Non-Cirrhotic Portal Hypertension and Incomplete Septal Cirrhosis

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"Non-Cirrhotic Portal Hypertension"
Problems with Liver Biopsy Diagnosis

(1) Uncommon (compared with hepatic fibrosis/cirrhosis)

(2) Histological changes subtle and patchy in distribution

(3) Spectrum of morphological changes
- Relationship between changes seen poorly understood
- Confusion about terminology

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

1. Definition and classification
2. Pathological features
3. Pathogenesis
4. Clinical aspects

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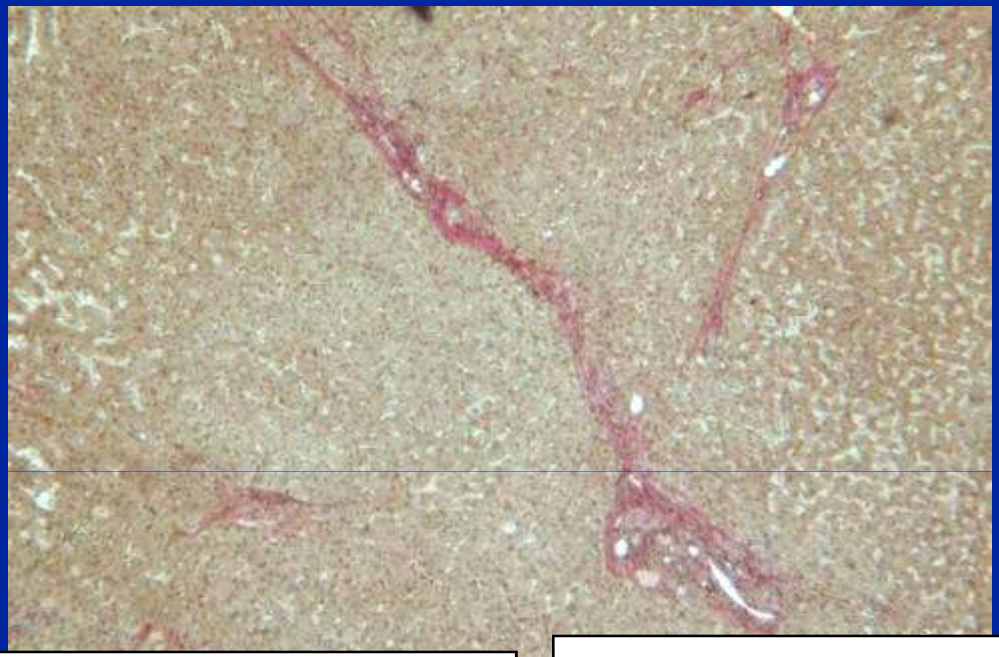
“Non-Cirrhotic Portal Hypertension”
Definition = Clinico-pathological

- Portal hypertension occurring in the absence of cirrhosis (or significant fibrosis)
- Abnormalities occur as a result of primary vascular lesions resulting in reduced venous flow
- Hepatic synthetic function generally well preserved

“Incomplete Septal Cirrhosis”
Definition = Morphological



Histological Features

- **Fibrous septa (periportal or perivenular)**
  - **Fragmented, blind –ending, thin**
  - **No nodules**
  - **Vascular relationships disturbed**

Pathogenesis

- **Part of the spectrum of NCPH (?late-stage disease)**
- **May also be part of the spectrum of true cirrhosis (incompletely developed or partially regressed)**
- **A possible “bridge” between NCPH and cirrhosis**

Classification of Portal Hypertension
(from Roskams et al Histopathology. 2003;42:2-13)

<table>
<tr><th>Relationship to liver</th><th>Vessels involved</th><th>Relationship to sinusoids</th><th>Cirrhosis</th></tr>
<tr><td>Pre-hepatic</td><td>Portal veins (large)</td><td rowspan="2">Presinusoidal</td><td>No</td></tr>
<tr><td rowspan="4">Intrahepatic</td><td>Portal veins (small)</td><td rowspan="4">Yes</td></tr>
<tr><td>Sinusoids</td><td>Sinusoidal</td></tr>
<tr><td>Hepatic veins (small)</td><td rowspan="2">Post-sinusoidal</td></tr>
<tr><td>Hepatic veins (large)</td></tr>
<tr><td>Post-hepatic</td><td></td><td></td><td>No</td></tr>
</table>

Primary Hepatic Vascular Diseases associated with Portal Hypertension (Non - Cirrhotic)

Site of vessel	Pathological changes	Clinical Syndromes
Portal vein (large)	Thrombosis	Portal vein thrombosis
Portal vein (small)	Obliteration/loss • possibly related to previous thrombosis ("hepato-portal sclerosis")	"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

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Hepatic vein (large)	Thrombosis	Budd-Chiari syndrome

“Idiopathic” Non- Cirrhotic Portal Hypertension

Definition

1. Evidence of portal hypertension (e.g. varices, splenomegaly)
2. Patent portal and hepatic veins
3. No cirrhosis (or significant fibrosis) on liver biopsy
4. No risk factors for chronic liver disease (e.g. alcohol, viral hepatitis)

Alternative Terms

- Idiopathic portal hypertension
- Non-cirrhotic portal hypertension
- Non-cirrhotic intrahepatic portal hypertension
- Hepatoportal sclerosis
- Non-cirrhotic portal fibrosis

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

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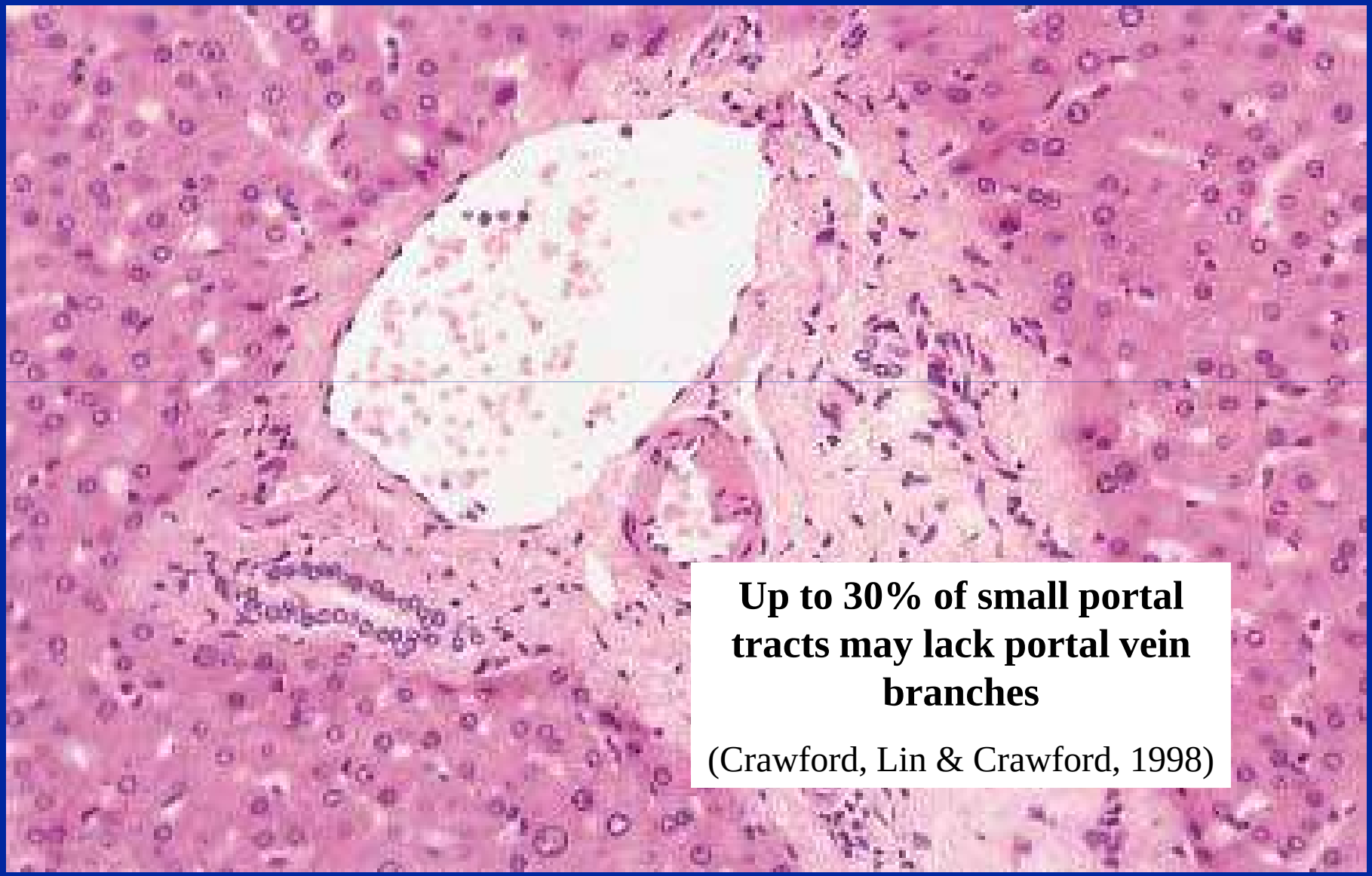
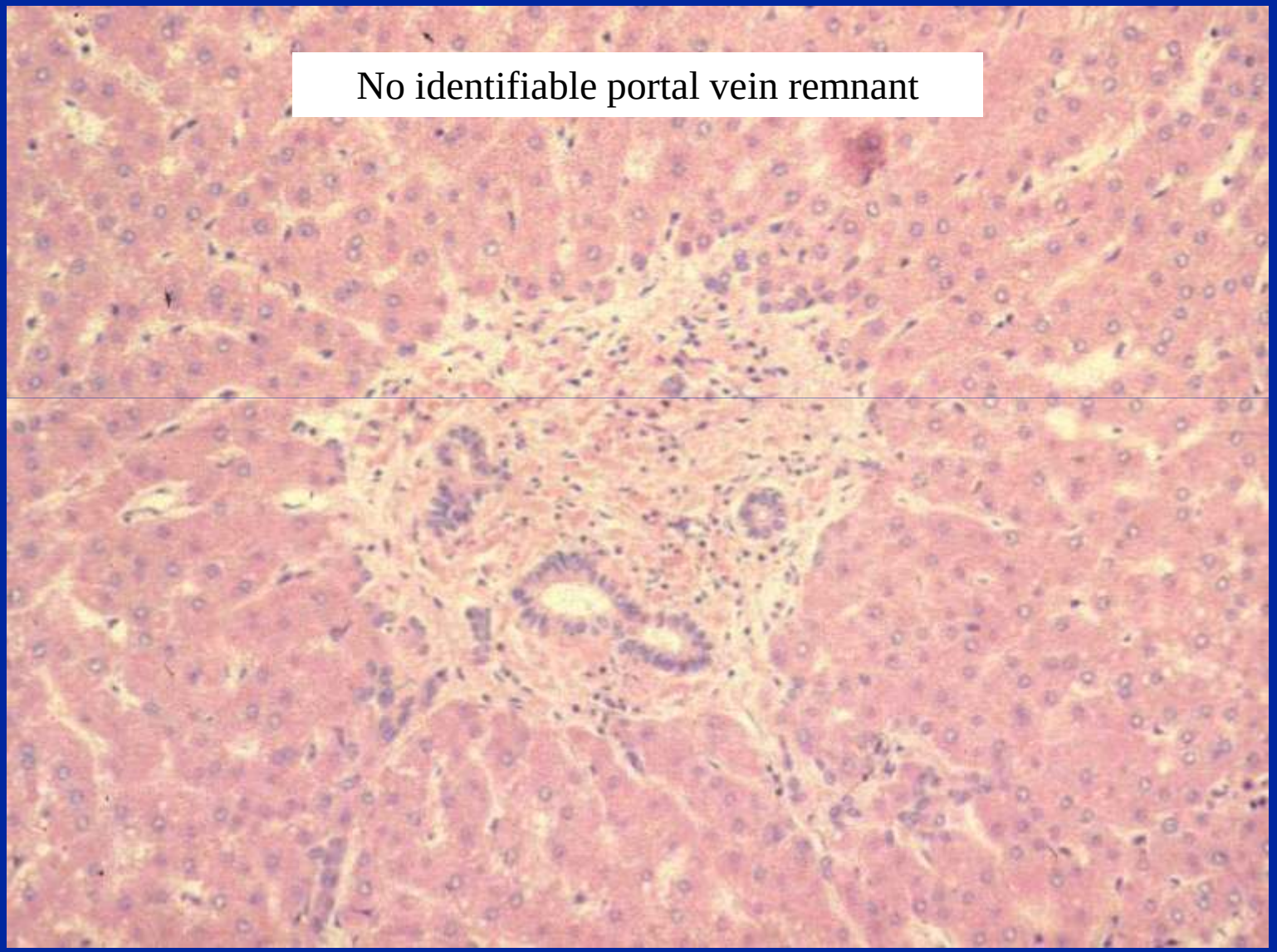
Normal Portal Tract



Up to 30% of small portal tracts may lack portal vein branches

(Crawford, Lin & Crawford, 1998)

Non-Cirrhotic Portal Hypertension
Portal Tract Sclerosis

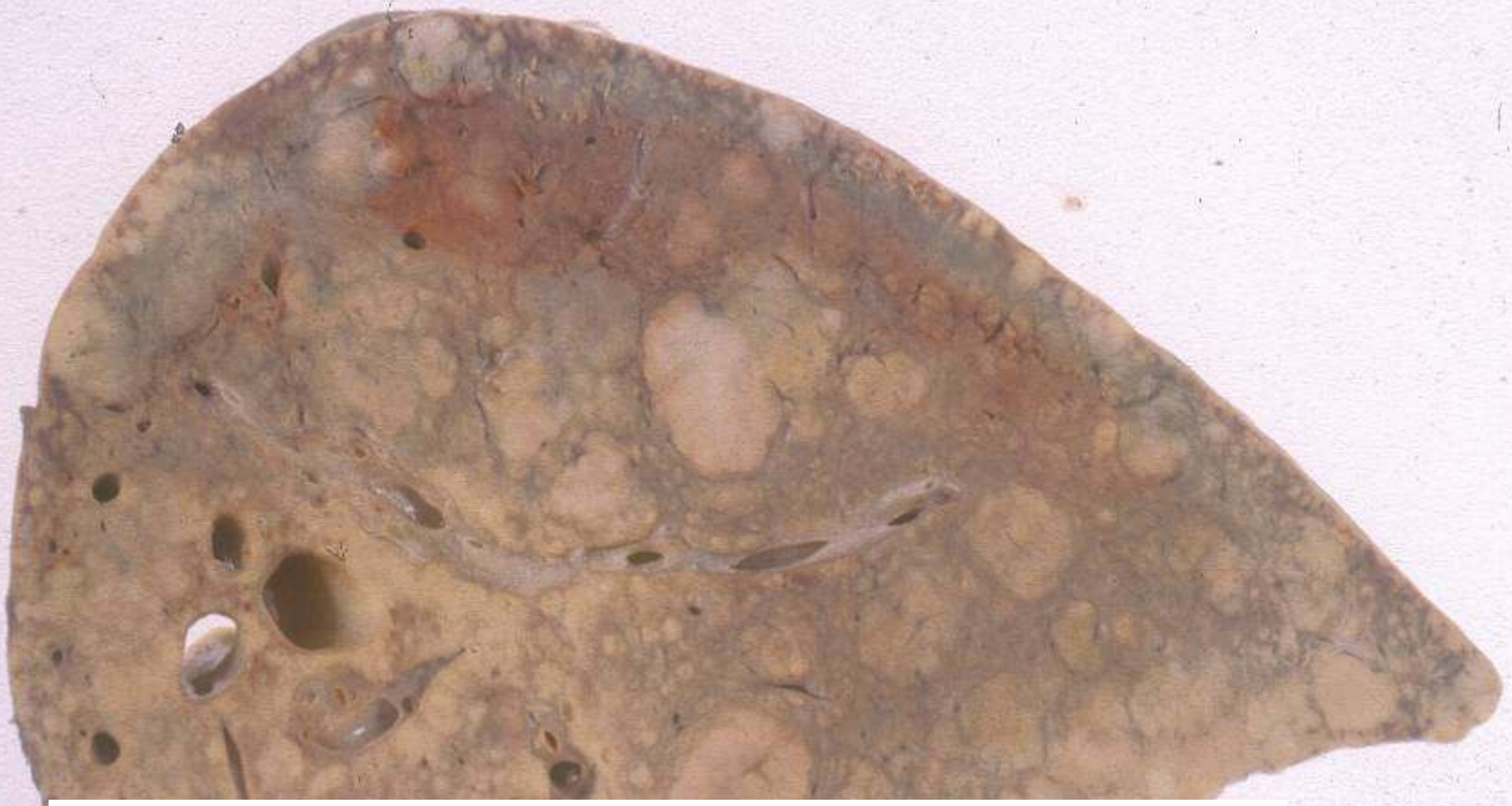


Non – Cirrhotic Portal Hypertension
A case requiring liver transplantation

Clinical Summary

- Female, age 62.
- Presumed alcoholic liver disease with cirrhosis.
- Recurrent variceal bleeds. Patent portal vein.
- Transjugular intrahepatic porto-systemic shunts inserted (x2).
- No previous biopsy
- Liver transplantation

Nodular Regenerative Hyperplasia

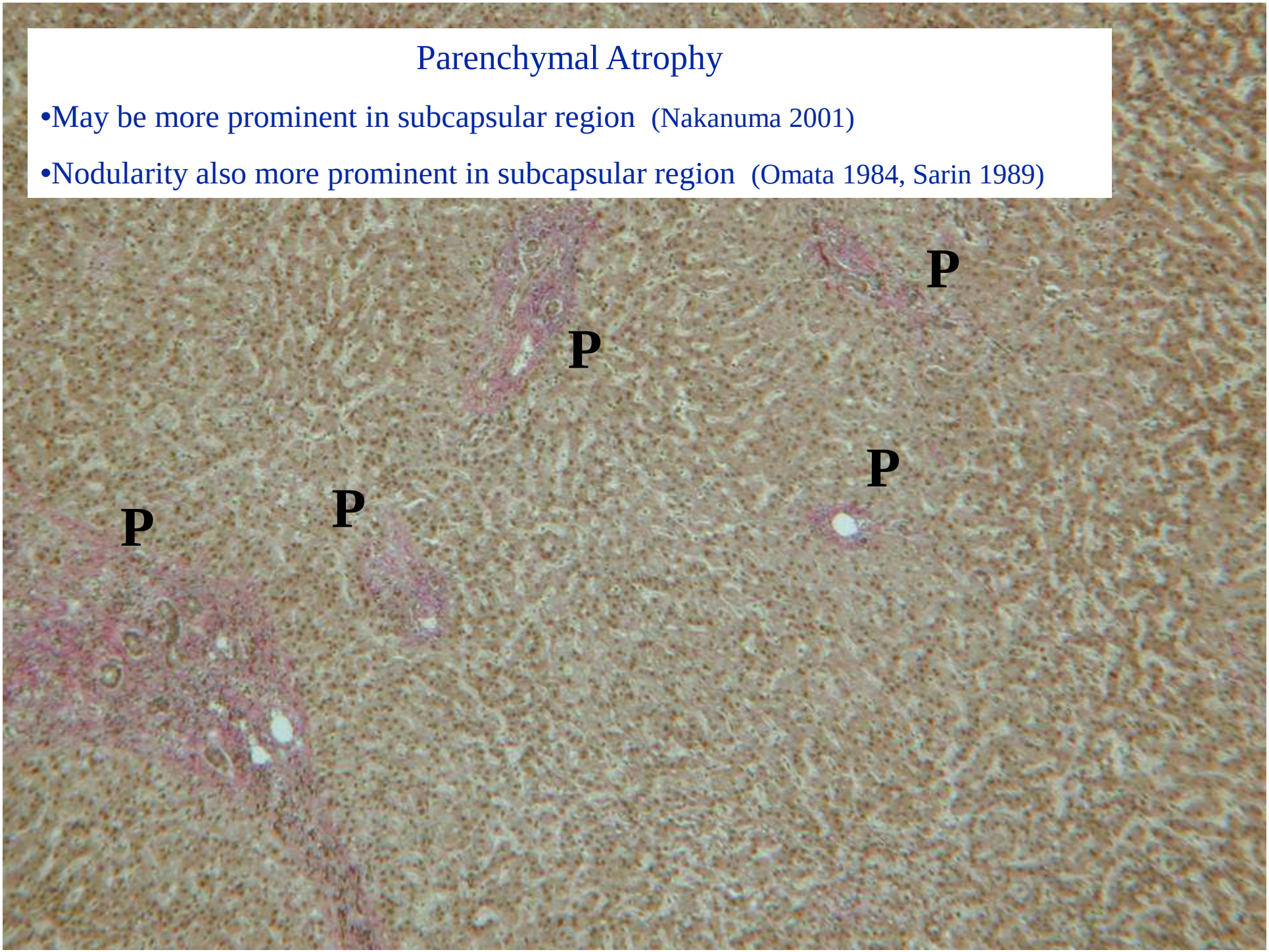


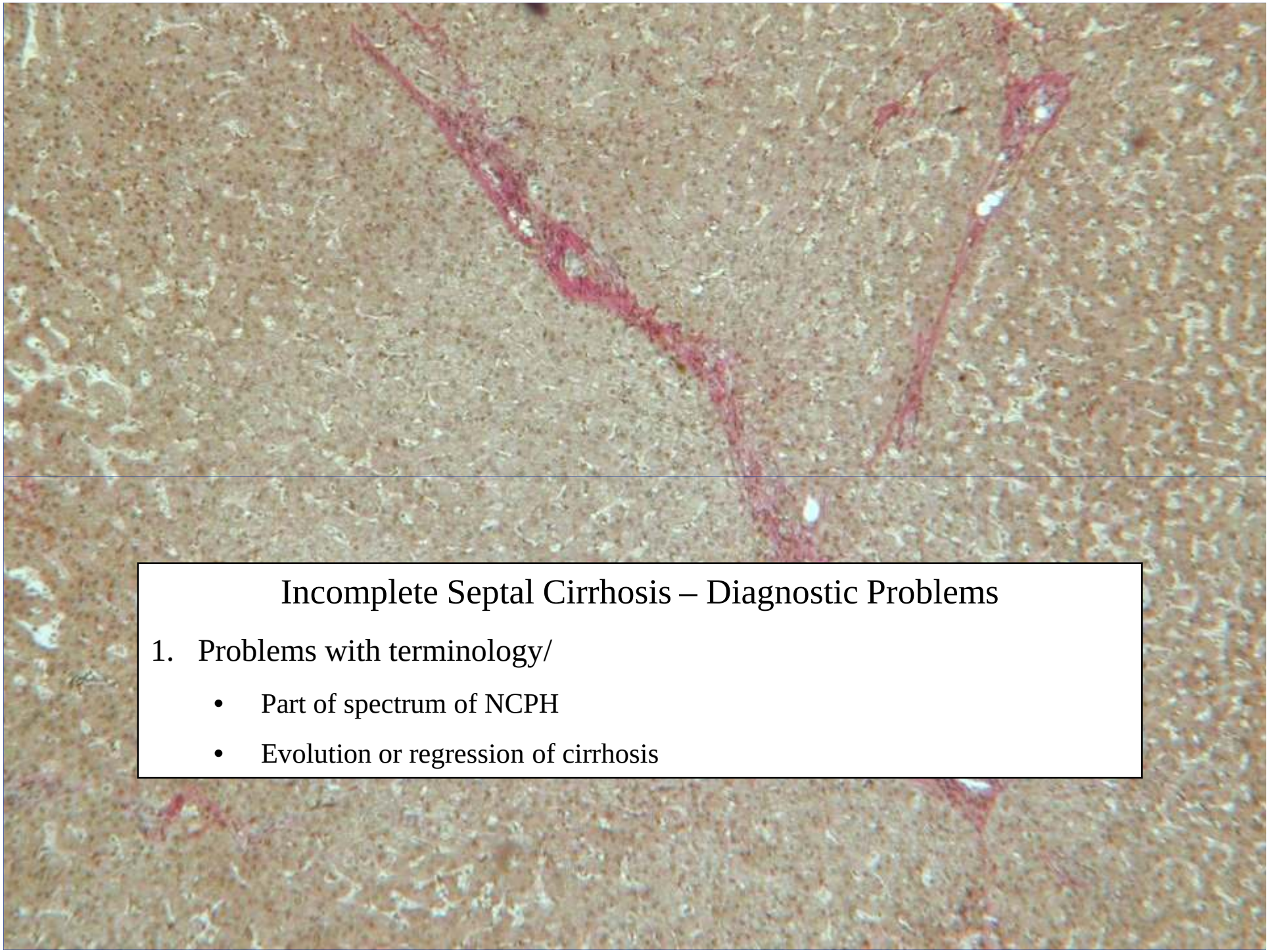
- Hyperplastic nodules typically small –1-3 mm diameter
- Occasionally much larger – up to several centimetres (largest nodule 7 cm diameter in series reported by Hikada, 2005)
- Malignant transformation very uncommon

Normal Vascular Relationships – No Significant Fibrosis

Parenchymal Atrophy

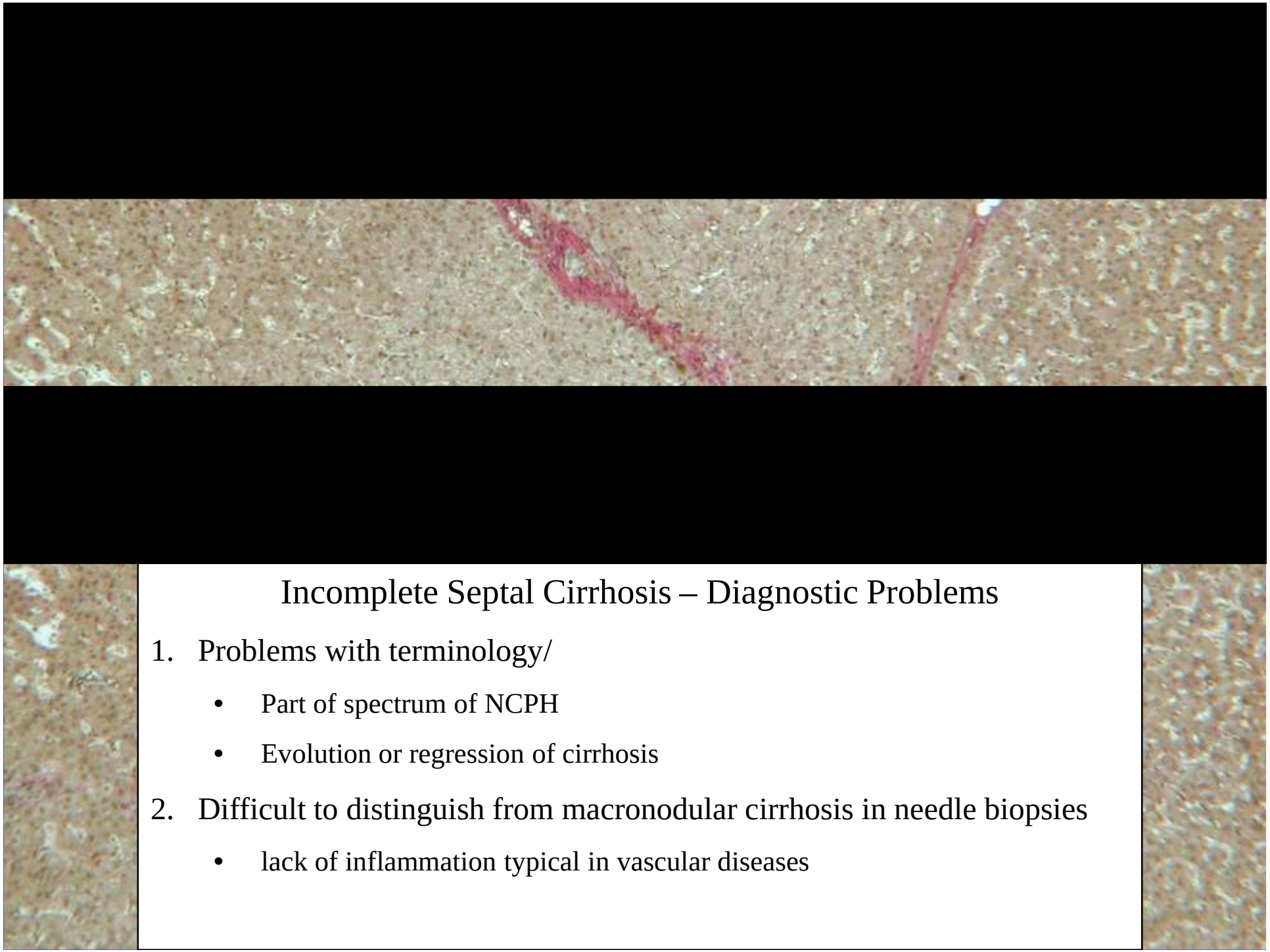
- May be more prominent in subcapsular region (Nakanuma 2001)
- Nodularity also more prominent in subcapsular region (Omata 1984, Sarin 1989)





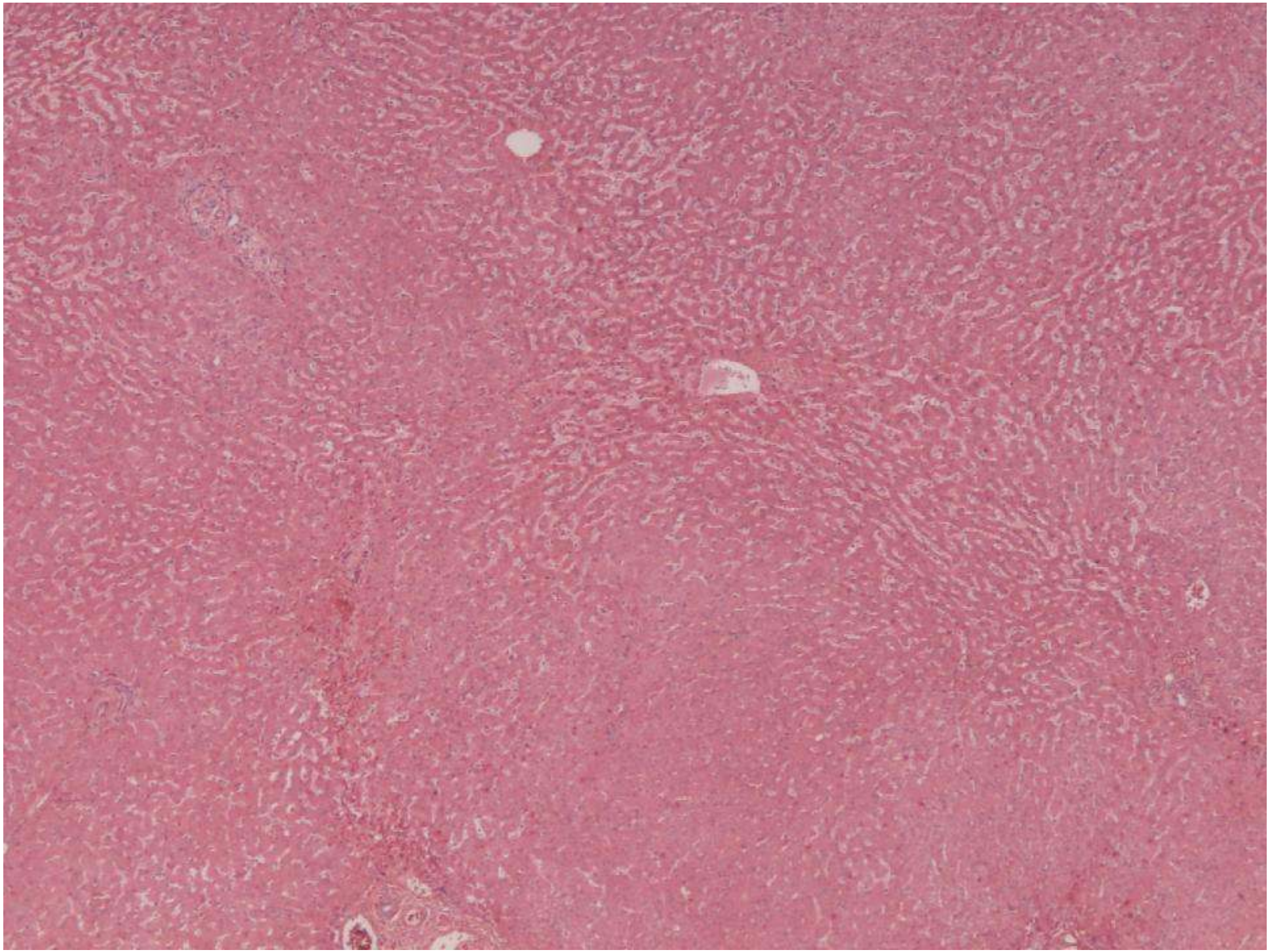
Incomplete Septal Cirrhosis – Diagnostic Problems

1. Problems with terminology/
    - Part of spectrum of NCPH
    - Evolution or regression of cirrhosis

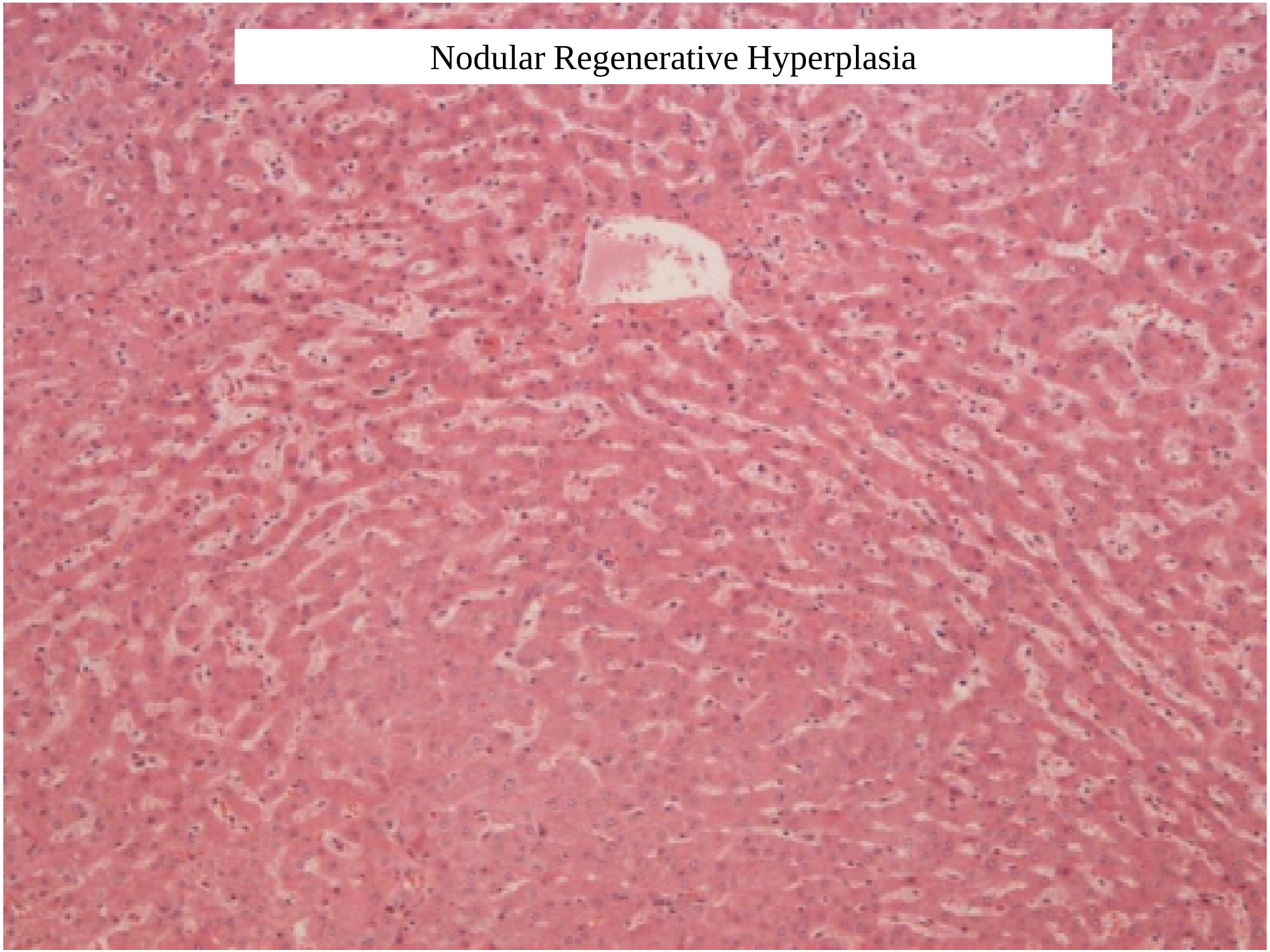


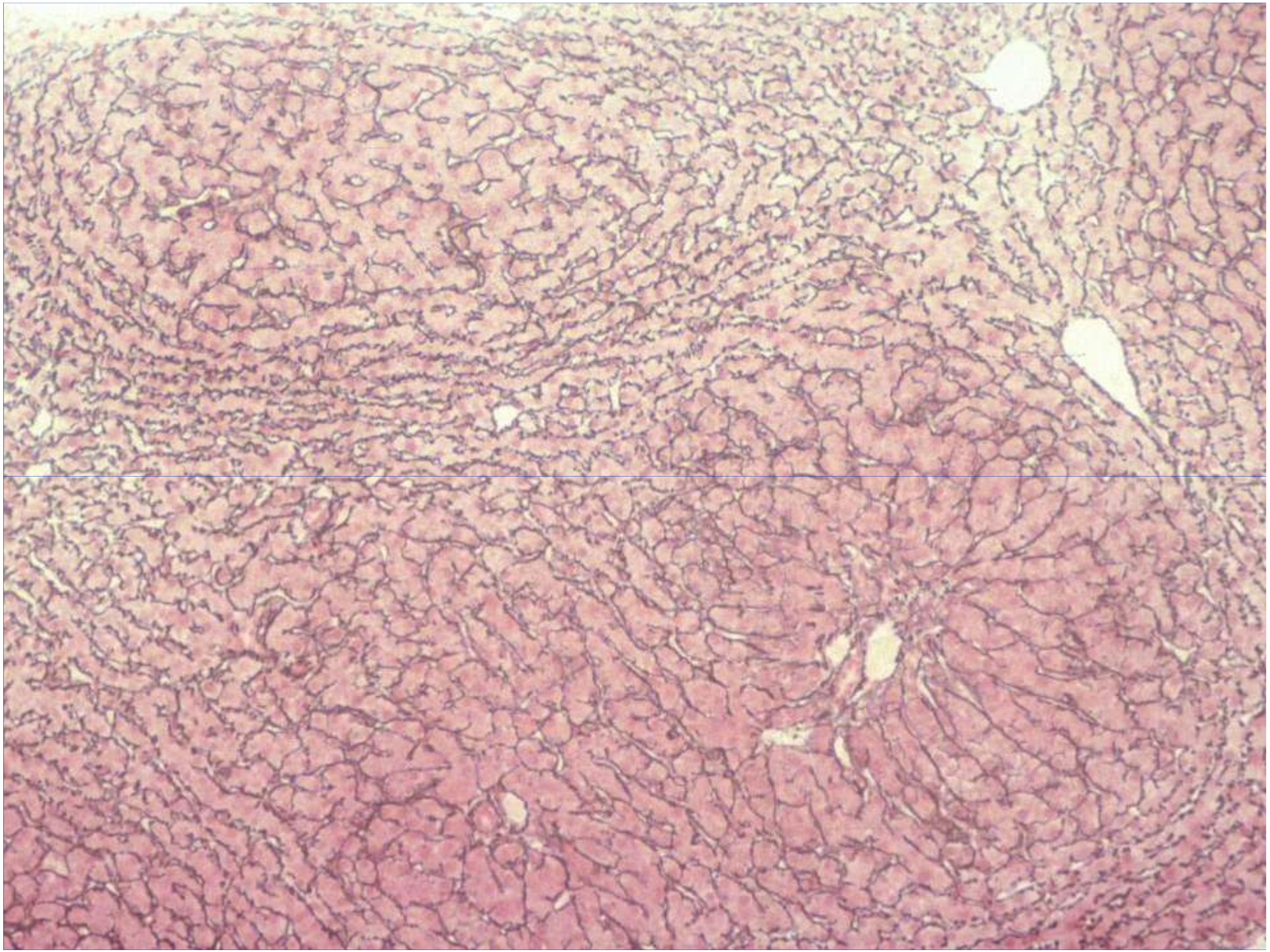
Incomplete Septal Cirrhosis – Diagnostic Problems

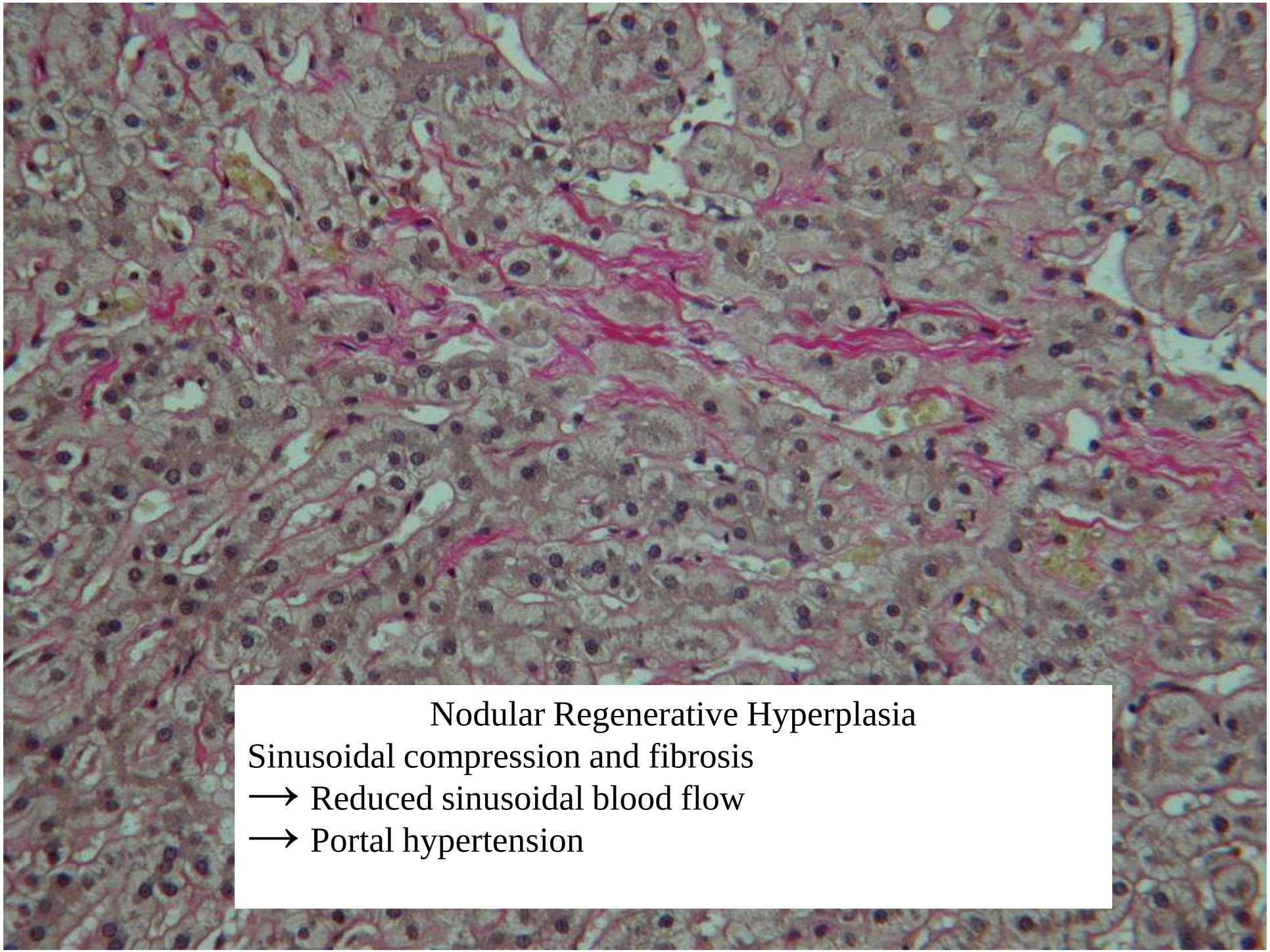
1. Problems with terminology/
   - Part of spectrum of NCPH
   - Evolution or regression of cirrhosis
2. Difficult to distinguish from macronodular cirrhosis in needle biopsies
   - lack of inflammation typical in vascular diseases



Nodular Regenerative Hyperplasia





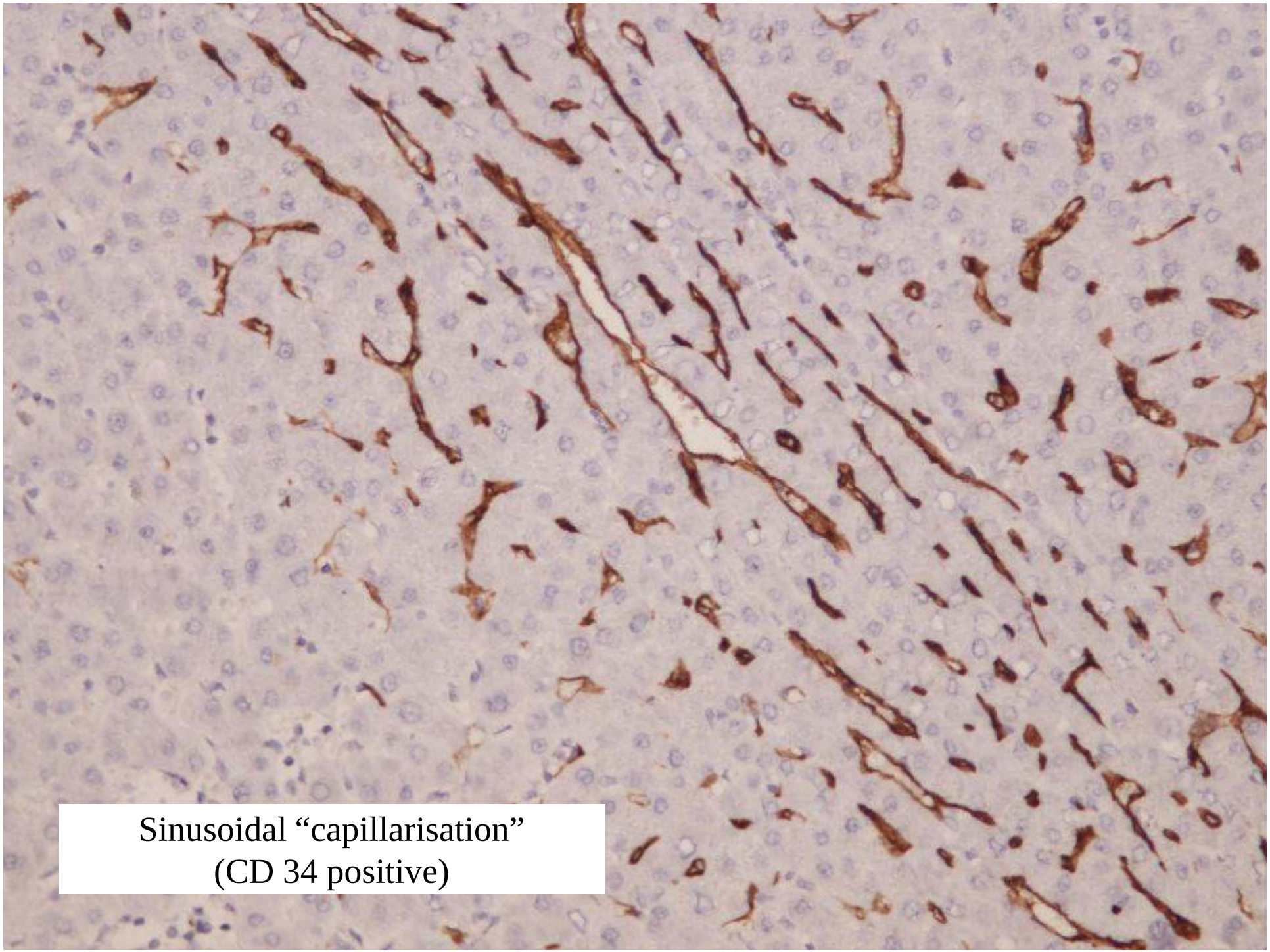


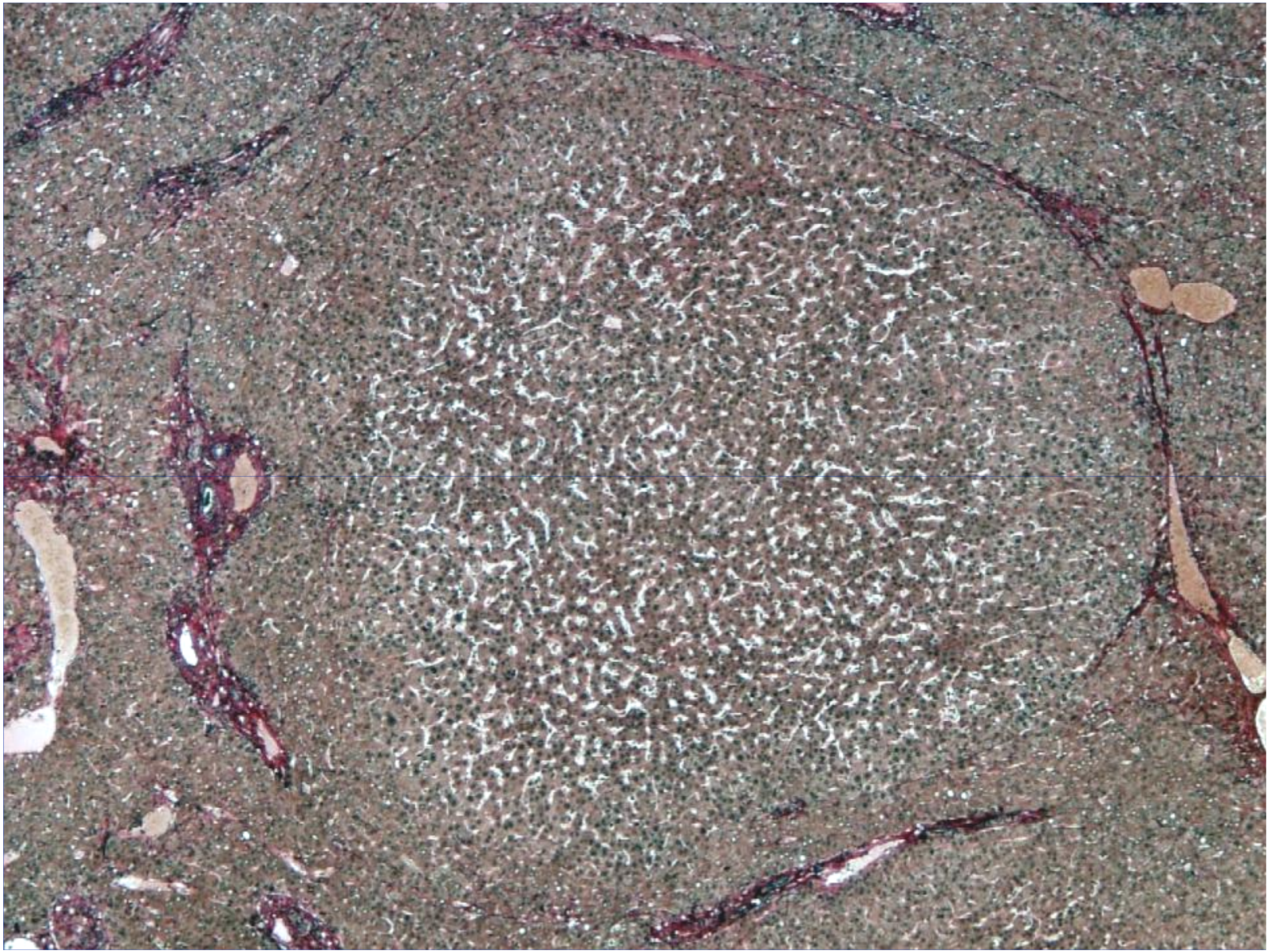
Nodular Regenerative Hyperplasia

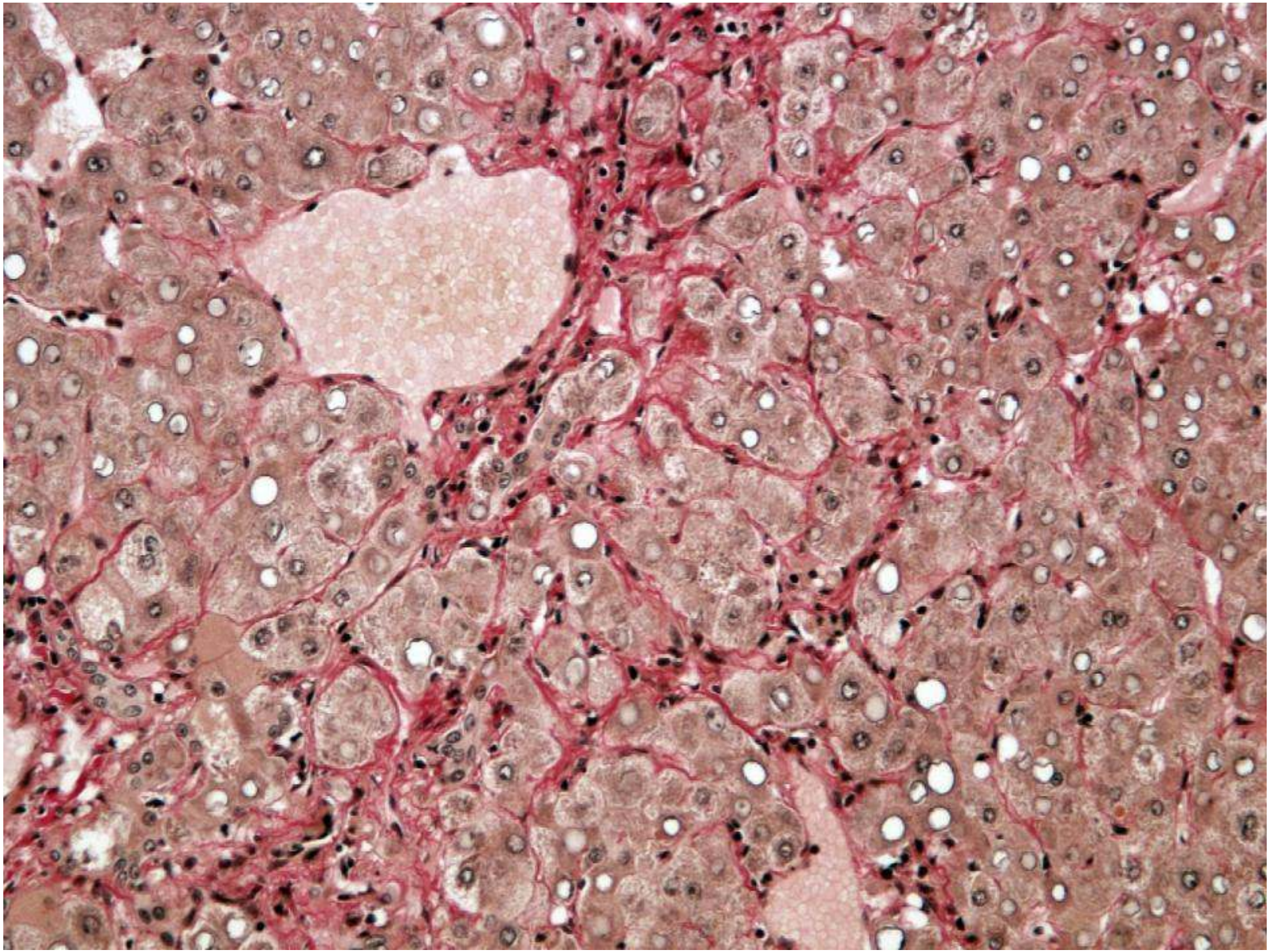
Sinusoidal compression and fibrosis

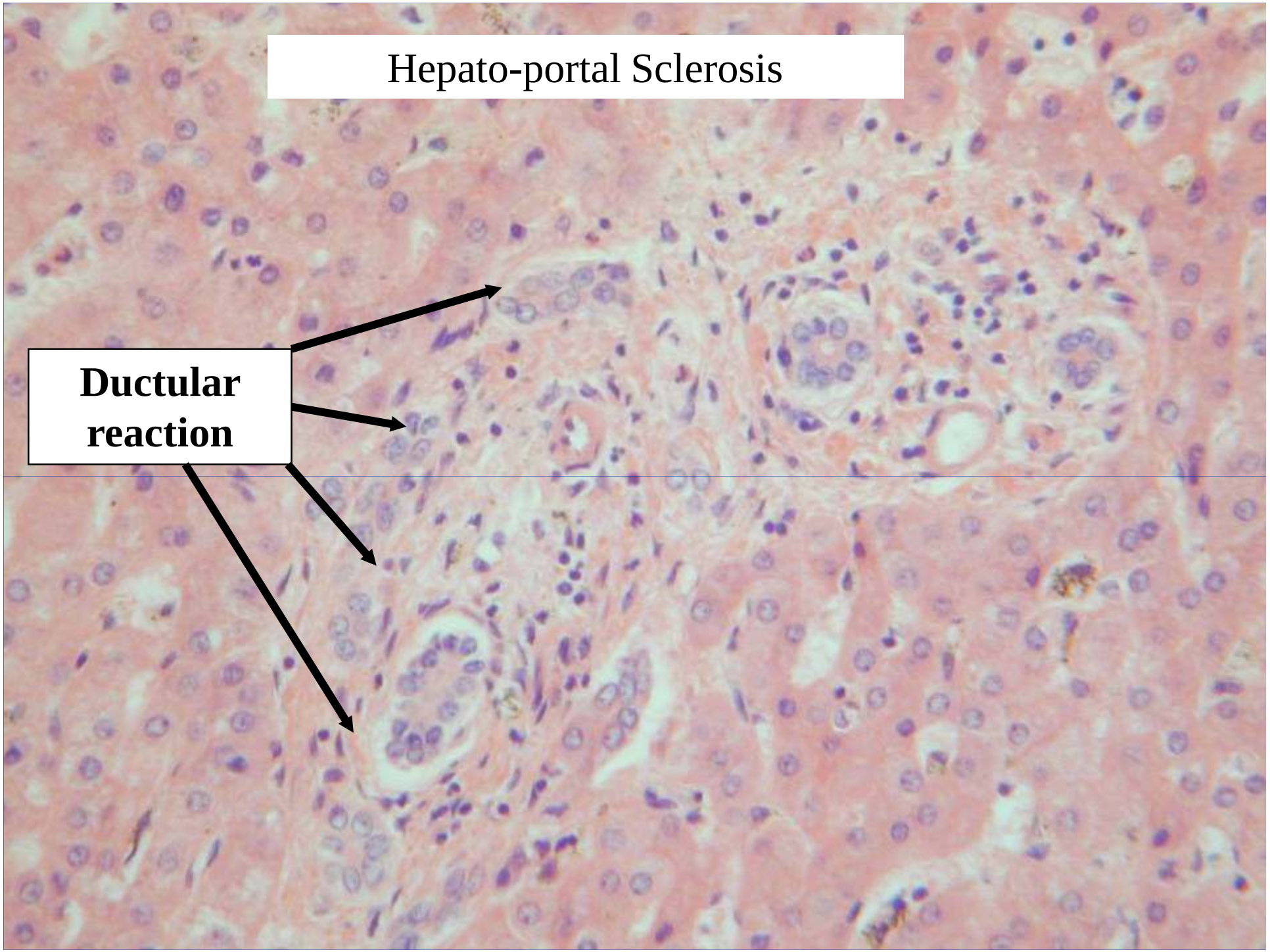
⟶ Reduced sinusoidal blood flow

⟶ Portal hypertension

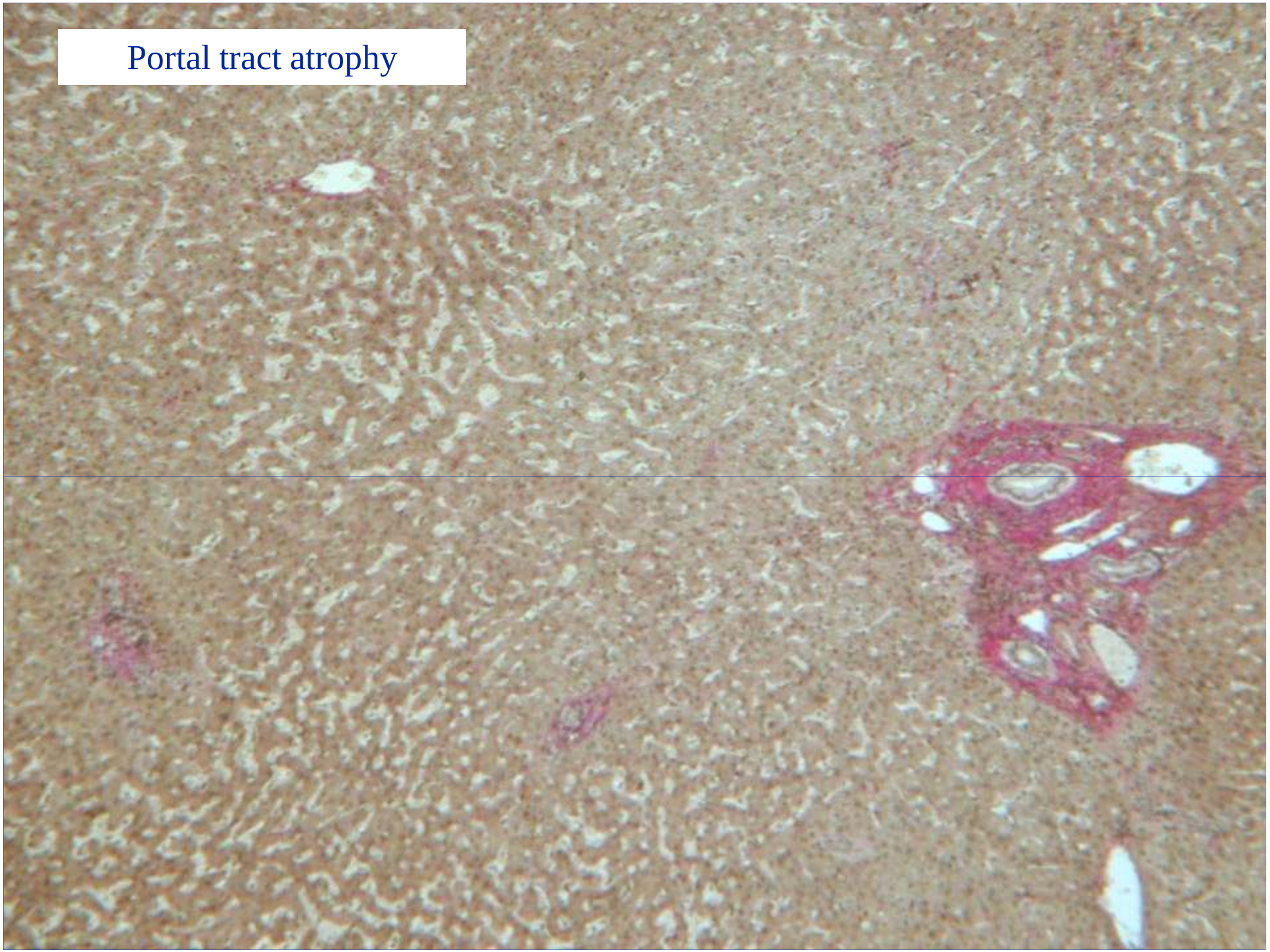

Sinusoidal “capillarisation”
(CD 34 positive)



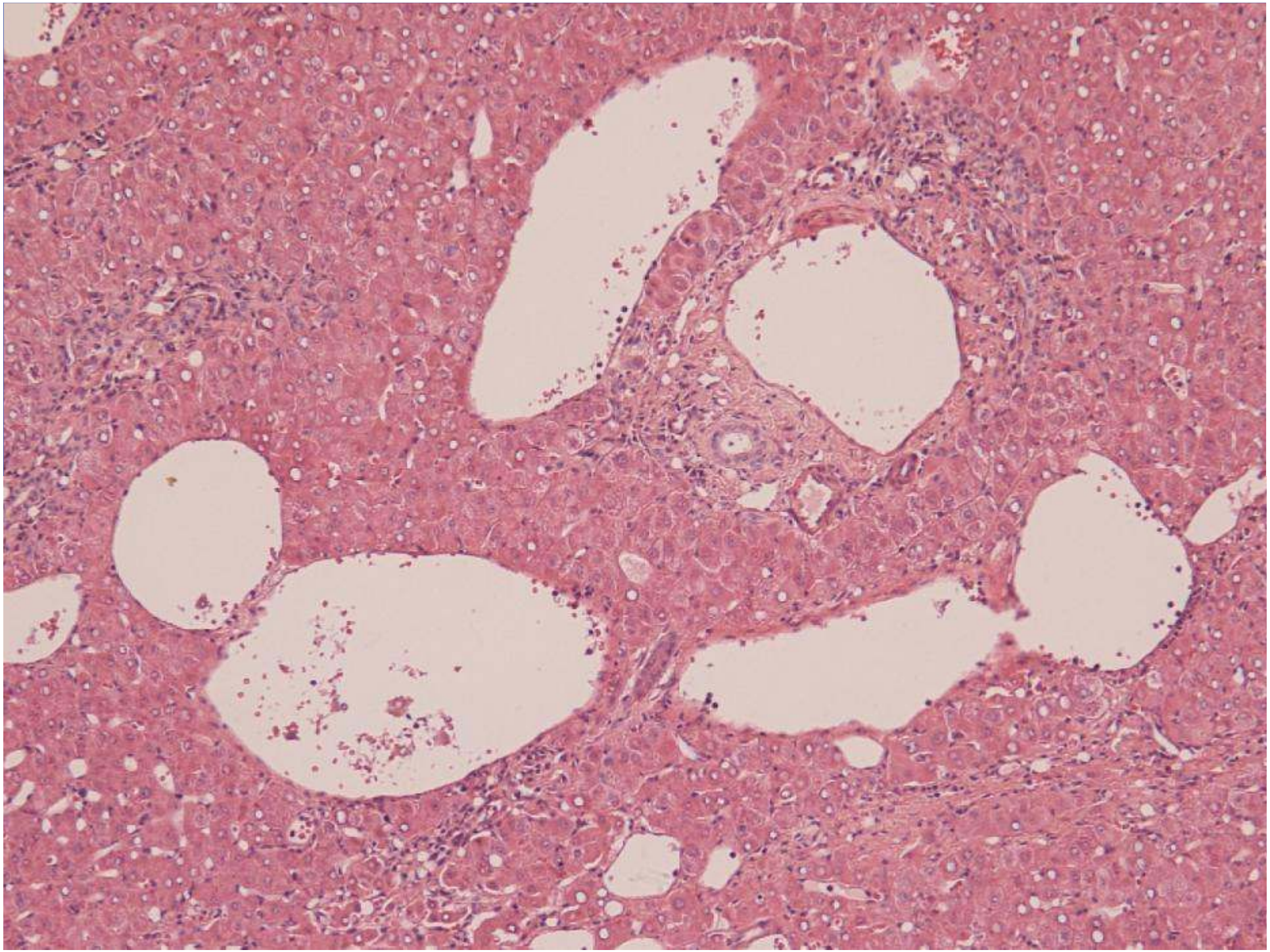


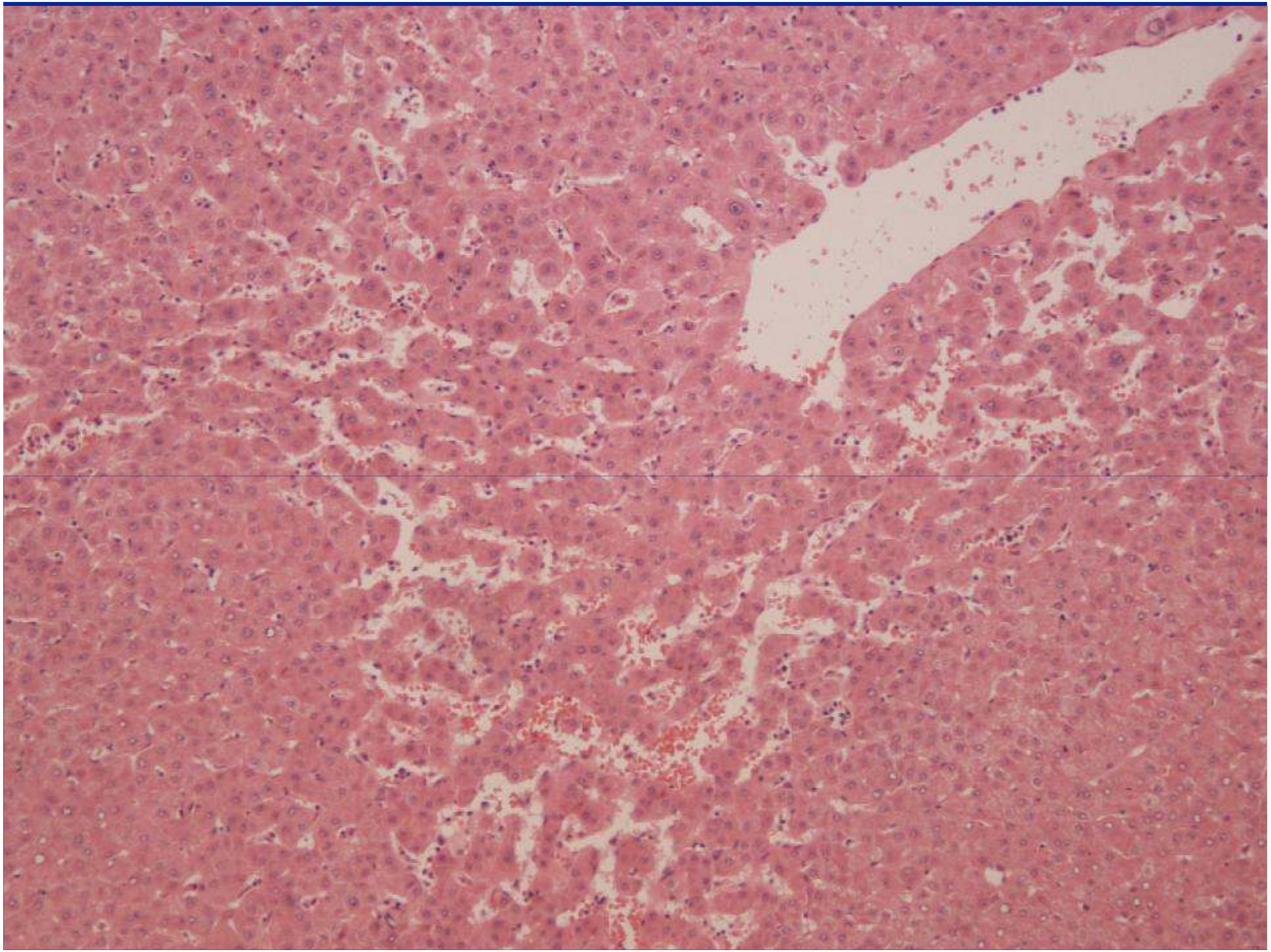

Hepato-portal Sclerosis
Ductular reaction

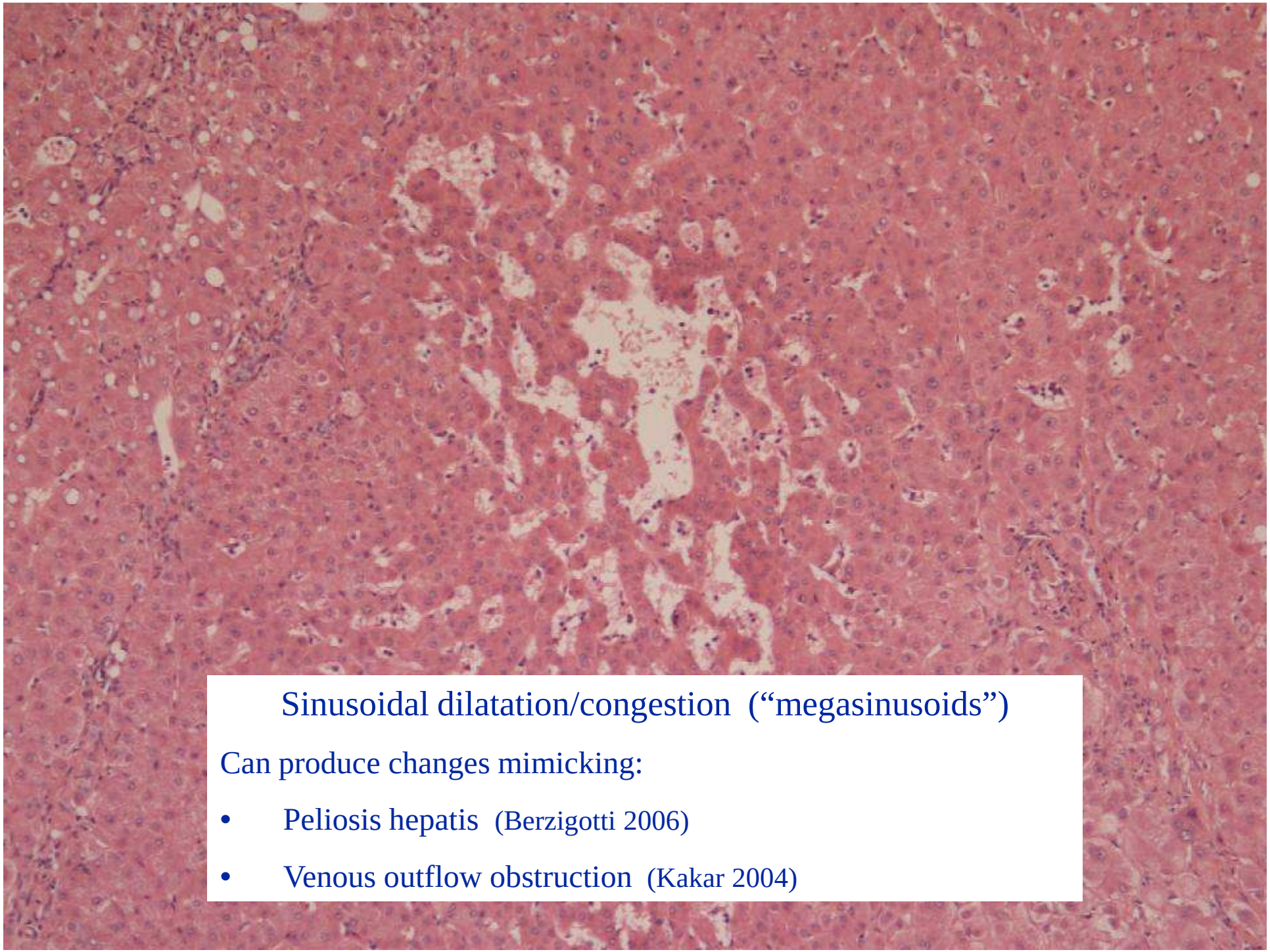
Portal tract atrophy




Portal vein ectasia – “herniation” into adjacent liver parenchyma
• Shunt vessels
• ? Derived from inlet venules (Hikada 2005)







Sinusoidal dilatation/congestion ("megasinusoids")

Can produce changes mimicking:

- Peliosis hepatis (Berzigotti 2006)
- Venous outflow obstruction (Kakar 2004)

Non – Cirrhotic Portal Hypertension
A case requiring liver transplantation

Histological Findings

- Normal vascular relationships
- Parenchymal atrophy
- Nodular regeneration
  (without fibrosis)
- Delicate non-linking fibrous septa
- Portal vein obliteration
- Portal vein ectasia (shunt vessels)
- Sinusoidal dilatation/congestion

- **NO** features of alcoholic liver disease

Non – Cirrhotic Portal Hypertension
Histological Features (+ alternative terms)

Histological Findings

- Normal vascular relationships
- Parenchymal atrophy
- Nodular regeneration (without fibrosis)

} Nodular regenerative hyperplasia

- Delicate non-linking fibrous septa — Incomplete septal cirrhosis
- **Portal vein obliteration** — **Hepato-portal sclerosis**
- Portal vein ectasia (shunt vessels)
- Sinusoidal dilatation/congestion

The Spectrum of Non-Cirrhotic Portal Hypertension

Nakanuma Et Al Histopathology 1996; 28: 195-204

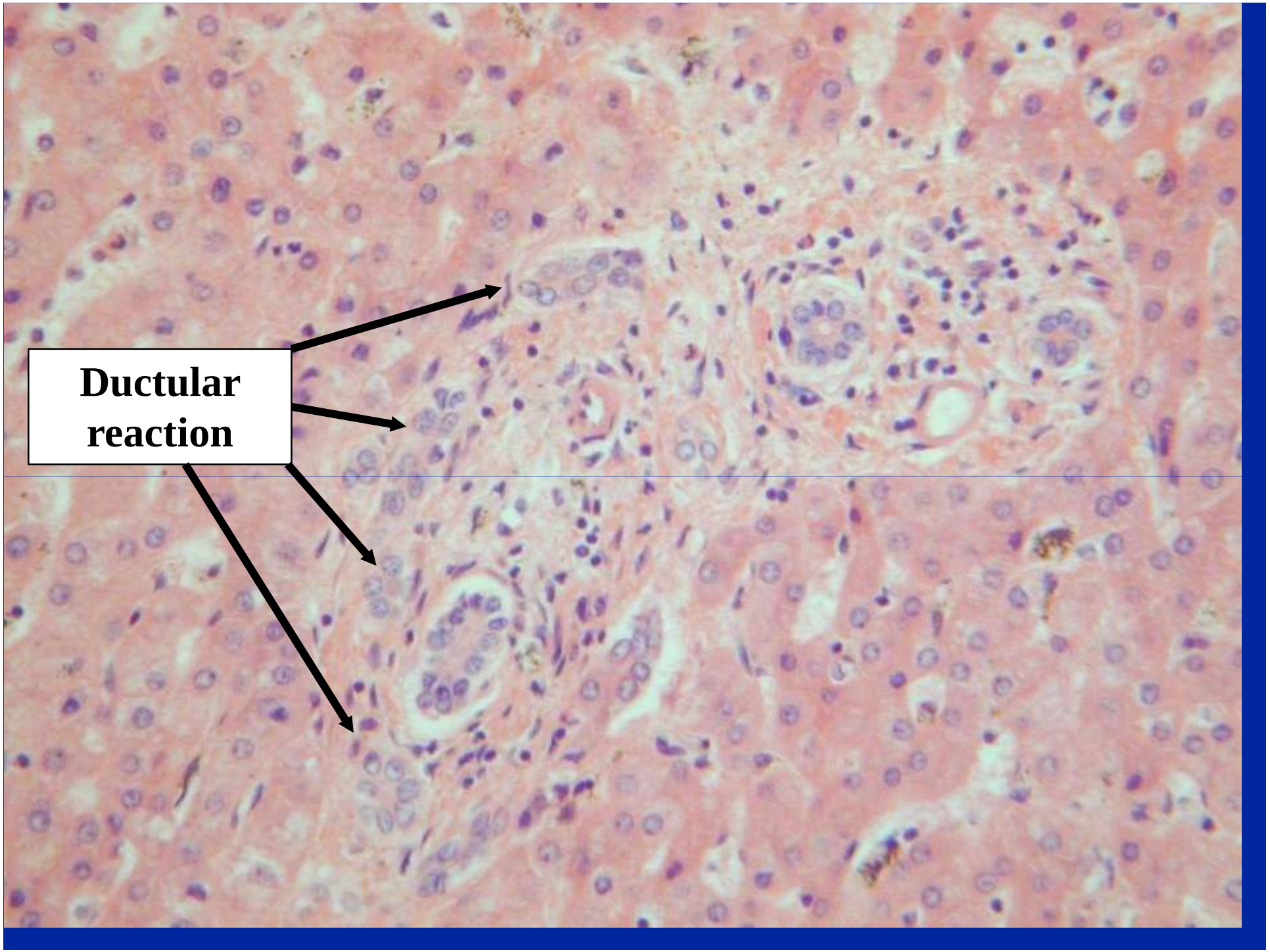
	Idiopathic portal hypertension (n=66)	Nodular regenerative hyperplasia (n=14)	Partial nodular transformation (n=2)	Incomplete septal cirrhosis (n=25)
Portal fibrosis/ venous obliteration	**100%**	**100%**	**100%**	**100%**
Nodular hyperplasia without fibrosis	**41%**	**100%**	**100%**	**32%**
Intralobular fibrous septa	**94%**	**86%**	**100%**	**100%**

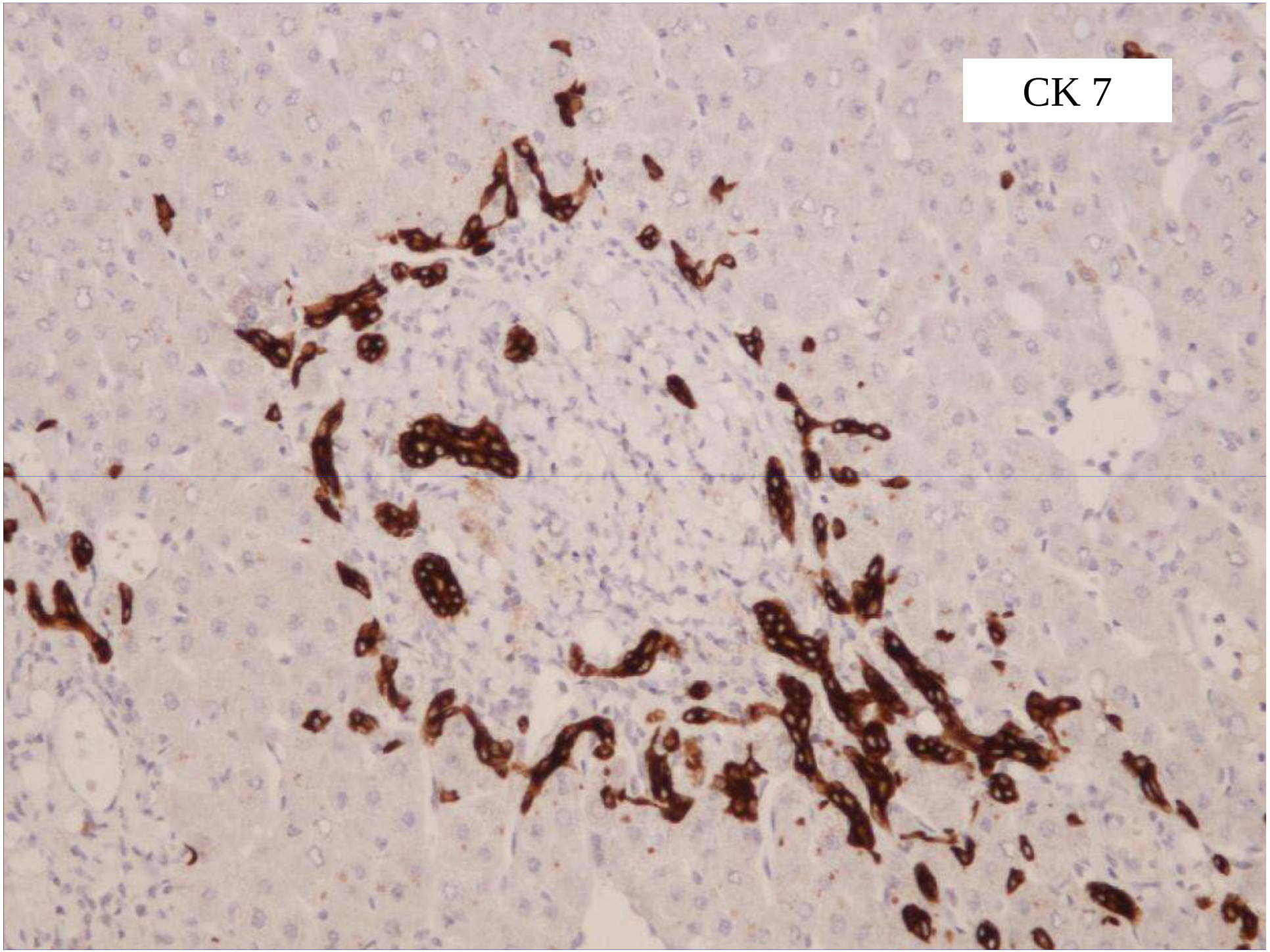
"Biliary Features" in NCPH (Portal Hypertensive Biliopathy)

(Dhiman. Gut 2007; 56: 1001-1008)

- Mainly seen as complication of **extrahepatic** portal vein obstruction
- Can also occur in intrahepatic NCPH, usually to a lesser degree

	Extrahepatic Portal Vein Obstruction	**"Idiopathic" NCPH**
Frequency	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


Ductular reaction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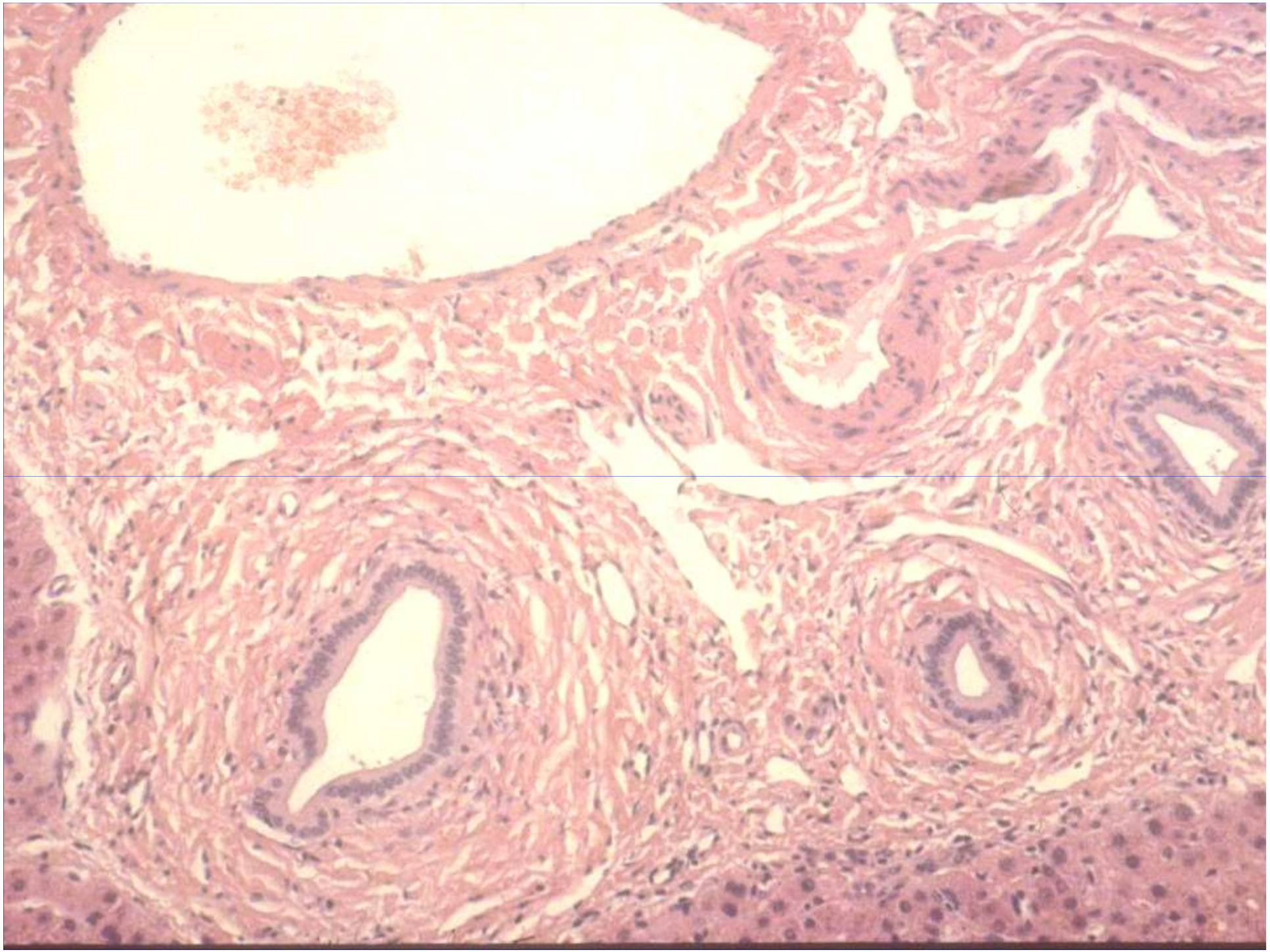
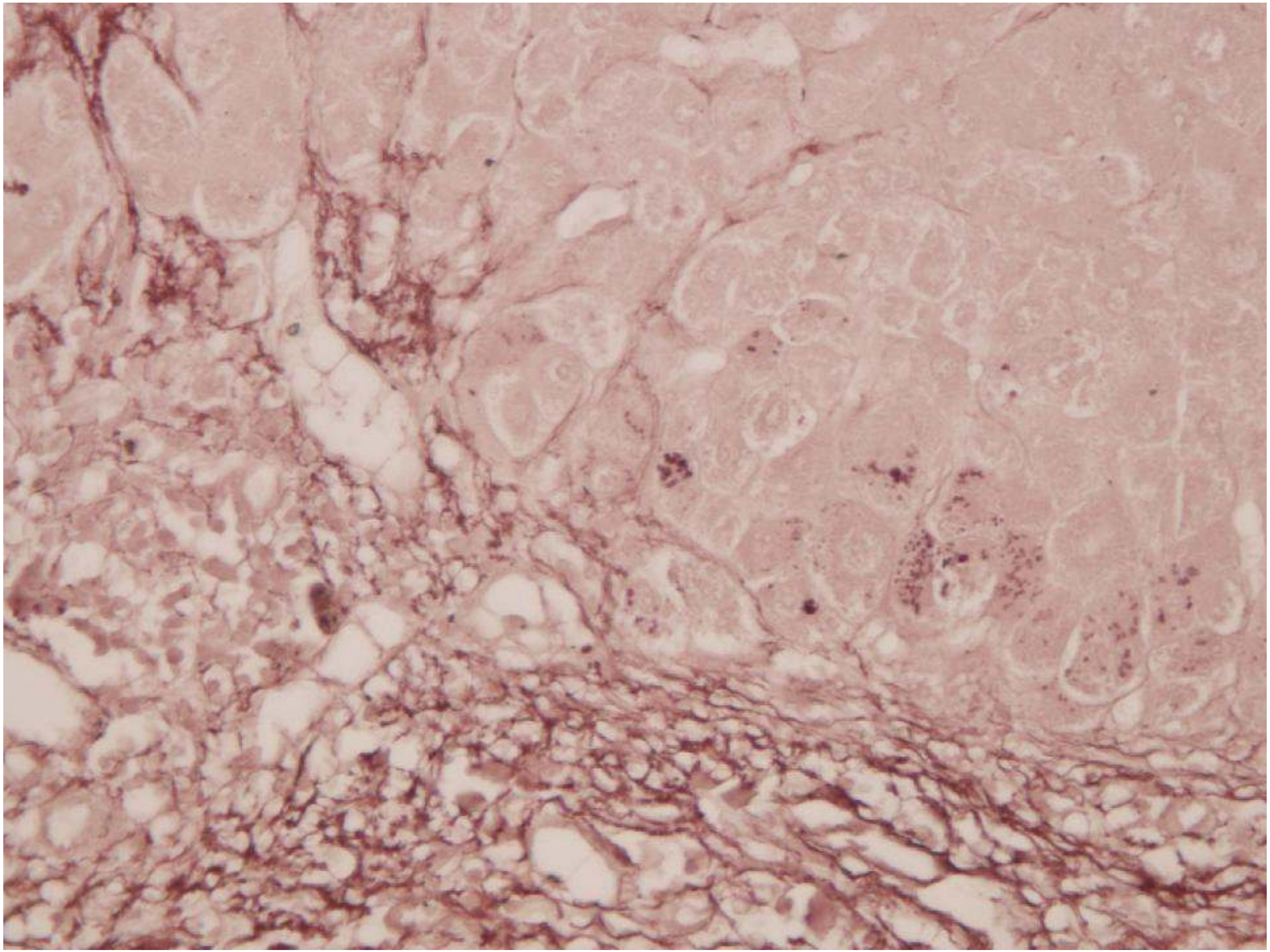




“Biliary Features” in “Idiopathic” NCPH - Histological Changes

(Nakanuma 1996, Dhiman 2002 , Dhiman 2007)

Histological Feature	Frequency
Periductal fibrosis	48% (Nakanuma 1996)
Bile duct loss	10% (Nakanuma 1996)
Ductular reaction	82% (Dhiman 2002)
Copper-associated protein	Common

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

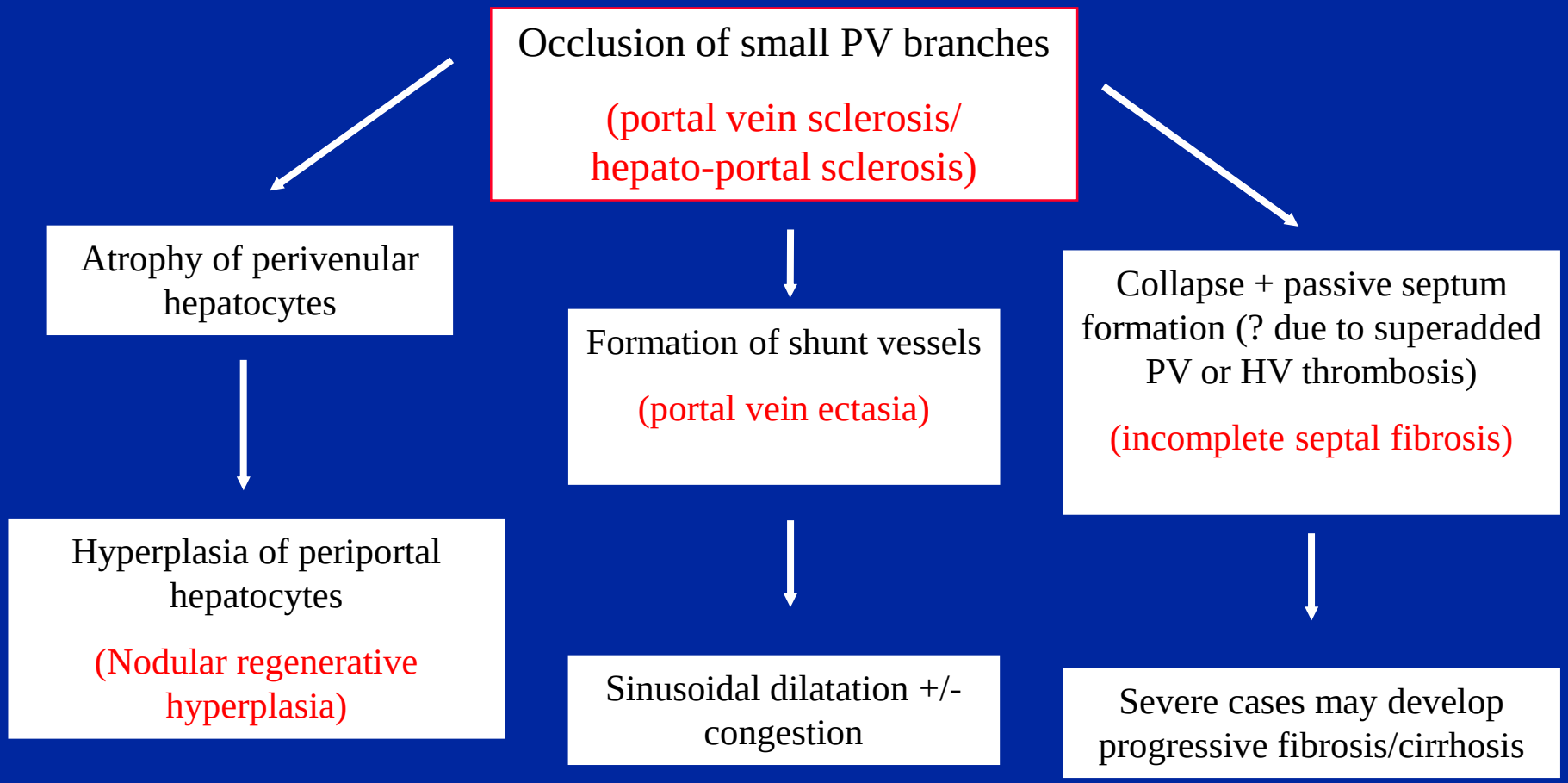
1. Definition and classification

2. Pathological features

3. Pathogenesis
   - "Primary" NCPH (evolution of changes, underlying mechanisms)
   - "Secondary" NCPH
   - Vascular lesions in pathogenesis of cirrhosis

4. Clinical aspects

Non-cirrhotic portal hypertension (hepatoportal sclerosis) Pathogenesis + Histological Features



Evolution of Morphological Changes in “Idiopathic” NCPH

- Difficult to verify in serial biopsies, due to problems with sampling variability

- In studies documenting histological features NRH is the most common abnormality (> 90%)
- Incomplete septal cirrhosis mainly seen in severe/longstanding disease
  - Present in 13/24 patients at liver transplantation (Krasinskas 2005, Fiel 2007)
    (22/24 had atrophy/NRH)

- One case report suggesting evolution from IPH (liver biopsy age 17) to incomplete septal cirrhosis requiring liver transplantion (age 30)
  (Bernard . J Hepatol 1995)

Hepato-Portal Sclerosis/ Nodular Regenerative Hyperplasia - Pathogenesis

1. Thrombotic occlusion of small portal veins
   - Prothrombotic tendency in up to 20-50% of patients (Hillaire 2002, Valla 2008, Morris 2010)
   - Anti-phospholipid antibodies common (77% of patients – Klein 2003)
     - Anti- cardiolipin antibodies most frequent (46% of patients – Klein 2003)

2. Endothelial-mesenchymal transition (Nakanuma 2009)
   - Expression of pSmad2 and S100A4 in endothelium of small portal veins in "idiopathic" portal hypertension
   - Associated with reduced expression of CD 34

Hepato-Portal Sclerosis/ Nodular Regenerative Hyperplasia - Pathogenesis

3. Sinusoids as possible primary site of injury:
   - 17/28 patients described by Hillaire et al (2002) had NRH and peri-sinusoidal fibrosis without obviously portal vein occlusion (cf Nakanuma 1996)
   - Increased intrasinusoidal CD8+ T cells in 14/44 NRH patients – associated with apoptosis of sinusoidal endothelial cells (Ziol 2004)
   - Intrasinusoidal T cells present in 90% of patients with NRH associated with immunodeficency syndromes (Malamut 2008)

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

1. Definition and classification

2. Pathological features

3. Pathogenesis
   - "Primary" NCPH
   - "Secondary" NCPH (mainly NRH)
   - Vascular lesions in pathogenesis of cirrhosis

4. Clinical aspects

Non-Cirrhotic Portal Hypertension Secondary to Other Diseases

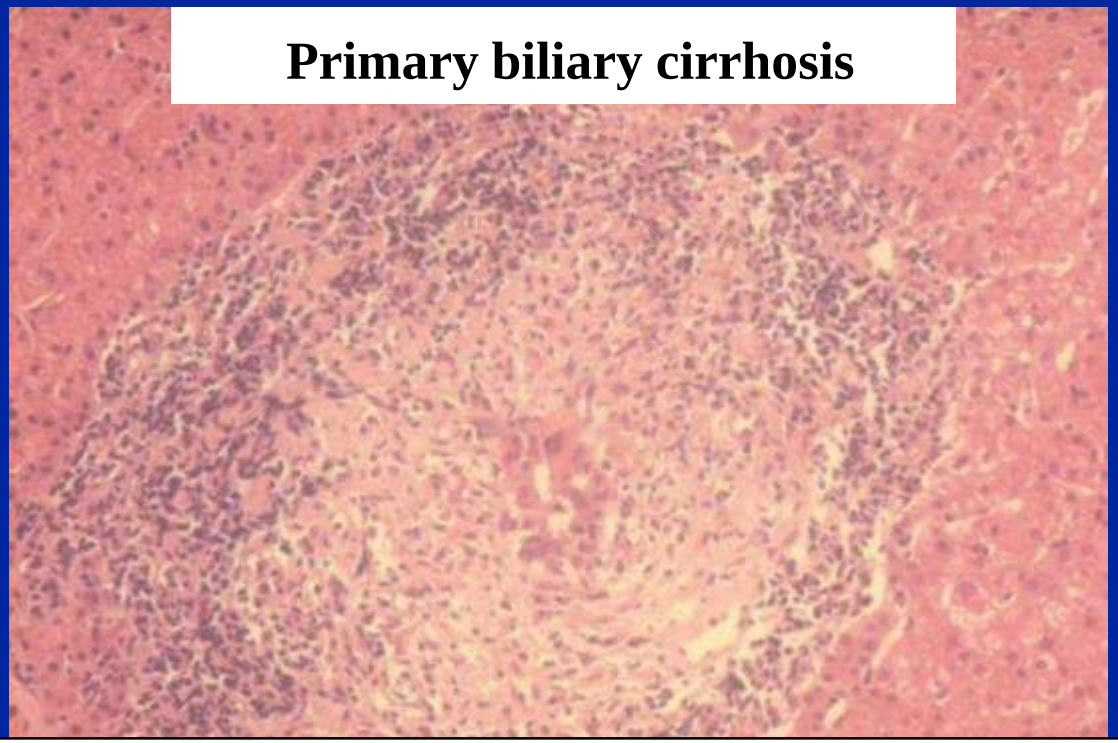
Disease	Examples	Mechanisms/ comments
1. Rheumatic/ Connective Tissue Diseases	Rheumatoid arthritis, SLE, systemic sclerosis, polyarteritis nodosa, Wegener's	Portal veins damaged as "bystander effect", secondary to hepatic arteritis Anti-phospholipid antibodies may predispose to portal vein thrombosis
2. Haematological diseases	Myeloproliferative and lymphoproliferative diseases	? underlying thrombotic tendency Also associated with Budd-Chiari syndrome
3. Immunodeficiency Syndromes	HIV (Mallet 2007, Schiano 2007, Maida 2008, Tateo 2008, Mendizabeh 2009,Vispo 2010) Other (e.g. CVID) (Malamut 2008, Ward 2008)	? anti-retroviral induced endothelial injury +/- thrombosis Some cases have progressed to liver transplantation

Non-Cirrhotic Portal Hypertension Secondary to Other Diseases

Disease	Examples	Mechanisms/ comments
4. Drugs	Azathioprine, Oxaliplatin, 6-TG	Drug-induced endothelial injury Overlap with “sinusoidal obstruction syndrome” and “veno-occlusive disease”
5. Chronic biliary diseases (pre-cirrhotic)	PBC, PSC, biliary obstruction	Severe portal hypertension may occur in the absence of advanced fibrosis. 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.
6. Post-transplant		Common finding in late-post transplant biopsies Possible mechanisms include previous rejection, drug toxicity, regeneration in reduced-sized grafts

Portal Vein Occlusion/Loss - Secondary Causes

Primary biliary cirrhosis



Portal Vein Lesions in PBC

- Possible mechanism for pre-cirrhotic portal hypertension (NRH also commonly present)
- May also be involved in pathogenesis of hepatic fibrosis/cirrhosis, particularly if associated with occlusive lesions in hepatic venules

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

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   - Vascular lesions in pathogenesis of cirrhosis
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Vascular Lesions in the Evolution (and Regression) of Cirrhosis
(from Wanless, Arch Pathol Lab Med 2000; 124: 1599-1607)

A. Normal liver

B. Obliteration of small portal and hepatic veins
(e.g. secondary to inflammation)
⟶ Parenchymal ischaemia

C. Loss of ischaemic parenchyma (“extinction”)
⟶ Atrophy
⟶ Approximation of vascular structures
⟶ Fibrosis (sinusoidal)

Vascular Lesions in the Evolution (and Regression) of Cirrhosis
(from Wanless, Arch Pathol Lab Med 2000; 124: 1599-1607)

D. (i) Fibrous septa replace areas of parenchymal extinction
(ii) Obliterated small veins disappear

E. Septa elongated by expansion of regenerating hepatocytes
⟶ Curved septa

F. Remodelling and resorption of fibrosis
⟶ thinning & fragmentation of septa
("incomplete septal cirrhosis", "hepatic repair complex")

Non-Cirrhotic Portal Hypertension & Incomplete Septal Cirrhosis

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Non-Cirrhotic Intrahepatic Portal Hypertension - Clinical Aspects

- Many cases probably asymptomatic
  - Only 1/64 cases diagnosed with NRH at autopsy were diagnosed prior to death (Wanless 1990)
- Most cases have portal hypertension with preserved synthetic function
  - Prognosis better than cirrhotic patients with a similar severity of portal hypertension (Merkel 1992)
- Cholestatic LFTs common
  - Raised Alk Phos in 25 % of cases of NRH reviewed by Reshamala (2006)
  - Abnormal LFTs (mainly cholestatic) presenting feature in 76% NRH cases reported by Morris (2010). Only 9.5% had portal hypertension as presenting feature
  - Alk Phos levels higher in patients with symptomatic portal hypertensive biliopathy (Dhiman 2007)

Non-Cirrhotic Intrahepatic Portal Hypertension - Clinical Aspects

- Progression to liver failure occurs in some cases
  - Several studies describing patients who developed liver failure requiring liver transplantation - 44 in 5 series (du Mortier 2001, Ibarrolar 2003, Krasinskas 2005, Fiel 2007, Geramizadeh 2008)
  - 21/24 patients reported by Krasinskas and Fiel had an incorrect pre-transplant diagnosis of cirrhosis

Non-Cirrhotic Intrahepatic Portal Hypertension
Outcome & Prognostic Factors
(Eapen. Dig Dis Sci 2010)

34 Patients (median follow-up 88 months)

- 18 (53%) developed decompensated liver disease
- 10 deaths, 3 liver transplants
- Transplant-free survival at 10 years = 69%

Factors predicting reduced survival:

- Older age (at presentation)
- Hepatic encephalopathy (at presentation)
- Portal vein thrombosis (after presentation)