Hepatic vascular diseases

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Abstract

Hepatic vascular diseases often present with non-specific and subtle histologic changes that could be easily overlooked during the evaluation of liver biopsies and surgical material. A liver biopsy typically samples small vasculature and thus is not a sensitive tool to evaluate the histopathology of large blood vessels. Vascular disease is rarely clinically suggested in the differential diagnosis of a case, and the indication for the liver biopsy is usually "elevated liver enzymes" or "cirrhosis". Hence, when evaluating liver diseases, pathologists may overlook subtle histopathologic changes associated with vascular disease and instead focus on hepatitis, biliary disease or cirrhosis. Pathologists evaluating liver biopsies should be familiar with vascular diseases and their clinical implications. Recognizing hepatic vascular disorders is critical in order to trigger appropriate medical management. This review provides a brief overview of relatively common hepatic vascular diseases that surgical pathologists may encounter in practice.

Keywords acute ischaemia; Budd-Chiari syndrome; congestive hepatopathy; hepatic vascular diseases; non-cirrhotic portal hypertension; peliosis hepatis

Introduction

The liver is a highly vascular organ receiving about 25% of the total cardiac output with a dual supply from the portal vein and hepatic artery. Not surprisingly, given the enormous blood flow, the liver is susceptible to a wide range of circulatory disturbances and various vascular injuries.[1] Depending on where blood flow is impaired, hepatic vascular disorders can be grouped into impaired hepatic inflow, outflow, or impaired intrahepatic blood flow (Table 1).[2,3] Hepatic inflow can be impaired via hepatic artery compromise and/or obstruction of the portal vein. Intrahepatic blood flow disturbances can occur as a result of cirrhosis and sinusoidal occlusion. Hepatic outflow impairment can be secondary to hepatic vein obstruction due to, for example, thrombosis. Primary hepatic vascular diseases are rare and form a heterogeneous group with a spectrum of diverse histologic features. Furthermore, due to the intimate association of the hepatic vasculature with the parenchyma, vascular changes can be seen in essentially every type of hepatic disorder.[4] Thus, in any liver biopsy, it is important to consider vascular pathology. If pathologic changes associated with vascular disease are noted in the liver biopsy, then the pathologist must determine whether the issue is secondary to intrinsic hepatic disease, primary hepatic vascular disease, or a combination of both.

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Impaired hepatic inflow

Acute ischaemia

Also known as ischaemic hepatitis, shock liver or hypoxic hepatitis, sudden and severe hypo-perfusion of any cause can result in liver ischaemia. Common causes include acute cardiac failure, circulatory shock due to sepsis, hypovolaemia, severe trauma, and burns. Diagnosis is usually straightforward when circulatory issues are clinically obvious. When circulatory issues are clinically subtle and liver dysfunction is significant, diagnosis may be challenging. In this setting transaminase elevation may reach the levels of that seen in patients with viral or toxic hepatitis, and acute ischaemia may not be part of the clinical differential diagnosis.[5]

Histologically, ischaemia leads to well-demarcated areas of coagulative necrosis that are typically seen in the perivenular region (zone 3) and less frequently in zone 2. The periportal region (zone 1) usually remains unaffected (Figure 1). Reticulin stain highlights intact cord-sinusoid pattern with condensation of zone 3 reticulin fibres as a result of perivenular hepatocellular dropout. The other helpful clue to liver ischaemia is the presence of apoptotic bodies in the zone between the normal and necrotic hepatocytes. Inflammation is usually scant or absent.[4] Abundant ceroid-laden macrophages may be seen in the affected area. Larger, well-defined areas of coagulative necrosis are considered infarcts, which typically occur as a result of systemic hypoperfusion in combination with obstruction of portal or hepatic veins. Ischaemic necrosis can be histologically indistinguishable from acetaminophen induced necrosis.

Non-cirrhotic portal hypertension

Portal hypertension is a clinical syndrome defined by a portal-caval venous pressure gradient exceeding 5 mm Hg.[6] Causes may be pre-hepatic, intra-hepatic, or post-hepatic.[7] Though one of the most common intrahepatic causes is cirrhosis, portal hypertension can occur in patients with non-cirrhotic livers. Portal hypertension in the absence of cirrhosis is referred to as non-cirrhotic portal hypertension (NCPH). Worldwide, the most common cause of NCPH is schistosomiasis. Common causes in the Western world include chronic liver diseases such as alcohol, non-alcoholic steatohepatitis, primary biliary cholangitis, primary sclerosing cholangitis, sarcoidosis, portal vein thrombosis and Budd-Chiari syndrome. Patients with these conditions may develop portal hypertension clinically before histologic cirrhosis fully developed. If all conditions have been excluded, the diagnosis of idiopathic non-cirrhotic portal hypertension (INPH) can be established.

NCPH is histologically and clinically under-recognized. Clinically, patients with NCPH present features of portal hypertension, such as gastrointestinal bleeding and splenomegaly. Imaging studies may show a nodular liver with thickened portal

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Distribution of vascular injury in hepatic vascular diseases

	Blood inflow	Intrahepatic blood flow		Blood outflow
	Non-cirrhotic portal hypertension	Cirrhosis	Sinusoidal obstruction Syndrome	Congestive hepatopathy/ Budd-Chiari Syndrome
Large portal vein	−	−	−	−
Small portal vein	++	++	+/−	+
Sinusoidal injury	+/−	++	++	++
Small hepatic vein	+/−	++	++	++
Large hepatic vein	−	−	−	++

Table 1

veins, which can frequently lead to the misdiagnosis of cirrhosis, so that a liver biopsy is required to distinguish cirrhosis and non-cirrhotic portal hypertension.

INCPH is confusing because many different names have been used to describe this entity. In the Indian subcontinent, it is known as non-cirrhotic portal fibrosis, whereas in Japan it is referred to as idiopathic portal hypertension. In the Western world it is known as hepatoportal sclerosis, idiopathic portal hypertension, incomplete septal cirrhosis, and nodular regenerative hyperplasia.

The aetiology of INCPH is broad and include immunological disorders (systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis), chronic infections (HIV), medication or toxic injury (azathioprine), genetic disorders (Turner syndrome), and hypercoagulable states.[6,7] The histologic features of INCPH are heterogeneous and non-specific. The two most commonly observed histologic features of INCPH are obliterative portal venopathy (OPV) and nodular regenerative hyperplasia (NRH). In OPV, there is obliteration or luminal narrowing of a few or several of the portal vein branches with dense deposits of elastic fibres in the vessel wall. Thickening of portal venules can be extensive and may cause the venules to resemble the hepatic artery of the same portal tract (Figure 2a, b).[8]

NRH, also known as micronodular transformation, is characterized by the transformation of the normal hepatic parenchyma into regenerative nodules in the absence of fibrosis. These nodules are small ranging from 1 to 3 mm in diameter and have mild or complete absence of fibrosis (Figure 3a). Nodularity is a consequence of alterations in small portal veins. Regenerative nodules are composed of hyperplastic hepatocytes arranged up to two cell thick plates and are separated by small, atrophic hepatocytes. The atrophied hepatocytes are compressed into parallel plates between the individual nodules. The compressed hepatocytes can be best visualized on a reticulin stain, which highlights the nodules with expanded liver cell plates and adjacent zones of reticulin compression associated with atrophied hepatocytes (Figure 3b).[9] Some degree of perisinusoidal fibrosis or periportal fibrosis may be observed. Between the hepatic lobules, thin fibrous septae can be seen. Sinusoidal dilatation may be visible in areas of hepatocellular atrophy. NRH presents with only mild

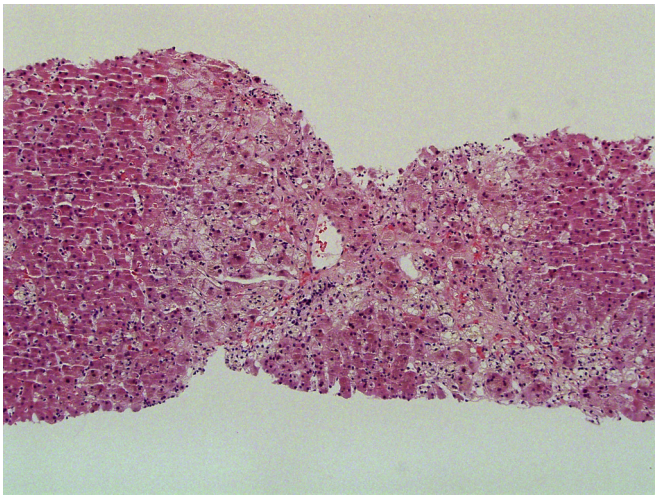

Figure 1 Acute ischaemia. Well-demarcated coagulative necrosis around central vein.

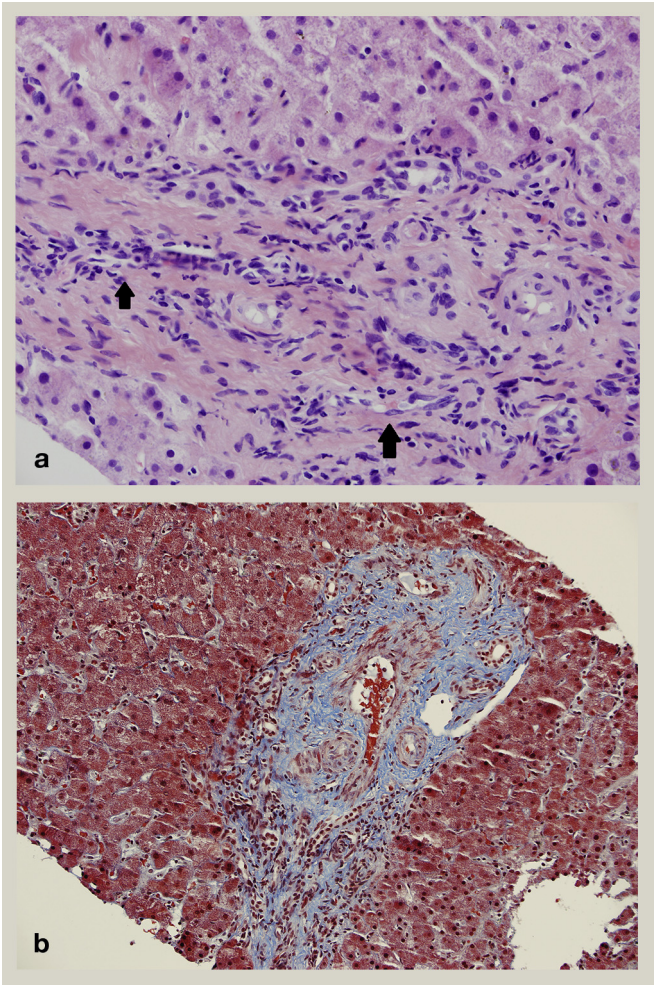

Figure 2 Idiopathic non-cirrhotic portal hypertension. (**a**). Obliterative portal venopathy shows narrowing of portal veins (arrows) in the portal triad. Venules resemble arteres. (**b**). Trichrome stain shows fibrosis around the portal vein, but no evidence of cirrhosis.

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