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Idiopathic Noncirrhotic Portal Hypertension

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Overview:

Cirrhosis is the most common cause of portal hypertension but a heterogeneous group of clinical entities, collectively referred to as non-cirrhotic portal hypertension (NCPH), can also lead to elevation of the portal venous pressure in the absence of cirrhosis. Common causes of NCPH are nonalcoholic or alcoholic steatohepatitis, primary biliary cholangitis, primary sclerosing cholangitis, congenital hepatic fibrosis, extra-hepatic portal vein thrombosis, and Budd-Chiari syndrome. Table 1 lists common causes of NCPH.

Idiopathic noncirrhotic portal hypertension (INCPH) is characterized by the elevation of portal venous pressure with no known cause. This entity has been ascribed various terms such as hepatoportal sclerosis, idiopathic portal hypertension, noncirrhotic portal fibrosis, incomplete septal cirrhosis, nodular regenerative hyperplasia (NRH) and obliterative portal venopathy (OPV). Because of the ambiguity of the nomenclature, the term INCPH was proposed to encompass these entities. Additionally, INCPH is considered a unifying term because it includes both clinical and histopathological aspects. Furthermore, the term “idiopathic” is controversial because the entity is seen in association with certain diseases. However, because the pathogenesis of INCPH remains uncertain, the term may still be applicable.

The incidence of INCPH varies throughout the world. In India in the 1980s, it was estimated to be present in 23% of patients with portal hypertension although

currently it is reported to be lower. In the Western world, the incidence ranges from 3-5% among patients having portal hypertension. There is a male predominance with a younger age of onset in India (25-35 years old) as compared to patients in the United States and Europe where there is a 3:1 female to male ratio and the median age of onset is 40 years.

Due to the low level of clinical suspicion for this disease, INCPH may be missed or may be confused with other diseases. This leads to INCPH being under-recognized and its incidence to be underestimated. Because such patients present with signs of portal hypertension, the frequent assumption is that the liver is cirrhotic. Awareness of the existence of this entity by both clinicians and pathologists is paramount because management of the portal hypertension is critical and may be the only treatment necessary.

The most frequent presentation of INCPH is with esophago-gastric variceal bleeding and hypersplenism among patients in India. Chronic elevation of aminotransferases is reported to occur in only 19% of patients in the West. Splenomegaly along with liver test abnormalities are considered to be the main presenting signs in Western patients and portal hypertensive bleeding is less common. Many studies have shown that no clinical or laboratory alterations are pathognomonic of INCPH. Hepatic encephalopathy is rare and ascites occurs in only half of the patients. The prevalence of hepatopulmonary syndrome is 10%. The liver function is typically well maintained during the course of the disease. As a result, mortality from variceal bleed is low compared to that of a variceal bleed in cirrhotic patients. Nonetheless, the major cause of mortality in INCPH patients is GI bleeding. The survival of these patients lies between those with cirrhosis and the normal healthy population of comparable age with a 2-year and 5-year survival of almost 100% noted after successful eradication of esophagogastric varices.

On radiological imaging studies, ultrasound may show a nodular liver and thickening of portal vein walls, lending to the misdiagnosis of cirrhosis. Transient elastography (Fibroscan®) typically shows lower stiffness values (~9.2 kPA) as compared to those with cirrhosis (>14kPA). No specific changes are seen on Magnetic Resonance Imaging either. Regenerative nodules appear hyperintense on T1-weighted images and iso- or hypointense on T2-weighted images.

Portal vein thrombosis is a common complication of INCPH. In a follow up study, some patients with INCPH were noted to have developed portal vein thrombosis on follow-up 5 to 7 years later. This is attributed to the low portal vein flow secondary to the presinusoidal increase of hepatic resistance.

Etiology:

The etiology of INCPH is multifactorial but five different types of conditions are postulated to give rise to INCPH:

1. Immunological.
    a. Systemic sclerosis – the disease promotes fibrogenesis
    b. Systemic lupus erythematosus – immunoglobulins interfere with prostacyclin formation, which then increases microthrombi formation
    c. IgA anticardiolipin antibody elevation leading to obliteration of small blood vessels
    d. Primary hypogammaglobulinemia – INCPH is known to occur in up to 70% of patients.
2. Infection: Bacterial infection of the gut with repeated septic embolization lead to subsequent obstruction of small portal venules. This theory is supported by the high prevalence of INCPH in low socioeconomic areas. E. coli infection in the portal vein leads to the development of clinical and histological characteristics of INCPH. Among HIV+ patients, INCPH occurs in some who have had prolonged exposure to anti-retroviral

agents, particularly didanosine. On the other hand, the presence of hypercoagulability by itself may lead to INCPH. It is believed that there is endothelial and mitochondrial damage due to didanosine.

3. Medications and toxins: Among the drugs that have been implicated are azathioprine, 6-thioguanine, 6-mercaptopurine, arsenic as Fowler's solution, and others. An underlying susceptibility is needed to develop this disorder when exposed to implicated drugs. In a recent study, four single nucleotide polymorphisms at the two genes coding enzymes of purine metabolism were shown to have a cumulative risk of developing INCPH. If all 4 SNPs are present, the risk approaches 100% in HIV patients who were exposed to didanosine.
4. Genetic disorders: This theory is supported by familial aggregation of INCPH. INCPH is also found to occur in several congenital disorders such as Adams-Oliver syndrome and Turner's disease. Furthermore, there is a high prevalence of HLA-DR3+ in families who have a high incidence of INCPH.
5. Thrombophilia: A 54% prevalence of pro-thrombotic disorders is found in INCPH. This is supported by the high prevalence and incidence of portal vein thrombosis in Western patients with INCPH.

Pathogenesis:

There are two theories as to why INCPH develops. Studies by Wanless have suggested that OPV is the primary lesion in the development of intrahepatic hemodynamical changes. This leads to parenchymal remodeling resulting in hepatocyte atrophy in areas with reduced portal vein blood supply and compensatory hyperplasia in the better perfused areas. Portal vascular channels (shunt vessels) shunt blood from the obliterated portal segments toward unaffected portal tracts. On the other hand, Hillaire's hypothesis is that the prothrombotic disorder acts directly on the sinusoidal and portal vein wall,

inducing fibrosis and obstruction, that then lead to secondary alterations in the microarchitecture.

Pathology:

Gross: The liver may appear normal, enlarged, or sometimes even shrunken. The capsular surface may be nodular and the cut surface may have vague nodularity but without fibrosis. In patients who required liver transplantation for INCPH, the liver weights were below one kilogram.

Histology: Liver biopsy is essential in making a diagnosis of INCPH. There are no pathognomonic histological features in INCPH. The features are heterogeneous. The features observed are:

1. OPV, which is luminal narrowing or obliteration of some or majority of portal vein branches accompanied by dense deposits of elastic fibers. Portal venules may be thickened to such an extent that they resemble the hepatic artery in the same portal tract. This is termed phlebosclerosis.
2. NRH, less commonly known as micronodular transformation, in which nodules are composed of hyperplastic hepatocytes and are surrounded by atrophic hepatocytes. This feature is best seen on a reticulin stain.
3. Increased numbers of portal vascular channels along the edge of the portal tract. These vascular structures appear, and may function as, paraportal shunt vessels.
4. Irregular and unusually large and widely dilated portal veins that frequently herniate into the surrounding parenchyma.
5. Sinusoidal dilatation with formation of megasinusoids.
6. Peri-portal and peri-sinusoidal fibrosis resulting in densely fibrotic portal tracts having rounded borders. When fibrous septa are present, these end blindly in the lobule and do not bridge with other portal tracts, unlike those seen in cirrhosis.

7. Irregular distribution of portal tracts with some appearing to be remnants of portal tracts whereas others appearing be approximating each other. The latter are associated and result from parenchymal loss.

Of note, not all the features listed above may be seen on a biopsy. Frequently, combinations of histological features are present, the most frequent are those of concurrent OPV and NRH.

Management:

The treatment is primarily controlling the portal hypertension and preventing bleeding from esophageal varices. These include the use of non-selective beta blockers, endoscopic variceal ligation, sclerotherapy, splenectomy or partial splenic embolization, or sometimes shunt surgery and transjugular intrahepatic porto-systemic shunt. In some patients, anticoagulation for thrombophilic INCPH patients might be beneficial. In rare instances, liver transplantation has been performed. This latter group consisted mostly of patients thought to have cirrhosis prior to transplantation although liver transplantation may be done if the portal hypertension is medically refractory.

Summary:

INCPH, although a rare condition, is under-recognized in the Western world. Lack of awareness as well as the lack of familiarity of the histological features among pathologists may contribute to the underestimation of this condition. OPV and NRH changes may be subtle but if given the clinical information of portal hypertension, the pathologist should look for these changes. As long as the complications of portal hypertension are properly managed, the disease has a good prognosis.

Table 1. Common causes of non-cirrhotic portal hypertension.

Sinusoidal obstruction syndrome
Nonalcoholic steatohepatitis
Alcoholic hepatitis
Budd-Chiari syndrome
Schistosomiasis
Sarcoidosis
Primary biliary cholangitis
Primary sclerosing cholangitis
Congenital hepatic fibrosis
Cystic fibrosis
Hepatic arterio-portal fistula/splanchnic arterio-venous fistula
Extrahepatic portal vein obstruction
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
Splenic vein thrombosis
Massive splenomegaly
Right-sided heart failure/constrictive pericarditis
Pylephlebitis

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