

Primary Sclerosing Cholangitis

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Duct injury · Periductal fibrosis · Cholangiographic strictures

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Learning objectives

- Define PSC by its affected ducts and characteristic fibrosing lesion.
- Explain established associations and proposed immune mechanisms.
- Connect duct pathology with cholangiography, manifestations, and complications.
- Differentiate PSC from primary biliary, IgG4-related, and secondary cholangitis.

PSC is a chronic fibrosing cholangiopathy

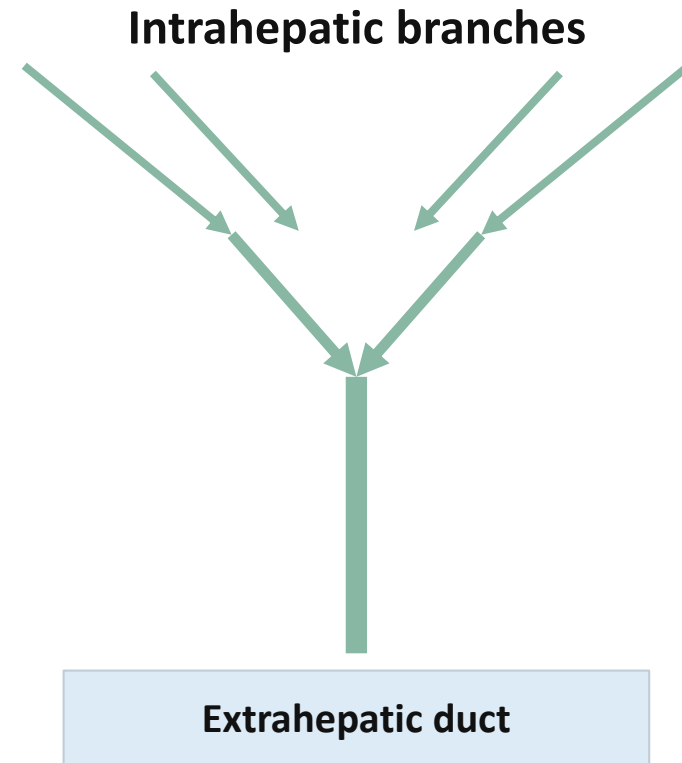
Inflammation and obliterative fibrosis of major bile ducts

- Large intrahepatic and extrahepatic bile ducts are principal targets.
- Irregularly preserved duct segments may become dilated.
- This combination produces a recognizable obstructive biliary phenotype.

Anatomical distribution determines the phenotype

- Major intrahepatic ducts are affected.
- Extrahepatic ducts are also affected.
- Small portal-tract ducts may show secondary cholestatic changes rather than the defining large-duct lesion.

SCHEMATIC — major duct anatomy

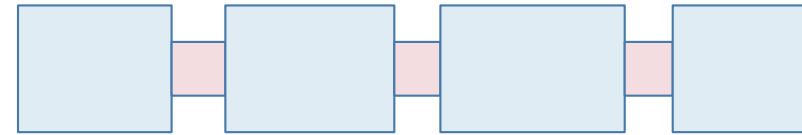


Large ducts: Principal lesions

Alternating injury creates the beaded duct

- Inflammation and fibrosis narrow affected segments.
- Relatively preserved segments remain patent or dilate.
- Multiple strictures alternating with dilatations explain the characteristic appearance.

SCHEMATIC — alternating diameter



Dilated segment

Fibrotic stricture

Imaging appearance: “beading”

Injury and scarring are linked but distinct

Inflammatory component

- Cholangiocyte epithelial damage
- Acute neutrophilic activity may coexist with chronic inflammation
- Periductal edema may worsen narrowing

Fibrosing component

- Persistent periductal collagen deposition
- Concentric scar progressively constricts a duct
- End-stage lesions can obliterate the lumen

Who develops PSC?

- Typical presentation occurs from the third through fifth decades.
- Male predominance is approximately 2:1.
- These are population tendencies, not diagnostic requirements.

CHARACTERISTIC ASSOCIATIONS

Age at presentation

3rd–5th decades

Sex distribution

~2:1 male predominance

IBD / ulcerative colitis

~70% have IBD

PSC is strongly associated with inflammatory bowel disease

- Inflammatory bowel disease is reported in approximately 70% of PSC patients.
- Ulcerative colitis is the particularly strong association.
- The enteric association is relevant both clinically and mechanistically.

Association is not proof that colitis directly causes PSC.

The gut–liver association raises a mechanistic question

Why should bowel inflammation accompany bile-duct damage?

- Ulcerative colitis provides a setting for mucosal T-cell activation.
- A proposed mechanism is migration of gut-activated lymphocytes to the liver.
- The putative cross-reactive biliary antigen remains hypothetical.

Familial clustering suggests genetic susceptibility

- First-degree relatives have increased risk of PSC.
- This supports a heritable component without specifying a single causative variant.
- Disease development is thought to require both genetic and environmental contributions.

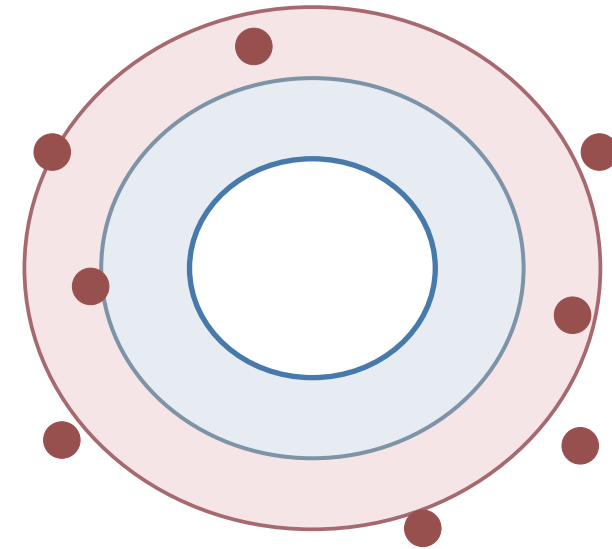
Immunogenetic associations support immune involvement

- HLA-B8 and other major histocompatibility complex alleles are associated with PSC.
- Circulating autoantibodies and local immune cells provide additional evidence.
- Association with immune loci does not identify the complete causal pathway.

T cells are observed in the periductal stroma

- Lymphocytes occur around injured ducts.
- Immune-mediated damage is a biologically plausible disease model.
- Observed infiltration does not alone establish the initiating event.

SCHEMATIC — duct cross-section

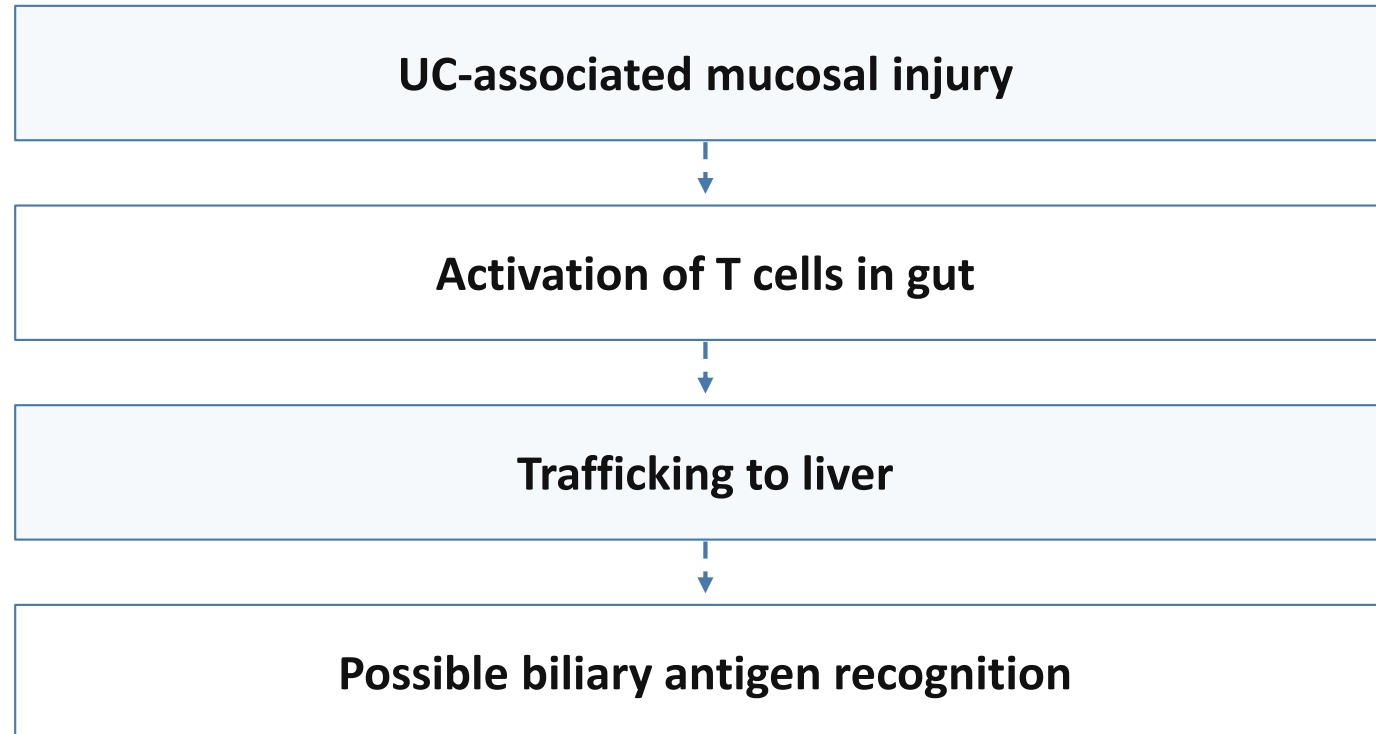


Injured epithelium

Periductal inflammatory cells

Gut-activated T-cell trafficking: A proposed model

PROPOSED mechanism, not an established sequence



This hypothesis is discussed; Causality remains unproven.

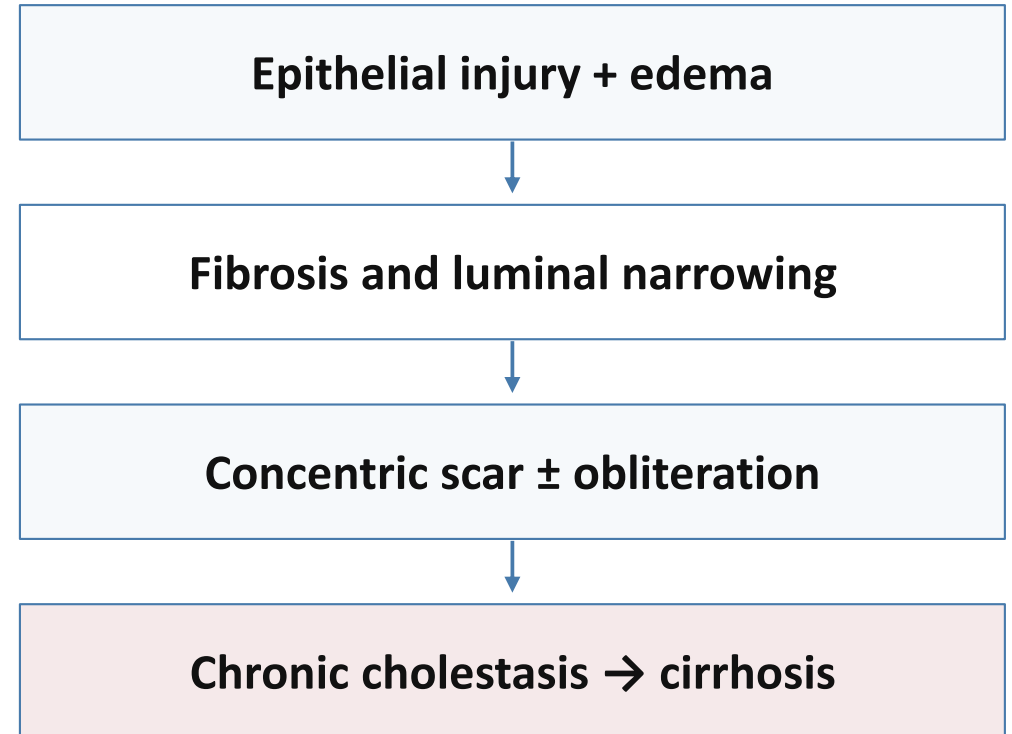
Microbial or infectious triggers have been proposed

- Infection is one hypothesized environmental trigger.
- Changes in the intestinal microbiome may influence cholangiocyte biology.
- Neither idea currently accounts definitively for all PSC cases in the source discussion.

PSC pathogenesis is multifactorial

- Genetic susceptibility contributes to risk.
- Environmental and gut-related factors are proposed triggers.
- Immune-cell recruitment and bile-duct injury lead to a fibrosing response.

SCHEMATIC — structural progression



PANCA is common but not disease-specific

- Perinuclear antineutrophil cytoplasmic antibodies occur in approximately 65% of patients.
- The source describes reactivity to a nuclear-envelope protein.
- PSC lacks the characteristic autoantibody signature seen in PBC.

A serologic association is not interchangeable with a diagnostic test.

Autoantibodies: PSC and PBC are not equivalent

Primary sclerosing cholangitis

- PANCA commonly detectable
- No highly characteristic PSC-specific antibody profile
- Antimitochondrial antibody generally absent

Primary biliary cholangitis

- Antimitochondrial antibody is a central association
- PDC-E2 is the key mitochondrial antigen
- Antibody profile is much more disease-characteristic

Large ducts show epithelial injury

- Injured biliary lining is the initiating morphologic compartment.
- Luminal integrity and bile passage are affected.
- Inflammation is centered on the bile duct wall and adjacent stroma.

SCHEMATIC — morphologic triad

Injury

Epithelial damage

Inflammation

Chronic $\pm$ neutrophils

Repair/scarring

Concentric fibrosis

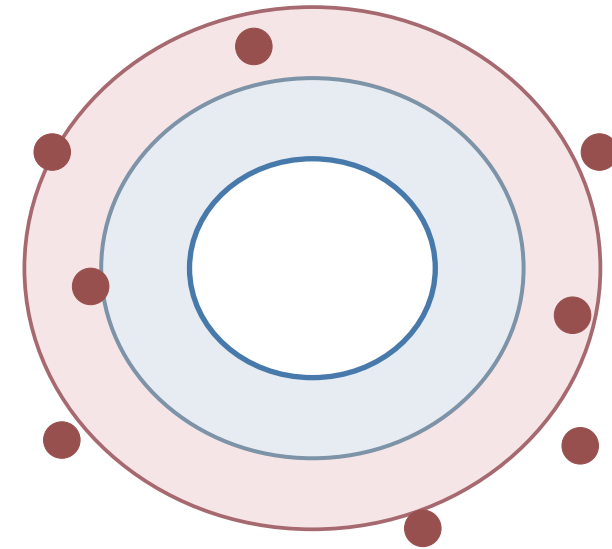
Acute and chronic inflammation can coexist

- Neutrophilic infiltrates may be superimposed on chronic inflammation.
- The mixed response is described in the large intrahepatic and extrahepatic ducts.
- The inflammatory tissue changes contribute to narrowing before fixed fibrosis dominates.

Edema can constrict a bile duct

- Inflammation produces mural and periductal edema.
- Swelling reduces the available luminal diameter.
- Subsequent fibrosis may convert reversible narrowing into a fixed stricture.

SCHEMATIC — duct cross-section



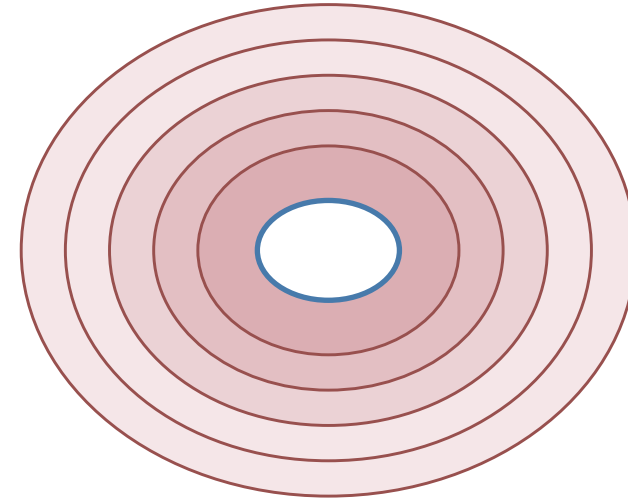
Injured epithelium

Periductal inflammatory cells

Progressive periductal fibrosis causes stricture

- Periductal collagen accumulates during chronic injury.
- The residual lumen is increasingly narrow.
- Multiple fibrotic segments interrupt biliary drainage at different levels.

SCHEMATIC — concentric periductal fibrosis



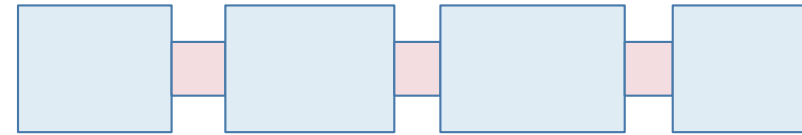
Concentric scar

Atrophic duct lumen

Duct dilatation coexists with strictures

- Segments that remain patent can become expanded.
- This creates an irregular rather than uniformly narrow biliary tree.
- The combined appearance is the basis of cholangiographic beading.

SCHEMATIC — alternating diameter



Dilated segment

Fibrotic stricture

Imaging appearance: “beading”

Lithiasis can complicate dilated ducts

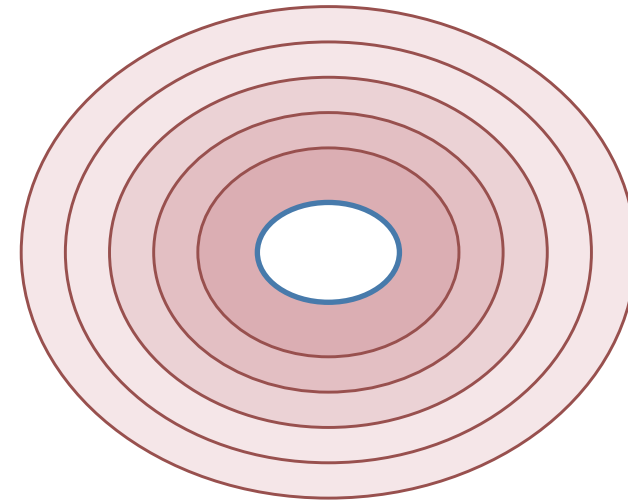
- Stones may develop within dilated biliary segments.
- The coexistence of strictures and lithiasis complicates bile drainage.
- Biliary obstruction can contribute to episodes of ascending cholangitis.

Stones in PSC are a consequence of distorted duct architecture.

“Onion-skin” fibrosis: The signature microscopic pattern

- Concentric rings of periductal fibrosis encircle an injured duct.
- The ductal epithelium progressively degenerates.
- The residual lumen may be severely narrowed.

SCHEMATIC — concentric periductal fibrosis



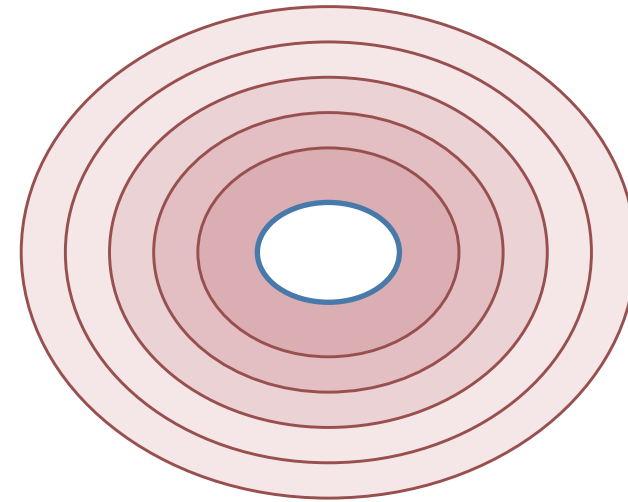
Concentric scar

Atrophic duct lumen

Duct atrophy follows concentric scarring

- Repeated injury and fibrosis reduce residual duct caliber.
- Ducts may become increasingly atrophic within a fibrotic cuff.
- The morphologic process advances toward duct obliteration.

SCHEMATIC — concentric periductal fibrosis



Concentric scar

Atrophic duct lumen

The “tombstone” scar is an end-stage duct lesion

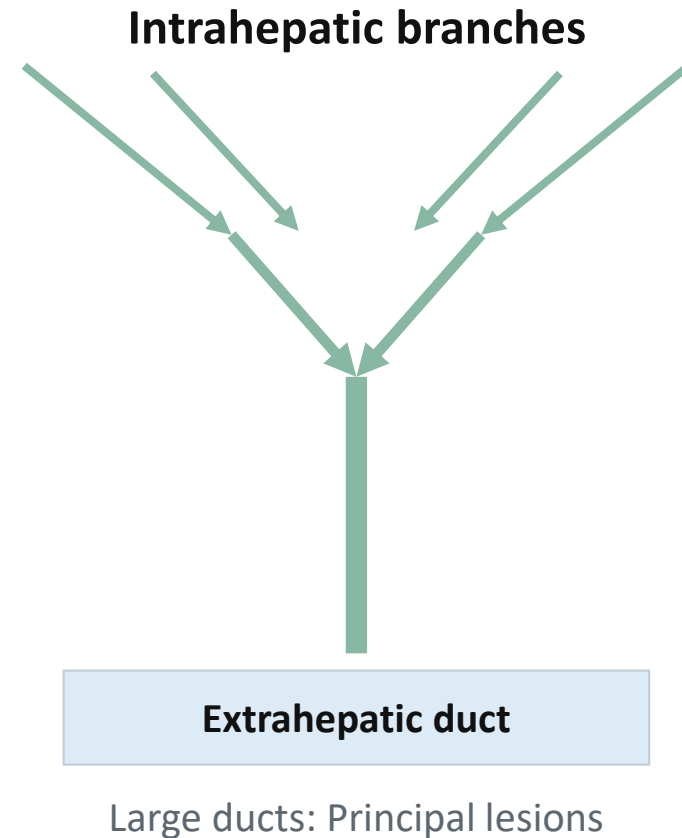
A bile duct may be replaced by a solid fibrous scar

- Progressive periductal fibrosis can completely obliterate a lumen.
- The resulting scar reflects chronic duct loss rather than simple acute edema.
- Recognizing a vanished duct depends on adequate tissue context.

Routine biopsy may miss the principal PSC lesion

- Needle biopsy preferentially samples peripheral, smaller portal tracts.
- The defining large-duct inflammatory lesion may lie outside the sampled tissue.
- Therefore, secondary cholestatic changes can predominate in a biopsy.

SCHEMATIC — major duct anatomy



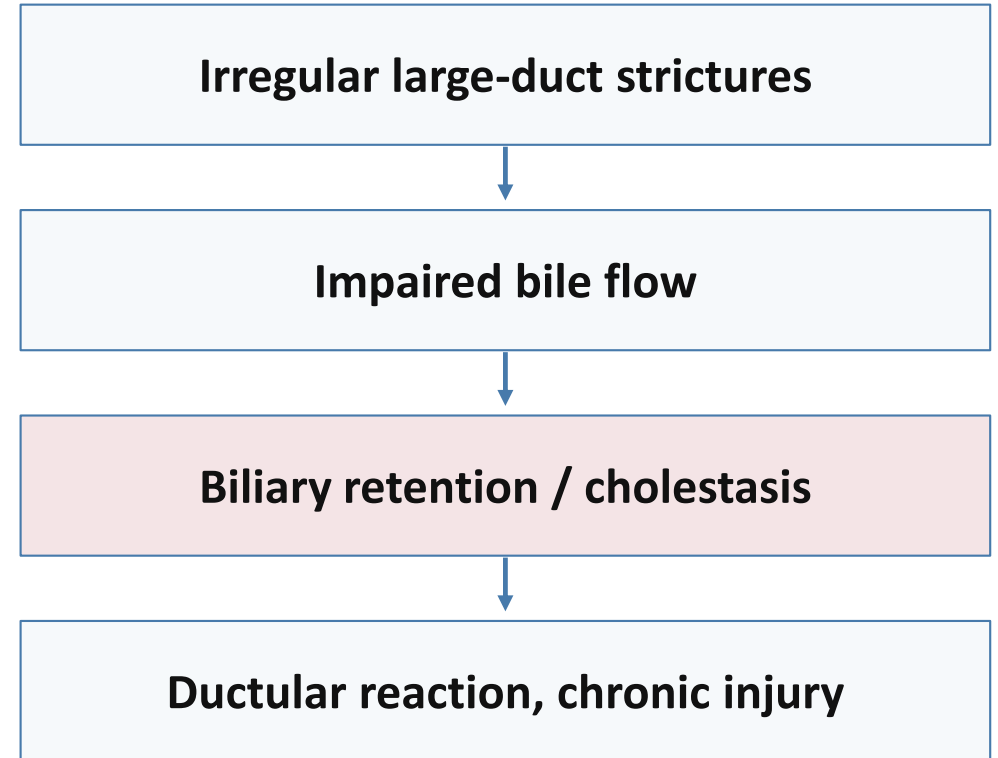
Smaller bile ducts often show indirect injury

- Small intrahepatic ducts are not the principal directly inflamed structures in classic PSC.
- Mild epithelial injury may nevertheless occur.
- A prominent ductular reaction reflects chronic cholestatic stress.

Ductular reaction signals impaired bile drainage

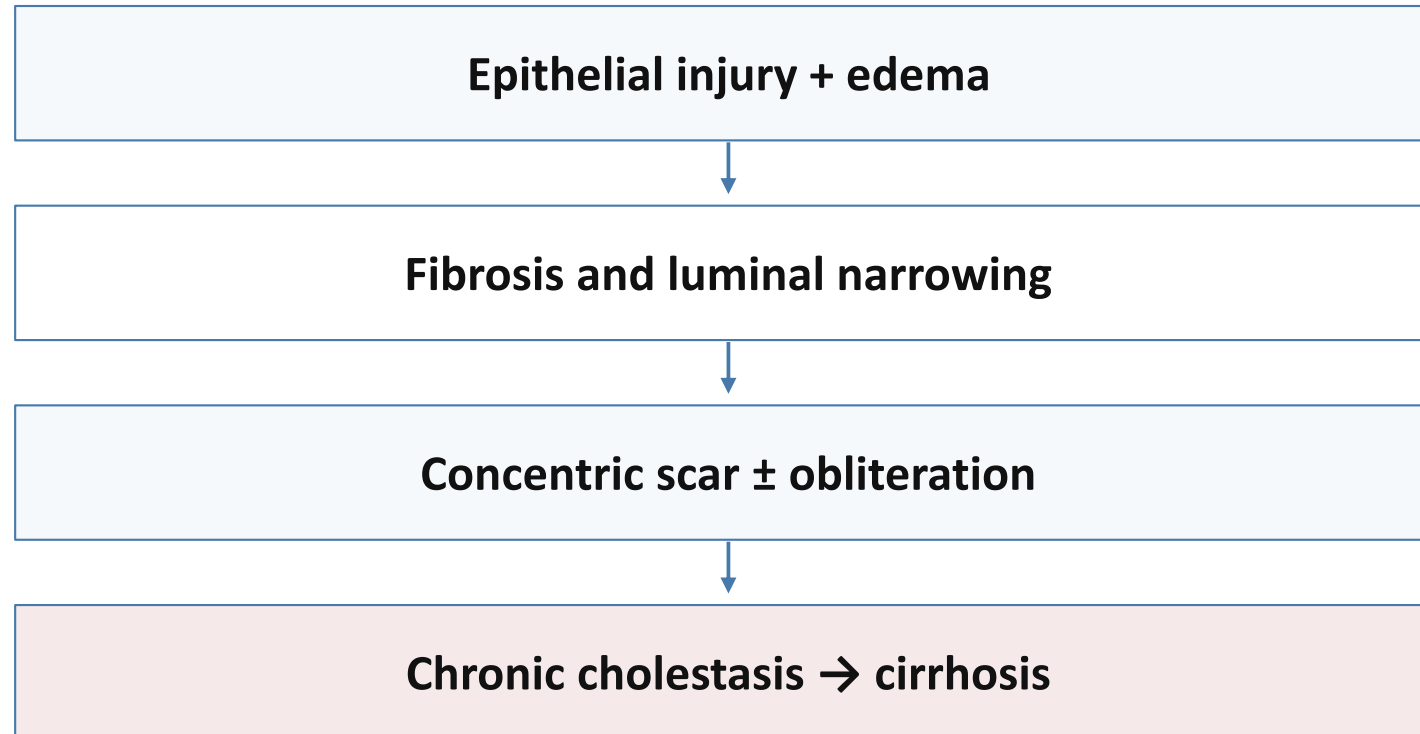
- Duct narrowing impedes normal passage of bile.
- Intrahepatic bile retention accompanies chronic obstructive cholangiopathy.
- Smaller portal areas may react even when the most conspicuous strictures are proximal.

SCHEMATIC — consequence chain



Structural disease evolves toward biliary cirrhosis

SCHEMATIC — structural progression



This is a conceptual sequence; Individual rates of progression vary.

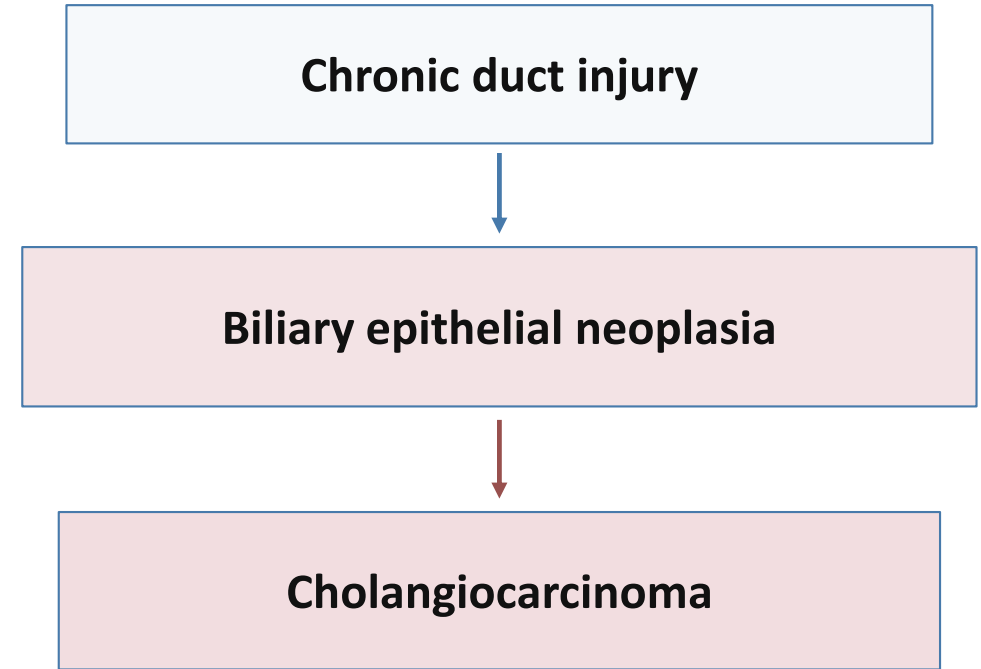
Biliary cirrhosis is the major fibrotic endpoint

- Long-standing duct injury sustains cholestatic hepatocellular stress.
- Fibrosis can extend and eventually remodel the liver.
- End-stage biliary cirrhosis contributes to transplant indications.

Chronic epithelial injury creates a neoplastic risk

- Biliary intraepithelial neoplasia may develop.
- Dysplastic epithelial change can precede cholangiocarcinoma.
- Risk assessment must consider malignancy, not fibrosis alone.

SCHEMATIC — disease-linked pathways



The sequence is a biologic concept, not a claim that all lesions progress.

Cholangiocarcinoma is a feared complication

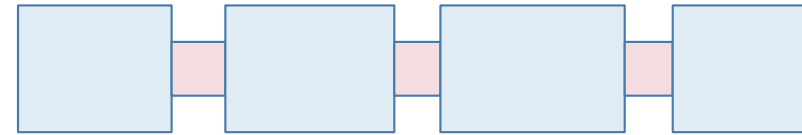
A lifetime cholangiocarcinoma risk of 20%

- The figure is a textbook estimate, not a personalized prediction.
- Persistent biliary epithelial injury is the relevant pathologic context.
- Malignancy may complicate the protracted natural history.

Cholangiography reveals the main duct abnormality

- Irregular strictures alternate with preserved or dilated segments.
- Large intrahepatic and extrahepatic branches can be involved.
- This imaging pattern supplies the main diagnostic visualization.

SCHEMATIC — alternating diameter



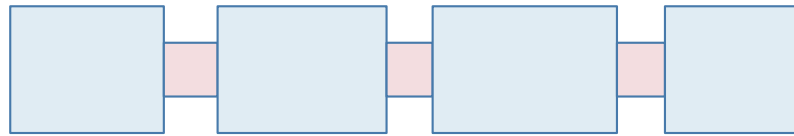
Dilated segment

Fibrotic stricture

Imaging appearance: “beading”

Why cholangiography looks “beaded”

SCHEMATIC — alternating diameter



Dilated segment

Fibrotic stricture

Imaging appearance: “beading”

This figure is an editable schematic, not a patient cholangiogram.

MRCP and ERCP visualize the ductal pattern

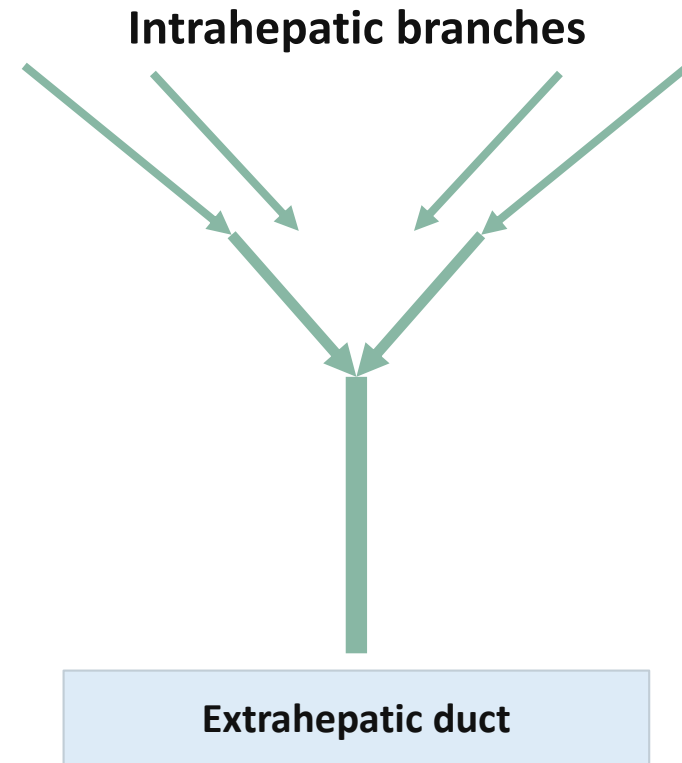
- Magnetic resonance cholangiopancreatography (MRCP) delineates biliary architecture.
- Endoscopic retrograde cholangiopancreatography (ERCP) can also demonstrate strictures and dilatations.
- The Robbins account emphasizes characteristic morphology on duct imaging.

The source excerpt does not compare procedural indications or safety.

Large-duct PSC involves both biliary compartments

- Intrahepatic large ducts may contain multiple narrow segments.
- Extrahepatic duct strictures may coexist.
- Their combined involvement distinguishes classic disease from small-duct PSC.

SCHEMATIC — major duct anatomy



Large ducts: Principal lesions

Small-duct PSC can have normal cholangiography

- A subset has disease confined to smaller intrahepatic ducts.
- The large-duct imaging examination may appear normal.
- An accompanying history of inflammatory bowel disease is common in the source description.

SCHEMATIC — different anatomical targets

LARGE-DUCT PSC

Inflammation → fibrosis → visible strictures

SMALL-DUCT PSC

Small ducts only; Cholangiography normal

Small-duct disease may evolve to large-duct PSC

- Small-duct PSC is not synonymous with a permanently isolated process.
- Some patients subsequently develop the characteristic large-duct phenotype.
- Disease subtype and evolution need to be distinguished.

PSC may be detected before symptoms

- Nearly half of patients are reported asymptomatic when first identified.
- Persistently increased alkaline phosphatase is a common detection route.
- Routine monitoring in ulcerative colitis can lead to discovery.

SCHEMATIC — interpretation framework

Cholestatic presentation / raised ALP



Characteristic duct strictures and dilations



Assess PSC and relevant mimics

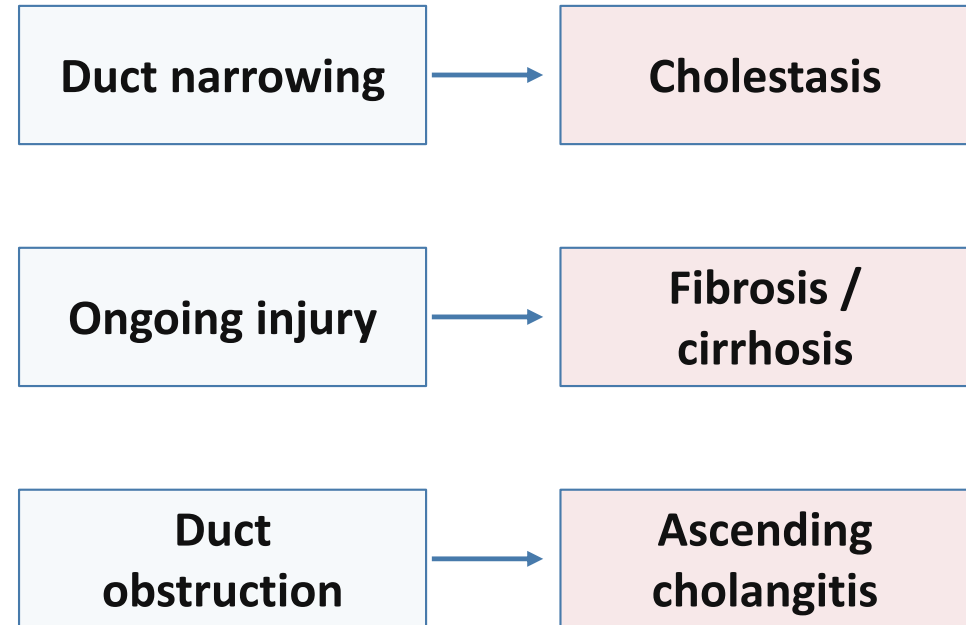
Persistent alkaline phosphatase elevation is a clue

- A biochemical cholestatic pattern can prompt further evaluation.
- Alkaline phosphatase elevation does not by itself diagnose PSC.
- The decisive source-described pattern is ductal alteration on imaging.

Three clinical complaints recur

- Fatigue is a common presentation.
- Pruritus reflects symptomatic cholestatic disease.
- Jaundice may indicate clinically evident impaired bile excretion.

SCHEMATIC — clinicopathologic links



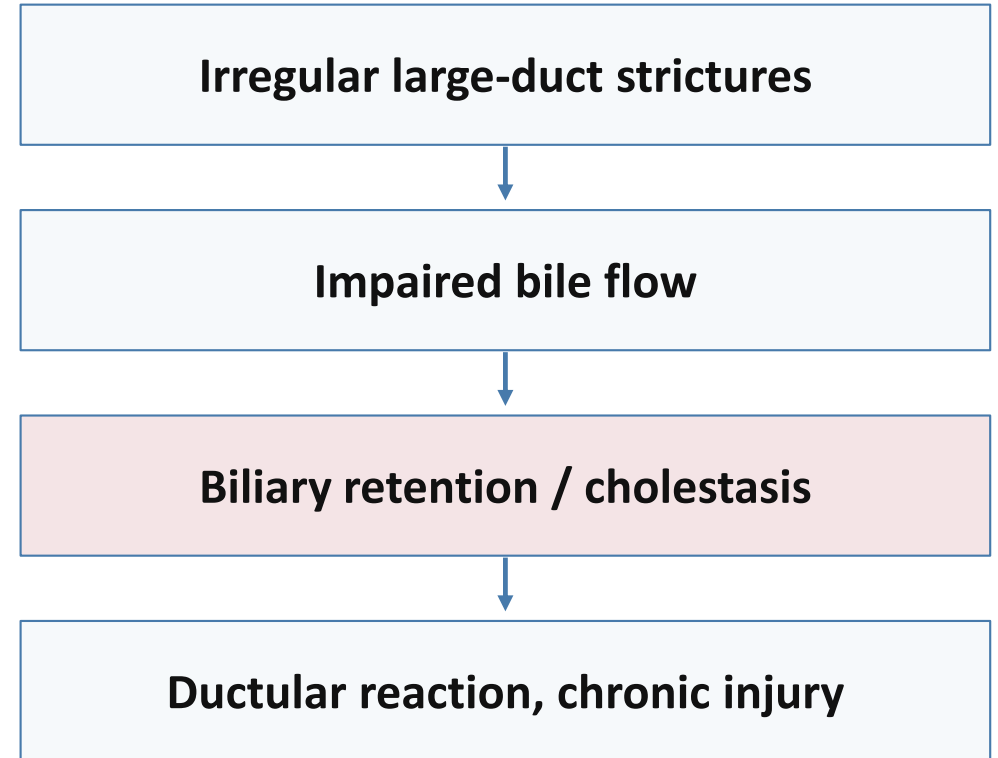
Pruritus accompanies chronic cholestasis

- PSC-associated duct narrowing reduces effective biliary flow.
- Cholestatic disease can produce substantial itching.
- Symptomatic control is distinct from correction of the underlying duct injury.

Jaundice links duct disease to bile retention

- Strictures restrict movement of bile through the tree.
- Retention becomes clinically manifest in some patients.
- Jaundice has to be interpreted alongside the broader cholestatic presentation.

SCHEMATIC — consequence chain



Ascending cholangitis may be the first presentation

- Infected or inflamed obstructed ducts can create an acute clinical episode.
- Ascending cholangitis may reveal previously unrecognized PSC.
- It must be recognized as a complication rather than the defining chronic lesion.

Biliary-associated disease extends beyond the liver

- Chronic cholecystitis can accompany PSC.
- Chronic pancreatitis is also described in association with duct involvement.
- Pancreatic and gallbladder findings may influence the differential diagnosis.

Case: Biochemical detection in ulcerative colitis

A patient with ulcerative colitis has persistently elevated alkaline phosphatase but no jaundice.

- What cholangiographic pattern would make PSC likely?
- Which duct compartments would you assess?
- Why is the absence of symptoms not reassuring?

Case interpretation: Characteristic duct architecture

**Multiple irregular biliary strictures alternating with dilatations suggest classic
PSC.**

- Disease can be present before the classical symptoms develop.
- Large-duct imaging is central to the source-described diagnostic approach.
- A normal study raises a different question: Could this be small-duct PSC?

PSC and PBC: Compare the major clinical patterns

Feature	Primary sclerosing cholangitis	Primary biliary cholangitis
Typical sex	~70% male	~90% female
Median age	~30 years	~50 years
Common association	Inflammatory bowel disease	Sjögren syndrome; autoimmune disorders
Characteristic serology	pANCA may be present; AMA typically negative	AMA frequently positive
Ductal imaging	Large-duct beading / strictures	Usually normal large ducts

The principal duct targets separate PSC from PBC

- PSC: Predominantly large intrahepatic and extrahepatic ducts.
- PBC: Small- and medium-sized intrahepatic ducts.
- The different targets explain why large-duct imaging separates the conditions.

SCHEMATIC — primary duct targets

PBC	PSC
Small intrahepatic bile ducts	Large intrahepatic and extrahepatic ducts
Florid duct lesions	Periductal concentric fibrosis

Morphology: Concentric sclerosis or florid duct lesion

PSC morphology

- Large-duct epithelial injury and periductal concentric fibrosis
- Progressive narrowing and duct obliteration
- Secondary ductular reaction in smaller portal tracts

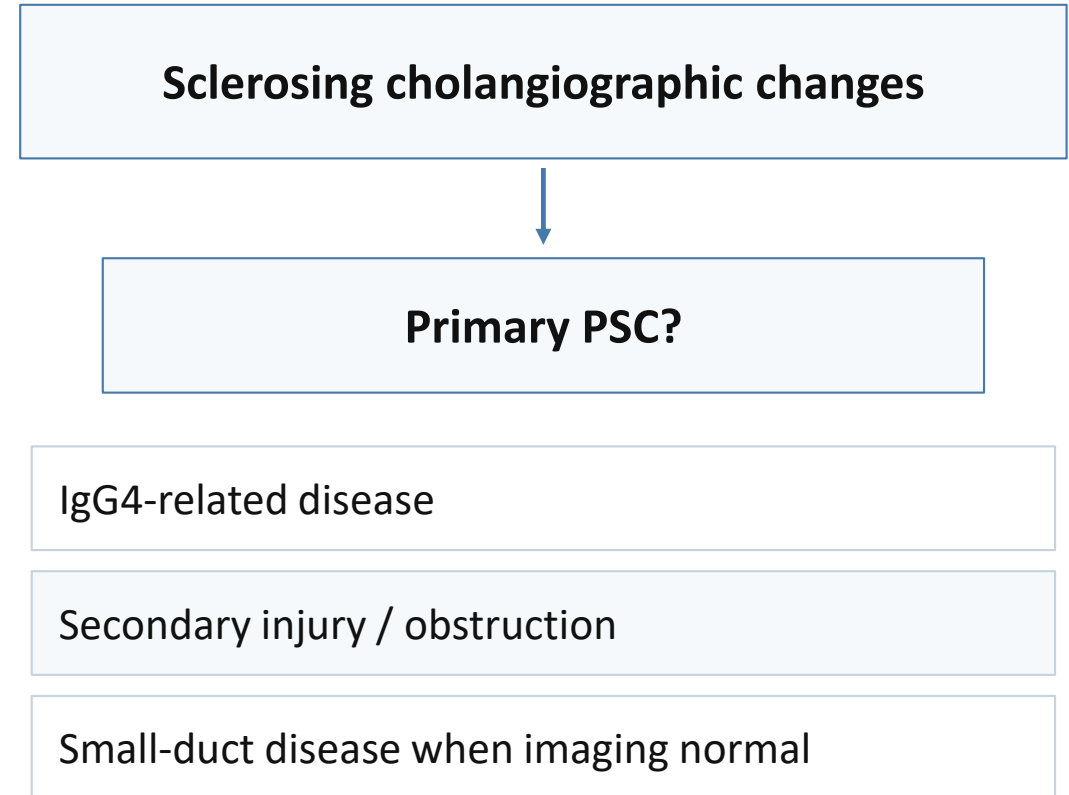
PBC morphology

- Inflammatory destruction of small intrahepatic ducts
- Granulomatous florid duct lesions
- Progressive small-duct loss / ductopenia

IgG4-related sclerosing cholangitis is a key mimic

- The biliary picture may resemble classic PSC.
- It is often associated with pancreatitis.
- It by responsiveness to corticosteroids.

CLINICAL DIFFERENTIAL — editable teaching schema



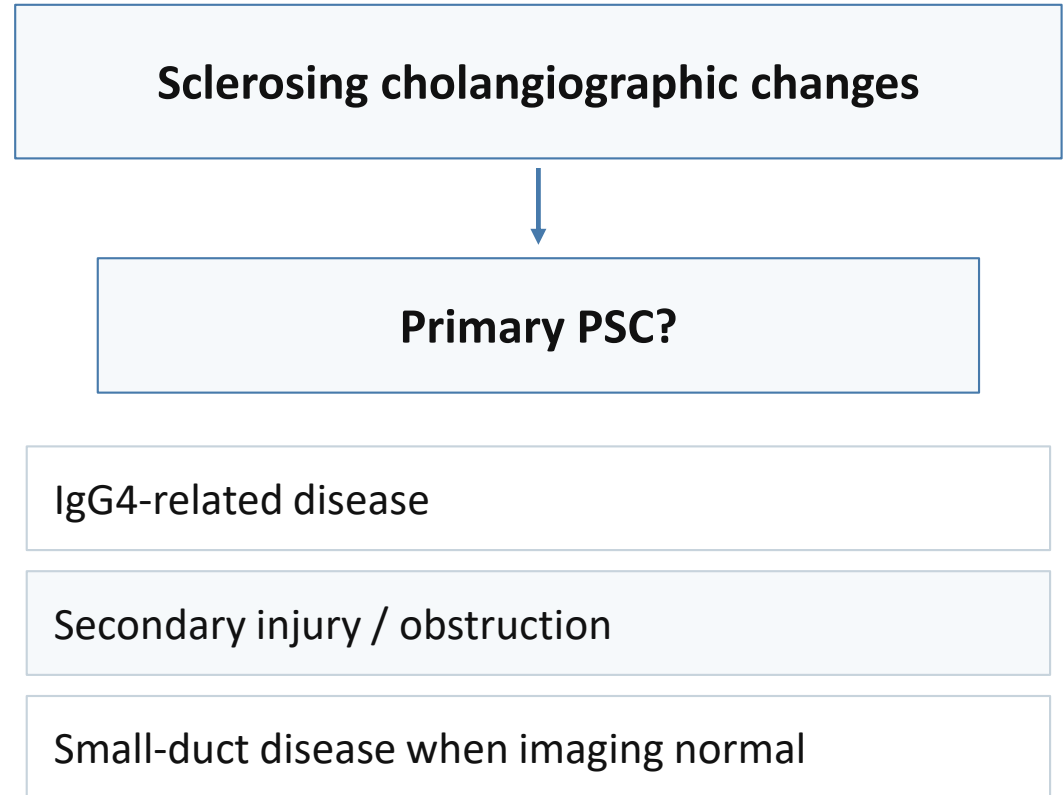
PSC may overlap with autoimmune hepatitis

- Concomitant autoimmune hepatitis in 5%–10% of PSC cases.
- This is an overlap context, not the usual phenotype of isolated PSC.
- Its presence complicates clinicopathologic interpretation.

Secondary sclerosing cholangitis must be considered

- A PSC-like sclerosing duct pattern is not necessarily primary.
- Long-standing obstruction and ischemic injury are alternative causes.
- A focused causal assessment prevents erroneous attribution to PSC.

CLINICAL DIFFERENTIAL — editable teaching schema



Drug injury and infection may mimic PSC

- Ketamine is an example of a drug linked with secondary sclerosing injury.
- CMV, HIV, and COVID-19 are among infections discussed as causes.
- The mechanism and context differ from primary disease.

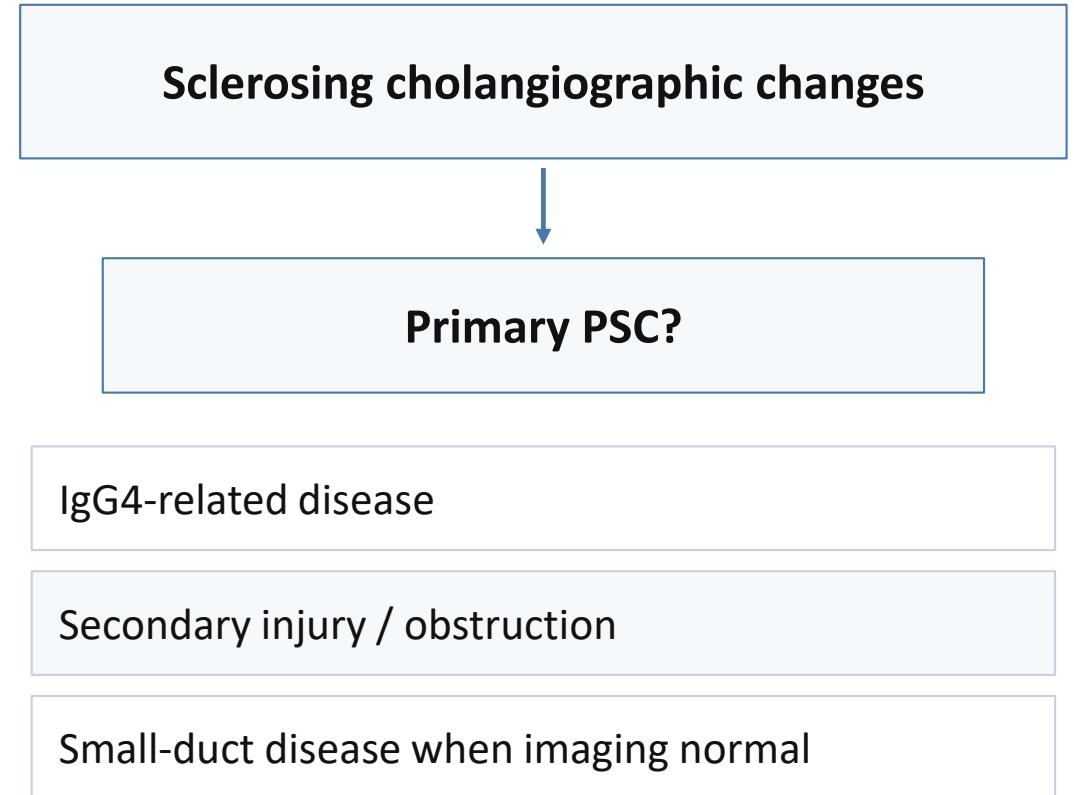
Transporter defects belong in the secondary differential

- Late-onset bile transporter defects can produce a PSC-like biliary phenotype.
- MDR3 deficiency is the example named.
- The existence of a phenocopy means imaging must be interpreted in context.

A careful differential begins with disease context

- Exclude obstructive or ischemic causes.
- Consider IgG4-related sclerosing disease and pancreatic findings.
- Recognize small-duct PSC when classic imaging changes are absent.

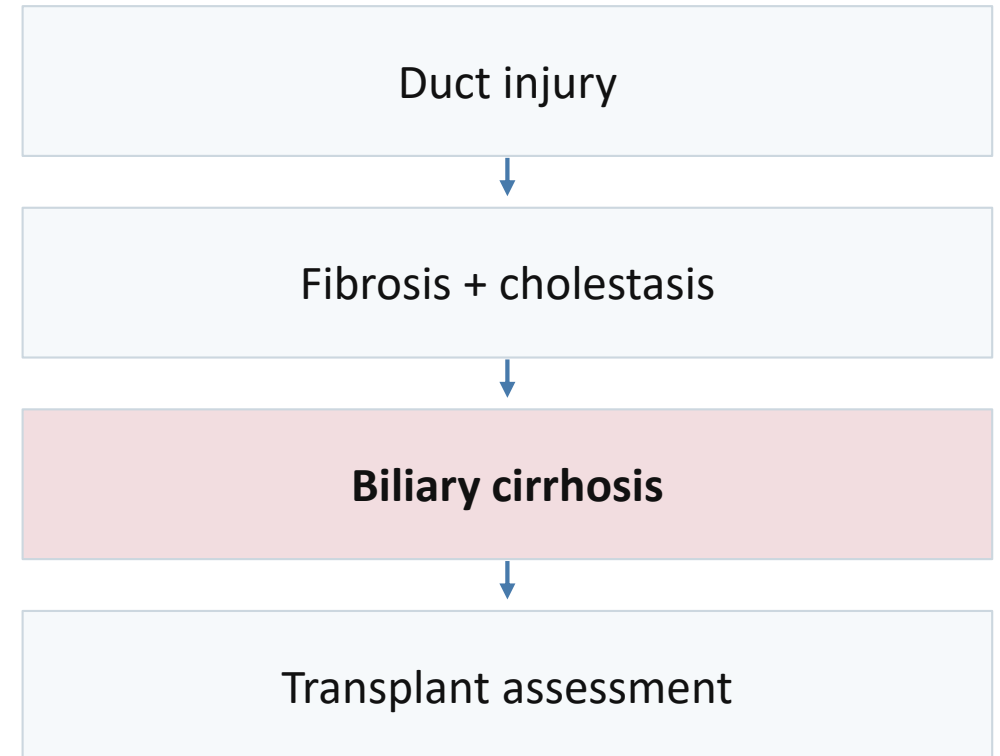
CLINICAL DIFFERENTIAL — editable teaching schema



The clinical course can be prolonged and progressive

- The source describes a course extending approximately 10–15 years toward cirrhosis.
- This is a general natural-history summary, not a fixed time for an individual.
- Fibrosis, cholestatic symptoms, and malignant complications can all affect outcomes.

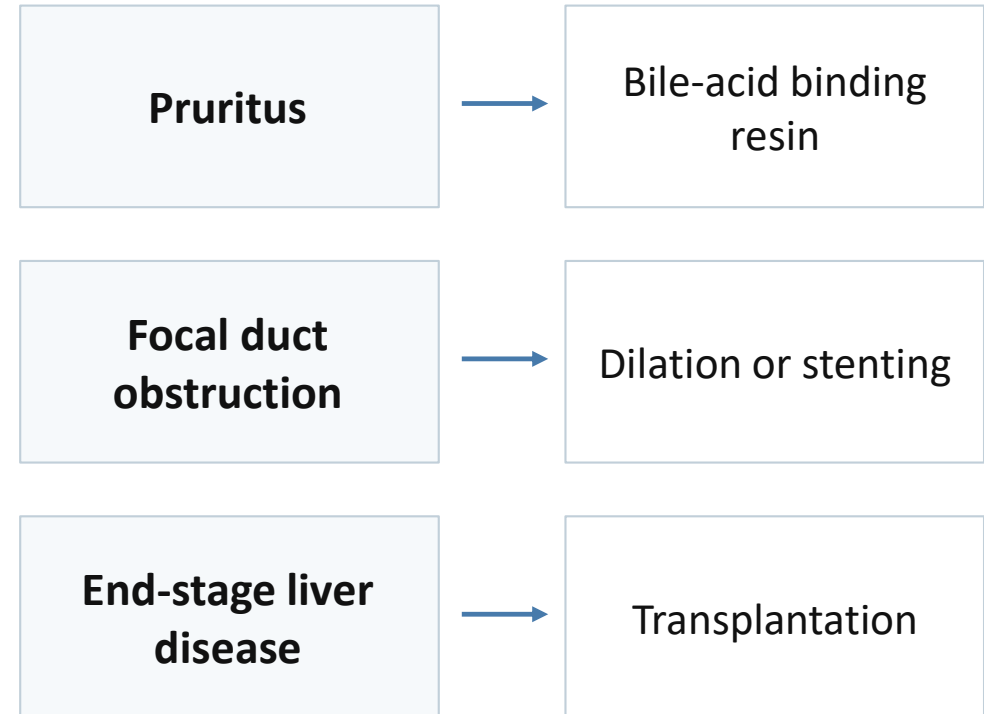
SCHEMATIC — long-term course



Management addresses distinct clinical problems

- Cholestyramine is used to relieve pruritus.
- Endoscopic dilation or stenting may relieve biliary obstruction.
- Liver transplantation is used for end-stage disease.

SCHEMATIC — management target, not cure



A medical cure is not established account

- No established medical therapy that reverses PSC.
- Ursodeoxycholic acid is discussed in relation to clinical trials.
- Relief of symptoms or strictures does not imply elimination of underlying disease.

This slide reflects the supplied textbook, not an independently updated treatment guideline.

Case: Progressive strictures and cholangitis

A patient with established PSC develops jaundice and episodes of ascending cholangitis.

- What duct-level process may explain deterioration?
- Which intervention directly addresses an obstructed segment?
- Why does management also require long-term risk assessment?

Case interpretation: Injury, obstruction, consequence

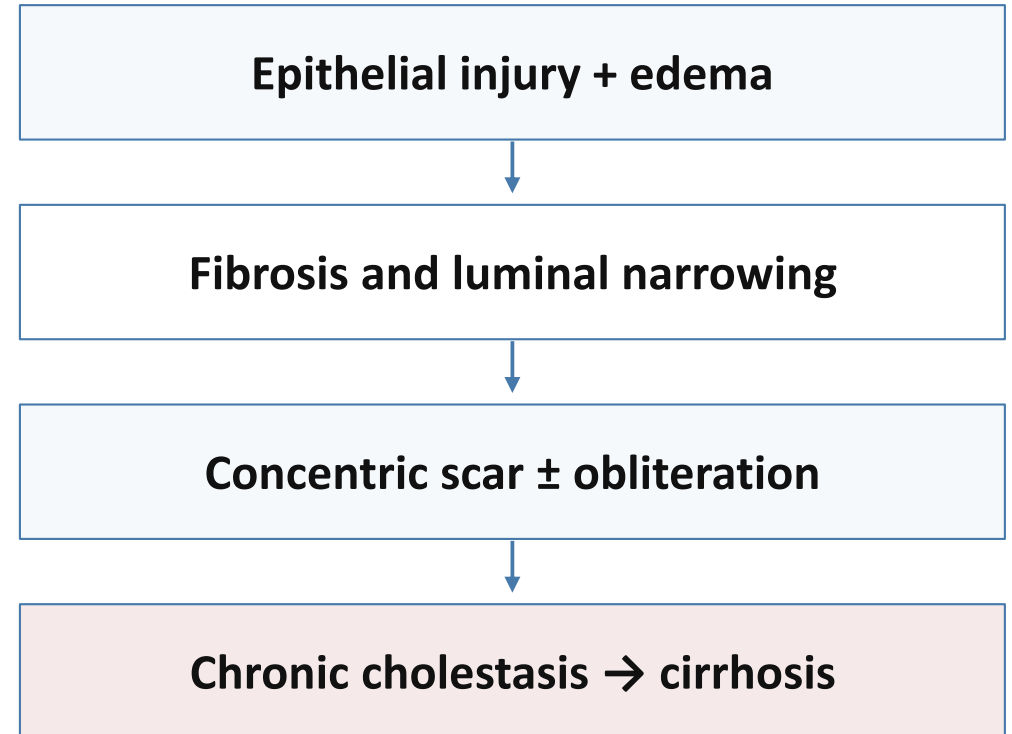
Worsening stricture can impair drainage, while chronic injury continues.

- Endoscopic dilation or stenting may address obstruction.
- Repeated injury can sustain fibrosis and eventually biliary cirrhosis.
- Cholangiocarcinoma remains a significant associated long-term risk.

Integrating the disease in one causal map

- Susceptibility and uncertain environmental triggers are associated with immune injury.
- Large-duct inflammation and concentric fibrosis produce irregular strictures.
- Cholestasis, complications, and biliary cirrhosis follow downstream.

SCHEMATIC — structural progression



Four high-yield distinctions

- PSC primarily injures large intrahepatic and extrahepatic ducts.
- “Onion-skin” periductal fibrosis and cholangiographic beading are characteristic.
- Ulcerative colitis is a strong association; PANCA is not a specific diagnostic signature.
- Always consider IgG4-related and secondary sclerosing conditions, plus cholangiocarcinoma risk.

Principal reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Source section: primary sclerosing cholangitis within autoimmune cholangiopathies.
- All native diagrams are conceptual schematics, not clinical images or microscopic specimens.
- Management and numerical risk estimates reflect the supplied textbook account.