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Department of Pathology

Pediatric Medical Liver Disease

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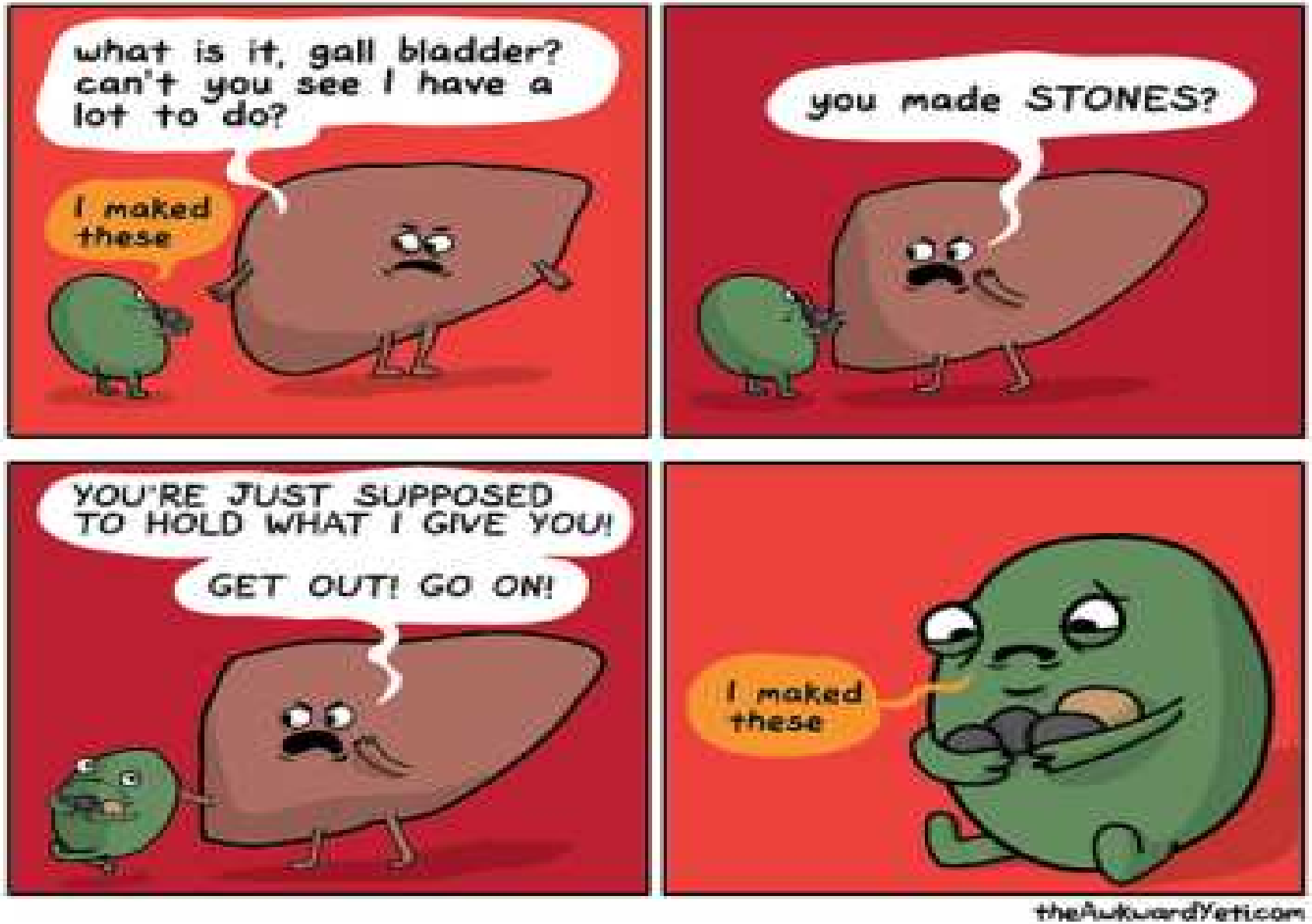
PRESENTATION OUTLINE:

I. Cholestatic Liver Disease
   - A. Neonatal hepatitis
   - B. Progressive familial intrahepatic cholestasis
   - C. Paucity of intrahepatic ducts/Alagille syndrome
   - D. Extrahepatic biliary atresia
   - E. α-1 Anti-trypsin deficiency
   - F. Ductal plate malformations/ARPKD
   - G. Wilson's disease


what is it, gall bladder? can't you see I have a lot to do?
I maked these
you made STONES?
YOU'RE JUST SUPPOSED TO HOLD WHAT I GIVE YOU!
GET OUT! GO ON!
I maked these
theAwkwardYeti.com

I. Examples of cholestatic diseases:

Mechanical obstruction		Non-obstructive intrahepatic cholestasis		Systemic illness
Extrahepatic	*Intrahepatic*	*Small bile duct/canalicular*	*Hepatocellular*	
Malignant • Cholangiocarcinoma • Pancreatic carcinoma • Ampullary carcinoma • Gall bladder carcinoma • Metastases to lymph nodes in porta hepatis Benign • Choledocholithiasis • Primary sclerosing cholangitis • Chronic pancreatitis • AIDS cholangiopathy • Congenital – Choledochocele	Malignant • Metastatic malignancy Benign • Abscess • Primary sclerosing cholangitis • Suppurative cholangitis ★ Congenital fibrosis	• Primary biliary cirrhosis • Primary sclerosing cholangitis • Vanishing bile duct syndrome – Chronic rejection in liver transplants – Sarcoidosis – Drugs • Inherited – Benign recurrent cholestasis ★ Progressive familial intrahepatic cholestasis – Gilbert's syndrome – Crigler-Najjar syndrome – Dubin-Johnson syndrome – Rotor syndrome • Cholestasis of pregnancy	• Viral • Alcoholic hepatitis • Drug induced • Autoimmune • Malignant infiltration • Vascular occlusion – Budd-Chiari syndrome – Portal vein thrombosis • Metabolic/Hereditary – NAFLD/NASH – Iron overload ★ Wilson's disease ★ Alpha$_1$-antitrypsin deficiency – Galactosaemia – Tyrosinaemia – Cystic fibrosis	• Right heart failure • Haemolysis

AIDS = acquired immunodeficiency syndrome; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis.

A. Neonatal Hepatitis

--Multifactorial disorder with myriad pathogenetic mechanisms

--Diagnosis of exclusion based on adjunct testing :

- Laboratory investigation
- Electron microscopy
- Imaging studies
- Infectious disease work-up
- Clinical features
- Etc.

TABLE 12.2. Conditions Associated with Neonatal Hepatitis.

Idiopathic neonatal hepatitis

Infections, including cytomegalovirus, herpes virus, enterovirus (coxsackie B- and echovirus), rubella, hepatitis B, varicella, reovirus, paramyxovirus, parvovirus B19, toxoplasmosis, syphilis, toxoplasmosis, and bacterial sepsis (*Escherichia coli* and *Listeria*)

Metabolic conditions (see Table 12.3)

Endocrine, hypopituitarism

Obstructive, including biliary atresia, choledochal cyst

Chromosomal, including trisomy 17-18 syndrome, 21, and Monosomy X

Immune and hemolytic disorders (ABO and Rh incompatibility, spherocytosis, neonatal lupus erythematosus)

Total parenteral nutrition

TABLE 12.3. Metabolic Causes of Hepatitis (Neonatal or Acute).

- Alpha-1-antitrypsin deficiency
- Tyrosinemia
- Bile acid synthesis disorders (oxysterol 7α hydroxylase deficiency, 3β hydroxy steroid deydrogenase deficiency and oxosteroid 5β reductase deficiency)
- Alagille syndrome
- Cystic fibrosis
- Peroxisomal disorders (Zellweger syndrome, Refsum disease, di- and trihydroxycholestanoic acidemia)
- Familial intrahepatic cholestatic syndromes (progressive familial intrahepatic cholestasis II, North American Indian childhood cirrhosis)
- Fructosemia
- Galactosemia
- Mitochondrial mtDNA depletion
- Neonatal hemochromatosis
- Gaucher disease
- Niemann–Pick disease type C
- Wilson's disease[1]
- Indian childhood cirrhosis[1]
- Ornithine transcarbamylase deficiency[1]

[1]Acute hepatitis pattern.

Common Histological Features of Idiopathic Neonatal Hepatitis (INH):

--Pronounced giant cell transformation

--Portal and lobular inflammatory infiltrates

--Apoptotic bodies

-- Bile ductular reaction

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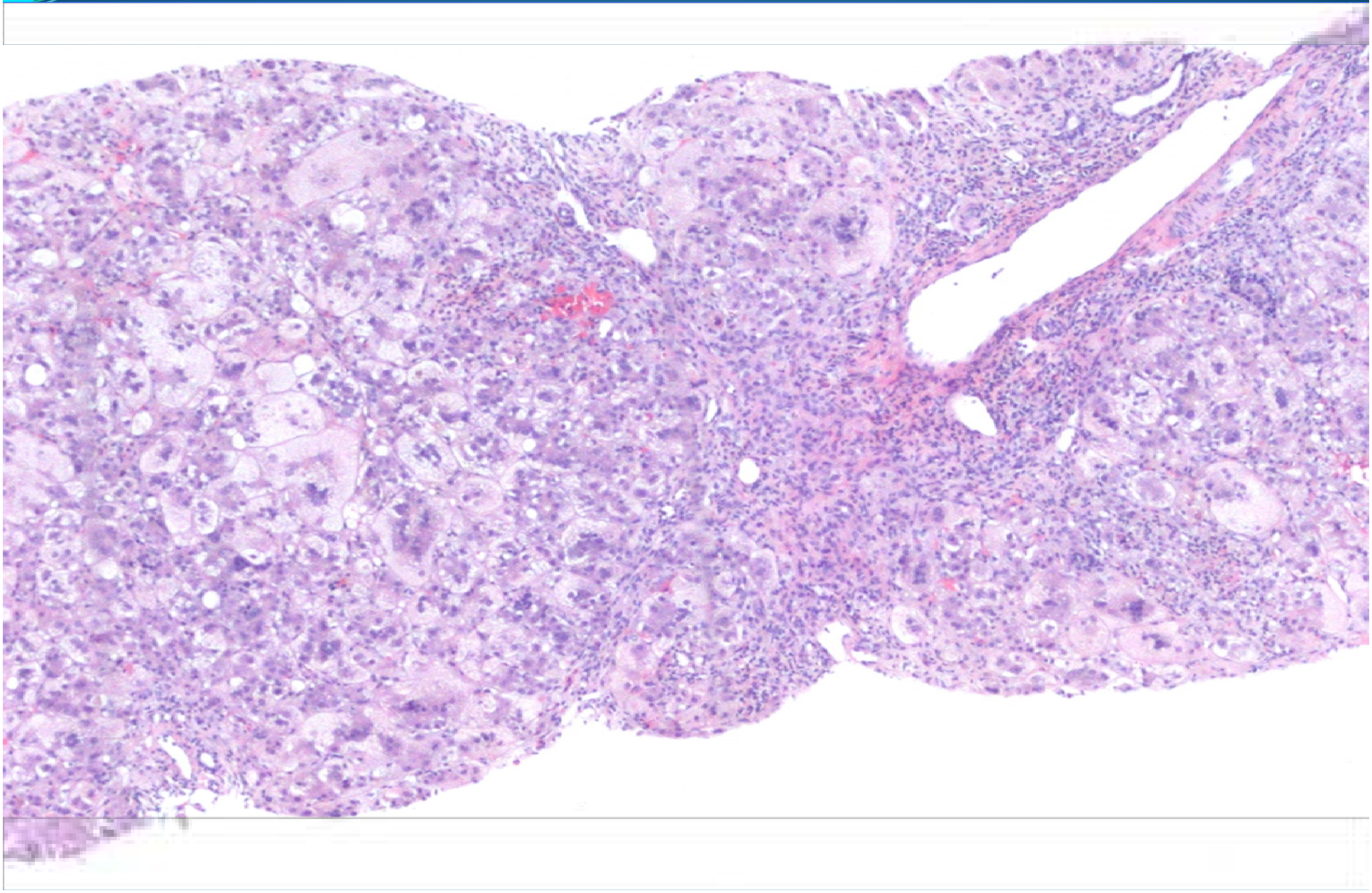
INH: Giant cell transformation, portal/periportal infiltrate with lobular spill (H&E x 4)



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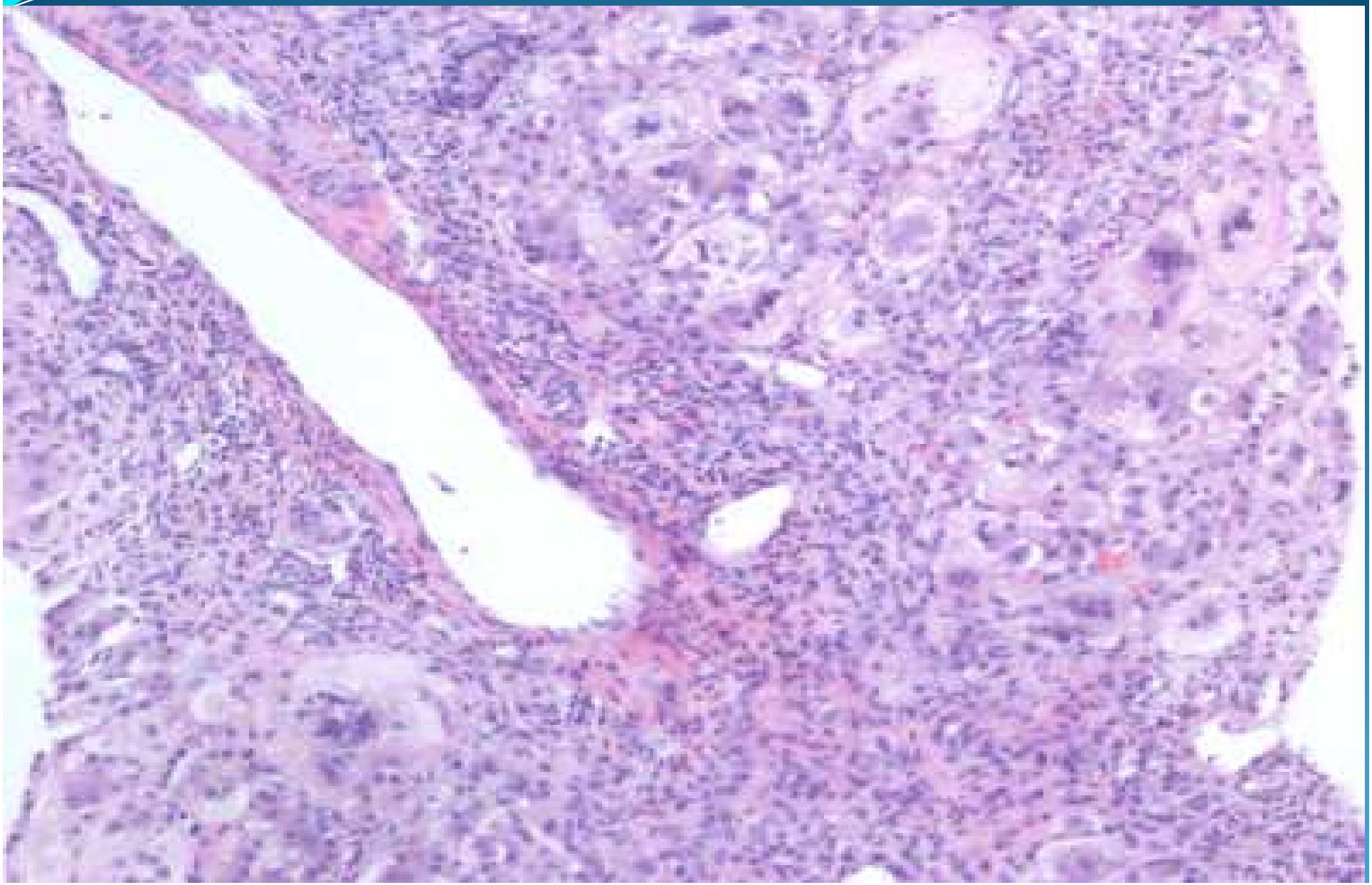
INH: Feathery degeneration of hepatocytes, canalicular cholestasis and inflammation (H&E x 10).



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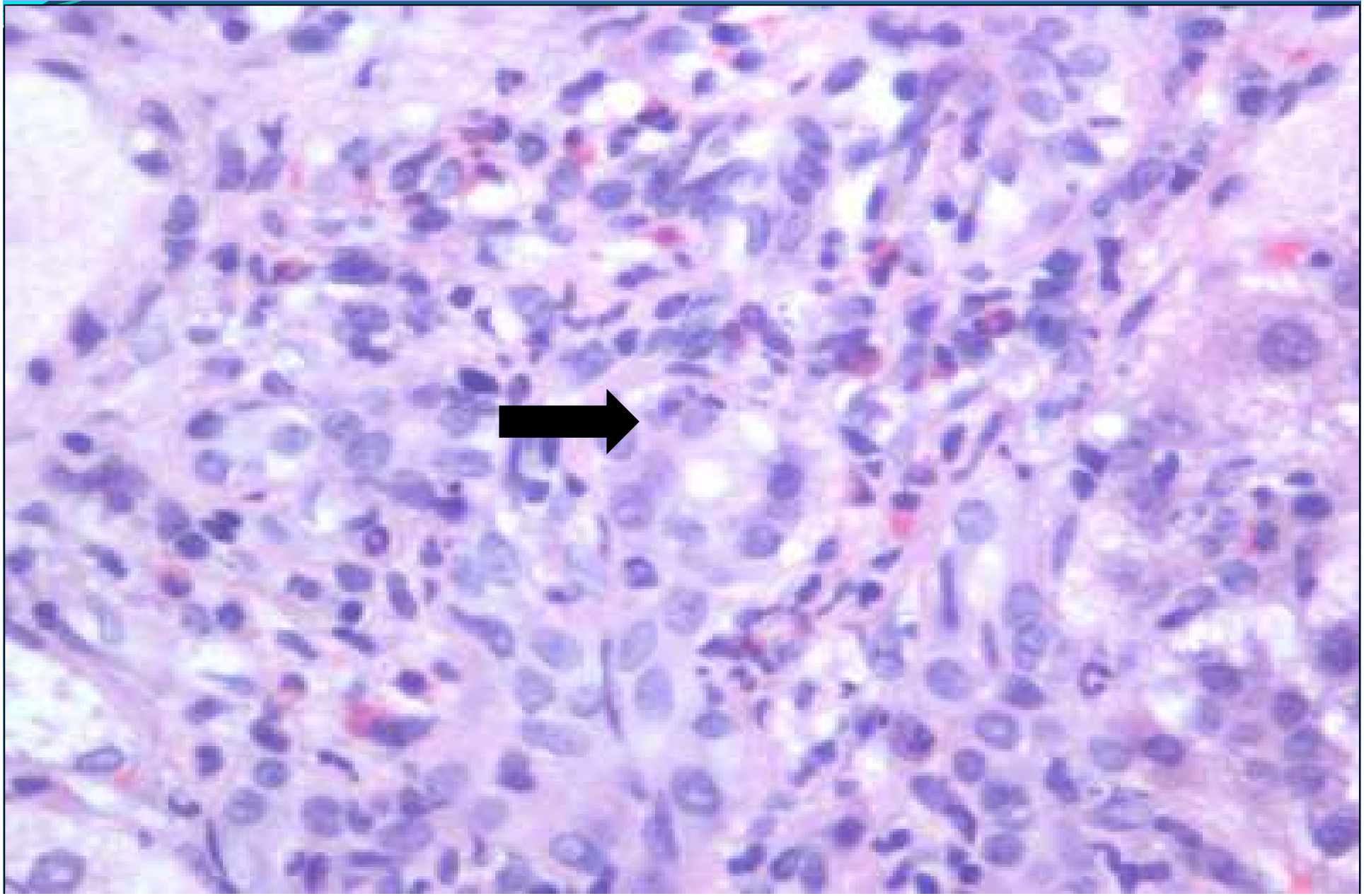
INH: Mixed acute/chronic inflammation with eosinophils. Note neutrophil in bile duct epithelium (arrow) (H&E x 40).



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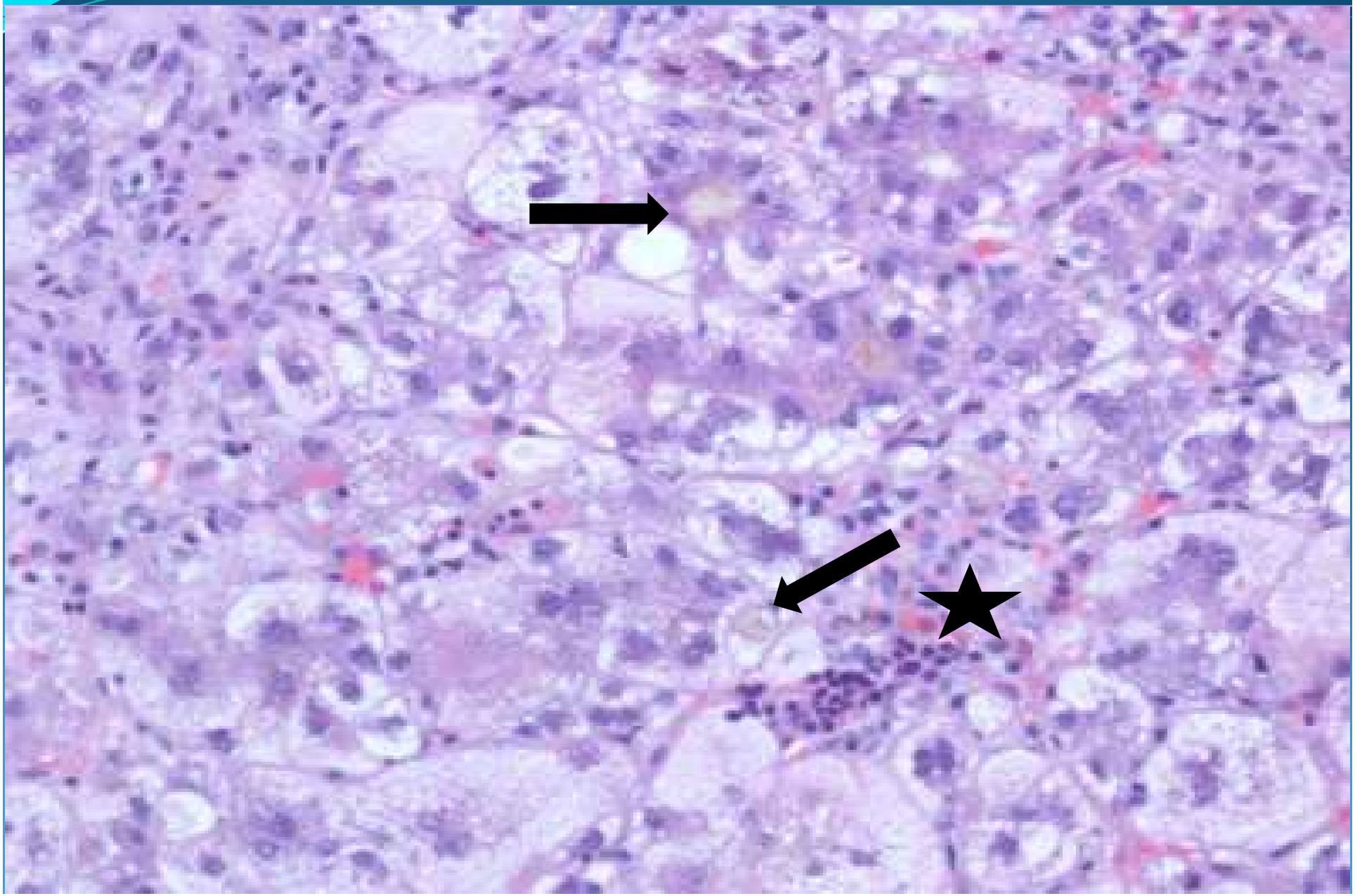
INH: Canalicular and cytoplasmic cholestasis (arrows), extramedullary hematopoiesis (star), and giant cell transformation (H&E x 20)



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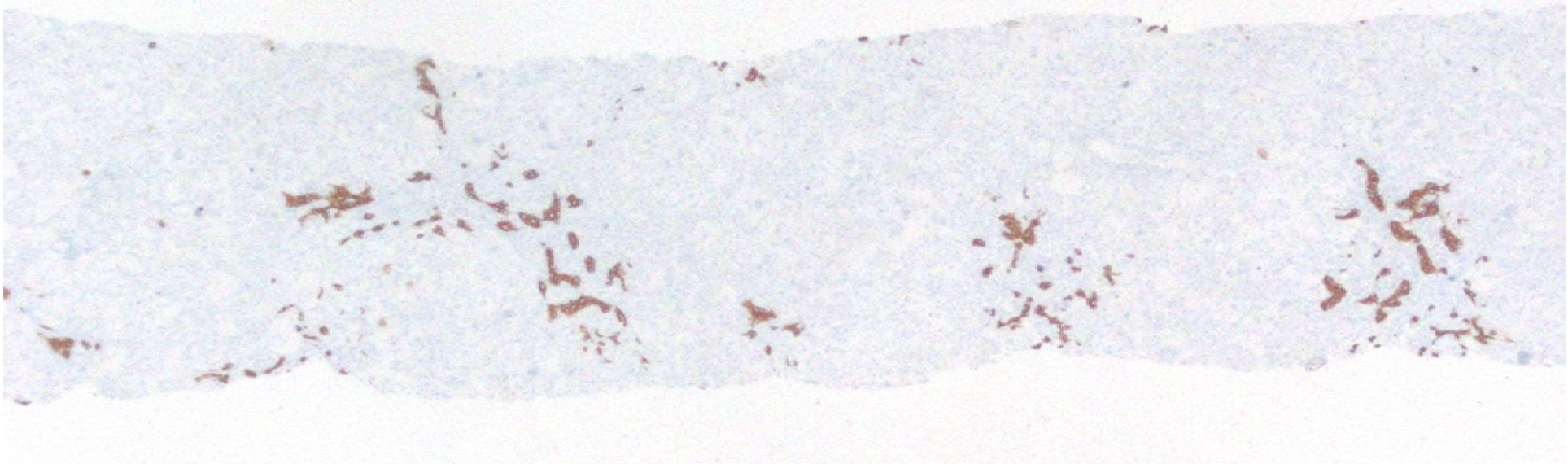
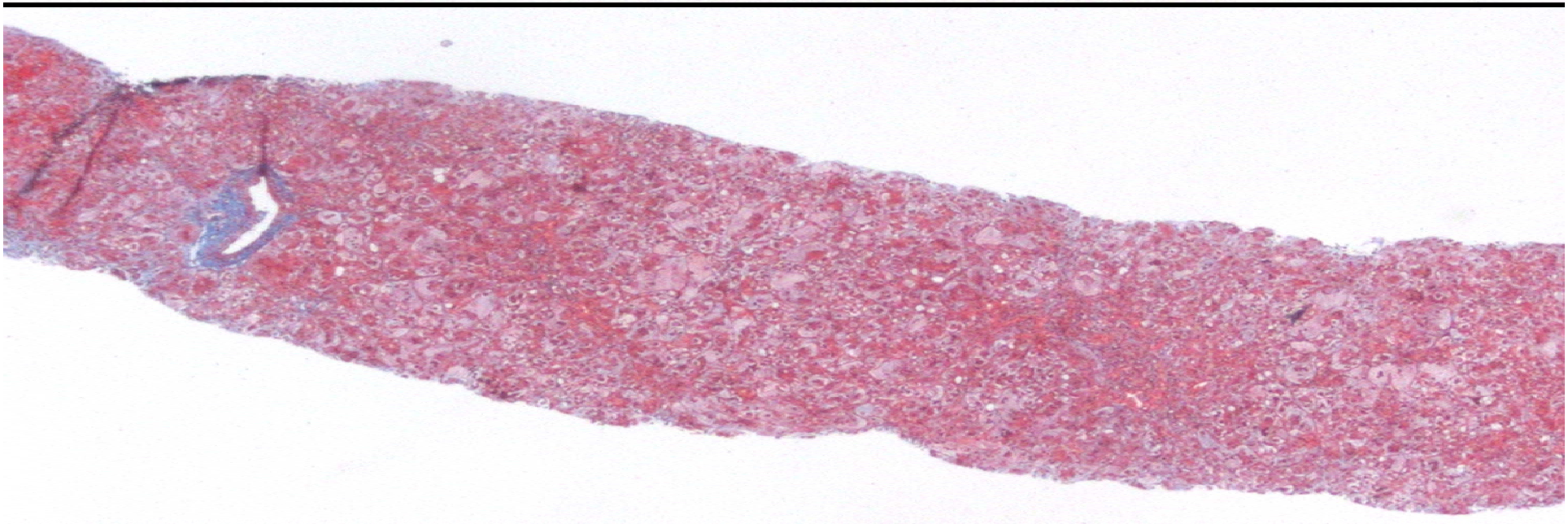
INH: Moderate ductular proliferation (CK7 x 2) but no fibrosis (Masson trichrome x 2)





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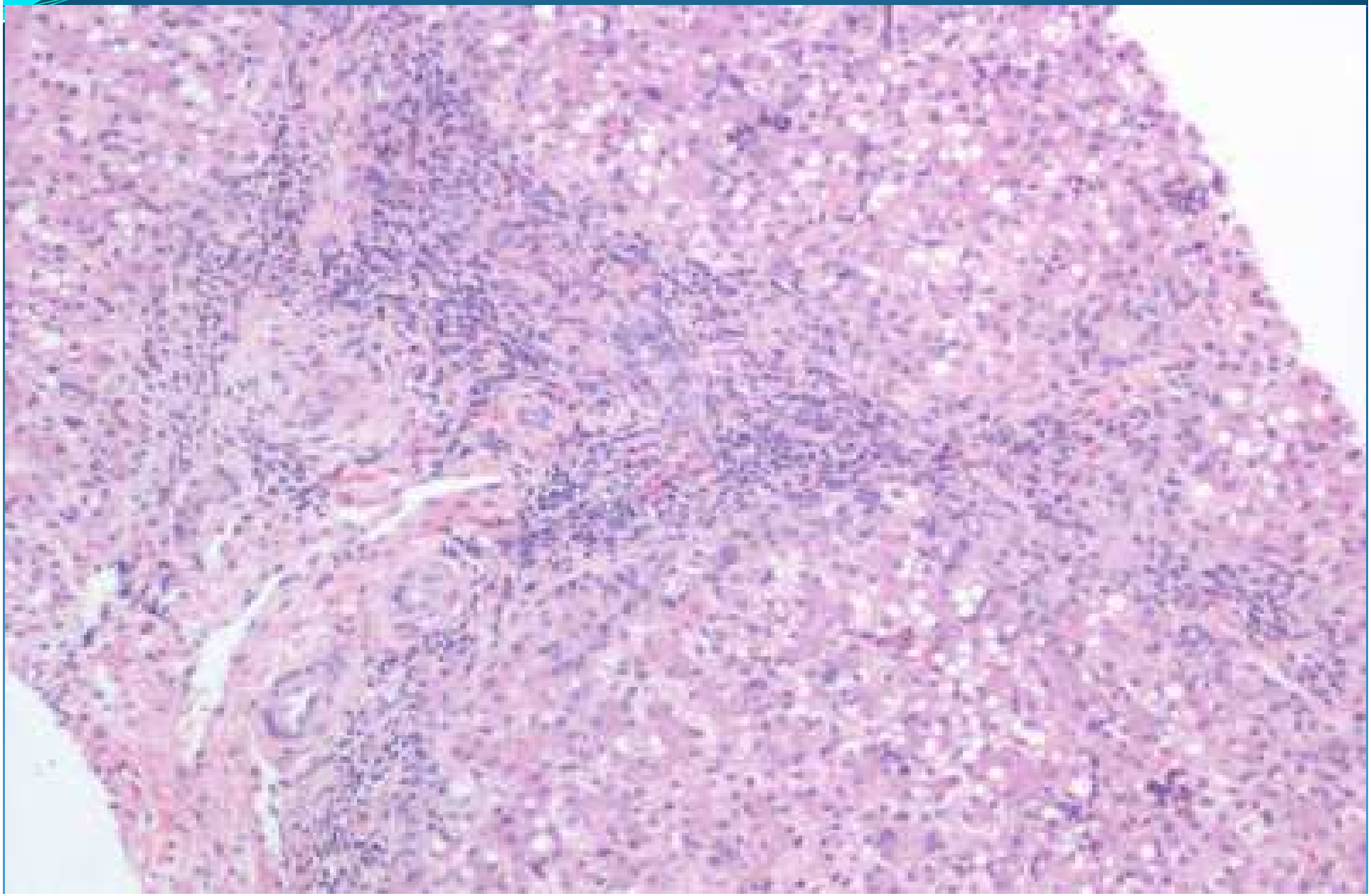
INH: Microvesicular steatosis (H&E x 10).



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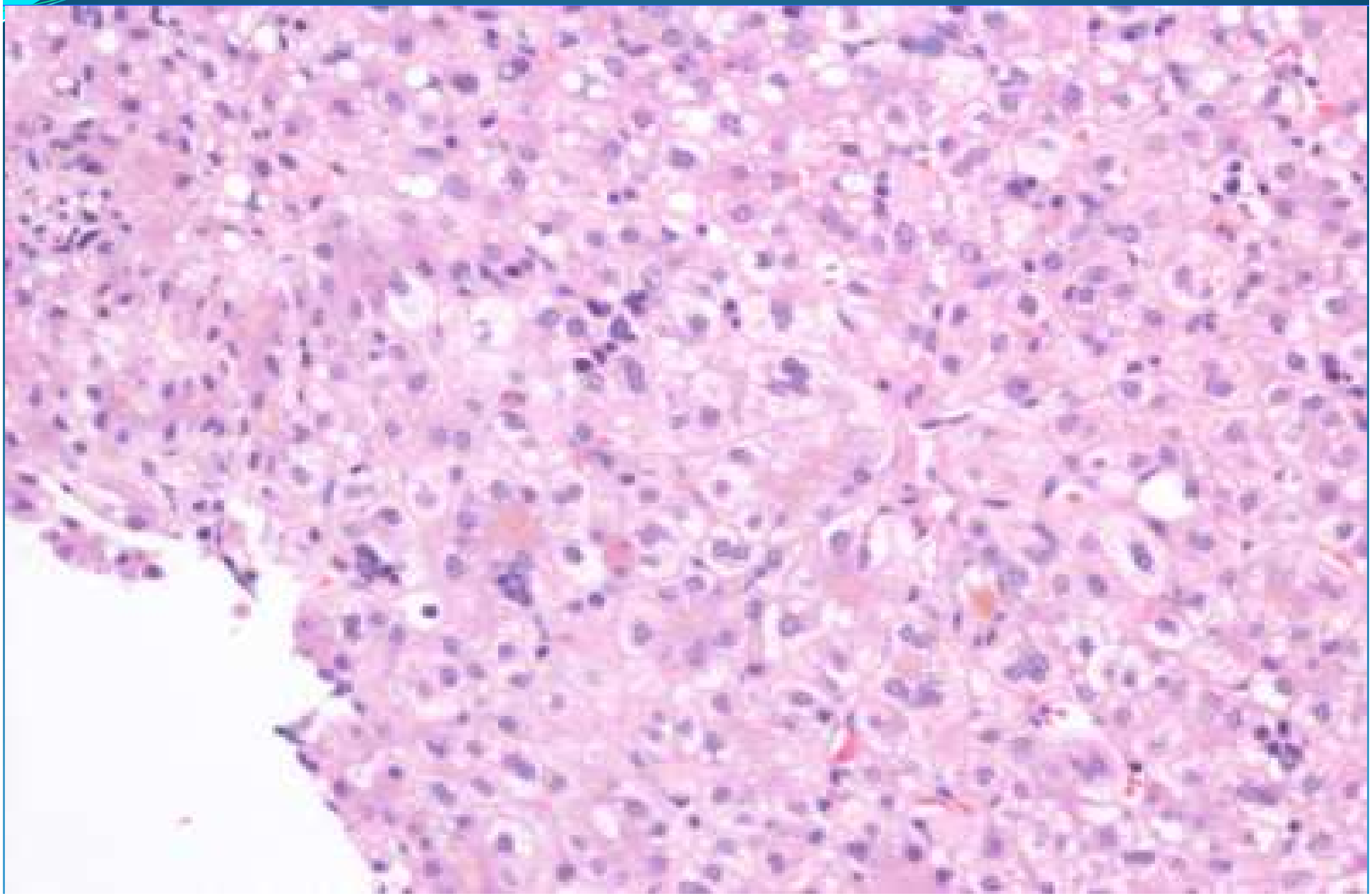
INH: Canalicular and cytoplasmic cholestasis, apoptotic body, and feathery degeneration with focal giant cell transformation (H&E x 20).



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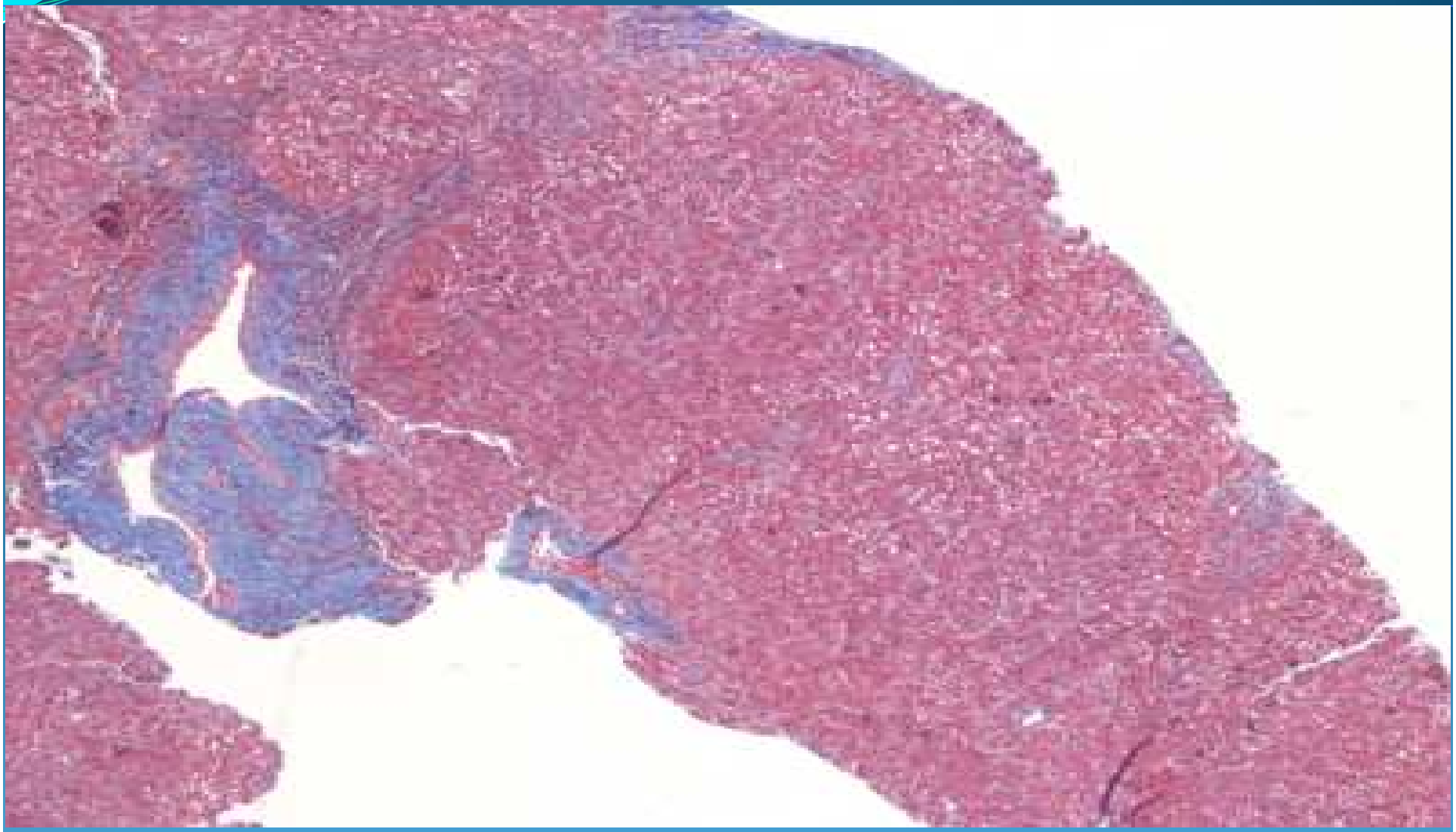
Stage 2 fibrosis (Masson trichrome x 4).



INH: As possible causes are numerous, diagnosis often descriptive with suggestions for additional testing to determine etiology.

Helpful ancillary tests:

--Special stains:

iron, copper;

infections (CMV/HSV/Adenovirus) immunostains as CK7/CKAE1/AE3)

--Electron microscopy

--Quantification studies (iron/copper)

--Viral RT-PCR

--Serology

B. Progressive Familial Intrahepatic Cholestasis (PFIC):

--Originally described in 1965 in Byler kindred of Pennsylvania Amish
--Different subtypes classified on molecular profile

--All 3 types are caused by recessive mutations in different genes

--Benign recurrent intrahepatic cholestasis also described in 1965, now recognized as milder form of PFIC

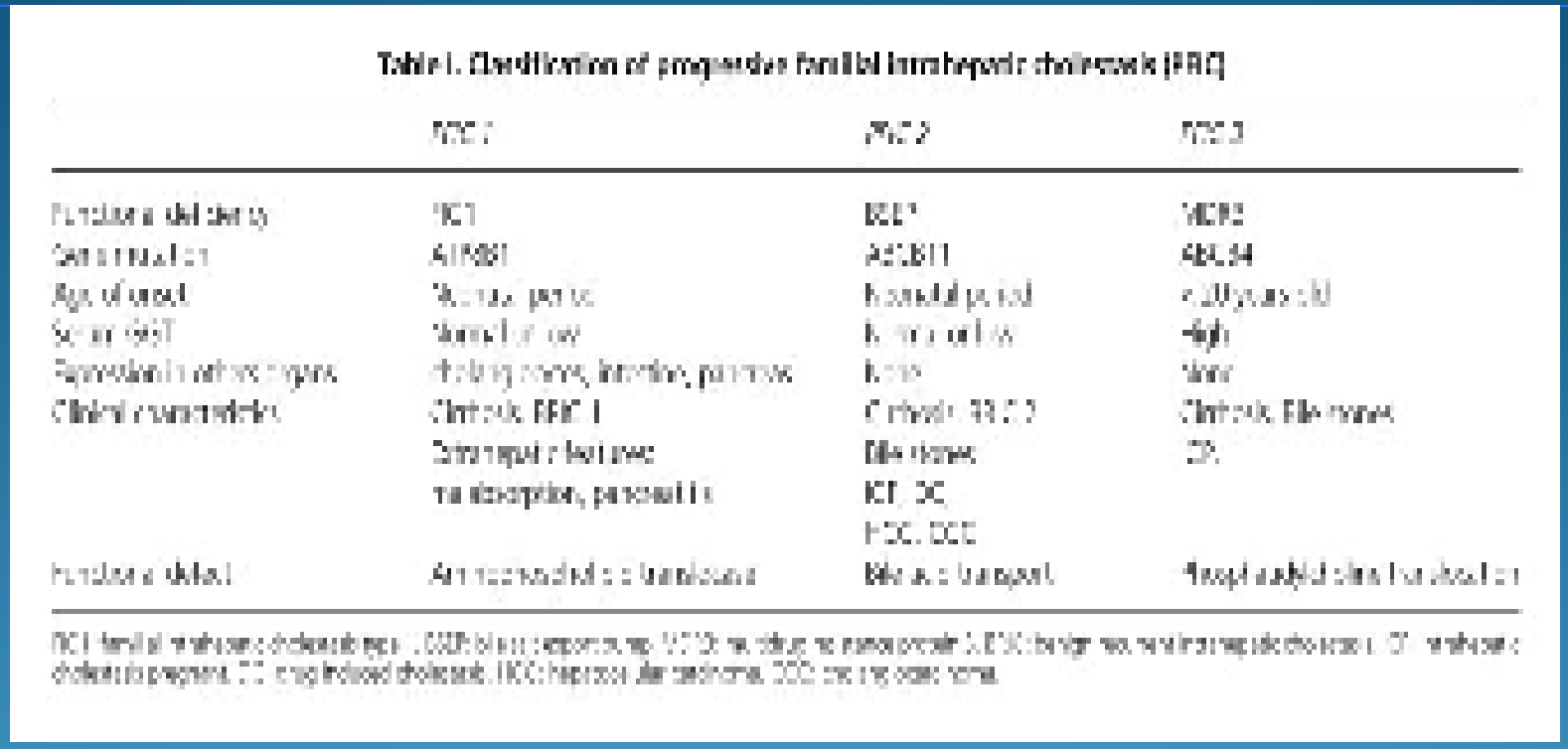


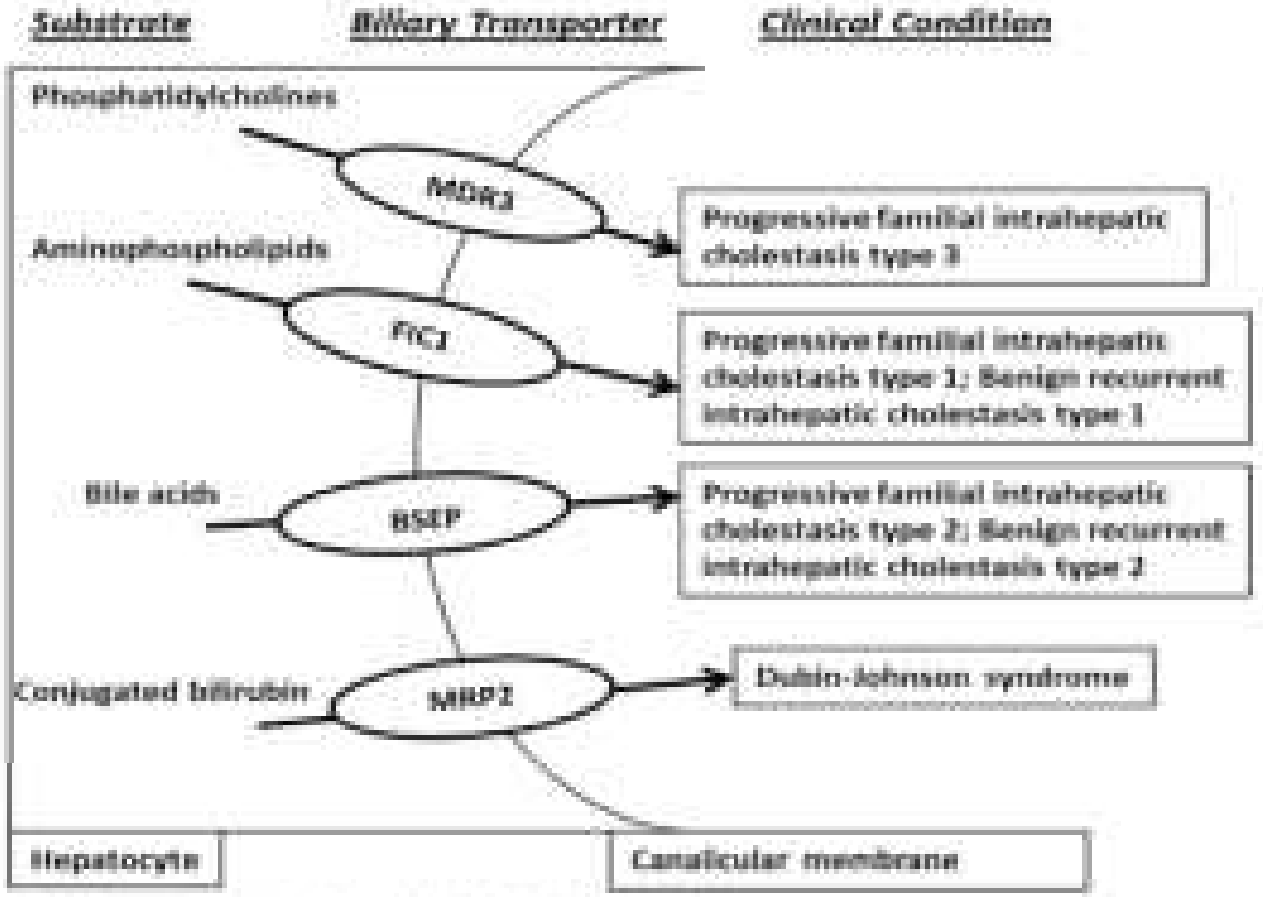
Table I. Classification of progressive familial intrahepatic cholestasis (PFIC)

	PFIC 1	PFIC 2	PFIC 3
Functional abnormality	FIC1	BSEP	MDR3
Gene mutated	ATP8B1	ABCB11	ABCB4
Age of onset	Neonatal period	Neonatal period	>2 years old
Serum GGT	Normal or low	Normal or low	High
Extrahepatic manifestations	Diarrhea, pancreatitis, deafness	None	None
Clinical characteristics	Clinically PFIC 1 Severe pruritus Malabsorption, steatorrhea	Clinically PFIC 2 Bile stones HCC, CC FHC, CCC	Clinically Bile stones CC
Functional defect	Abnormal canalicular translocase	Bile salt transport	Phospholipid transfer to bile

FIC1 familial intrahepatic cholestasis type 1, BSEP bile salt export pump, PFIC progressive familial intrahepatic cholestasis, MDR3 multidrug resistance protein 3, CC cirrhosis, HCC hepatocellular carcinoma, CCC cholangiocellular carcinoma

PFIC I often shows ductopenia on histology
PFIC II may display a hepatitic pattern
PFIC III may present with cirrhosis
All three types may lead to neoplasia.

Canalicular membrane surface proteins, their substrates, and known associations with pediatric disease.



David Brandsough, and Cara Mack Pediatrics in Review 2012;33:281-282

PediatricsinReview

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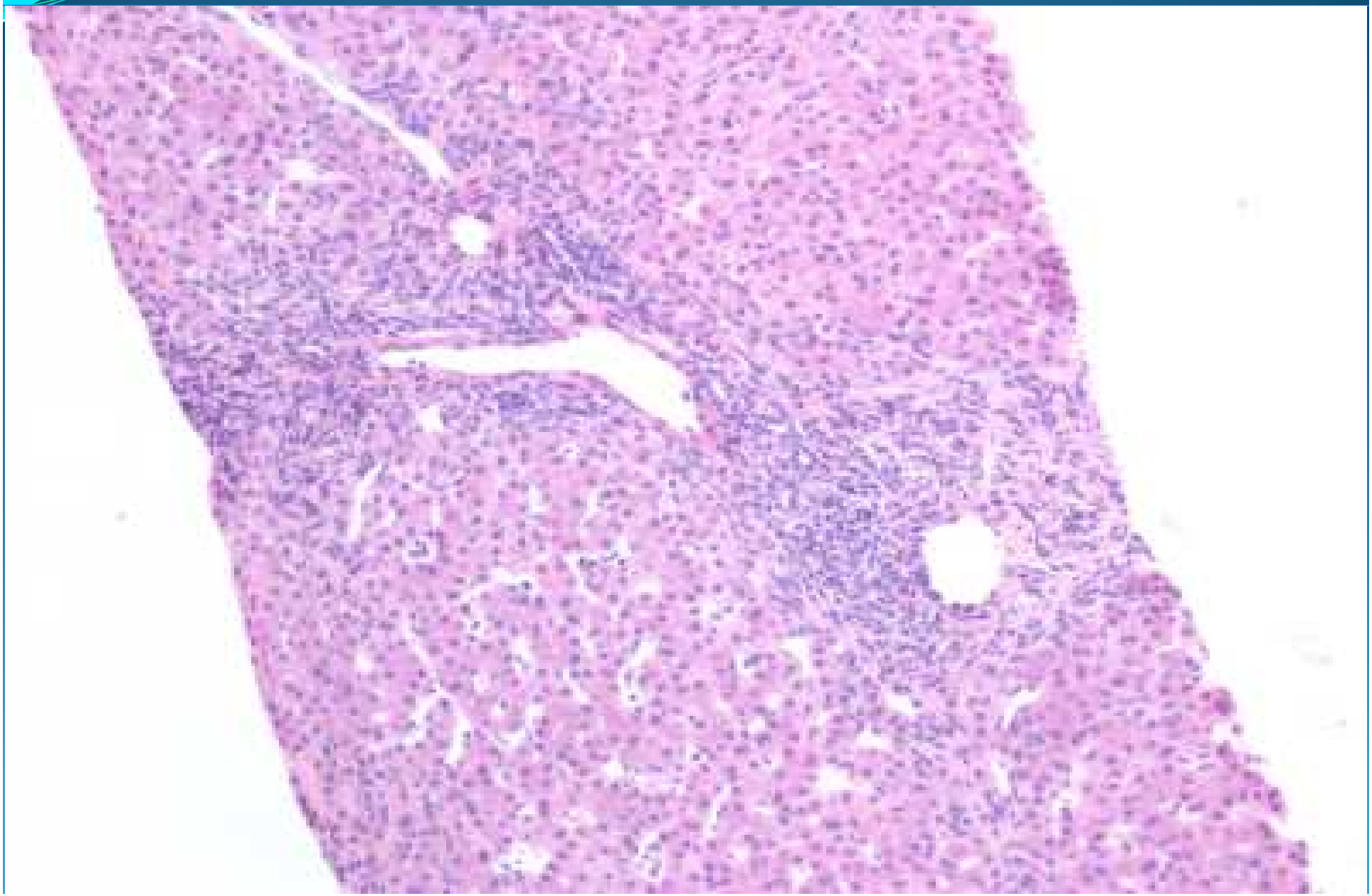
PFIC I: Portal inflammation and ductopenia (H&E x 10)



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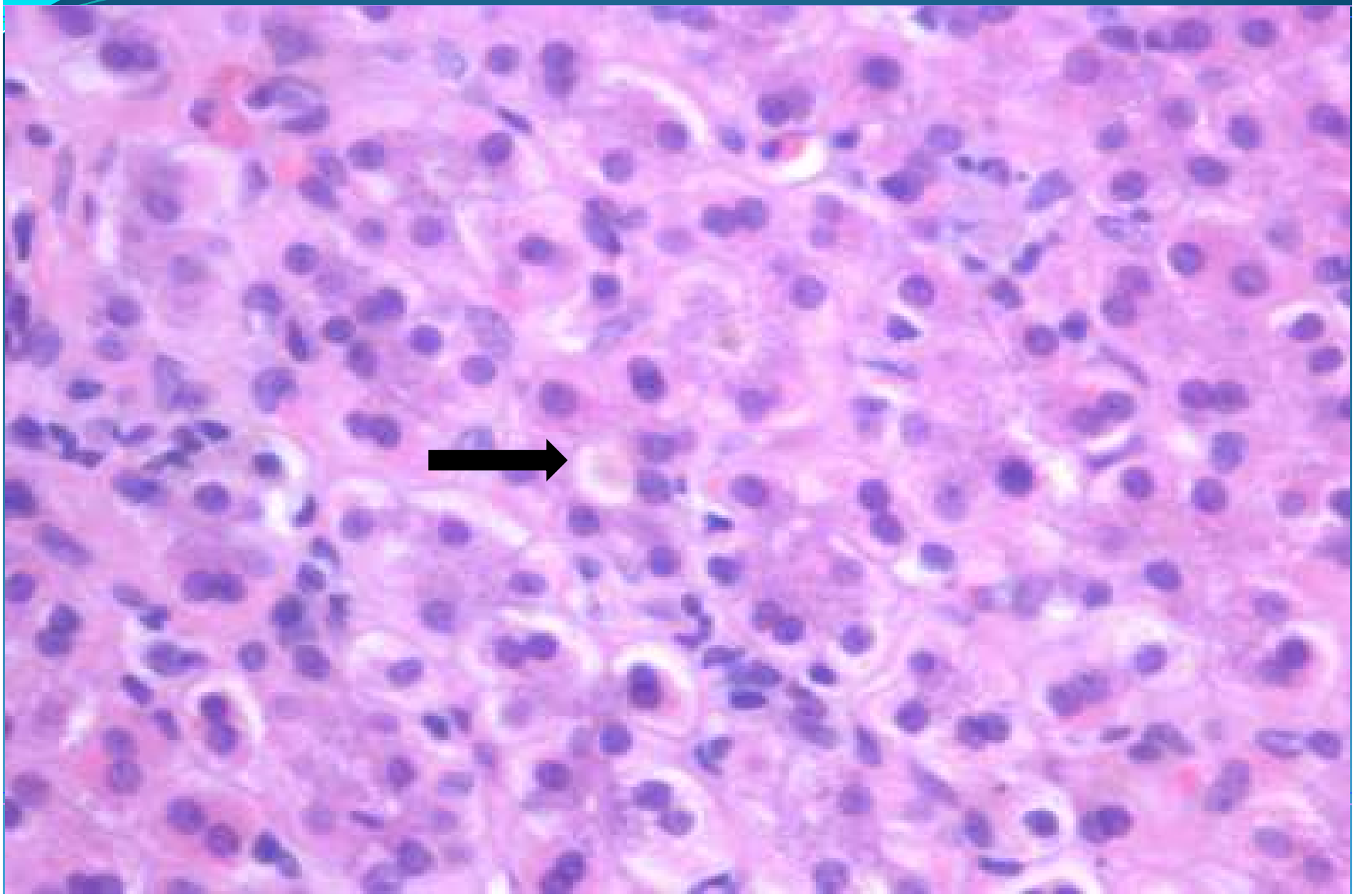
PFIC I: Pale canalicular bile (arrow) (H&E x 40).



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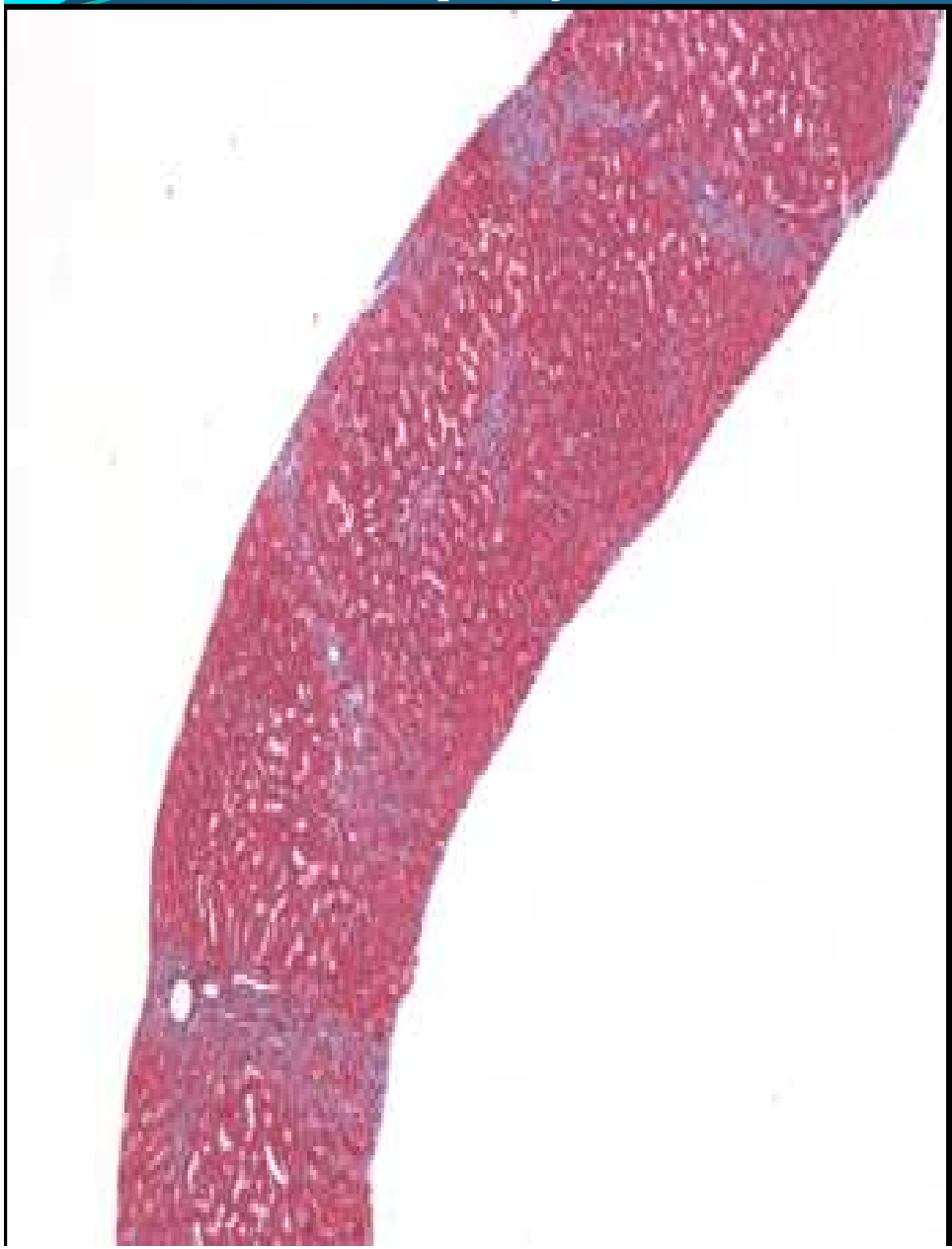
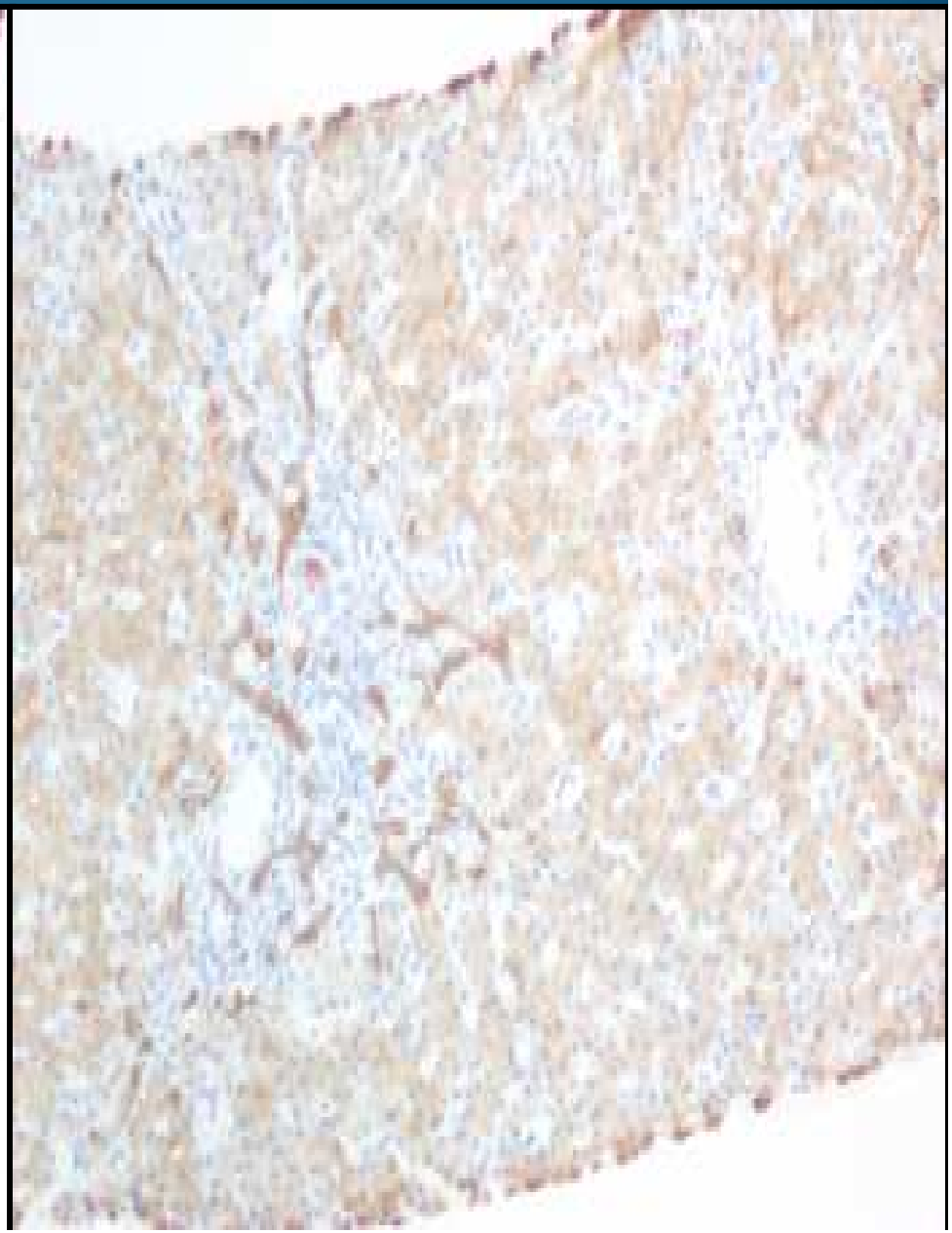
PFIC I: Mild to moderate portal and lobular fibrosis (Masson trichrome x 4); CK7 highlights ductular proliferation and hepatocytes (x 10).





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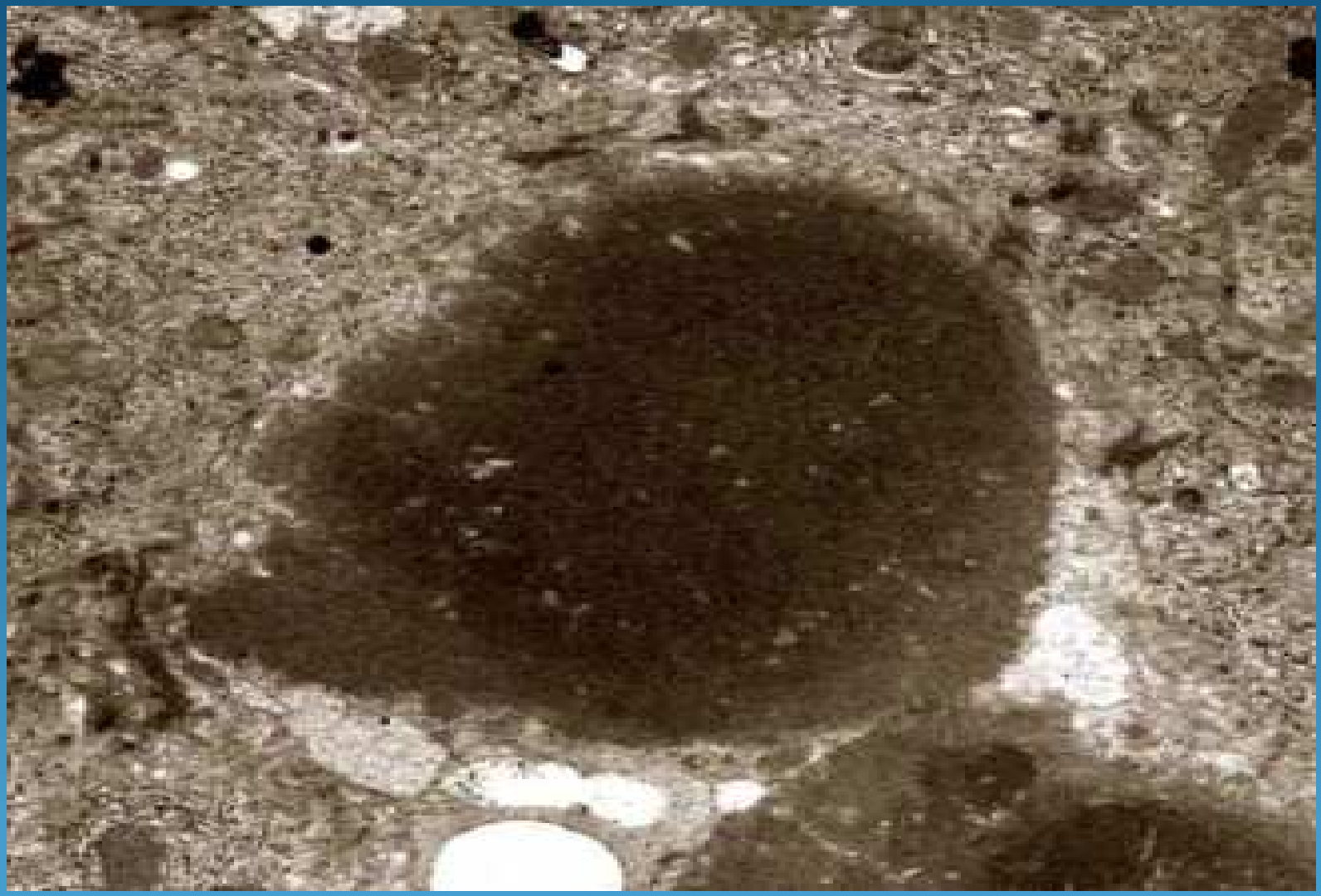
Ultrastructural feature of normal bile



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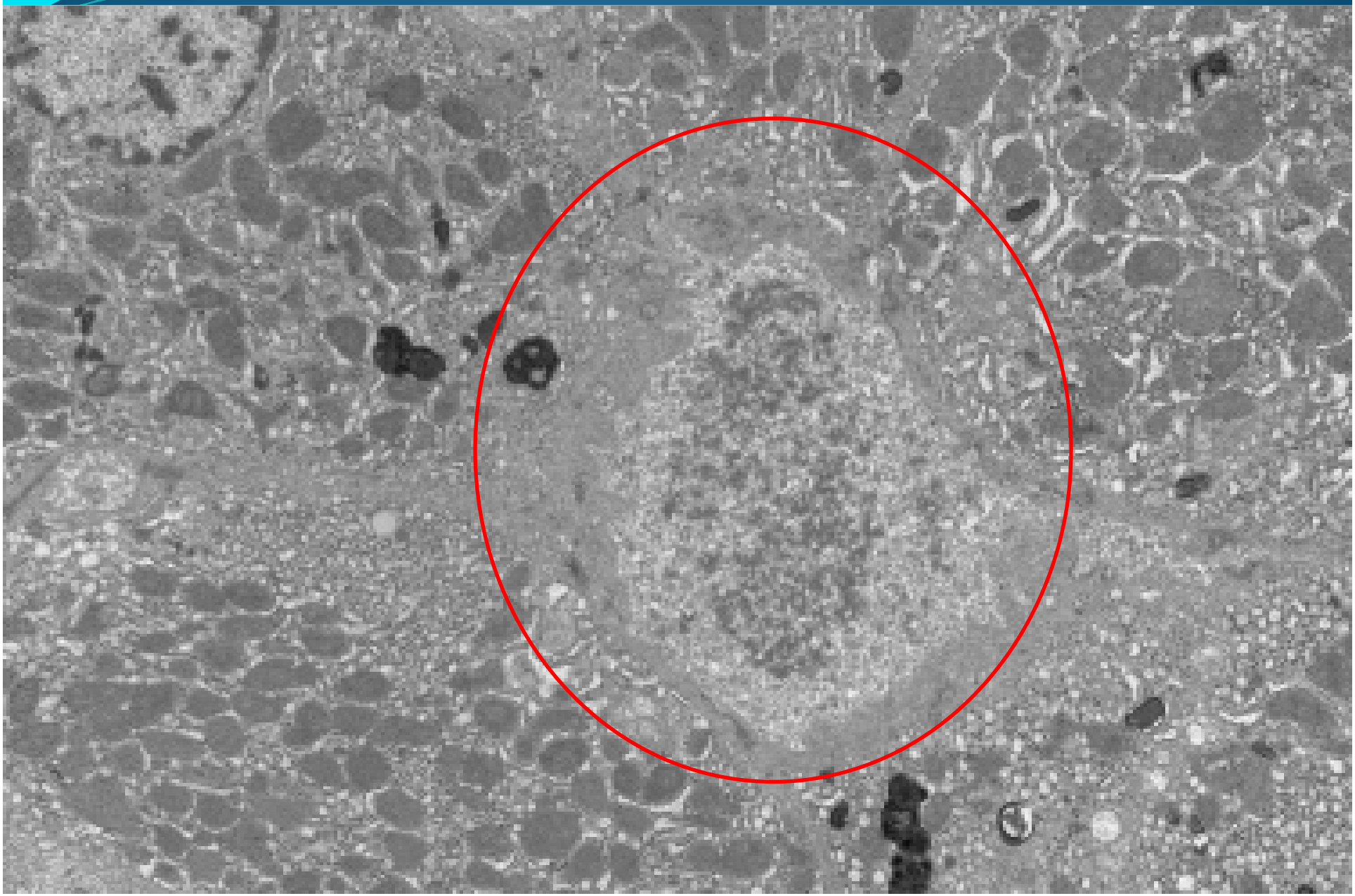
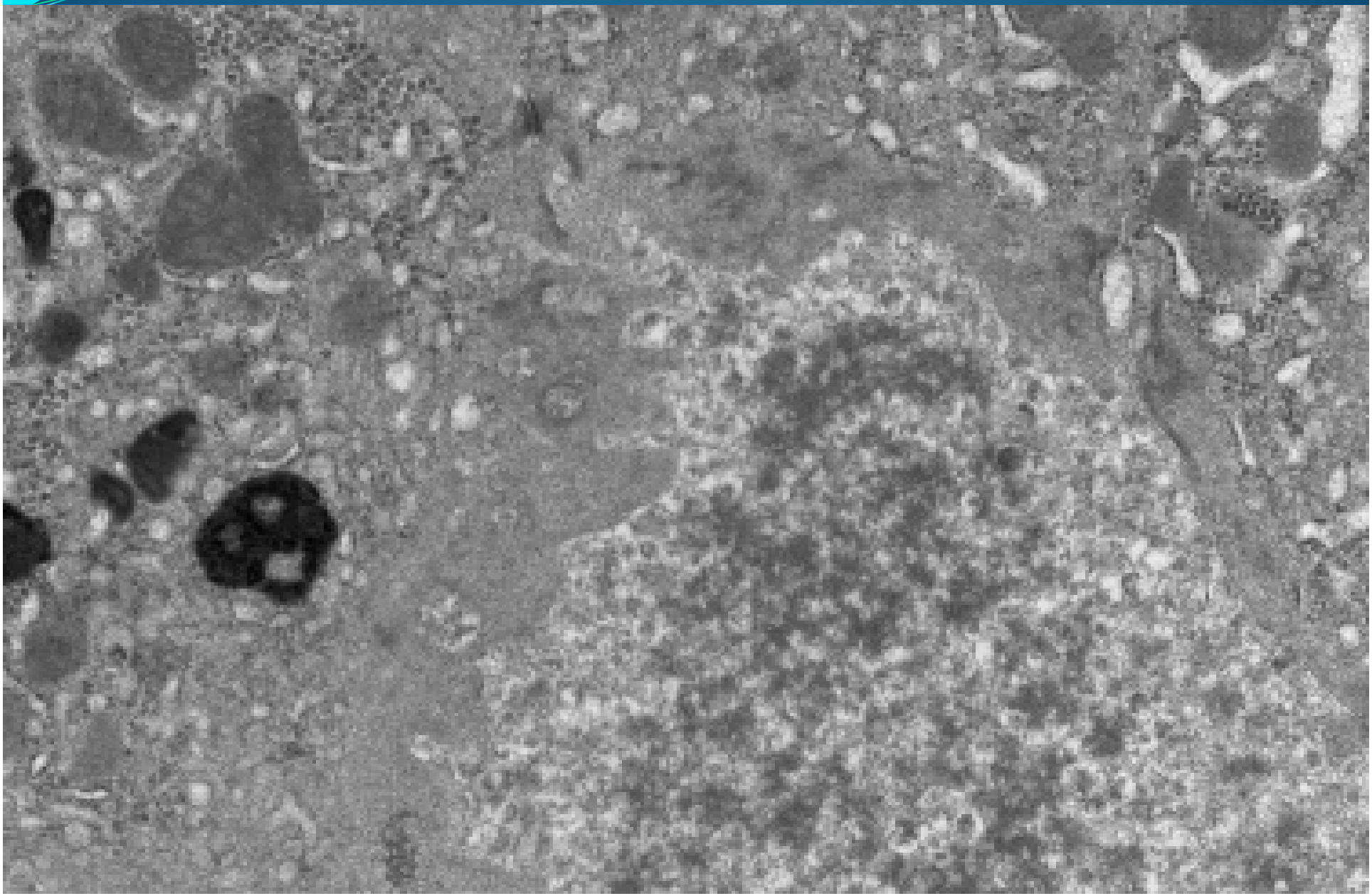
Granular (Byler) bile in PFIC I liver found on electron microscopy.





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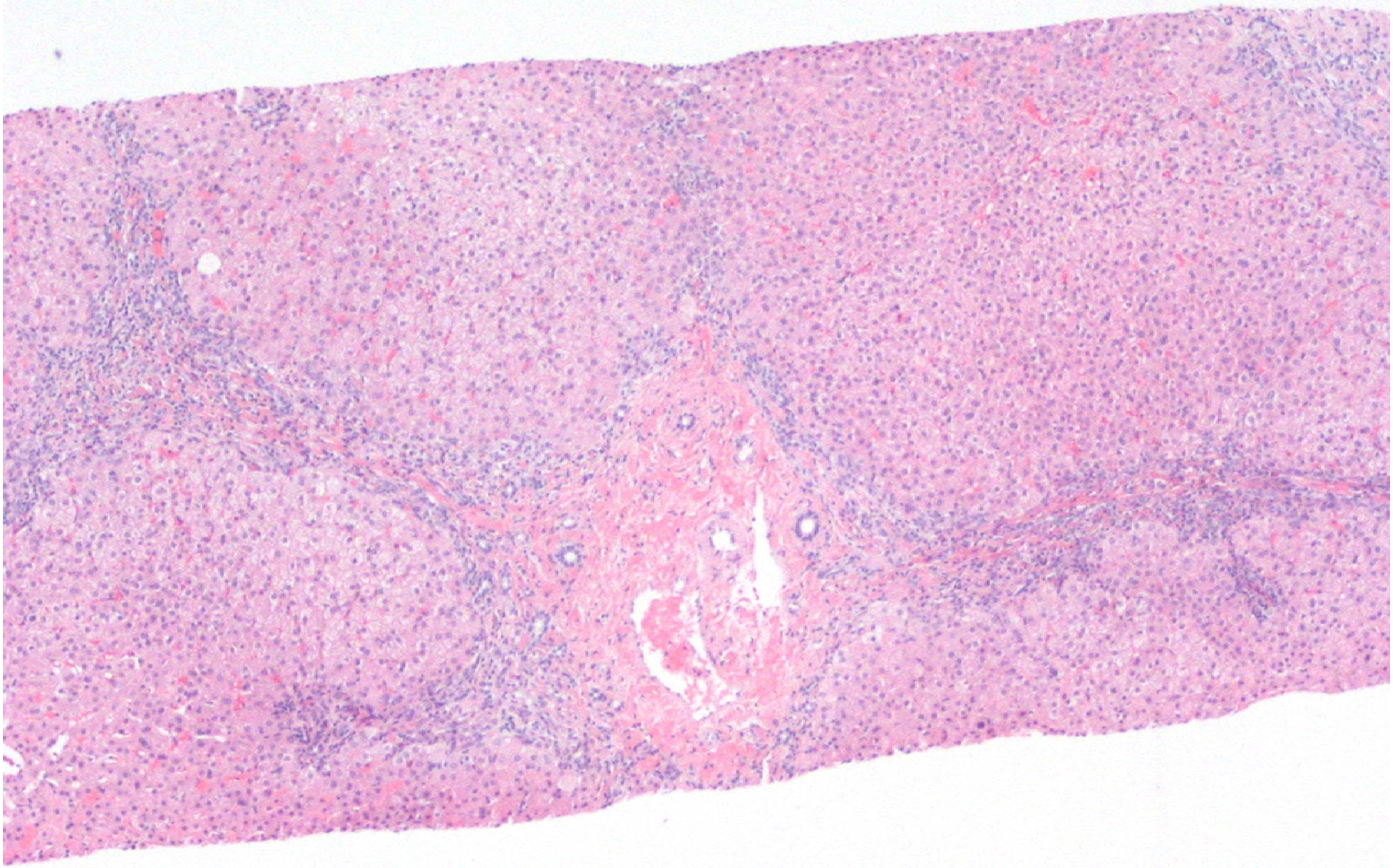
PFIC III: Chronic active hepatitis with brisk inflammation and portal-portal bridging (H&E x 4).



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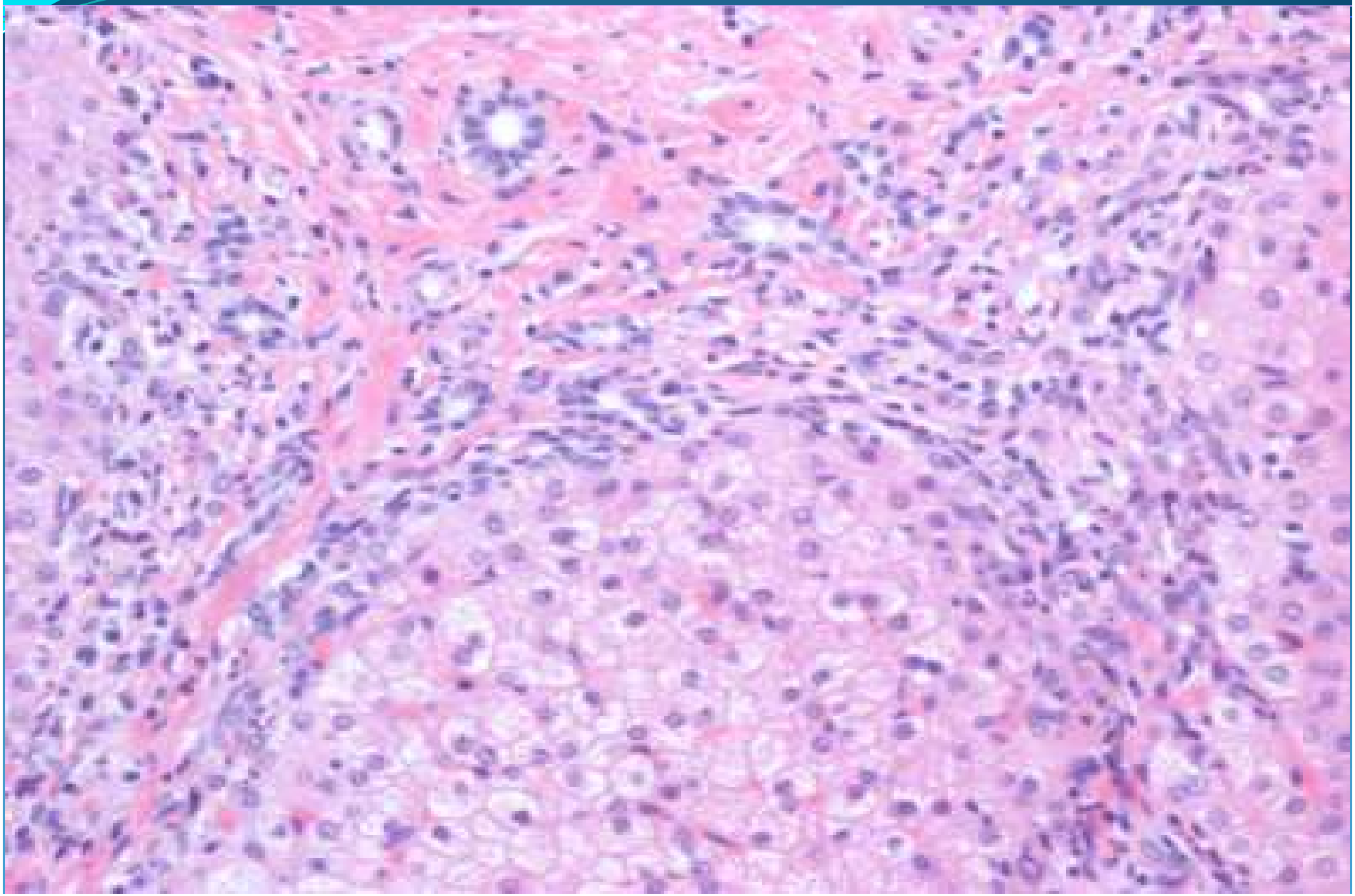
PFIC III: Ductular hyperplasia and interface hepatitis (H&E x 20).



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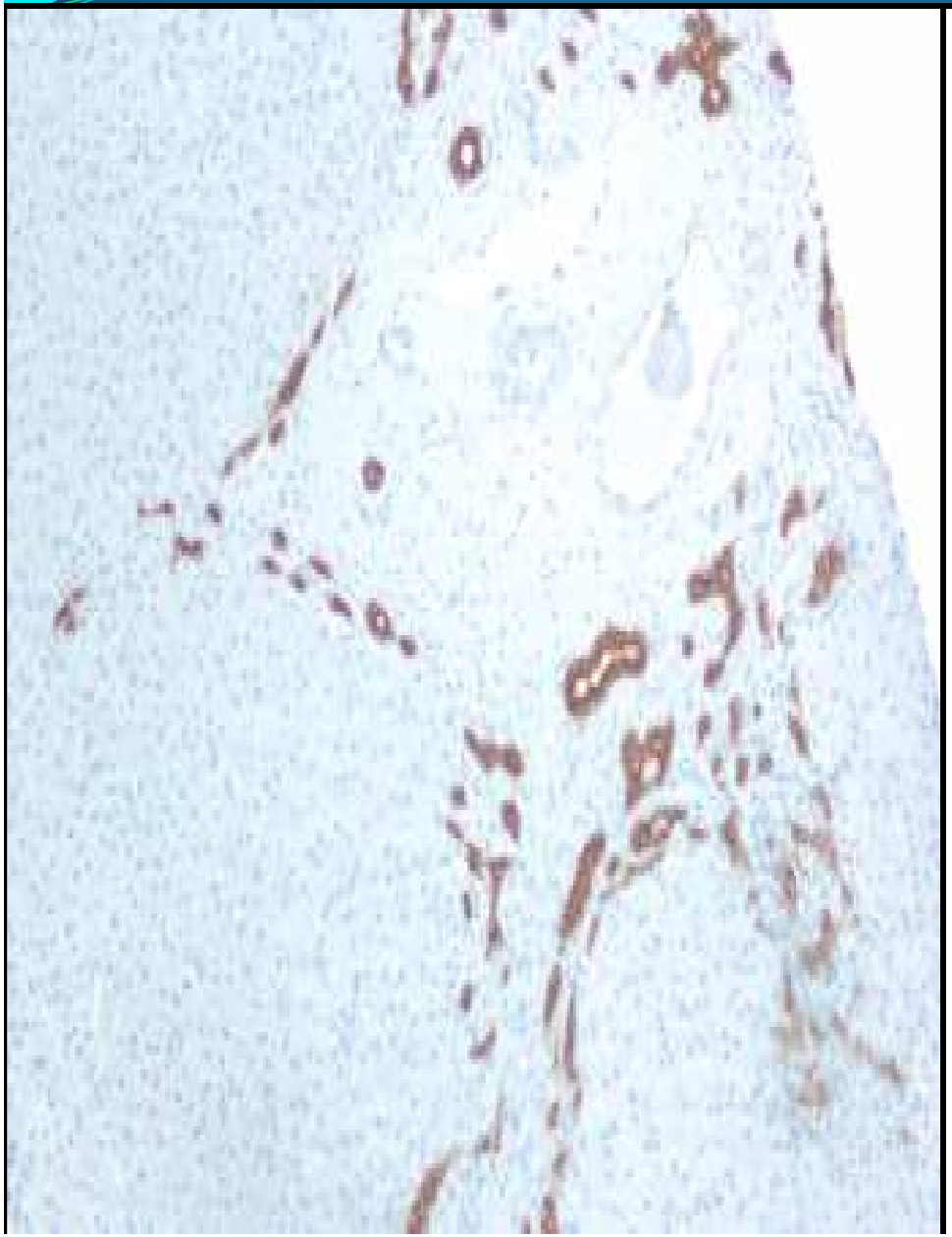
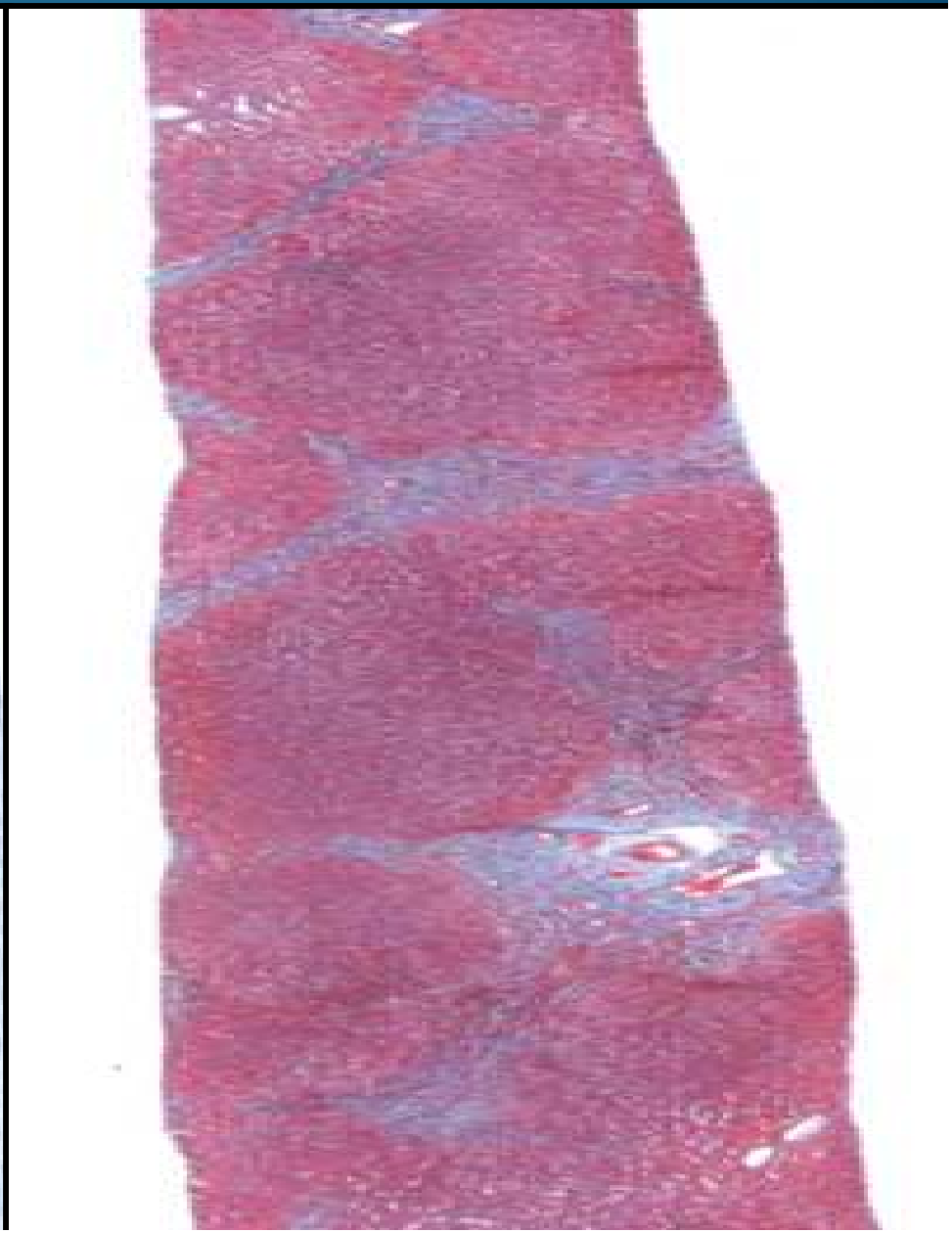
PFIC III: Ductular proliferation highlighted by CK7 (x 10); bridging fibrosis on Masson trichrome (x 4).





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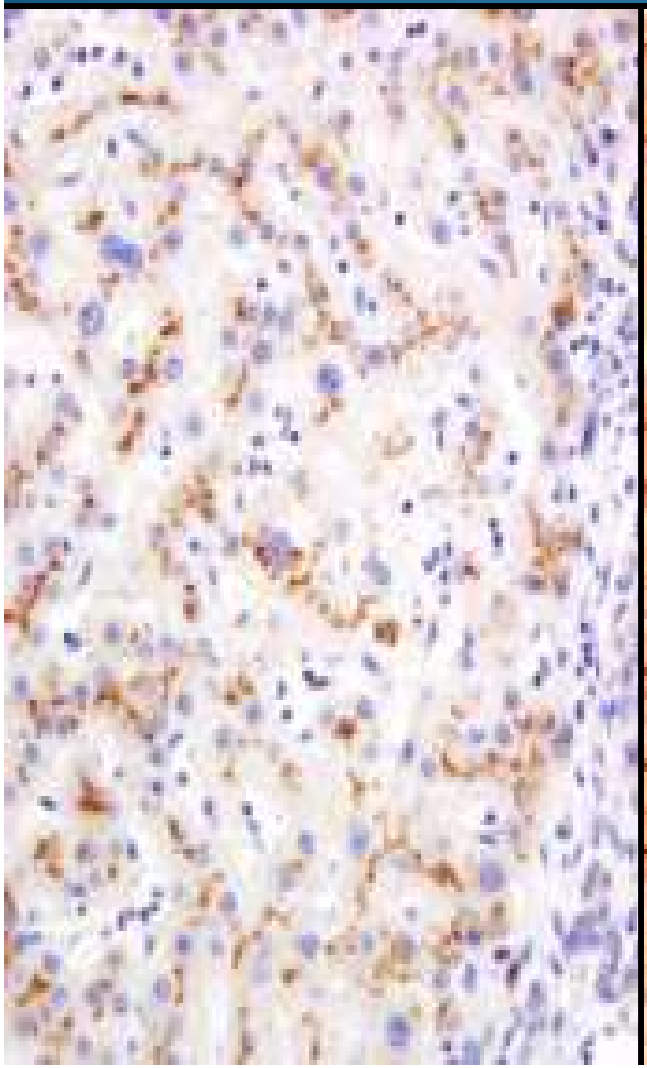
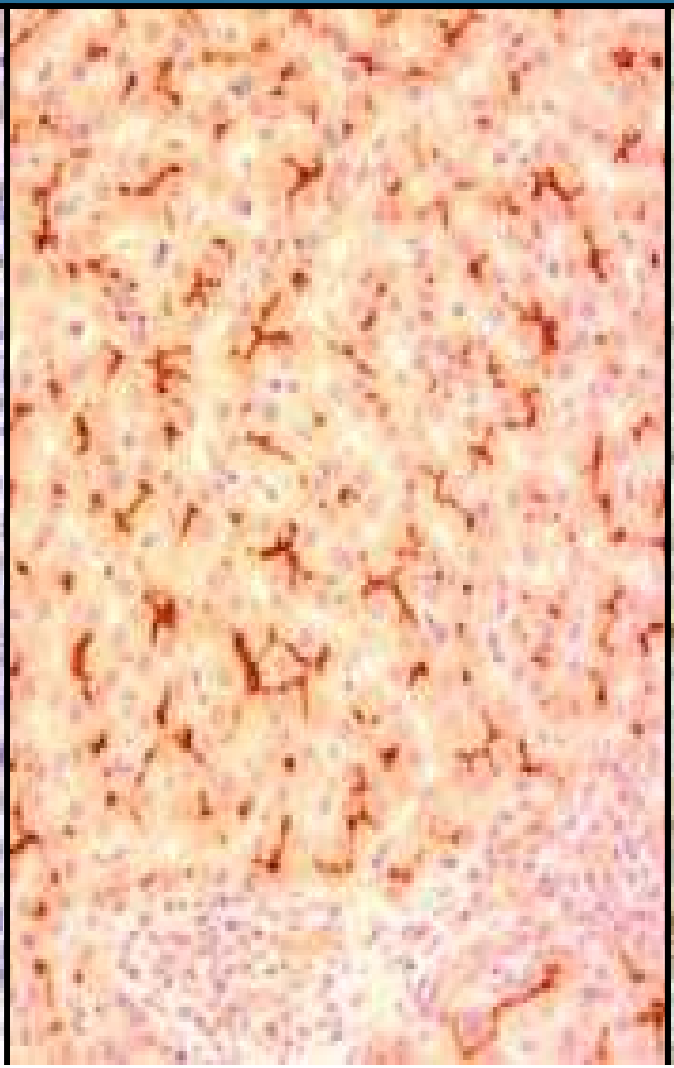
Applicable Antibodies:

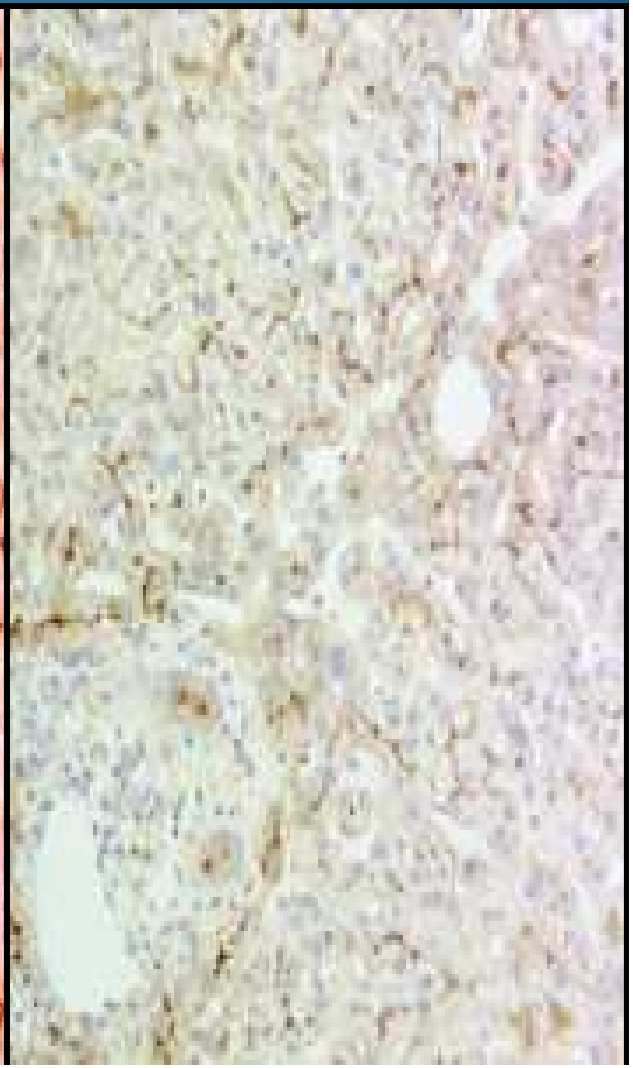
BSEP



MDR3



GGT



C. Paucity of Intrahepatic Bile Ducts

Two general groups:

1. Syndromic
   --Alagille syndrome (arteriohepatic dysplasia)
2. Non-syndromic
   --Diseases in which paucity is associated with another identifiable condition:
   --Infection (CMV, HSV, rubella)
   --Immune abnormality , e.g. GVHD
   --Hepatotoxicity
   --Metabolic diseases (Zellweger syndrome, bile acid metabolism)
   --Chromosomal abnormalities (45XO; trisomy 17, 18, 21)
   --Extrahepatic biliary atresia
   --Sclerosing cholangitis
   --Langerhans cell histiocytosis
   --Primary biliary cirrhosis

C. Paucity of Intrahepatic Bile Ducts: Alagille syndrome epidemiology:

Etiology	• Autosomal dominant genetic disease • Mutations in the JAG-1 gene on chromosome 20p12 are responsible for AGS in more than 90 percent of patients; others have mutations in NOTCH-2
Incidence	• Approximately 1/100,000 live births
Gender Ratio	• There is equal gender distribution
Age Predilection	• The majority of patients present before six months of age
Risk Factors	• Mutation in the *Jagged1 (JAG1)* or *NOTCH2* gene
Treatment	• Currently no curable treatment exists and medical management depends on diagnosing and treating disease in each affected organ system
Prognosis	• Predicting prognosis is difficult; however, it is dependent on the severity of liver damage and cardiac complications
Findings on Imaging	• ERCP: Narrowing of the extrahepatic biliary ducts and uniform narrowing of the intrahepatic ducts with reduced arborization • Cholescintigraphy: Delayed visualization of gastrointestinal tract • MR: Peripheral pulmonary stenosis. Structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy • CT: Peripheral pulmonary stenosis; Butterfly vertebrae

Table 1: Summary table of syndromic Alagille syndrome

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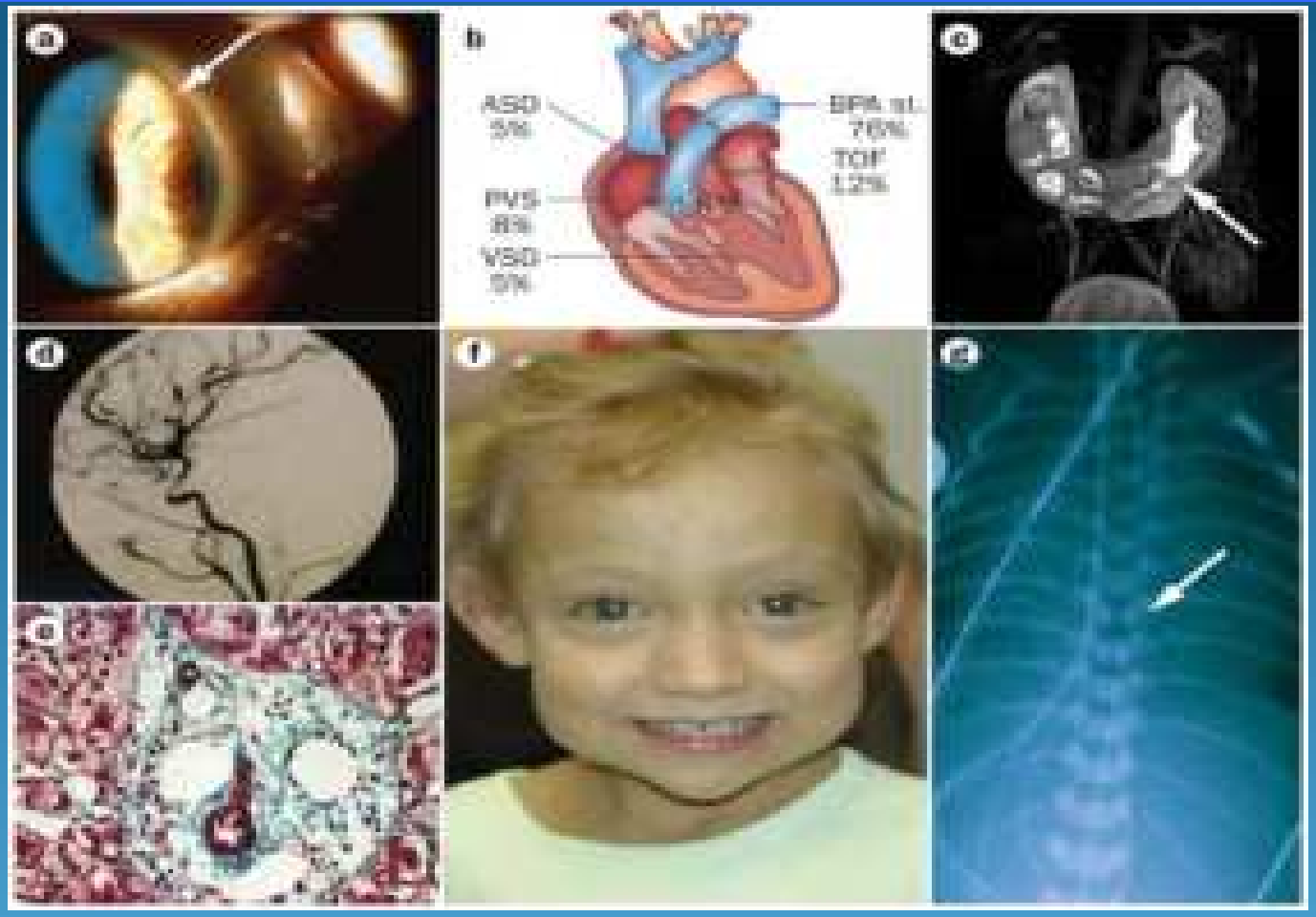
Features of Alagille Syndrome:



A |Slit-lamp eye exam with posterior embryotoxon (arrow). B | Classical cardiac abnormalities with frequency. C | MRI of ren arcuatus. D | Cerebral angiogram with moyamoya disease. E | Trichrome stain on liver demonstrating paucity of bile ducts. F | Characteristic facies: broad forehead, pointed chin, deep-set eyes. G | Butterfly vertebral bodies (arrow).

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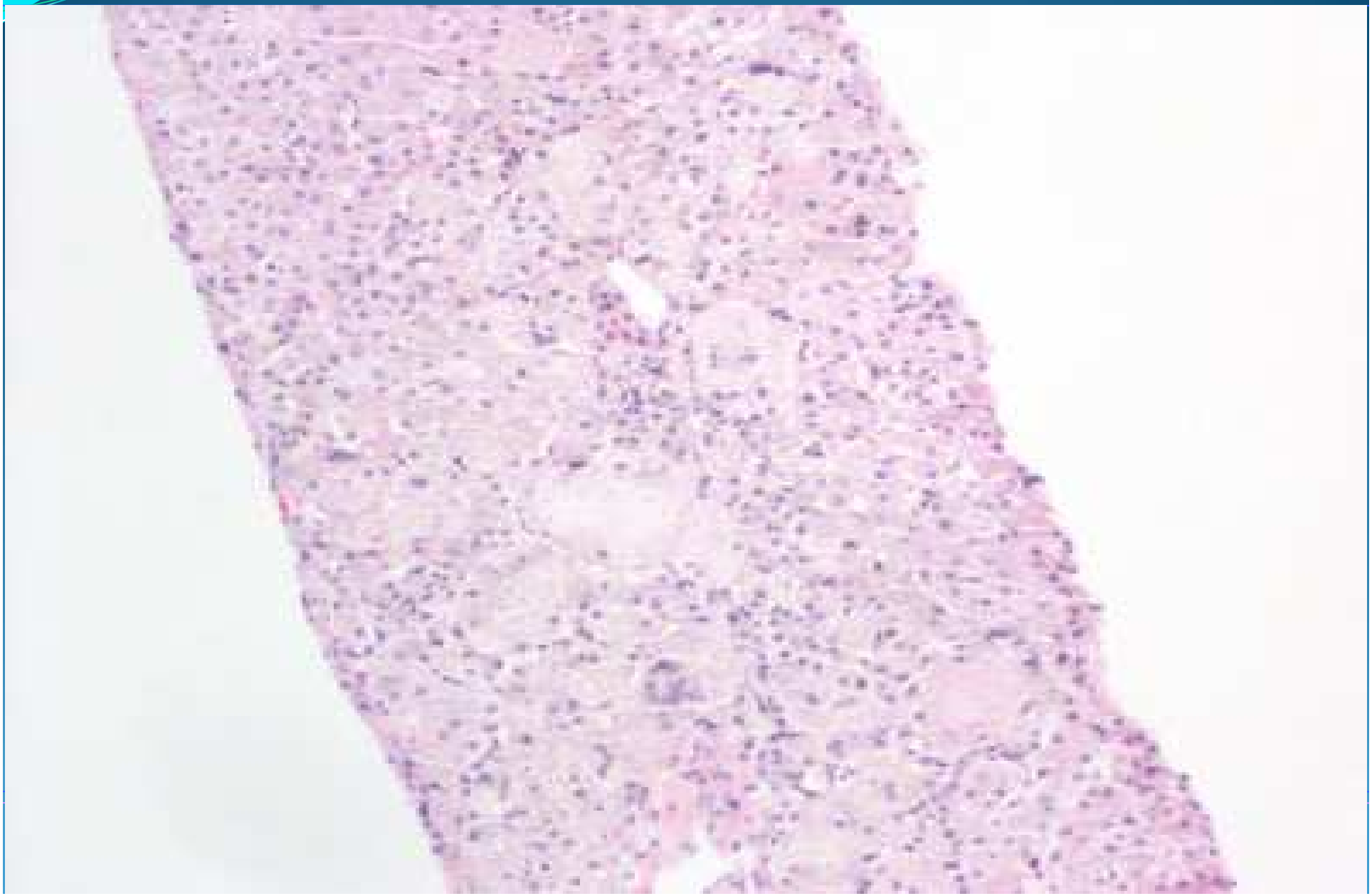
Alagille syndrome (AS): Cholestasis and giant cell transformation (H&E x 10).



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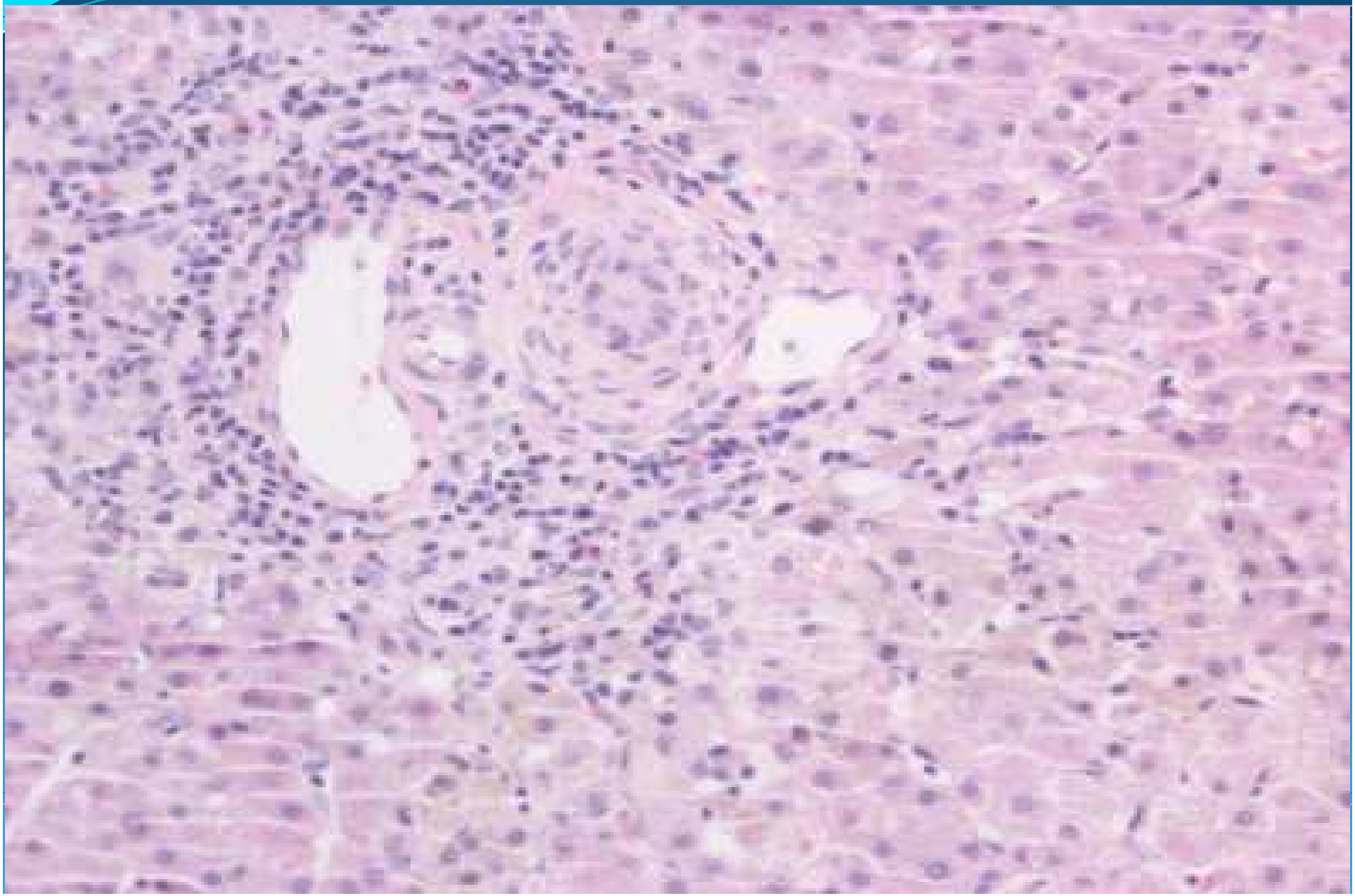
AS: Portal tract with no bile ducts (H&E x 20).



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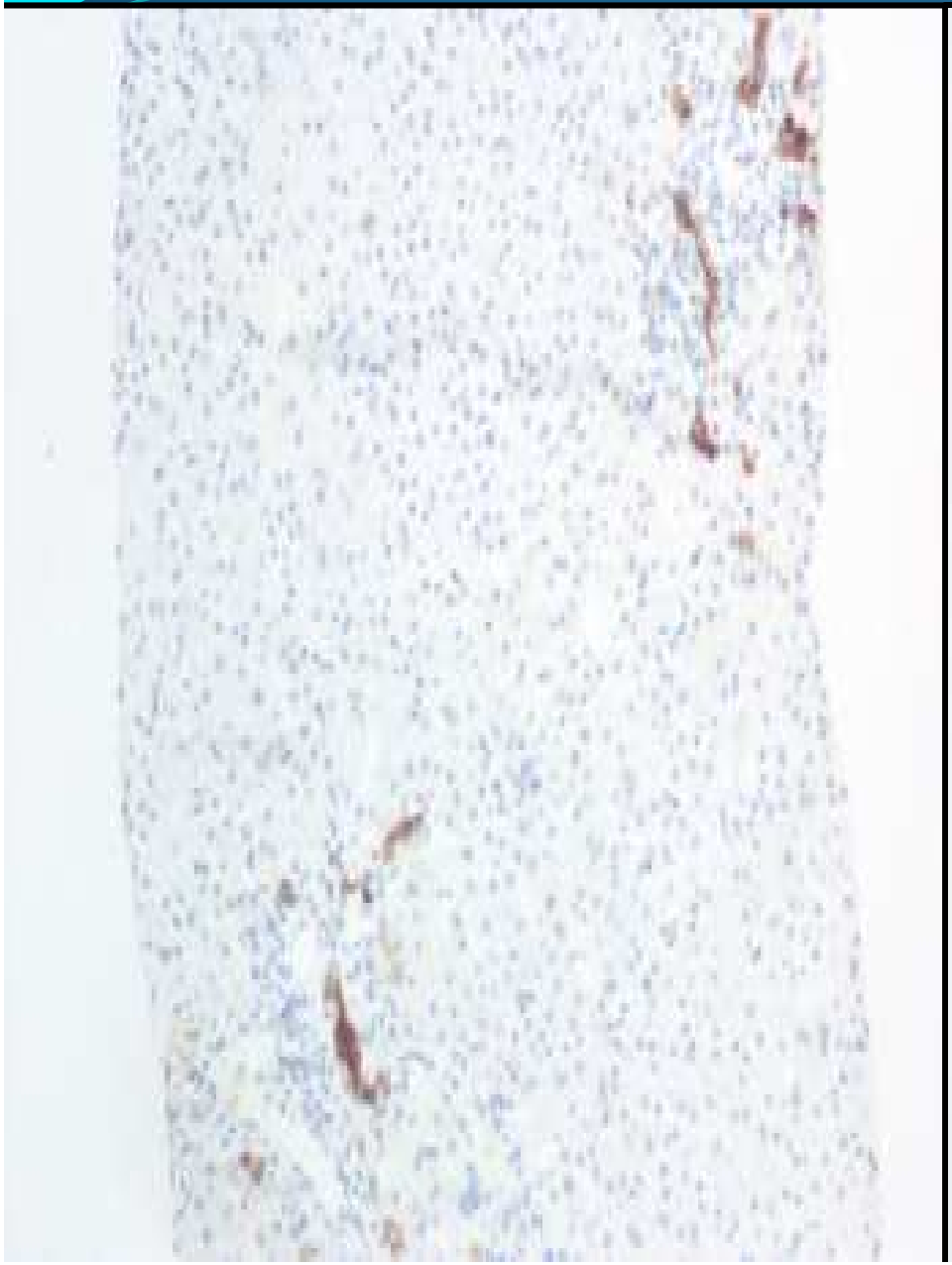
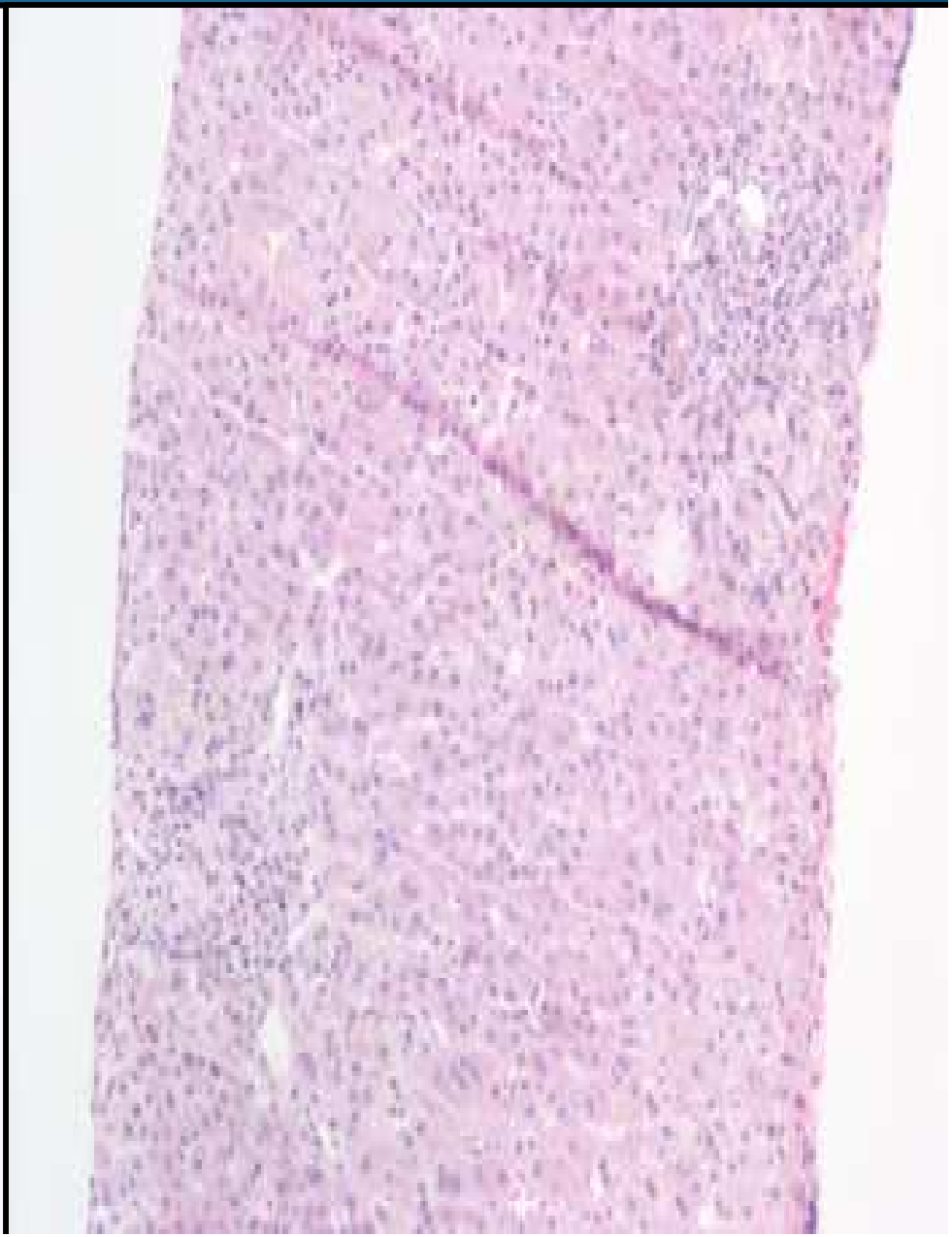
AS: Portal tracts with CK7 and H&E demonstrating proliferating ductules but no bile ducts (each x 10).





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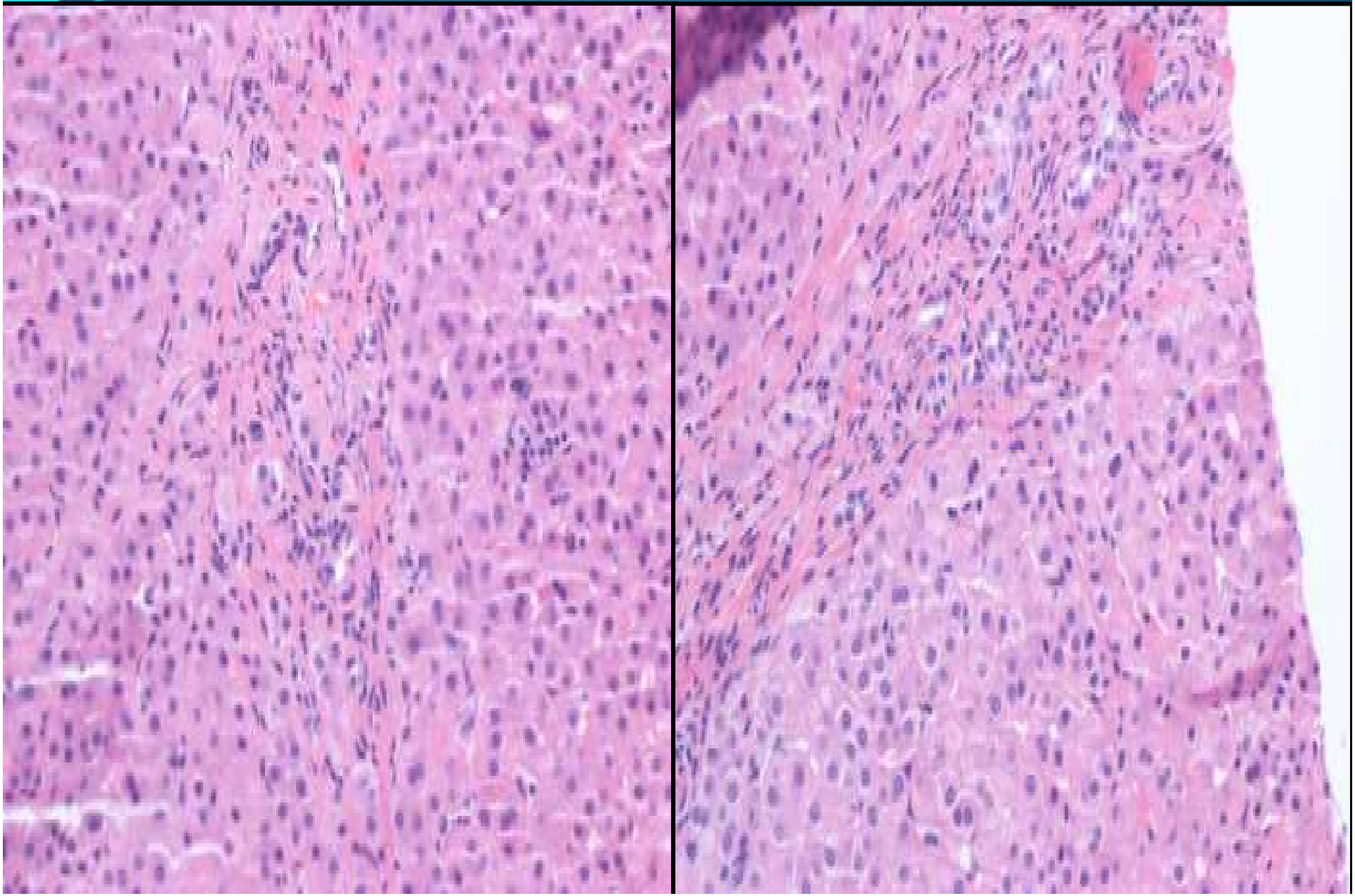
AS: No bile ducts in portal tracts (H&E x 20).



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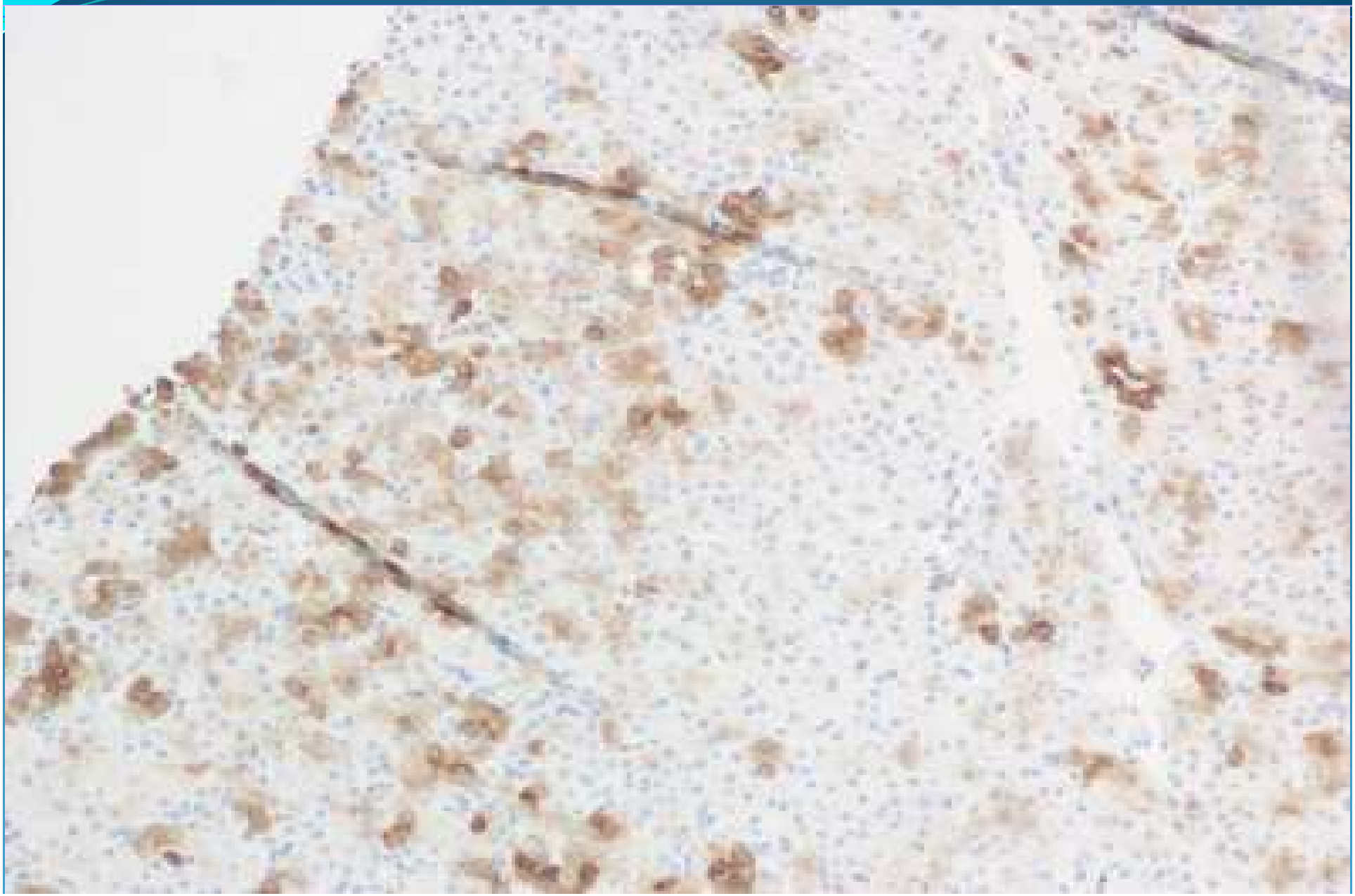
AS: CK7 in hepatocytes and one possible bile duct in portal tract (x 20).



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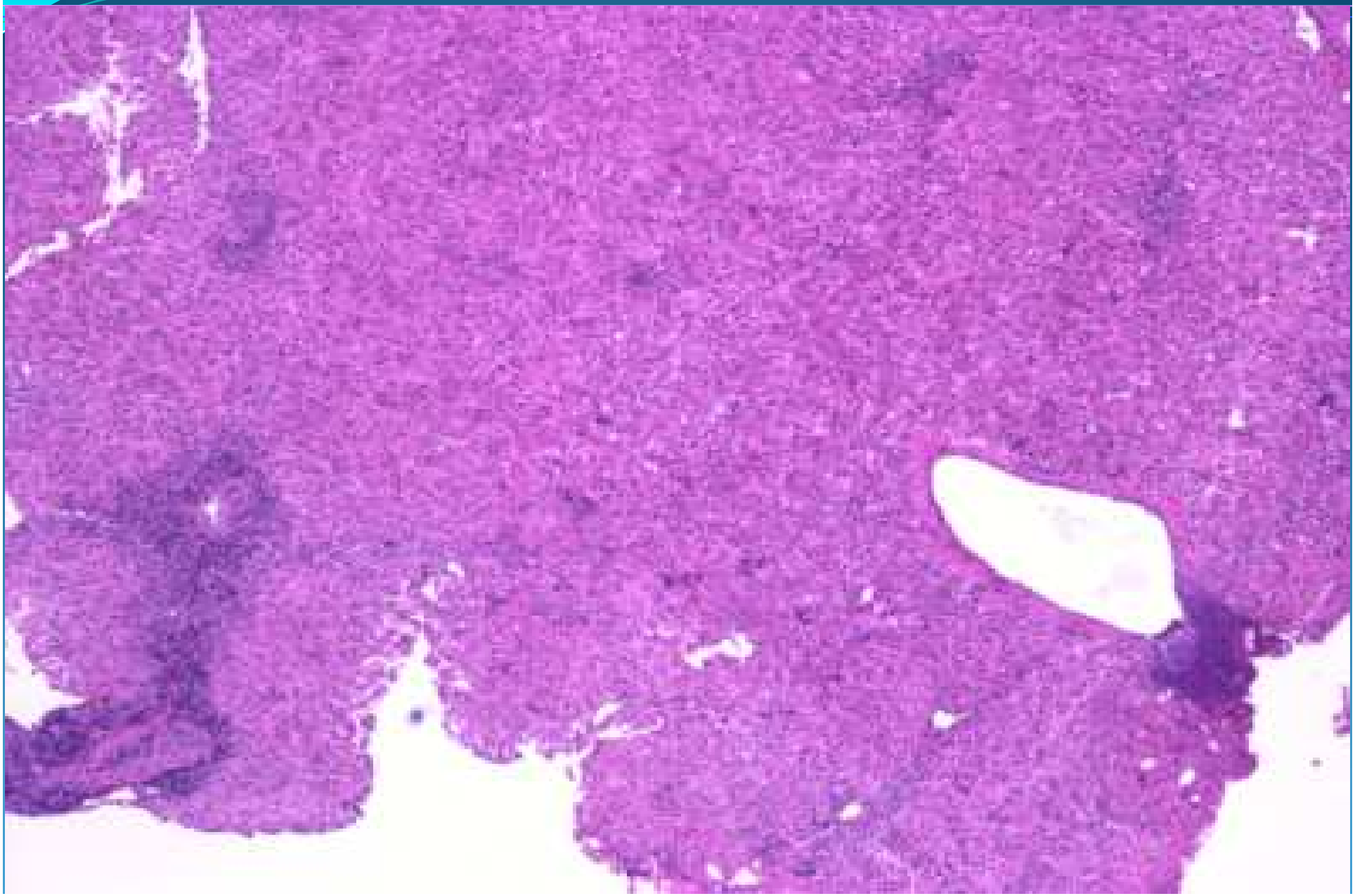
Non-syndromic paucity of bile ducts: intense periportal inflammation (H&E x 4)



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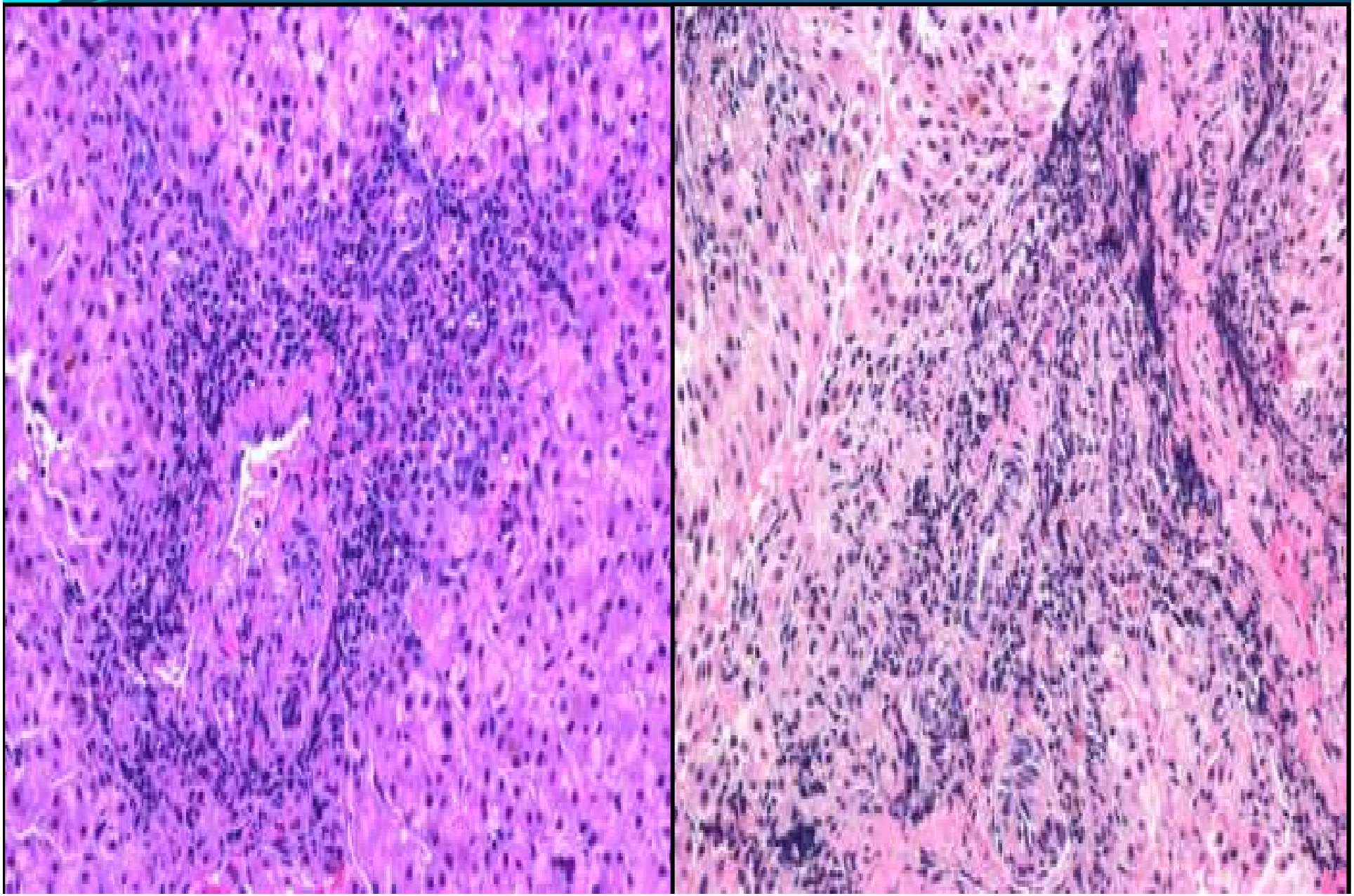
Non-syndromic paucity of bile ducts (H&E x 20).



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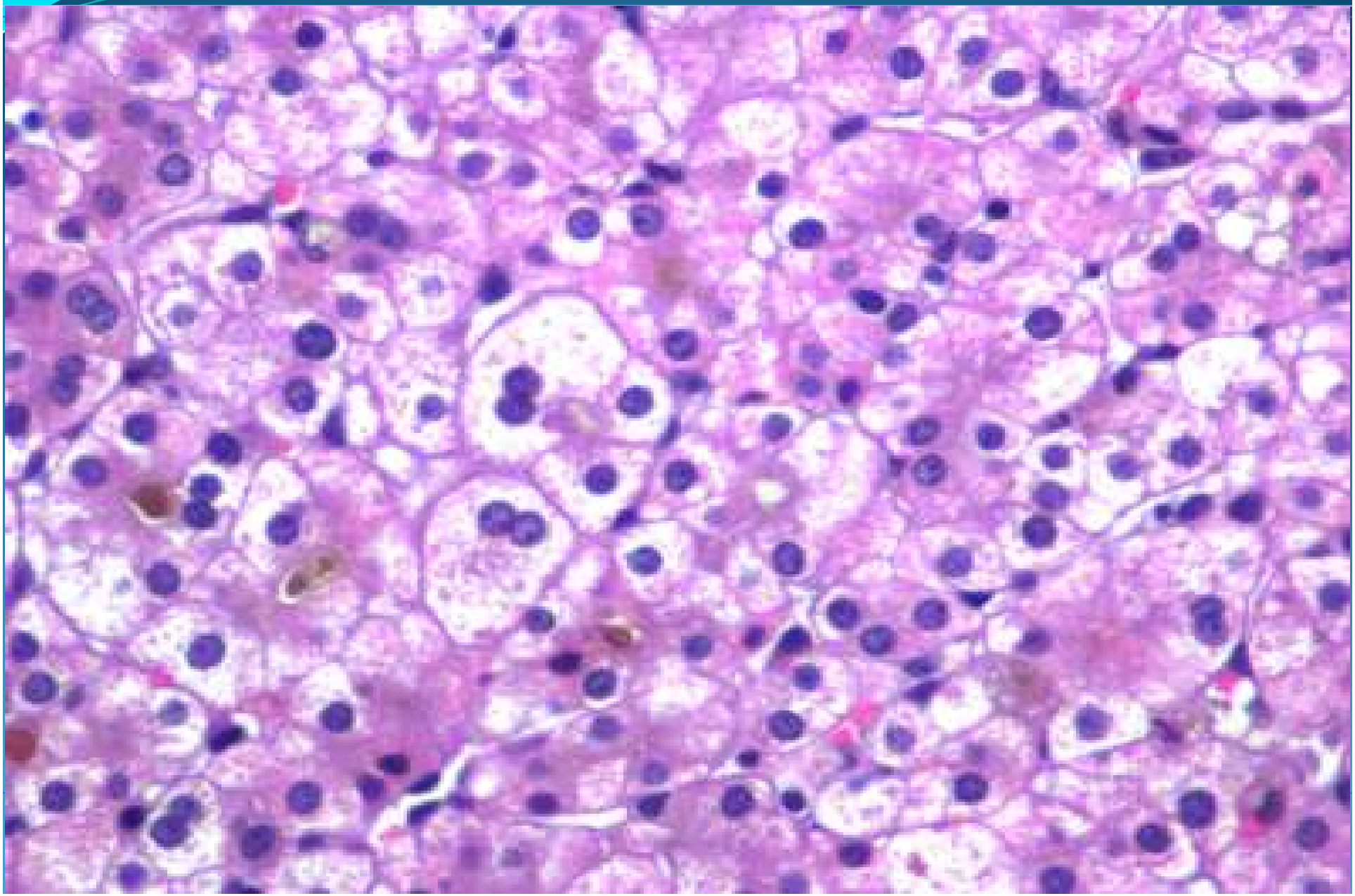
Non-syndromic paucity of bile ducts: Cytoplasmic and canalicular cholestasis with plugging (H&E x 40).



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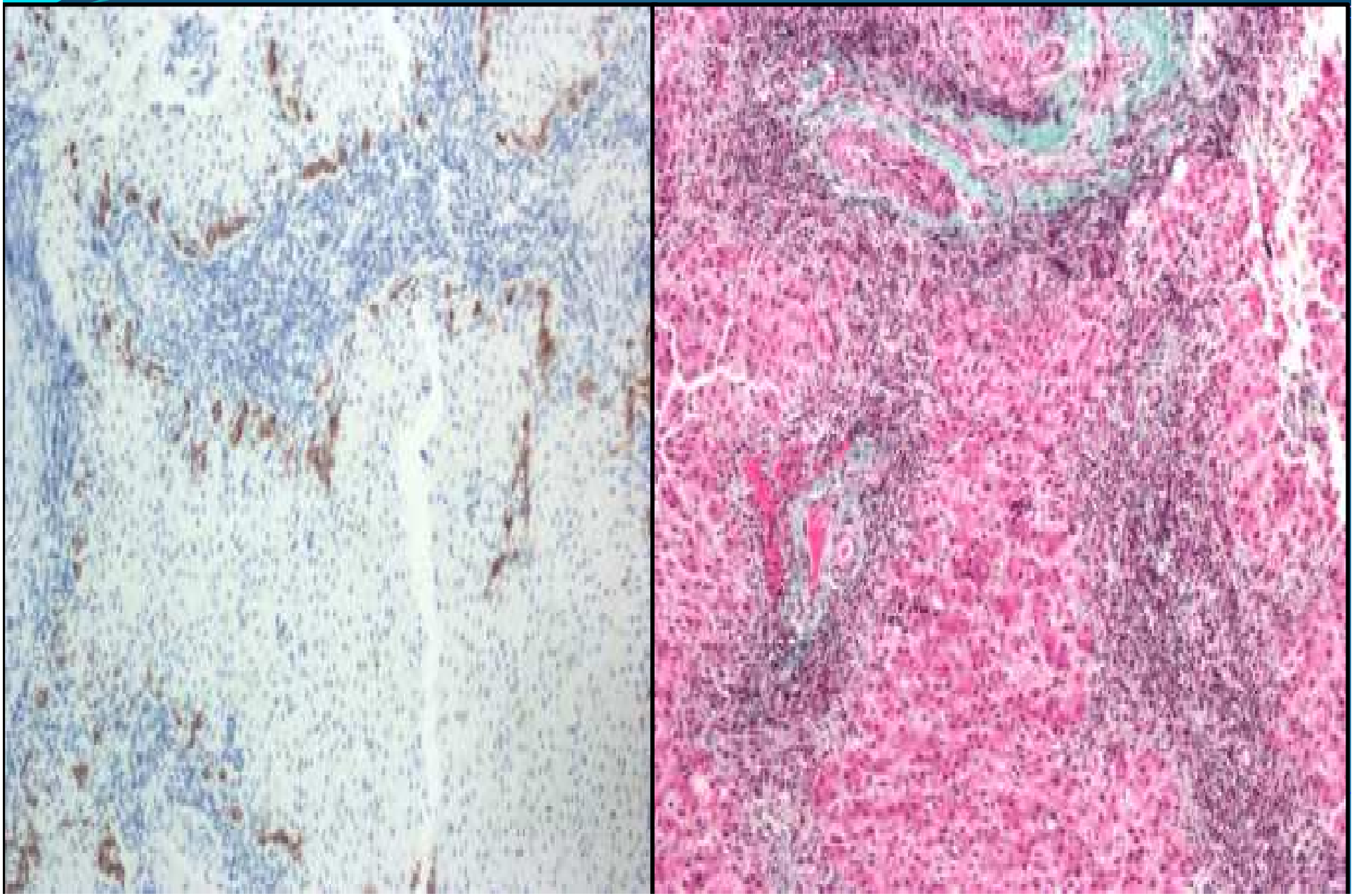
Non-syndromic paucity of bile ducts: Ductular proliferation highlighted on CK7; portal fibrosis on Masson trichrome (each x 10).



D. Extrahepatic Biliary Atresia:

Gene	IHBD	EHBD	Gallbladder
Jagged/Notch pathway	Abnormal	No findings	No findings
Hes1	No findings	Hypoplasia	Agenesis
HNF6	Ductal plate malformation IH biliary cysts	Abnormal	Agenesis
HNF1ß	Rarefaction of small IHBD Dysplasia of large IHBD	Undefined	Abnormal epithelium Dilated cystic duct
Foxf1	Normal	Undefined	Small or absent Without epithelial cells
Foxm1b	Agenesis	Undefined	Undefined

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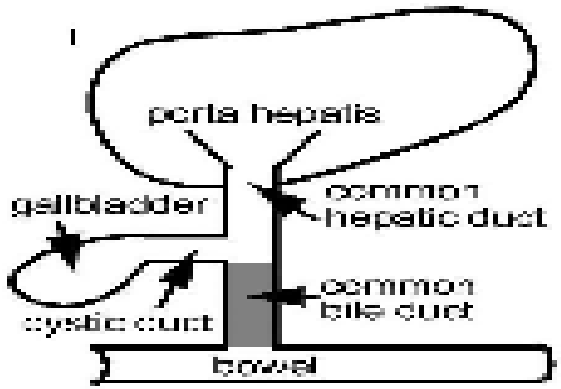
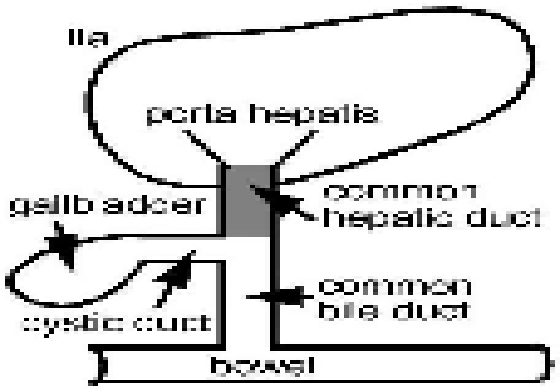
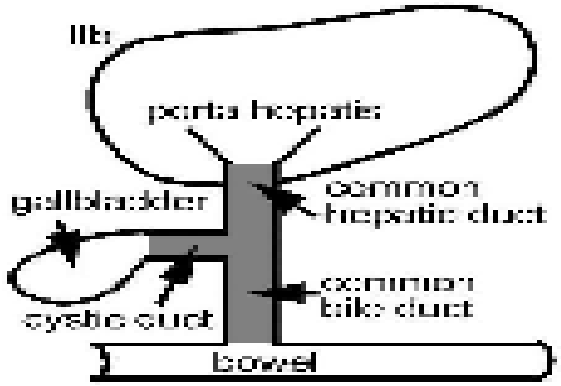
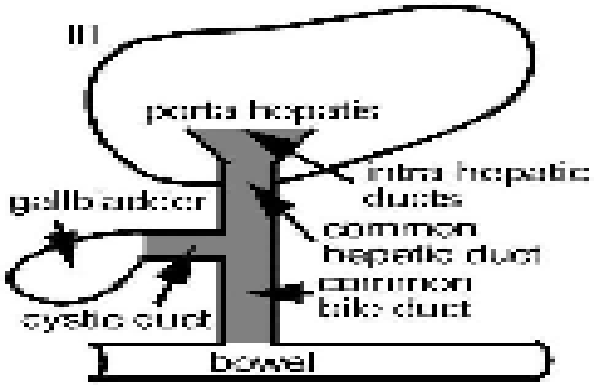
Extrahepatic biliary atresia types









Zukotynski, K, Babyn, P, Coombs, B, et al. Biliary atresia imaging. Medscape. http://emedicine.medscape.com/article/406335-overview#a4

Type I: Obliteration of common bile duct with patent proximal bile ducts.
Type IIa: Atresia of hepatic duct with cystic bile ducts at porta hepatis.
Type IIb: Atresia of cystic duct, common bile duct, and hepatic ducts.
Type III: Atresia of extrahepatic biliary tree and intrahepatic ducts of porta hepatis.

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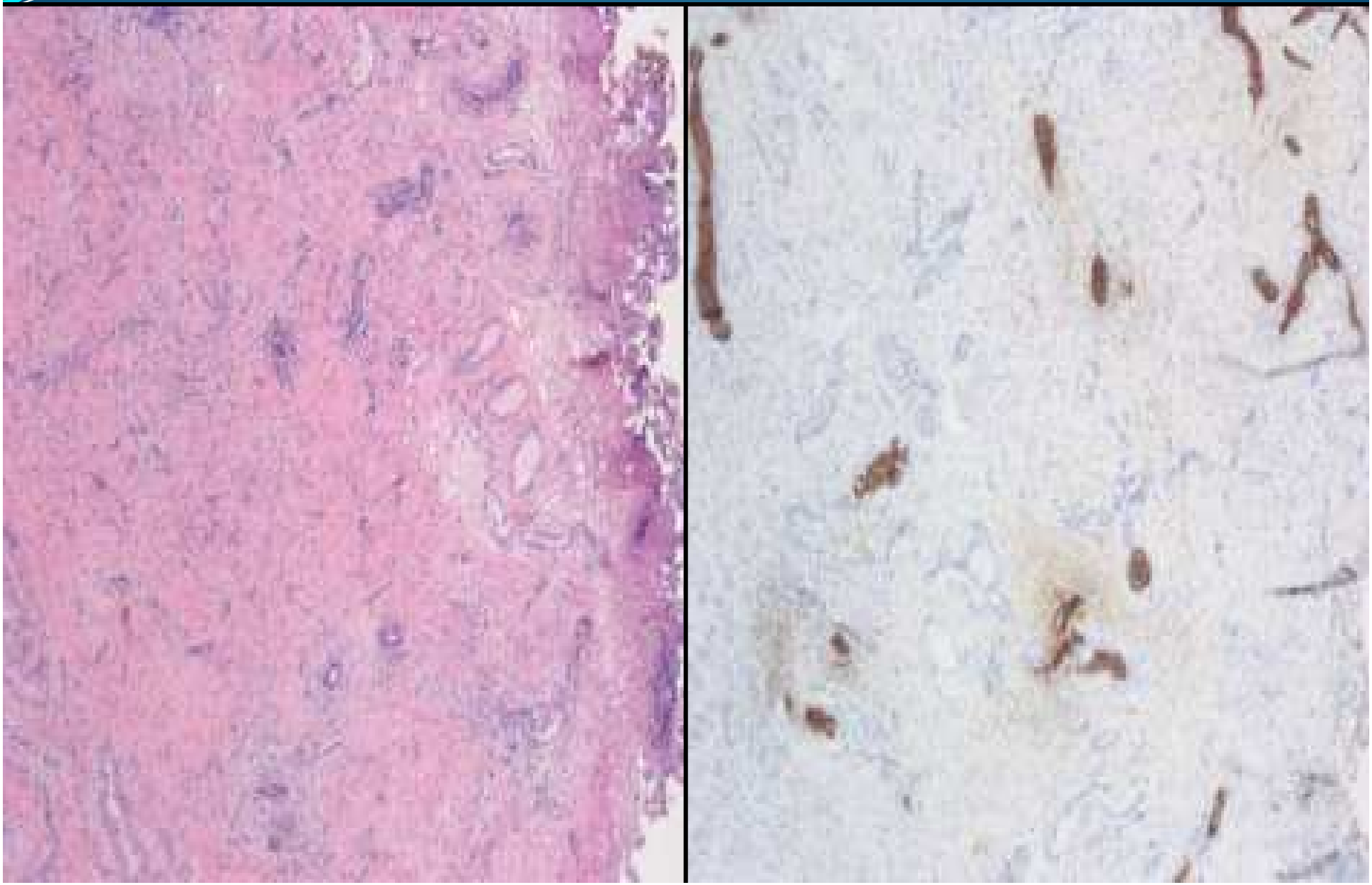
Common bile duct biopsy in biliary atresia. Left: Markedly fibrotic stroma with small ductular structures displaying pinpoint lumens. Right: CK7 stain (each x 4).



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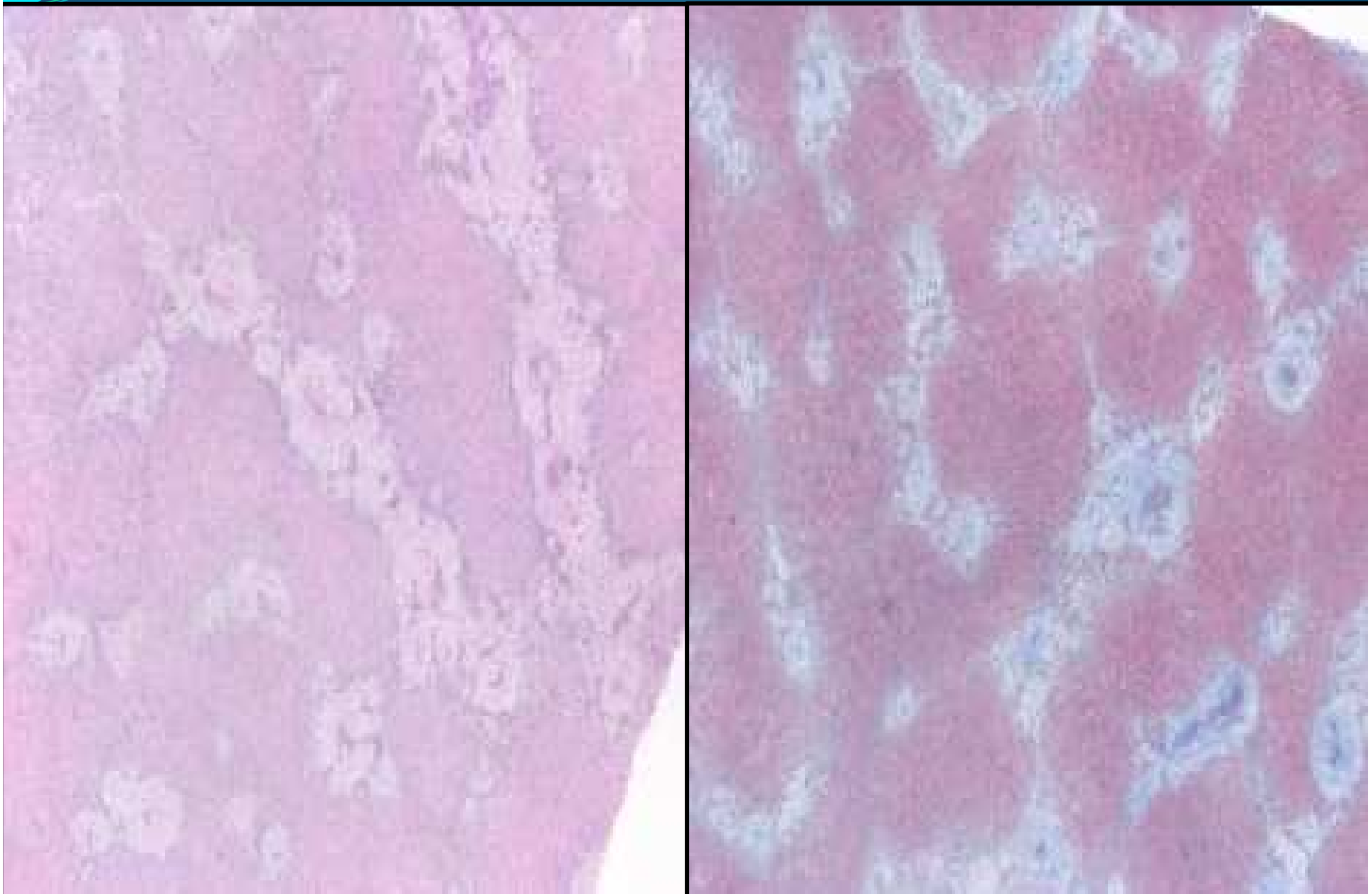
Biliary atresia: Liver wedge biopsy with bridging fibrosis.
Left, H&E x 2; Right, trichrome x 2.



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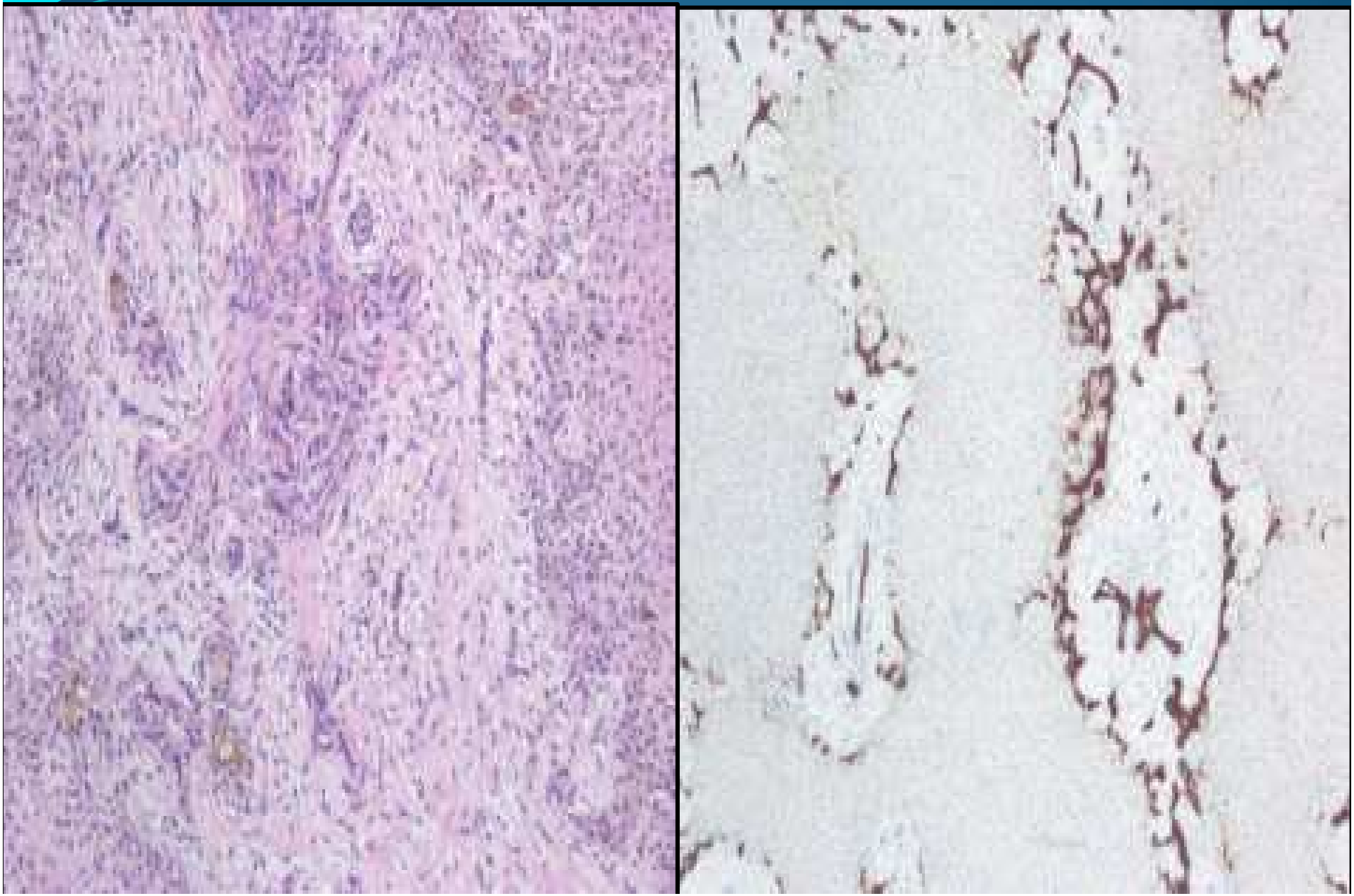
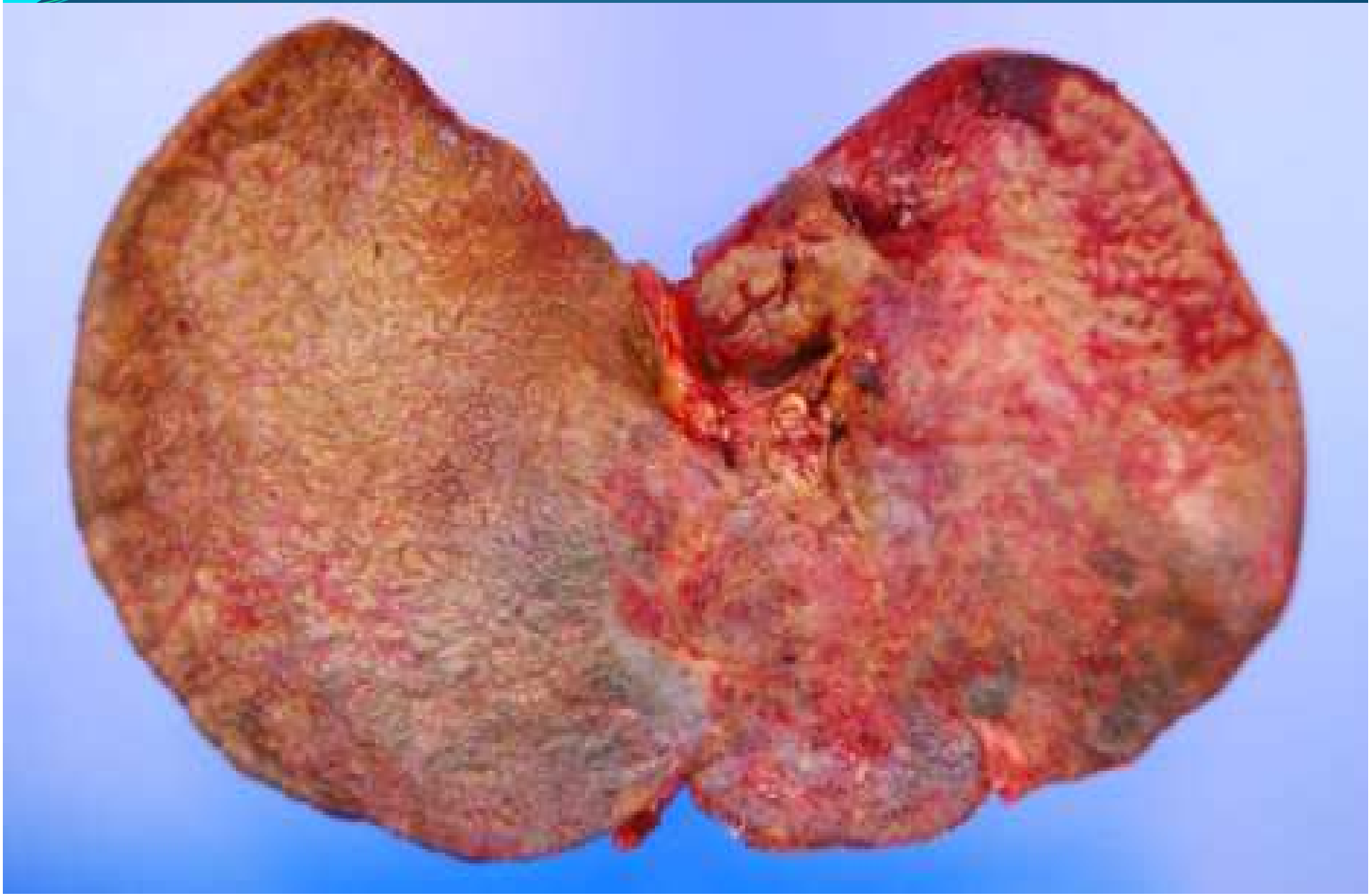
Biliary atresia: Ductal bile plugging; ductular proliferation on CK7 (H&E x 10, CK7 x 4).



Liver resection after failed Kasai procedure.



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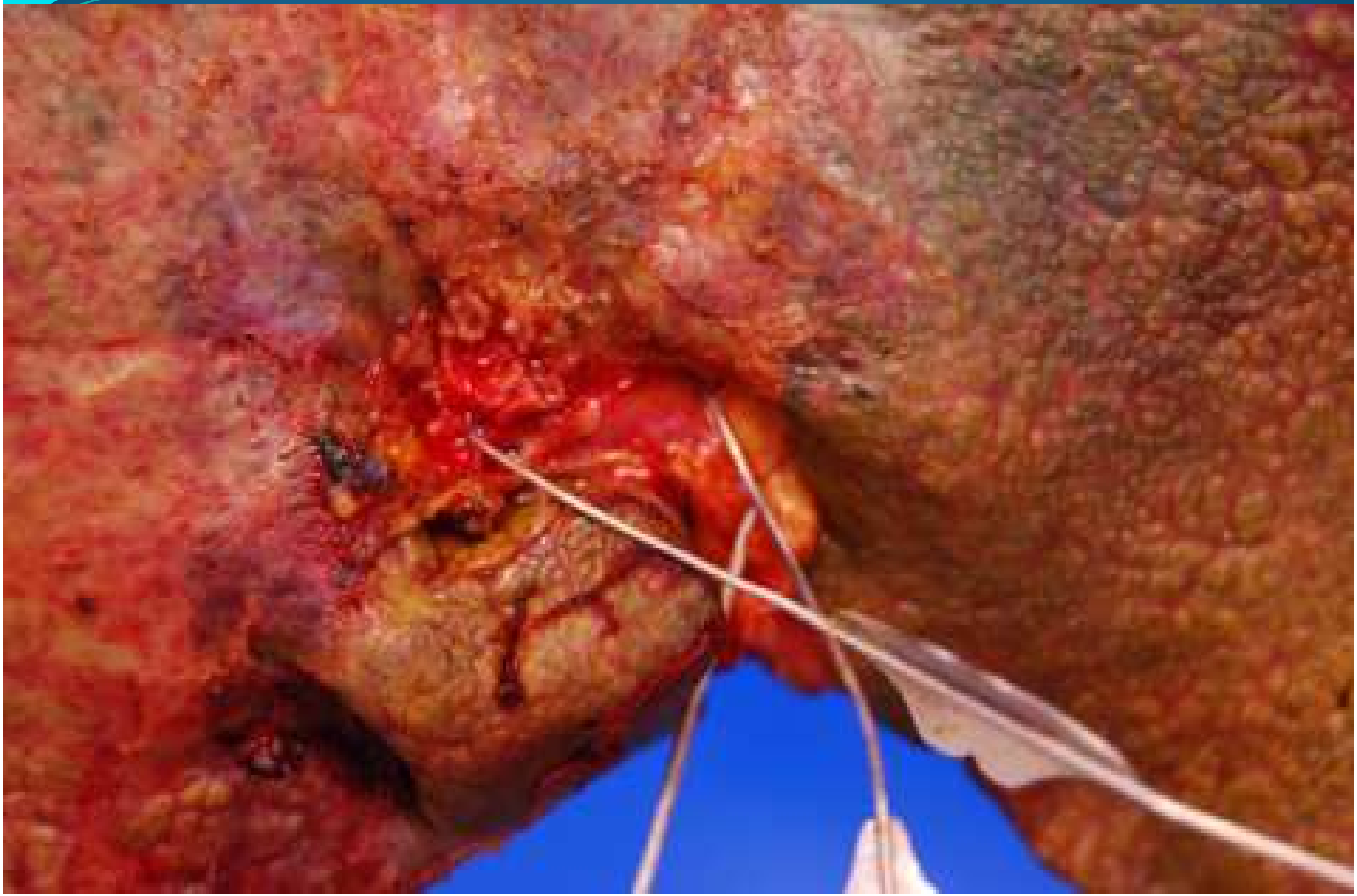
Probes demonstrate no luminal connection of intrahepatic biliary tree with small intestine anastomosis.



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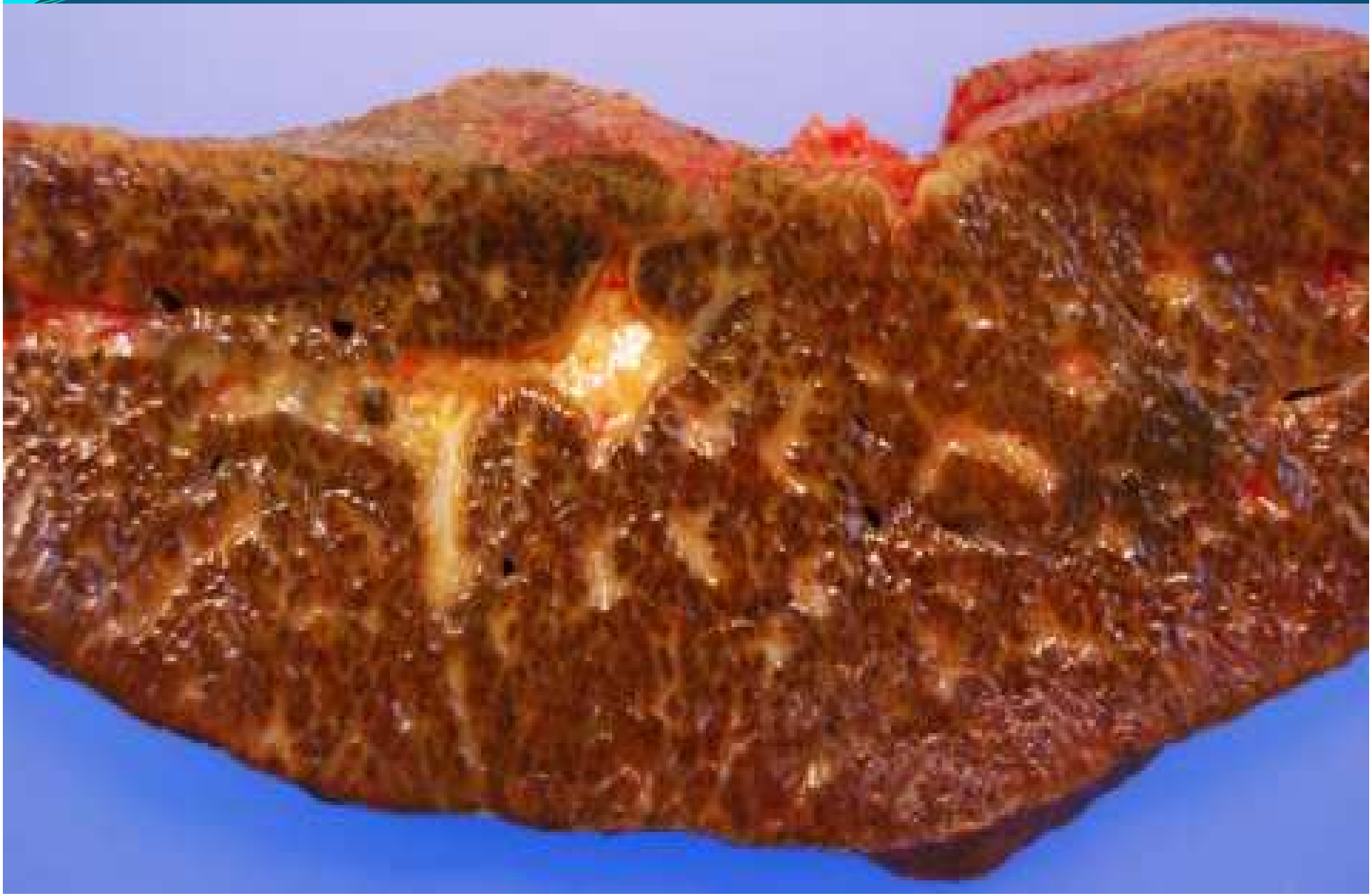
Macronodular cirrhosis with diffuse cholestasis and fibrosis.



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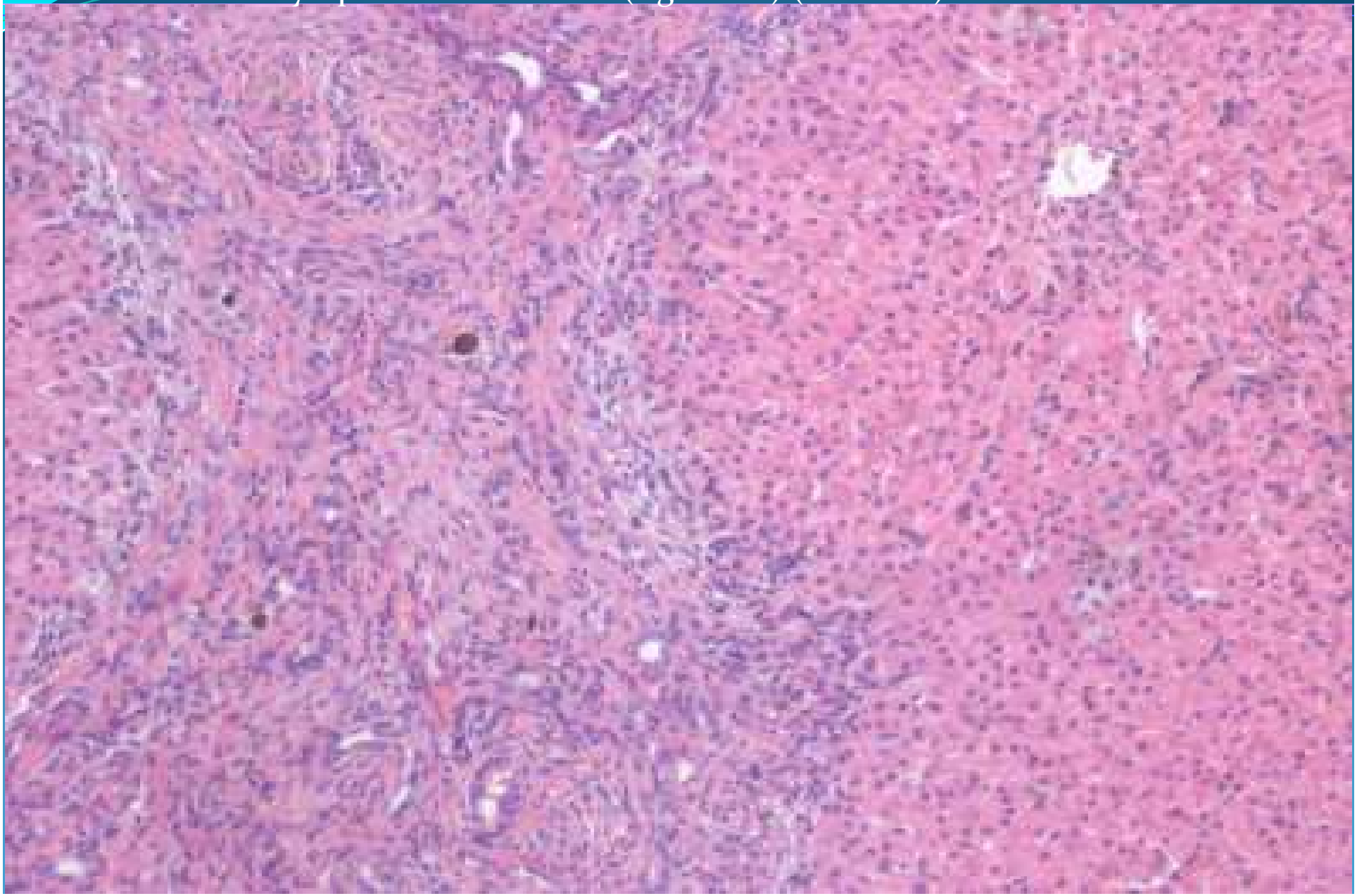
EHBA: Portal fibrosis and proliferating ductules with ductal plugging and mild interface inflammation; hepatocytes have cytoplasmic cholestasis (right side) (H&E x 10).



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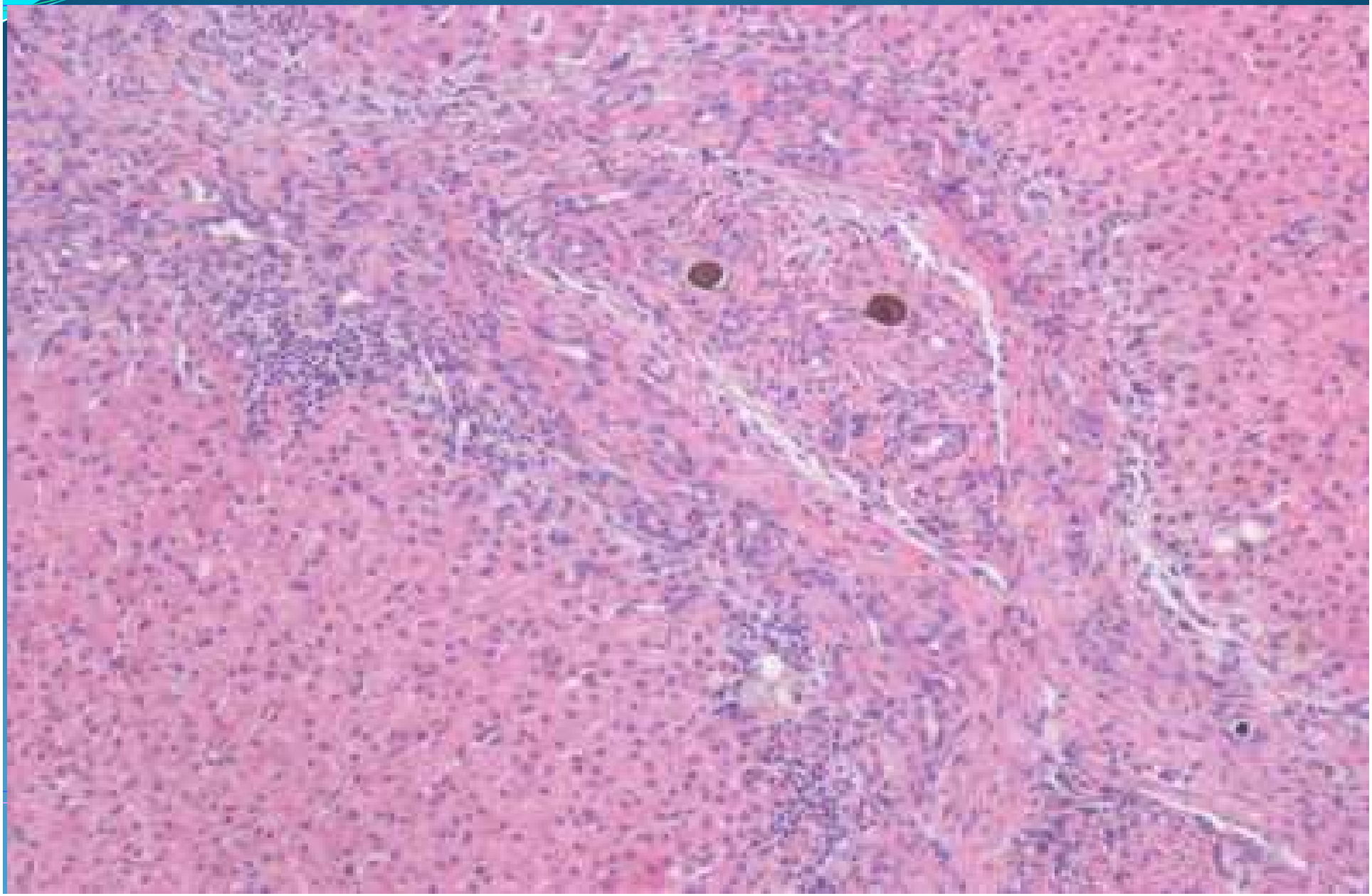
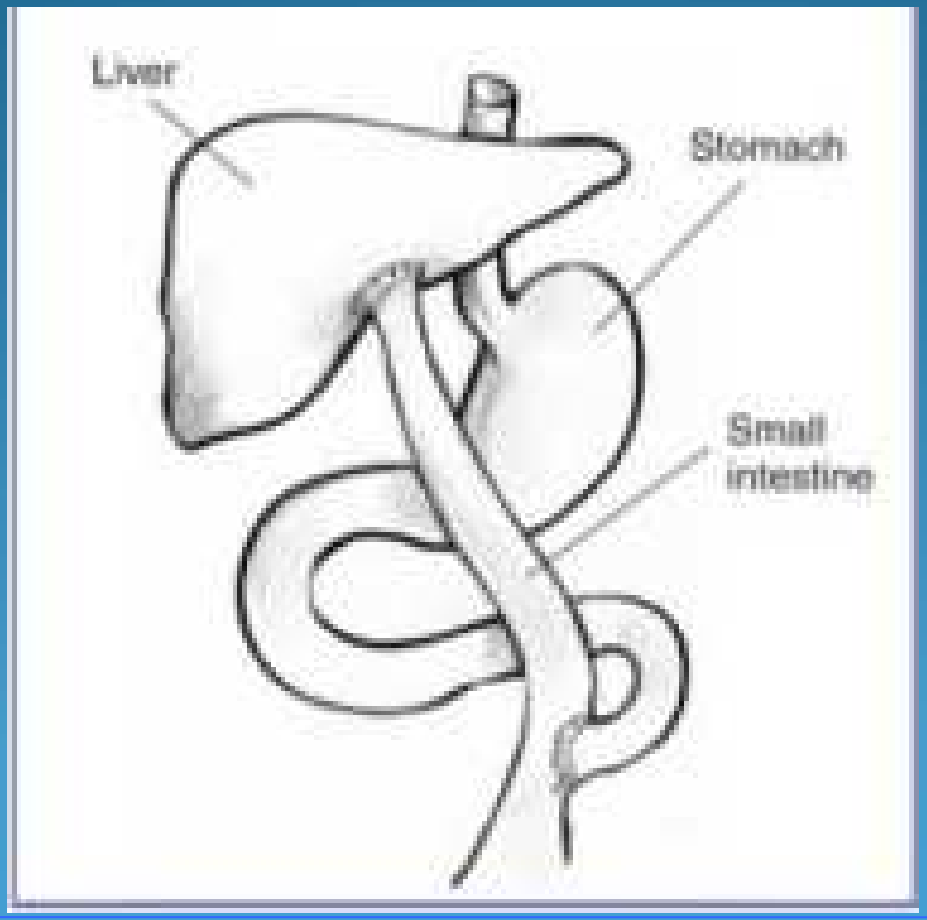
Biliary atresia: Portal fibrosis and proliferating ductules with ductal plugging and mild interface inflammation; hepatocytes display cytoplasmic cholestasis (H&E x 10).



Treatment for Extrahepatic Biliary Atresia:
--Kasai hepatoportoenterostomy:



Complications after Kasai procedure:

1. Ascending cholangitis (most common)
2. Portal hypertension
3. Intrahepatic biliary cavities
4. Poor growth and malnutrition

****Biliary atresia is most common reason for pediatric liver transplant in the US**

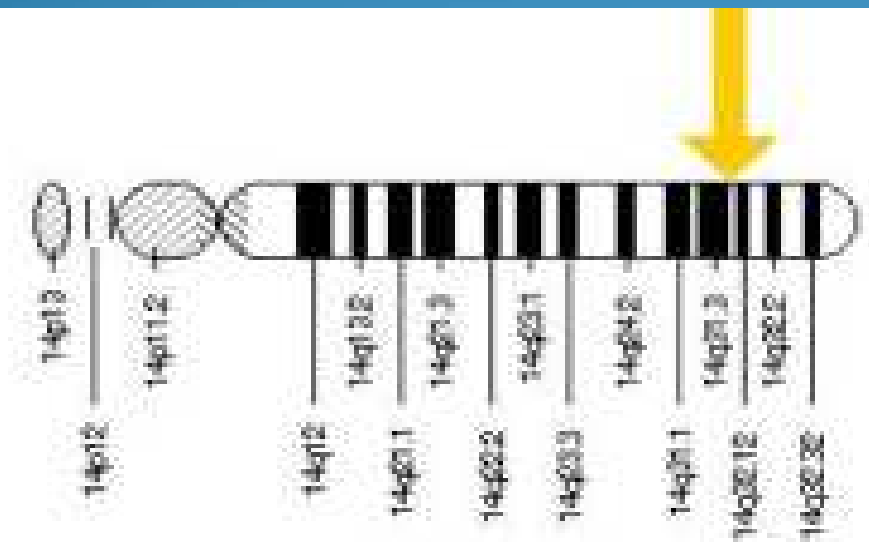
E. α-1 Anti-trypsin Deficiency

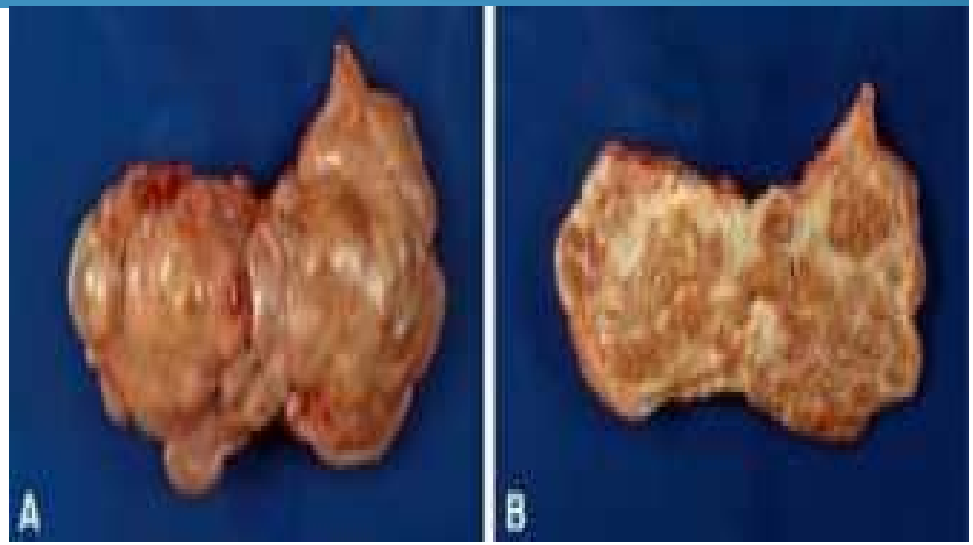
--Common cause of neonatal cholestasis

--Autosomal recessive disease causing low serum levels of alpha-1-antitrypsin (AAT) and leading to emphysema (80%, usually 20-39 years) and liver disease

--α1AT: 394 amino acid plasma glycoprotein synthesized predominantly by hepatocytes and encoded by gene at 14q31.3

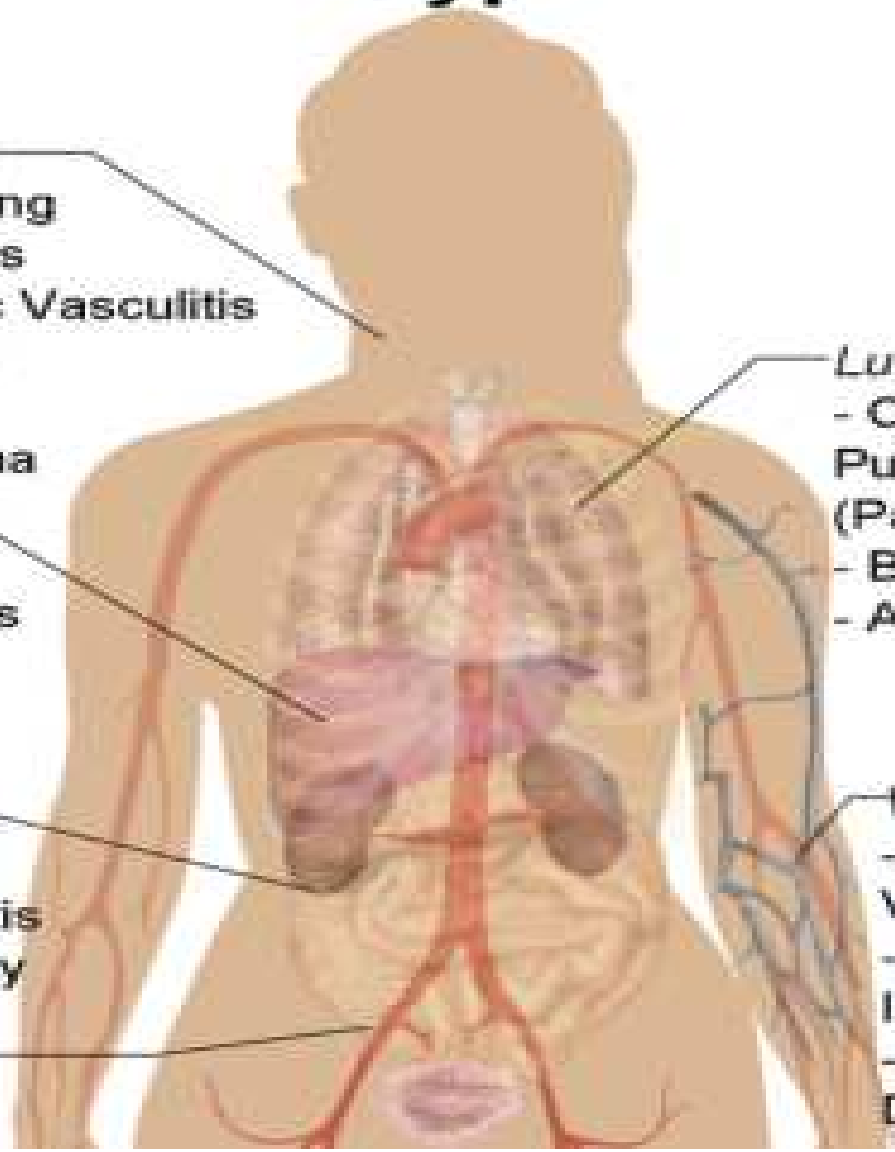
--α1AT: Protease inhibitor (Pi) that inhibits neutrophil elastase released at sites of inflammation; also inhibits trypsin





Conditions Associated with

Alpha-1 Antitrypsin Deficiency



Skin
- Necrotising Panniculitis
- Systemic Vasculitis
- Psorasis
- Urticaria
-angioedma

Liver
- Cirrhosis
- Neonatal Hepatitis
- Hepatocellular Carcinoma

Kidneys
- Proliferative Glomerulonephritis
- IgA Nephropathy

Intestines
- Inflammatory Bowel Disease

Lungs
- Chronic Obstructive Pulmonary Disease (Panacinar Emphysema)
- Bronchiectasis
- Asthma

Vascular
- ANCA-positive Vasculitis
- Abdominal and Intracranial aneurysms
- Arterial fibromuscular Dysplasia

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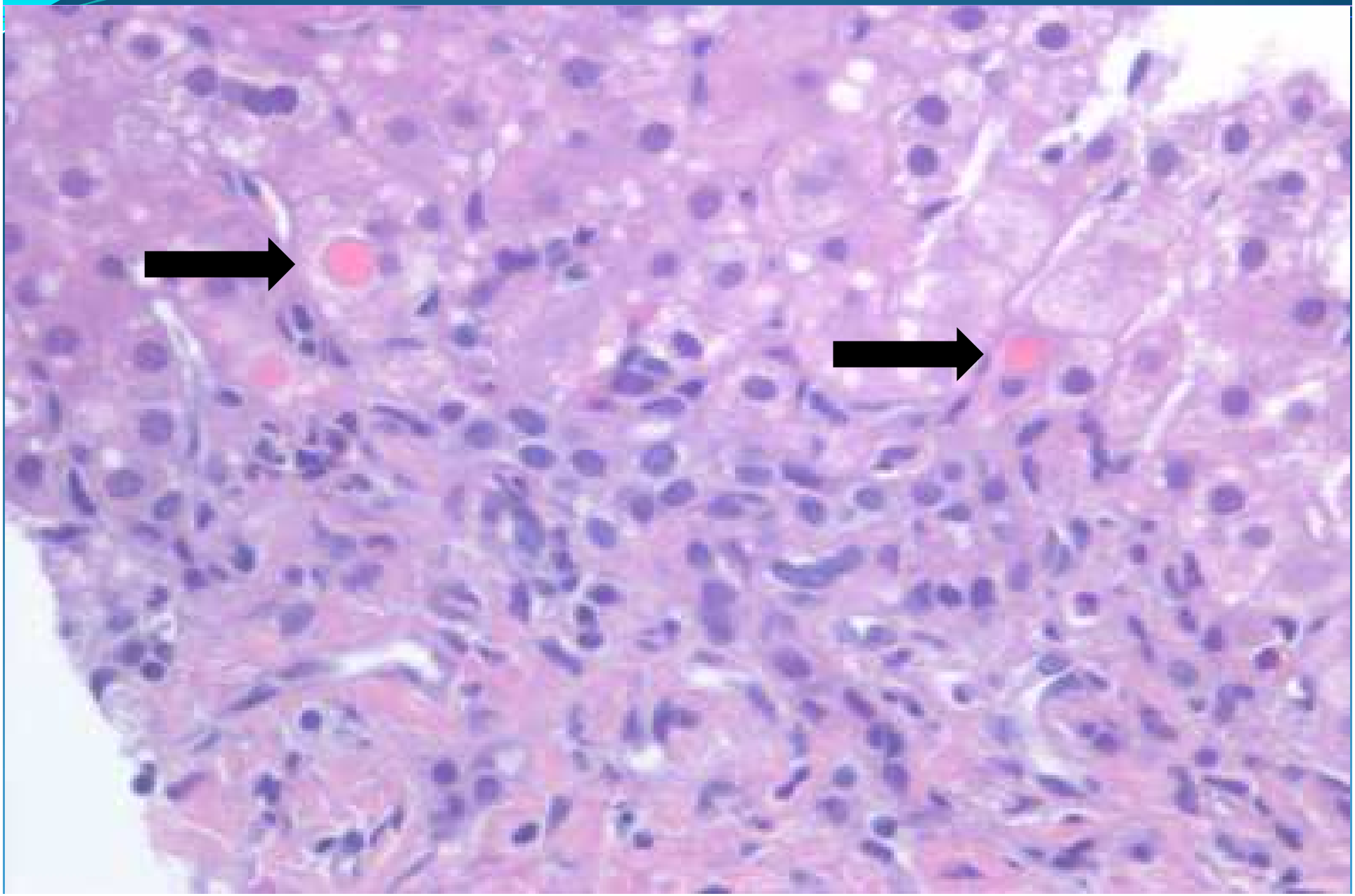
α1AT: Liver displays bright intracytoplasmic eosinophilic globules in hepatocytes (arrows) near the limiting plate (H&E x 20).



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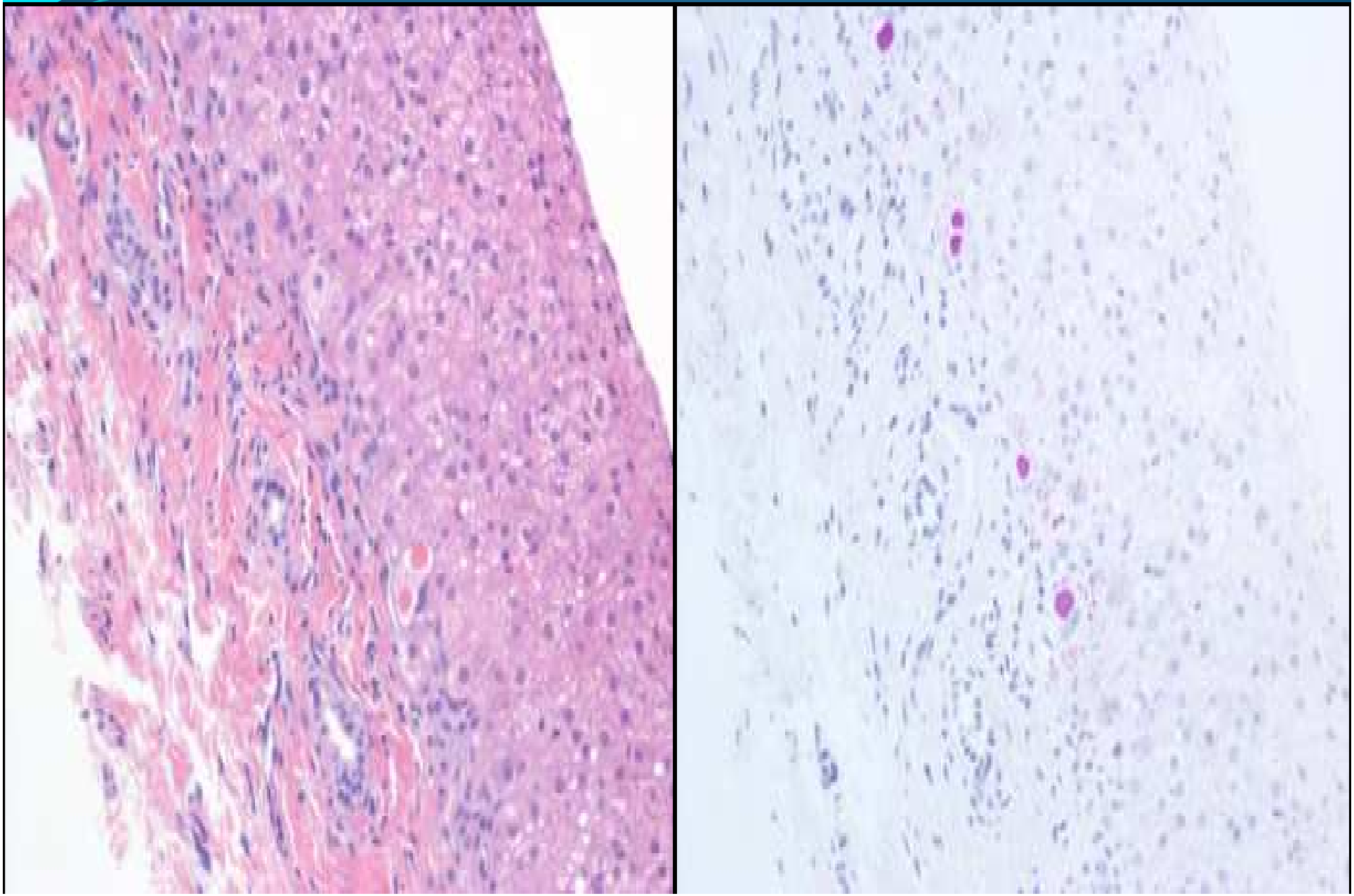
α1AT: H&E (left) and PAS-Diastase (right) demonstrating accumulations of α-1 antitrypsin material (each x 20).



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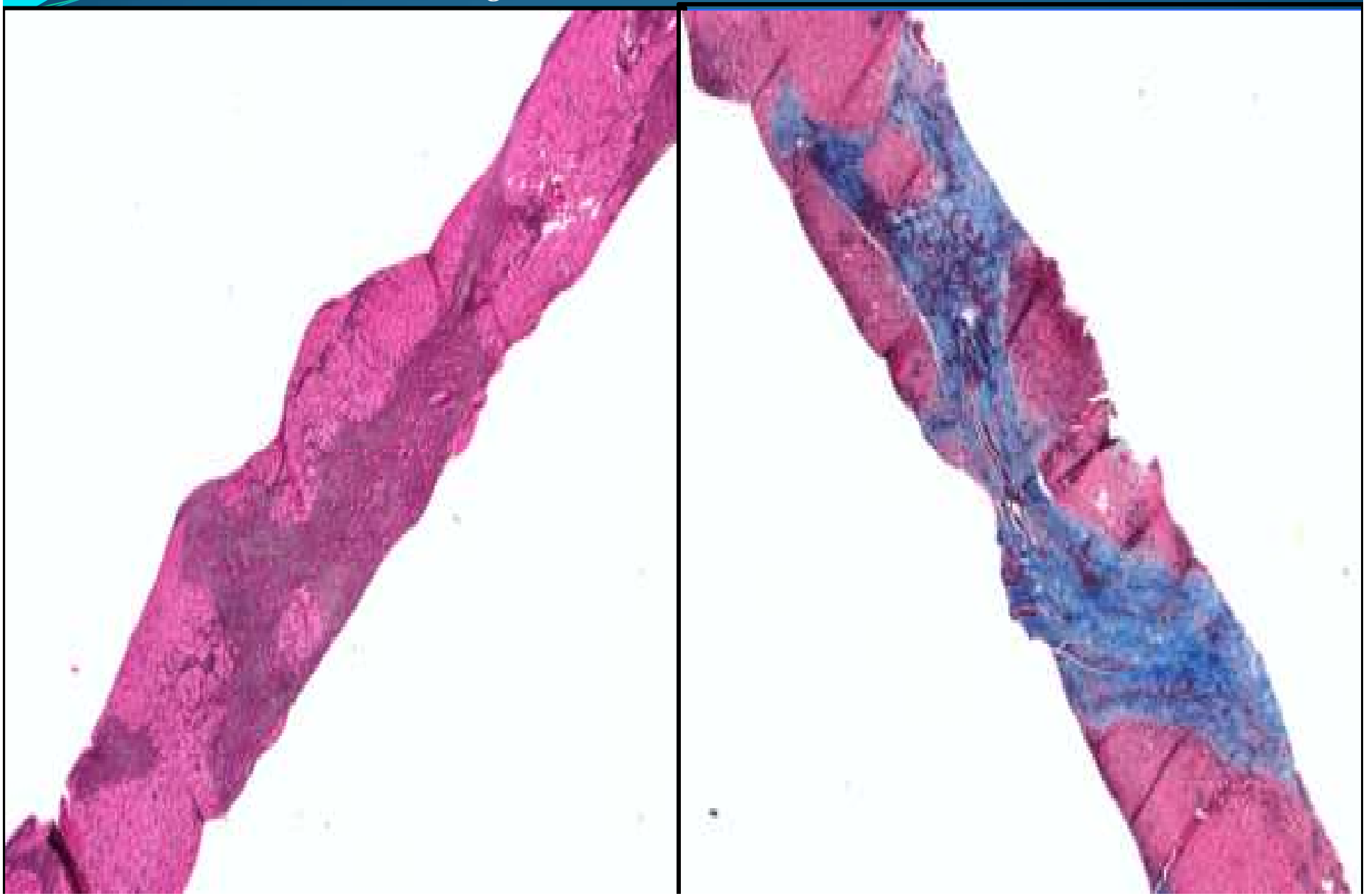
α1AT: Liver with α-1 antitrypsin deficiency showing marked fibrosis on reticulin (left) and Masson trichrome (right) (each x 2).



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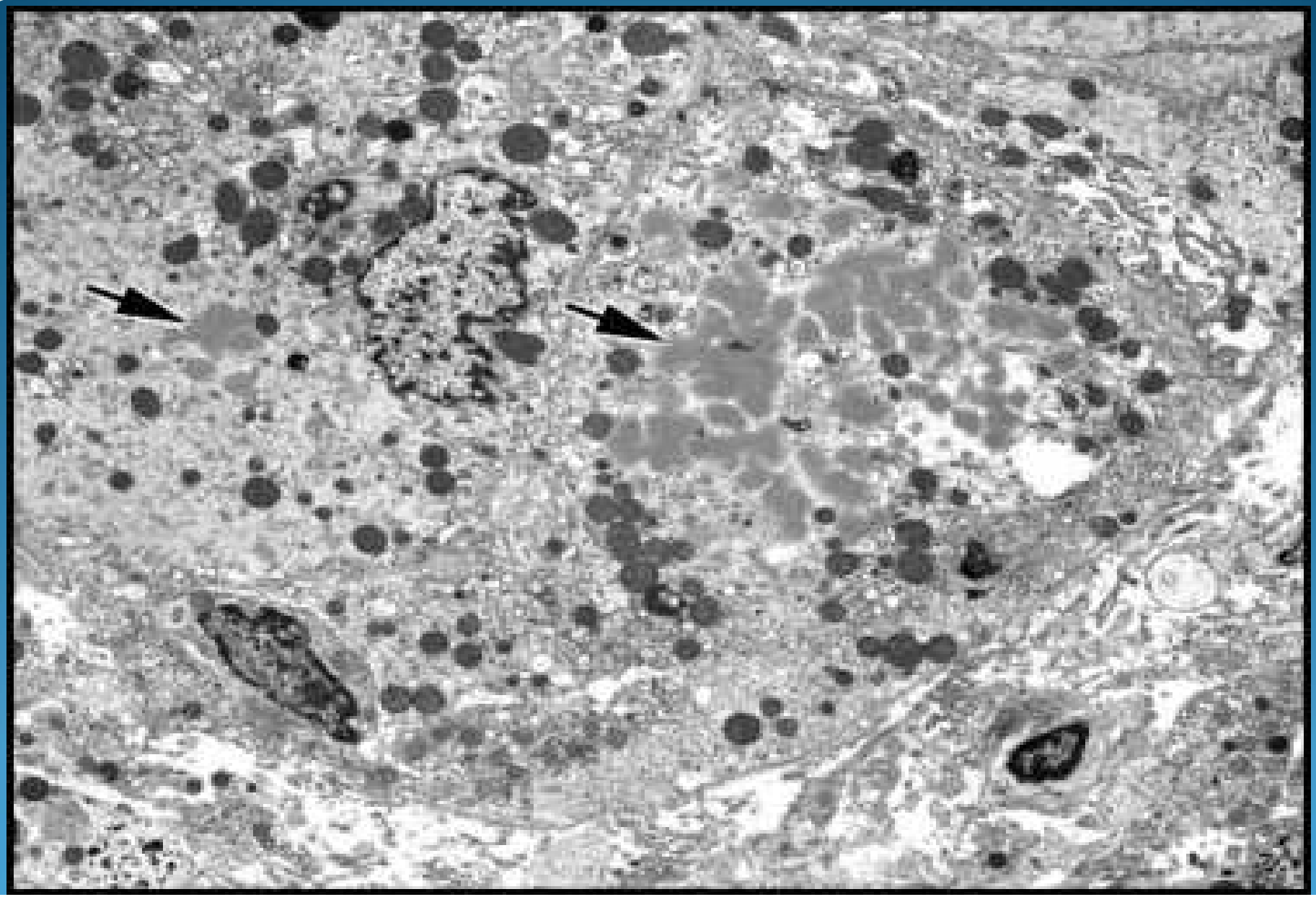
α1AT: Electron micrograph with accumulations of α-1 antitrypsin (arrows).



Diagnostic Tests for Alpha$_1$-Antitrypsin (AAT) Deficiency and Associated Disease Risks.

Table 1. Diagnostic Tests for Alpha$_1$-Antitrypsin (AAT) Deficiency and Associated Disease Risks.*

Inherited Genetic Variants†	Protein Phenotype‡	Serum Protein Level§	Molecular Genotype¶	Risk of COPD	Risk of Liver Disease
ZZ	Z	Very low	ZZ	Very high	High
ZNull	Z	Very low	Z/non-S, non-Z	Very high	Unknown
MZ	MZ	Intermediate	Z/non-S, non-Z	Possibly increased	Possibly increased
MNull	M	Intermediate	Non-S, non-Z/non-S, non-Z	Unknown	None
SZ	SZ	Low	SZ	Increased	Possibly increased
NullNull	None	None	Non-S, non-Z/non-S, non-Z	Very high	None

Silverman EK, Sandhaus RA. N Engl J Med 2009;360:2749-2757.

The NEW ENGLAND JOURNAL of MEDICINE

α1AT treatment:

--Augmentation therapy or infusion of purified α-1 anti-trypsin from pooled human plasma

--Liver transplantation

F. Ductal Plate Malformation & Polycystic Kidney Disease:

A. Small interlobular ducts

--Congenital hepatic fibrosis, ARPKD

--Biliary hamartomas

B. Medium interlobular ducts

--AD Polycystic Liver Disease

--Isolated form caused by 2 genes:

--*SEC63* and *PRKCSH*

--Associated with ADPKD caused by 2 genes:

--*PKD1* and *PKD2*

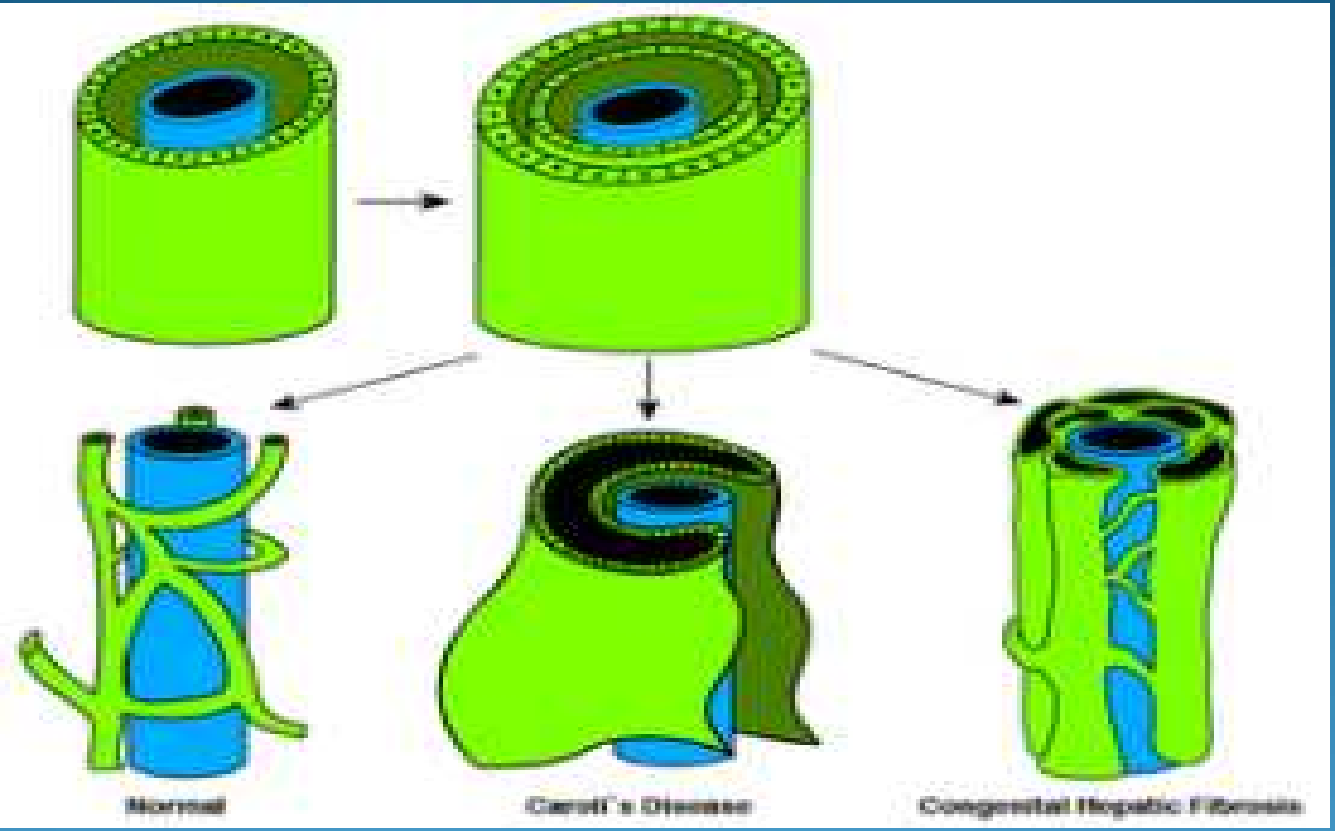
C. Large-sized intrahepatic ducts

--Caroli's disease

D. Large extrahepatic ducts

--Choledochal cysts

Normal bile duct development



References: Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine - Kyoto/JP

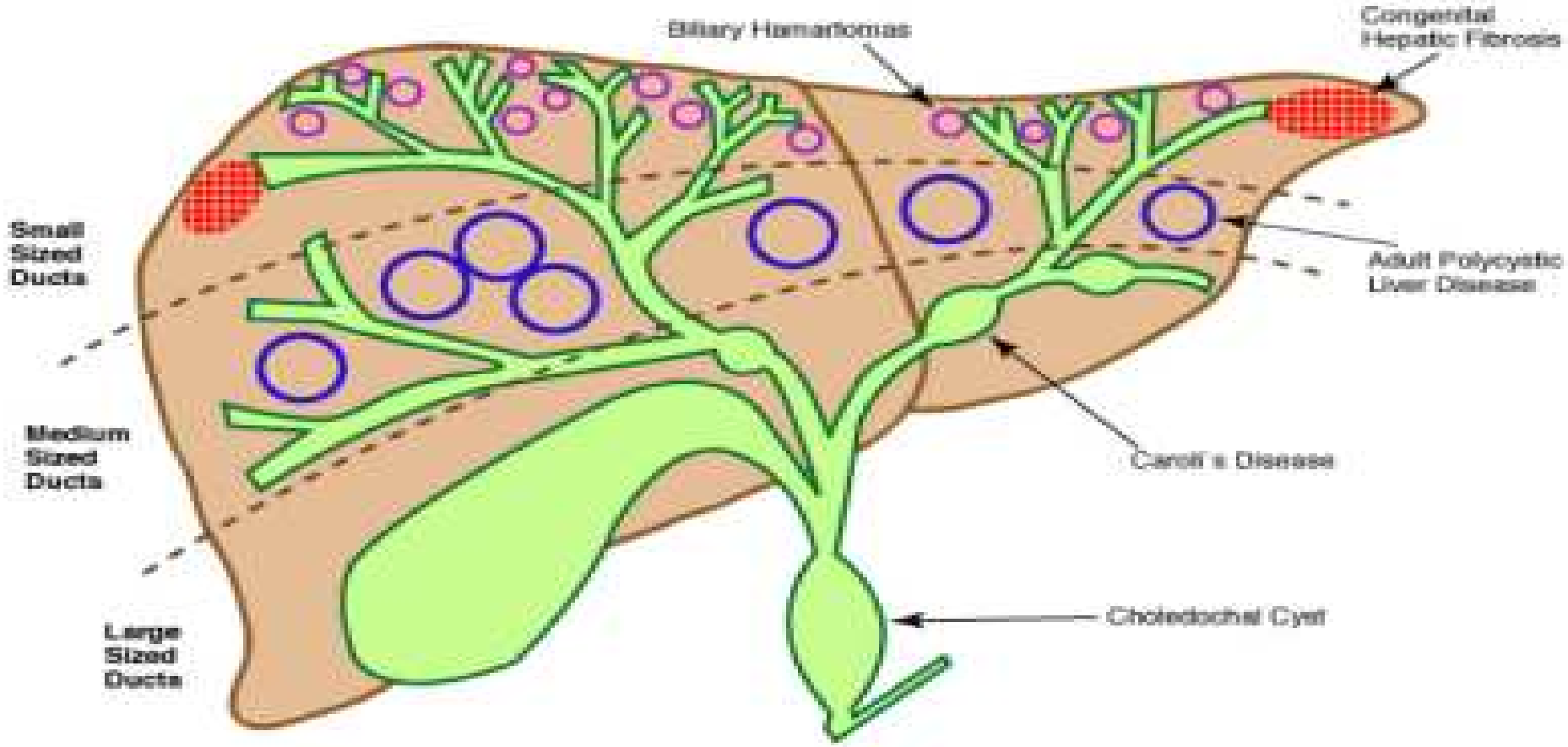


Fig. 2: Types of ductal plate malformation depending on duct size affected. References: Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine - Kyoto/JP

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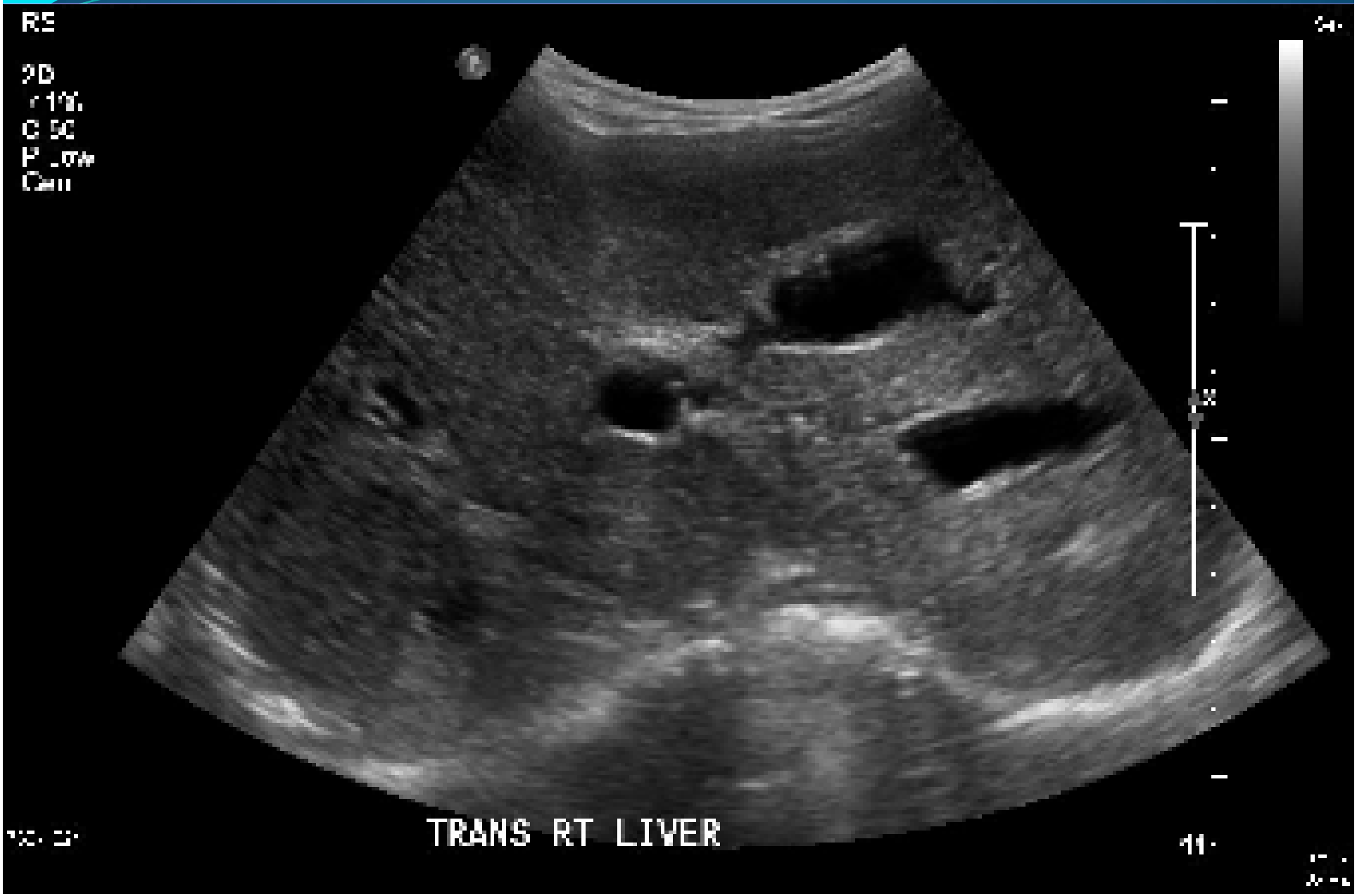
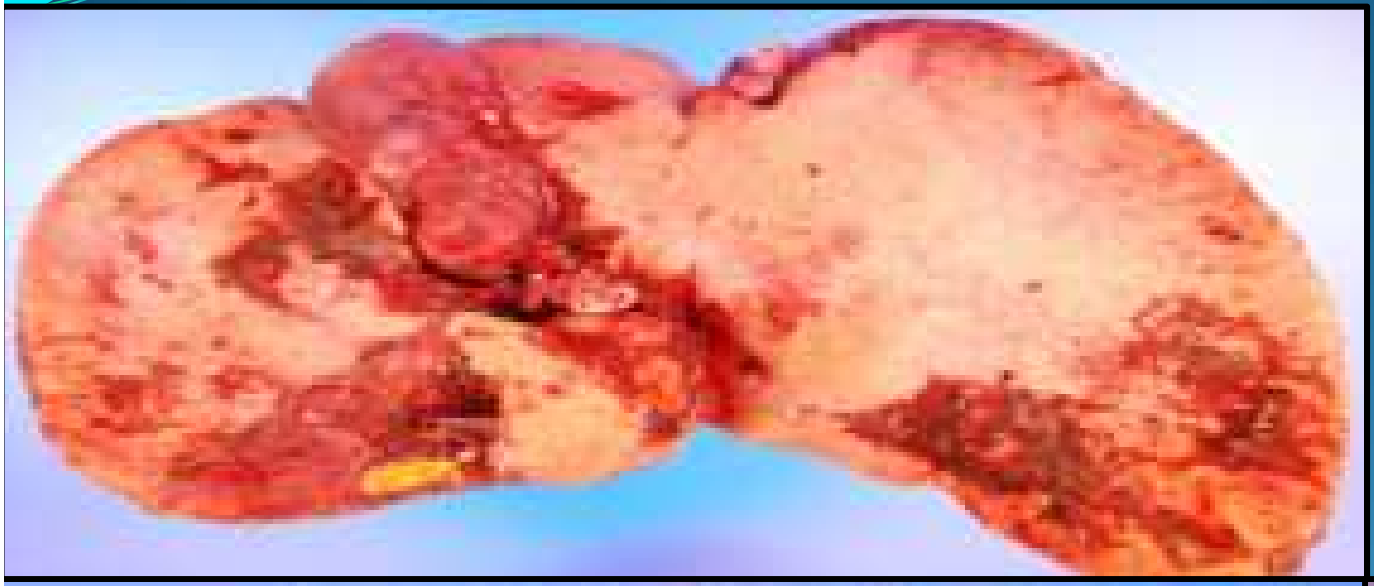
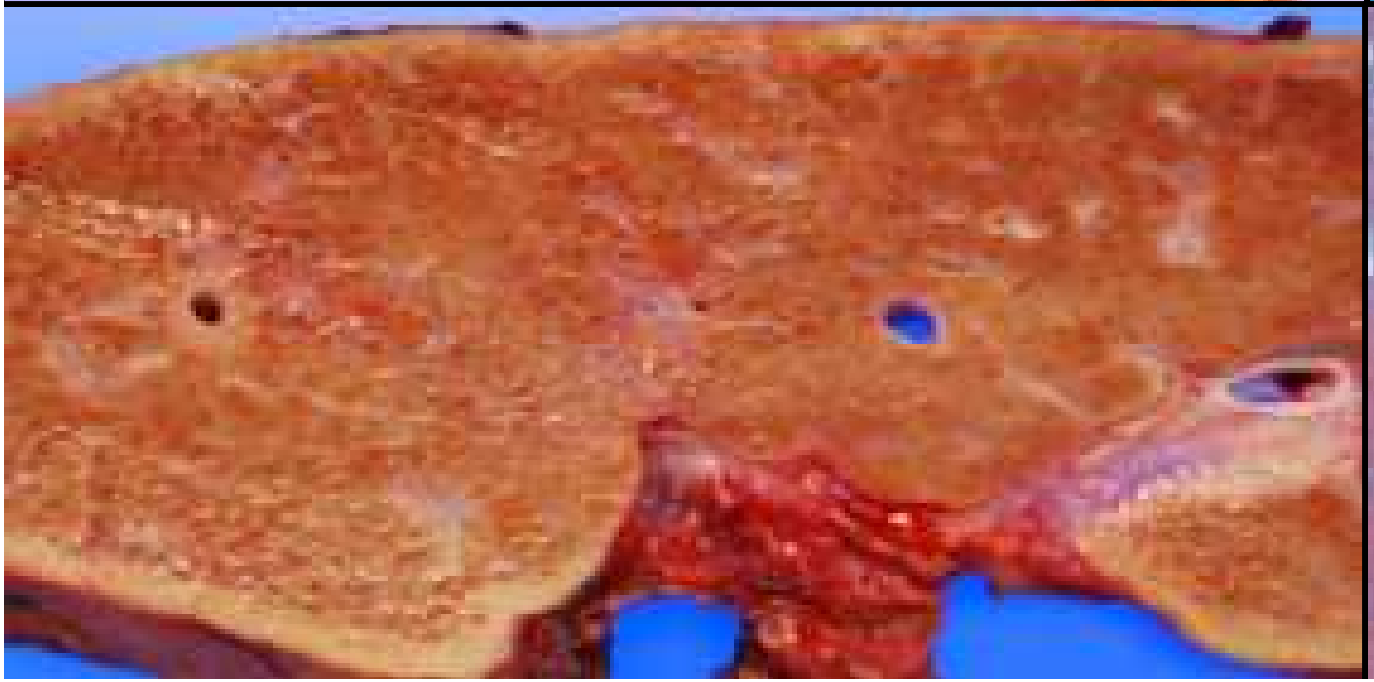
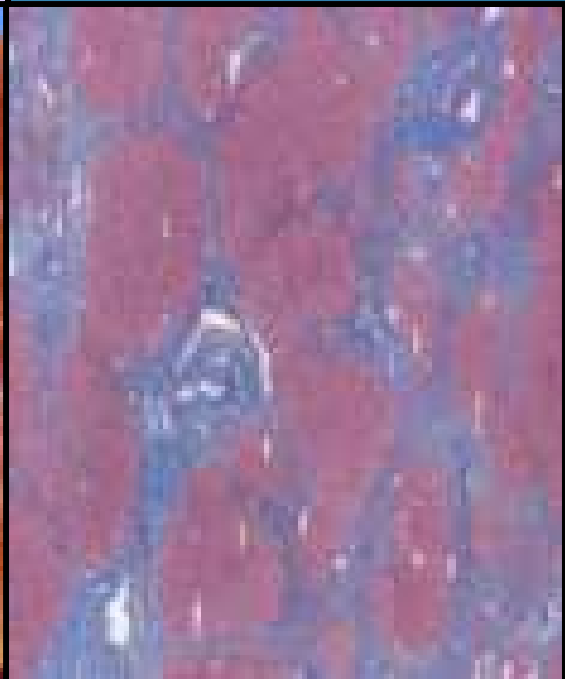
Liver ultrasound showing dilated intrahepatic ducts.





ARPKD/CHF: Cirrhosis with ductal plate malformation. Note macronodular architecture of parenchyma and grey bands of **fibrosis** (x 2).





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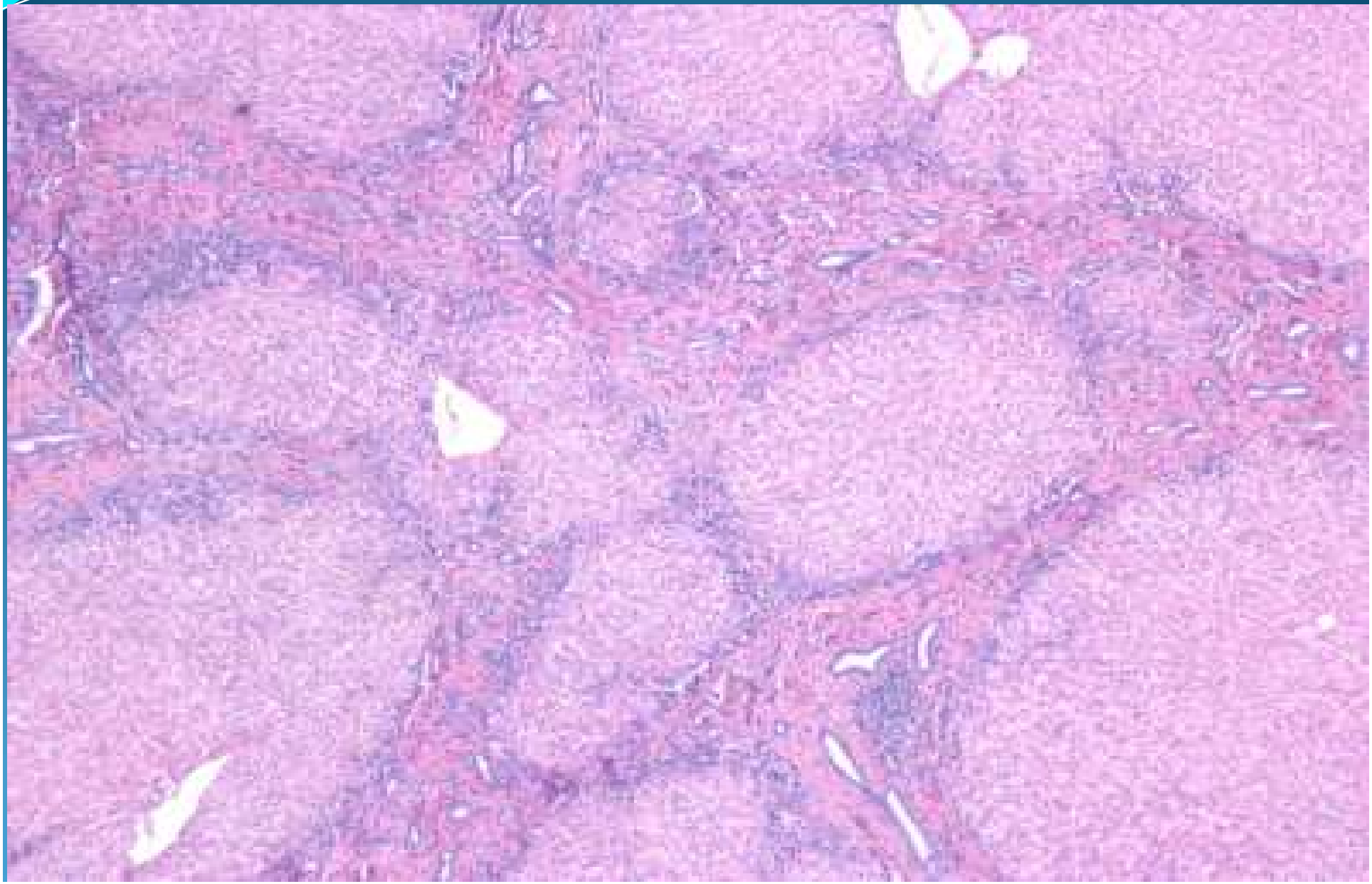
ARPKD/CHF: Dense bands of fibrosis, inflammatory infiltrates , and marked ductular proliferation (H&E x 4).



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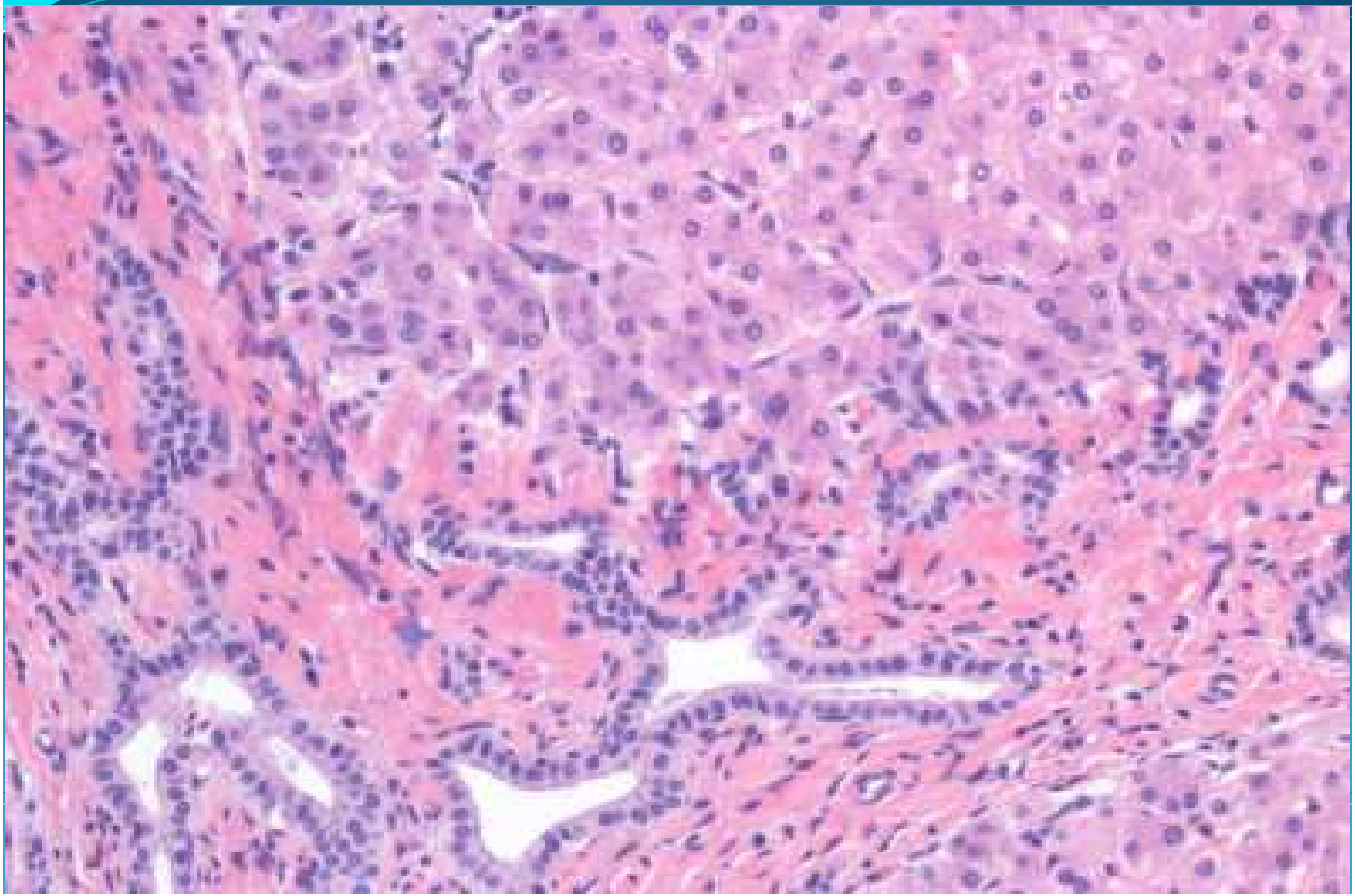
ARPKD/CHF: Dilated enlarged ducts at edge of limiting plate (H&E x 20).



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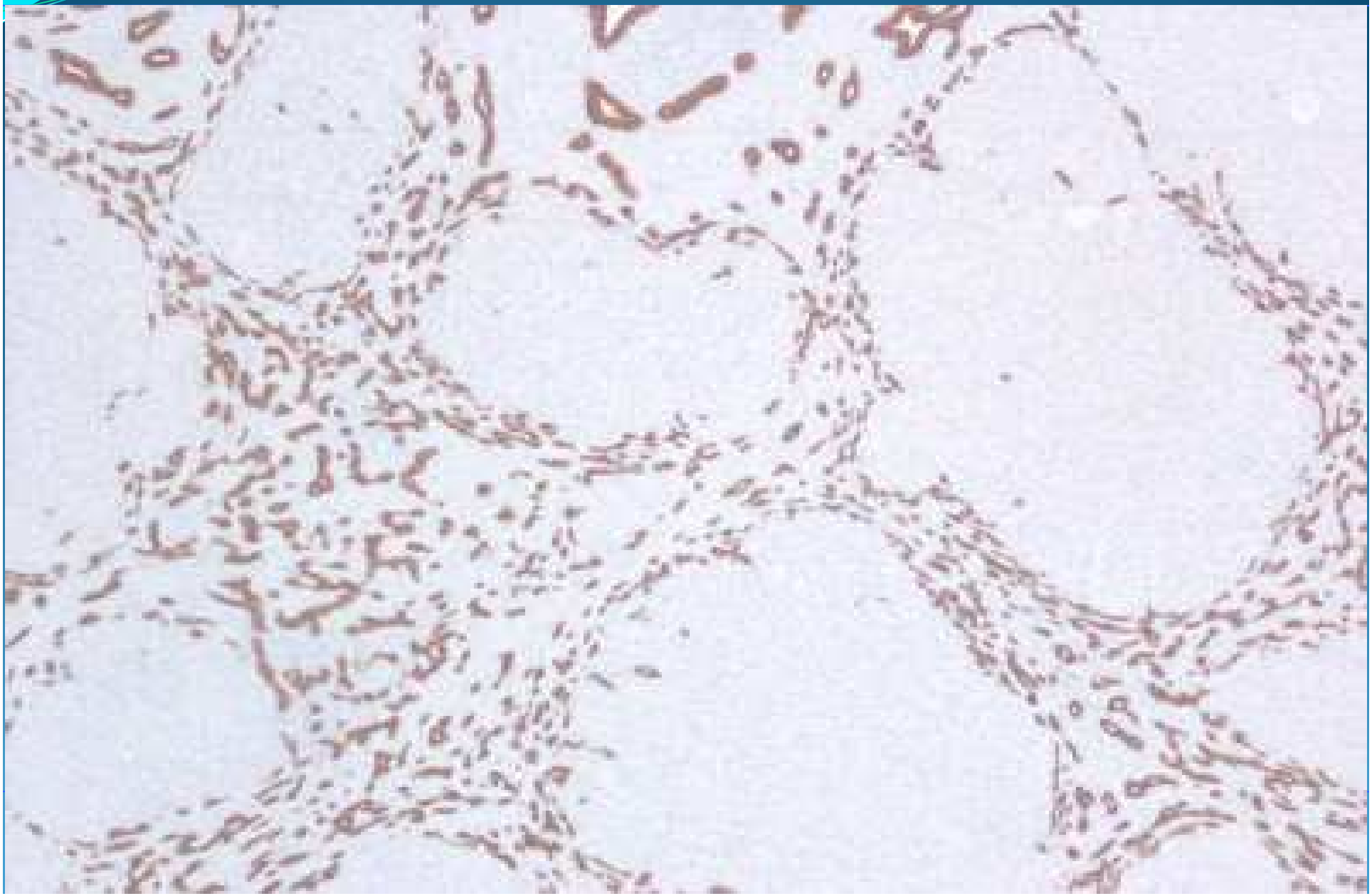
ARPKD/CHF: CK7 positive in florid proliferation of small, intermediate and large ducts (x 4).



ARPKD features:

--Early mortality most common due to pulmonary complications: 30-50% perinatal mortality, 80-95% 5 year survival after the first month of life

--1:20,000 births

--Usually no cysts other than kidney/liver, but liver is always affected with ductal plate malformation and congenital hepatic fibrosis

--Caused by mutations in PKHD1 gene at locus 6p12

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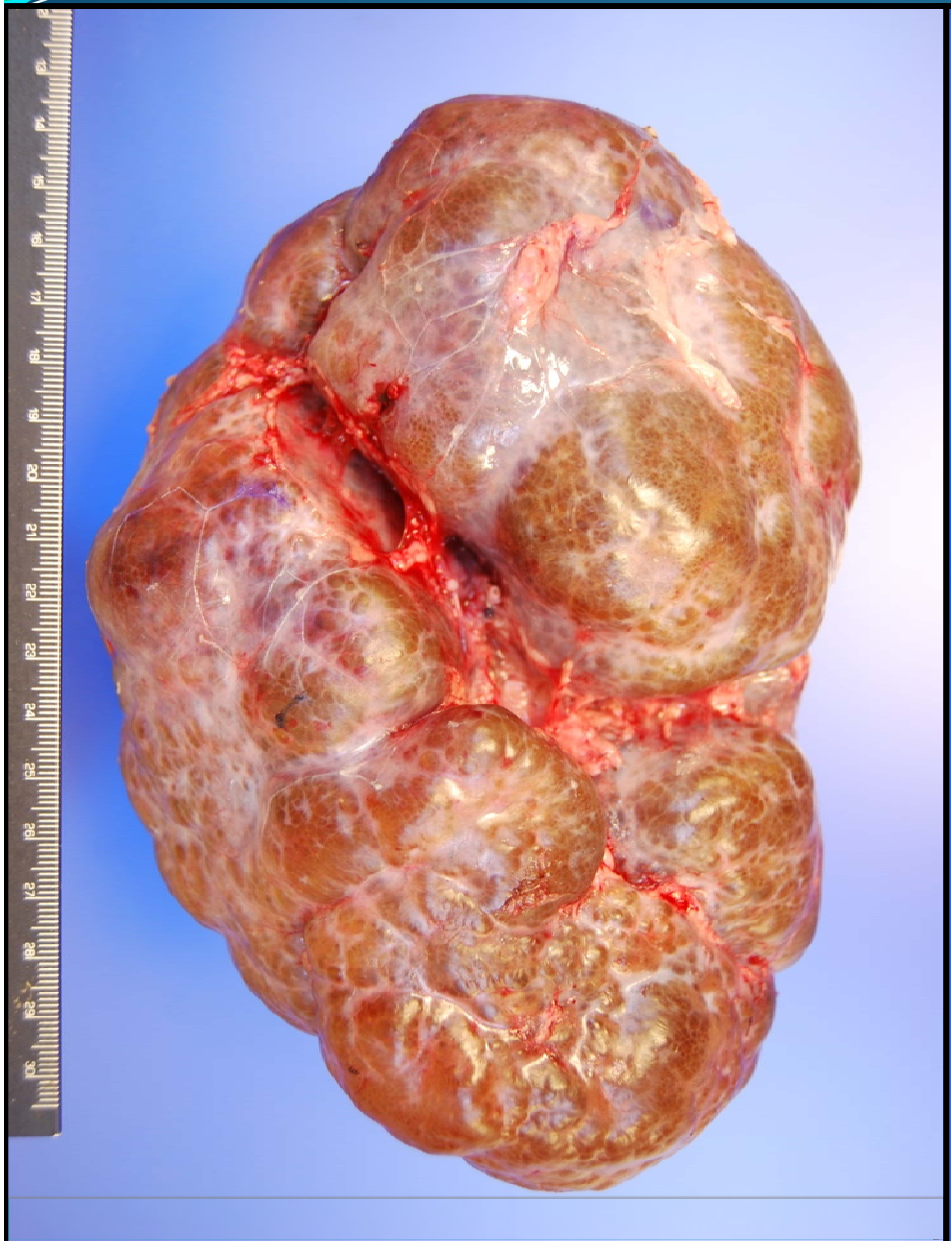
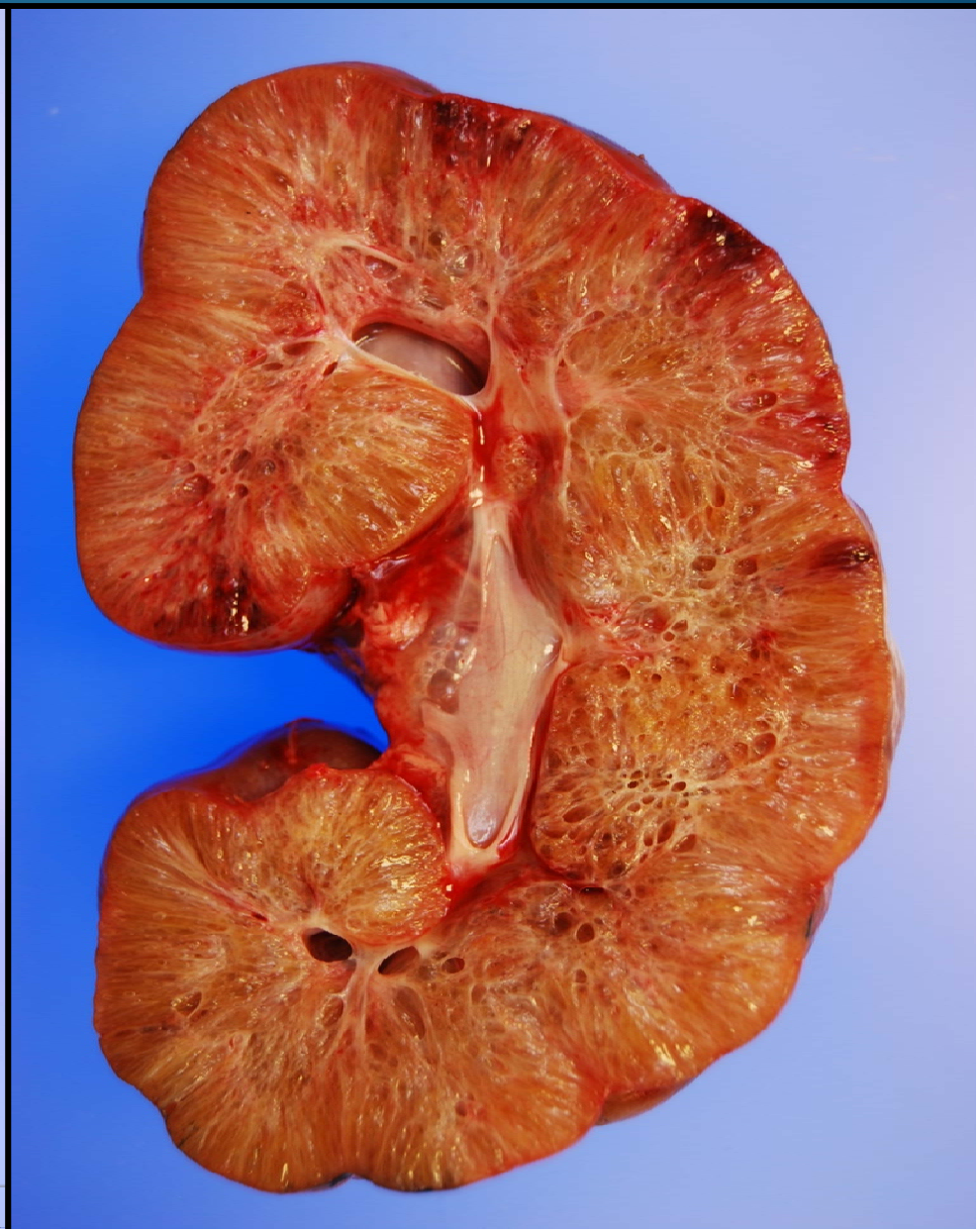
ARPKD: External and cut surfaces of kidney. Note effacement of entire cut surface and perpendicular orientation of cysts to renal capsule.





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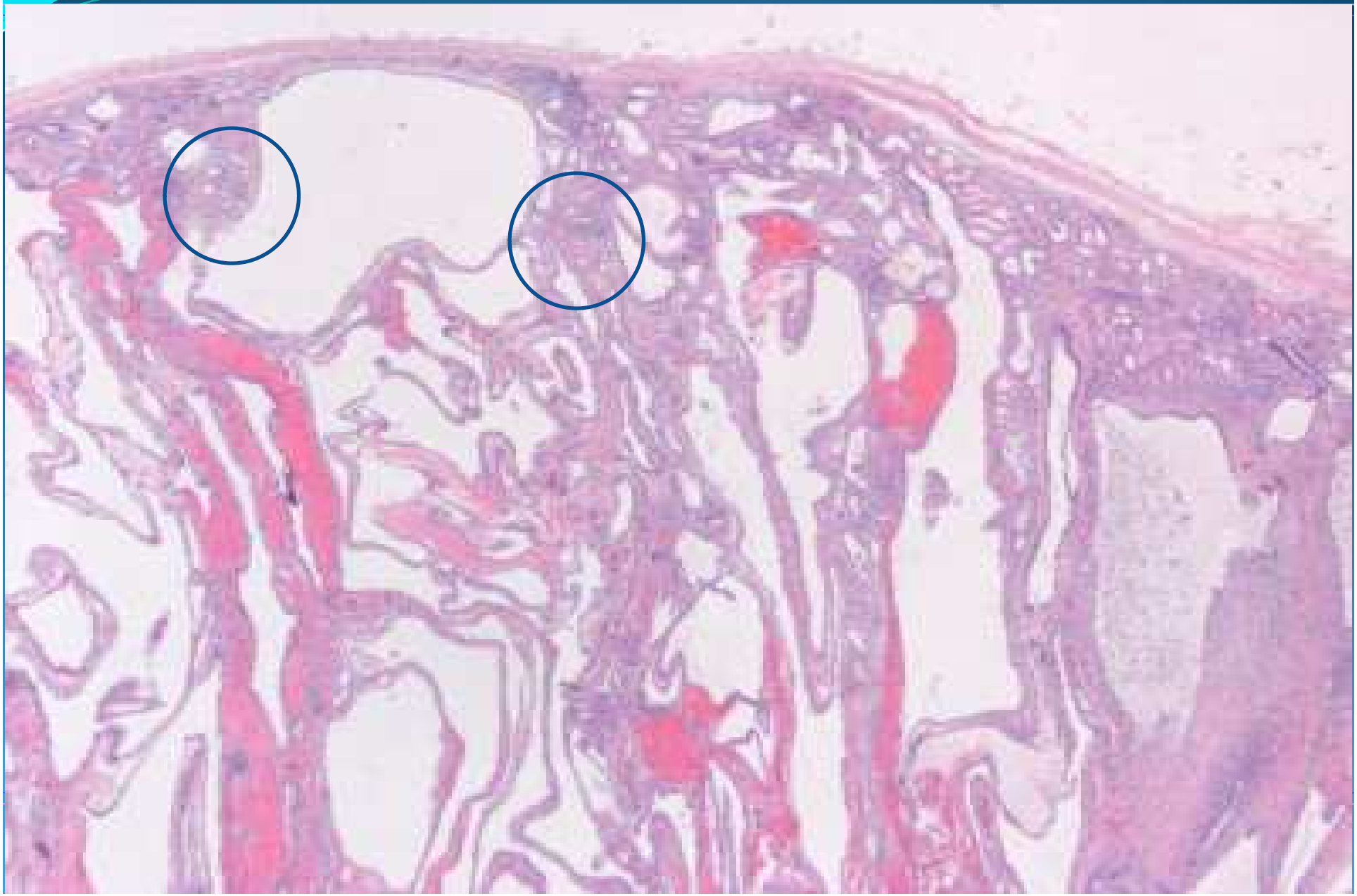
ARPKD: Kidney histology with multiple cystic structures (H&E x 2). Note presence of few glomeruli (circled).



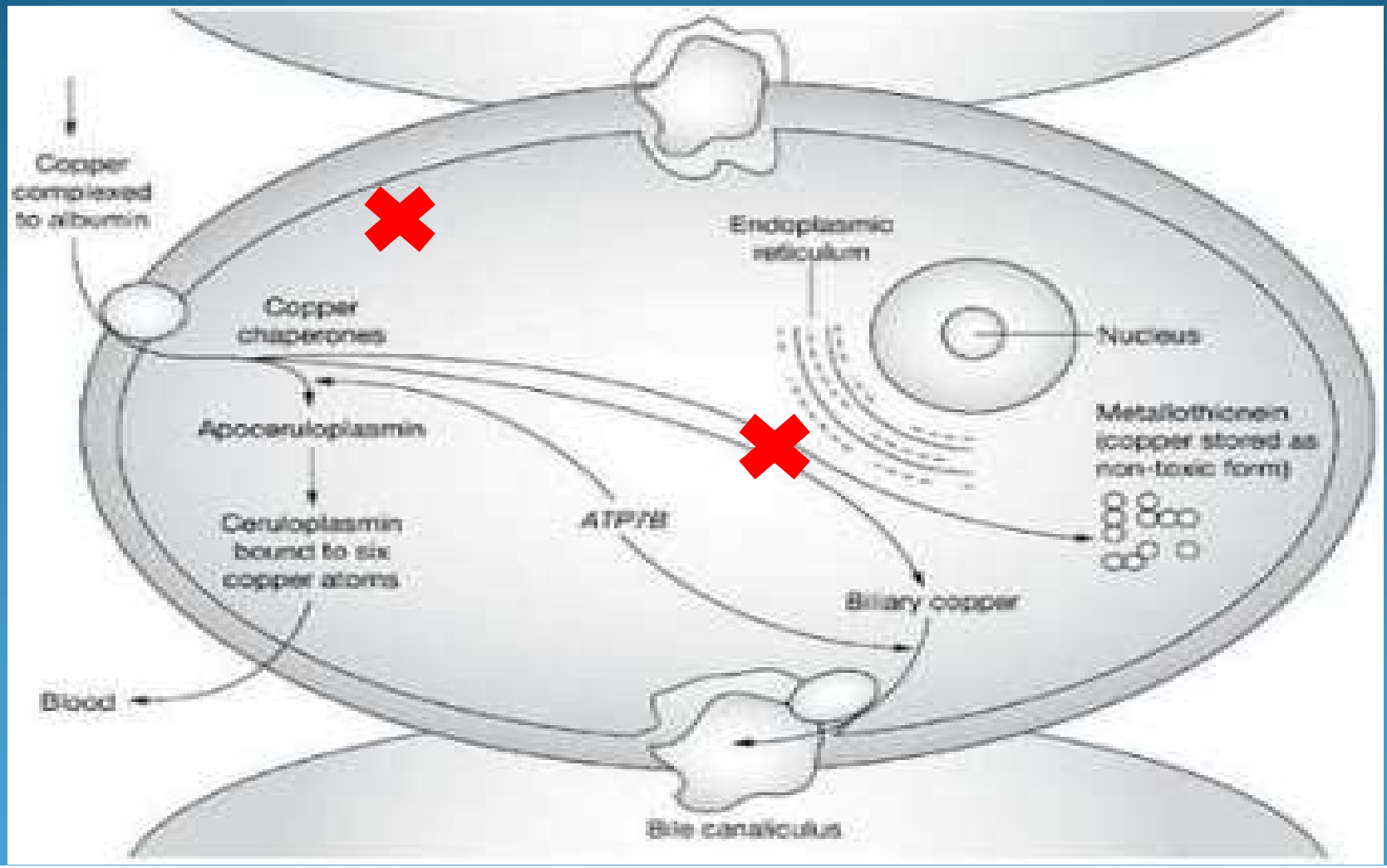
G. Wilson Disease (Hepatolenticular degeneration)

--AR disorder, 1:30,000; causes toxic copper accumulation in liver, brain and eyes

--Genetic abnormality on 13q14 producing ATP7B, a transmembrane copper-transporting ATPase

--Diagnosis: serum ceruloplasmin <20 mg/dL (<5), increased copper on liver biopsy, urinary copper excretion >50µg/24 hr, liver copper quantification >250 µg/g dry weight

Wilson disease: Abnormal *ATP7B* functionality leads to failure of conversion of apoceruloplasmin to ceruloplasmin and failure of conjugated copper to be excreted in bile. Results in toxic accumulation of copper in hepatocytes.



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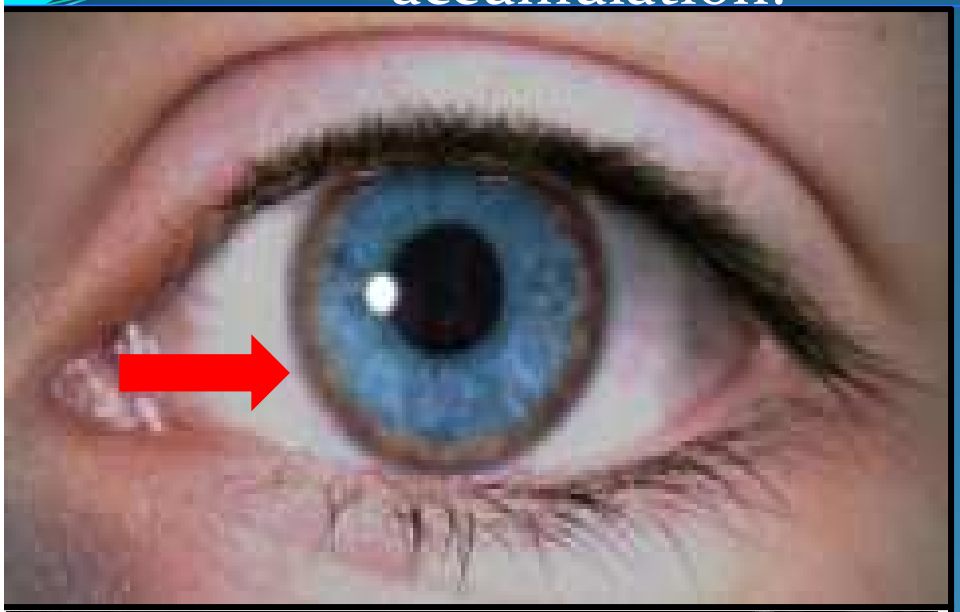
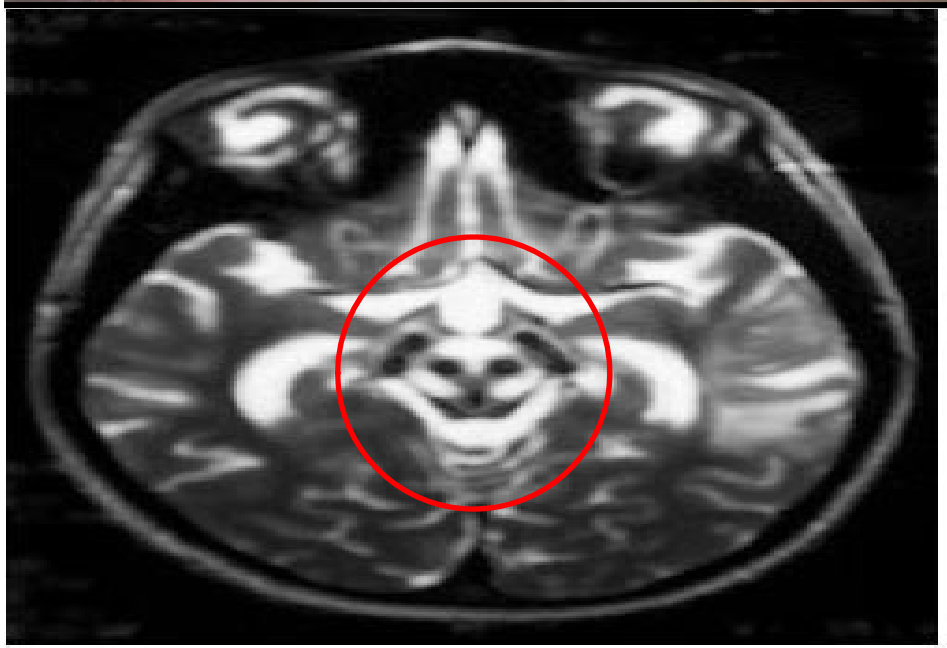
Wilson disease: Additional sites of abnormal copper accumulation:



Kayser-Fleischer rings in eyes result from copper accumulating in Descemet's membrane at corneoscleral junction (limbus).



The 'Giant panda face' is typical on MRI when copper accumulates in midbrain.

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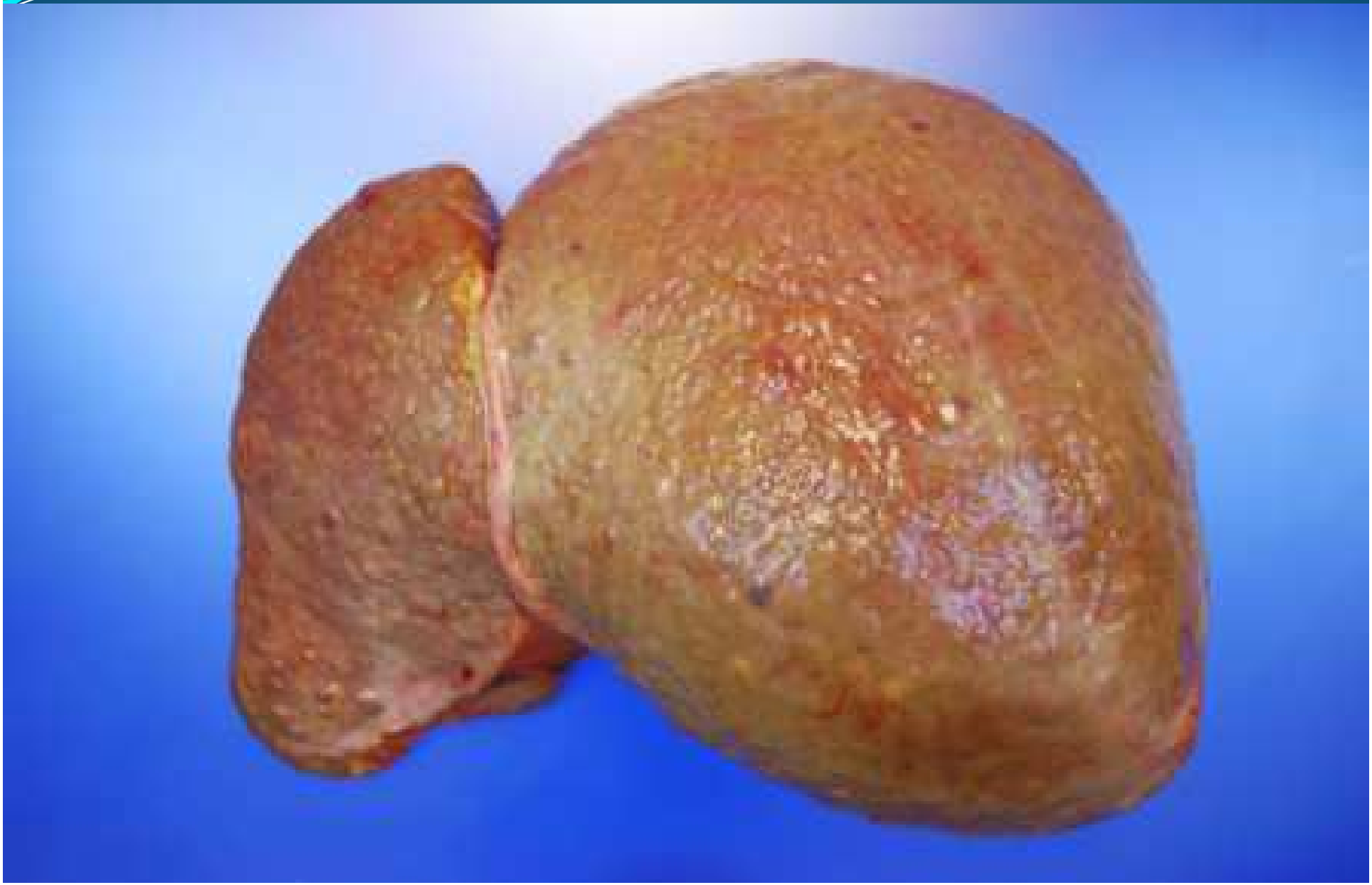
Wilson disease: Liver explant from WD patient with fulminant hepatic failure.



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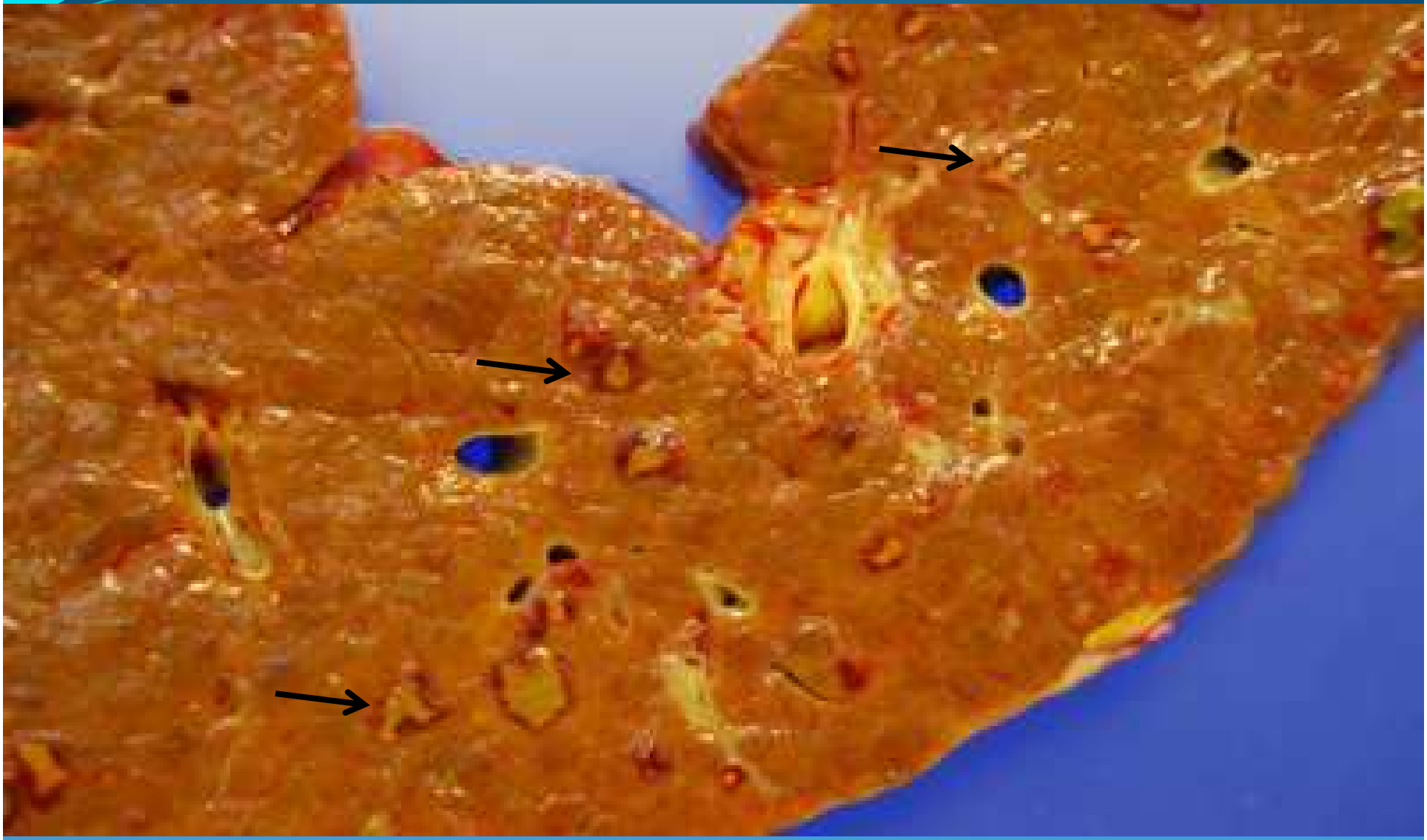
Wilson disease: Macronodular cirrhosis with scattered necrosis (arrows).



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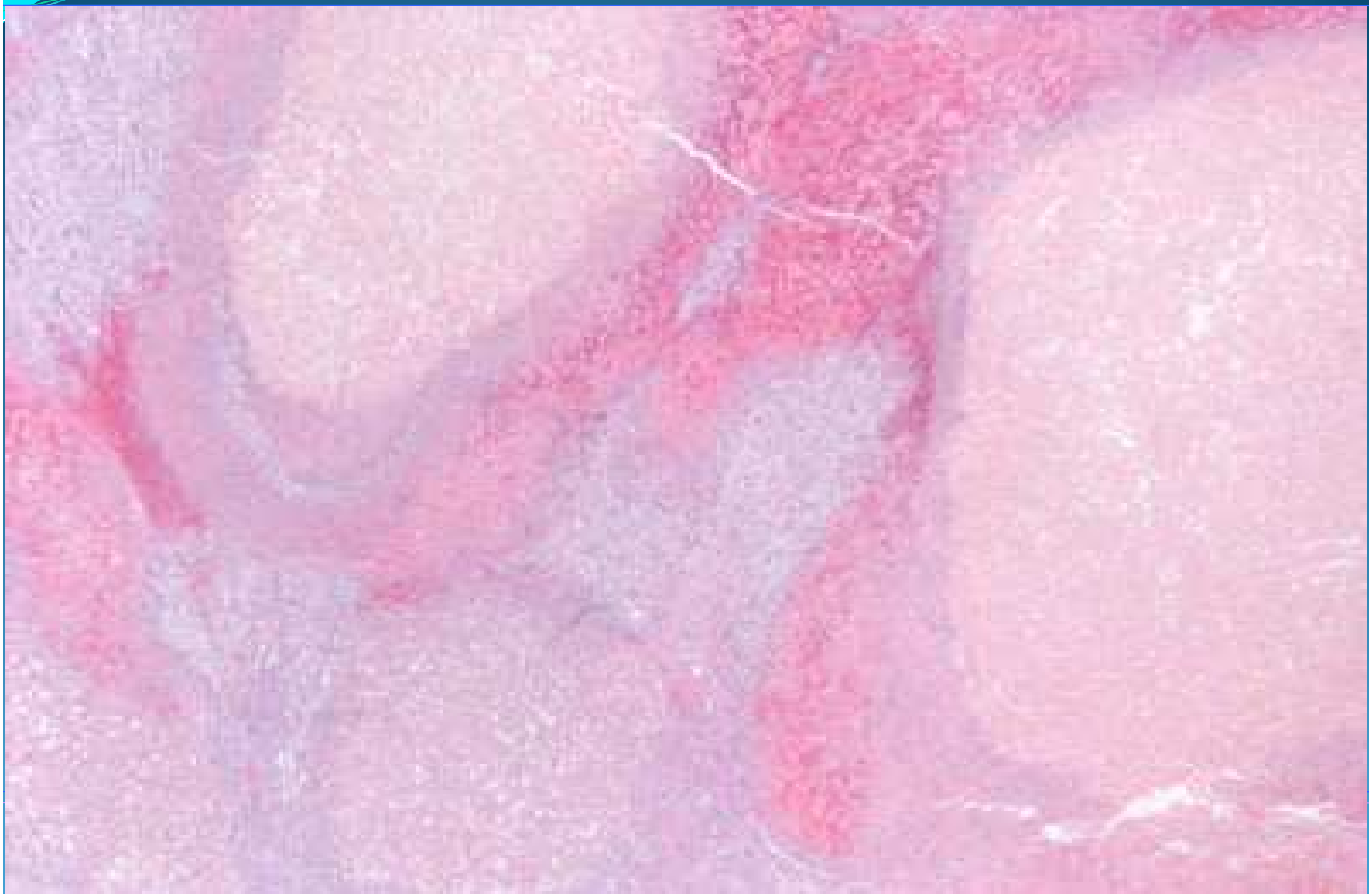
Wilson disease: Necrosis surrounded by hemorrhage (H&E x 2).



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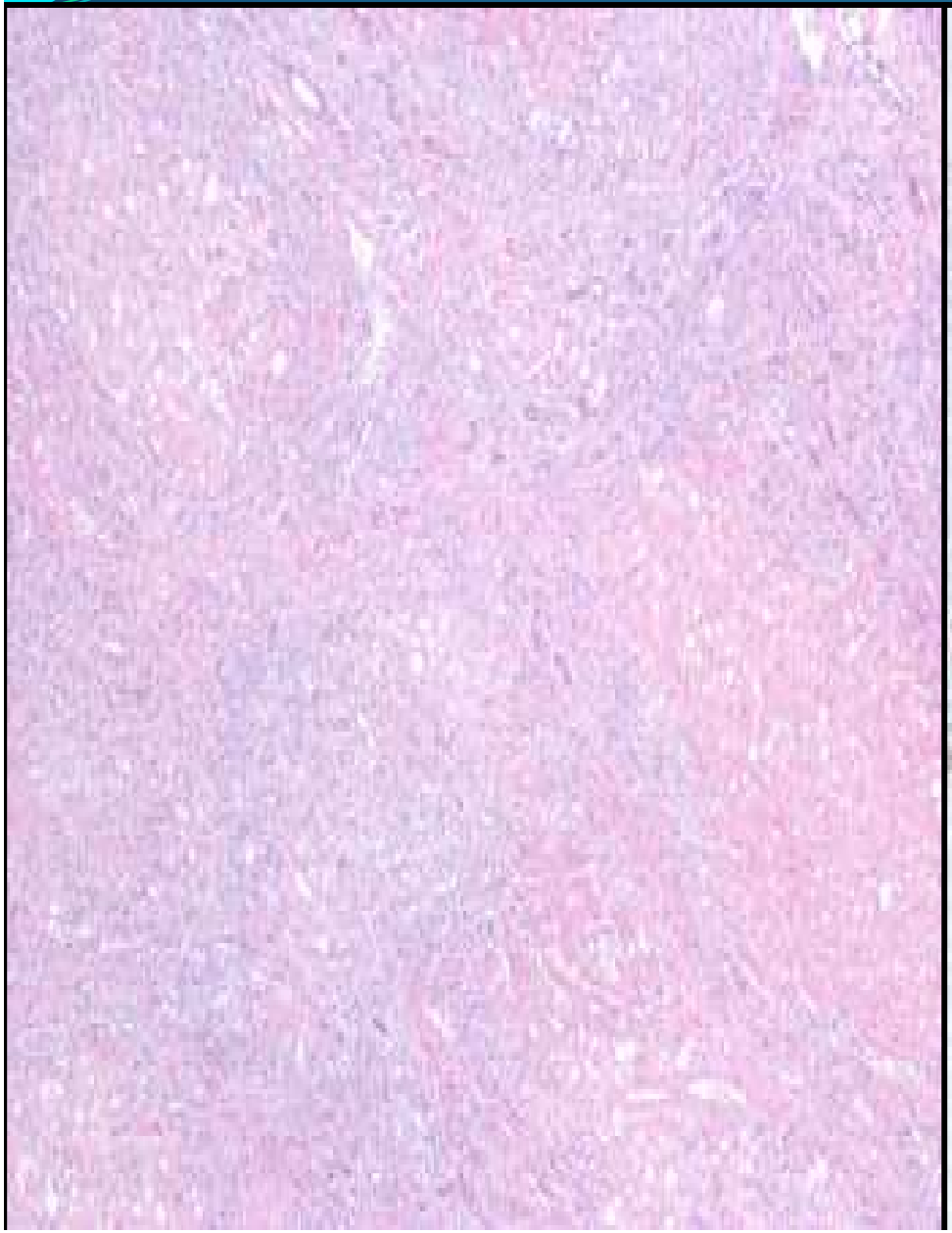
Wilson disease: Effacement of normal architecture with bands of fibrosis containing proliferating bile ductules (Right: H&E x 4; Right, CK7 x 4).



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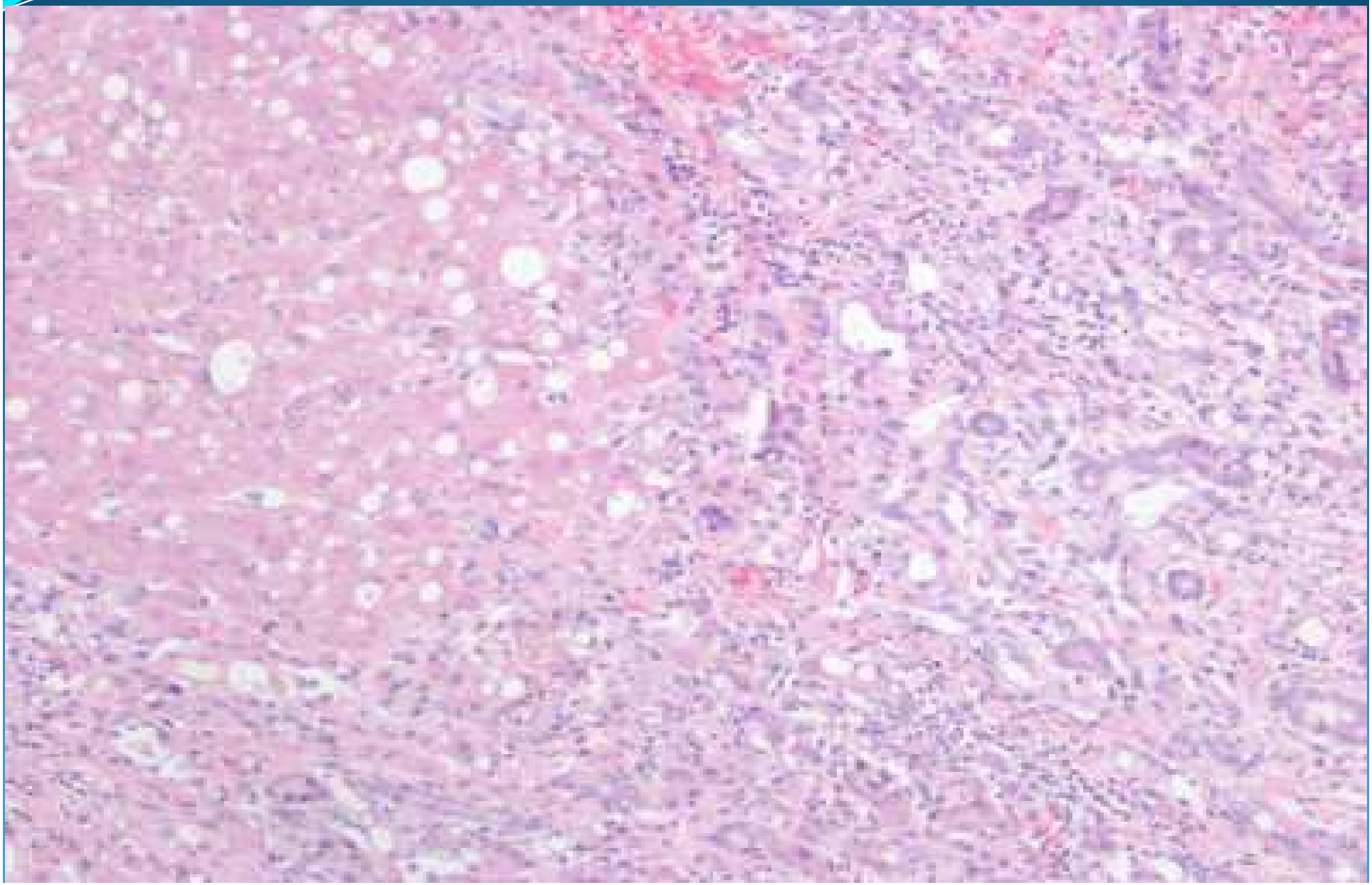
Wilson disease: Steatosis, proliferating bile ductules and hepatocytic cholestasis (H&E x 10).



PHOENIX CHILDREN'S Hospital
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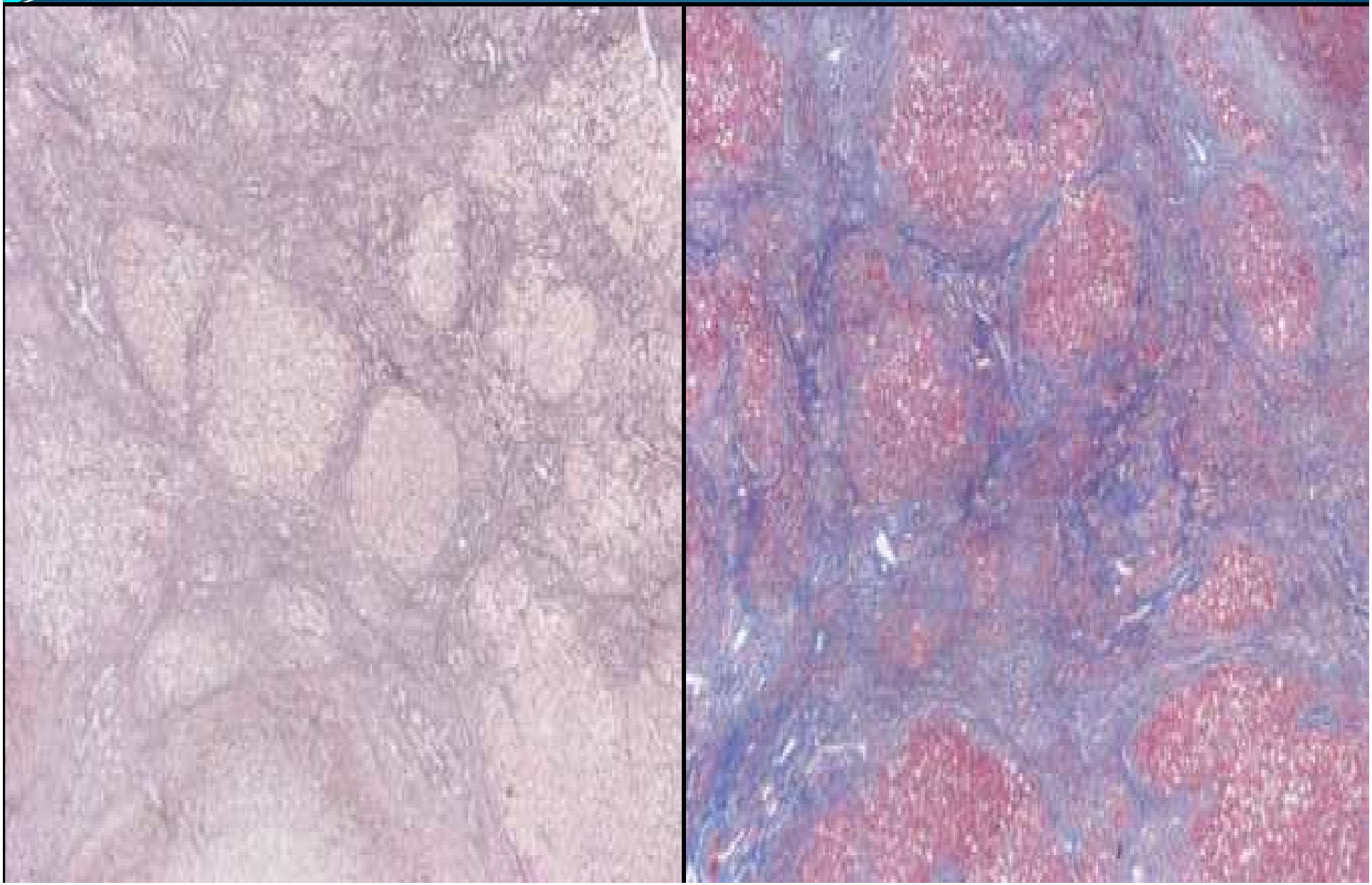
Wilson disease: Reticulin (left) and Masson trichrome (right) demonstrate dense bands of fibrosis (each x 2).



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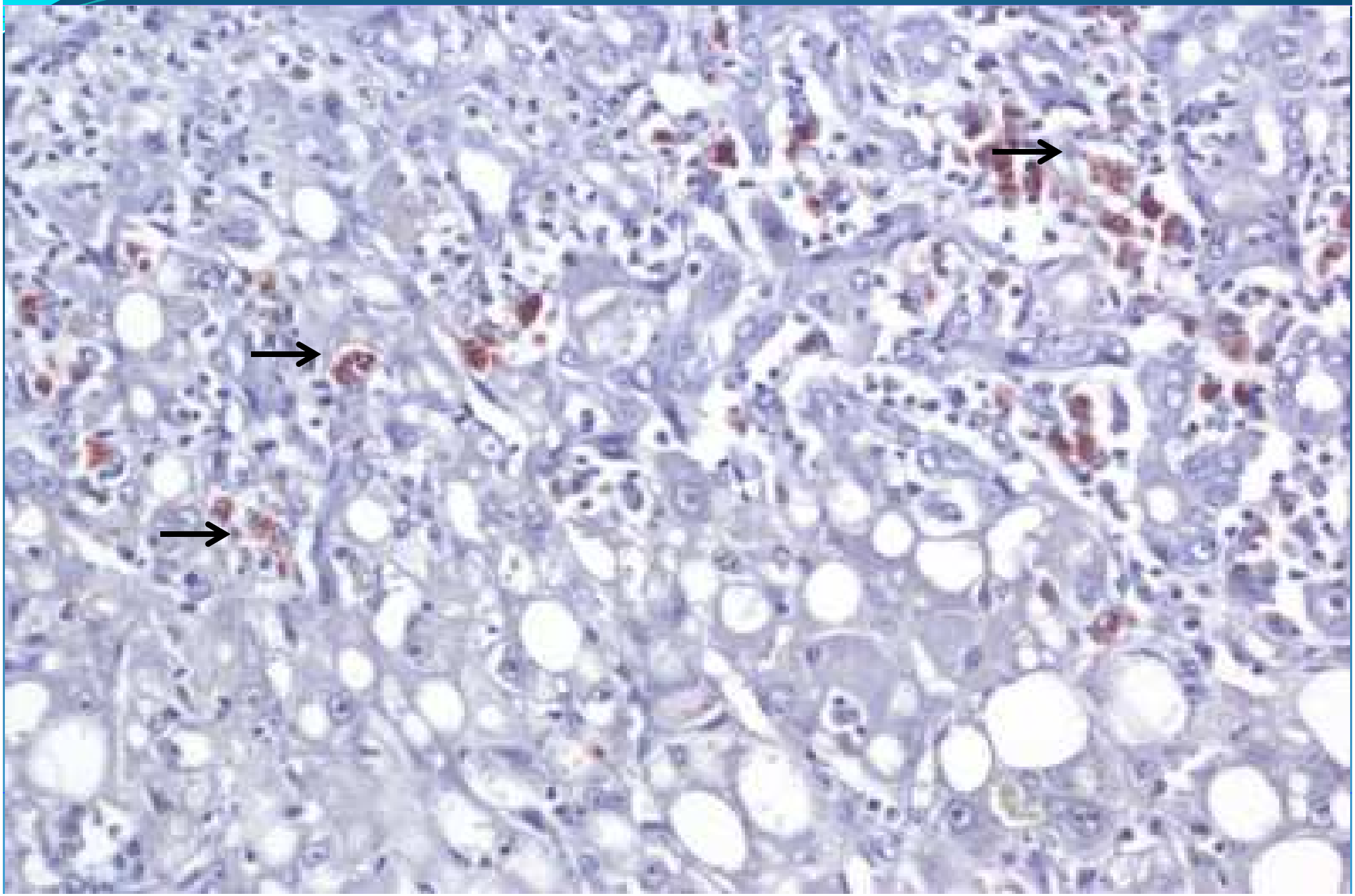
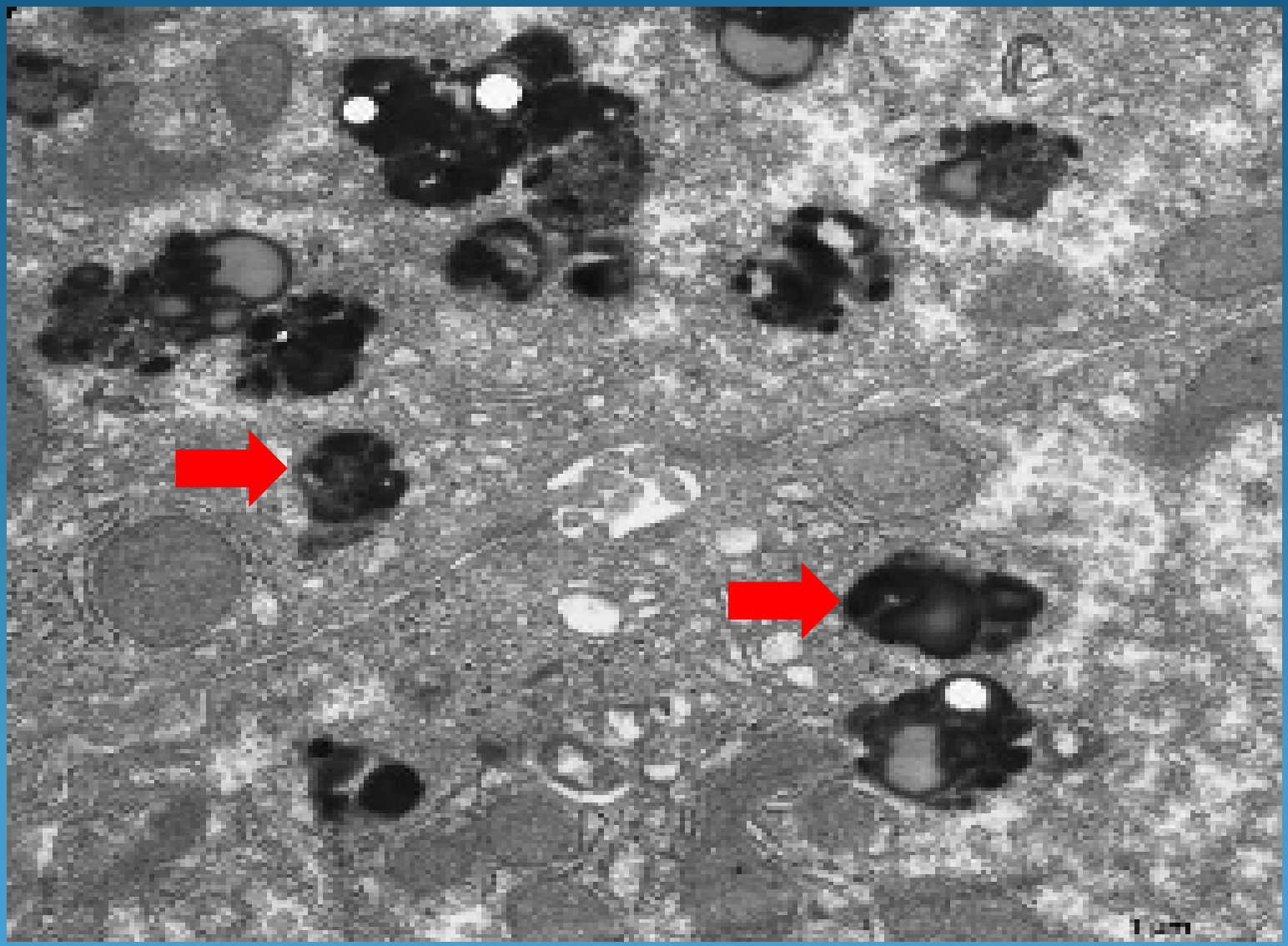
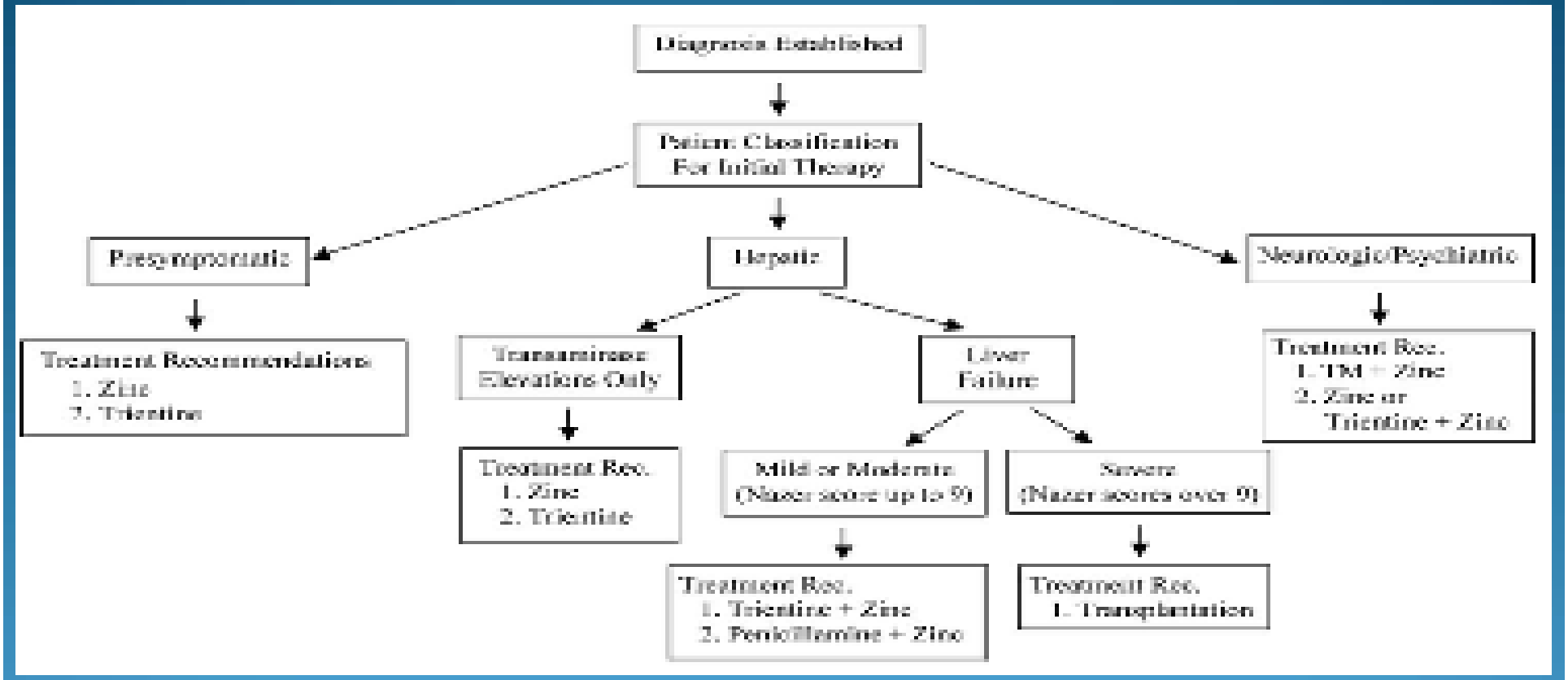
Wilson disease: Red-brown accumulations of copper in hepatocytes and Kupffer cells. (arrows) (rhodanine x 20).



Wilson disease: Electron-dense deposits (arrows) of copper.



Treatment for Wilson's Disease:



Long-term copper chelation therapy and/or liver transplantation

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