Primary biliary cirrhosis and other ductopenic diseases

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Ductopenia and its morphologic consequences

Several distinct conditions are associated with a reduction in the number of small and medium-sized intrahepatic bile ducts (ie, <100 μm in diameter). Some of these are the result of a developmental failure; this includes syndromic (Alagille's syndrome) and nonsyndromic paucity of intrahepatic bile ducts. There are also acquired disorders (often referred to as vanishing bile duct syndromes) that lead to ductopenia, some of which are associated with necroinflammatory destruction of the bile duct epithelium; in others, there is no obvious necroinflammatory process [1].

The degree of ductopenia is highly variable; when mild, it may be overlooked during liver biopsy examination. When there is marked bile duct loss, a diagnosis of ductopenia can often be made without a formal bile duct count, but an objective measure of the degree of ductopenia is helpful. In heavily inflamed portal tracts, residual bile duct radicles may occasionally be obscured by inflammatory cells [2]. In this setting, it is useful to use immunohistochemistry for antigens that are expressed by bile duct epithelial cells (and not by hepatocytes); anticytokeratins 7 or 19 are useful markers [3]. Outlining the basement membranes of residual bile ducts can also be helpful using either the periodic acid-Schiff diastase stain or by immunolocalization of collagen type IV [1]. In quantifying bile duct elements within liver biopsies, it is convenient to express the number of bile ducts either as a ratio to portal tracts or to other structures within the portal tracts—in particular, the hepatic arteries. Crawford et al [4] have shown that in normal adult human liver, on average, within a portal tract there are profiles of two bile ducts, two hepatic arteries, and one portal vein. Hepatic arteries may be unaccompanied by a bile duct of similar diameter (in up to 25% of portal tracts). Some investigators use a duct to tract or a duct to artery ratio of less than 0.5 to establish a diagnosis of ductopenia [1]. Small ductules as part of a ductular reaction (see later) should not be included in the quantitative analysis. Most authorities accept that a minimum of 10 portal tracts in a biopsy specimen is required to make a firm diagnosis.

Specific bile duct lesions may be seen in ductopenic conditions, and these are described later. However, there are histologic sequelae that are common to the various ductopenic disorders associated with ductopenia [3]. These are manifestations of cholestasis and include the accumulation of bilirubin in hepatocytes (both within the cytoplasm and in canaliculi) and in Kupffer cells. The hepatocellular accumulation is seen predominantly in the perivenular zones, although in longstanding cholestasis it may be seen in periportal cells. Bile pigment accumulation is termed bilirubinostasis, which should be distinguished from cholate stasis, which refers to the changes that accompany bile acid retention and which are more frequently
seen in periportal hepatocytes that accompany bile acid retention. Cholate stasis leads to swelling of hepatocytes and is often accompanied by accumulation of copper and copper-associated protein, the latter being a polymerized form of metallothianein. The copper and its binding protein accumulate in lysosomes; the latter can be demonstrated using Shikata's orcein stain (Fig. 1). Other methods that detect copper rather than the binding protein, including rhodanilne, are more capricious and generally less sensitive. The swollen cells may be surrounded by a pericellular halo, and the cells may express cytokeratins 7 and 19. The accompanying cytoskeletal injury may lead to the formation of Mallory bodies; this is thought to be a consequence of microtubular dysfunction by retained bile acids [3].

![Copper-associated protein in periportal hepatocytes; stage 4 primary biliary cirrhosis (Shikata's orcein).](image)

Fig. 1. Copper-associated protein in periportal hepatocytes; stage 4 primary biliary cirrhosis (Shikata's orcein).

One of the other striking changes that occurs in chronic cholestasis, and therefore a feature of ductopenic disorders, is the so-called ductular reaction [2]. Ductular reactions have been described as either typical or atypical. The former is seen in acute biliary obstruction and represents a true proliferation of mature well-formed ducts; these are confined to the portal tracts. By contrast, in chronic cholestatic disorders such as those associated with ductopenia, the so-called atypical ductular reaction is seen and is characterized by the presence of anastomosing duct-like structures at the interface between the portal tract and the parenchyma (Fig. 2). The derivation of these structures is the subject of considerable debate, but it seems likely that they result in part from a metaplastic process whereby hepatocytes undergo a transformation to bile duct–like cells and in part by expansion of a stem cell population that is thought to be present at the level of the canals of Hering [5,6]. The ductules express cytokeratins 7 and 19 [2], tissue polypeptide antigen [7], chromogranin, and integrins normally expressed by bile ducts (VLA2, VLA3, and VLA6) [2]. The stimulus for this reaction remains uncertain but it is likely that bile salt accumulation plays a role. Metaplastic changes may also be seen deeper in the parenchyma; the resulting “cholestatic rosettes” are composed of hepatocytes that express bile duct–type cytokeratins. The ductular reaction is accompanied by so-called cholangioliitis with an accumulation of polymorphs around the ductular structures. Furthermore, there is an accompanying activation of hepatic stellate cells and probably portal tract (myo)fibroblasts. These cells produce interstitial collagens, and other matrix proteins accumulate, leading to periportal fibrosis. There is some evidence of a direct relationship between the ductular structures and the development of fibrosis; ductules express transforming growth factor β2 and this may directly stimulate hepatic stellate cells [8].
Chronic cholestasis in ductopenia leads to progressive fibrosis at the interface with expansion of the portal tracts and subsequently portal-to-portal bridging fibrosis. This leads to a so-called monolobular cirrhosis in which the fibrous septa outline classic lobules.

**Differential diagnosis of ductopenia**

Ductopenia in infancy and childhood may be associated with developmental abnormalities of intrahepatic ducts, including ductal plate malformations [9]. It may also be seen in extrahepatic biliary atresia; this is possibly a secondary phenomenon, although it may represent an overlap with intrahepatic atresia and the ductal plate malformation [10].

Ductopenia may also be caused by intrauterine infection with cytomegalovirus, rubella and syphilis, and by a diverse range of metabolic disorders including α₁-antitrypsin deficiency, transporter protein mutations (the progressive familial intrahepatic cholestases), and abnormalities of bile acid metabolism [11]. This article focuses on ductopenia in the adult, the differential diagnosis of which is associated with the following diseases or conditions:

- Primary biliary cirrhosis
- Autoimmune cholangitis
- Primary sclerosing cholangitis
- Secondary sclerosing cholangitis
- Idiopathic adulthood ductopenia
- Ischemia (vasculitis, intra-arterial chemotherapy)
- Allograft rejection
- Graft-versus-host disease
- Drugs/toxins
- Sarcoidosis
Neoplastic disease (Hodgkin's disease)

Cytomegalovirus (CMV) infection

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) most commonly affects middle-aged women and is characterized histologically by necroinflammation of small and medium-sized bile ducts and ductopenia [12]. The term PBC is considered inappropriate by some as cirrhosis occurs only very late in the disease; the term chronic nonsuppurative destructive cholangitis [13] has been proposed as an alternative, although autoimmune cholangiopathy may be preferable [14]. Biopsies from patients with PBC show a spectrum of changes ranging from the classic granulomatous and lymphocytic bile duct lesion seen most frequently in the early stages of the disease to biliary fibrosis and cirrhosis [14]. Although the disease is more common in women, the clinical and histologic manifestations are identical in both sexes [15], the clinical course of the disease is also similar between adult patients, regardless of age [16]. There is a marked geographical variation in incidence, with the highest prevalence rate being seen in northern Europe; in some areas, the prevalence is greater than 60 cases per 1,000,000 individuals [17]. Part of this variation may reflect different levels of awareness of the disease, but there does appear to be a genuine geographical variation and, in some countries, clustering of cases has been noted [18].

The disease is insidious in onset and cases may be identified during routine medical examination when an isolated, elevated alkaline phosphatase level is noted [19]. The disease ultimately progresses in almost all cases, with an average life span of 20 years following the initial diagnosis. Several other immune-mediated disorders, most notably Sjogren's syndrome, are often also seen in patients with PBC, implying there may be a common mechanism responsible for damaging ducts in lacrimal and salivary glands and in the liver [20]. Other associations include CREST syndrome, thyroiditis, celiac disease, and seropositive and seronegative arthritis [12].

PBC affects bile ducts less than 100 µm in diameter. Bile ducts may be infiltrated by lymphocytes, and this is accompanied by vacuolar degeneration of the epithelial cells, apoptosis, and disruption of the basement membrane. The apoptosis appears to involve CD40-Fas interactions [21] and granzyme B [22] and is associated with upregulation of WAF1 and p53 in cholangiocytes [23].

The accompanying portal tract inflammatory infiltrate includes lymphocytes (CD8- and CD4-positive T cells with occasional CD103-positive cells), plasma cells, eosinophils, and mast cells (Fig. 3) [24]. Antigen-presenting CD83-positive dendritic cells can also be identified within the infiltrate [25]. There may be some proliferation of bile duct epithelium with stratification, and this may be accompanied by duct ectasia. Epithelioid granulomas closely opposed to injured bile ducts are a characteristic, if not pathognomic, finding of PBC [26]. Although these may arise as part of an immune-mediated injury to the ducts, some contain foamy histocytes, suggesting that rupture of the ducts with release of bile acids and phospholipids may contribute to their development. Occasionally, there may be periductal edema and an infiltration of neutrophils; this may raise the differential diagnosis of bile duct obstruction (see Fig. 3).
As the disease progresses, injured ducts disappear. Remnants of bile duct epithelium may be seen particularly when immunohistochemistry is used for bile duct–type cytokeratins. Ultimately, however, these remnants disappear; a lymphoid aggregate may be present at the site of the previous duct or there may be condensation of the surrounding extracellular matrix [3]. The portal tract inflammation may be accompanied by interface hepatitis of the type seen in autoimmune hepatitis (AIH) [27]. When this is florid and accompanied by significant lobular inflammation, the possibility of an overlap syndrome is raised. In progressive disease, there are features of cholate stasis with copper-associated protein accumulation and a ductular reaction. Recent evidence suggests that whereas reduced expression of the hepatobiliary transporters OATP2, NTCP, and BSEP may contribute to the cholestasis in some forms of chronic liver disease, this does not apply to PBC [29]. Within the lobules there may be liver cell dropout and Kupffer cell prominence. Epithelioid granulomas may be seen within the lobules; these are noncaseating and, on reticulin-stained preparations, show little central matrix deposition, which may be helpful in distinguishing PBC from sarcoidosis [28]. Significant hepatocytic regenerative activity may be seen, even during the early phases of the disease; this may lead to nodular regenerative hyperplasia [30], which may occasionally be sufficiently severe to lead to (noncirrhotic) portal hypertension.

Progressive necroinflammatory changes occurring at the edge of portal tracts is accompanied by fibrosis. Initially, this is seen around cholangiolar structures within the ductular reaction, but, as the disease progresses, the ductules may disappear and the picture then becomes one of periportal and perisepetal fibrosis occurring in a pericellular manner. As this progresses, there is the development of portal-to-portal bridging fibrosis [31], outlining the classic lobule (monolobular cirrhosis). A true cirrhosis, in which there is distortion of the relationship between vascular structures, occurs very late in the disease and often is not present in explant tissue taken at the time of orthotopic liver transplantation. When nodules are present, they are frequently surrounded by a halo effect, which develops on the basis of edema within the matrix at the interface.

Hepatocellular carcinoma may develop after cirrhosis has occurred. Although the overall incidence of this complication is less than that for other forms of cirrhosis, this appears to
result from the high preponderance of PBC in women; when age- and sex-matched cirrhotic groups are compared, the incidence appears to be similar to that of the hepatitis C virus [32].

The histologic changes of PBC may be highly variable throughout the liver. This poses a particular problem with needle biopsy specimens; the classic bile duct lesions with granulomatous involvement of interlobular bile ducts are seen in only a small proportion of patients. Examination of explant tissue has emphasized the heterogeneity of the disease throughout the liver; within an individual specimen, there may be areas showing early classic bile duct lesions with no significant fibrosis adjacent to areas showing nodule formation. Despite this, staging systems are commonly used to describe the degree of injury [33,34], which divide the histologic changes into four successive but overlapping stages. Stage 1 disease indicates that the histologic changes are restricted to the portal tracts; stage 2, necroinflammation at the interface with ductular proliferation; stage 3, the presence of septal fibrosis; and stage 4, the presence of an established micronodular cirrhosis. Given the variable spread of changes within an individual liver, such staging systems are probably of limited value in predicting prognosis, and biopsy interpretation serves mainly to confirm the diagnosis and to identify whether, in broad terms, there is early (stages 0–2) or more progressive (stages 3–4) disease.

The histologic changes in PBC may be modified by therapy. Ursodeoxycholic acid treatment has been associated with a reduction in the prevalence of bile duct lesions, granulomas, and lobular inflammation [35]. PBC may recur after orthotopic transplantation, with rates of up to 50%. Because ductopenia and progressive cholestasis are also features of chronic rejection, granulomatous bile duct lesions should be identified to confirm the diagnosis of recurrent disease [36].

There has been considerable recent interest in the pathogenesis of PBC. The histologic features noted previously point to an immune-mediated mechanism for the bile duct injury. It has been suggested that the disease may represent a form of graft-versus-host disease caused by fetal microchimerism, but this hypothesis has not been supported by recent studies [37]. More likely, it represents an organ-specific autoimmune disease. Supportive evidence comes from (1) cosegregation with other organ-specific autoimmune diseases, in particular Sjögren's syndrome and autoimmune thyroiditis [38]; (2) the high preponderance among women; and (3) the immunogenetic association with certain major histocompatibility complex (MHC) loci [39], polymorphisms of interleukin 1 [39], and cytotoxic T-lymphocyte-associated antigen-4, or CTLA-4 [40]. The most compelling evidence is the presence of circulating autoantibodies in almost all PBC patients. These include antibodies to the nuclear membrane pore proteins gp210α and p62, lamin B receptor, and thyroid antigens [41]. However, the most characteristic antibodies of PBC are antimitochondrial antibodies (AMA). These antibodies were first identified in 1965 using immunofluorescence [42]. Immunofluorescence remains the most commonly used method for their detection, but ELISA and immunoblotting using recombinant proteins appear to be more sensitive; more than 94% of PBC patients are AMA positive using the latter approach [43]. The antigens to which AMA bind are members of the 2-oxoacid dehydrogenase complex, located within the matrix of the inner mitochondrial membranes where they catalyze important steps in intermediary metabolism [44].

The antigenic targets include the E2 subunit of pyruvate dehydrogenase complex (PDC-E2), branched chain 2-oxoacid dehydrogenase complex (BCOADC-E2), oxoglutarate
dehydrogenase complex (OGDC-F2), and dihydrolipoamide dehydrogenase binding protein (E3BP); anti-PDC-E2 is the most common and probably most important of these [44]. The three-dimensional structure of PDC-E2 has been characterized [45] and the epitopes for antibody binding have been mapped using truncated peptides [46]; this has demonstrated that the immunodominant epitope is located within the inner lipoyl domain of the protein. A T-cell response to identical epitopes in PDC-E2 has been described using T-cell clones derived from liver tissue or peripheral blood mononuclear cells from PBC patients; stimulation of T-cell lines can also be seen with BCOADC-E2 and E3BP [47]. Until recently, it has been unclear how either B- or T-cell responses to proteins within the inner mitochondrial membranes could be involved in the pathogenesis of biliary disease. It is now clear that IgA-class AMA could interact with mitochondria during transcellular trafficking; such antibodies have been shown to inhibit enzyme activity [45]. Furthermore, several groups have demonstrated that PDC-E2 and E3BP are upregulated in cholangiocytes early in the course of PBC and are aberrantly expressed at the apical cell membrane [48]. This may occur because of increased synthesis, decreased degradation, and/or abnormal targeting of the proteins. The membrane immunoreactivity is accompanied by expression of MHC proteins, adhesion molecules, and costimulatory molecules, and there is thus an appropriate repertoire for recognition by autoreactive T cells.

This aberrant expression of mitochondrial proteins in PBC is restricted to bile duct and salivary gland epithelia. One possible explanation for this has been suggested by the recent studies of Odin et al [49]. Many "autoantigens" are modified during apoptosis; teleologically, this can be seen as a protective mechanism. Odin et al showed that, in a variety of cell types, PDC-E2 was undetectable at the cell surface following apoptosis. By contrast, the protein was found on apoptotic isolated rat cholangiocytes and in human salivary epithelial cells; this appears to be due to a lack of glutathiolation and/or Bcl2-dependant oxidation. This does not, of course, explain why only a small proportion of the population develop AMA and PBC; it seems likely that this occurs only in genetically predisposed individuals. An alternative hypothesis for the development of AMA and T-cell responses to PDC-E2 is that it represents molecular mimicry [50]. PDC-E2 is highly conserved across many species, and previous studies have demonstrated that AMA from PBC patients can cross-react with E coli PDC-E2. This has led to the suggestion that either chronic bacteriuria or colonic infection with rough colony mutants of E coli may be a triggering event. Functional studies, however, suggest that molecular mimicry is unlikely to be important in the B-cell responses in PBC, although it may play a role at the T-cell level.

Other infections have been suggested as triggering events in PBC, including Mycobacterium gordonae [51] and Helicobacter species [52]. Although many other rigorous polymerase chain reaction–based studies have failed to demonstrate any such association [53], Harada et al [54] have found Propionibacterium acnes within microdissected granulomas from PBC livers. Mason et al [55] detected antibodies to retroviral elements in the serum of PBC patients; this was not disease specific, however, and similar findings were observed in SLE, chronic viral hepatitis, and primary sclerosing cholangitis (PSC). There is some preliminary evidence that a transmissible agent derived from lymphoid tissue in PBC patients can induce PDC-E2 expression on biliary epithelial cells [56], although the precise nature of this agent remains uncertain.
Using ab initio quantum chemistry, Long et al [57] have drawn attention to the possibility that anti–PDC-E2 autoantibodies may arise following modification of the molecule by environmental organic compounds.

The understanding of the immune mechanisms involved in the development of PBC is likely to be enhanced by the recent description of an animal model of autoimmune cholangiopathy [58].

**Overlap syndromes and autoimmune cholangitis**

Variant forms of PBC have been identified. In some patients, there are clinical, biochemical, and histologic features that indicate an overlap syndrome of PBC and AIH. Recent evidence suggests that it is more likely that these occur consecutively rather than simultaneously in an individual patient [59]. Histologically, such patients show (1) either diagnostic bile duct lesions of PBC or ductopenia/ductular reaction and (2) florid interface hepatitis with significant intra-acinar inflammation (Fig. 4). Assessing the incidence of PBC/AIH overlap is clearly influenced by the criteria used for the diagnosis; one recent study suggested that it occurred in almost 10% of PBC patients [60].

![Fig. 4. Primary biliary cirrhosis/autoimmune hepatitis overlap with ductopenia and florid lymphocytic-type interface hepatitis (hematoxylin-eosin). (See also Color Plate 4.)](image)

**Color Plate 4.** Primary biliary cirrhosis/autoimmune hepatitis overlap with ductopenia and florid lymphocytic-type interface hepatitis (hematoxylin-eosin). (See also page 373, Fig. 4 in article by A.D. Burt.)

AMA-negative PBC was first identified by Brunner and Klinge [61] who described three patients with histologically typical PBC but who were negative for AMA and positive for
antinuclear factor (Fig. 5). Other groups have subsequently described similar patients with the term *autoimmune cholangitis* [62,63]. The histologic changes are indistinguishable from AMA-positive PBC. Some of these patients have circulating autoantibodies to BCOADC-E2, and some have AMAs shown on immunoblotting when indirect immunofluorescence was negative [12]. Serum antibodies against carbonic anhydrase, a cytosolic enzyme found in bile duct epithelial cells, has been described in autoimmune cholangitis but these do not appear specific [64].

Fig. 5. Antimitochondrial antibody–negative primary biliary cirrhosis (autoimmune cholangitis). Granulomas are seen within an expanded portal tract with evidence of bile duct injury (hematoxylin-eosin).

**Primary sclerosing cholangitis**

PSC is characterized by a fibroinflammatory process which may involve any part of the biliary tract [65]. The extrahepatic and large intrahepatic ducts are most commonly affected, but the disease may also involve small intrahepatic ducts, and in a small proportion of patients (<10%) there may be exclusively small-duct disease [66]. All forms of the disease are associated with progressive ductopenia and chronic cholestasis. It is important to distinguish PSC from secondary sclerosing cholangitis, which may complicate surgical procedures on the bile ducts, or cholangitis associated with infections, ischemia, or iatrogenic cholangiopathy. This disease affects a younger age group than PBC [67] and can be seen in infancy and childhood [68]. The male-to-female ratio is approximately 3 to 1 and more than three fourths of cases are associated with a chronic inflammatory bowel disease, in particular with ulcerative colitis [67]. There is a variable clinical course; progression to cirrhosis may occur within 5 years, however, in some patients, the course is slower [69]. Other diseases associated with PSC include Riedel's thyroiditis, mediastinal and retroperitoneal fibrosis, hypereosinophilic syndrome, and orbital pseudotumor [2].

The classic bile duct lesion of PSC is fibro-obliteration of medium-sized or larger bile ducts [65–67]. There is periductal “onion-skin” fibrosis; this is accompanied by atrophy of the bile duct epithelium (Fig. 6). In time, the epithelium disappears and is replaced by a fibrous scar, the so-called tombstone lesion. Progression of the disease occurs in a manner similar to that described for PBC, and an analogous staging system can be used. Thus, in stage 1, the changes are confined within the portal tracts and biopsies may show classic fibro-obliterative lesions or show less-specific inflammatory changes around bile ducts. Lymphoid follicles may be present; but granulomas are not a common feature, although they are described in a small
proportion of cases [70]. Some small and medium-sized ducts may show degeneration of the epithelium without obvious surrounding fibrosis, but the basement membrane is frequently thickened in this setting. In stage 2 disease, there is a ductular reaction, the extent of which is determined, at least in part, by the severity of extrahepatic PSC and therefore large-duct obstruction. There may be considerable interface hepatitis of the form seen in AIH, and this may lead to a suggestion of a PSC/AIH overlap syndrome (see later). As in PBC, stage 3 disease denotes more extensive fibrosis around the portal tracts and the formation of septa, and stage 4 implies the development of an established cirrhosis. As with PBC, this occurs late in the disease and is characteristically a monolobular, micronodular cirrhosis [71]. Large ducts, particularly those at the hilum, may show saccular dilatation [72]. They may ulcerate or be associated with cholangitic abscesses and large biliary concretions [73]. Areas of liver cell atrophy may also be present, possibly as a result of a vasculitis—in particular, phlebitis of the portal veins. An inflammatory pseudotumor may be found around large, dilated hilar ducts, and there may be a xanthogranulomatous tissue reaction, which, on macroscopic examination, is bile stained.

Fig. 6. Small-duct primary sclerosing cholangitis. There is concentric fibrosis around the interlobular bile duct radicles and accompanying degeneration of cholangiocytes (hematoxylin-eosin). (See also Color Plate 5.)

Color Plate 5. Small-duct primary sclerosing cholangitis. There is concentric fibrosis around the interlobular bile duct radicles and accompanying degeneration of cholangiocytes (hematoxylin-eosin). (See also page 375, Fig. 6 in article by A.D. Burt.)

There is evidence that immune mechanisms may be involved in the pathogenesis of PSC [74,75]. Patients with this disease commonly have elevated serum immunoglobulins and
there may be circulating autoantibodies [76]—in particular, antineutrophil cytoplasmic antibodies and antitropomyosin. There is also evidence of circulating immune complexes and complement activation. Furthermore, the presence of overlap syndromes with AIH strongly suggests an immune-mediated basis. There does appear to be a familial predisposition, and there is a close association between the presence of HLA DRW-52 and the development of PBC [77]; immunogenetic studies have pointed to a specific epitope on the DRβ chain which confirms susceptibility to the disease [78]. Although it had been assumed that the disease occurred in response to toxins (including endotoxin) from the diseased colon in patients with ulcerative colitis, it now appears that the two are independent diseases with common risk factors [79]. There is no strong relationship between the severity of ulcerative colitis and development of PSC, and the interval between the onset of inflammatory bowel disease and PSC varies considerably. The possibility of other infective etiologies has been considered, including the hypothesis that CMV [80] or Reo [81] virus may be involved, but these claims have not been substantiated. Helicobacter species have been detected by molecular techniques in some cases with PSC, but the significance of this in pathogenesis of the disease remains uncertain [52].

Some patients show a marked interface hepatitis and lobular inflammation in PSC. Furthermore, there may be clinical and biochemical overlap between PSC and AIH; when a well-characterized cohort of 114 patients with PSC were assessed using the International Autoimmune Hepatitis Group criteria for AIH, two patients had definite AIH [82]. According to the criteria, 33% of the patients had probable AIH, although the number is reduced when the recent modification to the scoring system is applied. Such PSC/AIH overlap is most frequently seen in children [83]. Almost half of children with a diagnosis of AIH have bile duct lesions on radiologic examination, and there are well-documented cases of progression from a hepatitic illness to a ductopenic process with chronic cholestasis and the development of biliary cirrhosis [84].

Like other chronic necroinflammatory conditions of the biliary tract, such as Clonorchis infestation in PSC, hyperplastic and dysplastic changes may arise in the cholangiocytes. Cholangiocarcinoma develops from this in up to 20% of patients with PSC [85]. Fleming et al recently suggested that bile duct dysplasia within liver biopsies represents a useful marker of current or developing malignancy [86].

**Idiopathic adulthood ductopenia**

Some adult patients may have evidence of ductopenia on liver biopsy but no clinical, biochemical, or serologic findings to indicate the specific cause. Such patients are, by definition, AMA negative; they have normal ERCP, no drug history, and no evidence of sarcoidosis or chronic inflammatory bowel disease. Ludwig [87] referred to this condition as idiopathic adulthood ductopenia. The clinical features are variable; in some patients, there is progressive cholestasis leading to a biliary cirrhosis, but Moreno et al [88] described patients with asymptomatic elevations of serum liver enzymes and an indolent clinical course. Burak et al [89] recently described five cases within three generations of an extended family; others have also described familial disease [90]. Therefore, it is possible that at least some idiopathic adulthood ductopenia may be a manifestation of a genetic abnormality of bile acid metabolism or intrahepatic transporter proteins. It has also been suggested that some cases may represent late presentation of nonsyndromic, infantile paucity of bile ducts [90]. It is
likely, however, that idiopathic adulthood ductopenia represents a heterogeneous group of conditions.

**Drug-induced ductopenia**

Many therapeutic agents cause jaundice and some may lead to prolonged cholestasis. With some drugs, jaundice occurs early; this may persist or increase over time, even after withdrawal of the drug. In most cases, jaundice eventually subsides, but in a small proportion of patients, there is progressive cholestasis, and this may be complicated by biliary fibrosis and cirrhosis. More commonly in drug-induced ductopenia, the jaundice subsides early, but there is biochemical evidence of persisting cholestasis. These patterns of drug-induced cholestasis may be associated with ductopenia [91]. The pathogenesis remains uncertain; some cases of ductopenia may represent immune-mediated injury, whereas in others there may be direct cytotoxicity to biliary epithelium by xenobiotic metabolites. Over 30 therapeutic agents have been implicated in drug-induced ductopenia, the best example being the antipsychotic agent chlorpromazine [92]. There are more than 40 cases of chlorpromazine-induced ductopenia described in the literature, but given the widespread use of this drug in psychiatric practice, it appears to be a relatively rare event. Other agents that have been associated with ductopenia are as follows [91]:

- Ajmaline
- Amoxycillin-clavulanic acid
- Arsenicals
- Carbamazepine
- Chlorpromazine
- Cotrimoxazole
- Cyamemazine
- Erythromycin
- Flucloxacillin
- Methyltestosterone
- Phenytoin
- Prochlorperazine

The histologic changes vary in severity and are in part determined by the duration of the disease and by the degree of ductopenia. In some patients, there may be severe cholate stasis, florid ductular reaction, and a progressive biliary-type fibrosis and cirrhosis [92].
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