma, adrenal cortical carcinoma, and ovarian clear cell carcinoma and a panel of immunostains (hepatocyte antigen (HepPar1), arginase (**Fig. 22.33**), PAX8, and SF-1) may be needed to establish the diagnosis.

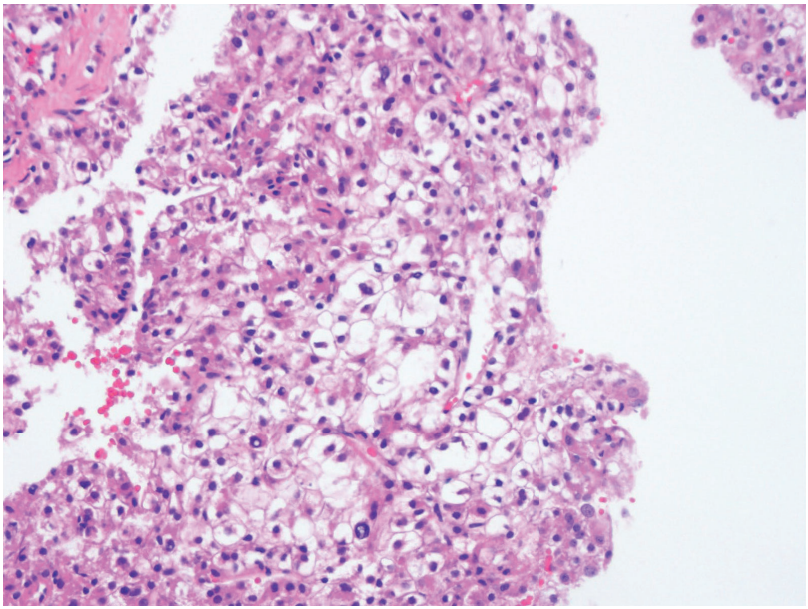

Fig 22.32 Clear cell hepatocellular carcinoma. Note more than 50% of the tumor cells have clear cell morphology.

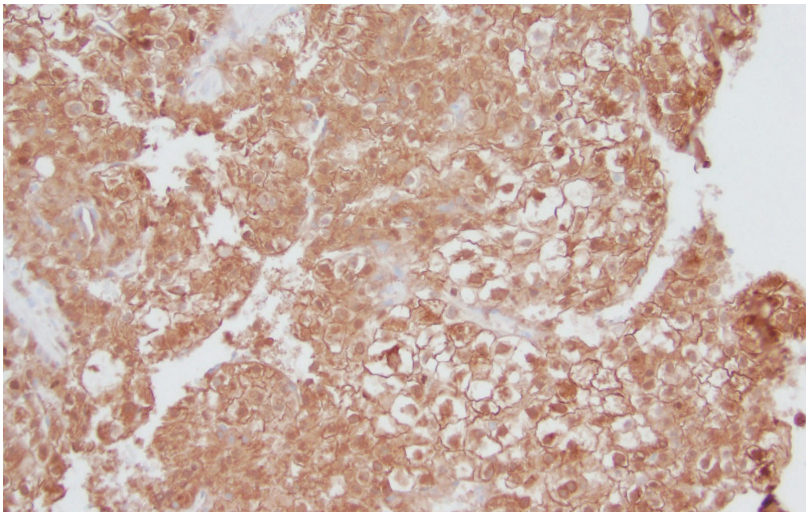

Fig 22.33 Immunoreactivity for arginase helps aid in the diagnosis of clear cell hepatocellular carcinoma.

iii. Macrotrabecular HCC

Macrotrabecular HCC is defined as HCC with 50% of tumor exhibiting the macrotrabecular growth pattern (> 6 cells thick) **(Fig. 22.24)**.[62] Recently, Jeon Y et al. suggested HCCs harboring at least 30% of this macrotrabecular pattern had a poor prognosis.[63] Additionally, it has distinct clinical features (high serum AFB level) and a higher rate of lymphovascular invasion.[63, 64]

iv. Scirrhous HCC

Scirrhous variant of HCC is a rare primary malignancy of the liver with a reported prevalence of 0.2-4.6%.[65, 66] Scirrhous HCC is associated with low serum AFP levels and less delayed washout during CT.[67] It occurs less frequently in cirrhotic livers and shows less frequent capsule formation, but higher rates of venous invasion.[67, 68] The scirrhous variant of HCC has a long-term outcome similar to conventional or usual HCC in patients after surgical resection. [66, 67] Histologically, it shows nodular growth with dense dissecting fibrous bands between tumor nodules. The fibrosis often extends along the sinusoid-like blood spaces with atrophic tumor trabeculae with hyalinization and fibrous lamellations. Sixty-five percent of scirrhous HCC are positive for cytokeratin 7 and 25% are negative for hepatocyte antigen (HepPar 1).[68] Radiographically and histologically, scirrhous HCC may mimic intrahepatic cholangiocarcinoma and fibrolamellar HCC.

v. Fibrolamellar carcinoma

Fibrolamellar carcinoma is a rare primary malignancy of the liver accounting for 0.8% to 16% of all hepatocellular malignancies.[69] It occurs more frequently in young patients with a median age of 22 years at diagnosis and is not associated with risk factors such as chronic liver disease or cirrhosis.[70] The primary tumor size is often large (median 13 cm) with 43% of cases having nodal metastases and 33% harboring distant metastases.[70] Serum AFP levels are often not elevated. The tumor equally involves the right and left lobes.[70] Histologically, fibrolamellar carcinoma consists of large polygonal tumor cells with abundant eosinophilic granular cytoplasm, large vesicular nuclei, and prominent nucleoli (**Fig. 22.34**). Striking intratumoral lamellar fibrous bands are present.[71] Immunohistochemically, the tumor cells are positive for hepatocellular markers (such as HepPar1, arginase, glypican-3), cytokeratin 7, and CD68.[72] Honeyman et al. reported a novel somatic recurrent 400 kb deletion in these tumors on the short arm of chromosome 19, resulting in a *DNAJB1-PRKACA* gene fusion which can be detected by a break-apart fluorescent in situ hybridization (FISH) assay

with high sensitivity and specificity.[72, 73] Fibrolamellar carcinoma is usually treated with surgical resection and has a better prognosis compared to conventional or usual HCC.

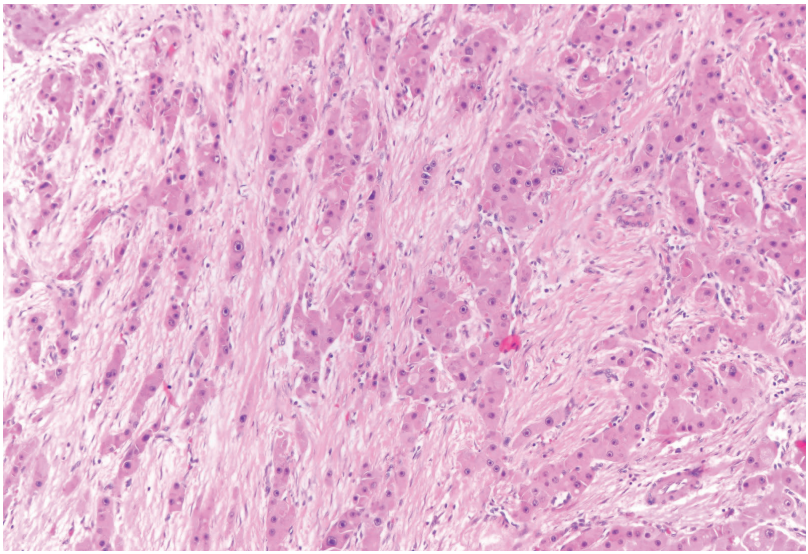

Fig 22.34 Fibrolamellar hepatocellular carcinoma demonstrating classic histologic features including cords of densely eosinophilic tumor cells with prominent nucleoli embedded in a fibrous stroma.

vi. Neutrophil-rich HCC

Neutrophil-rich HCC is a recently recognized rare malignancy of the liver.[74] It is characterized by the presence of numerous intratumoral neutrophils. Clinically, these patients have increased absolute neutrophil counts in the peripheral blood, elevated CRP, and IL-6.[75] These tumors have been shown to produce granulocyte colony stimulating factor (G-CSF).[75]

vii. Lymphocyte-rich HCC

Lymphocyte-rich HCC or lymphoepithelioma-like HCC is a rare primary malignancy of the liver accounting for less than 5% of all hepatocellular malignancies.[76] Lymphocyte-rich HCC has a relatively low frequency of male sex, tends to present with early-stage disease, and as a solitary tumor only.[76] Histologically, these tumors consist of trabeculae and/or sheets of tumor cells with dense lymphocytic infiltrates (**Fig. 22.35**) which are

composed mainly of cytotoxic T-cell infiltrations.[76] They do not differ in frequencies of microsatellite instability, *BRAF* mutation, and DNA hypermethylation. They are not associated with Epstein-Barr virus (EBV) infection.[76] It has a favorable prognosis with a 94.1% 5-year survival rate in one series. [76, 77]

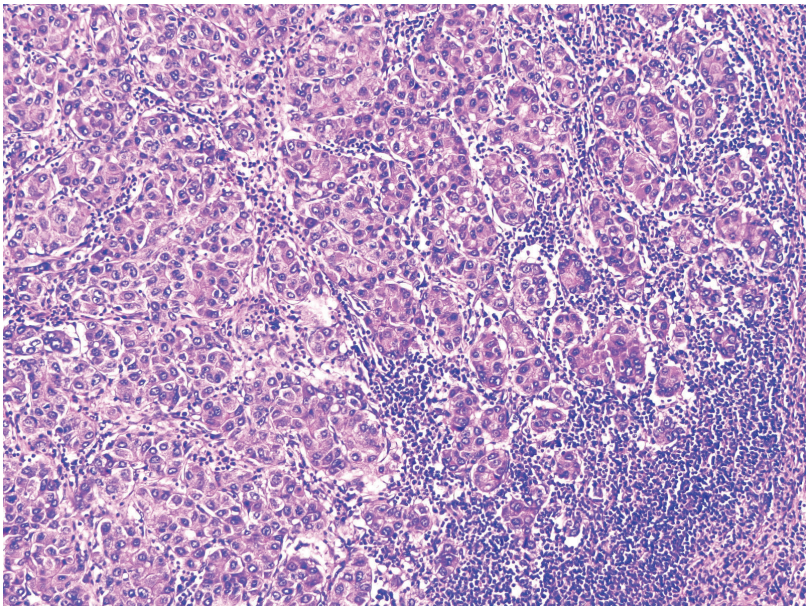

Fig 22.35 Lymphocyte-rich hepatocellular carcinoma with prominent intratumoral and peritumoral lymphocytic infiltration.

viii. Chromophobe HCC

Chromophobe HCC with abrupt anaplasia is a rare variant accounting for 6% of all HCCs.[78] Histologically, these tumors may contain pseudocysts and the cytoplasm of the lesional cells has a 'chromophobe appearance' where the tumoral cytoplasm is not stained as deeply as in typical hepatocellular carcinoma.[78] Most of the tumor cells have small and round nuclei with small inconspicuous nucleoli. Clusters of cells with marked nuclear anaplasia can be seen irregularly distributed within the tumor. This variant has been shown to harbor alternative lengthening of telomeres.[78] The prognostic significance of this variant remains unclear as there are only small series reported.

ix. Cirrhotomimetic HCC

Cirrhotomimetric HCC or diffuse-type HCC is an uncommon growth pattern where HCC infiltrates and replaces cirrhotic parenchyma. It may evade radiographic detection in up to 27% cases.[53, 79] On gross examination, these tumors may appear as a slight discoloration in an otherwise cirrhotic liver or as a predominant mass with many surrounding small nodules.[79] Histologically, these tumors consist of many small nodules encircled by fibrous bands mimicking the architecture of cirrhotic liver. The tumor nodules can show trabecular, pseudoglandular, solid/compact growth patterns and cytoplasmic clearing.[79] Cirrhotomimetic HCC confined to one lobe and with clear cell morphology appears to have good prognosis after liver transplantation.[79]

These HCC variants/subtypes are summarized in **Table 22.4**.

Table 22.4: HCC subtypes/variants.

	Frequency	Clinical association	Histology	Other features	Prognosis
Steatohepatitic[54]	5-20%	Metabolic syndrome or alcohol use, background of fatty liver disease	Resembling steatohepatitis: steatosis, ballooning, Mallory hyaline, chicken-wire fibrosis	IL6/JAK/STAT3 activation	Similar
Clear cell[61]	3-7%	None	Glycogen accumulation in 80% of tumor cells		Better
Macrotrabecular[64]	5%	High serum AFP	Macrotrabecular pattern in 50% of tumor		Worse
Scirrhous[62]	0.2-4%	Mimics cholangiocarcinoma	Dense intratumoral fibrosis in >50% of tumor		Similar
Chromophobe[78]	3%	None	Light, almost clear cytoplasm, bland nuclei, focal nuclear atypia		Not clear yet
Fibrolamellar[71]	1%	Young age (median age 25 years), no background liver disease	Large eosinophilic tumor cells with prominent nucleoli, dense intratumoral fibrosis	PKA activation due to DNAJB1-PRKACA fusion	Similar to HCC in non-cirrhotic liver

Neutrophil-rich[74]	<1%	Elevated white blood cell count, C reactive protein, IL-6	Marked intratumoral neutrophilic infiltrate	Tumor produces G-CSF.	Worse
Lymhocyte-rich[80]	<1%	None	Dense intratumoral lymphocytic infiltrate	Not EBV-related	Better

3. Biliary tumors

A. Bile duct hamartoma

a. Clinical features: Also known as von Meyenburg complexes, bile duct hamartomas are benign bile duct proliferations that fall on a spectrum of diseases which include those of ductal plate malformation, congenital hepatic fibrosis, and autosomal dominant polycystic hepatorenal disease. Indeed the exact nature of these lesions, namely whether they represent true neoplasms, simple malformations, or reactive processes has never been definitively settled although most doubt a neoplastic origin. That said, these typically diminutive lesions are not exceptionally uncommon and can reportedly be appreciated in 5.6% of adult autopsies.[81] In contrast to bile duct adenomas [**Table 22.5**], bile duct hamartomas are more frequently multifocal with a higher number of lesions being more closely associated with genetic polycystic disease. Given their propensity to occur, or rather be readily appreciated in, the immediate subcapsular liver parenchyma, they are often encountered by the pathologist at the time of frozen section secondary to an operative concern for malignancy.

b. Pathologic features: Histologically, bile duct hamartomas are composed of proliferations of variably sized dilated bile ducts lined by bland biliary epithelium. The stroma interspersed between these epithelial elements is typically hyalinized and the irregular ductal structures often contain luminal bile **(Fig. 22.36)**. No significant nuclear atypia or notable mitotic activity should be noted as these features should raise a concern for malignancy.

Table 22.5: Comparison of benign bile duct lesions of the liver.

	Bile duct hamartoma	**Bile duct adenoma**
Location	subcapsular	subcapsular
Focality	multifocal	unifocal
Ducts	dilated ducts with bile	ducts with diminutive lumens
Epithelium	bland cuboidal	bland cuboidal
Stroma	hyalinized	stroma poor
Associations	ductal plate disorders	none

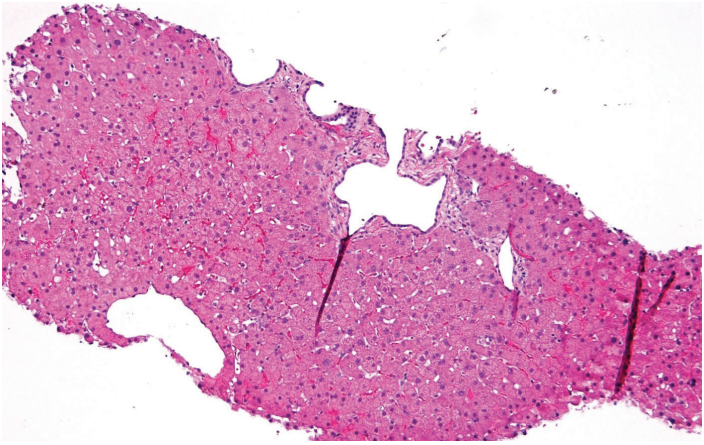

Fig 22.36 Biopsy demonstrating a bile duct hamartoma, composed of multiple irregularly dilated ducts embedded in a hyalinized stroma.

B. Bile duct adenoma

a. Clinical features: Bile duct adenomas are almost universally an incidental finding and are most frequently encountered during visual inspection of the liver in the operating room. It is in this setting that pathologists most often become acquainted with them as they often raise the suspicion of metastatic disease to our surgical colleagues. These lesions are most often solitary, subcapsular, and appear as well-defined nodules measuring approximately 5.8 mm on average.[82] Similarly to bile duct hamartomas (von Meyenburg complexes), the neoplastic nature of these lesions has been heavily scrutinized with the prevailing belief being these lesions represent a reactive process involving peribiliary glands.[83-85]

b. Pathologic features: Complementing their well-defined gross appearance, bile duct adenomas are well-circumscribed but lack an appreciable capsule. These lesions are composed of disordered proliferations of bile ducts, similar in appearance to ductules, containing bland cuboidal epithelium **(Figs. 22.37 and 22.38)**. In contrast to bile duct hamartomas, these tubular structures lack well-defined lumen and lack luminal bile. The epithelial components typically contribute to a majority of the lesion and the associated stroma is characteristically minimal. When present, the stroma may appear inflammatory in nature or fibrotic. Distinguishing bile duct adenomas from potential metastatic foci, these benign lesions should demonstrate an absence of nuclear hyperchromasia, pleomorphism, or

notable mitotic activity. Finally, a clear cell form of bile duct adenoma has been described which may call to mind metastatic renal cell carcinoma.[86] Fortunately, bile duct adenomas, including the clear cell form, demonstrate an immunohistochemical profile similar to biliary epithelium including expression of CK7 and CK19 so exclusion of a distant metastasis is typically possible if not by clinical and histologic means then by ancillary testing.

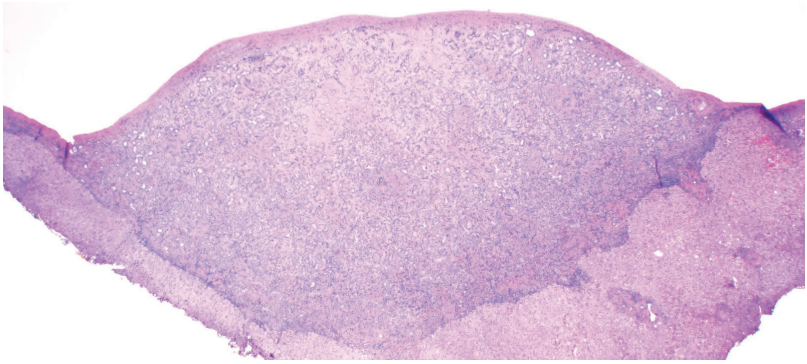

Fig 22.37 Wedge biopsy of bile duct adenoma showing subcapsular location and discrete borders with surrounding liver. Low power view.

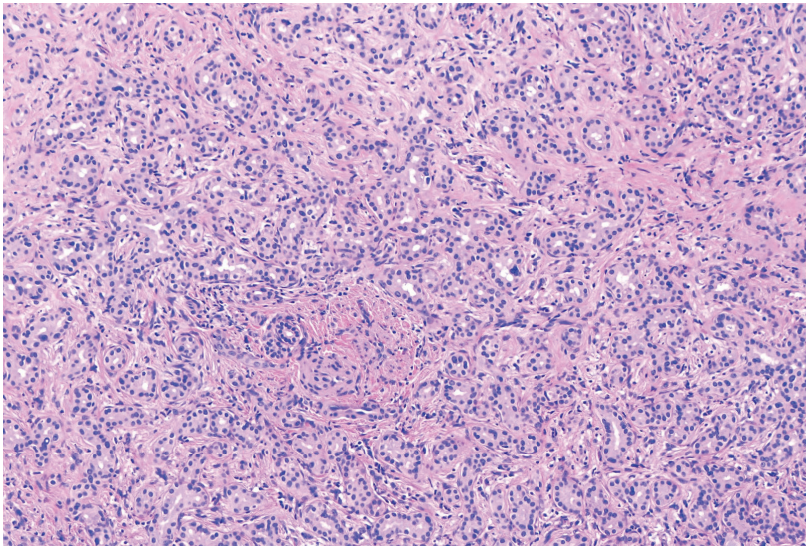

Fig 22.38 High power view of bile duct adenoma demonstrating compact ducts without atypia.

C. Mucinous cystic neoplasm

a. Clinical features: Mucinous cystic neoplasms of the liver have gone by many designations in the past including and perhaps most prominently biliary cystadenoma. These mucinous lesions are analogous to their pancreatic counterparts which are more commonly encountered. With that in mind, mucinous cystic neoplasms are almost exclusively encountered in female patients and present radiographically as large multiloculated cysts measuring approximately 10 cm in average diameter.[87] Characteristically, these cystic lesions should not appear to be continuous with the biliary system. While they can occur over a wide age range, most patients are in their 5th of 6th decade of life.[87,88] Mucinous cystic neoplasms are of themselves benign lesions, however, they do harbor a risk of malignant transformation which has been estimated to be approximately 6%.[89] It is this risk of associated carcinoma that drives the management of these cystic lesions with complete surgical resection being the treatment of choice.

b. Pathologic features: Given their cystic habitus, mucinous cystic neoplasms are not typically amenable to conventional biopsy techniques and instead may be sampled through a fine needle aspiration biopsy. The end result for the pathologist is often minute fragments of cyst wall which may or may not demonstrate the associated lining. This lining ranges from simple cuboidal, reminiscent of normal biliary epithelium, to tall columnar with mucinous features. Despite the name of mucinous cystic neoplasm, clear cut mucinous lining may not be appreciated. Should the biopsy contain the underlying connective tissue of the cyst wall, ovarian-type stroma may be appreciated, and is required for a definitive diagnosis **(Fig. 22.39)**. As mentioned previously, these cystic lesions may harbor an associated invasive component. While fine needle biopsy has been shown to be quite specific for the detection of an associated malignancy, sensitivity is lacking, likely secondary to sampling restrictions.[87] Beyond frank invasion, mucinous cystic neoplasms may also demonstrate a full range of neoplasia with high-grade neoplasia often exhibiting complex architectural changes such as micropapillary or papillary formations.

The largest role for ancillary testing in these lesions on biopsy may be demonstration of the aforementioned ovarian-type stroma. This condensed population of spindle cells underlying the epithelium frequently expresses estrogen and progesterone receptors as well as alpha-inhibin, the latter of which may be focal.[90] Finally, while cyst fluid analysis is a well-accepted diagnostic test in pancreatic cysts, measuring hepatic cyst contents for analytes such as CA19-9 and CEA remains controversial.[91]

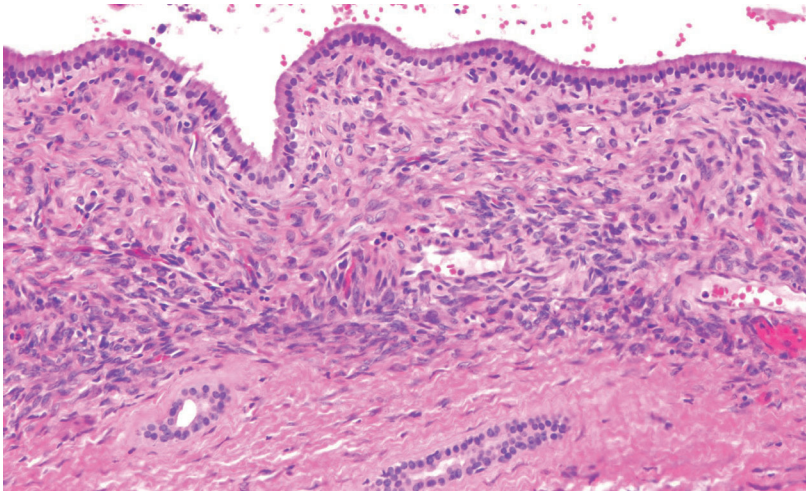

Fig 22.39 Mucinous cystic neoplasm of the liver demonstrating the characteristic subepithelial ovarian-type stroma. The lining in this case is notably biliary and benign bile ducts can be appreciated within the cyst wall.

D. Intraductal papillary neoplasm

a. Clinical features: Just as mucinous cystic neoplasms of the liver are complimentary to their pancreatic counterpart, so is the relationship between hepatic intraductal papillary neoplasms and intraductal papillary mucinous neoplasms of the pancreas.[92] [**Table 22.6**] These lesions can just as well occur in both sexes with some studies suggesting a slight male predominance.[93, 94] Predisposing factors have been identified including lithiasis, helminth infections, and primary sclerosing cholangitis with the former two being more widely reported in Asian cohorts.[95] Intraductal papillary neoplasms can form large cystic dilations of pre-existing bile ducts and often retain this connection to the biliary system. Indeed they can be appreciated involving the intrahepatic or extrahepatic bile ducts, with the latter being more common. While considered precursor lesions, a significant proportion of these neoplasms are found to have an associated invasive component, with an incidence as high as 28% in Western populations.[93]

Table 22.6: Comparison between hepatic mucinous cystic neoplasms and intraductal papillary neoplasms.

	Mucinous cystic neoplasm	Intraductal papillary neoplasm
Sex	strong female predominance	slight male predominance
Association with biliary inflammatory processes	absent	present
Risk of associated invasive carcinoma	low	high
Continuity with bile ducts	absent	present
Ovarian-type stroma	present	absent
Pancreatic analogue	MCN*	IPMN**

*MCN, mucinous cystic neoplasm; **IMPN, intraductal papillary mucinous neoplasm

b. Pathologic features: Biopsy evaluation of potential intraductal papillary neoplasms typically consist of specimens obtained by advanced endoscopic techniques such as those guided by endoscopic ultrasound. Histologic assessment often demonstrates varying degrees of anastomosing papilla lined by a variety of epithelial types **(Fig. 22.40)**. This lining may be of an intestinal, pancreato-biliary, gastric, or oncocytic type, with the former two being more frequently encountered both in Western and Eastern populations.[93, 94] While it has been suggested that these particular subtypes carry a prognostic significance as they do in intraductal lesions of the pancreas, this remains unclear in the liver.

The intestinal subtype typically consists of long papilla lined by pseudostratified cells with hyperchromatic ovoid nuclei and expresses CDX2 by immunohistochemistry. This subtype appears to be most closely associated with risk factors for chronic bile duct inflammation. The papilla of the pancreato-biliary subtype tend to be more architecturally complex and are lined with cuboidal cells with more limited cytoplasm and rounded nuclei. Epithelial elements reminiscent of pyloric glands define the gastric subtype while the oncocytic variant consists of complex branching papilla lined by more cuboidal cells with abundant eosinophilic cytoplasm with round nuclei. These latter lesions have also been referred to as intraductal

oncocytic papillary neoplasms. Cases with mixed epithelial types are not infrequently encountered.

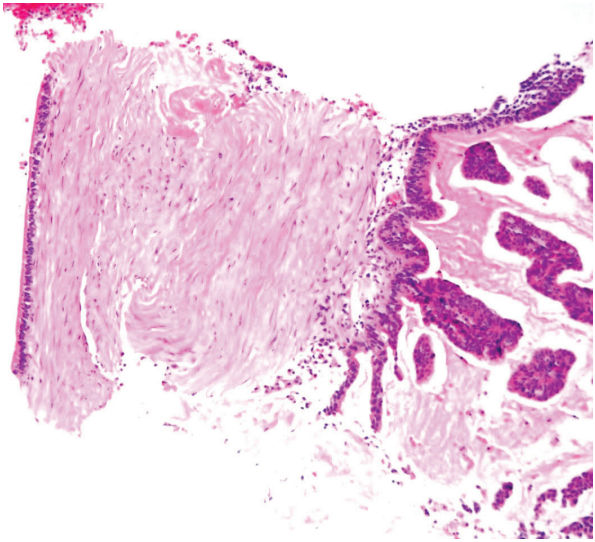

Fig 22.40 Biopsy demonstrating an intraductal papillary neoplasm of bile ducts. The papillary neoplastic proliferation on the right contrasts with the benign biliary epithelium on the left.

While identification of an associated invasive component should be reported if present on an initial biopsy, a diagnosis of an intraductal papillary neoplasm is enough to warrant an oncologic resection if surgically feasible.

E. Biliary adenofibroma

a. Clinical features: A rare entity, biliary adenofibromas are most often incidental findings in adult patients with the largest series reflecting an age range from 46 to 83 years old.[96] Although considered benign, progression to epithelial dysplasia or malignant transformation into conventional cholangiocarcinoma has been reported.[97, 98]

b. Pathologic features: Biliary adenofibromas typically range from 7-16 cm in size and consist of irregular proliferations of tubules and microcysts lined by simple cuboidal epithelium with distinct biliary characteristics.[96] Epithelial cells typically contain a moderate degree of amphophilic

cytoplasm with round regular nuclei lacking prominent nucleoli. Mitotic activity is rare and occasionally luminal apocrine snouting can be appreciated. These epithelial elements are embedded in a dense fibrotic stroma and are well demarcated from the surrounding liver. Given the overlapping features with benign bile duct adenomas on the benign side and small duct-type intrahepatic cholangiocarcinoma, a biopsy diagnosis of biliary adenofibroma is strongly discouraged. A definitive diagnosis of such relies upon the ability to assess not only the cytologic features of the tumor but also its relationship with the surrounding liver, a luxury not afforded on biopsy specimens.

F. Intrahepatic cholangiocarcinoma

Only second to hepatocellular carcinoma, cholangiocarcinoma is one of the most commonly encountered primary malignant tumors of the liver, accounting for approximately 15% of such cases.[99] There has been a rise in the incidence of these tumors worldwide over the last few decades, including in the United States.[100] Over that time period, we have also come to recognize that intrahepatic cholangiocarcinomas represent two distinct types of hepatic tumors, small duct and large duct types, which are worth separate discussions here [**Table 22.7**].

Table 22.7: Comparison between small duct and large duct type of intrahepatic cholangiocarcinoma.

	Small duct type	**Large duct type**
Location	peripheral	hilar
Predisposing factors	viral hepatitis	helminth infection, lithiasis, primary sclerosing cholangitis
Histology	tight tubular or cholangiolar	columnar cells with mucin
Precursor	unknown	biliary intraepithelial neoplasia, intraductal papillary neoplasia
Immunohistochemistry	CD56, N-cadherin	S100P
Molecular alterations	*IDH1*, *IDH2*	*KRAS*

a. Small duct type intrahepatic cholangiocarcinoma

i. Clinical features: The small duct type of intrahepatic cholangiocarcinoma has gone by several names in the literature including cholangiolocarcinoma or ductular type. These tumors occur as frequently in men as they do in women and typically present as mass forming lesions located in the peripheral aspects of the liver. Given this propensity for a peripheral location, these tumors can become quite substantial in size before they become clinically symptomatic. Risk factors for these small duct type tumors are similar to hepatocellular carcinoma with viral hepatitis being a significant contributing factor.[101] Given the population in which these tumors arise it should come as no surprise that the primary differential diagnosis often includes atypical hepatocellular carcinoma on imaging studies.

ii. Pathologic features: Biopsies of this cholangiocarcinoma type most often demonstrate a proliferation of low cuboidal cells with scant eosinophilic to amphophilic cytoplasm. These tumor cells are often monotonous in appearance however some degree of nuclear atypia is invariably present **(Fig. 22.41)**. Multiple architectural growth patterns can occur with the most common being a tubular proliferation. Other recognized patterns include solid or micropapillary forms. Tumors cells are almost always accompanied by a desmoplastic stroma. Distinction from large duct type is typically made on a morphologic and topographical bases, however, N-cadherin and CD56 are more commonly expressed in small duct type.[101, 102] Molecular findings also demonstrate divergent features between these two groups with small duct type cholangiocarcinoma exhibiting a higher frequency of *IDH1* and *IDH2* mutations.[103]

Despite our deeper understanding of intrahepatic cholangiocarcinomas there continues to be a lack of definitively specific markers of biliary origin. Therefore, it is of utmost importance that the diagnosis of cholangiocarcinoma only be made in the appropriate clinical setting. This most often includes lack of a recognizable primary elsewhere on imaging studies as well as endoscopy.

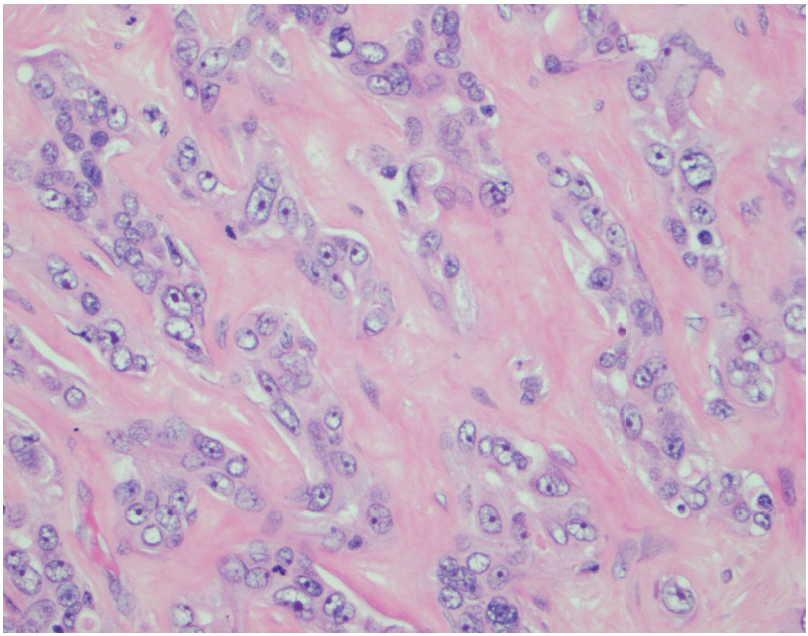

Fig 22.41 Intrahepatic cholangiocarcinoma of the small duct-type typically consists of infiltrating tubules of atypical cuboidal cells set in a relatively paucicellular stroma.

b. Large duct type intrahepatic cholangiocarcinoma

i. Clinical features: In contrast to small duct type tumors, large duct type cholangiocarcinomas occur more often in the hilar region of the liver and share many risk factors with extrahepatic cholangiocarcinomas. This includes causes of chronic biliary inflammation such as chronic helminth infections, lithiasis, and primary sclerosing cholangitis.[104] Due to their obstructive nature and close approximation with large caliber bile ducts these tumors often present early on with symptoms including cholangitis. Despite this fact, large duct type tumors are typically of a higher stage at presentation and carry a worse overall survival compared to small duct type.[103]

ii. Pathologic features: Histologic assessment of biopsies obtained from large duct type intrahepatic cholangiocarcinomas will demonstrate similar features as extrahepatic cholangiocarcinomas. Namely, these tumors typically consist of medium to large sized infiltrating glands lined by more

columnar epithelium with some degree of notable apical cytoplasm **(Fig. 22.42)**. Mucin production is not infrequently encountered. Biopsies may also demonstrate evidence of precursor lesions including biliary intraepithelial neoplasia or intraductal papillary neoplasms. Just as in small duct type, this variety is also almost always accompanied by a desmoplastic stroma. Immunohistochemically, these tumors are more likely to express CK20 and S100P compared to their peripheral counterparts and also more frequently harbor *KRAS* mutations.[103, 105, 106]

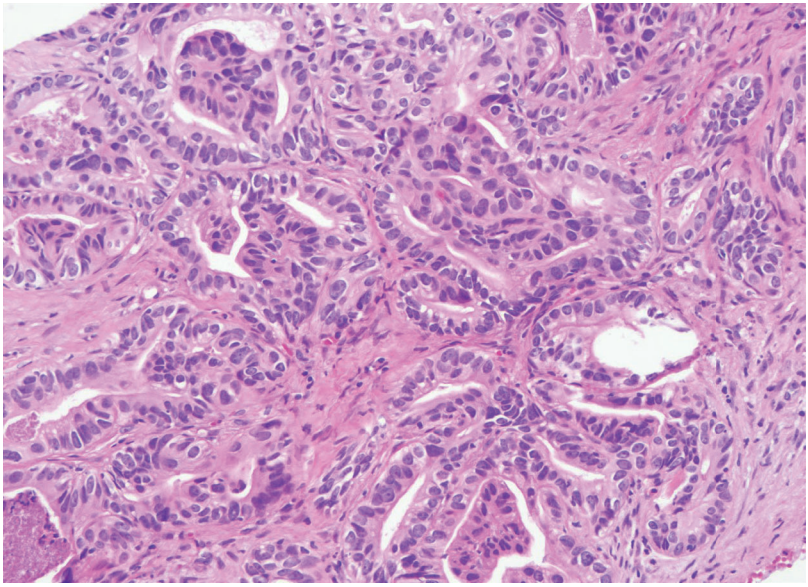

Fig 22.42 Biopsy of a large duct-type intrahepatic cholangiocarcinoma with more columnar cells with apical cytoplasm set in a desmoplastic stroma.

4. Combined (mixed) hepatocellular-cholangiocarcinoma and other variations of hepatocellular carcinoma

A. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA)

cHCC-CCA is a rare primary liver carcinoma which shows a variable degree of differentiation toward hepatocellular and cholangiocellular carcinoma. It accounts for 2-5% of primary liver cancers and represents a diagnostic challenge, especially in biopsy material[107]. This entity has been reviewed recently and a 2018 consensus has been incorporated in the 2019

WHO classification.[108, 109] The current classification and criteria may not be perfect, but it does provide a survival guide to assist pathologists in their routine workup of liver biopsies potentially containing a cHCC-CCA. The term "cHCC-CCA with stem cell features" is no longer recommended.[107, 109]

The clinicodemographic features of cHCC-CCA are similar to HCC and intrahepatic cholangiocarcinoma (iCC).[107] In addition, the imaging features overlap with those of HCC and iCCA.[107] Transarterial chemoembolization (TACE) of primary liver cancer has been associated with a higher frequency of cHCC-CCA.[110]

cHCC-CCA does not have specific macroscopic features and its gross appearance depends on the major component and the distribution and ratio of HCC and CCA constituents. Histologically, two patterns (mixed/combined and biphenotypic) may be encountered. The mixed/combined tumors contain two closely located or intermingled HCC and CCA components with the transitional zone of these two components showing small uniform tumor cells (so-called cancer stem cells) located in the periphery of hepatocellular carcinoma nests or trabeculae **(Figs. 22.43 and 22.44)**. The biphenotypic tumors are often referred to as intermediate cell carcinomas and consist of monotonous tumor cells with scant cytoplasm and morphologic features between that of hepatocytes and cholangiocytes. The tumor cells in these intermediate cell carcinomas are often arranged in strands in a fibrous stroma and express both hepatocellular markers (such as hepatocyte antigen, arginase, and AFP) and cholangiocytic marker (such as cytokeratin 19).

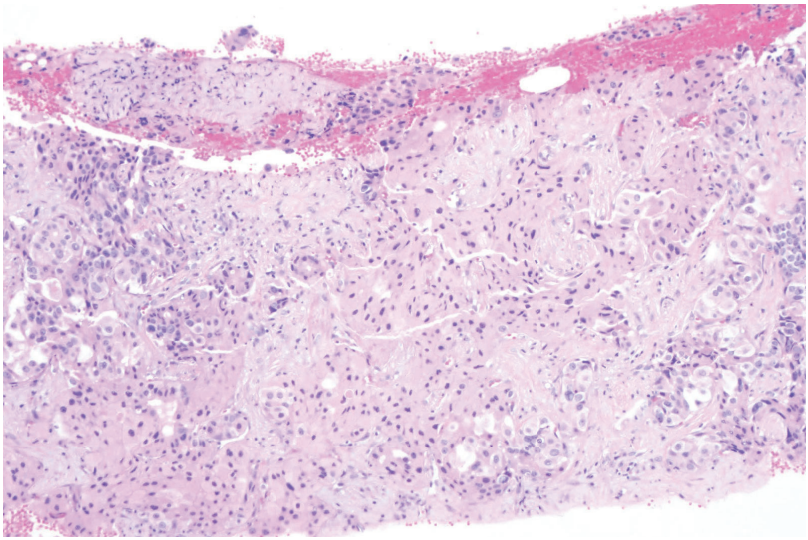

Fig 22.43 Biopsy of a combined hepatocellular-cholangiocarcinoma demonstrating distinct areas of hepatocyte differentiation accompanied by glandular portions of tumor with a biliary phenotype.

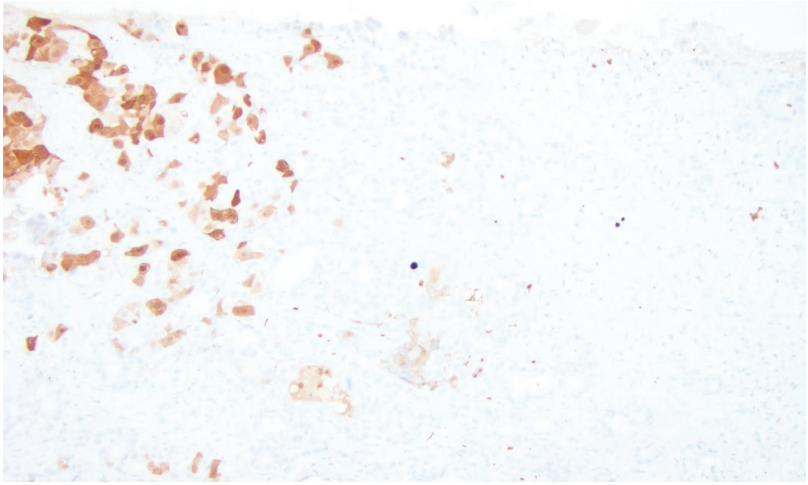

Fig 22.44 The hepatocellular differentiation apparent on H&E stain depicted in fig. 22.43 is confirmed by its immunoreactivity for arginase.

B. Other variations of HCC

Cholangiolocarcinoma can be a component of cHCC-CCA if an HCC component is present. Otherwise, it is best considered as a subtype of iCCA. Rare cases of primary liver cancer can have neuroendocrine components (**Figs. 22.45 and 22.46**) in addition to HCC or iCCA, thus they should be diagnosed as mixed neuroendocrine-non-neuroendocrine neoplasm after each component is confirmed by immunohistochemical markers. Carcinosarcoma is extremely rare and shows two components, the carcinomatous (HCC and/or CCA) and the sarcomatous component. Undifferentiated carcinoma lacks definitive morphological and immunohistochemical features of any differentiation beyond epithelial nature.

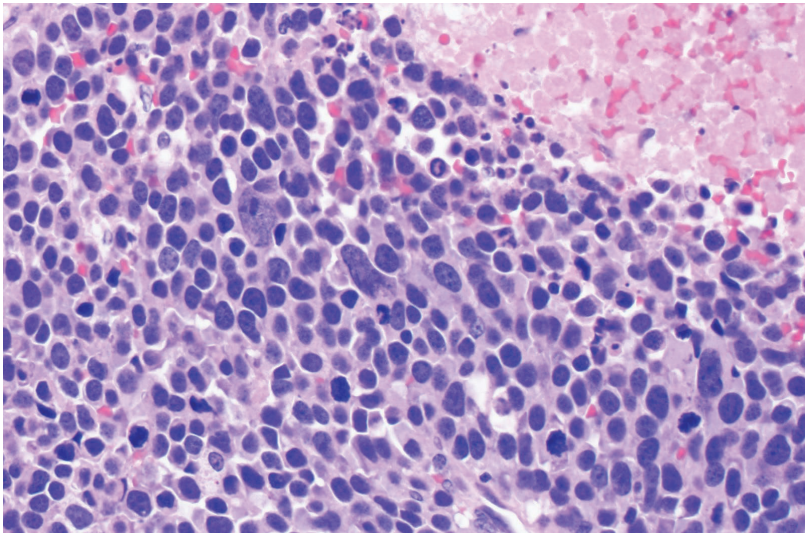

Fig 22.45 Liver mass consisting of a sheet-like growth of epithelioid cells without glandular or squamous differentiation. Tumor necrosis is present. The tumor cells have a high nuclear/cytoplasmic ratio and fine chromatin, suggestive of neuroendocrine differentiation.

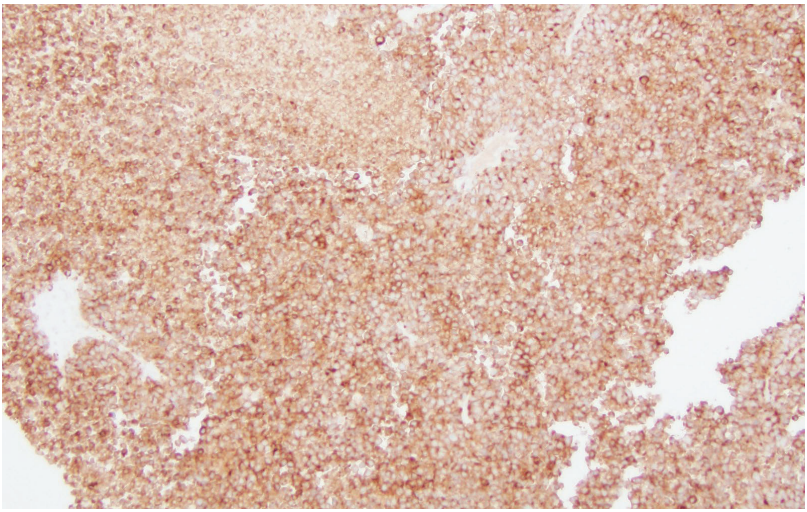

Fig 22.46 Immunochemistry for synaptophysin confirms the neuroendocrine differentiation in the area depicted in fig. 22.45, supporting the diagnosis of high-grade neuroendocrine carcinoma.

Checklist for pathologists when encountering a primary liver carcinoma that cannot be easily classified as pure HCC or CCA:

- Two closely located components with suggestive morphology of HCC and adenocarcinoma (glandular) on H&E stain, confirmed by immunostains for hepatocellular and cholangiocytic, consider cHCC-CCA.
- Nests or trabecular with peripherally located small cells resembling stem cells and centrally located HCC component, confirmed by immunostains for hepatocellular (center) and cholangiocytic (periphery), consider cHCC-CCA.
- Monotonous cells with scant cytoplasm arranged in strands in a fibrous stroma, confirmed to express hepatocellular and cholangiocytic markers at the cellular level, consider cHCC-CCA (biphenotypic).
- Two or more than components (HCC or CCA with additional neuroendocrine component), confirmed by immunostains for hepatocellular and/or cholangiocytic, and neuroendocrine markers, consider mixed neuroendocrine-non-neuroendocrine neoplasm (MiNENs).

- Carcinomatous and sarcomatous components, consider carcinosarcoma.
- Carcinoma without morphology and immunohistochemical evidence of glandular, hepatocellular, or neuroendocrine differentiation, consider undifferentiated carcinoma.
- Tumor with slender, malignant ductules in a tubular, cord-like, anastomosing pattern within a dense stroma, consider cholangiolocarcinoma.

5. Other tumors

A. Angiomyolipoma

a. Clinical features: While not nearly as common as those of the kidney, the liver represents the second most common site of involvement by angiomyolipomas. These rare tumors typically present as solitary liver lesions in young adults although they have been reported in patients over a wide age range.[111] There is a consistent female predominance which is quite striking in some large series, with a female to male ratio of 5:1.[112] As with most indolent liver tumors, hepatic angiomyolipomas are most often encountered as incidental findings. Radiographically, the possibility of a hepatic angiomyolipoma may be raised if a liver lesion is noted to contain a notable lipomatous component, a characteristic which is usually best appreciated by magnetic resonance imaging. The clinical association with tuberous sclerosis is not nearly as strong with hepatic lesions as with renal tumors, however, approximately 10% of liver cases may be associated with this syndrome.[112] In these cases, patients typically present with concurrent lesions in the kidney as well.

b. Pathologic features: As the name suggests, angiomyolipomas of the liver characteristically contain elements with vascular, myoid, and lipomatous differentiation **(Figs. 22.46)**. These components may occur in various proportions and any single constituent may predominate, particularly on biopsy specimens. Vascular elements most notably consist of medium sized arteries with ill-formed and disorganized appearing muscular walls. The lipomatous components may range from what appears to be well-formed mature adipose tissue to more epithelioid cells containing flocculent lipid droplets. Smooth muscle elements are also variable in presentation although more spindled myoid cells closely approximating large vessels is the most typical appearance. Hepatic angiomyolipomas may occasionally contain foci of pigmentation thought to represent either melanin or hemosiderin.

Foci of extramedullary hematopoiesis are not infrequently encountered, a finding not associated with renal angiomyolipomas.

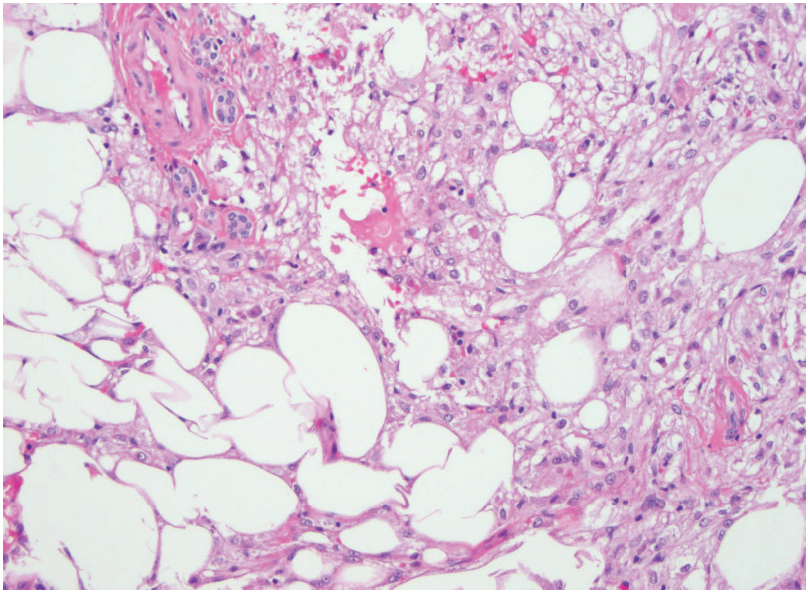

Fig 22.46 Angiomyolipoma of the liver containing vacuolated smooth muscle-like cells, adipocytes, and irregular vessels. Entrapped bile ducts can also be appreciated.

Varying forms of hepatic angiomyolipomas do occasionally occur and tumors with clear cell, eosinophilic (**Fig 22.47**), and cellular pleomorphism have been described. Those with eosinophilic and epithelioid features raise perhaps the most significant diagnostic dilemma as they may appear initially as hepatocellular carcinoma (**Figs. 22.48 and 22.49**). Immunohistochemical studies are of utility in these cases with a vast majority of angiomyolipomas expressing several markers of melanocytic derivation including HMB45 and Melan A as well as the myoid marker smooth muscle actin (SMA). Caution should be exercised in small biopsies however as expression of these markers may be patchy and particularly diminished in lipomatous foci. Additionally, angiomyolipomas are also known to express KIT, such that a gastrointestinal stromal tumor may also enter the differential diagnosis.[113] As with angiomyolipomas from other sites, and other tumors in the PEComa family, hepatic angiomyolipomas frequently exhibit alterations in the mTOR pathway.[114]

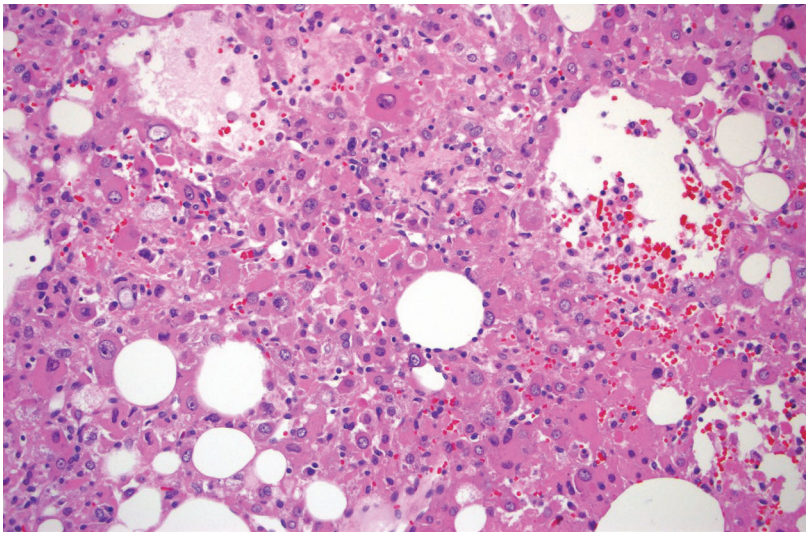

Fig 22.47 The neoplastic cells in this angiomyolipoma are epithelioid and contain abundant eosinophilic cytoplasm, mimicking a hepatocellular carcinoma.

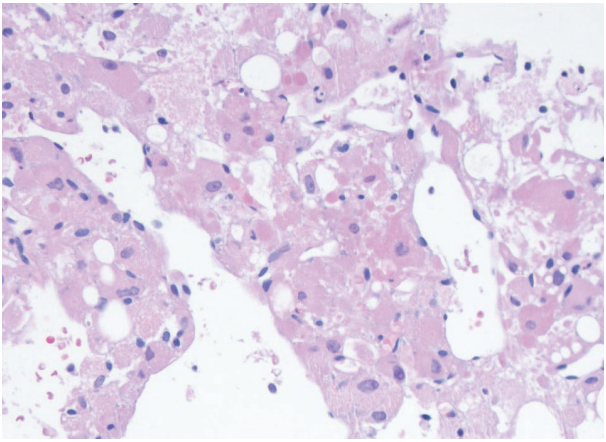

Fig 22.48 Small biopsies can pose a diagnostic challenge. This biopsy depicts epithelioid cells with eosinophilic to amphophilic cytoplasm, mimicking hepatocellular neoplasia.

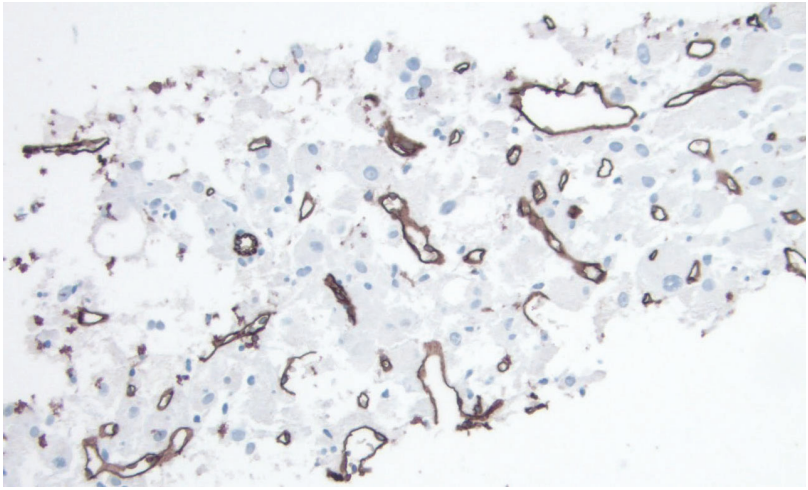

Fig 22.49 Immunoreactivity for CD34 can be observed in vessels in an angiomyolipoma (depicted in fig. 22.48), which may lead to a misdiagnosis of hepatocellular carcinoma.

6. Pediatric liver tumors

A. Hepatoblastoma

a. Clinical features: Hepatoblastoma is the most common malignant liver tumor of children, representing over 90% of primary hepatic malignancies in persons under the age of 5 years.[115] This is a disease of early childhood with a majority of cases occurring prior to the age of 2 years. Rare instances of hepatoblastoma involving older children and adults are occasionally reported.[116] While most cases are unassociated with an underlying familial syndrome, these liver tumors can occasionally be appreciated in individuals with Beckwith-Wiedemann syndrome or familial adenomatous polyposis (FAP). The most well recognized risk factor in the development of these tumors is prematurity and low birth weight, particularly less than 1000 grams.[117] This finding is thought to explain, at least in part, the increasing incidences in developed countries. Patients most often present with abdominal enlargement secondary to an underlying mass which may be associated with pain or vomiting. Laboratory testing is extremely helpful in the clinical investigation of these lesions as they are often associated with dramatically elevated serum AFP levels. Indeed, a lack of elevated serum AFP often suggests an alternative diagnosis or the presence of the so-called

small cell undifferentiated subtype of hepatoblastoma. The overall survival at 5 and 10 years has been estimated at 82% an 81% respectively, however this varies considerably depending on a number of factors including histologic type, age and serum AFP at diagnosis, and the presence of metastasis.[118]

b. Pathologic features: The histologic findings of hepatoblastoma are complex but are worth understanding as the various microscopic permutations carry both therapeutic and prognostic implications. Furthermore, as the treatment strategy for most of these tumors involves a biopsy to confirm the diagnosis followed by neoadjuvant chemotherapy, the initial evaluation of these tumors is often done on limited tissue. The overall classification of hepatoblastomas includes those composed solely of epithelial components and those consisting of both epithelial and mesenchymal elements, with this latter group representing nearly half of the lesions. After this major division the epithelial component is further classified into a number of categories including fetal, embryonal, macrotrabecular, cholangioblastic, and small cell undifferentiated.[119]

When present, the mesenchymal component of hepatoblastomas often consists of osteoid or immature cartilage or skeletal muscle. Occasionally, the stromal component may appear more primitive and appear as undifferentiated spindle cells. Immunohistochemistry for β-catenin may be helpful in confirming the neoplastic nature of these foci.[120] This is particularly helpful in the post-treatment setting when reactive ossification may occur. Beyond these stromal components the presence of other heterologous tissues in mixed tumors, including those composed of endodermal or neuroectodermal derivatives, has been termed teratoid hepatoblastomas. The significance of these findings is unclear.

Fetal components are said to resemble developing liver in late stages. This pattern consists of nests and cords of polygonal tumor cells forming thin trabecula. The cytoplasm is relatively ample and ranges from clear to eosinophilic and tumors often demonstrate alternating zones of each **(Fig. 22.50)**. Tumor cell nuclei are small and round with fine chromatin. Mitotic activity is typically sparse in this pattern although some cases may demonstrate notable mitotic activity, a finding that has been termed the crowded or mitotically active fetal pattern. Overall, fetal components resemble immature hepatocytes and are considered to be the well-differentiated pattern of hepatoblastoma. In fact, tumors recognized as consisting solely of the fetal pattern may be treated with surgical resection alone without need for chemotherapy.

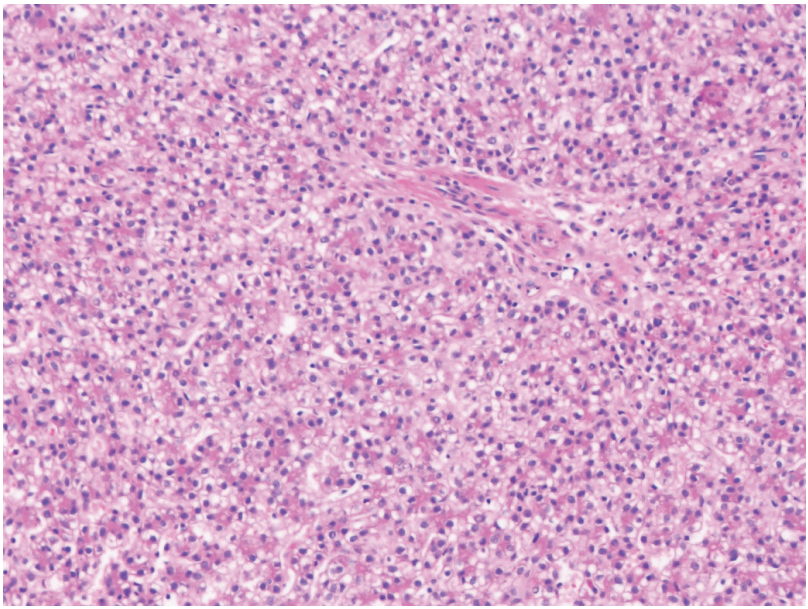

Fig 22.50 Fetal pattern of hepatoblastoma composed of cuboidal cells with alternating clear to eosinophilic cytoplasm.

The embryonal pattern of hepatoblastoma recapitulates the developing liver of early gestation and has a blastemal appearance. Just as in nephroblastoma, This component often consists of sheets, nests, or tubular configurations composed of epithelioid cells with scant cytoplasm. Here the tumor cell nuclei are notably enlarged compared to the fetal components with coarser chromatin **(Fig. 22.51)**. In this pattern mitotic activity is more often notable. While fetal components often readily express HepPar1, expression of this protein is typically diminished or even absent in embryonal areas. Both elements may express nuclear β-catenin.

More uncommon patterns include macrotrabecular and cholangioblastic. The former often resembles the cytology of fetal components but forms large thickened trabecula with plates over 5-20 cells thick.[119, 121] Cholangioblastic components consist of neoplastic cells demonstrating differentiation along a cholangiocyte lineage. These foci are often found adjacent to hepatocellular components and appear as small duct-like structures.[122] Cholangioblastic foci commonly express nuclear β-catenin just as the fetal or embryonal patterns but will also demonstrate reactivity

for cytokeratins 7 and 19. The significance of these patterns is not well understood but recording their presence is recommended.[119]

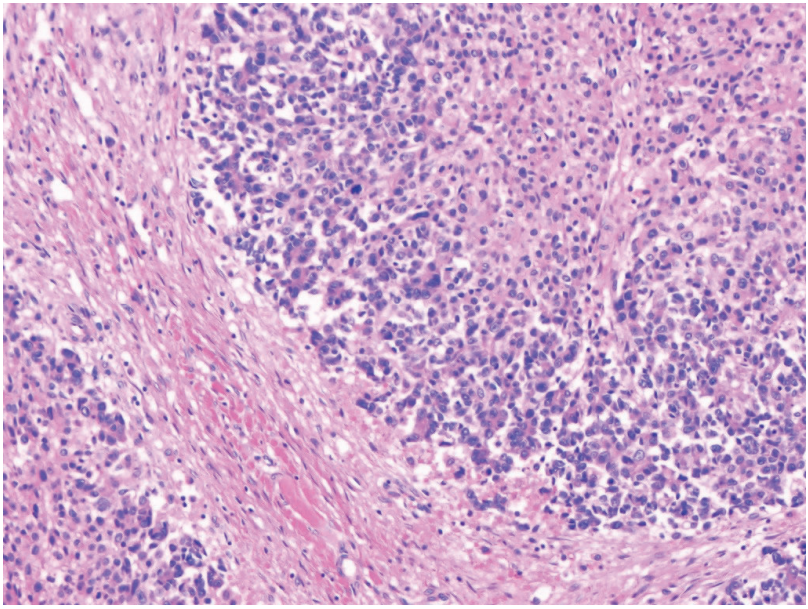

Fig 22.51 Hepatoblastoma with a prominent embryonal pattern demonstrating coarser chromatin and notable nucleomegaly compared to the fetal component in the upper right.

The small cell undifferentiated pattern consists of sheets of prototypical small round blue cells with no discernable architectural pattern. Nucleoli are inconspicuous and tumor cells may be accompanied by a variably myxoid matrix. Notable cell turnover exemplified by increased mitotic activity and apoptosis is typically present. This pattern may represent the tumor as a whole or may be found as individual foci accompanied by other patterns such as fetal or embryonal. The proportion of small cell undifferentiated component should be reported. This pattern may demonstrate a loss of SMARCB1 (INI1) by immunohistochemistry and when it comprises the whole tumor these lesions share many overlapping clinical and molecular features with malignant rhabdoid tumors of liver. This includes a lack of elevated serum AFP, chromosomal alterations at 22q11, and a poor prognosis. Indeed these small cell undifferentiated tumors may be more closely related to rhabdoid tumors than their current classification as hepatoblastomas.[123]

B. Mesenchymal hamartoma of the liver

a. Clinical features: Although these tumors of childhood represent the second most common benign liver tumor after vascular lesions in this age group, they remain quite rare with some accounts estimating they represent approximately 6% of total pediatric liver tumors.[124] The typical clinical presentation involves noticeable abdominal distension by an apparent underlying mass, while symptoms such as pain or vomiting are uncommon. These tumors characteristically affect young children with 85% of these lesions occurring in individuals under the age of 3 years.[125] Cases of mesenchymal hamartoma identified in the prenatal period as well as examples in adults have been reported but are the exception.[126-129] Radiographic studies most often demonstrate a multiloculated cystic tumor with solid components, although the proportions of these two constituents can be quite variable. While considered benign, mesenchymal hamartomas have been known to be associated with concurrent undifferentiated embryonal sarcomas, a highly malignant liver tumor.[130] These sarcomas are also known to arise in individuals in which a preceding mesenchymal hamartoma was not completely resected.[131]

b. Pathologic features: Biopsy specimens of mesenchymal hamartomas are relatively rare as the diagnosis is often suggested by radiographic studies and confirmed pathologically following resection, which is the treatment of choice. However, in cases with limited cystic components, or those arising outside of the typical age range, a biopsy may be pursued.

Histologically, these tumors are composed of haphazard arrangements of branching bile ducts associated with mesenchymal elements. These stromal elements often condense around the aforementioned bile ducts and are variably myxoid to fibrous with the former being more common. The mesenchymal cells are often stellate in character. Varying proportions of hepatocytes may be present, consisting of small clusters and cords to large aggregates **(Fig. 22.52)**. Well-formed bile ducts will be absent as will any significant cytologic atypia or mitotic activity. While distinct areas of necrosis should be present, the radiographically appreciated cysts typically consist of hydropic degeneration of mesenchymal components and lack a true epithelial lining. As in many pediatric liver tumors, foci of extramedullary hematopoiesis are almost invariably present and are not a specific finding[132]. While malignant transformation appears to be rare, and may only be appreciated on resection, particular attention should be given so as to ensure a lack of features to suggest an undifferentiated embryonal sarcoma.

Immunohistochemistry has little role in the diagnosis of hepatic mesenchymal hamartoma as the constituents of the tumor will retain expression of their normal counterparts. Additionally, while not often utilized diagnostically, these tumors have been shown to harbor chromosomal rearrangements involving 19q13.[133]

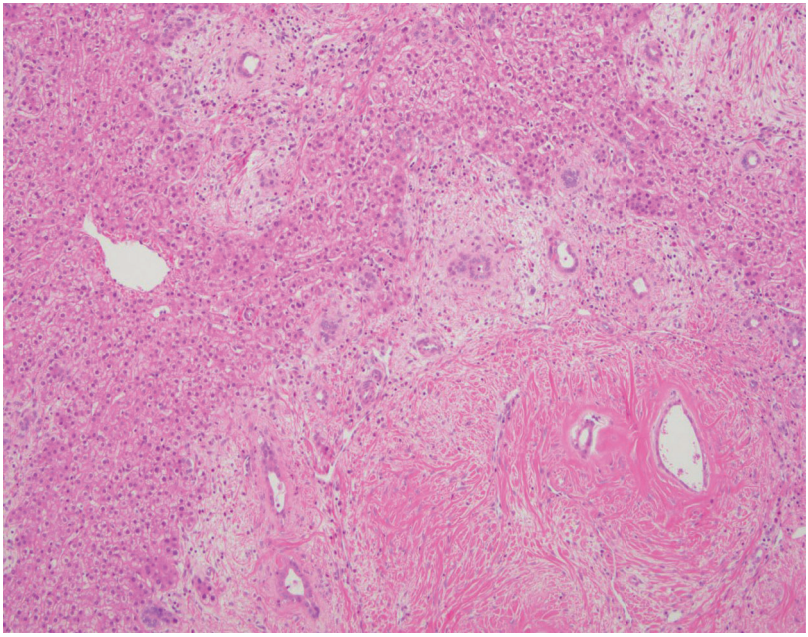

Fig 22.52 Mesenchymal hamartoma of the liver composed of proliferations of bile ducts associated with a variably myxoid to fibrous stroma. Sheets and cords of hepatocytes can also be appreciated in this case.

C. Undifferentiated embryonal sarcoma

a. Clinical features: Of the classic liver tumors of childhood, undifferentiated embryonal sarcomas more typically arise in older children with a median age of 9 years.[134] In fact, these tumors have also been known to occur in young adults with exceptional cases in the elderly also being reported.[135] Infrequently encountered, these tumors represent approximately 6% of all hepatic tumors in children.[124] Of the malignant liver tumors of childhood, only hepatoblastoma and hepatocellular carcinoma are more common.[124] Radiographically, undifferentiated embryonal sarcoma may appear as a cystic lesion on MRI or CT, a finding attributed to their high-

water content. However, other imaging modalities such as ultrasound may demonstrate the true solid nature of these tumors. These contradictory findings are said to strongly suggest the diagnosis radiographically. While these tumors were once thought to impart a grave prognosis, survival has drastically improved with the development of modern chemotherapeutic agents with a 5-year overall survival of 86%.[134]

b. Pathologic features: Embryonal sarcomas are composed of atypical spindled to stellate cells embedded in a typically myxoid stroma **(Fig. 22.53)**. Occasional multinucleated tumor giant cells may be appreciated but can be rather patchy in distribution. The most characteristic feature is the presence of intracellular and extracellular hyaline deposits which may be highlighted by PAS with diastase. Should the edge of the tumor be represented in biopsy material one may appreciate entrapped bile ducts or cords of hepatocytes. This should not be confused with a mesenchymal hamartoma.

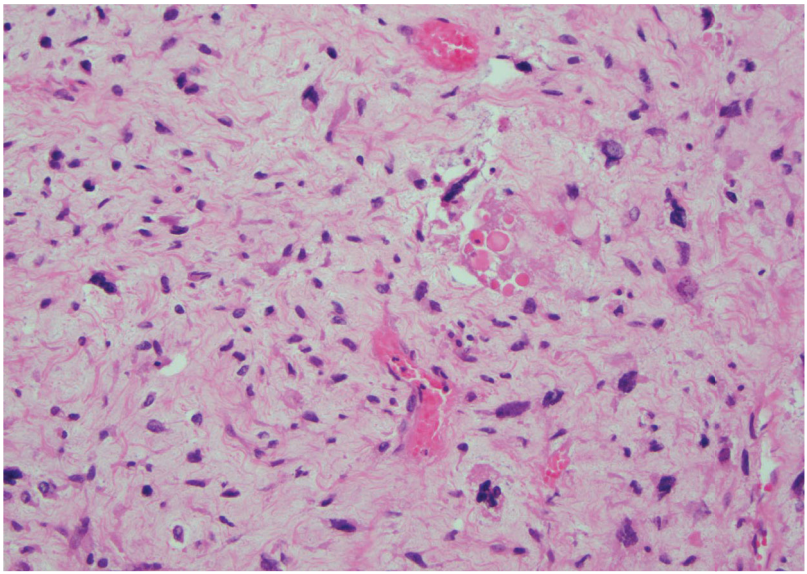

Fig 22.53 Undifferentiated embryonal sarcoma of the liver with variably sized pleomorphic cells associated with a myxoid stroma. Multiple extracellular hyaline globules can also be appreciated.

The primary role of immunohistochemistry in the diagnosis of embryonal sarcoma is in its utility to exclude other tumors in the differential diagnosis. While these sarcomas are known to variably express a number of markers including cytokeratins, alpha-1 antitrypsin, glypican-3, and desmin, they lack reactivity for HepPar1, myogenin, and MyoD1.[136] These latter findings, along with the tumor morphology, help exclude tumors of hepatocellular origin and perhaps more importantly rhabdomyosarcoma.

D. Rhabdoid tumor

a. Clinical features: Analogous to their renal counterparts, malignant rhabdoid tumors of the liver occur in young children with a median age of 8 months.[137] While the imaging findings of these rare tumors overlap significantly with the relatively more common hepatoblastoma, rhabdoid tumors are not typically associated with a significantly increased serum AFP. It is this laboratory finding that often first suggests an alternative diagnosis other than hepatoblastoma. Unfortunately these aggressive tumors are associated with an almost universal mortality rate with only rare case reports of individuals surviving long term.[137] Surgical resectability, the use of actinomycin, and older age at diagnosis have been associated with humble increases in survival.[138]

b. Pathologic features: Histologically, malignant rhabdoid tumors of liver demonstrate features equivalent to rhabdoid tumors of kidney. Namely, they consist of sheets of discohesive epithelioid cells with abundant eosinophilic cytoplasm. This cytoplasm often exhibits paranuclear accentuations known to be composed of collections of intermediate filaments. Nuclei are eccentric and enlarged with vesicular chromatin and prominent nucleoli which are typically solitary **(Fig. 22.54)**.

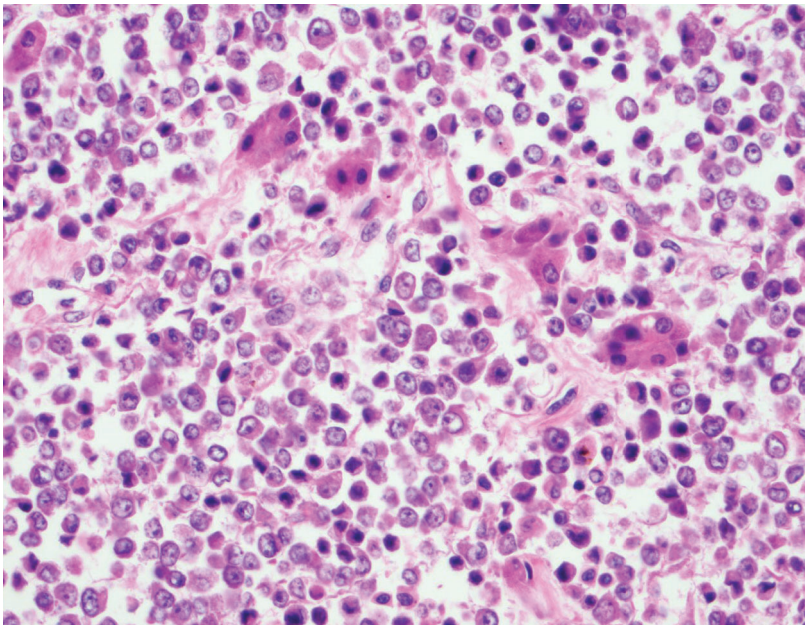

Fig 22.54 Rhabdoid tumor of the liver composed of sheets of dyscohesive epithelioid cells with eccentric nuclei and prominent nucleoli. Entrapped hepatocytes highlight the infiltrative nature of this tumor.

The most characteristic immunophenotypic feature of these tumors is loss of expression of SMARCB1 (INI1). This correlates with the consistent cytogenetic finding of alterations of 22q11 appreciated in many cases as well as similar lesions of the central nervous system.[139] Beyond this defining feature, extrarenal rhabdoid tumors are known to consistently express vimentin which is often accompanied by reactivity for keratins.[140]

Caution should be advised in making a definitive diagnosis of rhabdoid tumor of liver based solely on the loss of SMARCB1 expression. Hepatoblastomas composed almost exclusively of small cell undifferentiated components have also been shown to possess this finding.[123, 141] Furthermore, these tumors often occur in the same age group and present with unremarkable serum AFP levels. It is in this scenario that histologic assessment is crucial as the aforementioned classic morphology is still considered to be required to make a diagnosis of malignant rhabdoid tumor.[119]

E. Rhabdomyosarcoma

a. Clinical features: Rhabdomyosarcomas represent a heterogeneous group of mesenchymal tumors with the embryonal subtype being the most common variant to involve the liver. While these tumors may occasionally present as a liver parenchymal mass, they are more likely to arise in association with large caliber extrahepatic bile ducts. Given the involvement of the biliary system it is not unexpected that many patients initially present with jaundice.[142] Although rhabdomyosarcoma of the soft tissue is one of the most frequently encountered soft tissue sarcomas in children, those arising in association with the liver are quite rare and large series are lacking. Rare examples of other subtypes of rhabdomyosarcoma have also been reported in the liver including spindle cell/sclerosing and alveolar rhabdomyosarcomas.[143, 144]

b. Pathologic features: Embryonal rhabdomyosarcomas involving the liver or bile ducts are usually of the botryoid subtype. This name is given to them as they appear as coalescing subepithelial nodules of tumor imparting a grape-like appearance. Biopsies of these tumors may very well be performed from within the bile duct lumen and appear as cellular proliferations underlying biliary epithelium. The tumor is often more cellular around these structures and stromal condensation around vessels can also be occasionally appreciated. Tumor cells are small and round to spindled with limited eosinophilic cytoplasm and are typically embedded in a myxoid stroma (**Fig. 22.55**). Cross striations may be appreciated but are not always evident. While these tumor cells often appear bland and somewhat hyperchromatic, foci of anaplasia may be appreciated.

Other types of rhabdomyosarcoma have somewhat different histologic findings. Alveolar rhabdomyosarcoma typically consists of nests of round cells separated by fibrous septa with cystic changes imparting an alveolar appearance (**Fig. 22.56**). These tumors can occasionally be solid in nature and multinucleated tumor giant cells can also be seen. Spindle cell/sclerosing rhabdomyosarcoma may demonstrate a variety of histologic patterns with spindle cells forming intersecting fascicles or whorled appearance. Foci with cord-like patterns composed of more round cells embedded in a densely hyalinized stroma impart the sclerosing moniker.

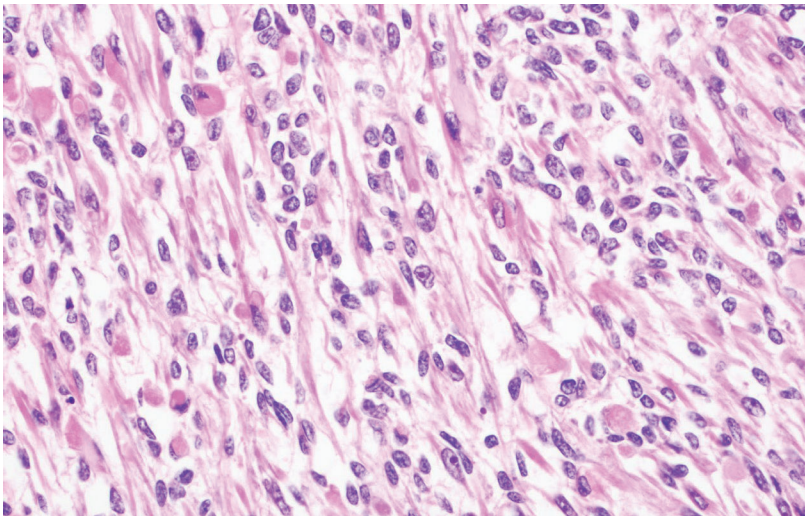

Fig 22.55 Embryonal rhabdomyosarcoma consisting of nests of round cells separated by fibrous septa with cystic changes. Pictures courtesy of Dr. Archana Shenoy, University of Florida.

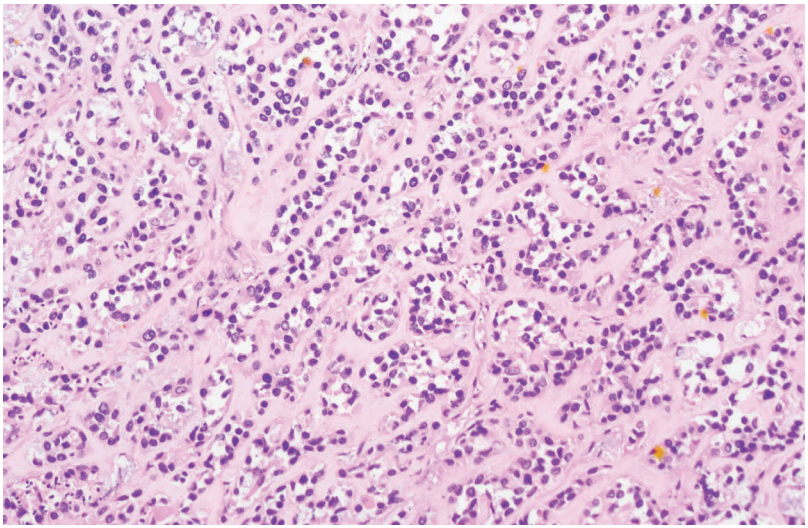

Fig 22.56 Alveolar rhabdomyosarcoma consisting of small round to spindled cells with limited eosinophilic cytoplasm which are typically embedded in a myxoid stroma. Pictures courtesy of Dr. Archana Shenoy, University of Florida.

When confronted with an apparently undifferentiated round cell to spindled tumor, rhabdomyosarcoma should always be on the differential as this diagnosis is easily missed. Immunohistochemistry should demonstrate some markers of muscle differentiation including desmin, MyoD1, and myogenin. The latter marker may be patchy with some tumor types exhibiting diffuse reactivity such as alveolar rhabdomyosarcoma and more limited expression in embryonal and spindle cell/sclerosing. Molecular studies may also be helpful as the alveolar type typically harbors *FOXO1* fusions. Fusions involving *NCOA2* and *VGLL2* have been reported in some of the spindle cell/sclerosing variants.[145, 146]

Finally, a definitive diagnosis of rhabdomyosarcoma via biopsy of a liver mass in an adult should only be made with extreme caution. As with many epithelial tumors, hepatocellular carcinomas or cholangiocarcinomas with sarcomatoid components may demonstrate rhabdomyoblastic features complete with immunophenotypic evidence of myogenic differentiation.[147]

F. Calcifying nested stromal-epithelial tumor

a. Clinical features: Calcifying nested stromal-epithelial tumor of the liver is a rare entity of which we have limited understanding. These tumors can be appreciated over a wide age range from children to young adults. There appears to be a female predominance with 71% of cases occurring in girls or young women.[148] These tumors may present with a variety of symptoms and several have been associated with a Cushing-type syndrome.[149] Others have been associated with Beckwith-Wiedemann syndrome.[150]

Radiographically these tumors are typically large and often contain areas of calcification.[151]

b. Pathologic features: As the name suggests, these tumors are composed of circumscribed nests of epithelial cells which are bland in character with eosinophilic cytoplasm and vesicular chromatin. Surrounding these nests are bland spindled cells which often form a cuff around these islands. Foci of calcification or ossification are often appreciated. Seemingly entrapped bile ducts may also be apparent in the stroma. Mitotic activity is typically rare but can be brisk in occasional cases.[152] Immunohistochemical studies will demonstrate some degree of keratin expression and most tumours will exhibit nuclear reactivity for WT-1 and β-catenin. A lack of expression of markers of hepatocellular differentiation, such as HepPar1, aide in the differential diagnosis of hepatoblastoma.

7. Metastases

While much of this text is devoted to primary tumors of the liver, secondary hepatic involvement by distant malignancies is far more common. Indeed the liver is the most common site for metastatic disease with carcinomas representing a bulk of these lesions. The most common primary tumor to metastasize to the liver is colorectal adenocarcinoma with other frequent primary sites including pancreas, breast, lung and stomach.[153] Beyond carcinomas, hepatic involvement by metastatic neuroendocrine tumors is also frequently encountered. Less commonly, non-epithelial tumors such as melanoma or sarcoma may also metastasize to the liver.

Before determining the specific site of origin of a presumed metastasis the first question that needs to be answered is whether or not a lesion present on a biopsy represents a metastasis at all. Clinical and radiographic features such as a history of malignancy, multifocal liver involvement, and a lack of background liver disease favor metastasis while the presence of solitary lesions in the background of cirrhosis should raise the possibility of primary tumors. While it is well established that the incidence of involvement by metastatic disease is far less common in cirrhotic livers, this factor by itself should not exclude this possibility.[154] If a review of a patient's relevant history is not helpful, cautious use of ancillary tests may be helpful but should not be considered absolute.

Immunohistochemical markers of hepatocellular differentiation such as HepPar1 and arginase may prove helpful in some situations but pathologists should be aware than any tumor with hepatoid features, including metastasis from the stomach, colon, or pancreas, may also express these markers.[155] A more novel ancillary test, albumin RNA in-situ hybridization, initially showed extraordinary results in its ability to distinguish hepatocellular carcinoma and intrahepatic cholangiocarcinomas from metastasis.[156] However, even this promising marker has been shown to also be expressed in a limited set of metastatic adenocarcinomas.[157] Additional markers which have been recently recognized and may aide in the differential are bile salt export protein (BSEP) and multidrug resistance protein 3 (MDR3), which appear as of now to be quite specific for hepatocellular carcinoma.[158, 159]

References

1. Mocchegiani F, Vincenzi P, Coletta M, et al. Prevalence and clinical outcome of hepatic haemangioma with specific reference to the risk of rupture: A large retrospective cross-sectional study. Dig Liver Dis. 2016;48:309-314.
2. Glinkova V, Shevah O, Boaz M, Levine A, Shirin H. Hepatic haemangiomas: Possible association with female sex hormones. Gut 2004;53:1352-1355.
3. Kim GE, Thung SN, Tsui WM, Ferrell LD. Hepatic cavernous hemangioma: Underrecognized associated histologic features. Liver Int. 2006;26:334-338.
4. Song JS, Kim YN, Moon WS. A sclerosing hemangioma of the liver. Clin Mol Hepatol. 2013;19:426-430.
5. Lin J, Bigge J, Ulbright TM, Montgomery E. Anastomosing hemangioma of the liver and gastrointestinal tract: An unusual variant histologically mimicking angiosarcoma. Am J Surg Pathol. 2013;37:1761-1765.
6. Makhlouf HR, Ishak KG. Sclerosed hemangioma and sclerosing cavernous hemangioma of the liver: A comparative clinicopathologic and immunohistochemical study with emphasis on the role of mast cells in their histogenesis. Liver 2002;22:70-78.
7. Lau K, Massad M, Pollak C, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: Insights from an internet registry in the study of a rare cancer. Chest 2011;140:1312-1318.
8. Mehrabi A, Kashfi A, Fonouni H et al. Primary malignant hepatic epithelioid hemangioendothelioma: A comprehensive review of the literature with emphasis on the surgical therapy. Cancer 2006;107:2108-2121.
9. Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: A clinicopathologic study of 137 cases. Cancer 1999;85:562-582.
10. Agostini-Vulaj D, Pehlivanoglu B, Weiss SW et al. Intrasinusoidal spread of hepatic epithelioid hemangioendothelioma: Implications for the diagnosis in minimal samples. Am J Surg Pathol. 2019;43:573-579.
11. Doyle LA, Fletcher CD, Hornick JL. Nuclear expression of camta1 distinguishes epithelioid hemangioendothelioma from histologic mimics. Am J Surg Pathol. 2016;40:94-102.
12. Mani H, Van Thiel DH. Mesenchymal tumors of the liver. Clin Liver Dis. 2001;5:219-257.

13. Zocchetti C. [liver angiosarcoma in humans: Epidemiologic considerations]. Med Lav. 2001;92:39-53.
14. Gaballah AH, Jensen CT, Palmquist S, et al. Angiosarcoma: Clinical and imaging features from head to toe. Br J Radiol. 2017;90:20170039.
15. Koyama T, Fletcher JG, Johnson CD, Kuo MS, Notohara K, Burgart LJ. Primary hepatic angiosarcoma: Findings at ct and mr imaging. Radiology 2002;222:667-673.
16. Hertzanu Y, Peiser J, Zirkin H. Massive bleeding after fine needle aspiration of liver angiosarcoma. Gastrointest Radiol. 1990;15:43-46.
17. Kang TW, Lee MW, Choi D, et al. Safety of percutaneous biopsy for hepatic angiosarcoma: Results of a multicenter korean survey. J Vasc Interv Radiol. 2016;27:846-851.
18. Yasir S, Torbenson MS. Angiosarcoma of the liver: Clinicopathologic features and morphologic patterns. Am J Surg Pathol. 2019;43:581-590.
19. Wiland HO, Pai RK, Purysko AS. Hepatic angiosarcoma mimicking sinusoidal obstruction syndrome/venoocclusive disease: A pathologic-radiologic correlation. Ann Diagn Pathol. 2012;16:275-279.
20. Gill RM, Buelow B, Mather C, et al. Hepatic small vessel neoplasm, a rare infiltrative vascular neoplasm of uncertain malignant potential. Hum Pathol. 2016;54:143-151.
21. Zen Y, Sofue K. Sinusoidal-type angiosarcoma of the liver: Imaging features and potential diagnostic utility of p53 immunostaining. Am J Surg Pathol. 2019;43:1728-1731.
22. Weihrauch M, Bader M, Lehnert G, et al. Mutation analysis of k-ras-2 in liver angiosarcoma and adjacent nonneoplastic liver tissue from patients occupationally exposed to vinyl chloride. Environ Mol Mutagen 2002;40:36-40.
23. Przygodzki RM, Finkelstein SD, Keohavong P, et al. Sporadic and thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in k-ras-2. Lab Invest. 1997;76:153-159.
24. Gouw AS, Zeng W, Buiskool M, et al. Molecular characterization of the vascular features of focal nodular hyperplasia and hepatocellular adenoma: A role for angiopoietin-1. Hepatology 2010;52:540-549.
25. Mathieu D, Kobeiter H, Maison P, et al. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118:560-564.
26. Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: A report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990;11:787-797.

27. Libbrecht L, Cassiman D, Verslype C et al. Clinicopathological features of focal nodular hyperplasia-like nodules in 130 cirrhotic explant livers. Am J Gastroenterol. 2006;101:2341-2346.
28. Bioulac-Sage P, Cubel G, Taouji S, et al. Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol. 2012;36:1691-1699.
29. Chang CY, Hernandez-Prera JC, Roayaie S, Schwartz M, Thung SN. Changing epidemiology of hepatocellular adenoma in the united states: Review of the literature. Int J Hepatol. 2013;2013:604860.
30. Søe KL, Søe M, Gluud C. Liver pathology associated with the use of anabolic-androgenic steroids. Liver 1992;12:73-79.
31. Bannasch P. Hepatocellular glycogenosis and hepatic neoplasms. Toxicol Pathol. 2010;38:1000-1002.
32. Klompenhouwer AJ, de Man RA, Thomeer MG, Ijzermans JN. Management and outcome of hepatocellular adenoma with massive bleeding at presentation. World J Gastroenterol. 2017;23:4579-4586.
33. Bioulac-Sage P, Laumonier H, Couchy G, et al. Hepatocellular adenoma management and phenotypic classification: The bordeaux experience. Hepatology 2009;50:481-489.
34. Nault JC, Couchy G, Balabaud C, et al. Molecular classification of hepatocellular adenoma associates with risk factors, bleeding, and malignant transformation. Gastroenterology 2017;152:880-894.e886.
35. Terkivatan T, Ijzermans JN. Hepatocellular adenoma: Should phenotypic classification direct management? Nat Rev Gastroenterol Hepatol. 2009;6:697-698.
36. Rebouissou S, Franconi A, Calderaro J, et al. Genotype-phenotype correlation of ctnnb1 mutations reveals different ß-catenin activity associated with liver tumor progression. Hepatology 2016;64:2047-2061.
37. Evason KJ, Grenert JP, Ferrell LD, Kakar S. Atypical hepatocellular adenoma-like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas. Hum Pathol. 2013;44:750-758.
38. Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology 2007;46:740-748.
39. Larson BK, Guindi M. A limited immunohistochemical panel can subtype hepatocellular adenomas for routine practice. Am J Clin Pathol. 2017;147:557-570.

40. Bedossa P, Burt AD, Brunt EM, et al. Well-differentiated hepatocellular neoplasm of uncertain malignant potential: Proposal for a new diagnostic category. Hum Pathol. 2014;45:658-660.
41. Kakar S, Evason KJ, Ferrell LD. Well-differentiated hepatocellular neoplasm of uncertain malignant potential: Proposal for a new diagnostic category--reply. Hum Pathol. 2014;45:660-661.
42. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: Consider the population. J Clin Gastroenterol 2013;47 Suppl:S2-6.
43. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365:1118-1127.
44. Liu P, Xie SH, Hu S, et al. Age-specific sex difference in the incidence of hepatocellular carcinoma in the united states. Oncotarget 2017;8:68131-68137.
45. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123-133.
46. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol 2020;72:250-261.
47. Tang A, Bashir MR, Corwin MT, et al. Evidence supporting li-rads major features for ct- and mr imaging-based diagnosis of hepatocellular carcinoma: A systematic review. Radiology 2018;286:29-48.
48. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15:599-616.
49. Colecchia A, Scaioli E, Montrone L, et al. Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment. J Hepatol 2011;54:300-305.
50. Zhou L, Rui JA, Wang SB, et al. Outcomes and prognostic factors of cirrhotic patients with hepatocellular carcinoma after radical major hepatectomy. World J Surg. 2007;31:1782-1787.
51. Lang H, Sotiropoulos GC, Brokalaki EI, et al. Survival and recurrence rates after resection for hepatocellular carcinoma in noncirrhotic livers. J Am Coll Surg. 2007;205:27-36.
52. Jonas S, Bechstein WO, Steinmüller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 2001;33:1080-1086.

53. Han YS, Choi DL, Park JB. Cirrhotomimetic type hepatocellular carcinoma diagnosed after liver transplantation--eighteen months of follow-up: A case report. Transplant Proc. 2008;40:2835-2836.
54. Salomao M, Yu WM, Brown RS, Emond JC, Lefkowitch JH. Steatohepatitic hepatocellular carcinoma (sh-hcc): A distinctive histological variant of hcc in hepatitis c virus-related cirrhosis with associated nafld/nash. Am J Surg Pathol. 2010;34:1630-1636.
55. Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitch JH, Moreira RK. The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol. 2012;43:737-746.
56. Olofson AM, Gonzalo DH, Chang M, Liu X. Steatohepatitic variant of hepatocellular carcinoma: A focused review. Gastroenterology Res. 2018;11:391-396.
57. Singhi AD, Jain D, Kakar S, Wu TT, Yeh MM, Torbenson M. Reticulin loss in benign fatty liver: An important diagnostic pitfall when considering a diagnosis of hepatocellular carcinoma. Am J Surg Pathol. 2012;36:710-715.
58. Takahashi A, Saito H, Kanno Y, et al. Case of clear-cell hepatocellular carcinoma that developed in the normal liver of a middle-aged woman. World J Gastroenterol. 2008;14:129-131.
59. Yang SH, Watanabe J, Nakashima O, Kojiro M. Clinicopathologic study on clear cell hepatocellular carcinoma. Pathol Int. 1996;46:503-509.
60. Liu Z, Ma W, Li H, Li Q. Clinicopathological and prognostic features of primary clear cell carcinoma of the liver. Hepatol Res. 2008;38:291-299.
61. Li T, Fan J, Qin LX, et al. Risk factors, prognosis, and management of early and late intrahepatic recurrence after resection of primary clear cell carcinoma of the liver. Ann Surg Oncol. 2011;18:1955-1963.
62. Ziol M, Poté N, Amaddeo G, et al. Macrotrabecular-massive hepatocellular carcinoma: A distinctive histological subtype with clinical relevance. Hepatology 2018;68:103-112.
63. Jeon Y, Benedict M, Taddei T, Jain D, Zhang X. Macrotrabecular hepatocellular carcinoma: An aggressive subtype of hepatocellular carcinoma. Am J Surg Pathol. 2019;43:943-948.
64. Calderaro J, Couchy G, Imbeaud S, et al. Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification. J Hepatol. 2017;67:727-738.
65. Omata M, Peters RL, Tatter D. Sclerosing hepatic carcinoma: Relationship to hypercalcemia. Liver 1981;1:33-49.

66. Farooq A, Merath K, Paredes AZ, et al. Outcomes of patients with scirrhous hepatocellular carcinoma: Insights from the national cancer database. J Gastrointest Surg. 2020;24:1049-1060.
67. Lee JH, Choi MS, Gwak GY, et al. Clinicopathologic characteristics and long-term prognosis of scirrhous hepatocellular carcinoma. Dig Dis Sci. 2012;57:1698-1707.
68. Matsuura S, Aishima S, Taguchi K, et al. 'scirrhous' type hepatocellular carcinomas: A special reference to expression of cytokeratin 7 and hepatocyte paraffin 1. Histopathology 2005;47:382-390.
69. Kassahun WT. Contemporary management of fibrolamellar hepatocellular carcinoma: Diagnosis, treatment, outcome, prognostic factors, and recent developments. World J Surg Oncol. 2016;14:151.
70. Chakrabarti S, Tella SH, Kommalapati A, et al. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. J Gastrointest Oncol. 2019;10:554-561.
71. Graham RP, Torbenson MS. Fibrolamellar carcinoma: A histologically unique tumor with unique molecular findings. Semin Diagn Pathol. 2017;34:146-152.
72. Graham RP, Yeh MM, Lam-Himlin D, et al. Molecular testing for the clinical diagnosis of fibrolamellar carcinoma. Mod Pathol. 2018;31:141-149.
73. Honeyman JN, Simon EP, Robine N, et al. Detection of a recurrent dnajb1-prkaca chimeric transcript in fibrolamellar hepatocellular carcinoma. Science 2014;343:1010-1014.
74. Torbenson MS. Morphologic subtypes of hepatocellular carcinoma. Gastroenterol Clin North Am. 2017;46:365-391.
75. Joshita S, Nakazawa K, Koike S, et al. A case of granulocyte-colony stimulating factor-producing hepatocellular carcinoma confirmed by immunohistochemistry. J Korean Med Sci. 2010;25:476-480.
76. Chan AW, Tong JH, Pan Y, et al. Lymphoepithelioma-like hepatocellular carcinoma: An uncommon variant of hepatocellular carcinoma with favorable outcome. Am J Surg Pathol. 2015;39:304-312.
77. Yuan L, Aucejo F, Menon K, Liu X. Lymphoepithelioma-like hepatocellular carcinoma: Report of three cases and review of literature. J Med Cases 2015;6:297-303.
78. Wood LD, Heaphy CM, Daniel HD, et al. Chromophobe hepatocellular carcinoma with abrupt anaplasia: A proposal for a new subtype of hepatocellular carcinoma with unique morphological and molecular features. Mod Pathol. 2013;26:1586-1593.

79. Clayton EF, Malik S, Bonnel A, et al. Liver transplantation and cirrhotomimetic hepatocellular carcinoma: Classification and outcomes. Liver Transpl. 2014;20:765-774.
80. Torbenson M, Ng I, Park YN et al. Hepatocellular carcinoma. In: WHO Classification of Tumours of the Digestive System. 5th ed. Lyon: IARC 2019; p.230.
81. Redston MS, Wanless IR. The hepatic von meyenburg complex: Prevalence and association with hepatic and renal cysts among 2843 autopsies [corrected]. Mod Pathol. 1996;9:233-237.
82. Allaire GS, Rabin L, Ishak KG, Sesterhenn IA. Bile duct adenoma. A study of 152 cases. Am J Surg Pathol. 1988;12:708-715.
83. Hughes NR, Goodman ZD, Bhathal PS. An immunohistochemical profile of the so-called bile duct adenoma: Clues to pathogenesis. Am J Surg Pathol. 2010;34:1312-1318.
84. Bhathal PS, Hughes NR, Goodman ZD. The so-called bile duct adenoma is a peribiliary gland hamartoma. Am J Surg Pathol. 1996;20:858-864.
85. Aishima S, Tanaka Y, Kubo Y, Shirabe K, Maehara Y, Oda Y. Bile duct adenoma and von meyenburg complex-like duct arising in hepatitis and cirrhosis: Pathogenesis and histological characteristics. Pathol Int. 2014;64:551-559.
86. Albores-Saavedra J, Hoang MP, Murakata LA, Sinkre P, Yaziji H. Atypical bile duct adenoma, clear cell type: A previously undescribed tumor of the liver. Am J Surg Pathol. 2001;25:956-960.
87. Arnaoutakis DJ, Kim Y, Pulitano C, et al. Management of biliary cystic tumors: A multi-institutional analysis of a rare liver tumor. Ann Surg. 2015;261:361-367.
88. Devaney K, Goodman ZD, Ishak KG. Hepatobiliary cystadenoma and cystadenocarcinoma. A light microscopic and immunohistochemical study of 70 patients. Am J Surg Pathol. 1994;18:1078-1091.
89. Quigley B, Reid MD, Pehlivanoglu B, et al. Hepatobiliary mucinous cystic neoplasms with ovarian type stroma (so-called "Hepatobiliary cystadenoma/cystadenocarcinoma"): Clinicopathologic analysis of 36 cases illustrates rarity of carcinomatous change. Am J Surg Pathol. 2018;42:95-102.
90. Lam MM, Swanson PE, Upton MP, Yeh MM. Ovarian-type stroma in hepatobiliary cystadenomas and pancreatic mucinous cystic neoplasms: An immunohistochemical study. Am J Clin Pathol. 2008;129:211-218.

91. Soares KC, Arnaoutakis DJ, Kamel I, et al. Cystic neoplasms of the liver: Biliary cystadenoma and cystadenocarcinoma. J Am Coll Surg. 2014;218:119-128.
92. Zen Y, Fujii T, Itatsu K, et al. Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. Hepatology 2006;44:1333-1343.
93. Schlitter AM, Born D, Bettstetter M, et al. Intraductal papillary neoplasms of the bile duct: Stepwise progression to carcinoma involves common molecular pathways. Mod Pathol. 2014;27:73-86.
94. Kim KM, Lee JK, Shin JU, et al. Clinicopathologic features of intraductal papillary neoplasm of the bile duct according to histologic subtype. Am J Gastroenterol. 2012;107:118-125.
95. Jung G, Park KM, Lee SS, Yu E, Hong SM, Kim J. Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct. J Hepatol. 2012;57:787-793.
96. Arnason T, Borger DR, Corless C, et al. Biliary adenofibroma of liver: Morphology, tumor genetics, and outcomes in 6 cases. Am J Surg Pathol. 2017;41:499-505.
97. Sturm AK, Welsch T, Meissner C, Aust DE, Baretton G. A case of biliary adenofibroma of the liver with malignant transformation: A morphomolecular case report and review of the literature. Surg Case Rep. 2019;5:104. doi: 10.1186/s40792-019-0661-2.
98. Kaminsky P, Preiss J, Sasatomi E, Gerber DA. Biliary adenofibroma: A rare hepatic lesion with malignant features. Hepatology 2017;65:380-383.
99. Altekruse SF, Devesa SS, Dickie LA, McGlynn KA, Kleiner DE. Histological classification of liver and intrahepatic bile duct cancers in seer registries. J Registry Manag. 2011;38:201-205.
100. Shaib YH, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the united states: A true increase? J Hepatol. 2004;40:472-477.
101. Yu TH, Yuan RH, Chen YL, Yang WC, Hsu HC, Jeng YM. Viral hepatitis is associated with intrahepatic cholangiocarcinoma with cholangiolar differentiation and n-cadherin expression. Mod Pathol. 2011;24:810-819.
102. Kozaka K, Sasaki M, Fujii T, et al. A subgroup of intrahepatic cholangiocarcinoma with an infiltrating replacement growth pattern and a resemblance to reactive proliferating bile ductules: 'bile ductular carcinoma'. Histopathology 2007;51:390-400.
103. Liau JY, Tsai JH, Yuan RH, Chang CN, Lee HJ, Jeng YM. Morphological subclassification of intrahepatic cholangiocarcinoma:

Etiological, clinicopathological, and molecular features. Mod Pathol. 2014;27:1163-1173.
104. Aishima S, Oda Y. Pathogenesis and classification of intrahepatic cholangiocarcinoma: Different characters of perihilar large duct type versus peripheral small duct type. J Hepatobiliary Pancreat Sci. 2015;22:94-100.
105. Rullier A, Le Bail B, Fawaz R, Blanc JF, Saric J, Bioulac-Sage P. Cytokeratin 7 and 20 expression in cholangiocarcinomas varies along the biliary tract but still differs from that in colorectal carcinoma metastasis. Am J Surg Pathol. 2000;24:870-876.
106. Tsai JH, Huang WC, Kuo KT, Yuan RH, Chen YL, Jeng YM. S100p immunostaining identifies a subset of peripheral-type intrahepatic cholangiocarcinomas with morphological and molecular features similar to those of perihilar and extrahepatic cholangiocarcinomas. Histopathology 2012;61:1106-1116.
107. Brunt E, Aishima S, Clavien PA, et al. Chcc-cca: Consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentation. Hepatology 2018;68:113-126.
108. Sciarra A, Park YN, Sempoux C. Updates in the diagnosis of combined hepatocellular-cholangiocarcinoma. Hum Pathol. 2020;96:48-55.
109. Sempoux C, Kakar S, Kondo F, Schirmacher P. Combined hepatocellular-cholangiocarcinoma and undifferentiated primary liver carcinoma. Who classification of tumours of the digestive system. Lyon, France, 2019;p.260-262.
110. Zen C, Zen Y, Mitry RR, et al. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver Transpl 2011;17:943-954.
111. Goodman ZD, Ishak KG. Angiomyolipomas of the liver. Am J Surg Pathol. 1984;8:745-750.
112. Tsui WM, Colombari R, Portmann BC, et al. Hepatic angiomyolipoma: A clinicopathologic study of 30 cases and delineation of unusual morphologic variants. Am J Surg Pathol. 1999;23:34-48.
113. Makhlouf HR, Remotti HE, Ishak KG. Expression of kit (cd117) in angiomyolipoma. Am J Surg Pathol. 2002;26:493-497.
114. Huang SC, Chuang HC, Chen TD, et al. Alterations of the mtor pathway in hepatic angiomyolipoma with emphasis on the epithelioid variant and loss of heterogeneity of tsc1/tsc2. Histopathology 2015;66:695-705.
115. Darbari A, Sabin KM, Shapiro CN, Schwarz KB. Epidemiology of primary hepatic malignancies in U.S. Children. Hepatology 2003;38:560-566.

116. Zheng MH, Zhang L, Gu DN, Shi HQ, Zeng QQ, Chen YP. Hepatoblastoma in adult: Review of the literature. J Clin Med Res. 2009;1:13-16.
117. Tanimura M, Matsui I, Abe J, et al. Increased risk of hepatoblastoma among immature children with a lower birth weight. Cancer Res. 1998;58:3032-3035.
118. Feng J, Polychronidis G, Heger U, Frongia G, Mehrabi A, Hoffmann K. Incidence trends and survival prediction of hepatoblastoma in children: A population-based study. Cancer Commun. (Lond) 2019;39:62.
119. López-Terrada D, Alaggio R, de Dávila MT, et al. Towards an international pediatric liver tumor consensus classification: Proceedings of the los angeles cog liver tumors symposium. Mod Pathol. 2014;27:472-491.
120. Wei Y, Fabre M, Branchereau S, Gauthier F, Perilongo G, Buendia MA. Activation of beta-catenin in epithelial and mesenchymal hepatoblastomas. Oncogene 2000;19:498-504.
121. González-Crussi F, Upton MP, Maurer HS. Hepatoblastoma. Attempt at characterization of histologic subtypes. Am J Surg Pathol. 1982;6:599-612.
122. Zimmermann A. Hepatoblastoma with cholangioblastic features ('cholangioblastic hepatoblastoma') and other liver tumors with bimodal differentiation in young patients. Med Pediatr Oncol. 2002;39:487-491.
123. Vokuhl C, Oyen F, Häberle B, von Schweinitz D, Schneppenheim R, Leuschner I. Small cell undifferentiated (scud) hepatoblastomas: All malignant rhabdoid tumors? Genes Chromosomes Cancer 2016;55:925-931.
124. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Hum Pathol. 1983;14:512-537.
125. Stringer MD, Alizai NK. Mesenchymal hamartoma of the liver: A systematic review. J Pediatr Surg. 2005;40:1681-1690.
126. Kodandapani S, Pai MV, Kumar V, Pai KV. Prenatal diagnosis of congenital mesenchymal hamartoma of liver: A case report. Case Rep Obstet Gynecol. 2011;2011:932583.
127. Cignini P, Coco C, Giorlandino M, Bagolan P, Morini F, Giorlandino C. Fetal hepatic mesenchymal hamartoma: A case report. J Prenat Med. 2007;1:45-46.
128. Sharma M, Bansal P, Goyal NK. Adult hepatic mesenchymal hamartoma: An unusual case. J Lab Physicians 2014;6:124-126.

129. Cook JR, Pfeifer JD, Dehner LP. Mesenchymal hamartoma of the liver in the adult: Association with distinct clinical features and histological changes. Hum Pathol. 2002;33:893-898.
130. Lauwers GY, Grant LD, Donnelly WH, et al. Hepatic undifferentiated (embryonal) sarcoma arising in a mesenchymal hamartoma. Am J Surg Pathol. 1997;21:1248-1254.
131. Ramanujam TM, Ramesh JC, Goh DW, et al. Malignant transformation of mesenchymal hamartoma of the liver: Case report and review of the literature. J Pediatr Surg. 1999;34:1684-1686.
132. Ishak K, Goodman Z, Stocker J. Tumors of the liver and intrahepatic bile ducts. Washington, D.C.: Armed Forces Institute of Pathology, 2001.
133. Mathews J, Duncavage EJ, Pfeifer JD. Characterization of translocations in mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver. Exp Mol Pathol. 2013;95:319-324.
134. Shi Y, Rojas Y, Zhang W, et al. Characteristics and outcomes in children with undifferentiated embryonal sarcoma of the liver: A report from the national cancer database. Pediatr Blood Cancer 2017;64.
135. Ellis IO, Cotton RE. Primary malignant mesenchymal tumour of the liver in an elderly female. Histopathology 1983;7:113-121.
136. Kiani B, Ferrell LD, Qualman S, Frankel WL. Immunohistochemical analysis of embryonal sarcoma of the liver. Appl Immunohistochem Mol Morphol. 2006;14:193-197.
137. Trobaugh-Lotrario AD, Finegold MJ, Feusner JH. Rhabdoid tumors of the liver: Rare, aggressive, and poorly responsive to standard cytotoxic chemotherapy. Pediatr Blood Cancer 2011;57:423-428.
138. Horazdovsky R, Manivel JC, Cheng EY. Surgery and actinomycin improve survival in malignant rhabdoid tumor. Sarcoma 2013;2013:315170.
139. Biegel JA, Allen CS, Kawasaki K, Shimizu N, Budarf ML, Bell CJ. Narrowing the critical region for a rhabdoid tumor locus in 22q11. Genes Chromosomes Cancer 1996;16:94-105.
140. Fanburg-Smith JC, Hengge M, Hengge UR, Smith JS, Miettinen M. Extrarenal rhabdoid tumors of soft tissue: A clinicopathologic and immunohistochemical study of 18 cases. Ann Diagn Pathol. 1998;2:351-362.
141. Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, Gore L, Feusner JH. Small cell undifferentiated variant of hepatoblastoma: Adverse clinical and molecular features similar to rhabdoid tumors. Pediatr Blood Cancer 2009;52:328-334.

142. Davis GL, Kissane JM, Ishak KG. Embryonal rhabdomyosarcoma (sarcoma botryoides) of the biliary tree. Report of five cases and a review of the literature. Cancer 1969;24:333-342.
143. Akki AS, Harrell DK, Weaver KD, Esnakula AK, Shenoy A. Rare case of spindle cell/sclerosing rhabdomyosarcoma in adult liver. Pathology 2019;51:745-747.
144. Schoofs G, Braeye L, Vanheste R, Verswijvel G, Debiec-Rychter M, Sciot R. Hepatic rhabdomyosarcoma in an adult: A rare primary malignant liver tumor. Case report and literature review. Acta Gastroenterol Belg. 2011;74:576-581.
145. Mosquera JM, Sboner A, Zhang L, et al. Recurrent ncoa2 gene rearrangements in congenital/infantile spindle cell rhabdomyosarcoma. Genes Chromosomes Cancer 2013;52:538-550.
146. Alaggio R, Zhang L, Sung YS, et al. A molecular study of pediatric spindle and sclerosing rhabdomyosarcoma: Identification of novel and recurrent vgll2-related fusions in infantile cases. Am J Surg Pathol. 2016;40:224-235.
147. Akasofu M, Kawahara E, Kaji K, Nakanishi I. Sarcomatoid hepatocellular-carcinoma showing rhabdomyoblastic differentiation in the adult cirrhotic liver. Virchows Arch. 1999;434:511-515.
148. Benedict M, Zhang X. Calcifying nested stromal-epithelial tumor of the liver: An update and literature review. Arch Pathol Lab Med. 2019;143:264-268.
149. Heerema-McKenney A, Leuschner I, Smith N, Sennesh J, Finegold MJ. Nested stromal epithelial tumor of the liver: Six cases of a distinctive pediatric neoplasm with frequent calcifications and association with cushing syndrome. Am J Surg Pathol. 2005;29:10-20.
150. Malowany JI, Merritt NH, Chan NG, Ngan BY. Nested stromal epithelial tumor of the liver in beckwith-wiedemann syndrome. Pediatr Dev Pathol. 2013;16:312-317.
151. Schaffer LR, Shehata BM, Yin J, Schemankewitz E, Alazraki A. Calcifying nested stromal-epithelial tumor (cnset) of the liver: A newly recognized entity to be considered in the radiologist's differential diagnosis. Clin Imaging 2016;40:137-139.
152. Makhlouf HR, Abdul-Al HM, Wang G, Goodman ZD. Calcifying nested stromal-epithelial tumors of the liver: A clinicopathologic, immunohistochemical, and molecular genetic study of 9 cases with a long-term follow-up. Am J Surg Pathol. 2009;33:976-983.
153. de Ridder J, de Wilt JH, Simmer F, Overbeek L, Lemmens V, Nagtegaal I. Incidence and origin of histologically confirmed liver

metastases: An explorative case-study of 23,154 patients. Oncotarget 2016;7:55368-55376.
154. Cai B, Liao K, Song XQ, Wei WY, Zhuang Y, Zhang S. Patients with chronically diseased livers have lower incidence of colorectal liver metastases: A meta-analysis. PLoS One 2014;9:e108618.
155. Chandan VS, Shah SS, Torbenson MS, Wu TT. Arginase-1 is frequently positive in hepatoid adenocarcinomas. Hum Pathol. 2016;55:11-16.
156. Ferrone CR, Ting DT, Shahid M, et al. The ability to diagnose intrahepatic cholangiocarcinoma definitively using novel branched dna-enhanced albumin rna in situ hybridization technology. Ann Surg Oncol. 2016;23:290-296.
157. Nasir A, Lehrke HD, Mounajjed T, et al. Albumin in situ hybridization can be positive in adenocarcinomas and other tumors from diverse sites. Am J Clin Pathol. 2019;152:190-199.
158. Fujikura K, Yamasaki T, Otani K et al. Bsep and mdr3: Useful immunohistochemical markers to discriminate hepatocellular carcinomas from intrahepatic cholangiocarcinomas and hepatoid carcinomas. Am J Surg Pathol. 2016;40:689-696.
159. Lagana SM, Salomao M, Remotti HE, Knisely AS, Moreira RK. Bile salt export pump: A sensitive and specific immunohistochemical marker of hepatocellular carcinoma. Histopathology 2015;66:598-602.

Chapter Twenty-Three

Hematologic/Lymphoproliferative Disorders of Liver

Jinping Lai, MD, PhD

Abstract

The liver can be involved by various neoplastic hematologic/lymphoproliferative disorders. Primary hepatic lymphoma (PHL) is very rare, accounting for only 0.4% of extranodal lymphomas. However, the liver is frequently and secondarily involved by the advanced-stage lymphoma of any type. Hepatopathologists must be familiar with the full spectrum of hematolymphoid tumors/disorders involving the liver before signing cases out as inflammatory disease of the liver. PHL confined to the liver without extrahepatic involvement can present as solitary or multiple nodules raising consideration for carcinoma on imaging findings or may mimic benign inflammatory conditions posing a diagnostic challenge. This chapter describes clinical, morphologic, and immunophenotypic features of the common hematologic/lymphoproliferative neoplasms including B cell lymphoma, Hodgkin lymphoma, T/NK cell lymphoma, post-transplant lymphoproliferative disorders (PTLD), Epstein-Barr virus (EBV) positive inflammatory follicular dendritic cell sarcoma, mastocytosis, Langerhans cell histiocytosis, hairy cell leukemia, histiocytic sarcoma, plasma cell neoplasm and collision tumor of lymphoma and metastatic carcinoma in the liver, along with differential diagnosis, recommended ancillary testing and prognosis prediction. Some histologic mimics and diagnostic pitfalls are mentioned. A diagnostic checklist for pathologists is also listed.

Keywords: Diffuse large B-cell lymphoma (DLBCL); Extranodal marginal zone lymphoma; Small lymphocytic lymphoma/Chronic lymphocytic leukemia (SLL/CLL); Post-transplant lymphoproliferative disorders (PTLD); Hodgkin lymphoma; Hepatosplenic T-cell lymphoma; Anaplastic large cell lymphoma; T/NK cell lymphoma; Peripheral T-cell lymphoma

(PTCL); EBV positive inflammatory follicular dendritic cell sarcoma; Langerhans cell histiocytosis; Mastocytosis; Hairy cell leukemia; Histiocytic sarcoma; Plasma cell neoplasm; Collision tumors of lymphoma and carcinoma.

Introduction

Primary hepatic lymphoma (PHL) is very rare, accounting for only 0.4% of extranodal lymphomas.[1] However, the liver is frequently involved by the advanced-stage lymphoma of any type.[2] There is a strong association between pathogenesis of PHL and viral infection, such as chronic hepatitis (due to hepatitis B virus (HBV) and/or hepatitis C virus(HCV))[3,4], immunological disorders[5, 6] including immunodeficiency (human immunodeficiency virus (HIV) infection, post-transplant, iatrogenic immunosuppression)[7], and autoimmune disease (e.g. Felty syndrome, systemic lupus erythematosus, autoimmune cytopenia, and primary biliary cholangitis/cirrhosis (PBC))[8, 9].

Diffuse large B cell lymphoma (DLBCL) and extranodal marginal zone lymphoma are the most common types of primary hepatic B-cell lymphomas. Post-transplant lymphoproliferative disorders (PTLD), hepatosplenic T-cell lymphoma and NK- T cell lymphoma typically involve the liver as part of systemic disease. The liver is a characteristic primary site for the occurrence of EBV-positive inflammatory follicular dendritic cell sarcoma, previously known as inflammatory pseudotumor-like follicular/fibroblastic dendritic cell sarcoma.[2,10] Sometimes, Langerhans cell histiocytosis, mastocytosis, hairy cell leukemia, histiocytic sarcoma, plasma cell myeloma and myeloid sarcoma can uncommonly affect the liver.[2, 10, 11] Synchronous lymphoma and metastatic carcinoma with collision in the liver can be occasionally seen on a liver biopsy. Keeping in mind of these entities [**Table 23.1**] will help liver pathologists interpret the liver biopsy.

Table 23.1: Hematological and lymphoproliferative disorders of the liver.

B cell lymphoma
1. Diffuse large B cell lymphoma (DLBCL)
2. Extranodal marginal zone lymphoma
3. Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL)
4. Hairy cell leukemia
5. Post-transplant lymphoproliferative disorders (PTLDs)
6. T-cell/histiocyte rich large B cell lymphoma
Hodgkin Lymphoma
T cell lymphoma
1. Hepatosplenic T cell lymphoma
2. NK/T cell lymphoma (NK-TCL)
3. Peripheral T-cell lymphoma (PTCL)
4. Anaplastic large cell lymphoma (ALCL)
Others
1. EBV+ inflammatory follicular dendritic cell sarcoma
2. Mastocytosis
3. Histiocytic sarcoma
4. Langerhans cell histiocytosis
5. Myeloid sarcoma
6. Plasma cell neoplasm
7. Collision tumor of lymphoma and metastatic carcinoma in the liver

1. Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a diffuse neoplastic proliferation of large B lymphocytes lacking features of other defined types of large B-cell lymphoma.[12] DLBCL is the most common subtype of PHL, accounting for 46% to 96% of cases.[13-16] It usually occurs in older patients (mean age 64 years; range: 55–73) and is often associated with chronic viral infection (i.e., HBV, HCV, HIV, or EBV) and immunosuppression.[12] Patients with immunodeficiency are more prone to develop DLBCL, and the tumor may be EBV-positive, in which case the classification should change to EBV-positive DLBCL NOS.[12] Most cases clinically and radiographically present as solitary nodule (**Fig. 23.1**) or multiple discrete nodules (**Fig. 23.2**). Some patients may even present with acute liver failure.

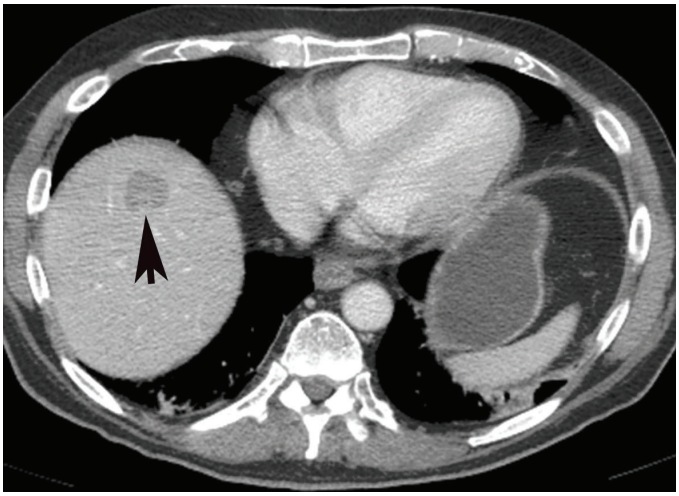

Fig 23.1 CT scans (Axial) of liver diffuse large B cell lymphoma in a patient clinically suspicious for metastatic carcinoma. This patient is a 71 year-old male with history of Merkel cell carcinoma showing a 2.6 cm hypodense nodule (arrow) within the right hepatic lobe at the dome (DLBCL histology in Figs 23.3 and 23.4 and immunostains in Fig 23.8.

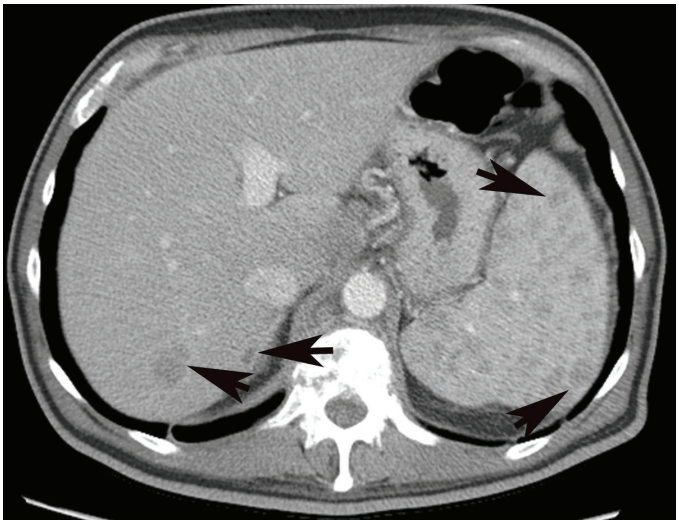

Fig 23.2 CT scan (Axial) of liver diffuse large B cell lymphoma in a 66 year-old male patient with history of high grade prostate carcinoma showing numerous nodules in the liver and spleen (arrows) (DLBCL histology in Fig 23.5 and immunostains in Fig 23.9).

Histopathology: Liver biopsy shows diffuse infiltrate of large lymphoid cells effacing the hepatic parenchyma (**Figs. 23.3 and 23.4**) or sinusoidal infiltrates of large atypical lymphoid cells (**Fig. 23.5**). The tumor cells have a high Ki-67 proliferation index (generally >40%) and should express one or more B-cell markers (CD19, CD20, CD79a, PAX5, or surface/cytoplasmic immunoglobulin). DLBCL can mimic active hepatitis histologically, with subtle portal, periportal, or sinusoidal infiltration (**Figs. 23.6 and 23.7**).[12,13] DLBCL must be subclassified into a germinal center B-cell type (GCB) or activated/non-germinal center B-cell type (ABC or non-GC) category, typically by using a panel of CD10, BCL6, and MUM-1 immunostains, because this designation may affect therapy. GCB DLBCLs are more often positive for CD10 (**Fig. 23.8**), GCET1, and LMO2, whereas the ABC type is generally strongly positive for MUM1 (IRF4) (**Fig. 23.9**) and FOXP1. Strong BCL6 positivity (>30%) with weak or negative MUM1 staining favors a GCB subtype. All other cases are considered non-GC type. The presence of EBV may not be hinted morphologically or apparent clinically and requires in situ hybridization for EBV-encoded small RNA (EBER) [17]. Classification as double-hit (or triple-hit) lymphoma (which most often occurs in GCB-type DLBCL) requires fluorescence ISH testing for *MYC*, *BCL2,* and *BCL6* rearrangements. It is also important to perform an immunostain for CD30 for therapeutic purposes.

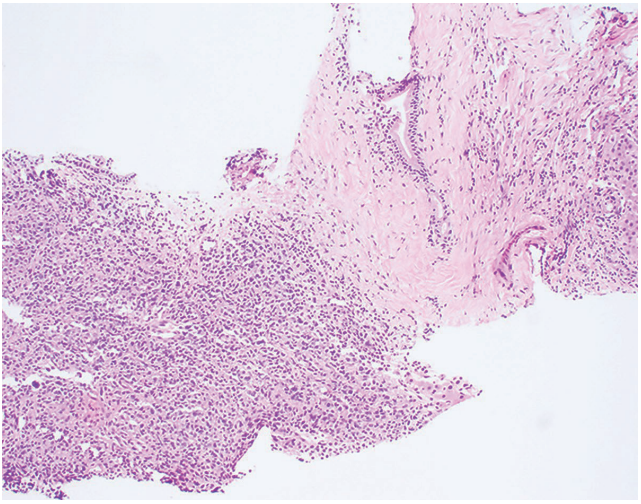

Fig 23.3 Primary hepatic DLBCL present in the patient in Fig 23.1. Liver biopsy showing large lymphoid cells effacing the hepatic parenchyma (H&E stain, 100x).

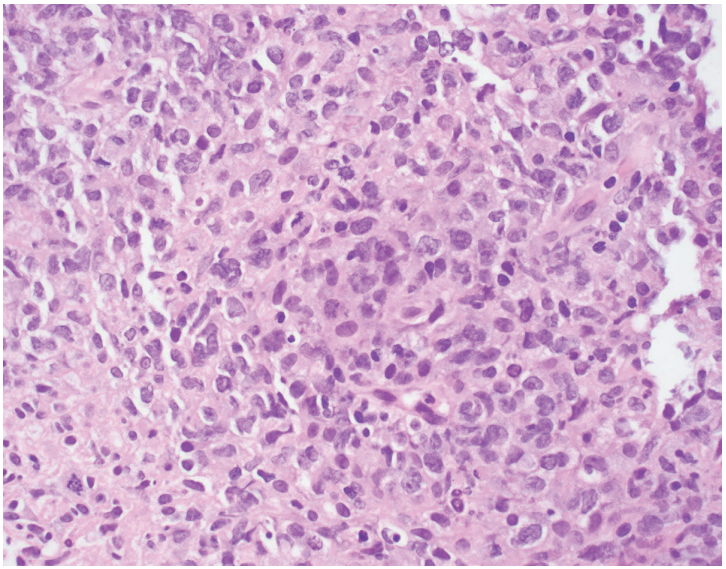

Fig 23.4 Liver biopsy of the patient of Fig 23.1 showing parenchyma and sinusoidal infiltration of DLBCL cells (H&E stain, 400x).

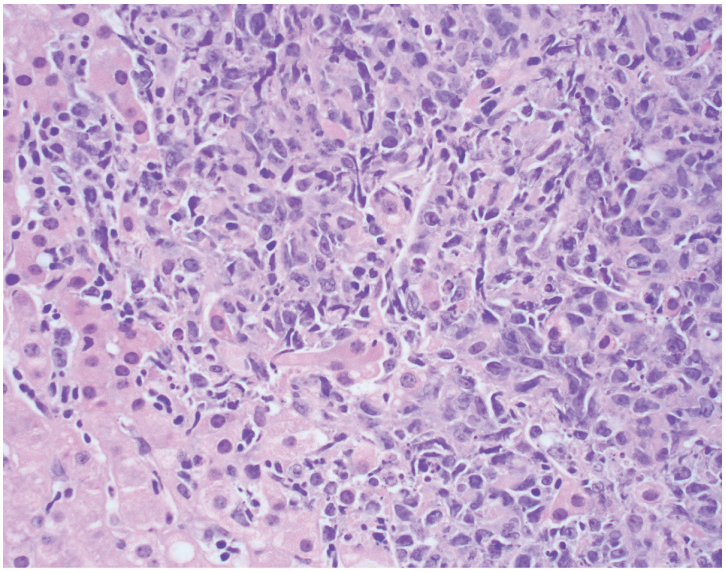

Fig 23.5 Liver biopsy of the patient of Fig 23.2 showing parenchyma and sinusoidal infiltration of DLBCL cells (H&E stain, 400x).

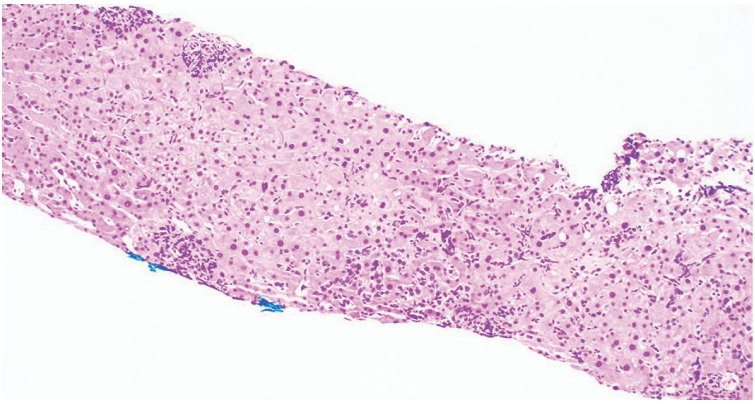

Fig 23.6 Liver biopsy of a 60-year-old male with unknown etiology of liver failure showing large B-cell lymphoma, with a predominantly sinusoidal infiltrating pattern (H&E stain, 100x).

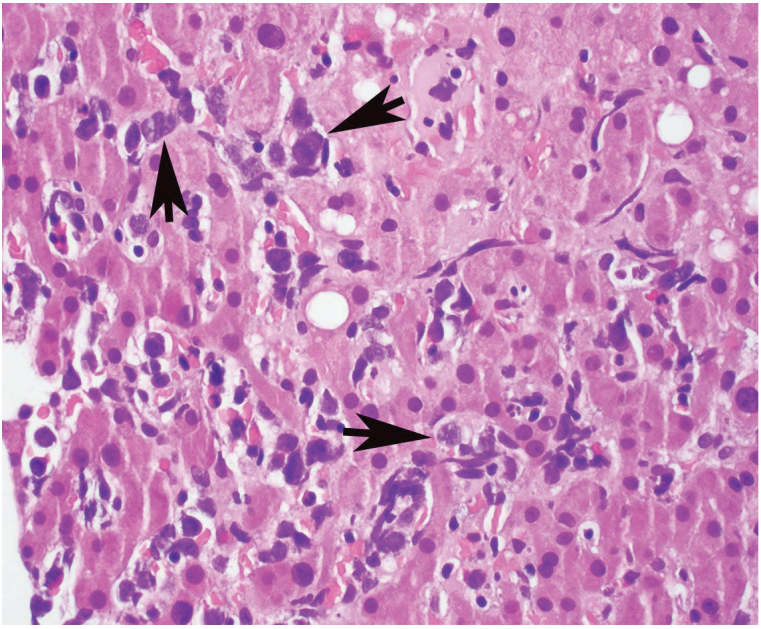

Fig 23.7 Liver biopsy of the 60-year-old male with unknown etiology of liver failure showing large B-cell lymphoma composed of atypical mononuclear cells (arrows) in a predominantly sinusoidal infiltrating pattern (H&E stain, 400x).

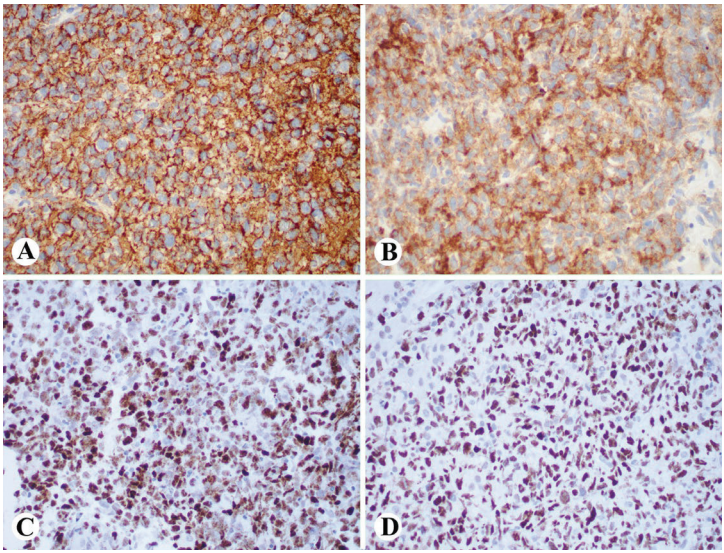

Fig 23.8 Immunostain of the tumor in the Fig 23.1 showing GCB type of DLBCL. The tumor cells are positive for CD20 (A), CD10 (B), BCL-6 (C) and Myc (D) (A-D, 400x).

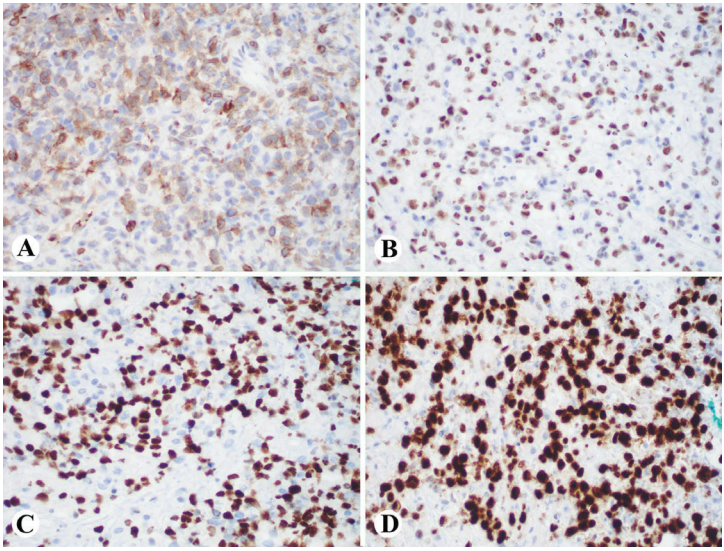

Fig 23.9 Immunostain of the tumor in the Fig 23.2 showing ABC type of DLBCL. The tumor cells are positive for BCL-2 (A), BCL-6 (B), Mum1 (C) and Myc (D) (A-D, 400x).

Prognosis and prediction: Primary hepatic DLBCLs generally are prognostically more favorable than nodal equivalents. Overall, about 65% the primary hepatic DLBCLs are ABC type. The ABC DLBCL subtype has worse prognosis than the GCB subtype.[12] Many other markers have been reported to be predictive of survival. These include *MYC* translocation,[18] CD5 expression[19], CD30 expression (excluding EBV-positive cases) [20], double MYC/BCL2 expression status [21] and EBV positivity.[22]

2. Extranodal marginal zone lymphoma

Primary hepatic marginal zone lymphoma is the second most common subtype of PHL .[13, 16, 23, 24] Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) involving the liver is an extranodal low-grade B-cell lymphoma recapitulating the cytoarchitectural features of MALT. It is composed of small lymphoid cells, often including marginal zone cells. Primary hepatic MALT lymphoma tends to form solitary or multiple nodules in older patients (mean age 62 years; range: 36–85).[13,24] Chronic viral infection or inflammatory liver disease seems to contribute to its pathogenesis, because several MALT lymphoma cases have been reported in association with chronic HBV, HCV, and PBC.[24, 25]

Histopathology: Liver biopsy from the lesion shows dense monotonous portal infiltrates surrounding reactive B-cell follicles with occasional infiltration of interlobular bile duct epithelium (lymphoepithelial lesions) (**Fig. 23.10**). Tumor cells are mainly small, with slightly irregular nuclear contour, dense chromatin, and scant cytoplasm, without evidence of germinal center differentiation (**Fig. 23.11**). Monocytoid cells, scattered immunoblasts and centroblast-like cells [26] could be present. Rarely, it can efface large portions of hepatic parenchyma. The neoplastic B-cells aberrantly coexpress CD43 in a subset of MALT lymphomas. In the setting of plasmacytic differentiation, which can be extreme, in situ hybridization or immunostaining for immunoglobulin kappa and lambda light chains can establish the presence of a monotypic cell population and support a diagnosis of lymphoma (**Fig. 23.12**). Genetic alteration of t(14;18)(q32;q21) IGH-MALT1 can be seen in 0 - 67% of the patients, t(3;14)(p14;q32) IGH-FOXP1, trisomy 3 and trisomy 18 could be seen in some patients.[26]

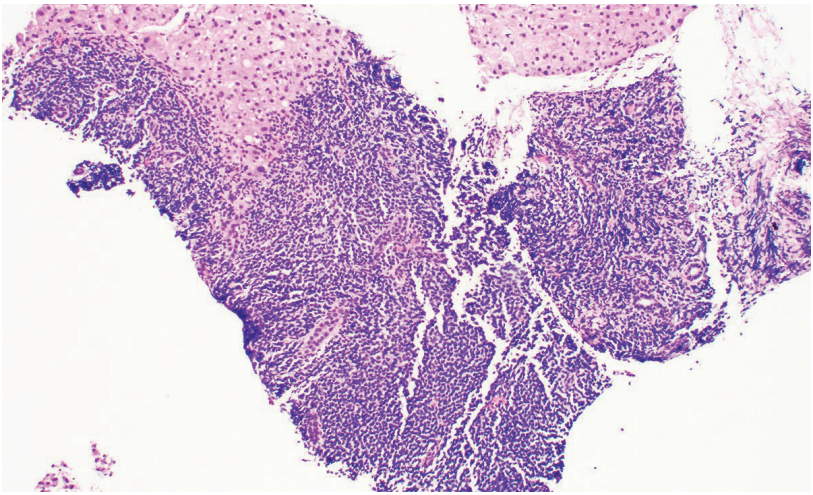

Fig 23.10 Extranodal marginal zone lymphoma. Liver biopsy showing portal infiltrates by dense monotonous small lymphoid cells (H&E, A, 100x).

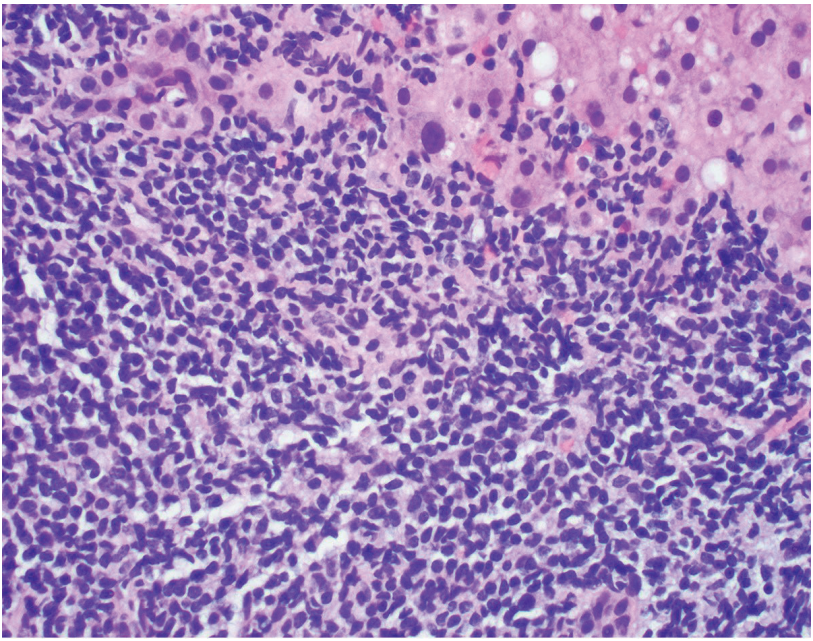

Fig 23.11 Extranodal marginal zone lymphoma. Liver biopsy showing portal infiltrates by dense monotonous small lymphoid cells (H&E, 400x).

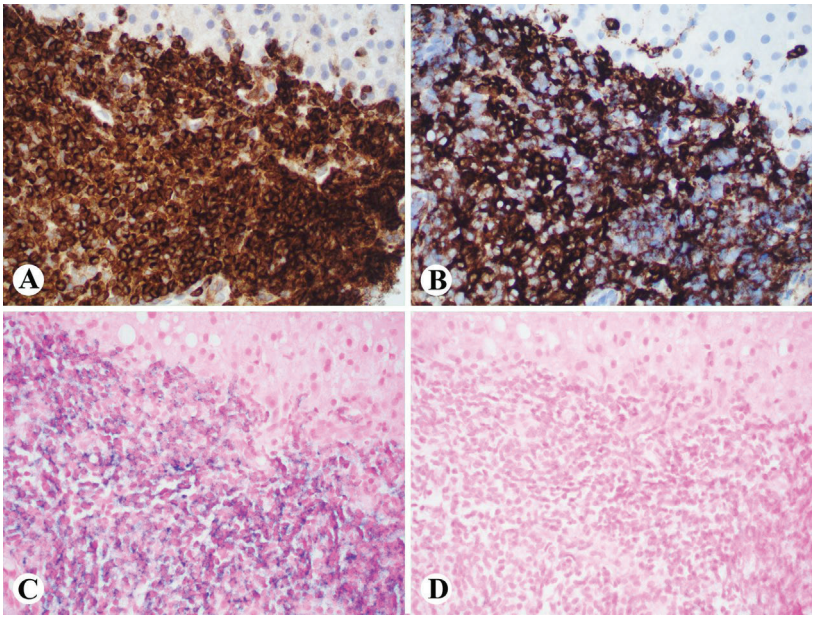

Fig 23.12 Immunostains and *in situ* hybridization of extranodal marginal zone lymphoma. The tumor cells are positive for CD20 (A), CD43 (B), and Kappa (C) and negative for Lambda (D) in situ hybridization. (A-D, 400x).

Prognosis and prediction: Primary hepatic MALT lymphomas have an indolent clinical course and are slow to disseminate. MALT lymphomas are sensitive to radiotherapy, and local treatment can lead to prolonged disease-free survivals.[26]

3. Post-transplant lymphoproliferative disorders (PTLDs)

PTLDs are characterized by abnormal, heterogeneous lymphoid proliferations (usually of B-cell origin and EBV-positive) that occur in the setting of iatrogenic immunosuppression to prevent rejection of transplanted solid organs or graft versus host disease (GVHD) following hematopoietic stem cell transplantation (HSCT). More than 20% of liver transplant PTLDs occur in the allograft.[27] Most PTLDs related to HSCT are of donor origin, whereas most PTLDs related to solid organ transplantation are of recipient origin. Symptoms of the patients are often nonspecific with fever, elevated liver function and graft dysfunction (in liver transplant patients). About 60-80% of the PTLDs are EBV-positive and arise as a result of impaired

immunity due to therapeutic immunosuppression, resulting in reactivation of a latent EBV infection or a poor response to a new EBV infection. The etiology of EBV-negative PTLDs is unknown.[28]

Histopathology: The liver PTLDs could include polymorphic PTLD (P-PTLD) and monomorphic PTLD (M-PTLD) and the histologic features and immunoprofile may vary. In the P-PTLD, the liver biopsy shows polyclonal B cells admixed with T cells. In M-PTLD, the liver biopsy shows morphology of lymphoma of clonal B cell (most often), T cell or plasma cell lineages. EBER *in situ* hybridization is almost always positive (**Fig. 23.13**). However, many late-onset B-cell PTLDs and most T-cell PTLDs are negative for EBER *in situ* hybridization.

Prognosis and prediction: The survival rate has been poor (30–60%),[29] but recent data suggest improving outcomes. Poor prognostic factors include late onset, M-PTLD, central nervous system (CNS) involvement, thoracic organ transplantation, elevated lactate dehydrogenase (LDH), and disseminated disease.[30, 31]

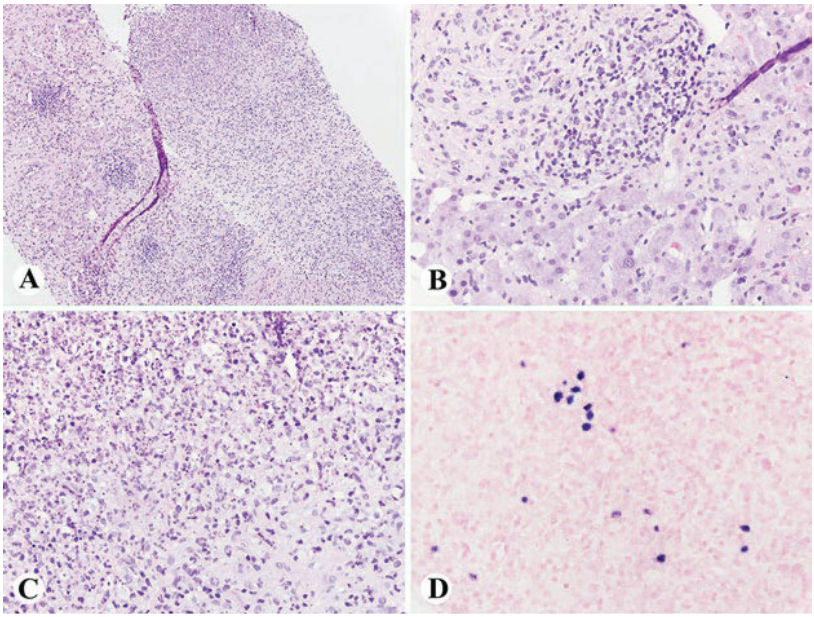

Fig 23.13 Polymorphic PTLD. A-C, histologically, the liver biopsy showing hepatic parenchyma with necrotic inflammatory infiltrate; D, EBER in situ hybridization showing EBER positive B cells (A, 100x, C-D, 400x).

4. Small lymphocytic lymphoma /chronic lymphocytic leukemia (SLL/CLL)

SLL/CLL usually presents in leukemic phase with secondary involvement of the liver. Although sinusoidal infiltration can occur, SLL/CLL usually manifests as prominent and monotonous appearing portal lymphocytic infiltrates (**Fig. 23.14**). Tumor cells are small with round nuclear contours and express CD5 and CD23, in addition to typical B-cell markers (CD19, CD20, CD79a and PAX-5) (**Fig. 23.15**). Cyclin D1 and SOX-11 stains are negative and should be performed to exclude mantle cell lymphoma (MCL). To differentiate SLL/CLL from other small cell B cell lymphomas, a panel of immunostains including CD20, PAX-5, CD3, CD5, CD10, CD23, Cyclin D1, and BCLl-2, and Kappa and Lambda *in situ* hybridization could be performed. In addition, LEF1 expression is relatively specific for CLL/SLL. Although majority of SLL/CLL cases are indolent, some cases may result in fulminant acute liver failure due to extensive parenchymal infiltration.[13]

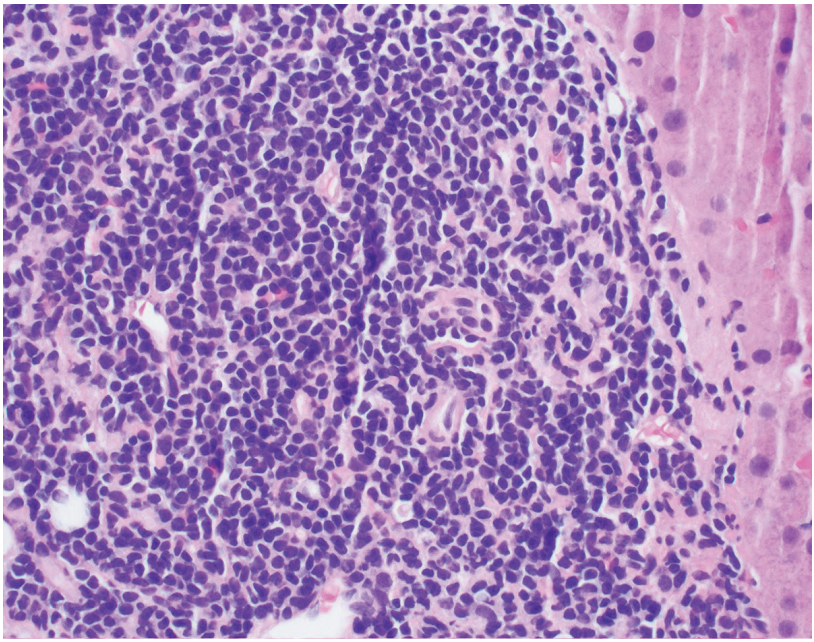

Fig 23.14 Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). The liver biopsy showing monotonous portal lymphocytic infiltrates (H&E stain, 400x).

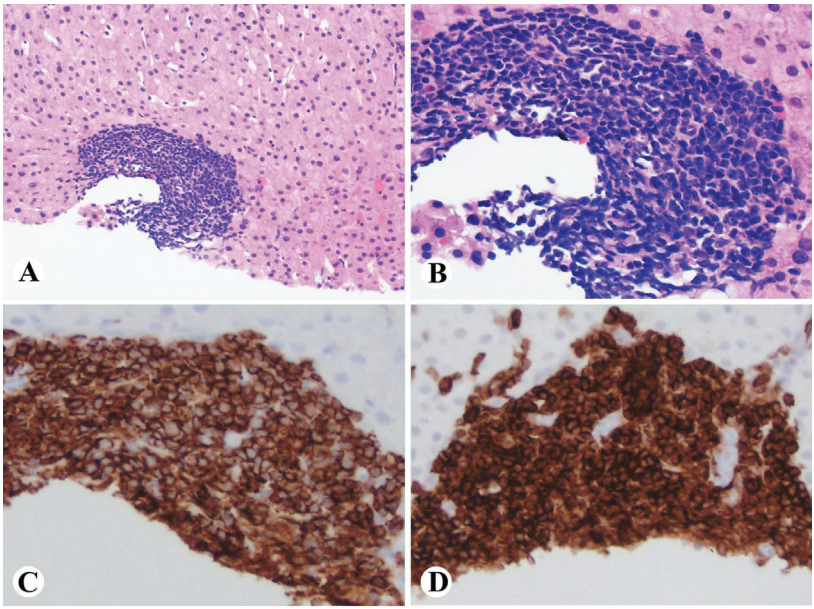

Fig 23.15 Another case of liver biopsy showing SLL/CLL. A-B, Dense monotonous small lymphoid cells present in the portal tract (H&E, A, 100x; B, 400x); C-D, CD20 (C) and CD5 (D) immunohistochemical reactivity highlighting the SLL/CLL cells (C-D, 400x).

5. Hairy cell leukemia (HCL)

HCL is an indolent neoplasm of small B-cells that predominantly affects middle aged to old males. Patients usually present with hepatosplenomegaly. Similar to CLL/SLL, HCL usually involves the liver as a leukemia, in the form of portal and sinusoidal infiltration (**Fig. 23.16A**). It can rarely form discrete nodules, however, the tumor cells are small to medium in size with abundant cytoplasm surrounding oval to indented nuclei (**Fig. 23.16B**). They are positive for the B cell markers and CD25 (**Fig. 23.16C**) and Annexin (**Fig. 23.16D**), usually negative for both CD10 and CD5. Flow cytometric evaluation (to include CD25, CD11c, and CD103) can be helpful for diagnosis. *BRAF* V600E or *MAP2K1* mutations are identified by both molecular methods and immunostains in most cases.[13]

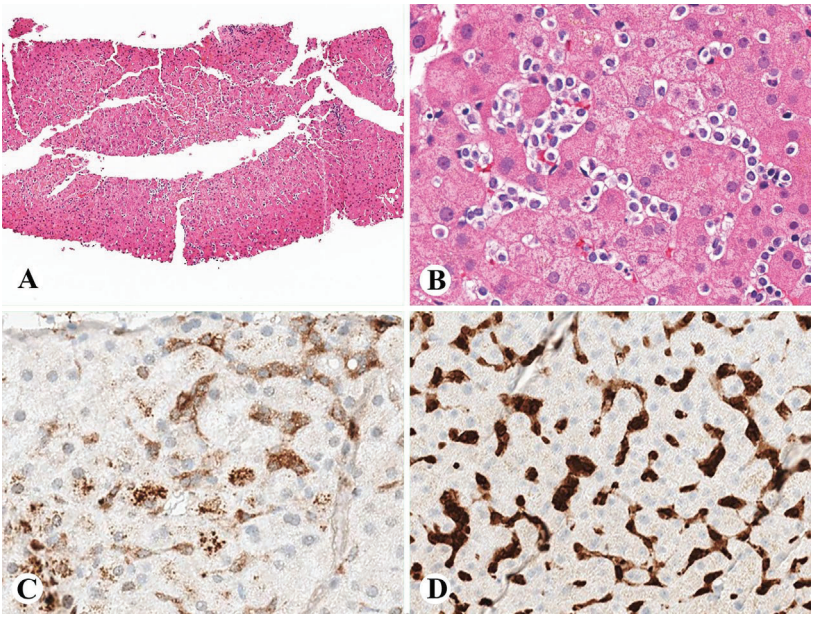

Fig 23.16 Liver involved by Hairy cell leukemia. A-B, Histologically, the liver biopsy showing predominant sinusoidal infiltrates of small to medium sized neoplastic cells; C-D, immunohistologically, the neoplastic cells are positive for CD25 (C) and Annexin (D) (A, 40x, B-D, originally 400x) (Courtesy of Dr. Yanxia Li, Midwest Diagnostic Pathology).

6. T-cell/histiocyte rich large B cell lymphoma

T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is traditionally considered as an aggressive B-cell lymphoma and was first included as a separate entity in the 2008 World Health Organization (WHO) classification.[32] In previous times THRLBCL represented a variant of DLBCL and the diagnostic criteria were only loosely defined. It is not surprising that cases of ordinary DLBCL with a T-cell-rich microenvironment were included in this category as well as cases of classical Hodgkin lymphoma (CHL) with aberrant CD20 expression. Keeping this in mind, it is even more surprising that the clinical presentation of THRLBCL is rather homogenous, usually affecting middle-aged male patients, presenting with advanced stage disease with frequent involvement of spleen and liver. THRLBCL exhibits many features that are similar to nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), indicating a

close relationship with regard to pathogenesis. NLPHL is an unusual subtype of Hodgkin lymphoma characterized by a distinct histopathological and clinical presentation. It mostly affects males and presents with localized disease and an indolent clinical course in the majority of cases. However, there are also patients with advanced NLPHL who frequently present with spleen and liver involvement, B-symptoms and a more aggressive clinical course. Different clinical presentations correlate with distinct histopathological characteristics.[32]

The histology of THRLBCL shows single scattered large blasts, which can have popcorn-like, but also centroblast-like or Hodgkin–Reed–Sternberg (HRS)-like nuclei. These blasts are found in an extensive background of histiocytes, which can have an epithelioid character admixed with reactive T-cells. Usually there are no to very few reactive naïve B cells in the microenvironment, which can be highlighted by IgD-immunostaining, since the tumor cells of THRLBCL are IgD-negative in most cases.[32]

Expression of most of the differentially expressed genes (*BAT3*, *HIGD1A*, *FAT10* and *CXCL13*) could be demonstrated in the tumor cells of NLPHL, THRLBCL-like NLPHL and THRLBCL, in varying number and intensity, indicating great similarity in the tumor cells of these lymphomas. It has also been observed that patients initially presenting with NLPHL show a picture of THRLBCL at relapse and vice versa.[32]

7. Classic Hodgkin lymphoma

Hodgkin lymphomas are divided into classical Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma. Although most Hodgkin lymphomas that arise in the liver are CHL, hepatic involvement by CHL is still uncommon and only rare cases of primary CHL have been reported. CHL usually forms discrete nodules with variable numbers of Hodgkin/Reed-Sternberg (HRS) cells in a background of mixed inflammatory cells (**Fig. 23.17**), often involving or surrounding portal tracts. CHL can rarely present as acute liver failure with extensive hepatic involvement. Although CHL is of B-cell origin, most B-cell markers (including CD20) are negative. One B-cell antigen consistently expressed by the malignant cells in CHL is PAX-5, although the staining can be weak and focal. The HRS cells are also positive for CD15 and CD30 in most cases (**Fig. 23.18**), sometimes with Golgi accentuation, and MUM-1 is also usually positive. Although some large B-cell non-Hodgkin lymphomas (NHLs) and anaplastic large cell lymphoma (ALCL) can mimic CHL, both morphologically and immunohistochemically, large B-cell NHLs are

positive for multiple B-cell markers, and ALCL does not express PAX-5.[13] EBER in situ hybridization could be positive in some CHL cases (**Fig. 23.18D**).

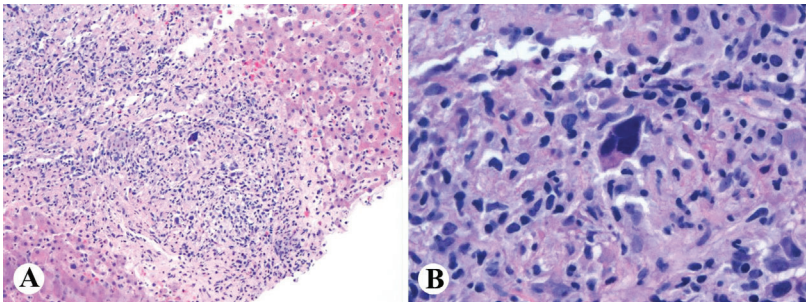

Fig 23.17 Liver involved by classical Hodgkin lymphoma. Histologically, Reed-Sternberg cells mixed with inflammatory cells present in the sinusoids and portal tracts (H&E, A, 100x; B, 400x) (Courtesy of Dr. Sharon Zhang, Clovis Medical Center).

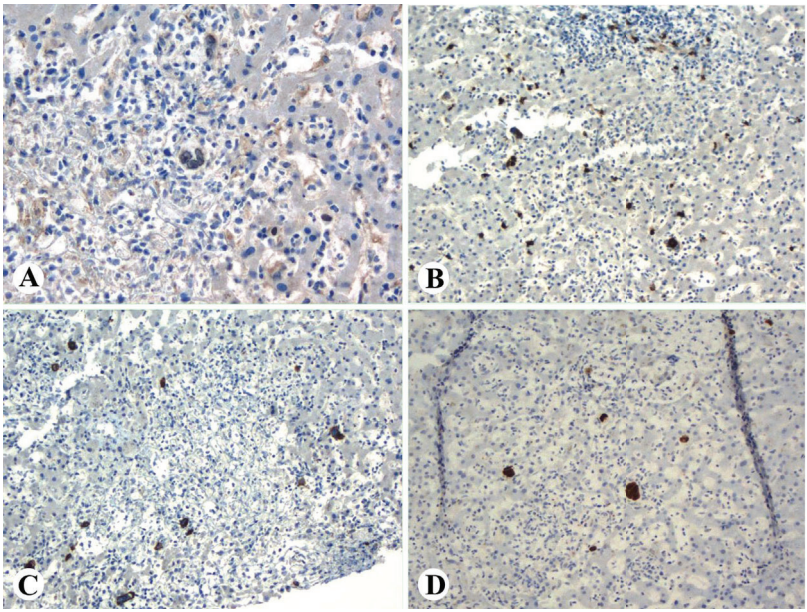

Fig 23.18 CHL immunostains and in situ hybridization: The Reed-Sternberg cells are positive for PAX5 (A), CD15 (B), CD30 (C) and EBER in situ hybridization (D) (A-D, 400x) (Courtesy of Dr. Sharon Zhang, Clovis Medical Center).

Due to frequent involvement of the portal tracts and surrounding the ducts, CHL can cause ductopenia or rarely vanishing ductal syndrome as a paraneoplastic phenomenon.

8. Hepatosplenic T-cell lymphoma (HSTCL)

HSTCL is an aggressive extranodal lymphoma characterized by a proliferation of cytotoxic T cells, usually γδ T cells, with a hepatosplenic presentation and no lymphadenopathy.[33] HSTCL usually occurs in young patients with a male predominance and presents with nonspecific systemic symptoms and hepatosplenomegaly. Patients usually manifest marked thrombocytopenia, often with anemia and leukopenia. As many as 20% of HSTCLs arise in the setting of chronic immune suppression, most commonly long-term immunosuppressive therapy for solid-organ transplantation or prolonged antigenic stimulation. A number of cases have been reported in patients, especially children, with immune disorders (including Crohn's disease, rheumatoid arthritis, and psoriasis) treated with azathioprine or mercaptopurine, often in combination with tumor necrosis factor (TNF) alpha inhibitors.[34]

Histopathology: The hallmark of liver involvement is marked sinusoidal dilatation by medium-sized malignant cells (often with 3 or 4 cells piling up) (**Fig. 23.19A**). Usually, there is little to no infiltration in portal tracts. In rare cases, a cytologically bland infiltrate can predominantly, or exclusively, involve portal tracts. The tumor cells have small inconspicuous nucleoli, and a rim of pale cytoplasm. Some degree of pleomorphism may occasionally be seen. The neoplastic cells are CD3+, CD5−, CD4−, CD8−/+, and usually TCRγδ+ and TCRαβ−. A minority of tumors are of TCRαβ type. The tumor cells express T-cell intracellular antigen 1 (TIA1) but are usually negative for granzyme B (**Fig. 23.19**) and perforin. Therefore, the cells appear to be mature, non-activated cytotoxic T cells with phenotypic aberrancy. CD56 immunostain may be positive in neoplastic cells, but EBV-encoded small RNA (EBER) ISH stain is most often negative. The lack of EBV and granzyme B staining is useful in distinguishing HSTCL from aggressive natural killer (NK)-cell leukemia/lymphoma.

In challenging cases, molecular and cytogenetic testing can be helpful, because HSTCL shows a recurrent cytogenetic abnormality (isochromosome arm 7q10 and, possibly, trisomy 8) and clonal T-cell receptor (TCR) gene rearrangement.[33]

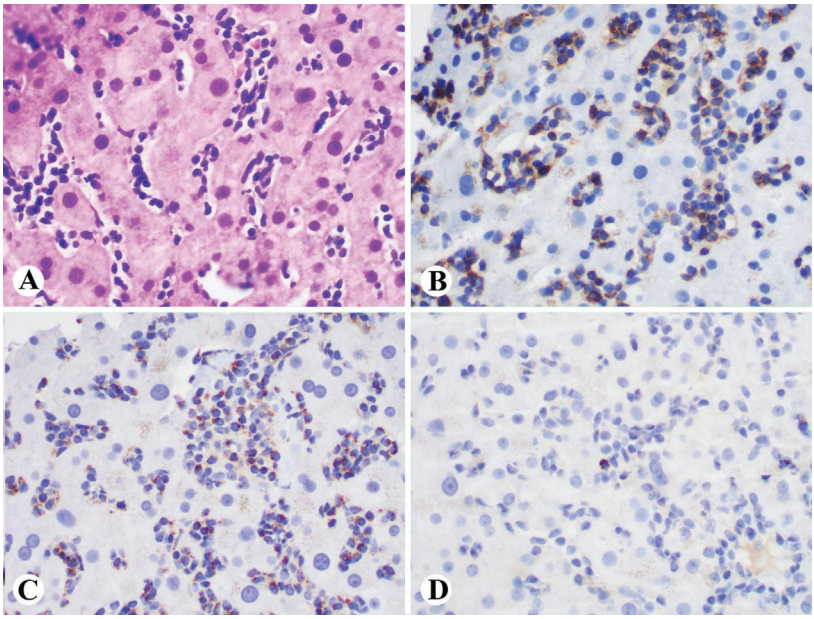

Fig 23.19 Hepatosplenic T-cell lymphoma. A, Liver biopsy showing sinusoidal dilatation with infiltration of medium-sized neoplastic cells (H&E stain); B-D, Immunohistochemically, the neoplastic cells are positive for CD3 (B) and TIA (C), and negative for Granzyme B (D). (A-D, 400x).

Prognosis and prediction: The disease is aggressive. Patients with HSTCL may initially respond to chemotherapy, but relapses are common. The median survival time is < 2 years. Platinum-cytarabine and pentostatin have been shown to be effective agents. Early use of high dose therapy followed by allogeneic HSCT may improve survival.[35,36]

9. A. Extranodal NK/T-cell lymphoma (ENKTL)

ENKTL is a neoplasm of NK cells or cytotoxic T cells characterized by extranodal occurrence, frequent presence of angioinvasion, and association with EBV infection. ENKTL of nasal type (ENKTL-NT) is uncommon in Europe and North America but is more prevalent in eastern Asian countries and among indigenous peoples of Central and South America. The liver may be involved in disseminated ENKTL-NT.[37,38]

Histopathology: Lymphoma cells infiltrate diffusely and frequently show an angiocentric and angiodestructive pattern. Coagulative necrosis and admixed apoptotic bodies are usually present. The cells tend to be medium in size and have irregular nuclei with pale to clear cytoplasm, but they can be small or large (**Fig. 23.20A**). ENKTL-NT is typically positive for CD2, cytoplasmic CD3, CD56, cytotoxic molecules (TIA1, granzyme B, and perforin) (**Fig. 23.20**), and EBV-encoded small RNA (EBER). ENKTL-NT is variably positive for CD7 but not for surface CD3, CD4, CD5, CD8, CD16, or CD57. Cases positive for surface CD3, CD5, CD8, and/or T-cell receptor constitute a T-cell subset of ENKTL-NT.

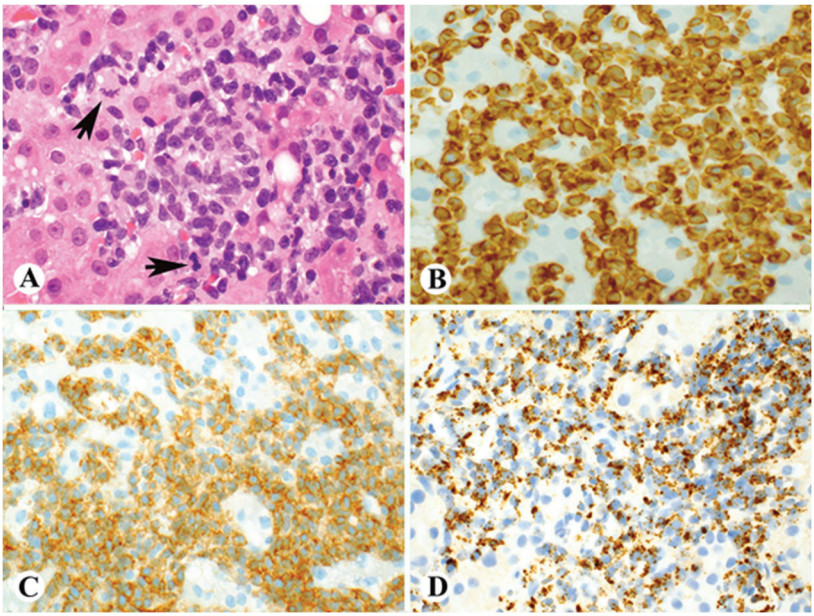

Fig 23.20 Extranodal NK/T cell lymphoma. A, histologically, liver biopsy showing parenchymal infiltrates of atypical lymphoid cells with pale cytoplasm which are medium in size and have irregular nuclei and brisk mitotic activity (arrows) (H&E stain); B-D, Immunohistochemically, the tumor cells are positive for CD3 (cytoplasmic) (B), CD56 (C) and TIA (D). (A-D, 400x). (Courtesy of Dr. Li Juan Wang, Brown University).

Prognosis and prediction: ENKTL-NT involving the liver has a dismal prognosis despite chemotherapy. Poor prognostic factors include high International Prognostic Index (IPI), high NK/T-cell lymphoma prognostic index, and high EBV viral load in peripheral blood.[13,37]

9. B. Chronic active EBV hepatitis in NK/T cells may mimic NK/T cell lymphoma

In the infectious mononucleosis associated EBV hepatitis, EBV typically infects B-cells through the EBV receptor (CD21). A liver biopsy most commonly shows a mild sinusoidal lymphohistiocytic infiltrate with only rare EBV-positive B-cells, which are best demonstrated by comparing a PAX-5 or CD20 immunostain with an EBV *in situ* hybridization.

Diagnosis of EBV-associated hepatitis, chronic active EBV infection, and EBV-associated lymphoproliferative diseases, is always challenging due to the overlapping symptoms and lack of diagnostic criteria. Recently we reported such a case of a 40-year-old man with unremarkable past medical history except mild EBV infection 2 years ago. He presented with fever of unknown origin for one month with jaundice for two days. Physical exams were unremarkable. His liver function tests were elevated with alanine transaminase (ALT) 559 U/L, aspartate transaminase (AST) 892 U/L, alkaline phosphatase 319 U/L and total bilirubin 4.4 mg/dL. Computer tomography of his chest, abdomen and pelvis did not show lymphadenopathy or hepatosplenomegaly. A liver biopsy showed moderately acute hepatitis with hemophagocytosis, EBV infected CD3 and CD4 positive T cells and CD56 positive natural killer (NK) cells (**Fig. 23.21**). CD20 was negative with appropriate control. The pathology diagnosis was consistent with reactivation of EBV hepatitis/chronic active EBV (CAEBV) infection but NK cell lymphoma needs to be excluded. Mild steatohepatitis was also present. His blood EBV DNA was 846,000 copies/mL at the time of liver biopsy and continued to increase to 2,000,000 copies/mL. Flow cytometric analysis of his bone marrow revealed an increased NK cell activity but no T/NK cell lymphoma was identified. Initial treatment with Rituxan, etoposide, and/or ruxolitimab/acyclovir failed or only had limited effect. However, subsequent valganciclovir greatly improved his conditions. In his three months follow up, the patient was doing well with almost normal liver function tests except mildly elevated ALT (95 IU/L) that was due to mild steatohepatitis. EBV DNA PCR was down to 2009 copies/mL.[39]

This case highlights that a histologic interpretation of NK/T cell infiltrate in the liver should be in the context of clinical setting as the differential diagnosis includes CAEBV vs EBV-associated lymphoproliferative disorders, two entities with quite different prognosis. However, during the disease course, CAEBV can lead to two lethal conditions: hemophagocytic lymphohistiocytosis and chemotherapy-resistant lymphoma. Clinical

follow up is recommended and it may be necessary to start treatment before these conditions develop in some cases.[40]

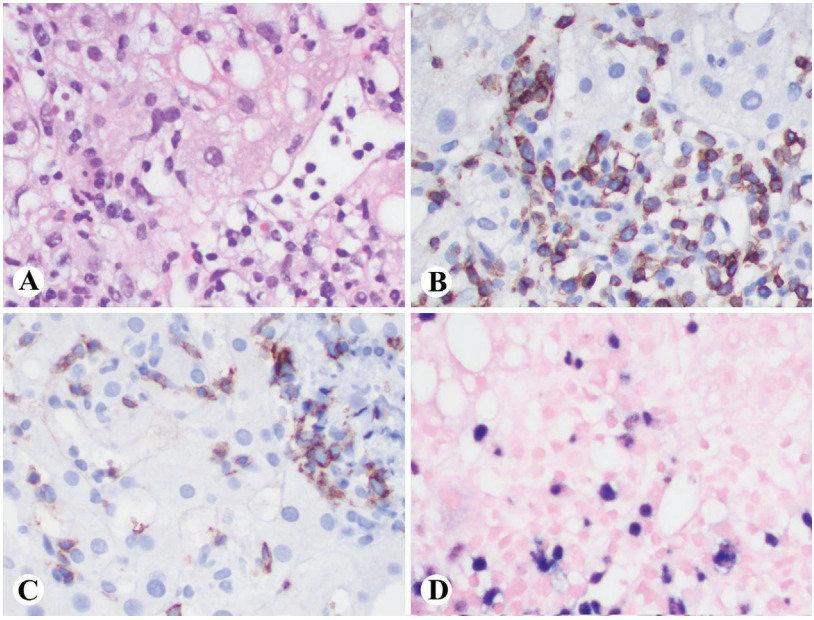

Fig 23.21 Chronic active EBV hepatitis in NK/T cells in a patient with history of mild EBV infection 2 years ago. A, histologically, the liver biopsy showing moderately active hepatitis with confluent lobular inflammation and sinusoidal lymphocytosis (H&E stain); B-C, Immunohistochemically, the inflammatory cells are positive for CD3 (B) and CD56 (C), negative for CD20 (data not shown); D, EBER *in situ* hybridization highlights some of the inflammatory cells. (A-D, 400x). (Flow cytometry negative for lymphoma).

10. Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

Primary hepatic peripheral T-cell lymphoma (PTCL) is exceedingly rare.[41] PTCL, NOS usually occurs in middle-aged men with or without discrete lesions. Malignant lymphoid infiltrate morphology varies from bland small lymphoid cells which may mimic hepatitis, to a mixture of small to large cells, to diffuse sheets of large cells. PTCL, NOS may completely obliterate the hepatic parenchyma (**Fig. 23.22**), but a liver biopsy may also show only scattered malignant T-cells in portal, periportal, and/or sinusoidal regions,

which can make diagnosis and immunophenotyping challenging. Gene rearrangement studies may be necessary to confirm the presence of a clonal T-cell population. Although EBV-associated lymphoproliferative disorders are mostly B-cell lymphomas, a rare case of primary hepatic PTCL associated with EBV infection has been reported.[41]

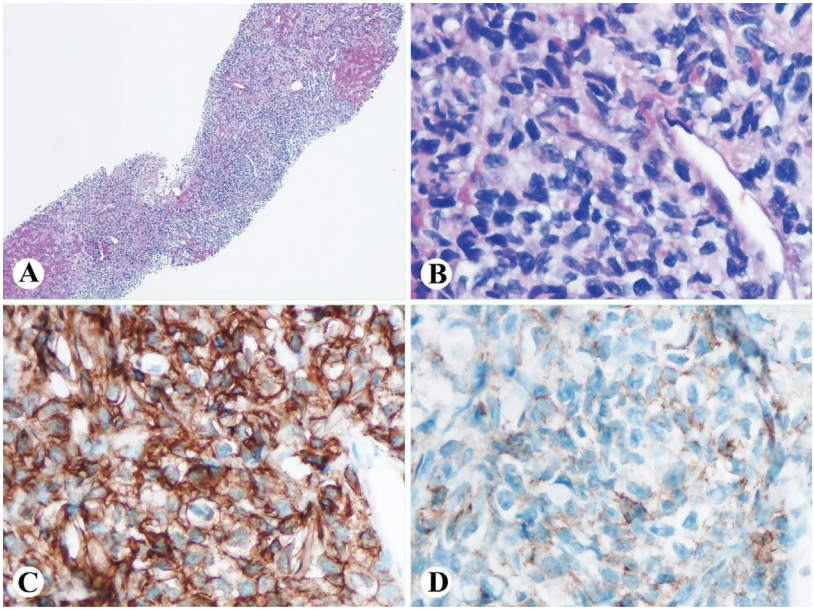

Fig 23.22 Liver peripheral T-cell lymphoma. A-B, Mass-forming atypical lymphoid cell infiltrates in the liver parenchyma (H&E stain, A, 100x; B, 400x); C-D, Immunoreactivity of the PTCL cells showing positive CD3 (C) and negative CD20 (D) (C-D, 400x).

11. Anaplastic large cell T –cell lymphoma (ALCL)

Anaplastic large cell T-cell lymphoma (ALCL) has a male predominance and four recently recognized genetic subcategories. The first subcategory is ALK-positive and characterized by ALK1 immunoreactivity that is corresponding to a rearrangement of the anaplastic lymphoma kinase (ALK) gene. The other three subcategories are ALK1 negative and include DUSP22-rearranged, TP63-rearranged and triple negative of ALK, DUSP22 or TP63 rearrangements. ALK-positive cases are most common in

younger patients (<30 years of age), whereas ALK-negative cases are seen in older patients (>40 years of age).[42]

Histopathology: Liver ALCL can show any of the three major growth patterns: mass lesion (most common) (**Fig. 23.23**), portal-based infiltrate, or sinusoidal infiltrate. Destructive appearance with areas of necrosis can be seen in the mass lesion. In most cases, the hallmark cells with striking cytological features including large size abundant cytoplasm and eccentrically located nuclei (horseshoe-shaped or wreath-like) can be seen (**Fig. 23.24**). In the immunoprofile, ALCL does not express all the pan-T-cell antigens. CD3 can be negative in about 50% of the cases, but CD2, CD3 and CD5 are the most helpful T-cell markers. About half of the cases are positive for CD4, and most of the cases are negative for CD8. The tumor cells are positive for ALK1 (ALK-positive cases), CD30 (**Fig. 23.25**), TIA-1, and Granzyme B. Nuclear and diffuse cytoplasmic staining for ALK1 is associated with t(2;5) (p23;q35), correlating with fusion of the *ALK* and *NPM* genes. Granular cytoplasmic ALK1 staining is associated with t(2;17) (p23:q23), correlating with fusion of the *ALK* and *CLTC* genes.[42]

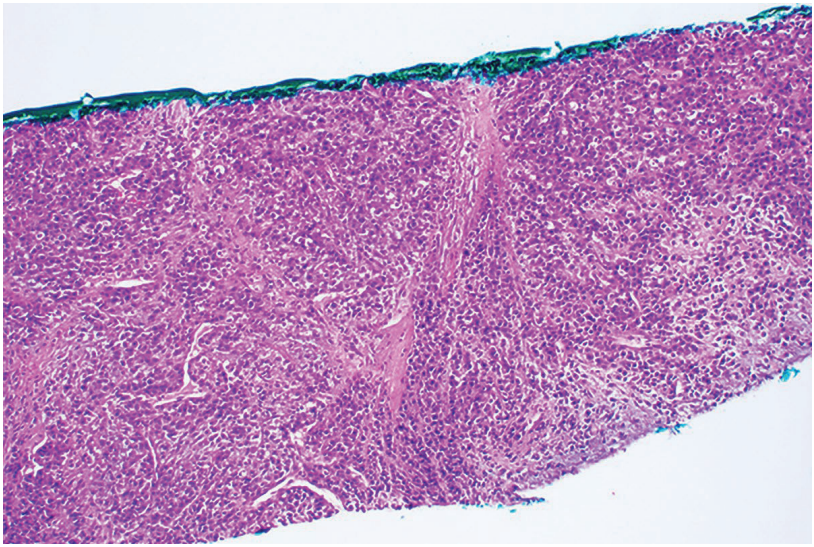

Fig 23.23 Liver anaplastic large cell T cell lymphoma (ALCL). Histologically, the liver biopsy shows mass-forming atypical epithelioid cells infiltrate (H&E stain, 100x).

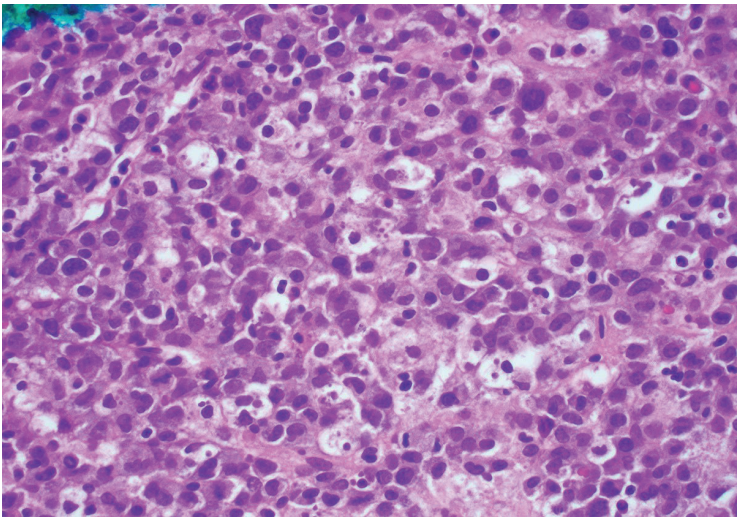

Fig 23.24 Liver anaplastic large cell T cell lymphoma (ALCL). High power view reveals that tumor cells contain abundant eosinophilic or clear cytoplasm, eccentric nuclei with some horseshoe shaped nuclei and abundant apoptoses (H&E stain, 400x).

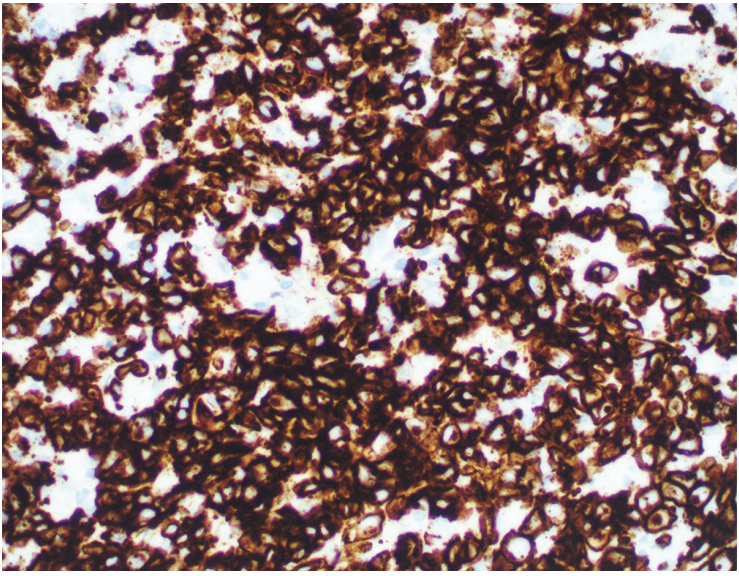

Fig 23.25 Liver anaplastic large cell T cell lymphoma (ALCL). The tumor cells are diffusely positive for CD30 on immunostain (400x).

Prognosis and prediction: ALCL cases with ALK and DUSP22 rearrangements have a favorable prognosis, the triple negative cases have an intermediate prognosis, and the TP63-rearraged cases tend to have a poor prognosis.[43]

12. EBV+ inflammatory follicular dendritic cell sarcoma

EBV-positive inflammatory follicular dendritic cell (FDC) sarcoma is a neoplasm of spindled FDCs with a rich lymphoplasmacytic infiltrate and a consistent association with EBV. It occurs predominantly in young to middle-aged Asian adults (mean age: 54.5 years), with a female predominance.[44] Patients are asymptomatic or present with abdominal discomfort, sometimes accompanied by constitutional symptoms such as malaise, weight loss, or low-grade fever.

Histopathology: The neoplastic spindled cells are inconspicuous or form loose whorled fascicles in the background of a prominent lymphoplasmacytic infiltrate (**Fig. 23.26**). The nuclei show vesicular chromatin and small distinct nucleoli. Nuclear atypia is highly variable, but at least some cells with overt atypia such as enlarged, irregularly folded or hyperchromatic nuclei are always found. Some tumor cells may even resemble Reed–Sternberg cells (**Fig. 23.27**). Necrosis and hemorrhage are often present and can be associated with histiocytic or granulomatous inflammation. In some cases, the tumor shows massive infiltration of eosinophils or numerous epithelioid granulomas. The blood vessels frequently show fibrinoid deposits in the vessel walls, a finding frequently seen in EBV-associated neoplasms. The neoplastic cells are often positive for FDC markers, but the staining can be focal, and application of a large panel of FDC markers, such as CD21, CD35, CD23 (**Fig. 23.28**), CXCL13, D2-40, CNA.42, and clusterin, may be required. Some cases may be negative for FDC markers but express actin, raising the possibility of fibroblastic reticular cell differentiation. EBV LMP1 protein expression is found in 70% of cases.

Prognosis and prediction: The tumor is indolent. Tumors occurring in the liver have a worse prognosis than those occurring in the spleen. Several series of this entity occurring in the liver revealed a tumor recurrence rate of 26% and a mortality rate of 6%.[44,45]

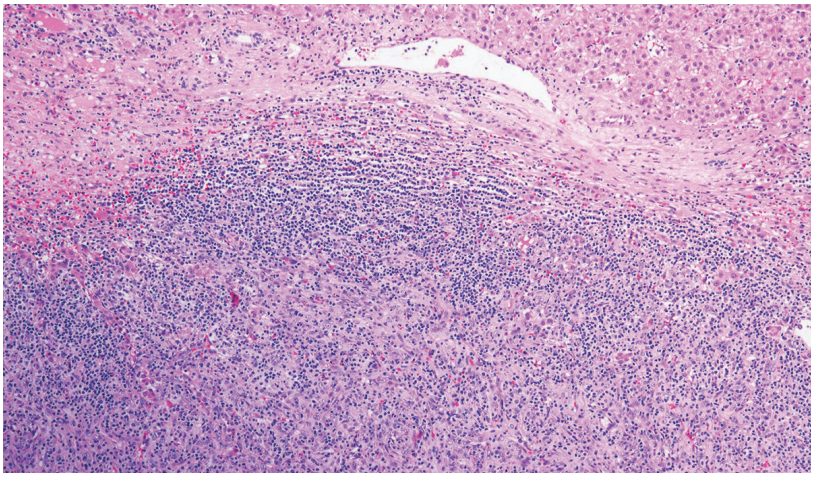

Fig 23.26 Histology of EBV positive inflammatory follicular dendritic cell sarcoma. Liver wedge biopsy shows mass-forming atypical neoplastic cells infiltrate within an inflammatory background. (H&E stain, A, 100x; B, 400x) (Courtesy of Dr. Jingping Yun, Cancer Center of Sun Yat-Sen University).

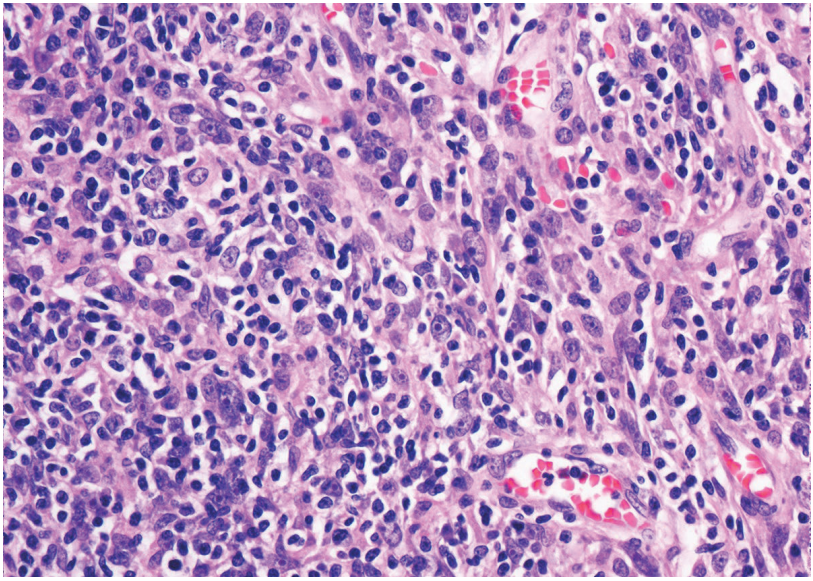

Fig 23.27 Histology of EBV positive inflammatory follicular dendritic cell sarcoma. High power view (H&E stain, 400x) (Courtesy of Dr. Jingping Yun, Cancer Center of Sun Yat-Sen University).

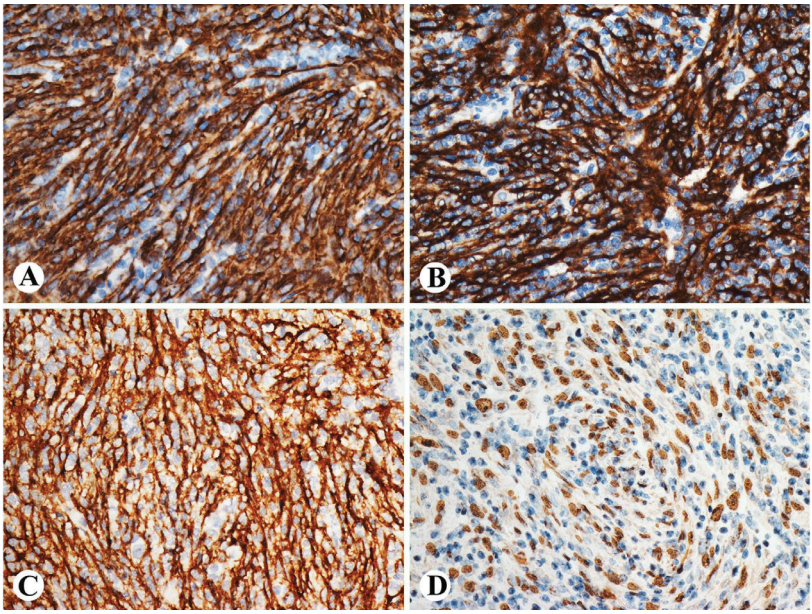

Fig 23.28 Immunostains of the liver lesion of Figs 23.26 and 23.27 demonstrating that the tumor cells are positive for CD21 (A), CD23 (B), CD35 (C) and EBER ISH stain (D) (A-D, 400x) (Courtesy of Dr. Jingping Yun, Cancer Center of Sun Yat-Sen University).

13. Systemic mastocytosis

Systemic mastocytosis is a neoplasm characterized by proliferation of clonally mutated (typically KIT-mutant) mast cells in various organs/tissues. Involvement of the liver in patients with systemic mastocytosis has also been reported.[46]

Histopathology: The main site of involvement of the liver is the portal triad. Mast cells may form subdiagnostic groups or even larger compact (diagnostic) infiltrates within the fibrotic portal tracts (**Fig. 23.29A and B**). Because mast cells are normally virtually absent from the sinusoids, the presence of loosely scattered mast cells in liver sinusoids is also highly suspicious for systemic mastocytosis. Immunohistochemically, mast cells show coexpression of tryptase and KIT (CD117) but also the typical aberrant expression of CD25 (**Fig. 23.29C and D**). However, a considerable number of tumors show an aberrant phenotype with weak expression of CD25 and

almost-missing expression of tryptase. Therefore, screening for systemic mastocytosis involving the liver should be performed using anti-KIT antibodies. The aberrant immunophenotype is not seen in other tissues/ organs.

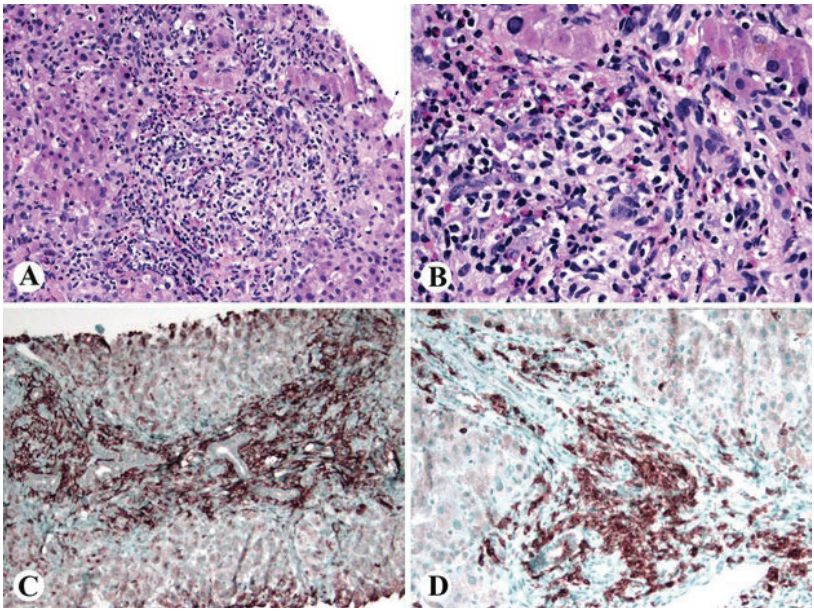

Fig 23.29 Liver mastocytosis. A-B, Predominant spindled mast cell infiltrates in the portal tract (H&E stain, A, 200x; B, 400x); C-D, Immunohistochemical reactivity of the mast cells showing positive CD25 (C) and CD117 (D) (C and D, 200x).

Prognosis and prediction: Prognosis depends on the type of systemic mastocytosis and is accordingly very unfavorable in patients with advanced systemic mastocytosis, whereas those with indolent systemic mastocytosis usually have an almost normal life expectancy.[47]

14. Histiocytic sarcoma (HS)

HS is a malignant proliferation of cells showing morphological and immunophenotypic features of tissue histiocytes. HS can occur in extranodal or nodal sites. Liver involvement of HS is extremely rare. Hornick et al reported 14 cases of extranodal HS, with only one case involving the liver.[48]

Histopathology: The tumors were generally composed of sheets of large epithelioid cells with abundant eosinophilic cytoplasm, oval to irregular

nuclei, vesicular chromatin, and large nucleoli. Binucleated cells were common, and tumor giant cells can be seen. Mitoses ranged from 1 to 64 per 10 HPF (median 11 per 10 HPF). Nearly all tumors show a striking inflammatory infiltrate, most often of neutrophils or lymphocytes.[48] Necrosis can be present and hemophagocytosis is occasionally observed. The tumor cells can sometimes be spindly. Variable numbers of reactive cells may be admixed. The tumor shows expression of one or more histiocytic markers, including CD163, CD68, and lysozyme, whereas Langerhans cell (CD1a, CD207 (langerin)), follicular dendritic cell (CD21, CD35), and myeloid cell (myeloperoxidase, CD13) markers are negative. There can be heterogeneous expression of S100.

Prognosis and prediction: HS is generally an aggressive neoplasm with poor response to therapy. Patients with localized disease and small primary tumors have a more favorable outcome.[49]

15. Langerhans cell histiocytosis (LCH)

LCH typically presents in children and is a clonal proliferation of cells with morphological and immunophenotypic features of Langerhans cells. LCH liver involvement is common in pediatric patients usually aged <2 years with multisystem disease. Liver involvement in adults is uncommon and usually occurs in the setting of multiorgan disease, and it manifests as hepatomegaly and abnormal liver function tests, in particular with evidences of cholestatic injury pattern.[50]

Histopathology: The hepatic parenchymal involvement may show Langerhans cell sinusoidal infiltrate, granulomatoid clusters, and confluent tumor masses (**Fig. 23.30**). LCH is characterized by proliferation of oval cells with deeply grooved or contoured nuclei, thin nuclear membranes, fine chromatin, and generally inconspicuous nucleoli (**Fig. 23.31**). Nuclear atypia may be minimal. The cells have a moderate amount of lightly eosinophilic cytoplasm. There are variable numbers of admixed eosinophils and histiocytes. The portal tracts, including the bile ducts, may be infiltrated by Langerhans cells, evolving to a pattern of sclerosing cholangitis with periductal fibrosis, ductopenia, and periportal ductular reaction. The diagnosis can be very subtle and easy to miss when the infiltrates are predominantly portal-based mimicking an ordinary hepatitis. In the late lesions, Langerhans cells may be sparse or absent. Immunophenotypically, LCH expresses CD1a, CD207 (langerin) and S100 (**Fig. 23.32)**.

Prognosis and prediction: Children with liver involvement as part of multisystem LCH have a high mortality rate. Adults with liver involvement may die from complications of sclerosing cholangitis. Tumors with BRAF p.V600E mutations are treatable using BRAF inhibitors,[51,52] and trial results are encouraging for this approach.

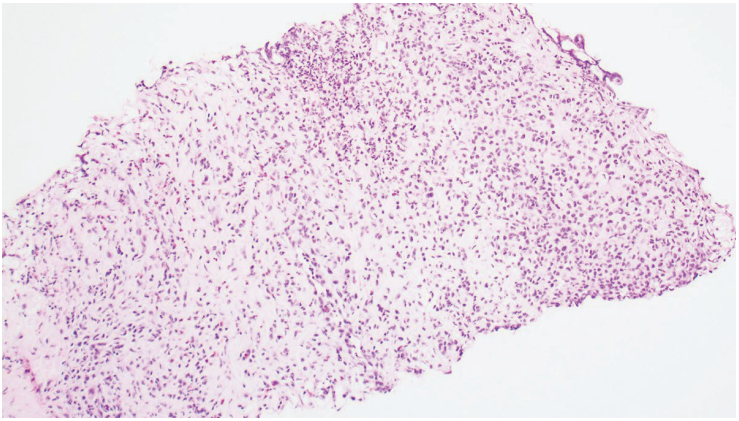

Fig 23.30 Histology of liver Langerhans cell histiocytosis. Liver biopsy shows mass-forming Langerhans cell infiltrate of the liver parenchyma (H&E stain, 100x) (Courtesy of Dr. Larry Wang, Children's Hospital Los Angeles).

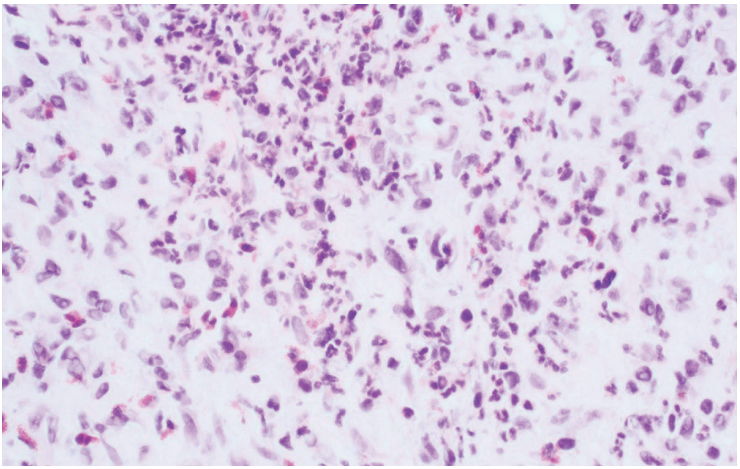

Fig 23.31 Histology of liver Langerhans cell histiocytosis. The Langerhans cells show pale cytoplasm, some contorted nuclei with fine chromatin admixed with

eosinophils and histiocytes (H&E stain, 400x) (Courtesy of Dr. Larry Wang, Children's Hospital Los Angeles).

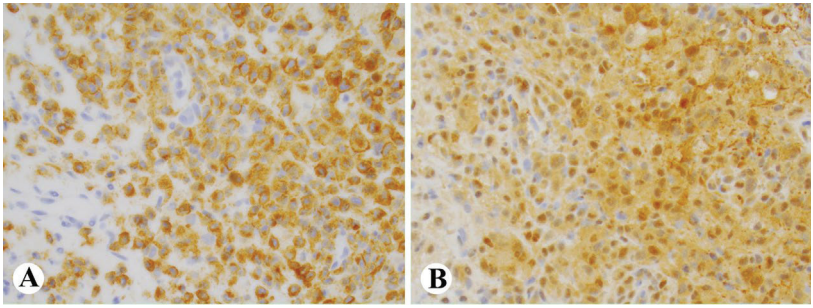

Fig 23.32 Immunostains of liver LCH of the Figs 23.30 and 23.31. The lesional cells are positive for Langerin (A), S100 (B) and CD1a (data not shown). (A-B, 400x). (Courtesy of Dr. Larry Wang, Children's Hospital Los Angeles).

16. Myeloid sarcoma

Myeloid sarcoma (MS) is a rare extramedullary presentation of myeloid malignancies, most commonly seen in association with acute myeloid leukemia (AML).[53] Although MS can develop in any organ, the involvement of the hepatobiliary system is rare. With clinical manifestations of jaundice, abdominal pain and other gastrointestinal symptoms, MS presenting at this location can be a challenge to diagnose, particularly in patients with no known history of hematologic malignancy. This may cause a delay in proper management.

Histopathology: The liver biopsy shows a diffuse monotonous infiltrate that destroys hepatic parenchyma (**Fig. 23.33**). The tumor cells have myeloblasts with a mild / moderate rim of basophilic cytoplasm, fine nuclear chromatin, and 2-4 nucleoli (**Fig. 23.34**). They are positive for myeloperoxidase (MPO), C-kit, CD34 (**Fig. 23.35**), CD56, and CD68, and negative for cytokeratin, CD3, CD20, CD23, CD138 and cyclin D1. Flow cytometry is helpful for blast identification and lineage assignment.[53]

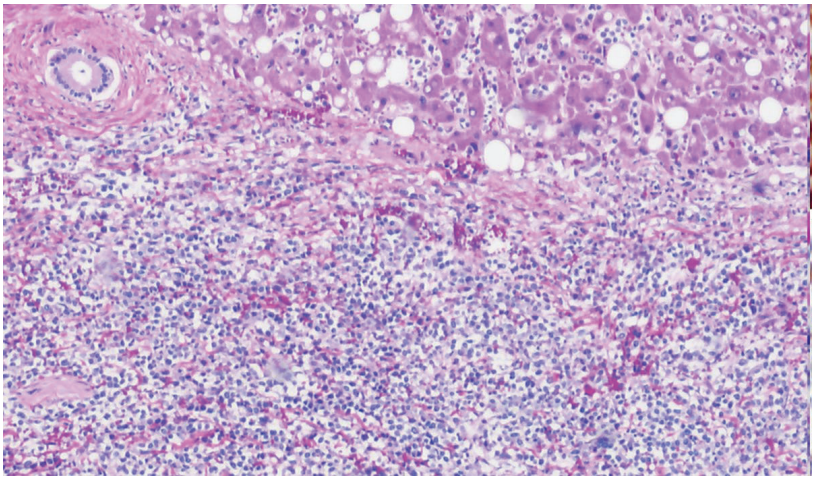

Figure 23.33 Liver involved by myeloid sarcoma (H&E stain, 100x).

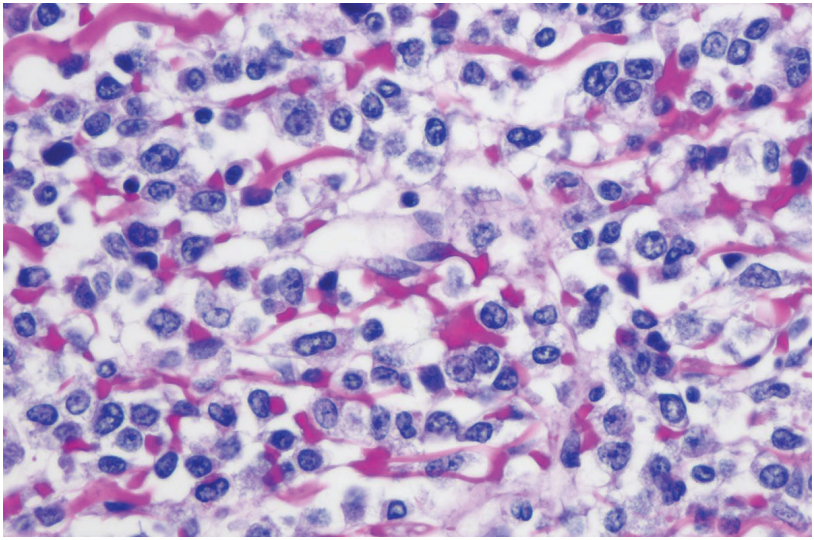

Figure 23.34 Liver involved by myeloid sarcoma (H&E stain, 400x).

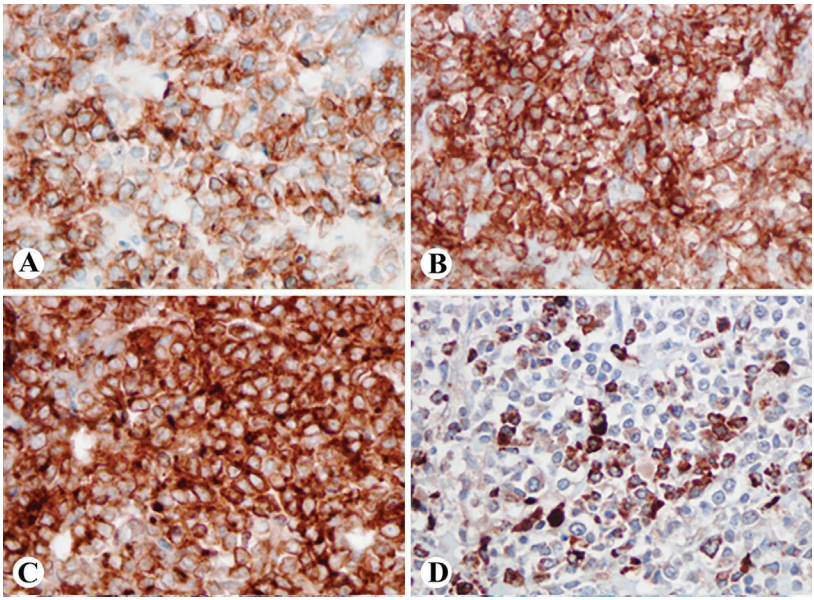

Figure 23.35 Immunohistochemical reactivity of liver involved by myeloid sarcoma. The tumor cells are positive for C-Kit (A), CD43 (B), CD34 (C) and MPO (D). (A-D, 400x).

Prognosis and prediction: It's not well studied. 55% of patients show chromosomal aberrations including trisomy 8, monosomy 7, MLL rearrangement, inversion 16, trisomy 4, or monosomy 16. Patients with isolated tumor and chromosome 7 abnormalities may have worse prognosis.[53]

17. Plasma cell myeloma initially presenting as liver failure

Primary extramedullary plasma cell neoplasm of the liver is rare. The prevalence of multiple myeloma (MM) leading to evidence of liver dysfunction is 0.4%, with only 4 case reports of MM leading to acute liver failure [54-57] identified in the English literature. In up to 40% of cases of MM, there is some degree of plasma cell infiltration of the liver; however, this is usually clinically silent and discovered on autopsy or incidentally on imaging. It is rare to have evidence of hepatic involvement on initial presentation. Recently, we reported the fourth case of MM with initial

manifestation of liver failure with a bilirubin of 3.1 mg/dL on admission, which peaked at 40 mg/dL within 2 weeks.

The patient was a 79-year-old Iranian man who presented with increasing fatigue, decreased appetite, and early satiety worsening over 1 month. He had no previous history of liver disease and denied alcohol use, travel outside of the United States, and risk factors for viral hepatitis. Tests for hepatitis A, B, and C, Epstein-Barr virus, and cytomegalovirus were negative, as were autoantibodies. Bilirubin continued to rise acutely during hospitalization, with total bilirubin measuring 10.6 mg/dL (direct 8.0 g/dL) on hospital day 8. Liver biopsy revealed extensive infiltrate of plasma cell neoplasm in the liver parenchyma (**Figs. 23.36 and 23.37**) with minimal steatosis and no evidence of fibrosis. The tumor cells were negative for CD45, positive for CD138, MUM1, BCL-2, and with Kappa light chain restriction (**Fig. 23.38**) supporting extramedullary plasma cell neoplasm involving liver. Subsequent bone marrow biopsy confirmed the diagnosis of MM with 90% kappa light chain-restricted plasma cells. Chemotherapy was attempted but limited due to marked bilirubinemia. The patient continued to decompensate and developed ascites, anasarca, and encephalopathy with asterixis. The patient died on the hospital day 24.[54] This case demonstrates the aggressiveness of this disease. In this case, worsening cholestasis rapidly progressing to overt liver failure was the initial presentation of MM. This phenomenon has been reported in only three other cases in the English literature.[55-57] Mechanisms of liver failure secondary to MM include direct invasion by plasma cells, plasmacytoma, light chain deposition, or amyloid deposition (the latter being the most prevalent). MM involving the liver more commonly occurs as an infiltrative disease, which is not radiologically detectable.

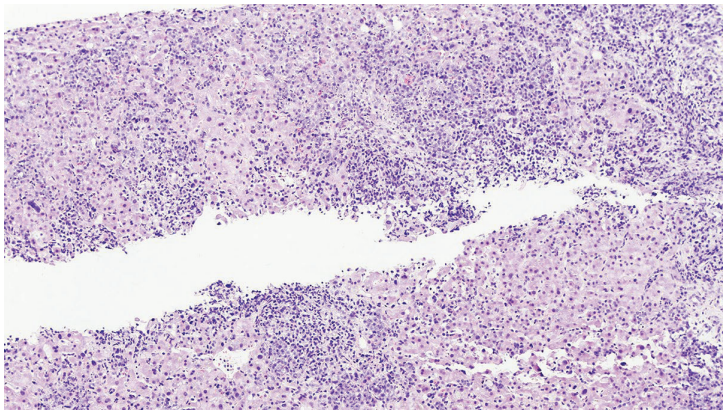

Fig 23.36 Liver plasma cell myeloma. Liver biopsy of a 79-year-old male presenting with liver failure shows extensive infiltrates in the parenchyma (H&E stain, 100x).

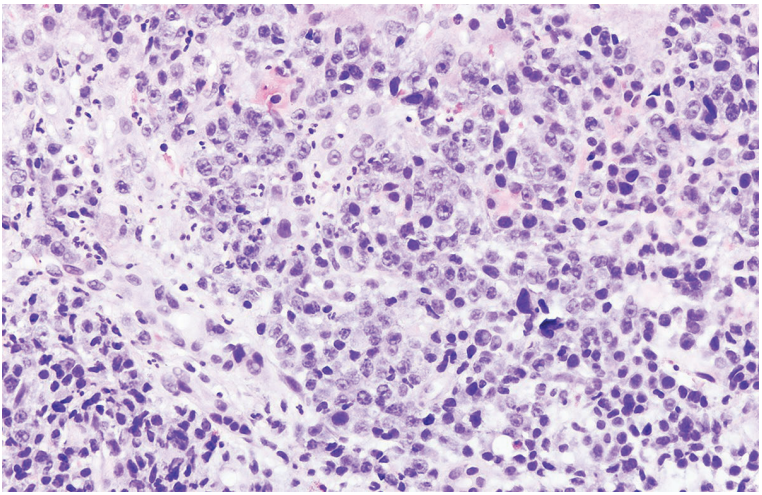

Fig 23.37 Liver plasma cell myeloma. High power view of the liver biopsy of Fig 23.36 reveals extensive infiltrates of atypical plasmacytoid cells (H&E stain, 400x).

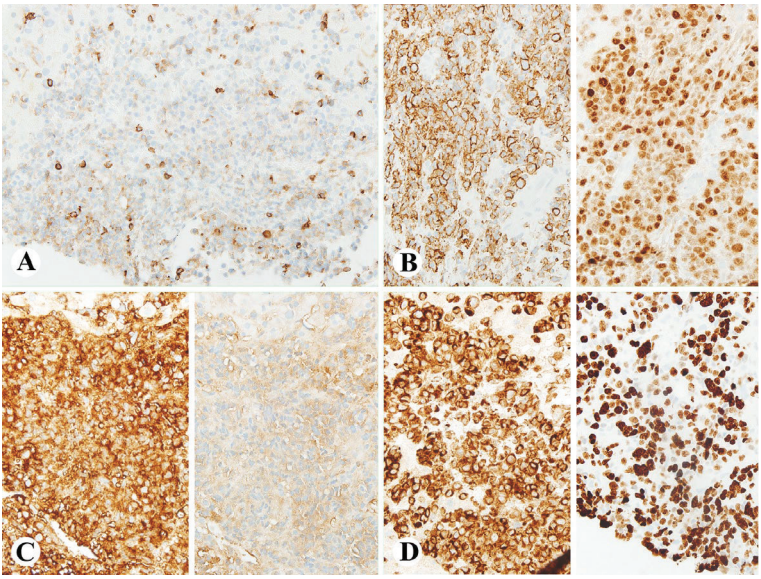

Fig 23.38 Immunostains and *in situ* hybridization of the liver plasma cell myeloma. The tumor cells are negative for CD45 (A), positive for CD138 (B, left), MUM1 (B, right), and Kappa (C, left), negative for Lambda (C, right), positive for Bcl-2 (D, left), and show high Ki-67 proliferative index (90%) (D, right). (A-D, 400x).

18. Collision tumors of lymphoma and metastatic carcinoma in the liver

Collision tumors are rare tumors composed of two histologically distinct neoplasms coinciding at the same location.[58] Most of these tumors represent collisions between carcinomas and sarcomas or lymphomas and rarely between two types of carcinomas. Recently, we reported an extremely rare case of liver collision tumor between chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and poorly differentiated adenocarcinoma of pancreatic origin in a 70-year-old man. Radiographically, the patient was found to have multiple liver nodules measuring up to 3.6 cm and a 5 cm cystic mass in the pancreatic tail adjacent to the splenic hilum. Computed tomography-guided biopsy of one the hepatic lesions revealed a collision tumor of poorly differentiated adenocarcinoma and CLL/SLL. Microscopically, some adenocarcinoma cells were present within the monotonous lymphoid components (**Fig. 23.39**). On immunohistochemical stains the lymphoid cells were diffusely positive for CD5, CD20, and CD23,

but were negative for CD10 and cyclin D1 which was consistent with the patient's clinical history of CLL. The adenocarcinoma cells were diffusely positive for CK7 and CK19, partially and weakly positive for CDX2. The histomorphology and immunophenotype of the adenocarcinoma are consistent with metastatic pancreatic adenocarcinoma.[58]

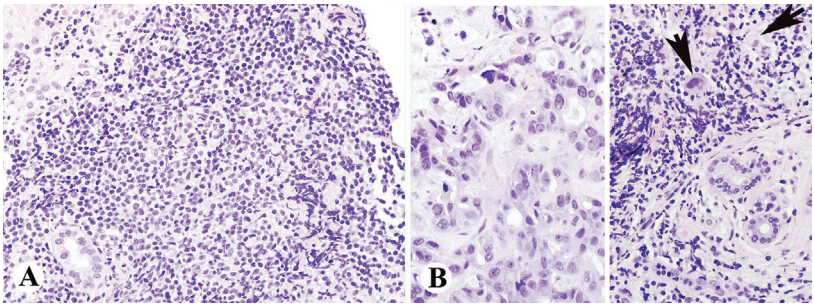

Fig 23.39 Histology of liver collision tumors of SLL/CLL and metastatic pancreatic adenocarcinoma. A, Portal tract with monotonous small lymphocytic infiltrates; B, next to the lymphoid proliferation (B, left) and within the lymphocytic infiltrate (arrows) are the atypical epithelial cells consistent with metastatic poorly differentiated pancreatic ductal adenocarcinoma (H&E stain, A and B, 400x).

Summary

Liver is commonly affected by infection and inflammatory process which mimic hematological and lymphoproliferative disorders. The knowledge on hematological and lymphoproliferative disorders has been explored with the use of immunohistochemistry, fluorescence in situ hybridization, and molecular modalities. Liver pathologists should exercise high vigilance and prudently use additional studies [**Table 23.2**] after a thorough histological assessment of the mononuclear infiltrates.

Table 23.2: Approach to work up for an atypical hepatic lymphoid infiltrate.

- First round
  - CD20, PAX-5, CD3, CD5, CD21, Cyclin D1, CD56, EBER ISH, and TdT (if lymphoblastic morphology)
- Second round
  - If MCL, then SOX-11 to subclassify
  - If a small B-lymphoid neoplasm is a consideration, then CD10, BCL-6, CD23, CD43, BCL-2, and Ki-67
  - If ALCL is a consideration, then CD4, CD30, EMA, and ALK
  - If DLBCL, then CD10, BCL-6, MUM-1, Ki-67, cMyc, BCL-2 and FISH for *MYC*, *BCL2*, and *BCL6*
  - If a mature T-cell neoplasm is a consideration, then work-up may include additional T-cell markers (i.e., CD2, CD4, CD7, CD8, TCRBF1, TCR gamma, TIA-1, granzyme B) and/or TCR clonality testing
  - If Hodgkin lymphoma is a consideration, then for CHL: CD30, CD15, and MUM-1, and for NLPHL: OCT2 and PD-1.[13]

Key points to pathologists:

- Always keep hematological and lymphoproliferative disorders in the differential diagnoses when encountering a liver biopsy with mononuclear cell infiltration, either in the portal tract and/or sinusoids. Histological features pointing towards a neoplastic process are: dense infiltrate, atypical infiltrate, destructive infiltrate, apoptosis of atypical cells, necrosis, and the presence of mitotic figures. Also, relative lack of tissue injury in the setting of dense infiltrate also raises the possibility of lymphoproliferative disorder.
- Although hepatic involvement by systemic lymphoma is common, rare cases of primary hepatic lymphoma (PHL) and secondary hepatic involvement by systemic lymphoma may be first encountered on liver biopsy. Diffuse large B-cell lymphoma and extranodal

marginal zone lymphoma of mucosa-associated lymphoid tissue are the most common PHLs.

- Epstein-Barr virus (EBV) typically infects B-cells through the EBV receptor (CD21) in the infectious mononucleosis associated EBV hepatitis. However, in the chronic active EBV hepatitis, the EBV may infect NK/T cells and may develop hemophagocytic lymphohistiocytosis and chemotherapy-resistant lymphoma. In this setting, close clinicopathologic correlation is the key to a correct diagnosis.
- T-cell or natural killer (NK)-cell lymphomas are less commonly diagnosed on liver biopsy; specific considerations include peripheral T-cell lymphoma, not otherwise specified; hepatosplenic T-cell lymphoma; aggressive NK-cell lymphoma and it's mimic of chronic active EBV hepatitis.
- Some other rare entities such as EBV+ inflammatory follicular dendritic cell sarcoma, mastocytosis, Hairy cell leukemia, Histiocytic sarcoma, Langerhans cell histiocytosis, myeloid sarcoma, and plasma cell myeloma may be unexpectedly seen in the liver biopsy.
- Langerhans cell histiocytosis and classic Hodgkin lymphoma (CHL) can present with cholestatic liver injury pattern. Thus, these should be carefully excluded in liver biopsy showing cholestatic features.
- Collision tumors of lymphoma and carcinoma may be seen in the liver biopsies too.

References

1. El-Fattah MA. Non-Hodgkin Lymphoma of the Liver: A US Population-based Analysis. J Clin Transl Hepatol. 2017;5:83-91.
2. Chan JKC and Fukayama M. Hematolymphoid tumors of the digestive system: Introduction. In WHO classification of Tumors Editorial Board. WHO classification of tumors- Digestive system tumors. International Agency for Research on Cancers, Lyon, France, 2019, p 376-377.
3. Omland LH, Jepsen P, Krarup H, et al. Liver cancer and non-Hodgkin lymphoma in hepatitis C virus-infected patients: results from the DANVIR cohort study. Int J Cancer 2012;130:2310-2317.
4. Bronowicki JP, Bineau C, Feugier P, et al. Primary lymphoma of the liver: clinicalpathological features and relationship with HCV infection in French patients. Hepatology 2003;37:781-787.

5. Bowman SJ, Levison DA, Cotter FE, et al. Primary T cell lymphoma of the liver in a patient with Felty's syndrome. Br J Rheumatol. 1994;33:157-160.
6. Salmon JS, Thompson MA, Arildsen RC, et al. Non-Hodgkin's lymphoma involving the liver: clinical and therapeutic considerations. Clin Lymphoma Myeloma 2006;6:27380.
7. Nart D, Ertan Y, Yilmaz F, et al. Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a liver transplant patient with hepatitis B cirrhosis. Transplant Proc. 2005;37:4408-4412.
8. Kikuma K, Watanabe J, Oshiro Y, et al. Etiological factors in primary hepatic B-cell lymphoma. Virchows Arch. 2012;460:379-387.
9. Dziadzio M, Chee R, McNamara C, et al. EBV-driven diffuse large B-cell lymphoma confined to the liver in a patient with a history of idiopathic CD4 lymphocytopenia. BMJ Case Rep. 2013;2013.
10. Cheuk W, Chan JK, Shek TW, et al. Inflammatory pseudotumor-like follicular dendritic cell tumor: a distinctive low-grade malignant intra-abdominal neoplasm with consistent Epstein-Barr virus association. Am J Surg Pathol. 2001;25:721-731.
11. Norsworthy KJ, Bhatnagar B, Singh ZN, et al. Myeloid Sarcoma of the Hepatobiliary System: A Case Series and Review of the Literature. Acta Haematol. 2016;135:241-251.
12. Chan WC, Lai J, Nakamura S, and Rosenwald A. Diffuse large B-cell lymphoma. In WHO classification of Tumors Editorial Board. WHO classification of tumors- Digestive system tumors. International Agency for Research on cancers, Lyon, France, 2019, p 402-405.
13. Choi WT and Gill RM. Hepatic lymphoma diagnosis. Surg Pathol Clin. 2018;11(2):389-402.
14. Ugurluer G, Miller RC, Li Y, et al: Primary hepatic lymphoma: a retrospective, multicenter rare cancer network study. Rare Tumors 2016;8:6502.
15. Peng Y, Qing AC, Cai J, et al: Lymphoma of the liver: clinicopathological features of 19 patients. Exp Mol Pathol. 2016;100: 276-280.
16. Lei KI.: Primary non-Hodgkin's lymphoma of the liver. Leuk Lymphoma 1998; 29: pp. 293-299.
17. Ishikawa E, Tanaka T, Shimada K, et al. A prognostic model, including the EBV status of tumor cells, for primary gastric diffuse large B-cell lymphoma in the rituximab era. Cancer Med. 2018.
18. Xu-Monette ZY, Dabaja BS, Wang X, et al. Clinical features, tumor biology, and prognosis associated with MYC rearrangement and Myc

overexpression in diffuse large B-cell lymphoma patients treated with rituximabCHOP. Mod Pathol. 2015;28:1555-1573.
19. Miyazaki K, Yamaguchi M, Suzuki R, et al. CD5-positive diffuse large B-cell lymphoma: a retrospective study in 337 patients treated by chemotherapy with or without rituximab. Ann Oncol. 2011;22:1601-1607.
20. Hu S, Xu-Monette ZY, Balasubramanyam A, et al. CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2013;121:2715-2724.
21. Galati G, Rampa L, Vespasiani-Gentilucci U, et al.Hepatitis C and double-hit B cell lymphoma successfully treated by antiviral therapy. World J Hepatol. 2016;8:1244–1250.
22. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–2390.
23. Chan R.C., Chu C.M., Chow C., et al: A concurrent primary hepatic MALT lymphoma and hepatocellular carcinoma. Pathology 2015;47: pp.178-181.
24. Bronowicki J.P., Bineau C., Feugier P., et al: Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. Hepatology 2003; 37: pp. 781-787.
25. Mizuno S., Isaji S., Tabata M., et al: Hepatic mucosa-associated lymphoid tissue (MALT) lymphoma associated with hepatitis C. J Hepatol. 2002;37:872-873.
26. Nakamura S and Delabie J. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) involving the digestive tract. In WHO classification of Tumors Editorial Board. WHO classification of tumors- Digestive system tumors. International Agency for Research on Cancers, Lyon, France, 2019, p 378-382.
27. Opelz G, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4:222-230.
28. Petrara MR, Giunco S, Serraino D, et al. Post-transplant lymphoproliferative disorders: from epidemiology to pathogenesis-driven treatment. Cancer Lett. 2015;369:37-44.
29. Kumarasinghe G, Lavee O, Parker A, et al. Post-transplant lymphoproliferative disease in heart and lung transplantation: Defining risk and prognostic factors. J Heart Lung Transplant. 2015;34:1406-1414.

30. Knight JS, Tsodikov A, Cibrik DM, et al. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. J Clin Oncol. 2009;27:3354-3362.
31. Trappe RU, Choquet S, Dierickx D, et al. International prognostic index, type of transplant and response to rituximab are key parameters to tailor treatment in adults with CD20-positive B cell PTLD: clues from the PTLD-1 trial. Am J Transplant. 2015;15:1091-1100.
32. Hartmann S, Eichenauer DA.Nodular lymphocyte predominant Hodgkin lymphoma: pathology, clinical course and relation to T-cell/histiocyte rich large B-cell lymphoma. Pathology 2020;52:142-153.
33. Gaulard P and Jaffe ES. Hepatosplenic T-cell lymphoma. In WHO classification of Tumors Editorial Board. WHO classification of tumors- Digestive system tumors. International Agency for Research on Cancers, Lyon, France, 2019, p 397-398.
34. Yabe M, Medeiros LJ, Daneshbod Y, et al. Hepatosplenic T-cell lymphoma arising in patients with immunodysregulatory disorders: a study of 7 patients who did not receive tumor necrosis factor-α inhibitor therapy and literature review. Ann Diagn Pathol. 2017;26:16-22.
35. Voss MH, Lunning MA, Maragulia JC, et al. Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience. Clin Lymphoma Myeloma Leuk. 2013;13:814.
36. Tanase A, Schmitz N, Stein H, et al. Allogeneic and autologous stem cell transplantation for hepatosplenic T-cell lymphoma: a retrospective study of the EBMT Lymphoma Working Party. Leukemia 2015;29:686-688.
37. Kim SJ, Jung HA, Chuang SS, et al. Extranodal natural killer/T-cell lymphoma involving the gastrointestinal tract: analysis of clinical features and outcomes from the Asia Lymphoma Study Group. J Hematol Oncol. 2013;6:86.
38. Jiang M, Chen X, Yi Z, et al. Prognostic characteristics of gastrointestinal tract NK/T-cell lymphoma: an analysis of 47 patients in China. J Clin Gastroenterol. 2013;47:e74-9.
39. Kwong S, Lu X, Liu X, Lai J. Reactivation of EBV hepatitis in T/NK cells mimicking liver T/NK cell lymphoma. Gastroenterol Res. 2020;13:81-84.

40. Arai A. Advances in the Study of Chronic Active Epstein-Barr Virus Infection: Clinical Features Under the 2016 WHO Classification and Mechanisms of Development. Front Pediatr. 2019;7:14.
41. Peng Y, Cai J, Yue C, Qing X. Primary hepatic Epstein–Barr virus-associated CD30-positive peripheral T-cell lymphoma of cytotoxic phenotype. Exp Mol Pathol. 2016;100:207-211.
42. Torbenson MS, McPhail ED. Hematopathology and the liver. In Torbenson MS, Zhang L, Moreira RK, Surgical Pathology of the Liver. Wolters Kluwer, Philadelphia, 2018, p686-687.
43. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-1480.
44. Ge R, Liu C, Yin X, et al. Clinicopathologic characteristics of inflammatory pseudotumorlike follicular dendritic cell sarcoma. Int J Clin Exp Pathol. 2014;7:2421-2429.
45. Lecuit T, Yap AS. E-cadherin junctions as active mechanical integrators in tissue dynamics. Nat Cell Biol. 2015;17:533-539.
46. Gilreath JA, Tchertanov L, Deininger MW. Novel approaches to treating advanced systemic mastocytosis. Clin Pharmacol. 2019;11:77-92.
47. Horny H-P, Akin C, Arber DA, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon (France): International Agency for Research on Cancer; 2017. p. 62-69.
48. Hornick JL, Jaffe SE, Fletcher CD. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. Am J Surg Pathol. 2004;28:1133-1144.
49. Pileri SA, Grogan TM, Harris NL, et al. Tumors of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 2002;41:1-29.
50. Abdallah M, Généreau T, Donadieu J, et al. Langerhans' cell histiocytosis of the liver in adults. Clin Res Hepatol Gastroenterol. 2011;35:475-481.
51. Arceci RJ, Allen CE, Dunkel IJ, et al. A phase IIa study of afuresertib, an oral panAKT inhibitor, in patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2017;64.
52. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent,

Phase 2, Openlabel VE-BASKET Study. JAMA Oncol. 2018;4:384-388.
53. Norsworthy KJ, Bhatnagar B, Singh ZN, Gojo I. Myeloid Sarcoma of the Hepatobiliary System: A Case Series and Review of the Literature. Acta Haematol. 2016;135:241-251.
54. Cull S, Westrich DJ Jr, Bhatia R, Lai J, Befeler AS. Multiple Myeloma Presenting as Acute Liver Failure. ACG Case Rep J. 2017;4:e85.
55. Rahhal F-E, Schade R-R, Nayak A, Coleman TA. Hepatic failure caused by plasma cell infiltration in multiple myeloma. World J Gastroenterol. 2009;15:2038–2040.
56. Yamamoto T, Maeda N, Kawasaki H. Hepatic failure in a case of multiple myeloma-associated amyloidosis (kappa-AL). J Gastroenterol. 1995;30:393–397.
57. Tabata S, Kurata M, Takeda J, et al. [Fatal hepatic failure due to AL amyloidosis in a patient with multiple myeloma]. Rinsho Ketsueki. 2012;53:1906–1910.
58. Al-Taee A, Lai J, Chen Y, Zhou Y, Jallad B. Hepatic Collision Tumor of Metastatic Pancreatic Adenocarcinoma and Chronic Lymphocytic Leukemia: A Case Report. J Gastrointest Cancer 2018;49:322-326.