

Practical Interpretation of Liver Biopsy, Volume 2

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Edited by

Xiuli Liu, Jinping Lai and 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.**

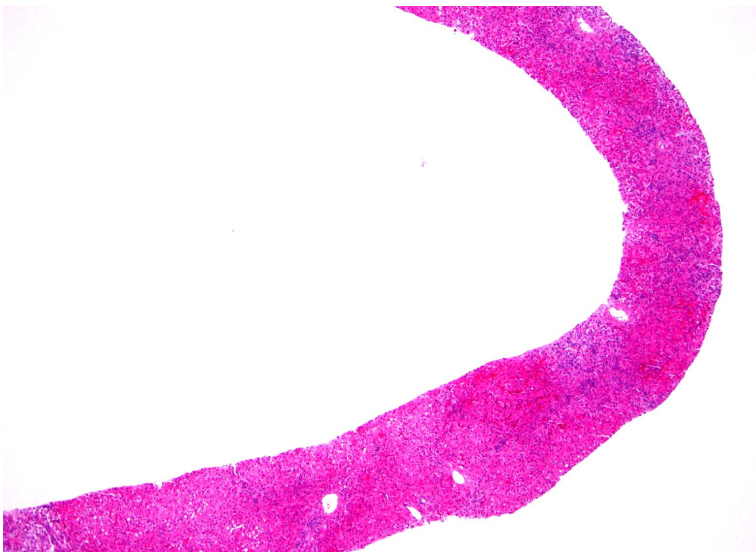


Fig 20.1 Features of focal nodular hyperplasia. Biopsy reveals benign liver parenchyma with nodular regeneration and fibrosis. Low power view.

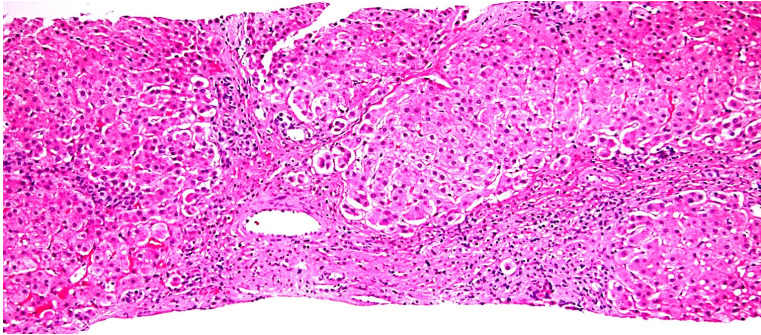


Fig 20.2 Features of focal nodular hyperplasia. Broad fibrous bands dissecting hepatocyte nodules. Intermediate power view.

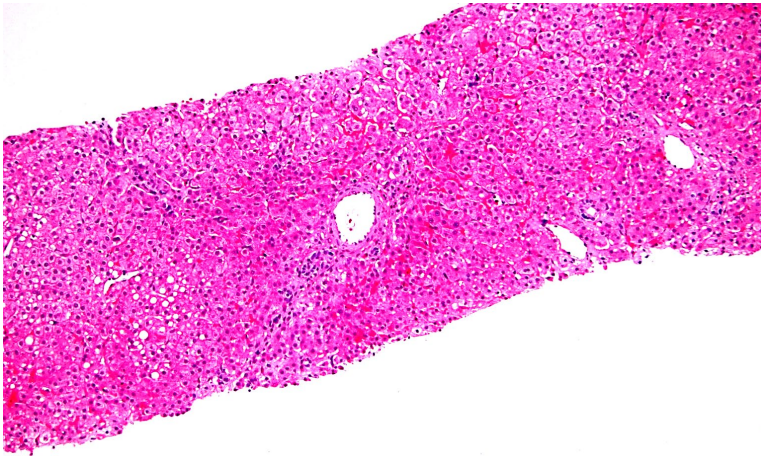


Fig 20.3 Features of focal nodular hyperplasia. Abnormal and thickened arterioles in the central scar.

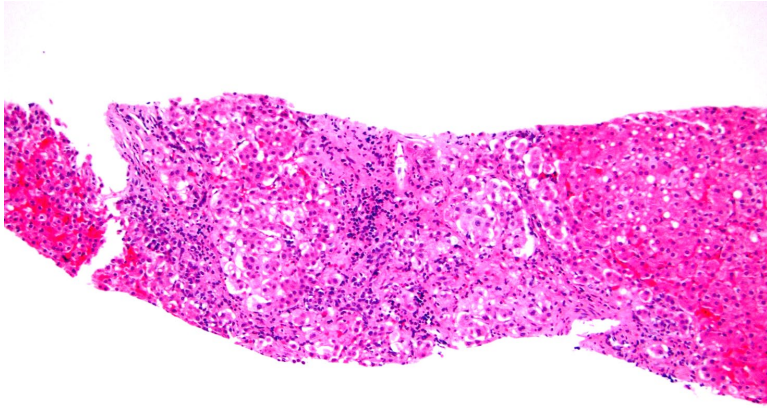


Fig 20.4 Features of focal nodular hyperplasia. Ductular reaction and cholate stasis manifested by enlarged and pale peri-septal hepatocytes are present.

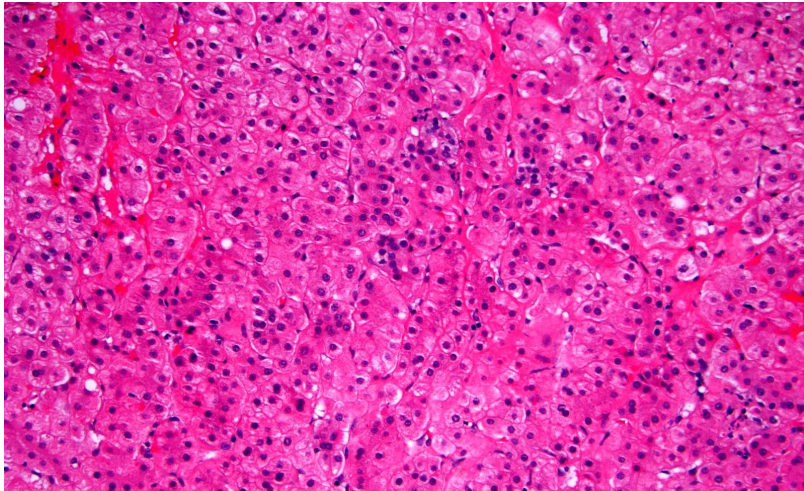


Fig 20.5 Hepatocyte proliferation with rosette formation in the hepatocyte nodules in focal nodular hyperplasia.

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.

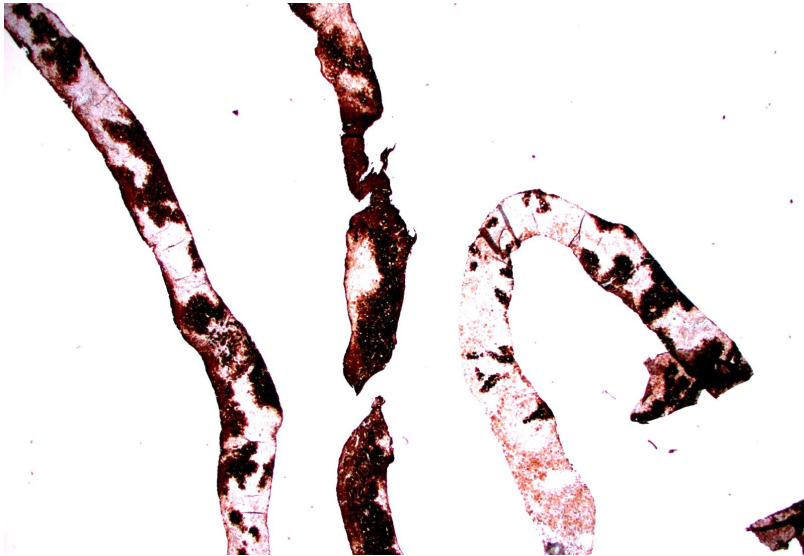


Fig 20.6 Map-like immunoreactivity of glutamine synthetase in lesional hepatocytes in focal nodular hyperplasia (immunohistochemical stain).

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.

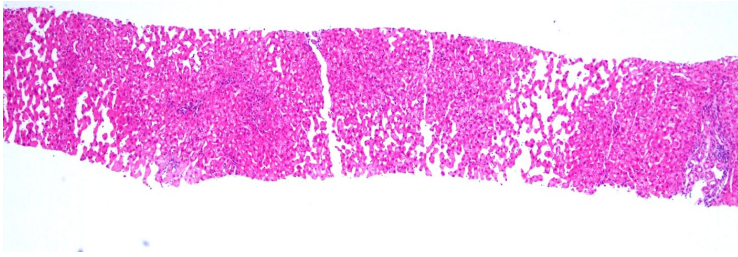


Fig 20.7 Features of inflammatory hepatocellular adenoma. Biopsy of liver mass reveals nodular regeneration and sinusoidal dilatation (telangiectasia). Low power view.

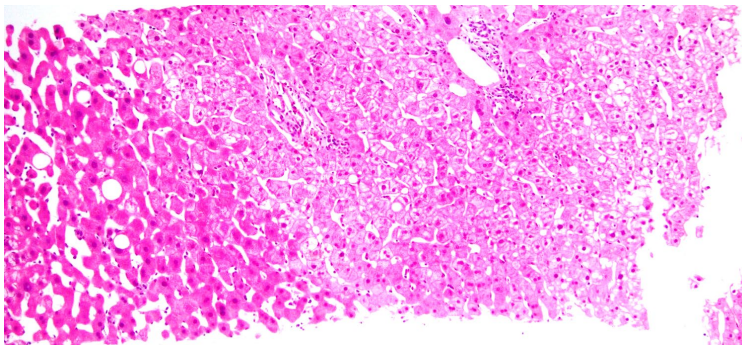


Fig 20.8 Features of inflammatory hepatocellular adenoma. Interface between portal tract-containing background liver (left) and lesional tissue with angiectasia. Intermediate power view.

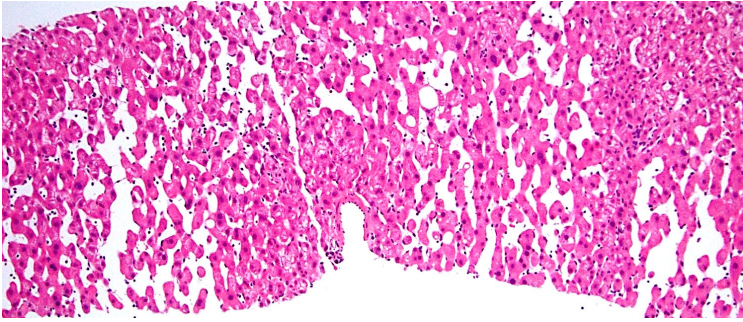


Fig 20.9 Sinusoidal dilatation in the lesional tissue in inflammatory hepatocellular adenoma.

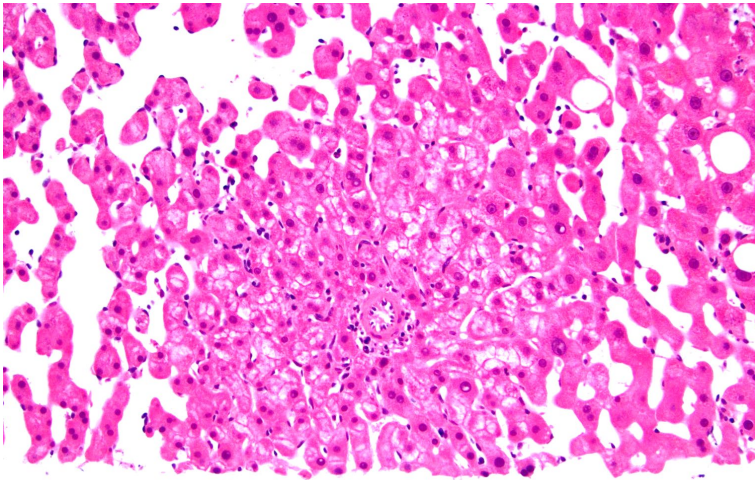


Fig 20.10 Isolated arteriole in the lesional tissue is a common finding in inflammatory hepatocellular adenoma.

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.

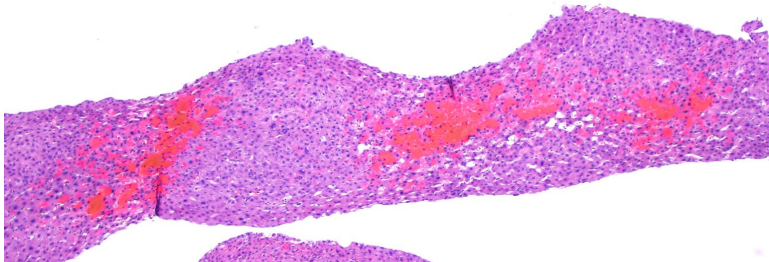


Fig 20.11 Nodular regenerative hyperplasia. Biopsy of the liver shows centrilobular hemorrhage and sinusoidal dilatation alternating with nodular regeneration



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**).

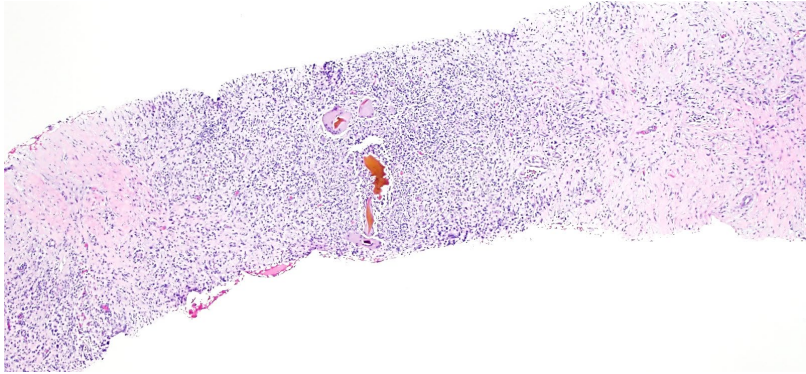


Fig 20.13 Fibrohistiocytic-type inflammatory pseudotumor. The biopsy from a liver mass shows fibrosis and inflammation with extravasated bile with giant cell response. Low power view.

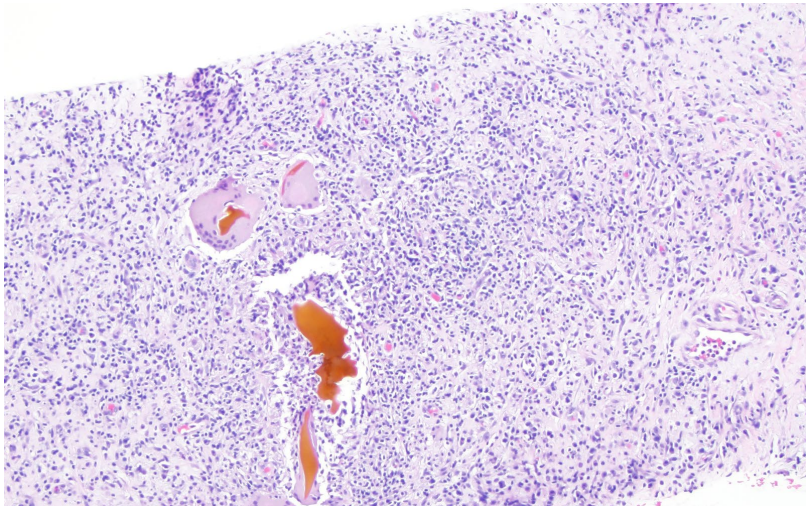


Fig 20.14 Fibrohistiocytic-type inflammatory pseudotumor. The biopsy from a liver mass shows fibrosis and inflammation with extravasated bile with giant cell response. Intermediate power view.

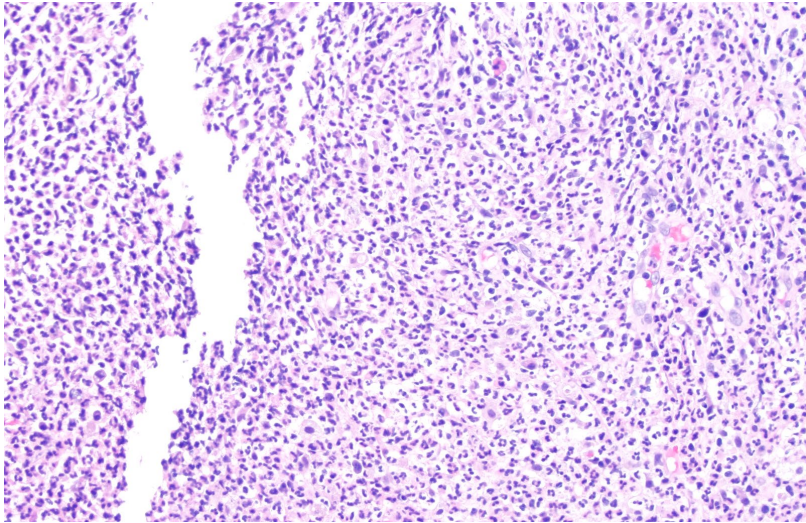


Fig 20.15 Fibrohistiocytic-type inflammatory pseudotumor. There is mixed mononuclear and neutrophilic inflammation.

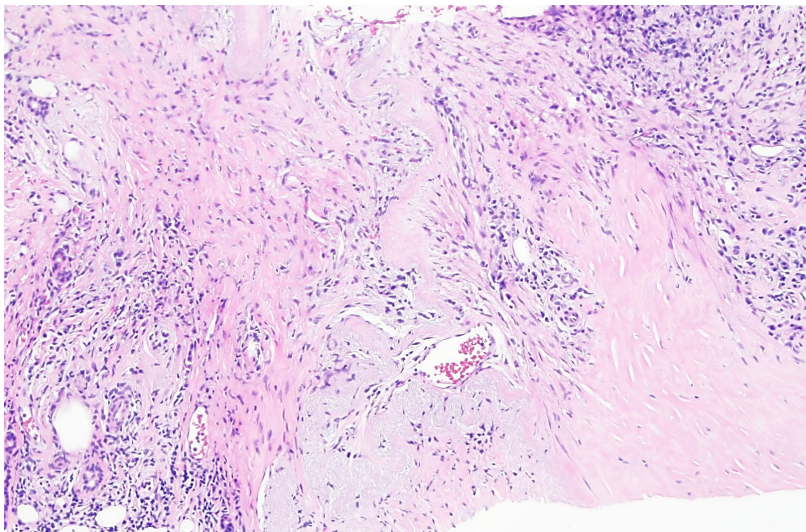


Fig 20.16 Fibrohistiocytic-type inflammatory pseudotumor. In the center of the lesion, there is fibrosis and elastosis, but less inflammation.



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

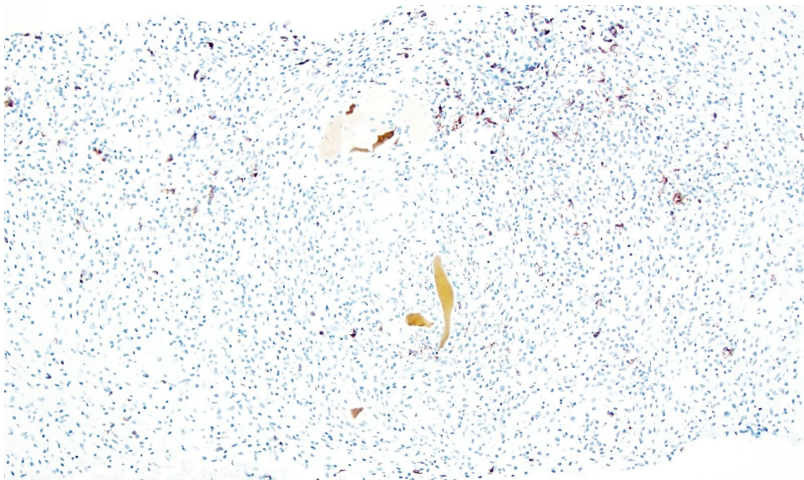


Fig 20.18 Inflammatory pseudotumor. Only few CD20 positive B cells are present (immunostain).