Pathology of non-cirrhotic portal hypertension and incomplete septal cirrhosis

Stefan G Hübscher

Abstract

This review will provide an overview of the pathological features of non-cirrhotic portal hypertension (NCPH) and incomplete septal cirrhosis (ISC), focussing on practical diagnostic approaches and problems. Although many liver diseases may be associated with portal hypertension in the absence of advanced fibrosis, the term NCPH is most widely used to describe a spectrum of changes resulting from occlusion of small portal vein branches, also referred to as "hepato-portal sclerosis" or "obliterative portal venopathy". Other histological manifestations of NCPH include parenchymal atrophy, nodular regenerative hyperplasia, formation of shunt vessels and foci of sinusoidal dilatation. In more severe cases, foci of parenchymal collapse may be associated with formation of delicate non-linking fibrous septa, corresponding to incomplete septal cirrhosis. Although ISC is generally considered to be part of the morphological spectrum of NCPH, it can also be regarded as part of the spectrum of true cirrhosis — either reflecting cirrhosis that is incompletely developed or partially regressed.

Keywords hepato-portal sclerosis; incomplete septal cirrhosis; liver biopsy; nodular regenerative hyperplasia; non-cirrhotic portal hypertension; obliterative portal venopathy

Introduction

The aim of this review is to provide an overview of the pathological features of non-cirrhotic portal hypertension (NCPH) and incomplete septal cirrhosis (ISC), focussing on practical diagnostic approaches and problems related to liver biopsy interpretation.

There are several reasons why liver biopsies from patients with non-cirrhotic portal hypertension are difficult to assess. Firstly, in western countries, NCPH is much less common as a cause of portal hypertension than hepatic fibrosis or cirrhosis and may thus not be considered in the differential diagnosis. Secondly, histological changes are often subtle and may not be recognized unless they are specifically looked for. They are also patchy in distribution and there are potential problems with sampling variability, particularly if small needle biopsy specimens are obtained. Finally, NCPH includes a spectrum of morphological manifestations — the relationship between the individual changes that are seen in NCPH is incompletely understood and there is confusion about the terminology used in this setting.

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Definition of non-cirrhotic portal hypertension and incomplete septal cirrhosis

The definition of non-cirrhotic portal hypertension is clinico-pathological — i.e. clinical signs of portal hypertension occurring in the absence of cirrhosis (or significant fibrosis). It is increasingly accepted that the abnormalities seen in NCPH occur as a result of primary vascular lesions that result in reduced portal venous blood flow. Hepatic synthetic function is generally well-preserved. This is in contrast to liver cirrhosis, where changes in portal venous blood flow are thought to occur as a complication of fibrosis and deranged liver architecture. Cirrhosis is also more typically associated with abnormalities of hepatic synthetic function. However, the distinction between NCPH and hepatic fibrosis/cirrhosis is not always clear-cut. On the one hand, the vascular lesions that occur in NCPH have also been implicated in the pathogenesis of liver fibrosis and cirrhosis. Conversely, patients with liver cirrhosis frequently develop veno-obliterative lesions resembling those seen in NCPH as a secondary phenomenon. The relationship between vascular lesions and hepatic fibrosis will be discussed further later.

The definition of incomplete septal cirrhosis (ICS) is purely morphological. It is characterized by fibrous septa, which are typically thin and fragmented or blind-ending (Figure 1) and are often associated with disturbed vascular relationships, of the type also seen in NCPH.[1] Complete cirrhotic-type regenerative nodules are not seen. The pathogenesis of ICS is poorly understood. It has been considered to be part of the spectrum of NCPH, possibly reflecting late-stage disease, but can also be regarded as part of the spectrum of true cirrhosis — either reflecting cirrhosis that is incompletely developed or partially regressed. Either way, ICS can be viewed as a bridge between NCPH and true cirrhosis.

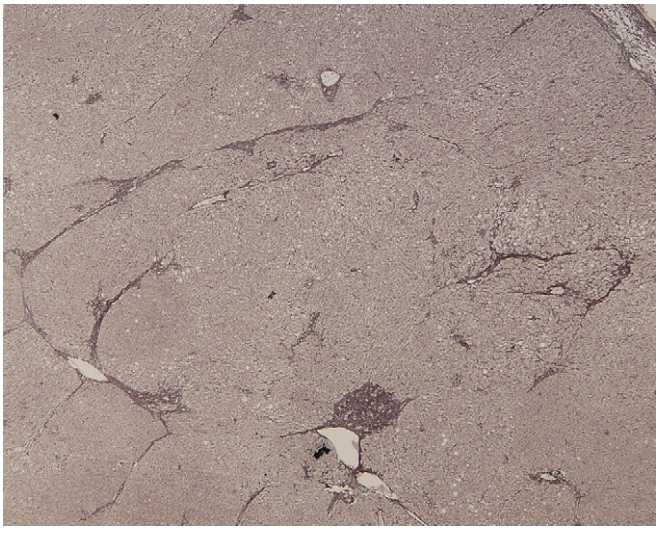

Figure 1 Incomplete septal cirrhosis. Hepatectomy specimen from a patient undergoing liver transplantation with a presumed diagnosis of "cryptogenic cirrhosis". There are delicate fibrous septa — some are blind-ending and others are associated with bridging fibrosis. The normal vascular relationships are disturbed, but cirrhotic-type nodule formation is not seen. Reticulin stain.

Classification of portal hypertension

Portal hypertension can be classified in a number of ways, as summarized in Table 1.[2] A useful approach to the classification and pathogenesis of portal hypertension is to consider the normal vascular anatomy of the portal venous circulation. The vessels involved include large portal vein branches (extrahepatic and intrahepatic), small portal veins, sinusoids and hepatic veins (small and large). Portal hypertension can also be classified according to the relationship of the site of vascular compromise to the liver itself (pre-, intra- or post-hepatic) or at a microscopic level, based on its relationship to sinusoidal blood flow. It is worth noting that portal hypertension occurring in cirrhosis can include elements that involve all of the main vascular compartments within the liver. Although the architectural changes occurring in cirrhosis are principally thought to affect hepatic sinusoidal blood flow, occlusive lesions in small portal and hepatic vein branches are commonly seen as a secondary phenomenon in cirrhosis, as is thrombosis of large portal veins.

The primary hepatic vascular diseases associated with non-cirrhotic portal hypertension can also be classified according to the site of the blood vessels involved (Table 2). The pathogenetic mechanisms involved include thrombosis (for which there are a number of recognized prothrombotic factors) and endothelial injury (e.g. chemotherapy-induced, resulting in sinusoidal obstruction syndrome/hepatic veno-occlusive disease). Whilst all of the vascular diseases listed in Table 2 may be associated with portal hypertension in the absence of cirrhosis, the term "non-cirrhotic portal hypertension" is most frequently applied to changes occurring as a result of occlusion of small intrahepatic portal vein branches (also referred to as "idiopathic" and intrahepatic non-cirrhotic portal hypertension).

A detailed discussion of all of the vascular diseases that may be associated with portal hypertension in the absence of cirrhosis is beyond the scope of this review. Instead, the remainder of the article will focus on so-called "idiopathic" NCPH. The criteria used to define idiopathic NCPH include clinical evidence of portal hypertension (e.g. oesophageal varices, splenomegaly), exclusion of known risk factors for cirrhosis (e.g. alcohol, viral hepatitis), radiological investigations demonstrating patent large portal and hepatic veins and the absence of cirrhosis (or significant fibrosis) on liver biopsy.[3] A number of alternative terms have been used — these include "idiopathic portal hypertension", "non-cirrhotic portal hypertension", "non-cirrhotic intrahepatic portal hypertension", "hepato-portal sclerosis", "obliterative portal venopathy" and "non-cirrhotic portal fibrosis".

Classification of portal hypertension

Relationship to liver	Vessels involved	Relationship to sinusoids
Pre-hepatic	Portal veins (large)	Presinusoidal
Intrahepatic	Portal veins (small)	Presinusoidal
Intrahepatic	Sinusoids	Sinusoidal
Intrahepatic	Hepatic veins (small)	Post-sinusoidal
Intrahepatic	Hepatic veins (large)	Post-sinusoidal
Post-hepatic	Hepatic veins (large)	Post-sinusoidal

Table 1

Pathological features

Typical histological features

The main features typically seen in NCPH are listed in Table 3 and illustrated in Figures 2–6. Recognition of any of these features in a biopsy without apparent cirrhotic fibrous septa should prompt consideration of NCPH and a systematic search for other features. The table also includes some of the terms that are most frequently used to describe individual pathological features of NCPH. Whilst some studies use these terms in a way which suggests that they represent distinct entities, there is an increasing acceptance that they are all part of an overlapping morphological spectrum.

There is increasing evidence to suggest that the primary lesion in NCPH is obliteration of small intrahepatic portal vein branches (hepato-portal sclerosis, obliterative portal venopathy). For example, morphometric studies by Nakanuma and colleagues showed that this lesion was present in 100% of cases which had previously been classified variously as idiopathic portal hypertension, nodular regenerative hyperplasia, partial nodular transformation and incomplete septal cirrhosis.[4]

The normal portal tract contains one or more branches of hepatic artery, bile duct and portal vein. The hepatic artery and bile duct branches are present in close proximity to one another and are usually roughly the same diameter. The portal vein branch is typically 2–3 times the calibre of the other two vessels and is variable in location.[5] Hepato-portal sclerosis is characterized by a portal tract containing normal bile duct and arterial branches, but lacking a recognizable or appropriately sized portal vein branch (Figure 2). Morphometric studies have shown that up to 30% of small portal tracts in normal livers may lack portal vein branches,[5] so the finding of occasional portal areas lacking an appropriately sized portal vein branch is not by itself diagnostic of NCPH. In many cases the portal tract stroma has a partly sclerotic appearance, possibly reflecting the site of an obliterated portal vein branch. Less frequently, occlusive lesions can be identified in small portal vein branches,[4,6,7] particularly if connective tissue stains are used to identify the walls of portal vein branches. Some portal veins that are still patent have muscular hypertrophy of the media (arterialization), probably in response to increased pressure (Figure 3).[2,4] Other portal tracts have an atrophic or hypoplastic appearance.[1] Lack of significant portal tract inflammation is another typical feature of hepato-portal sclerosis and is helpful in distinguishing NCPH from other chronic liver diseases in which portal inflammation is typically present. Because the sclerotic portal tract changes seen in NCPH are often subtle, they may be easily overlooked unless a conscious effort is made to look for appropriately sized portal vein branches.

Reduction in portal venous flow results in two other characteristic features of NCPH. The first is atrophy of liver cell plates, particularly in perivenular regions which are furthest away from

Classification of non-cirrhotic portal hypertension (NCPH) based on the primary site of blood vessel involvement. The term NCPH is most frequently used to describe cases associated with occlusion of small portal vein branches, also referred to as "hepato-portal sclerosis" or "obliterative portal venopathy"

Site of vessel involved	Pathogenesis/pathological changes	Clinical syndromes
Portal vein (large)	Thrombosis	Portal vein thrombosis
Portal vein (small)	Obliteration/loss • possibly related to previous thrombosis (hepato-portal sclerosis, obliterative portal venopathy)	"Idiopathic" non-cirrhotic portal hypertension
Sinusoid	Endothelial injury • usually caused by toxins (dilatation/congestion)	Sinusoidal obstruction syndrome
Hepatic vein (small)	Endothelial injury • usually caused by toxins (luminal occlusion)	Hepatic veno-occlusive disease
Hepatic vein (large)	Thrombosis	Budd—Chiari syndrome

Table 2

the portal venous inflow (Figure 4). In more severe cases, there may be more generalized atrophy resulting in a reduced size of the liver as a whole. At a microscopic level, this results in portal tracts being abnormally closely apposed to one another. Secondly, there is compensatory hyperplasia of periportal hepatocytes in areas still receiving adequate portal venous blood supply — nodular regenerative hyperplasia (NRH) (Figure 4).[8] The nodules are typically small (1—3 mm diameter) and rarely exceed 1—2 cm diameter. Infrequently, there are larger nodules that may present as focal lesions.[9] Features of parenchymal atrophy and NRH are often subtle and may not be readily appreciated in conventional H & E sections. Reticulin staining is helpful to highlight the changes present (Figure 4b). Atrophy and NRH are also typically patchy in distribution and are therefore prone to problems with sampling variability. At the periphery of hyperplastic nodules in NRH there are often foci of perisinusoidal fibrosis running alongside atrophic cell plates (Figure 5). This is associated with activation of perisinusoidal stellate cells, which express smooth muscle actin indicating transformation to myofibroblasts.[10] These changes may form the precursor for the development of incomplete fibrous septa seen as part of the spectrum of "incomplete septal cirrhosis" (see Figure 1). They also resemble the perisinusoidal/pericellular fibrosis typically seen in fatty liver disease. Recognition of the associated vascular/architectural changes of NCPH and lack of obvious features of fatty liver disease should help to point to the correct diagnosis.

Summary of the histological changes occurring in non-cirrhotic portal hypertension, including commonly used terms used to describe some of the main findings

Histological findings	Pathological terms
Portal vein obliteration Parenchymal atrophy	Hepato-portal sclerosis
Nodular regeneration (without fibrosis)	Nodular regenerative hyperplasia
Portal vein ectasia (shunt vessels) Sinusoidal dilatation/congestion	
Delicate non-linking fibrous septa	Incomplete septal cirrhosis

Table 3

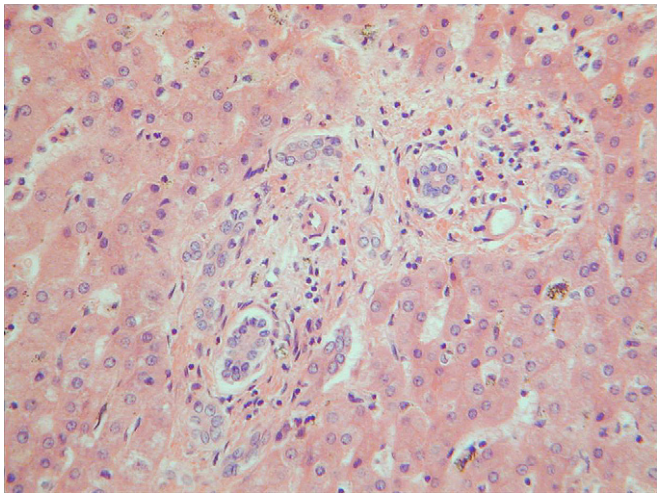

Figure 2 Obliterative portal venopathy. Two small portal tracts appear abnormally closely apposed. Both contain bile ducts and hepatic artery branches without accompanying portal veins. A ductular reaction is present at the periphery of the portal tract on the left.

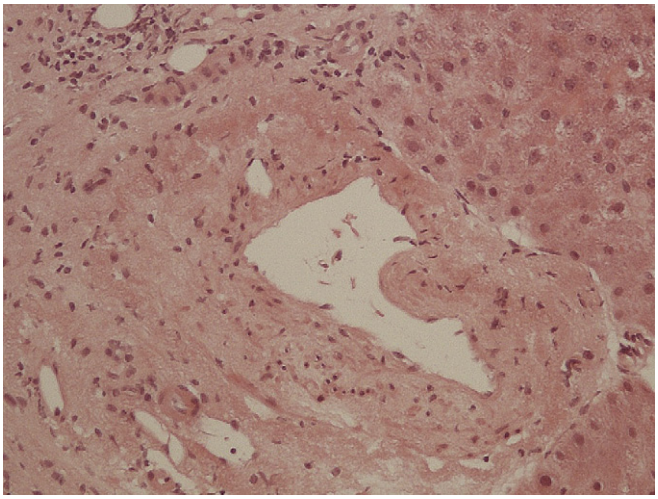

Figure 3 Muscular hypertrophy of a small portal vein branch has occurred in response to longstanding portal hypertension (arterialization).

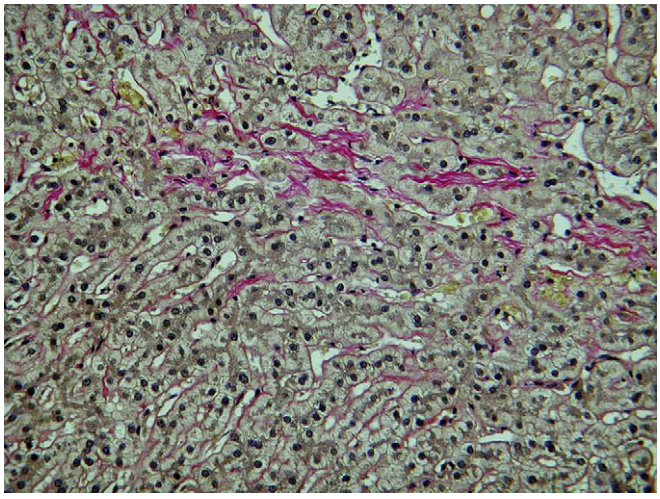

Figure 5 Perisinusoidal fibrosis in nodular regenerative hyperplasia. Collagen fibres are deposited in a perisinusoidal distribution alongside compressed liver cell plates at the periphery of a hyperplastic hepatocyte nodule. Focally there appears to be obliteration of the sinusoidal lumen. Haematoxylin van Gieson.

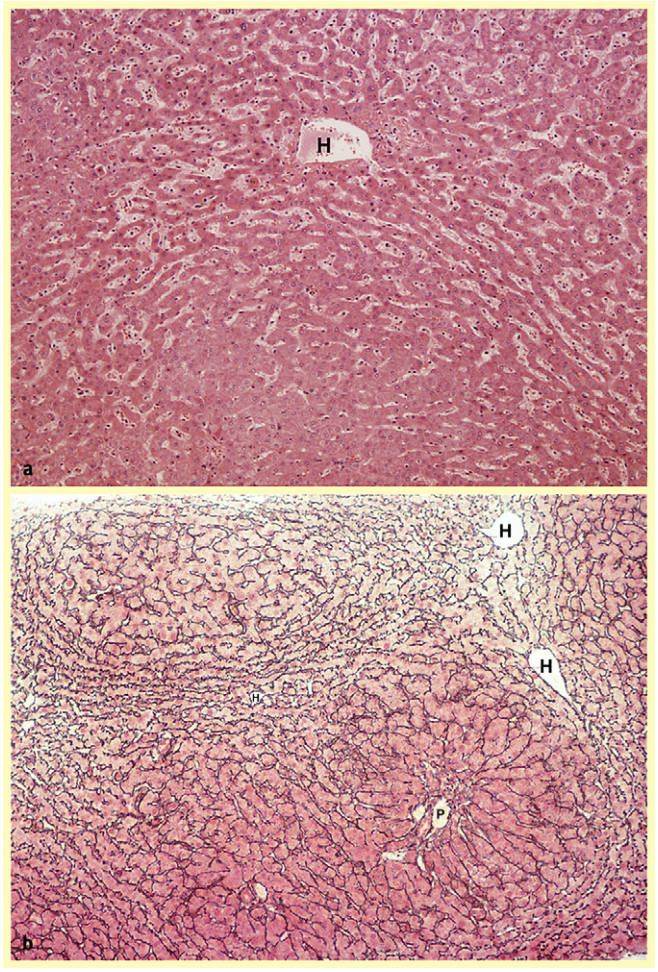

Figure 4 Nodular regenerative hyperplasia. (**a**) The liver cell plates adjacent to a small hepatic vein branch are atrophic. An adjacent hepatocyte nodule appears hyperplastic (H = hepatic vein). (**b**) Reticulin staining highlights the presence of a hyperplastic nodule of hepatocytes centred on a portal tract (P), with compression of liver cell plates in peripheral acinar regions (H = hepatic vein).

Another compensatory change following the obliteration of small portal vein branches is the development of portal vein shunt vessels, which appear as ectatic vein branches apparently herniating into the adjacent liver parenchyma (Figure 6). These shunt vessels may be derived from inlet venules[11] or from dilated branches of the peribiliary vascular plexus[12] and may also extend for some distance into the adjacent liver parenchyma. Shunt vessels also lead to the development of areas of parenchymal hyperperfusion, resulting in foci of sinusoidal dilatation with variable congestion, also referred to as "megasinusoids"[13] (Figure 7), which can mimic changes seen in peliosis hepatis[14] or venous outflow obstruction.[15]

Areas of parenchymal atrophy and/or parenchymal extinction may lead to the development of foci of collapse and passive septum formation resulting in the formation of delicate non-linking fibrous septa (incomplete septal cirrhosis) (see

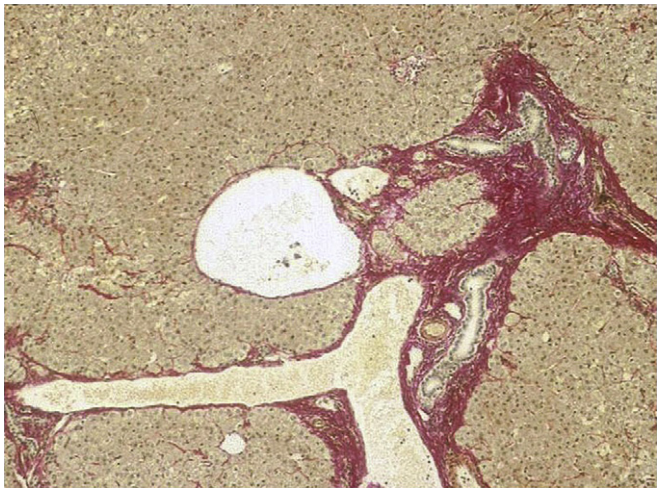

Figure 6 Periportal "shunt vessel". A dilated portal vein branch appears to herniate into the adjacent liver parenchyma. Haematoxylin van Gieson.

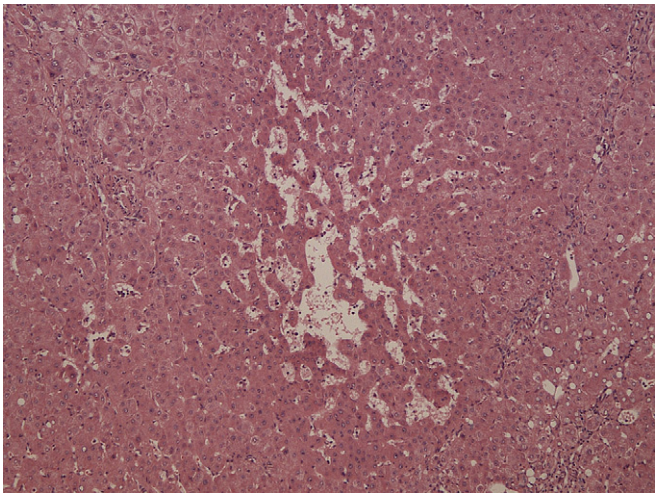

Figure 7 Sinusoidal dilatation is present in a centrilobular region. This is presumed to represent a localized area of hyperperfusion in an area where the portal venous blood supply is still intact.

Figure 1). In biopsies which are small and/or fragmented incomplete septal cirrhosis may be difficult to distinguish from inactive macronodular cirrhosis. As will be discussed later, there is evidence to suggest that cases in which vascular lesions are severe or widespread develop progressive fibrosis in some cases leading to cirrhosis.

A number of the features of NCPH, including atrophy, nodularity and fibrosis tend to be more pronounced in the subcapsular region of the liver,[4,6,10] possibly reflecting a regional variation in portal venous supply. This may result in the subcapsular region having an appearance resembling cirrhosis, whilst the remainder of the liver shows more subtle architectural changes more typically seen in NCPH. This has implications for assessing biopsy specimens obtained from the subcapsular region (including wedge biopsies), which may convey the misleading impression that the liver as a whole is cirrhotic.

Other histological features

Biliary features are commonly seen in patients with non-cirrhotic portal hypertension, for which the term "portal hypertensive biliopathy" has been used[16] (Table 4). Portal hypertensive biliopathy is mainly seen in patients with extrahepatic portal vein obstruction, where it results from cavernomatous transformation of the portal vein with the formation of choledochal varices leading to bile duct compression and changes resembling those seen in primary sclerosing cholangitis (PSC). Biliary features are also seen less frequently in patients with idiopathic NCPH.[4,6,16] The pathogenesis is uncertain, but one suggested mechanism is that vascular abnormalities in small portal tracts may compromise blood supply to bile ducts via the peribiliary vascular plexus. Cholestatic liver biochemistry is common, but symptomatic biliary tract disease is infrequent. The most common morphological changes are marginal zones of ductular reaction (see Figure 2) and periportal deposits of copper-associated protein. Foci of periductal fibrosis occur in up to 50% of patients resembling changes seen in PSC, but bile duct loss is infrequent.[4,17] Periportal accumulation of alpha-1-antitrypsin globules has also been described in idiopathic NCPH.[8]

Pathogenetic mechanisms

Primary non-cirrhotic portal hypertension

A proposed schema for the evolution of the histological changes occurring in NCPH is summarized in Figure 8. Assuming that occlusion of small portal vein branches is the "first hit", atrophy and foci of NRH occur as the earliest lesions, followed by formation of shunt vessels and foci of sinusoidal dilatation. Clinical signs of portal hypertension may relate both to the primary occlusive lesions in small portal veins and to secondary changes such as NRH and perisinusoidal fibrosis which further compromise sinusoidal blood flow. Areas of collapse, septum formation and the development of fibrosis occur as late events, and may produce changes that are difficult to distinguish from other causes of hepatic fibrosis or cirrhosis.

Summary of the "biliary features" that may be seen in non-cirrhotic portal hypertension ("portal hypertensive biliopathy"). These mainly occur as complication of extrahepatic portal vein obstruction, but can also occur in intrahepatic NCPH, usually to a lesser degree (from Dhiman. *Gut* 2007; 56: 1001–1008)[16]

	Extrahepatic portal vein obstruction	"Idiopathic" NCPH
Frequency of biliary features	94% (81–100%)	9–40%
Clinical manifestations	19% symptomatic (5–38%)	Rarely symptomatic Cholestatic LFTs common
Pathogenesis	Cavernomatous transformation of portal vein & formation of choledochal varices →bile duct compression	Mechanism uncertain • vascular abnormalities in small portal tracts may compromise blood supply to bile ducts via the peribiliary vascular plexus
Histological features	Resemble sclerosing cholangitis	Resemble sclerosing cholangitis

Table 4

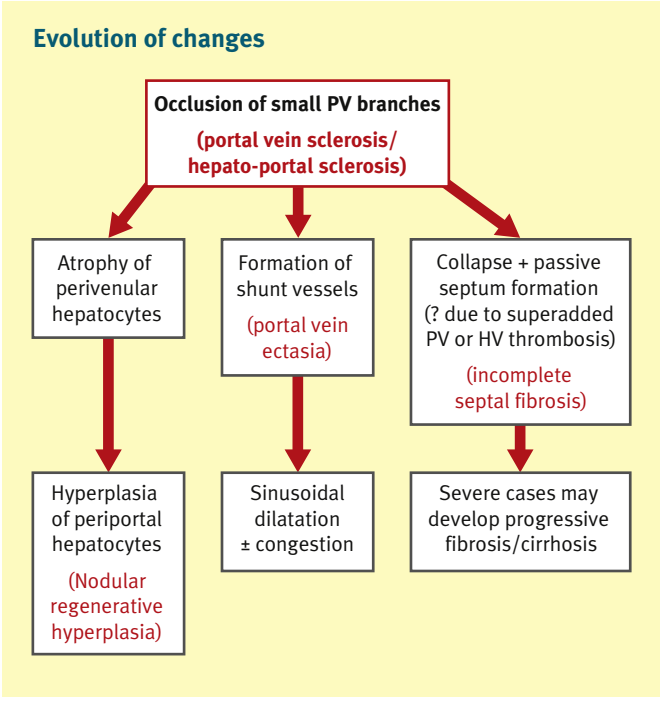

Figure 8 A proposed schema for the evolution of histological changes in NCPH. The "first hit" is occlusion of small portal vein branches. This results in atrophy of hepatocytes and foci of nodular regenerative hyperplasia in periportal regions. This is followed by formation of shunt vessels in areas where portal veins are still patent, leading to areas of sinusoidal hyperperfusion resulting in foci of sinusoidal dilatation. Areas of collapse, septum formation and the development of fibrosis occur as late events, and may produce changes that are difficult to distinguish from other causes of hepatic fibrosis or cirrhosis.

The evolution of morphological changes in idiopathic NCPH is difficult to demonstrate in serial biopsies. This is partly due to reluctance to biopsy patients on a regular basis, but also due to problems with sampling variability. However, in studies documenting histological features of NCPH, NRH is the most common abnormality, being present in >90% of cases. By contrast, incomplete septal cirrhosis is mainly seen in patients with severe or longstanding disease. In two recent studies of 24 patients undergoing liver transplantation for NCPH, incomplete septal cirrhosis was present in 13 (54%) cases[7,18] whilst NRH was present in 92% of cases. There is a single case report suggesting evolution from idiopathic portal hypertension to incomplete septal cirrhosis requiring liver transplantation over a 13-year period.[19] Another recent study suggested that obliterative portal venopathy detected in liver biopsies could precede the subsequent development of clinical signs of portal hypertension, in some cases by several years.[17]

The mechanism underlying occlusion of small portal vein branches is poorly understood. Thrombotic occlusion is the most likely mechanism and a pro-thrombotic tendency has been identified in 20–50% of patients.[3,17,20] Recognized pro-thrombotic factors include myeloproliferative disease, protein S or C deficiency and anti-phospholipid antibodies. A recent study postulated endothelial-mesenchymal transition as a mechanism for occlusion of small portal veins in idiopathic portal hypertension. Expression of mesenchymal markers such as pSmad2 and S100A4 was associated with reduced expression of the vascular endothelial marker CD34.[21]

Although obliterative portal venopathy is generally considered to be the most important mechanism in the pathogenesis of NCPH, sinusoids have also been suggested as a possible primary site of injury. In a study by Hillaire et al, 61% of patients with NCPH had NRH and perisinusoidal fibrosis without obvious portal vein occlusion.[3] This contrasts with a 96–100% prevalence of portal venopathy in two other studies.[4,17] One possible explanation for these disparate findings may be the patchy distribution of portal vein lesions and consequent sampling variability in needle biopsy specimens.[1] Wedge pressure studies have also suggested sinusoids as a possible site of obstruction[22] although this could represent sinusoidal compression secondary to NRH.[8] Other sinusoidal abnormalities described in patients with NCPH include increased intrasinusoidal T lymphocytes, in some cases associated with apoptosis of sinusoidal endothelial cells.[23,24]

Secondary NCPH

A number of the morphological changes seen in idiopathic NCPH have also been described as a secondary phenomenon in a range of other diseases associated with portal hypertension in the absence of advanced fibrosis or cirrhosis.[2,8] The most common manifestation is nodular regenerative hyperplasia. A summary of the main examples is presented in Table 5. For a more detailed discussion of other causes of NCPH, the reader is referred elsewhere.[2,8]

Amongst the various diseases listed in Table 5, there has been considerable recent interest in portal venopathy occurring in HIV-positive patients.[25] The main risk factor appears to be the cumulative exposure to anti-retroviral drugs, suggesting drug-induced toxic injury to endothelial cells as a likely mechanism. HIV-positive patients also have an increased prevalence of other prothrombotic factors such as protein S deficiency. Large portal vein thrombosis commonly occurs as a secondary event. It is also well-recognized that severe portal hypertension can occur in the absence of advanced fibrosis in patients with chronic biliary diseases such as primary biliary cirrhosis and primary sclerosing cholangitis,[26] where it has been postulated that portal vein occlusion may reflect collateral damage occurring as a consequence of injury to nearby bile duct branches. As discussed earlier, features of chronic biliary disease (including changes resembling PSC) can occur as a secondary phenomenon in patients with NCPH. In some cases where liver biopsies show combined features of chronic biliary disease and portal venous insufficiency, it may thus be difficult or impossible to determine the primary event on histological grounds alone and clinico-pathological correlation is therefore required.

Vascular lesions in the pathogenesis of cirrhosis

Elegant morphometric studies by Wanless and colleagues have led to the suggestion that occlusive lesions involving small portal and hepatic vein branches may be important in the evolution of hepatic fibrosis and cirrhosis.[27] A summary of the proposed mechanism is provided in Figure 9.[28] By contrast with NCPH where occlusion of small portal vein branches occurs as a primary event, probably related to portal vein thrombosis, the vascular occlusion occurring in chronic liver diseases associated with

Diseases in which features of non-cirrhotic portal hypertension (usually nodular regenerative hyperplasia) occur as a secondary phenomenon

Disease	Examples	Mechanisms/other features
Rheumatic/Connective tissue diseases	Rheumatoid arthritis, Systemic lupus erythematosus, Systemic sclerosis, Polyarteritis nodosa, Wegener's granulomatosis	Portal veins damaged as "bystander effect", secondary to hepatic arteritis. Anti-phospholipid antibodies may predispose to small portal vein thrombosis.
Haematological diseases	Myeloproliferative and lymphoproliferative diseases	May reflect underlying thrombotic tendency. Also associated with Budd–Chiari syndrome.
Immunodeficiency syndromes	HIV/AIDS, Other (e.g. common variable immunodeficiency)	Anti-retroviral drugs may cause toxic endothelial injury. Protein S deficiency also occurs in HIV-positive patients. Some cases have progressed to liver transplantation.
Drugs	Azathioprine, Oxaliplatin, 6-Thioguanine, Other chemotherapeutic agents	Drug-induced endothelial injury. Overlap with "sinusoidal obstruction syndrome" and "veno-occlusive disease".
Chronic biliary diseases (pre-cirrhotic)	Primary biliary cirrhosis, Primary sclerosing cholangitis, Biliary obstruction	Portal veins damaged as "bystander effect", secondary to bile duct injury. In cases with combined features of chronic biliary disease and portal venous insufficiency, primary event may be difficult to determine.
Gastrointestinal disease	Coeliac disease, Ulcerative colitis	IgA anti-cardiolipin antibodies derived from damaged intestine in coeliac disease may predispose to small portal vein thrombosis.
Other	Post-liver transplant	Possible mechanisms include previous rejection, drug toxicity, irregular regeneration in reduced-sized grafts. Common finding in late-post transplant biopsies. Frequently asymptomatic.

Table 5

inflammation and fibrosis can be viewed as a secondary event, most frequently related to portal tract inflammation. An important stage in the vascular pathogenesis of hepatic fibrosis is the development of areas of parenchyma ischaemia (also referred to as parenchymal "extinction lesions") which are thought to occur when there is a combination of obliteration of adjacent small portal and hepatic vein branches. These parenchymal extinction lesions form the basis for the development of fibrous septa. Areas of remodelling and resorption of fibrosis may lead to thinning and fragmentation of fibrous septa, corresponding to the picture of incomplete septal cirrhosis (also referred to as the "hepatic repair complex").

Clinical aspects

Many patients with NCPH are probably asymptomatic. In support of this suggestion, less than 10% of cases in which NRH was identified in a consecutive autopsy series had clinical features of portal hypertension prior to death.[29] In a recent study by Cazals-Hatem and colleagues, 21/59 of patients with a histological diagnosis of obliterative portal venopathy had no clinical signs of portal hypertension at the time of liver biopsy. Six of these 21 patients were subsequently found to have an extrahepatic portal vein thrombosis, whilst six of the remaining 15 patients developed portal hypertension during a median follow-up of 8.6 years.[17] Other aspects of this interesting study are discussed in the review on *Recent Advances in Medical Liver Disease* on pages 548–556 of this issue. These observations have implications for clinical management including the early detection of potentially treatable pro-thrombotic disorders.

Most patients with NCPH have portal hypertension with reasonably well-preserved hepatic synthetic function. The prognosis in such cases is better than cirrhotic patients with a similar severity of portal hypertension. As discussed earlier, cholestatic LFTs are common. Elevated serum levels of alkaline phosphatase (ALP) were identified in 25% of patients with NRH in one study[8] and abnormal LFTs were the presenting feature in 76% of NRH cases in another recent series.[20] ALP levels tend to be higher in patients with symptomatic portal hypertensive biliopathy.[16]

Although hepatic synthetic function is generally well-preserved, progression to liver failure occurs in some cases and may result in death from decompensated liver disease or the need for liver

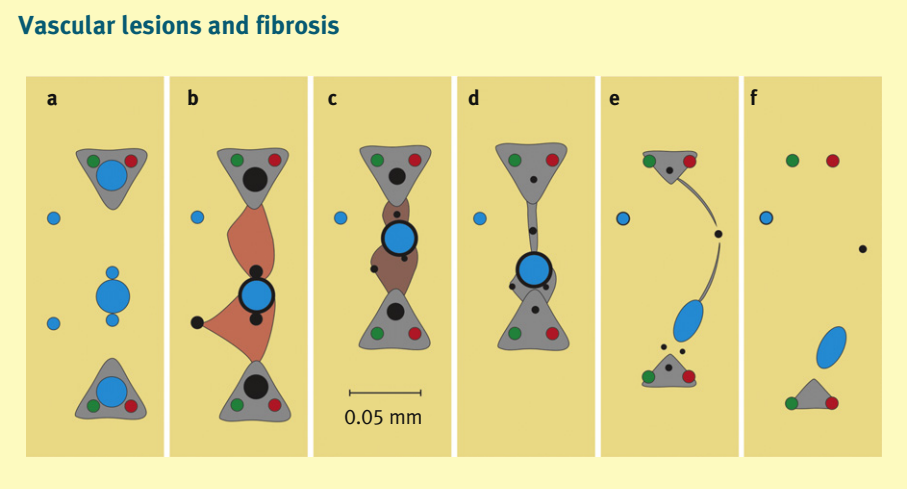

Figure 9 Vascular lesions in the pathogenesis of hepatic fibrosis and cirrhosis. (**a**) Normal liver with patent portal and hepatic veins (blue). (**b**) Obstruction of vein branches (shown in black) leads to areas in which hepatocytes are ischaemic (orange). (**c**) Loss of ischaemic hepatocytes leads to areas of collapse (brown), also referred to as "parenchymal extinction", with abnormally close apposition of portal tracts and hepatic veins. (**d**) Areas of parenchymal extinction are replaced by fibrous septa (grey), which form portal-portal linkages. Obliterated veins may now be incorporated into areas of fibrosis, where they are difficult to identify. (**e**) Hyperplasia of hepatocytes causes septa to elongate and become curved in shape. Resorption of fibrous tissue results in septa that are thin and fragmented ("incomplete septal cirrhosis"). (**f**) In some cases fibrous septa are completely resorbed. The vascular architecture remains abnormal with portal tract remnants that lack portal veins, obstructed hepatic vein remnants, and irregular arrangement of portal tracts and hepatic veins. (From Prof I Wanless, reproduced with permission.)

transplantation. A large proportion of patients undergoing liver transplantation for NCPH (21/24 in a combined series reported by Krasinskas and Fiel) have an incorrect pre-transplant diagnosis of cirrhosis (usually cryptogenic).[7,18] In many cases the incorrect pre-transplant diagnosis can be attributed to the lack of liver biopsy in the investigation of liver disease. Although the absence of portal vein thrombosis is generally required as a diagnostic criterion for idiopathic NCPH, there is evidence to suggest that portal vein thrombosis can occur as a secondary event in such cases[30] and may also be a factor predisposing to the development of liver failure.[22] Two recent studies documenting the natural history of NCPH have suggested that it does not always pursue a benign course[17,22] In the first study, 53% of patients followed up for a median of 88 months developed decompensated liver disease, with an overall transplant-free survival rate of 69% at 10 years,[22] whilst in the other recent study, 19% of patients progressed to end-stage liver disease (death or transplantation) over a mean period of 8.6 years.[17]

Conclusions

Liver biopsy plays an important role in the diagnosis and management of patients with non-cirrhotic portal hypertension. In addition to excluding the presence of significant fibrosis or cirrhosis, careful attention should be paid to identifying typical vascular and architectural changes of NCPH, such as obliteration of small portal veins and NRH, which are often subtle and patchy in distribution. In biopsy specimens that are small or fragmented, it can be difficult to distinguish NCPH with incomplete septal cirrhosis from inactive macronodular cirrhosis — this difficulty may also partly reflect the complex relationship that exists between vascular lesions and fibrosis in the liver. Liver biopsy may also identify other features of NCPH such as chronic biliary disease related to portal hypertensive biliopathy. In a small proportion of cases where the cause of portal hypertension is uncertain clinically, liver biopsy may point to a cause of chronic liver disease unrelated to NCPH. ◆

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Practice points

- The histological diagnosis of non-cirrhotic portal hypertension (NCPH) should involve more than simply excluding the presence of advanced fibrosis or cirrhosis
- Key lesions to recognize in NCPH are loss of small portal vein branches (obliterative portal venopathy), foci of parenchymal atrophy and nodular regenerative hyperplasia (NRH)
- Changes related to parenchymal atrophy and NRH are often subtle and may not be readily appreciated in routine H&E stained sections. Use of reticulin staining helps to highlight the relevant features
- The vascular and architectural changes that occur in NCPH are typically patchy in distribution and sampling variability may thus be a problem, particularly if small biopsies are obtained
- Histological features of NCPHT may precede the development of portal hypertension – an indication for clinical investigation and follow-up
- "Incomplete septal cirrhosis" is a rather poorly understood entity, which can be regarded as lying somewhere between NCPH and true cirrhosis