Idiopathic Non-Cirrhotic Portal Hypertension

M. Isabel Fiel, M.D.
Professor of Pathology
Icahn School of Medicine at Mount Sinai
New York, NY

Overview
1. Disease entities that cause non-cirrhotic portal hypertension
2. INCPH: definition, clinical presentation
3. Pathological features of INCPH
4. Etiology and Pathogenesis
5. Helpful clues and take away points

Cirrhosis is the most common cause of portal hypertension

Sinusoidal obstruction syndrome (SOS) and Veno-occlusive disease (VOD)

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Common causes of non-cirrhotic portal hypertension
- Sinusoidal obstruction syndrome
- NASH or ASH
- Budd-Chiari syndrome
- Schistosomiasis
- Sarcoidosis
- PBC and PSC
- Congenital hepatic fibrosis
- Cystic fibrosis
- Arterio-venous fistula
- Extrahepatic PV obstruction
- HHT (Osler-Weber-Rendu)
- Splenic vein thrombosis
- Massive splenomegaly
- Right-sided heart failure/constrictive pericarditis
- Pylephlebitis

Non-cirrhotic portal hypertension
- Elevation of portal venous pressure in the absence of cirrhosis
Budd-Chiari Syndrome

Steatohepatitis

ASH

NASH

Schistosomiasis

Primary biliary cholangitis

Primary sclerosing cholangitis

Ductal plate malformation-Congenital hepatic fibrosis

Osler-Weber-Rendu
Idiopathic Non-Cirrhotic Portal Hypertension (INCPH)

- INCPH is the proposed term to replace:
  - Hepatoporal sclerosis
  - Idiopathic portal hypertension
  - Non-cirrhotic portal fibrosis
  - Incomplete septal cirrhosis
  - Nodular regenerative hyperplasia
  - Obliterative portal venopathy
- Considered a unifying term because it includes both clinical and histopathological aspects
- “Idiopathic” is controversial because the entity is seen in association with certain diseases
- “Idiopathic” primarily because the pathogenesis is uncertain

Incidence
- India: 23% of patients with portal hypertension (1980s), male predominance, age 23-35 years
- Western world: 3-5% in those with portal hypertension, 3:1 female to male ratio, median age of onset is 40 years.

Clinical presentation
- Variceal bleeding - most frequent
- Hypersplenism
- Elevated aminotransferases
- Ascites
Pathological features of INCPH

Gross
- Normal, enlarged, sometimes shrunken
- Capsular surface may be nodular
- Cut surface may have vague nodularity but without fibrosis

The histology of INCPH is heterogeneous
- Obliterative portal venopathy (OPV)
- Nodular regenerative hyperplasia (NRH)
- Paraportal shunt vessels
- Unusually large and widely dilated portal veins that herniate into the surrounding parenchyma
- Sinusoidal dilatation (megasinusoids)
- Paraportal and perisinusoidal fibrosis → dense portal fibrosis
- Irregular distribution of portal tracts

NOT ALL FEATURES MAY BE SEEN ON A BIOPSY!

Obliterative portal venopathy
- Luminal narrowing or obliteration of some or majority or portal vein branches (phlebosclerosis)
- Dense deposits of elastic fibers
- Portal venules may be thickened that they resemble the hepatic artery in the same portal tract
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Nodular regenerative hyperplasia
- Diffuse micronodular transformation
- Compression of liver cell plates in between hyperplastic nodules
  - Crowding of reticulin fibers
- Nodules are composed of hyperplastic hepatocytes and are surrounded by atrophic hepatocytes
- Best seen on a reticulin stain

Increased numbers of portal vascular channels along the edge of the portal tract → paraportal shunt vessels
Irregular, unusually large, widely dilated portal veins that frequently herniate into the surrounding parenchyma

Sinusoidal dilatation with formation of megasinusoids

Irregular distribution of portal tracts
Densely fibrotic portal tracts

Densely fibrotic portal tracts
Blindly-ending fibrous septa

Densely fibrotic portal tracts
Blindly-ending fibrous septa
Etiology and Pathogenesis

- **Immunological:**
  - Systemic sclerosis
  - Systemic lupus erythematosus
  - IgA anticardiolipin antibody elevation → obliteration of small blood vessels
  - Primary hyoanemeglobulinemia → INCPH known to occur in up to 70% of patients.

- **Infectious**

- **Medications and toxins:**
  - Azathioprine, 6-thioguanine, 6-mercaptopurine, arsenic as Fowler’s solution

- **Genetic disorders**
  - Familial aggregation of INCPH
  - Occur in several congenital disorders such as Adams Oliver syndrome and Turner’s disease.
  - High prevalence of HLA-DR3+ in families who have high incidence of INCPH.

- **Thrombophilia:**
  - 54% prevalence of prothrombotic disorders
  - Supported by the high prevalence and incidence of portal vein thrombosis in Western patients with INCPH.

Theories of Pathogenesis

- OPV is the primary lesion → hepatocyte atrophy → portal vascular channels shunt blood from the obliterated portal segments to unaffected portal tracts (Wireless)

- Prothrombotic disorder acts directly on the sinusoidal and portal vein wall, → induce fibrosis and obstruction → secondary alterations in the microarchitecture (Hillaire)

- Aberrant vessels develop in order to compensate for portal circulatory insufficiency due to obliteration of portal vein branches
  - Decrease of intrahepatic collateral vessels → responsible for parenchymal atrophy and deterioration of liver function in the advanced stage of the disease
  - Liver cell atrophy → regenerative nodule formation

Development of OPV

1. Early lesions
   - Capillary dilatation and edema with microaneurysmal dilatation of the sinusoids at the limiting plate

2. Portal vein dilatation
   - Herniation of large thin-walled veins into the surrounding parenchyma

3. Late stage
   - Phlebosclerosis and portal fibrosis
   - Bile duct changes
   - Arterial abnormalities
   - Periportal stellate extension

Features of OPV may exist before signs of portal hypertension appear

- 59 patients, mean age 38 years
- OPV on liver biopsy
- Initial presentation:
  - Portal hypertension in 64%
  - Portal vein thrombosis in 22%
  - Abnormal liver tests in 20%

- Etiology:
  - 30% had pro-thrombotic disorders
  - 10% idiopathic
  - Remainder had immune-mediated disorders

- Median follow-up of 8.6 years
  - Features of portal hypertension worsened in 46%
  - Portal vein thrombosis in 44%
  - Portal hypertension was ultimately found in 88% of patients, respectively

Treatment of Non-Cirrhotic Portal Hypertension

- Prevention of recurrent bleeding
  - Beta adrenergic agents
  - High risk of re-bleeding, ascites
  - Endoscopic therapy
  - Surgical shunts
  - Rare development of encephalopathy
  - Liver transplantation
Summary

- INCPH is an uncommon disorder that causes portal HTN
  - Under-recognized
  - Lack of familiarity of the histological features may contribute to the underestimation of the incidence.
- Increasing recognition and incidence
  - Clinicians, radiologists and pathologists made aware that INCPH can mimic cirrhosis
  - Clinical input very important in making the diagnosis
- Heterogeneous histology
  - NRH and OPV are almost always part of the spectrum
- Liver synthetic function is preserved and liver transplantation is rarely performed unless compromised → small liver volume
- Liver needle biopsy may be helpful, however, the diagnosis may be missed unless there is strong clinical suspicion of this entity

Helpful clues and take-home points for INCPH

- Histological changes may be subtle.
- Diagnosis is difficult on a needle biopsy.
  - Clinical information of presence of portal hypertension.
  - When portal tracts are either too close or too far from each other.
  - When portal tracts have rounded borders.
  - When portal tracts have too many blood vessels.
  - When the diagnosis is suspected, order a reticulin stain as NRH and OPV frequently occur together.
  - When a biopsy looks “normal”, consider INCPH

THANK YOU