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Demystifying Idiopathic Adulthood Ductopenia: Diagnosis and Differential Diagnosis

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Abstract: Idiopathic adulthood ductopenia (IAD) is a rare chronic cholestatic liver disorder characterized by progressive loss of interlobular bile ducts in the absence of an identifiable etiology. Its histologic hallmark, ductopenia, is nonspecific and occurs across many cholestatic disorders, which complicates its recognition. IAD is therefore a diagnosis of exclusion, requiring thorough evaluation to rule out immune-mediated cholangiopathies, infections, genetic or metabolic diseases, drug-induced injury, and neoplasia. Advances in molecular diagnostics have increasingly uncovered monogenic cholangiopathies in adults previously classified as IAD, thereby narrowing the truly idiopathic category. In this article, we provide a comprehensive review of the disease, with emphasis on its clinical presentation, histopathologic characteristics, differential diagnoses, and emerging concepts.

Key Words: idiopathic adulthood ductopenia, cholestatic liver disorder, ductopenia, histology, liver

(*Adv Anat Pathol* 2026;00:000–000)

I diopathic adulthood ductopenia (IAD) is a rare chronic cholestatic liver disease characterized by the progressive loss of small intrahepatic bile ducts in the absence of an identifiable underlying cause, such as autoimmune, infectious, genetic, or drug-induced cholangiopathy. The term was first introduced by Ludwig et al¹ in 1988 based on 3 defining criteria: (1) its idiopathic nature, (2) clinicopathologic features resembling neonatal or infantile non-syndromic paucity of intrahepatic bile ducts but with adult onset, and (3) histology of ductopenia.

Despite overlapping morphology and terminology, IAD is distinct from vanishing bile duct syndrome (VBDS) and should not be conflated. VBDS refers to a ductopenic pattern secondary to an identifiable insult, most commonly drug-induced cholestasis or immune-mediated injury such as graft-versus-host disease (GVHD), allograft rejection, or primary biliary cholangitis (PBC), and may improve with removal or treatment of the underlying cause.²

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To date, only a limited number of IAD cases have been reported, and the disease is poorly understood. The pathogenesis, clinicopathologic features, therapeutic strategies, and prognosis of the disease remain insufficiently defined. Here, we reviewed the available literature on IAD, with the aim of synthesizing current knowledge, clarifying its diagnostic boundaries, and highlighting emerging insights relevant to patient management and future research. Given the diagnostic challenges and lack of standardized management strategies, advancing our understanding of IAD is essential both for improving outcomes in affected patients and for refining the broader classification of chronic cholestatic liver diseases.

PATHOGENESIS

By definition, the underlying etiology of IAD is unknown, although several potential causes have been proposed (Table 1).^{3–5} Bile duct loss may result from a variety of factors, including immunologic, ischemic, infectious, metabolic, genetic, and toxic processes.⁶ Cholangiocyte death represents a central pathogenic mechanism in ductopenic cholangiopathies, regardless of the underlying etiology.^{6,7}

Interestingly, IAD has also been reported in familial settings. For example, Burak et al⁸ described a series of adult-onset ductopenia affecting 5 members of an extended family across 3 generations, suggesting a potential genetic contribution to IAD. Indeed, a single missense mutation in the *ABCB4* gene was identified as the cause of ductopenic chronic cholestatic liver disease in adulthood that affected several siblings within one family.⁹ Moreover, *ABCB4* variants have also been detected in sporadic ductopenic cases.^{10,11} In addition, one study reported increased frequencies of multiple *HLA-DRB1* alleles in patients with mild IAD (defined as bile duct loss in <50% of portal tracts), further suggesting an immunogenetic basis of susceptibility.¹²

EPIDEMIOLOGY

In a large cohort of 2082 patients with small-duct biliary diseases, IAD accounted for only ~1% of cases, whereas PBC and primary sclerosing cholangitis (PSC) together comprised 93% of cases.¹³ A PubMed search identified 14 case reports published between 2000 and 2025, encompassing a total of 15 sporadic patients with IAD (Table 2). The reported patients ranged in age from 17 to 67 years, with a median age of 34 years and a mean age of 36.9 years. The sex distribution was equal (M:F = 1:1.1), in contrast to the earlier series by Ludwig,¹³ which showed a male predominance (M:F = 1.8:1), despite the same median age of 34 years.

CLINICAL PRESENTATIONS

As shown in Table 2, jaundice is the most frequently reported clinical sign/symptom, followed by pruritus and

TABLE 1. Potential Etiopathogenesis of IAD

Late-onset of nonsyndromic paucity of intrahepatic bile ducts
Autoimmune-related cholangiopathy
sd-PSC
Autoimmune cholangitis
Genetic defects
ABCB4 (MDR3)
ABCB11 (BSEP)
HLA-DR
Conditions with a potential specific etiology
Infections
Drugs or toxins
Paraneoplastic syndromes

ABCB indicates ATP-binding cassette subfamily B; BSEP, bile salt export pump; HLA, human leukocyte antigen; IAD, idiopathic adulthood ductopenia; MDR, multidrug resistance protein; sd-PSC, small-duct primary sclerosing cholangitis.

fatigue. About one-third of patients are asymptomatic at diagnosis, with IAD detected incidentally during evaluation for abnormal liver function tests. In most cases, symptoms and/or abnormal liver tests persist for more than 2 years, reflecting a chronic and progressive disease course. Overall, the clinical presentations of IAD are nonspecific and overlap with those of other chronic cholestatic liver diseases such as PBC and PSC. Its variable onset and frequent incidental detection underscore the diagnostic challenge that continues to obscure recognition of the disease.

LABORATORY FINDINGS

Laboratory findings in patients with IAD consistently show a cholestatic pattern of liver injury, characterized by elevated serum alkaline phosphatase (ALP), γ -glutamyl-transferase (GGT), and total bilirubin levels in nearly all reported cases (Table 2). In some instances, ALP and/or GGT levels exceeded 1000 U/L.^{18,22,23,25,27} Mild to moderate elevations in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (<300 U/L) have also been documented in most cases. In only one reported case,²⁷ both AST and ALT levels exceeded 300 U/L (AST 393, ALT 574). Workup for viral and autoimmune etiologies was uniformly negative, except for one case that tested positive for hepatitis C virus (HCV) antibody and RNA.²⁴ Notably, earlier studies have suggested that chronic HCV infection may be associated with bile duct damage and rarely cause ductopenia, particularly in the setting of advanced fibrosis, immunosuppression, or interferon therapy.^{24,28} Whether this case should be labeled as IAD is therefore debatable, although HCV as an independent cause of VBDS remains unproven.

IMAGING FINDINGS

The most common radiologic finding is a liver with a normal appearance. Reported abnormalities include hepatomegaly or hepatosplenomegaly, cirrhosis, and fatty liver (Table 2). Mild intrahepatic duct irregularities and cholelithiasis—potentially associated with biliary obstruction—have each been documented in a single case.^{22,24} Overall, the predominance of normal or nonspecific findings highlights the limited sensitivity of radiologic assessment for IAD and underscores the central role of histopathologic evaluation in establishing the diagnosis.

HISTOLOGIC DIAGNOSIS

The normal intrahepatic biliary tree is conventionally divided into large and small bile ducts according to their anatomic location and luminal caliber. Large intrahepatic bile ducts correspond to the first- and second-order branches situated distal to the septal ducts, and typically have relatively wide lumina (100 to 800 μ m in diameter). These ducts are lined by tall columnar or pseudostratified epithelium, often contain mucin-secreting cells, and are encased by a well-developed fibromuscular wall. Small bile ducts refer primarily to the interlobular and proximal septal ducts, with luminal diameters of <100 μ m. Interlobular bile ducts are lined by a single layer of cuboidal to low columnar nonmucinous epithelial cells and serve as the key structures for evaluating ductopenia in histopathologic assessment.²⁹

Histologically, IAD is defined by the absence of interlobular bile ducts in at least 50% of portal tracts on liver biopsy (Fig. 1A). Additional findings may include nonspecific portal inflammation, usually minimal to mild and predominantly lymphocytic, as well as sequelae of ductopenia such as cholestasis, cholate stasis, and copper deposition. Mild ductular reaction may be present, which must be distinguished from native bile ducts. The remaining bile ducts may exhibit variable degrees of epithelial injury. Periportal fibrosis and features of biliary cirrhosis can also be observed. Importantly, histologic hallmarks of other biliary disorders, such as granulomatous cholangiopathy, florid duct lesion, periductal concentric fibrosis, or suppurative cholangitis, should be absent.

PITFALLS IN HISTOLOGIC DIAGNOSIS

While IAD is conventionally defined by the absence of interlobular bile ducts in $\geq 50\%$ of portal tracts, it has been proposed that the disorder may exist along a spectrum.³⁰ Some authors classify cases with <50% duct loss as mild or type 1 IAD, although these cases fall outside the strict definition of IAD and may represent early or limited disease. These patients typically follow an indolent course and often respond to ursodeoxycholic acid (UDCA).¹⁹ In contrast, type 2 is characterized by more extensive ductopenia ($\geq 50\%$) and carries a higher risk of progression to decompensated biliary cirrhosis, ultimately necessitating liver transplantation.^{26,27,31}

In a healthy liver, the ratio of interlobular bile ducts to portal tracts ranges from 0.9 to 1.8. Ductopenia is diagnosed when this ratio falls below 0.5.²⁷ The diagnostic accuracy depends critically on adequate sampling, as evaluation requires a sufficient number of well-oriented and well-preserved portal tracts. It is generally recommended that 6 to 11 portal tracts be present for a reliable diagnosis.^{32,33} However, the diagnosis can be suggested when fewer portal tracts are available. Notably, in one published report,²³ only 3 portal tracts were evaluated, raising potential concerns regarding diagnostic reliability in that case. Another study demonstrates that unpaired hepatic artery-based assessment is more sensitive than the traditional criterion for diagnosing ductopenia, particularly in biopsies with limited portal tract sampling.³⁴

IDENTIFICATION OF INTERLOBULAR BILE DUCTS

In normal portal tracts, hepatic arteries, portal veins, and bile ducts typically form a classic portal triad (Fig. 1B). Portal dyads, in which one component (usually the portal

TABLE 2. Overview of Published Reports of IAD

Report	References	Age (y)/sex	Clinical presentation	Disease duration	Abnormal lab findings	Imaging findings	Biopsy findings	Treatment & Outcome
1	Li et al ¹⁴	24/M	Intermittent jaundice, fatigue, anorexia, dark urine	8 y	Elevated bilirubin and liver enzyme levels	Normal	Lack of bile ducts in 5 of 9 portal tracts, cholestasis, mild to moderate lymphocytic interlobular cholangitis	N/A
2	Zhang et al ¹⁵	27/F	Asymptomatic	5 y	Elevated AST, ALT, ALP, and GGT levels	Diffuse fatty liver or chronic liver injury	Lack of bile ducts in >50% of portal tracts, focal interface inflammation	UDCA, effective
3	Douglass et al ¹⁶	67/M	Abdominal pain, jaundice	10 d	Elevated AST, ALT, ALP, and bilirubin levels	Cirrhosis with perihepatic ascites	Lack of bile ducts in 8 of 10 portal tracts, cirrhosis, hepatocyte ballooning, cholestasis	Rapid deterioration, died of septic shock
4	Bilal et al ¹⁷	34/F	Asymptomatic	NA	Elevated ALP and GGT levels	Normal	Lack of bile ducts in 60% of portal tracts, mild steatosis, stage 2 fibrosis	UDCA, effective
5	Chomicki and		Dahmani ¹⁸	55/F	Chronic renal failure, mild jaundice, pruritus	NA	Elevated AST, ALT, ALP, and GGT levels	Normal
Bile ducts loss improved								
6	Kaung et al ¹⁹	50/M	Jaundice, scleral icterus	2 y	Elevated AST, ALT, ALP, GGT, and bilirubin levels	Normal	Lack of bile ducts in 4 of 15 portal tracts, cholestasis, mild periportal fibrosis	UDCA, ineffective
7	Yang et al ²⁰	17/M	Recurrent skin and scleral jaundice, pruritus	3 y	Elevated ALP and bilirubin levels	Hepatosplenomegaly	Lack of bile ducts in >50% of portal tracts, cholestasis, mild to moderate chronic hepatitis	UDCA, effective
8	Peniche-Moquel et al ²¹	20/M	Fatigue, weakness, pruritus	6 mo	Elevated AST, ALT, ALP, and GGT levels	Normal	Lack of bile ducts in >50% of portal tracts, sparse chronic inflammatory infiltrate	UDCA, mildly effective
9	Park et al ²²	19/M	Asymptomatic	4 y	Elevated AST, ALT, ALP, and GGT levels	Mild intrahepatic duct irregularities	Lack of bile ducts in 11 of 19 portal tracts, mild chronic inflammation	UDCA, effective
10	Zhang et al ²³	26/F	Fatigue, pruritus, jaundice	1.5 y	Elevated AST, ALT, ALP, GGT and, bilirubin levels	Mild	Hepatosplenomegaly	Lack of bile ducts in 3 of 3 portal tracts, cholestasis
UDCA, ineffective								
11	Dural et al ²⁴	53/M	Asymptomatic	NA	Elevated AST, ALT, ALP, and bilirubin levels, HCV ⁺	Cholelithiasis	Lack of bile ducts in all portal tracts, chronic cholestasis, mild spotty necrosis, and patchy portal fibrosis	N/A
12	Rios et al ²⁵	44/F	Fatigue, pruritus, jaundice, dark urine, pale stools	3 y	Elevated AST, ALT, ALP, and bilirubin levels	Hepatomegaly	Ductopenia, cholestasis, fibrosis	Liver transplant, no recurrent cholestasis for 7 y
13		30/F		4 mo		Mild hepatomegaly		

TABLE 2. (continued)

Report	References	Age (y)/sex	Clinical presentation	Disease duration	Abnormal lab findings	Imaging findings	Biopsy findings	Treatment & Outcome
14	Khanlou et al ²⁶ Dominguez-Antonaya et al ²⁷	44/F	Fatigue, jaundice, pruritus Right upper quadrant pain, jaundice, nausea	3 wk	Elevated AST, ALT, GGT, ALP, and bilirubin levels Elevated AST, ALT, GGT, ALP, and bilirubin levels		Lack of bile ducts, marked cholestasis, portal inflammation, fibrosis (biliary cirrhosis) Lack of bile ducts in 4 of 10 portal tracts, bile duct injury, and cholestasis. Repeat biopsy 10 mo later: no bile ducts in any of the portal tracts, replaced by concentric fibrosis and slight inflammatory infiltrate, bridging fibrosis	UDCA, ineffective; liver transplant, effective UDCA, ineffective initially but becoming effective 19 mo later
		44/F	Asymptomatic	2 y	Elevated ALP, GGT, and bilirubin levels	Normal	Lack of bile ducts in all 11 portal tracts, portal inflammatory infiltrate	UDCA effective

+ indicates positive; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; GGT, γ -glutamyltransferase; HCV, hepatitis C virus; IAD, idiopathic adulthood ductopenia; M, male; NA, not available; UDCA, ursodeoxycholic acid.

vein) is missing, are nearly as common as triads in peripheral liver tissue. Within individual portal tracts, interlobular bile ducts and hepatic arterial branches of comparable caliber run in parallel, a feature that is particularly useful for assessing bile duct loss.³⁵ Quantitatively, the mean ratio of bile duct to arterial branches, based on their respective volume fractions, is estimated at 1.72.³⁶

Mild ductopenia (< 50%) may be easily overlooked on liver biopsy.³⁷ Portal inflammation can also obscure the recognition of bile ducts on routine stains.⁶ In such cases, immunostaining for biliary cytokeratins (CK7 and CK19) can aid in bile duct identification. It should be noted that CK7 may become expressed in periportal and even intra-lobular hepatocytes (biliary metaplasia) in ductopenic conditions, which can occasionally complicate interpretation.³⁸ Reactive ductules also show CK7 and CK19 positivity and should not be mistaken for interlobular bile ducts. These small structures (< 15 to 20 μ m) lie along the periphery of portal tracts near the limiting plate, may be directly abut hepatocytes, and lack an accompanying hepatic artery.³⁴ In addition, EMA has been reported to highlight the brush border of true interlobular bile ducts but not proliferating ductules, which may serve as a useful adjunct marker to aid in their distinction.³⁹ However, its utility in this regard has not been validated by additional studies.

TREATMENT AND PROGNOSIS

UDCA remains the mainstay of medical therapy for IAD, with reported benefits on both biochemical and histologic parameters, as well as in reducing the need for liver transplantation in chronic cholestatic liver diseases.^{27,31} In published cases (Table 2), two-thirds (10/15) of patients received UDCA, of whom 70% demonstrated symptomatic and/or biochemical improvement. Among the 3 nonresponders, 1 had mild (type 1) IAD,¹⁹ 1 had cirrhosis,²⁶ and 1 had a liver biopsy containing only 3 portal tracts, limiting diagnostic accuracy.²³ All 7 responders had type 2 IAD. Notably, one patient had an initial biopsy that showed type 1 disease, but a repeat biopsy revealed type 2. This patient failed to respond to UDCA initially but became responsive 19 months later for unclear reasons.²⁷

The prognosis of IAD is heterogeneous, ranging from an indolent course to progressive disease. As summarized in Table 2, significant liver fibrosis was reported in 4 of 15 (27%) published cases. One patient died of septic shock,¹⁶ and 2 underwent liver transplantation with no disease recurrence.^{25,26} The remaining patient had bridging fibrosis.²⁷ In addition, periportal or stage 2 fibrosis was reported in 2 patients.^{17,19} Another patient was reported to have patchy portal fibrosis and mild spotty necrosis on liver biopsy, which could be attributed to concurrent HCV infection.²⁴

DIFFERENTIAL DIAGNOSIS

Pediatric Cholestatic Liver Diseases

The distinction of IAD from pediatric cholestatic liver diseases associated with bile duct paucity (Table 3) relies primarily on patient's age at presentation. These conditions can be broadly categorized as syndromic or nonsyndromic. Syndromic disorders, such as Alagille syndrome (Fig. 2A), typically involve multiple organs,⁴⁰ whereas nonsyndromic entities include biliary atresia (Fig. 2B),⁴¹ α -1 antitrypsin deficiency,⁴² cystic fibrosis,⁴³ and various forms of progressive familial intrahepatic cholestasis.⁴⁴ Despite considerable

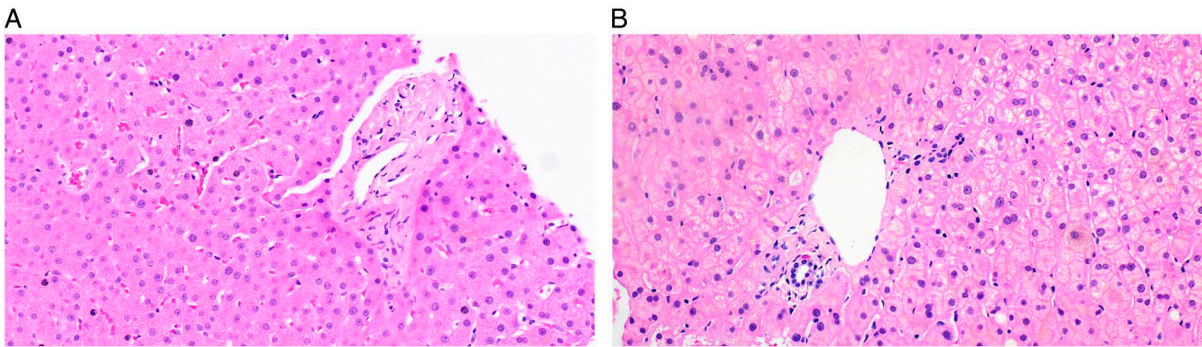


FIGURE 1. Idiopathic adulthood ductopenia (A). A liver biopsy from a 57-year-old patient showing no bile ducts in portal tracts. There is no significant portal or lobular inflammation (H&E, original magnification $\times 200$). B, A normal portal tract with bile duct, hepatic artery, and portal vein (H&E, original magnification $\times 200$).

heterogeneity in hepatic manifestations, neonatal cholestasis is the most common clinical presentation.^{45–50} Diagnosis is guided by age of onset, clinical features, and genetic findings. While most cases present in infancy or early childhood, milder or atypical phenotypes may remain unrecognized until adulthood.^{11,40,51} Such late-onset presentations can pose substantial diagnostic challenges, as they may mimic other causes of bile duct loss, including IAD. In these circumstances, molecular testing is essential for establishing an accurate diagnosis.^{11,52}

Primary Biliary Cholangitis (PBC)

PBC is a chronic autoimmune cholestatic liver disease and represents the most common cause of ductopenia in adults.^{43,53} While ductopenia typically develops in the late stages of the disease with bridging fibrosis or cirrhosis, it

also occurs in a minority of patients at earlier stages without significant fibrosis. It has been shown that early-stage ductopenia is associated with more pronounced biochemical abnormalities and poorer response to therapy.⁵⁴ Distinguishing ductopenic PBC from IAD relies primarily on the presence of serum antimitochondrial antibodies (AMA). In cases of AMA-negative PBC (also referred to as autoimmune cholangitis), hypergammaglobulinemia (predominantly elevated serum IgM levels) and PBC-specific antinuclear antibodies are helpful. Histologically, PBC is characterized by progressive destruction of intrahepatic bile ducts, most commonly manifesting as florid duct lesion and/or granulomatous cholangiopathy (Fig. 3).^{37,55} These classic histologic features should not be observed in IAD, although mild lymphocytic infiltrates can be seen.

TABLE 3. Pediatric Cholestatic Liver Diseases With Ductopenia

Disease	Pathogenesis	Clinical features	Liver histology
Alagille syndrome	Autosomal dominant (<i>JAG1</i> or <i>NOTCH2</i> genes)	Facial features, posterior embryotoxon, congenital heart defects, vertebral anomalies, hepatic involvement, renal and vascular abnormalities	Ductopenia, cholestasis, mild ductular reaction, progressive fibrosis leading to biliary cirrhosis
Biliary atresia	Viral infections, toxins, genetic variants, immune dysregulation, maternal microchimerism, vascular insults, developmental anomalies, idiopathic	Neonatal jaundice	Portal expansion with edema, prominent ductular reaction, and mixed inflammation with frequent neutrophils, cholestasis, occasional ductopenia, progressive fibrosis leading to biliary cirrhosis
Alpha-1 antitrypsin deficiency	Autosomal codominant (<i>SERPINA1</i> gene)	Neonatal jaundice, hepatitis, panacinar emphysema	PAS-positive, diastase-resistant globules in periportal hepatocytes, bile duct paucity
Cystic fibrosis	Autosomal recessive (<i>CFTR</i> gene)	Multisystem disease mainly affecting the lungs, gastrointestinal tract, and liver	Steatosis, cholestasis, inspissated eosinophilic concretions in dilated ductules, ductopenia, OPV, NRH, focal biliary fibrosis, biliary cirrhosis
Progressive familial intrahepatic cholestasis	Autosomal recessive (<i>ATP8B1</i> , <i>ABCB11</i> , <i>ABCB4</i> , <i>TJP2</i> , <i>NR1H4</i> , <i>MYO5B</i> genes)	Pruritus, jaundice	Cholestasis, ductular reaction, ductopenia, giant cell transformation, progressive fibrosis leading to cirrhosis

ABCB indicates ATP-binding cassette subfamily B; *ATP8B1*, ATPase phospholipid transporting 8B1; *CFTR*, cystic fibrosis transmembrane conductance regulator; *JAG1*, jagged canonical Notch ligand 1; *MYO5B*, myosin VB; *NOTCH2*, notch receptor 2; *NR1H4*, nuclear receptor subfamily 1 group H member 4; NRH, nodular regenerative hyperplasia; OPV, obliterative portal venopathy; PAS, periodic acid-Schiff stain; *SERPINA1*, serine protease inhibitor clade A member 1; *TJP2*, tight junction protein 2.

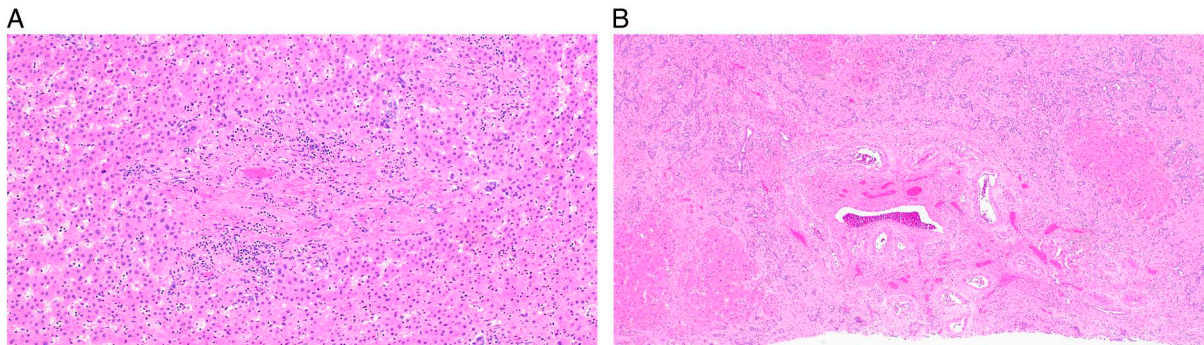


FIGURE 2. Examples of ductopenia in pediatric cholestatic liver diseases. A, Explant liver from a patient with Alagille syndrome showing absence of bile duct in a portal tract (H&E, original magnification $\times 100$). B, Explant liver from a patient with biliary atresia showing absence of bile ducts with cirrhosis and prominent ductular reaction (H&E, original magnification $\times 40$).

Small-Duct Primary Sclerosing Cholangitis (sd-PSC)

PSC is an idiopathic, progressive biliary disorder that primarily affects the extrahepatic and large intrahepatic bile ducts. In $< 10\%$ of patients, the disease is restricted to the small intrahepatic ducts, a variant referred to as sd-PSC.⁵⁶ Unlike classic large-duct PSC, sd-PSC does not exhibit the characteristic “beaded” appearance on cholangiography, as segmental strictures and dilatations of the intrahepatic and extrahepatic bile ducts are absent.⁵⁷ Nevertheless, sd-PSC shares histologic features with classic PSC, characterized by progressive ductopenia, chronic cholestasis, and progressive fibrosis. A histologic hallmark is concentric (“onion-skin”) fibrosis surrounding bile ducts, resulting in luminal narrowing, epithelial atrophy, and eventual obliteration of the ducts, which are replaced by a rounded fibrous scar (Fig. 4).⁵⁸ In the absence of this characteristic lesion or associated clinical conditions such as inflammatory bowel disease, distinguishing sd-PSC from IAD is essentially impossible, as both are diagnoses of exclusion. Interestingly, one reported IAD case demonstrated ductopenia with concentric fibrosis,²⁷ potentially representing sd-PSC. Studies have shown that 12.5% to 67% of sd-PSC cases eventually progress to large-duct disease over time.⁵⁹ Because of this potential evolution, periodic magnetic resonance cholangiopancreatography (MRCP) and clinical monitoring are recommended for patients with sd-PSC.⁶⁰ Although therapies such as UDCA and obeticholic acid can

improve liver biochemistry, long-term UDCA therapy has not shown a survival benefit.⁶¹

Ischemic Cholangiopathy

Ischemic cholangiopathy, also referred to as ischemic cholangitis, is defined by focal or diffuse bile duct injury resulting from impaired arterial blood supply.⁶² The biliary tree is nourished by the peribiliary vascular plexus, which originates from the hepatic arteries. Most cases of biliary ischemia are iatrogenic, but systemic and inflammatory diseases may also contribute. Major causes include liver transplantation (especially with hepatic artery thrombosis), transarterial chemoembolization, hepatic radiotherapy, arterial injury during cholecystectomy, systemic vascular diseases, hereditary hemorrhagic telangiectasia, AIDS-related cholangiopathy, and ICU-associated cholangiopathy.⁶³ Histologic findings vary with the severity and duration of ischemia. Early injury causes bile duct damage (Fig. 5A), which may lead to biliary obstruction or dilatation. Complete arterial occlusion, as observed in hepatic artery thrombosis, results in transmural bile duct necrosis (Fig. 5B) and biloma formation. Chronic or subacute ischemia leads to biliary strictures, periductal fibrosis, epithelial atrophy, and eventual ductopenia (Fig. 5C), mimicking PSC. In severe cases, ischemic injury extends into the hepatic parenchyma, causing zone 3 necrosis and cholestasis.⁵⁸ Differentiation from IAD relies primarily on the clinical history of injury to

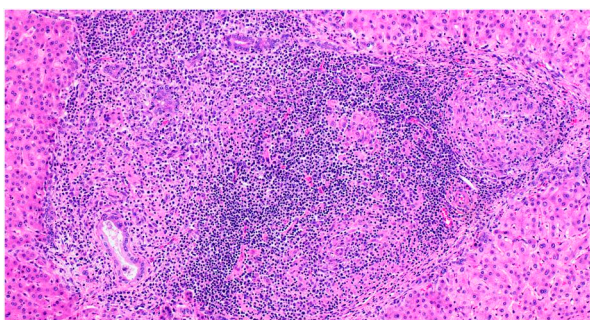


FIGURE 3. Florduct lesion and granulomatous portal inflammation in a patient with primary biliary cholangitis (H&E, original magnification $\times 100$).

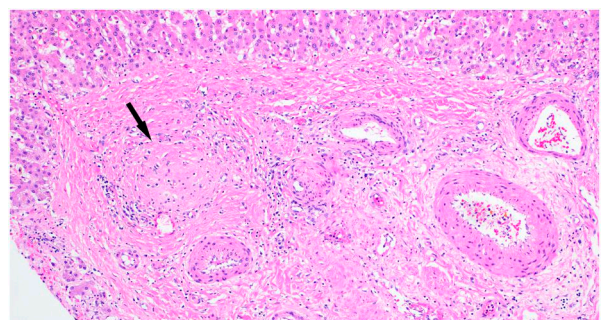


FIGURE 4. Fibro-obliteration of a medium-sized bile duct with a rounded scar (arrow) in a patient with primary sclerosing cholangitis (H&E, original magnification $\times 100$).

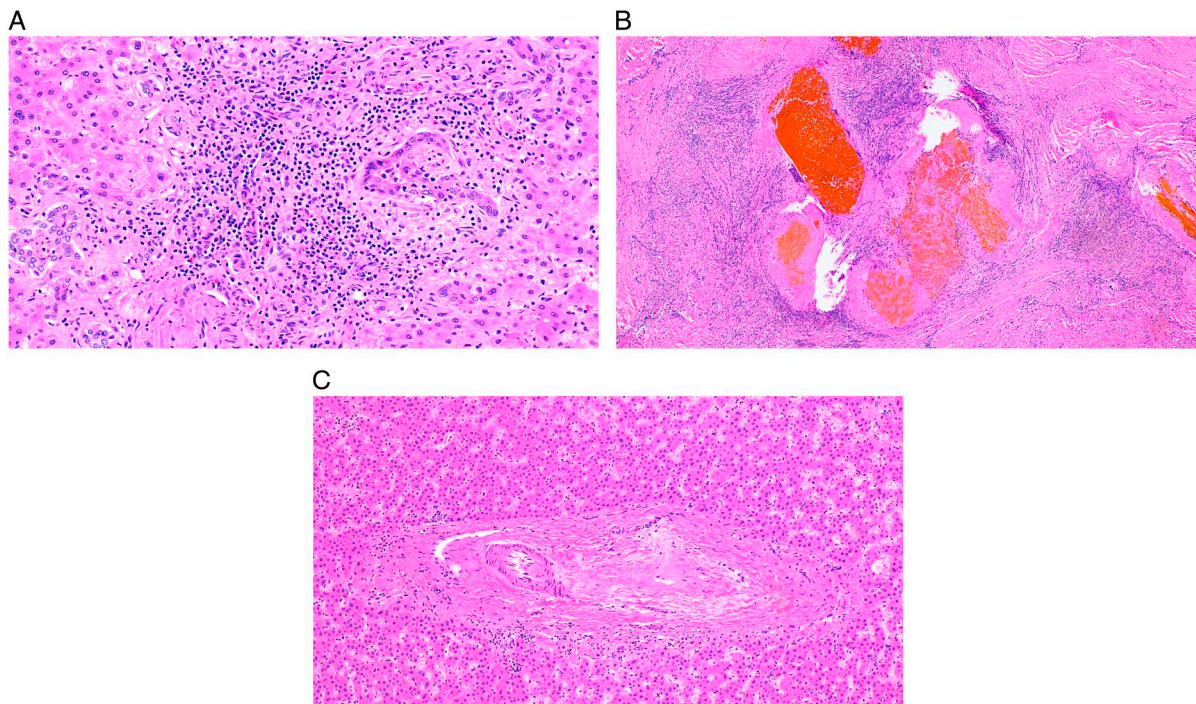


FIGURE 5. Explant liver from a patient with ischemic cholangiopathy complicated by recurrent cholangitis and biliary strictures. A, Portal tracts showing predominantly lymphocytic inflammation and bile duct injury (H&E, original magnification $\times 200$). B, Large bile ducts near the porta hepatis showing necrosis, inflammation, and fibrosis (H&E, original magnification $\times 40$). C, Some portal tracts showing fibrosis with no identifiable bile ducts (H&E, original magnification $\times 100$).

the hepatic artery. Bile duct necrosis is not a typical feature of IAD.

Drug-Induced Cholangiopathy

Drug-induced liver injury (DILI) encompasses a broad spectrum of injury patterns, depending on the cell populations affected.⁶⁴ Within this spectrum, drug-induced bile duct injury specifically targets the epithelium of the interlobular ducts, with agents such as amoxicillin/clavulanic acid and carbamazepine being most frequently implicated. The pathogenesis is thought to involve T-cell-mediated hypersensitivity reactions against the offending drug,⁶⁵ in which inflammation directed against cholangiocytes leads to bile duct injury and ductopenia, known as drug-induced cholangiopathy. Alternative terms used in the literature include drug-induced VBDS, drug-induced bile duct injury, drug-induced ductopenia, and disappearing intrahepatic bile ducts.⁶⁶ Patients typically present after a latency period of several days to weeks following drug exposure.⁶⁷

Histopathologic findings depend on the stage and severity of injury. In the acute phase, liver biopsy often shows mixed portal and periportal inflammatory cell infiltrates composed of lymphocytes, plasma cells, neutrophils, and eosinophils, along with bile duct injury characterized by cholangiocyte swelling, cytoplasmic vacuolization, nuclear irregularities, mitotic activity, and lymphocytic infiltration (Fig. 6A). Hepatocellular and canalicular cholestasis are common. In the chronic phase, progressive bile duct degeneration and loss occur (Figs. 6B, C),

sometimes accompanied by portal inflammation, fibrosis, cholestasis, and ductular reaction.⁶⁶

The heterogeneous clinical presentation of drug-induced cholangiopathy often complicates diagnosis, particularly when cholestasis develops long after drug exposure, obscuring the temporal association. Notably, some cases once classified as IAD may in fact represent unrecognized drug-induced VBDS.²⁹ Therefore, DILI should always be considered in the differential diagnosis of ductopenic liver disease, although its contribution may be overestimated relative to its true frequency.

Chronic Allograft Rejection

Chronic allograft rejection remains a major complication that threatens long-term graft survival following liver transplantation. It usually occurs > 3 months post-transplantation and is often preceded by episodes of acute T-cell-mediated rejection.^{68,69} Its pathogenesis involves the recipient's immune response in conjunction with progressive graft injury and repair processes, ultimately leading to vascular alterations within the graft.⁷⁰ The histologic hallmarks are progressive bile duct degeneration leading to ductopenia (Figs. 7A, B) and obliterative arteriopathy affecting large and medium-sized muscular arteries.^{68,71} although the latter is almost never observed in biopsy specimens.⁷² Distinguishing chronic ductopenic rejection from IAD relies primarily on the history of liver transplantation. Central perivenulitis, another histologic feature that can be seen in chronic rejection, is not observed in IAD.

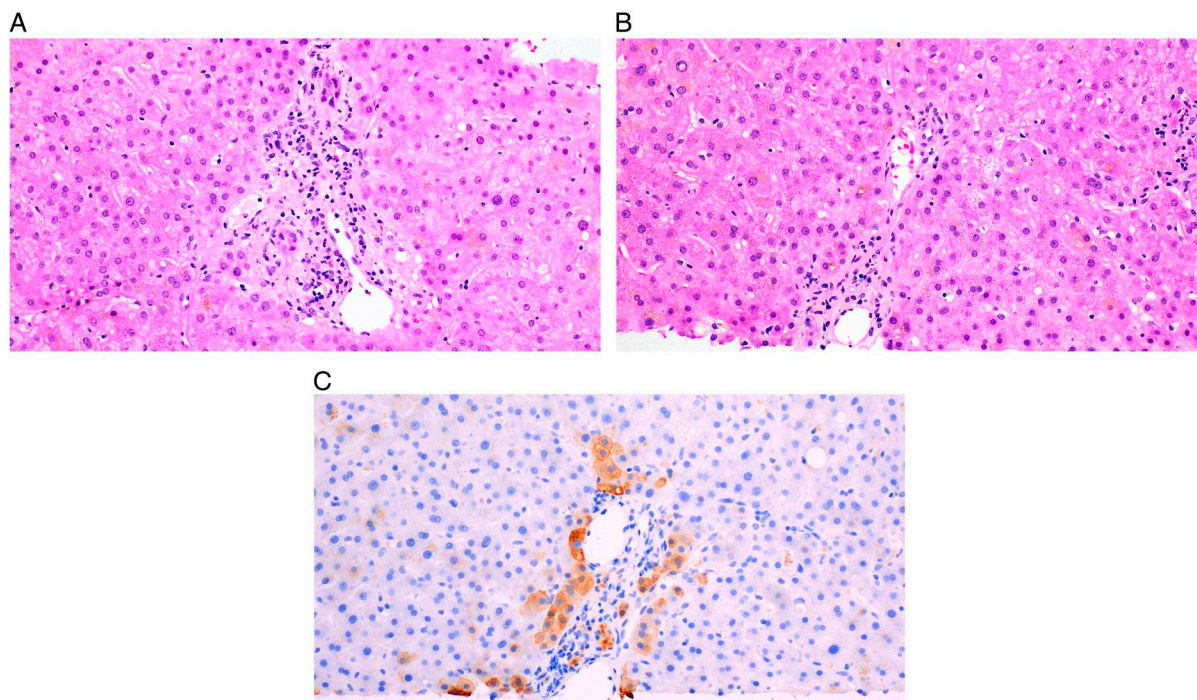


FIGURE 6. Vanishing bile duct syndrome secondary to drug-induced liver injury. A, The identifiable bile ducts show prominent features of injury (H&E, original magnification ×200). B, In the majority of portal tracts, bile ducts are absent (H&E, original magnification ×200). C, CK7 immunostaining confirms ductopenia and highlights biliary metaplasia in periportal hepatocytes (original magnification ×200).

Graft-Versus-Host Disease (GVHD)

GVHD is an immune-mediated condition in which donor-derived T cells attack host tissues. It is typically triggered by tissue injury caused by myeloablative or reduced-intensity conditioning regimens administered before hematopoietic cell transplantation (HCT).⁷³ Despite advances in transplant protocols, GVHD remains one of the most challenging complications after HCT and, although rare, following solid organ transplantation.⁷⁴ GVHD is divided into acute (≤ 100 d post-transplantation) and chronic (> 100 d) forms clinically,⁷³ but there is no rigid histologic dichotomy as the disease is a

continuous process. The primary histopathologic change of hepatic GVHD is bile duct injury and degeneration (Fig. 8A), which may progress to ductopenia in advanced stages (Fig. 8B). Nonsuppurative destructive cholangitis may be observed, resembling the features of PBC.⁷⁵ In addition to the cholangiopathic pattern, a hepatic variant has been described. This variant mimics viral hepatitis and is characterized by lobular injury with minimal or absent bile duct damage. It often emerges in specific clinical contexts, such as after immunosuppressive tapering or donor lymphocyte infusion.^{76,77} The key to distinguishing ductopenic GVHD from IAD lies in the

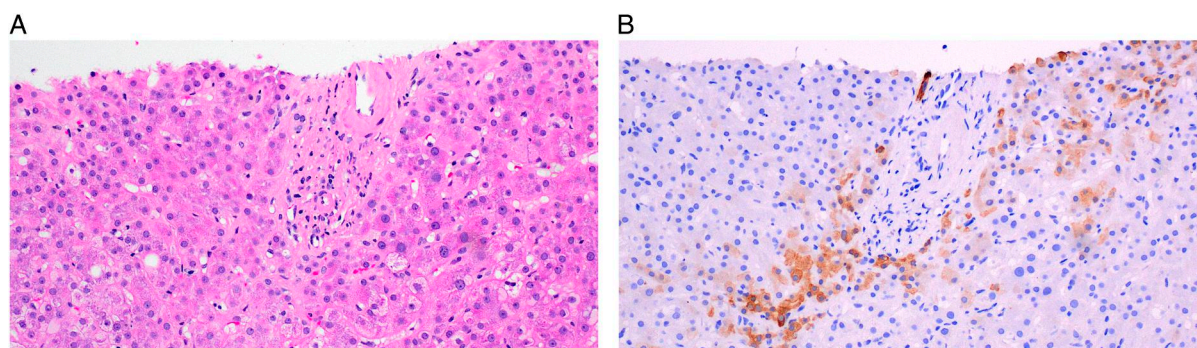


FIGURE 7. Chronic allograft rejection. A, Portal tracts showing no identifiable bile ducts (H&E, original magnification ×200). B, CK7 immunostaining confirming ductopenic rejection (original magnification ×200).

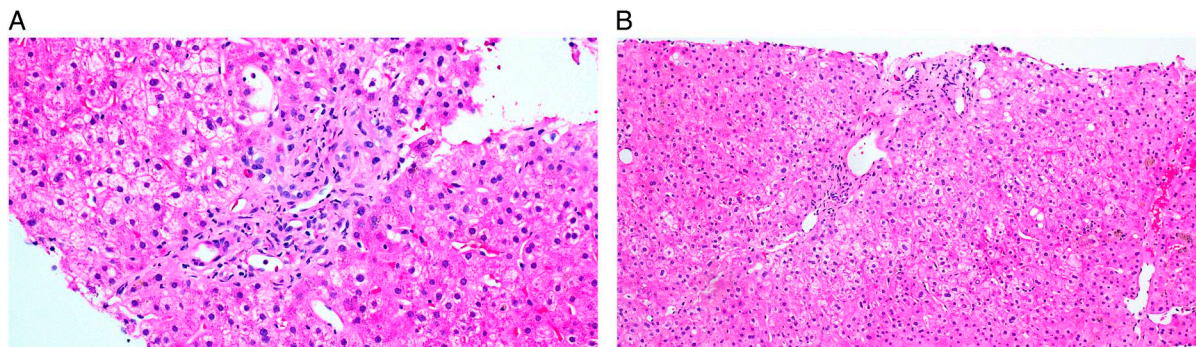


FIGURE 8. Graft-versus-host disease. A, Bile ducts show features of injury and degeneration (H&E, original magnification $\times 200$). B, Duct loss in advanced stages (H&E, original magnification $\times 100$).

history of HCT. Extrahepatic GVHD involvement (such as skin and gastrointestinal diseases) further aids in the differentials.

Viral Infections

Cytomegalovirus (CMV)

CMV is a ubiquitous pathogen that establishes lifelong latency following primary infection. In adults, CMV seroprevalence ranges from 40% to 90%.^{78,79} Immunosuppression facilitates viral reactivation, making CMV one of the most common opportunistic infections in transplant recipients.⁷⁸ Among viral pathogens, CMV is the best characterized cause of bile duct injury in both neonates and adults,^{80,81} and it has been implicated as an important trigger of VBDS following liver transplantation.⁸² The mechanisms are thought to involve both direct viral infection of cholangiocytes and indirect immune-mediated injury.⁶ Characteristic histologic findings include bile duct injury, along with mononucleosis-like inflammation and occasional granuloma formation. Diagnosis is supported by serologic testing and polymerase chain reaction (PCR) for viral DNA, as well as distinctive “owl’s eye” viral inclusions in hepatocytes (Fig. 9A), endothelium, and cholangiocytes (Fig. 9B).^{6,83} The infected cells are readily highlighted by immunohistochemistry, and when present in the lobules, may be accompanied by a microabscess defined as a cluster of neutrophils (Fig. 9C).

Human Immunodeficiency Virus (HIV)

HIV-related cholangitis, also referred to as acquired immunodeficiency syndrome (AIDS) cholangitis or AIDS-related sclerosing cholangitis, is a well-recognized late complication of advanced AIDS. Approximately 60% of cases are attributed to opportunistic infections, most commonly CMV and *Cryptosporidium parvum*, whereas the remaining 40% lack an identifiable cause.^{82,84} Proposed pathogenic mechanisms include direct biliary injury by opportunistic organisms, immune deficiency-related susceptibility to biliary damage, and direct cytopathic effect of HIV on the biliary epithelium. In addition to extrahepatic biliary abnormalities such as papillary stenosis of the common bile duct, sclerosing cholangitis, and long-segment biliary strictures,⁸³ VBDS has been reported in HIV-infected adults, most often in association with antiretroviral therapy, coinfections, or HIV-related lymphomas.^{85,86}

Epstein-Barr Virus (EBV)

EBV is a ubiquitous human lymphotropic herpesvirus that infects B lymphocytes. In immunocompetent individuals, cytotoxic T lymphocytes (CTLs) recognize and eliminate infected cells, thereby restricting their proliferation. In the setting of immunosuppression, however, EBV-infected cells can evade immune surveillance, leading to uncontrolled proliferation and, in some cases, even the development of malignancies.⁸⁷ Although EBV does not directly infect hepatocytes or cholangiocytes, CTL-mediated immune responses against infected B cells may cause collateral liver injury.⁸⁸ EBV infection can manifest as cholestatic hepatitis,^{89,90} sometimes accompanied by bile duct injury (Fig. 10A) and, rarely, progression to VBDS. Aberrant expression of HLA class II molecules has been proposed as a potential contributor to the immunopathogenesis of VBDS.⁹¹ For diagnosis, serologic testing, PCR for viral DNA, and in situ hybridization for viral RNA are useful tools (Fig. 10B).⁹²

COVID-19

COVID-19, caused by SARS-CoV-2, is primarily a respiratory illness but is now recognized as a multisystem disease. The virus gains cellular entry through angiotensin-converting enzyme 2 (ACE2), which is highly expressed in enterocytes, cholangiocytes, and, to a lesser extent, hepatocytes, thereby enabling widespread involvement of the gastrointestinal and hepatobiliary systems.⁹³ Hepatic manifestations of COVID-19 most often appear as mild hepatocellular injury with elevated transaminases during the acute phase. In severe or prolonged cases, cholestatic liver injury may emerge, mimicking sclerosing cholangitis, a condition now referred to as post-COVID-19 cholangiopathy or secondary sclerosing cholangitis associated with COVID-19.^{94,95} The reported incidence of post-COVID-19 cholangiopathy among hospitalized COVID-19 patients is $<1\%$.⁹⁶ Clinically, it typically presents with jaundice and marked elevations in serum ALP, GGT, and bilirubin levels.⁹⁴ Histopathology shows portal or periportal inflammation, fibrosis, and bile duct injury with cholangiocyte vacuolization, apoptosis/necrosis, regenerative changes, ductular reaction, and duct loss. Severe microvesicular steatosis has also been reported. The pathogenesis of post-COVID-19 cholangiopathy is likely multifactorial, involving ischemic injury, immune-mediated damage, and direct viral cytopathic effects on cholangiocytes.^{97–99}

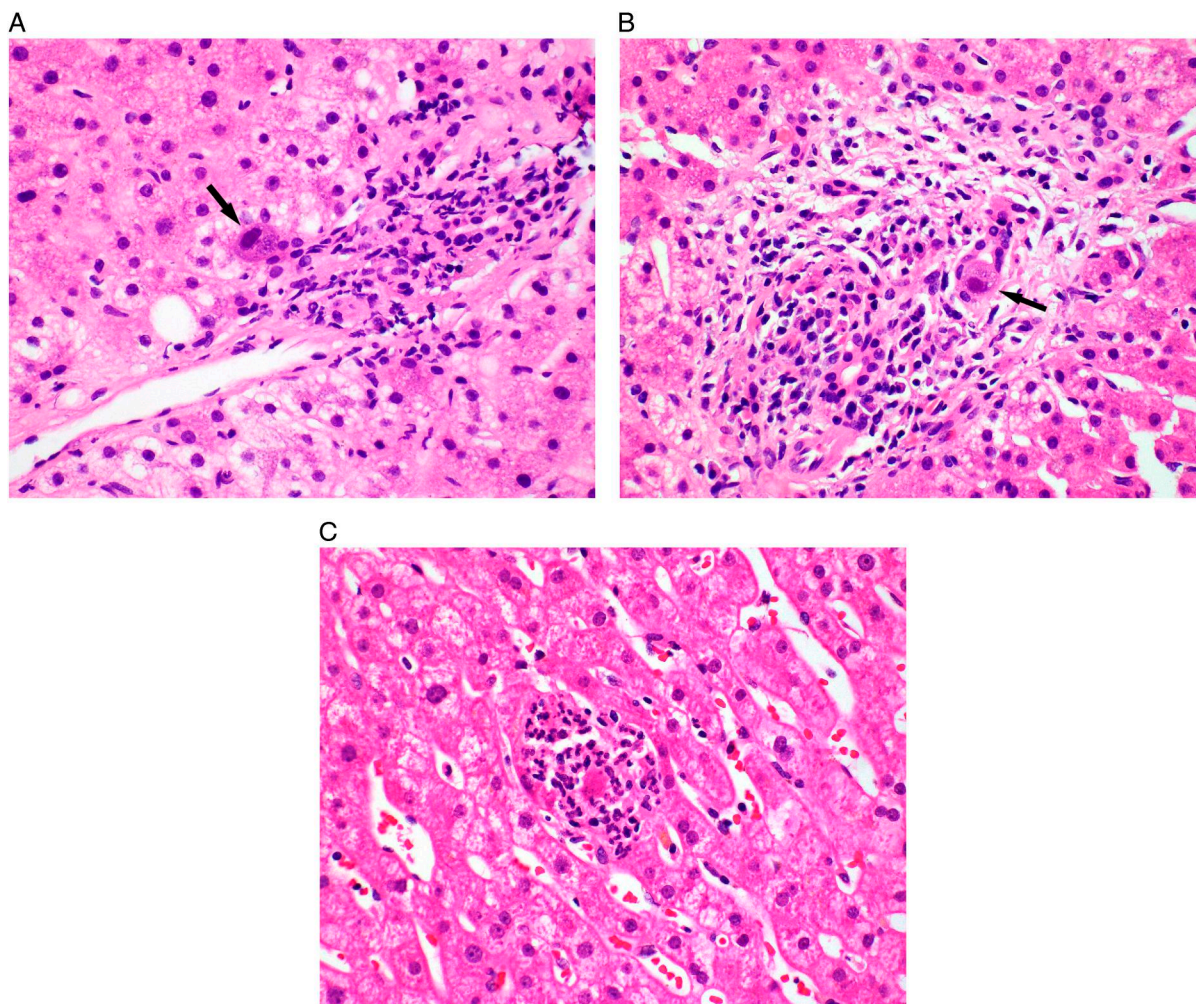


FIGURE 9. CMV hepatitis. A, Characteristic intranuclear and intracytoplasmic viral inclusions (arrow) in a hepatocyte (H&E, original magnification $\times 400$). B, CMV inclusions (arrow) in a bile duct (H&E, original magnification $\times 400$). C, A microabscess surrounding a CMV-infected hepatocyte (H&E, original magnification $\times 400$).

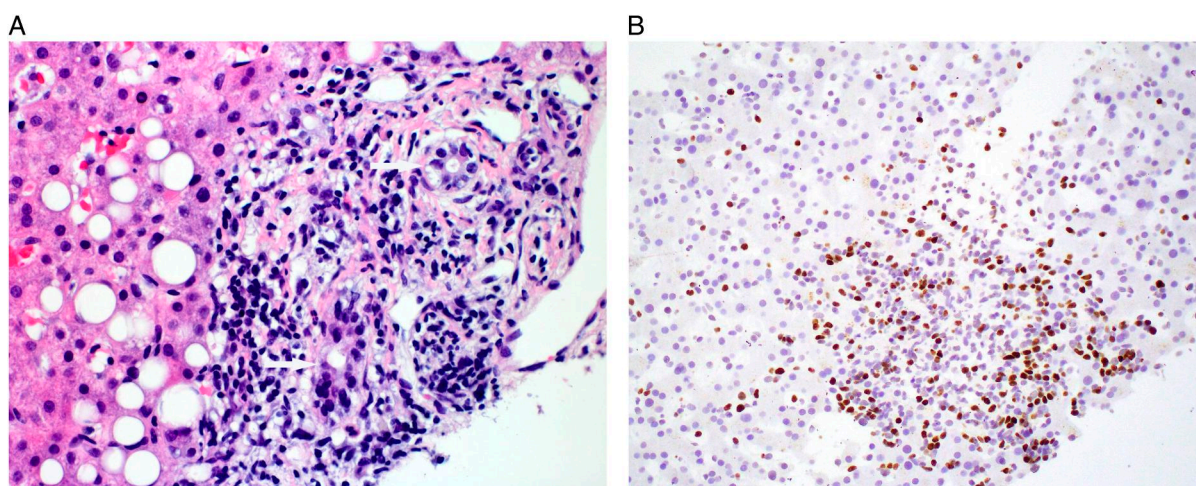


FIGURE 10. EBV hepatitis. A, Portal inflammation with bile duct injury (white arrows) (H&E, original magnification $\times 400$). B, In situ hybridization for EBV-encoded RNA (EBER) showing positive staining in portal and lobular lymphocytes (original magnification $\times 200$).

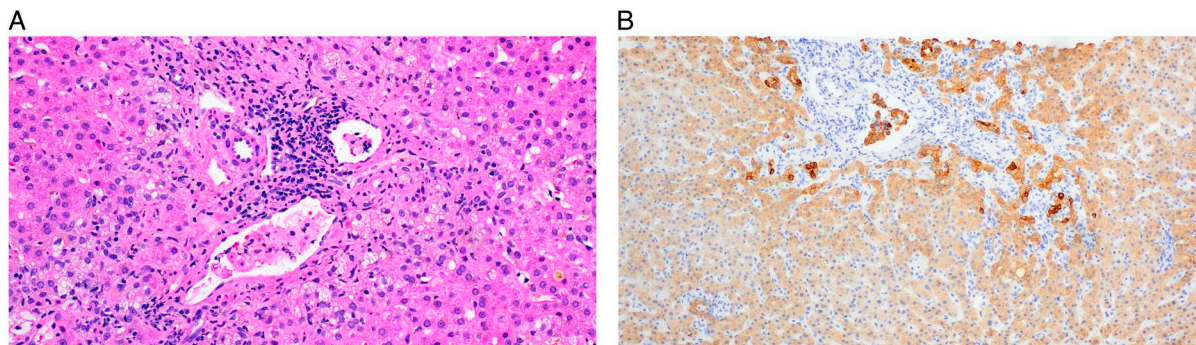


FIGURE 11. Extensive ductopenia and cholestasis in a patient with extrahepatic Hodgkin lymphoma. A, A mildly inflamed portal tract without an identifiable bile duct (H&E, original magnification $\times 100$). B, Pankeratin immunostaining confirming the absence of bile ducts (original magnification $\times 100$).

In addition, a rare case of VBDS was described following COVID-19 vaccination, presenting with progressive jaundice and multiorgan injury. Liver biopsy showed centrilobular cholestasis, bile duct damage, duct loss in some of the portal tracts, and positive C4d deposition in portal venous and capillary endothelial cells, resembling the pattern of antibody-mediated rejection seen in liver transplantation.¹⁰⁰ The patient gradually recovered with corticosteroids and plasmapheresis.

Hodgkin Lymphoma (HL)

HL is a malignant lymphoid neoplasm that predominantly affects young adults. Cholestasis as the sole manifestation of HL is uncommon, occurring in $<4\%$ of cases. It may result from hepatic infiltration, compression of the extrahepatic bile duct by bulky abdominal and periportal lymphadenopathy, or VBDS.¹⁰¹ HL-related VBDS was first reported by Hubscher et al in 1993,¹⁰² and can occur regardless of whether the liver is directly involved by lymphoma (Figs. 11A, B). It is considered a paraneoplastic phenomenon with presumed pathogenesis involving immune- and cytokine-mediated injury to bile ducts.^{103,104} Patients with HL-related VBDS typically present with jaundice, pruritus, and weight loss.¹⁰⁵ Although potentially reversible, VBDS in the setting of HL generally predicts poor overall survival, despite HL itself being otherwise highly curable.^{103,106,107}

Sarcoidosis

Sarcoidosis is a multisystem disorder characterized by non-necrotizing granulomas. Hepatic involvement is common, with liver biopsy revealing granulomas in 50% to 79% of patients with systemic sarcoidosis beyond the thoracic cavity.¹⁰⁸ Symptomatic hepatic sarcoidosis may present with abdominal pain, pruritus, hepatosplenomegaly, fever, night sweats, or weight loss.¹⁰⁹ In advanced stages, complications such as portal hypertension and liver failure can occur. Three major histologic patterns of hepatic involvement have been described: (1) cholestatic pattern, characterized by bile duct injury and ductopenia; (2) necroinflammatory pattern, marked by lobular necrosis and portal inflammation; and (3) vascular pattern, featuring sinusoidal dilatation and nodular regenerative hyperplasia. In addition, isolated granulomatous inflammation and varying degrees of fibrosis can be observed.¹¹⁰ Granulomas usually localize to the portal tracts, tend to

be larger than those seen in most other liver disorders, and may coalesce over time. They often contain multinucleated giant cells, surrounded by a lymphocytic cuff and with variable fibrin deposition.¹⁰⁹ Bile duct damage and ductopenia are strongly associated with cirrhosis and portal hypertension. Importantly, these changes may occur in the absence of granulomatous inflammation, suggesting alternative pathogenic mechanisms. Vascular injury has been proposed as a potential contributor to bile duct loss.¹¹¹

CONCLUSIONS

IAD is a rare but often underrecognized entity that remains diagnostically challenging. Given its nonspecific clinical presentations and overlapping histopathologic features with other cholangiopathies, IAD should be diagnosed only after systematic exclusion of alternative etiologies, particularly drug-induced cholangiopathy and sd-PSC. Molecular testing should be incorporated into the workup of patients with otherwise unexplained cholestatic liver disease with ductopenia. With ongoing advances in molecular diagnostics and other investigative modalities, it is expected that many cases previously classified as idiopathic will be reclassified with identifiable etiologies. Such progress will deepen our understanding of disease pathogenesis and ultimately guide the development of more effective, targeted therapeutic strategies.

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