

The Hepatic Vasculature: Missed Lesions, Missed Diagnoses

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Introduction

The possibility of overlooking hepatic vascular disease occurs both in evaluation of liver biopsies, and examining macroscopic specimens of the liver, surgical or autopsy. The standard approach to evaluating a liver biopsy involves assessment of portal tract architecture, bile duct features, and the hepatic parenchyma – sinusoids included. Giving specific attention to evaluating the hepatic microvasculature (portal veins, hepatic arteries, terminal hepatic veins) is mandatory. However, interpreting vascular lesions so identified is problematic.

The clinical indication for a percutaneous liver biopsy usually involves some version of “hepatitis”, “bile duct disease”, “fibrosis/cirrhosis”, or “neoplasia”. “Vascular disorder of the liver” is rarely in the clinical differential diagnosis, and will not be in the pathologist’s differential diagnosis either unless s/he thinks of it. Yet, vascular disorders can present clinically in a manner similar to the usual diagnostic entities above. Even more importantly, the liver biopsy is a very imperfect mechanism to diagnose vascular disorders. Identification of a hepatic vascular disorder as the etiology for a clinical condition is both challenging, and rewarding when demonstrated to be correct.

Table 1 gives disorders which merit at least cursory consideration in the differential diagnosis during histopathologic evaluation of hepatic tissue. This table is organized according to the pathophysiology of the vasculature. The differential diagnosis is less easily organized, since vascular disease can mimic essentially any of the more common hepatic conditions.

Table 1. Vascular Disorders of the Liver, to be considered in histopathologic evaluation of hepatic biopsies

Vascular Disorder	in the differential diagnosis of:
Portal Vein Obstruction To include: Hepatoportal Sclerosis	Fibrosis/Cirrhosis
Arterial Disease Arteritis (e.g., Polyarteritis Nodosa) Hepatic artery obstruction	Cholestasis, Hepatitis
Sinusoidal Disease (other than cirrhosis) Veno-occlusive Disease (Sinusoidal Obstruction Syndrome) Amyloidosis and light chain deposition disease Disseminated Intravascular Coagulation Sinusoidal spread of metastatic tumor	Hepatitis, Fibrosis/Cirrhosis
Hepatic Venous Outflow Obstruction (HVOO) Passive congestion and centrilobular necrosis Budd-Chiari Disease Congestive Heart Failure	Fibrosis/Cirrhosis
Nodular Regenerative Hyperplasia (NRH) Focal Nodular Hyperplasia (FNH)	Fibrosis/Cirrhosis Isolated hepatic neoplasm

It also is important to note that *vascular disease is inherent to essentially every hepatic disorder*. No one has articulated this perspective better than Dr. Ian Wanless (vis. reference 1), based on his meticulous histopathologic analysis of hepatic tissue in hepatitis, cirrhosis, and benign nodular disorders of the liver. I invite any pathologist to focus on the hepatic vasculature – portal venous, hepatic arterial, sinusoidal, and hepatic venous – in any hepatic disease of choice. Vascular lesions will be present.

Thus, the challenge is, first, to determine whether there is vascular pathology in a liver biopsy. If identified, the pathologist must then decide whether the vascular lesions are part-and-parcel of a more conventional hepatic disease, or represent what might be considered a “primary” vascular disorder of the

liver. Failure to recognize vascular disorders of the liver places the medical team at risk for subjecting the patient to a protracted course of ineffective diagnostic evaluation and intervention.

This discussion will *not* address hepatic transplantation pathology, in which hepatic arterial compromise, especially, constitutes a major diagnostic category. The differential diagnosis that includes Focal Nodular Hyperplasia is covered elsewhere in this symposium. Rather, this discussion will focus on the grab-bag of hepatitis, fibrosis/cirrhosis, and bile duct disease, in non-transplant patients.

Portal Vein Disease

Blockage of the extrahepatic portal vein may be insidious and well tolerated or may be a catastrophic and potentially lethal event; most cases fall somewhere in between. Occlusive disease of the portal vein or its major radicles typically produces abdominal pain and, in most instances, ascites and other manifestations of portal hypertension, principally esophageal varices which are prone to rupture. Hence, this condition falls under the differential diagnosis of cirrhosis/portal hypertension.

Extrahepatic portal vein obstruction may arise from the following conditions, but in about half of cases, no cause can be implicated.:

- *Banti syndrome*, in which subclinical occlusion of the portal vein (as from neonatal umbilical sepsis or umbilical vein catheterization) presents as variceal bleeding and ascites years later
- Intra-abdominal sepsis, for example, acute diverticulitis or appendicitis leading to *pylephlebitis* in the splanchnic circulation
- Thrombogenic disorders, including postsurgical thromboses, perinatal exchange transfusion (through the umbilical vein)
- Trauma
- Pancreatitis that initiates splenic vein thrombosis, which propagates into the portal vein

Ideally, portal vein occlusion is identified in a living patient by radiographic mechanisms. Involvement of a pathologist is usually at the time of post-mortem examination. In a deceased patient exhibiting ascites, intestinal congestion, splenomegaly, or other features of portal hypertension, *examination of the porta hepatis for portal vein thrombosis is mandatory*. Causes of portal vein thrombosis include cirrhosis, hepatocellular carcinoma, pancreatitis, and even intraabdominal sepsis.

Invasion of the portal vein system by primary or secondary cancer in the liver can progressively occlude portal inflow to the liver; tongues of hepatocellular carcinoma can even occlude the extrahepatic portal vein. These lesions may be identified radiographically. Identification of vascular invasion by hepatocellular carcinoma is a mandatory part of evaluating resected surgical specimens.

Idiopathic portal hypertension is a chronic, generally bland condition of impaired portal vein inflow and noncirrhotic portal hypertension. In those instances in which a cause can be identified, it may be associated with hypercoagulability of the blood, myeloproliferative disorders, peritonitis, chronic exposure to arsenicals, or autoimmune disorders. The presumed cause is a long-standing state of intrahepatic vascular inflammation and fibrosis, predominantly in the portal tree, leading to obliteration of intrahepatic vascular channels and ensuing portal tract fibrosis. The histologic manifestation is termed *hepatoportal sclerosis*, owing to dense fibrosis of intrahepatic portal tracts with obliteration of portal vein channels. Whether this histology represents a late stage of healed liver injury or a primary progressive disorder is unclear. Idiopathic portal hypertension has unusually high incidence in some parts of the world, for instance, up to 25% of the incidence of esophageal variceal bleeding in India are attributed to the presence of idiopathic portal hypertension.

Suspicion of hepatoportal sclerosis is raised when sclerotic portal tracts are identified in a patient with clinical evidence of portal hypertension, in the absence of histopathological features of cirrhosis. What constitutes sufficient evidence for hepatoportal sclerosis is a matter of opinion, since it remains unclear whether hepatoportal sclerosis should be viewed as a primary pattern of progressive non-bridging

intrahepatic fibrosis, or a healed state of more severe bridging intrahepatic fibrosis, now partially regressed.

Hepatic Artery Disease

Thrombosis or compression of a large intrahepatic branch of the hepatic artery by embolism or neoplasia may result in a localized intrahepatic infarct. The clinical scenario of a patient with a severe thromboembolic disorder, hepatocellular carcinoma, or disseminated metastatic cancer, is not subtle and the differential diagnosis is not likely to be difficult. The one situation in which the clinical presentation may be exceedingly confusing is polyarteritis nodosa, which may present with a bewildering array of intra-abdominal symptoms, features of “hepatitis”, or other localizing symptomatology (e.g., “cholecystitis”). The pathologist may have the first opportunity to identify the vasculitic lesion of polyarteritis nodosa, on a liver biopsy or resection of hepatic tissue.

Interruption of the main hepatic artery does not always produce ischemic necrosis of the organ, particularly if the liver is otherwise normal. Retrograde arterial flow through accessory vessels, when coupled with the portal venous supply, is usually sufficient to sustain the liver parenchyma. (The one exception is hepatic artery thrombosis in a transplanted liver, which generally leads to infarction of the major ducts of the biliary tree and loss of the organ.)

Impaired Blood Flow Through The Liver

The most common *intrahepatic cause* of blood flow obstruction is *cirrhosis*, for which this audience needs no elaboration. In addition, physical occlusion of the *sinusoids* occurs in a small but striking group of diseases. In *sickle cell disease*, the hepatic sinusoids may become packed with sickled erythrocytes, free in the sinusoids, or phagocytosed by Kupffer cells, leading to panlobular parenchymal necrosis.

Disseminated intravascular coagulation (DIC) may occlude sinusoids. This is usually inconsequential except for the spectacular periportal sinusoidal occlusion and parenchymal necrosis that may arise in pregnancy as part of *eclampsia*.

It is surprising the relative frequency with which a diagnosis of *amyloidosis* is first made by the pathologist examining a liver biopsy – and without antecedent clinical history that might raise suspicions of this disorder. In addition to alerting the clinical team of the need to work up the patient for the cause, the pathologist needs to characterize the amyloid deposits by immunohistochemistry.

Metastatic tumor cells (e.g., breast carcinoma, lymphoma, malignant melanoma) may fill the hepatic sinusoids in the absence of a mass lesion. The attendant obstruction to blood flow and massive necrosis of hepatocytes can lead to fulminant hepatic failure. An example of such a process was a patient referred for hepatic transplantation for presumed drug-induced acute hepatic failure. The patient succumbed to hepatic failure in the hours prior to transplantation, and was found at autopsy to have a liver 95% replaced by intrasinusoidal malignant melanoma. The small remainder of hepatocellular parenchyma had, indeed, been compromised by an unintended overdose of acetaminophen owing to the small hepatic reserve remaining, tipping the patient into “drug-induced hepatic failure”.

Passive Congestion and Centrilobular Necrosis

The condition of “congestive hepatopathy”, or “cardiac sclerosis”, is not usually an issue in evaluation of liver biopsies, since the clinical history is usually so striking. However, the pathologist may be called upon to verify that such “cardiac congestion” is the only apparent cause of hepatic compromise. Absence of other features of hepatitis, such as inflammatory portal tract disease, pan-lobular hepatocellular degeneration, or periportal fibrosis, is helpful.

Arguably, passive congestion of the liver occurs in virtually every non-catastrophic natural death, as the heart slowly fails. In such instances, the vascular channels of the liver, including the terminal hepatic vein, remain sharply defined. In the case of a more protracted circulatory compromise of the liver,

usually preterminal, *centrilobular necrosis* (of hepatocytes), without or with hemorrhage of erythrocytes into the hepatic plates, may occur.

It is those patients without a clear cardiac history, but with centrilobular hemorrhage and necrosis, that beg the issue of whether there is a primary hepatic vascular disorder. This situation may arise both in evaluation of a liver biopsy, or a post-mortem liver. The chief differential diagnosis is Sinusoidal Obstruction Syndrome, and other causes of Hepatic Venous Outflow Obstruction.

Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease)

Originally described in Jamaican drinkers of pyrrolizidine alkaloid-containing bush tea and named veno-occlusive disease, the disease is now called sinusoidal obstruction syndrome, and occurs primarily in the immediate weeks following bone marrow transplantation. The incidence approaches 25% in recipients of allogeneic marrow transplants, usually within the first 3 weeks. Sinusoidal obstruction syndrome can occur in cancer patients receiving chemotherapy, especially with agents such as gemtuzumab and ozagamicin, used in the treatment of acute myeloid leukemia, actinomycin D in the treatment of Wilm's tumors, dacarbazine - a drug that is activated by sinusoidal endothelial cells, and in patients who receive cytotoxic agents such as cyclophosphamide prior to bone marrow transplantation (discussed below). The mortality rates can be over 30%. Although histology is the gold standard for the diagnosis, a diagnosis of sinusoidal obstruction syndrome is frequently made on clinical grounds only (tender hepatomegaly, ascites, weight gain, and jaundice), owing to the high risk of liver biopsy in these patients.

Sinusoidal obstruction syndrome is characterized by obliteration of hepatic vein radicles by varying amounts of subendothelial swelling and fine reticulated collagen. In acute disease, there is striking centrilobular congestion with hepatocellular necrosis and accumulation of hemosiderin-laden macrophages. As the disease progresses, obliteration of the lumen of the venule is easily identified by using special stains for connective tissue (Fig. 18–48). In chronic or healed sinusoidal obstruction syndrome, dense perivenular fibrosis radiating out into the parenchyma may be present, frequently with total obliteration of the venule; hemosiderin deposition is evident in the scar tissue, and congestion is minimal.

Sinusoidal obstruction syndrome arises from toxic injury to the sinusoidal endothelium⁶⁶ which presumably starts with the depolymerization of actin in sinusoidal endothelial cells and increased production of metalloproteinases. Endothelial lining cells round up and slough off the sinusoidal wall, embolizing downstream and obstructing sinusoidal blood flow. This is accompanied by entry of erythrocytes into the space of Disse, necrosis of perivenular hepatocytes and downstream accumulation of cellular debris in the terminal hepatic vein. Proliferation of perisinusoidal stellate cells and subendothelial fibroblasts in the terminal hepatic vein follows, with fibrosis and deposition of extracellular matrix in the sinusoids.

Hepatic Venous Outflow Obstruction (other than Sinusoidal Obstruction Syndrome)

Obstruction of a single main hepatic vein by thrombosis is clinically silent. The obstruction of two or more major hepatic veins produces liver enlargement, pain, and ascites, a condition known as *Budd-Chiari syndrome*. Hepatic damage is the consequence of increased intrahepatic blood pressure, and an inability of the massive hepatic blood flow to shunt around the blocked outflow tract. *Hepatic vein thrombosis* is associated with primary myeloproliferative disorders (including polycythemia vera), inherited disorders of coagulation (e.g., deficiencies in antithrombin, protein S, or protein C, or mutations of factor V), antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and intra-abdominal cancers, particularly hepatocellular carcinoma. The occurrence of hepatic vein thrombosis in the setting of pregnancy or oral contraceptive use is usually through interaction with an underlying thrombogenic disorder. About 10% of cases are idiopathic in origin, presumably unrecognized thrombogenic disorders.

With acutely developing thrombosis of the major hepatic veins or the hepatic portion of the inferior vena cava, the liver is swollen and red-purple and has a tense capsule (Fig. 18–47). Microscopically, the

affected hepatic parenchyma reveals severe centrilobular congestion and necrosis. Centrilobular fibrosis develops in instances in which the thrombosis is more slowly developing. The major veins may contain totally occlusive fresh thrombi, subtotal occlusion, or, in chronic cases, organized adherent thrombi.

The challenge for the pathologist examining a liver biopsy with profound pericentral congestion is to distinguish between a Budd-Chiari syndrome pattern versus a Sinusoidal Obstruction Syndrome pattern. Terminal hepatic vein lumina will be visible in the former, and difficult to identify or absent in the latter.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia is a condition that presents with portal hypertension and its attendant symptomatology. Not uncommonly, the clinical presentation is muddled, in that a clear antecedent cause (such as a sub-clinical vasculitic condition such as rheumatoid arthritis) is not identified. A liver biopsy is obtained to identify a cause of portal hypertension, usually suspected to be "cirrhosis".

Instead, the pathologist observes essentially no intrahepatic inflammation, and a variable pattern of hepatocyte plate atrophy and regeneration, without significant hepatic fibrosis. *It is only identification of a curvilinear pattern to the plate atrophy* that the potential arises of Nodular Regenerative Hyperplasia. A reticulin stain can confirm the impression of curvilinearity. However, a liver biopsy is too limited in sampling, and diameter, to permit a definitive diagnosis of Nodular Regenerative Hyperplasia. Rather, the pathologist raises the possibility, and only then can a clinical history be pieced together that does, or does not, support this interpretation.

Nodular Regenerative Hyperplasia affects the entire liver with roughly spherical nodules, in the absence of fibrosis. Microscopically, plump hepatocytes are surrounded by rims of atrophic cells, confirmed on reticulin staining. The presumed cause is a smoldering subclinical pattern of intrahepatic vascular occlusion; this leads to variable but pan-hepatic atrophy of regions of the parenchyma. Better-vascularized regions then hypertrophy, in the form of nodules. This lesion occurs in association with conditions affecting intrahepatic blood flow, including solid organ (particularly renal) transplantation, bone marrow transplantation, and vasculitic conditions. The common factor in both lesions appears to be heterogeneity in hepatic blood supply, arising from focal obliteration of portal vein radicles with compensatory augmentation of arterial blood supply.

Conclusion

In the end, the hepatic pathologist must grow comfortable with the fact that intravascular thrombosis and occlusion may occur in virtually any condition of hepatitis and as a key component of progressive fibrosis and cirrhosis. It is a heightened suspicion for vascular disease per se that gives opportunity for the pathologist to make a singular contribution to the diagnostic evaluation of a patient with intrinsic vascular disease, and hence their clinical management.

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