ELSEVIER
SAUNDERS

Clin Liver Dis 12 (2008) 203–217

CLINICS IN
LIVER DISEASE

Vanishing Bile Duct Syndrome

Nancy S. Reau, MD*, Donald M. Jensen, MD

Center for Liver Diseases, Section of Gastroenterology, Department of Medicine, University of Chicago Medical Center, 5841 S. Maryland, MC7120, Chicago, IL 60637, USA

Perhaps no condition associated with chronic cholestasis is less understood than vanishing bile duct syndrome (VBDS). Although the array of insults resulting in poor bile flow is vast, most adult patients who have chronic cholestasis have either primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). A small but significant portion of patients has neither of these disease entities, however, and in some cases a cause cannot be identified. VBDS refers loosely to the group of acquired disorders associated with progressive destruction and disappearance of the intrahepatic bile ducts and, ultimately, cholestasis. This is a final common pathologic pathway, resulting from multiple etiologies including autoimmune disorders, medications, genetic abnormalities, infectious diseases, and neoplastic disorders. The diagnosis typically is suggested by the clinical features and histologic findings. The prognosis and treatment depend on the cause of the initiating insult and degree of injury. This article reviews the multiple causes, postulated pathophysiology, clinical features, and treatment options for this syndrome.

''Ductopenia'' is a descriptive term for the loss of small intrahepatic bile ducts from any cause. Ductopenia, or bile duct paucity, was well recognized as a common pathologic feature in multiple disease states involving both adult and pediatric populations. Not until 1988, however, was idiopathic adulthood ductopenia (IAD), first described by Ludwig in a case series of three patients. This acquired disorder has now become synonymous with VBDS [1].

Anatomy

The biliary system is a series of ducts responsible for transportation of bile from the liver, where it is produced by the hepatocytes, to the small intestine, where it assists in digestion. The diameter of these channels increases

* Corresponding author.
E-mail address: nreau@medicine.bsd.uchicago.edu (N.S. Reau).

1089-3261/08/$ - see front matter
doi:10.1016/j.cld.2007.11.007 *liver.theclinics.com*

progressively from the periphery of the liver to the hepatic hilum. The bile ducts may be separated into intra- and extrahepatic systems (Fig. 1). The ducts located in the hepatic parenchyma (those proximal to the right and left hepatic ducts) represent the intrahepatic system [2]. The intrahepatic system is further divided by size. The intrahepatic large bile ducts (segmental and area ducts) are grossly visible, whereas the intrahepatic small bile ducts (septal and interlobular ducts, ductules, and canal of Hering) require magnification for identification. With the assistance of a light microscope, the interlobular and proximal septal bile ducts up to approximately 100 mm in diameter can be visualized. Histologically, the liver is organized into hexagonal lobules with a portal tract containing a branch of the hepatic artery, portal vein, and a bile duct, at each apex. The interlobular bile ducts usually reside near a similar-sized arterial branch, making this ratio useful when evaluating for biliary damage [2]. Few disease states involve both systems, leading to a natural taxonomic separation between the intra- and extrahepatic biliary tree [3].

Embryology and development

Around the fourth week of gestation a hepatic diverticulum arises from the foregut. This is the embryologic precursor of the liver, gallbladder, and biliary system. Endodermal cells give rise to hepatoblasts, which form cords, ultimately differentiating into hepatocytes and a layer of duct progenitors called the "ductal plate." This plate becomes bilayered. Lumina then

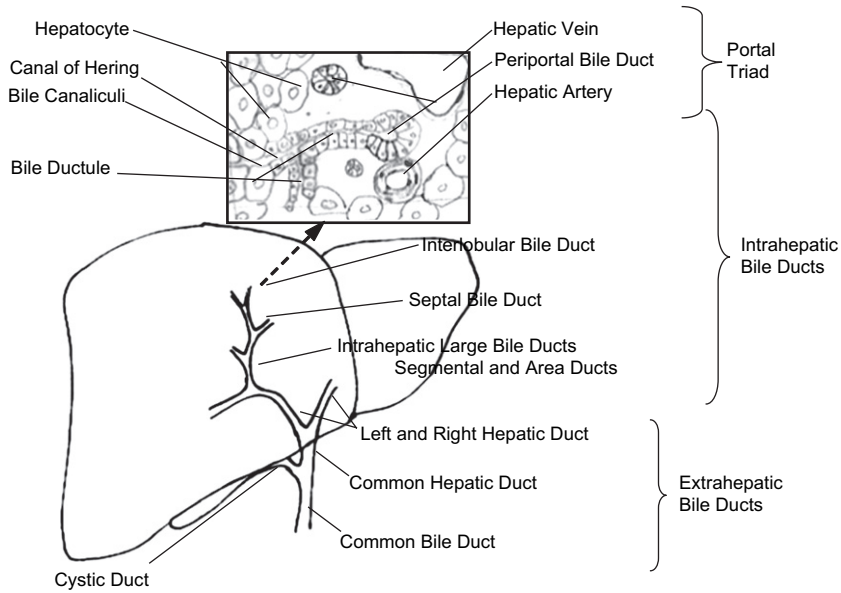

Fig. 1. Normal biliary anatomy.

form, ultimately growing into a complex network of ducts [4,5]. Malformations of the ductal plate have been implicated in several liver diseases.

Pathology

"Ductopenia" refers to the absence of interlobular bile ducts from within the portal tracts [3]. Loss of a bile duct is recognized in an individual portal tract when no duct is identified in proximity to the parallel hepatic arterial branch. (Fig. 2) By definition, ductopenia, or small duct damage, exists when there is loss of interlobular bile ducts in more than 50% of portal tracts in a pathologic specimen that is adequate for interpretation [1]. An adequate biopsy size is 3 cm in length and 16 gauge in caliber to yield a sufficient number of portal tracts, because diagnostic accuracy declines with specimen size, especially when smaller than 2 cm in length [6]. At least 11 portal tracts are required for accurate semiquantitative assessment, although 20 or more is ideal [7]. Diagnostic yield can be increased by immunostaining for biliary elements. Several stains, including cytokeratin 7 and 19, epithelial membrane antigen, and blood group–related antigen, have proven useful, especially in the presence of inflammation (Fig. 3) [2]. Ductular proliferation also may coexist with interlobular duct loss, and thus ductules must be distinguished from bile ducts. The size and location of the biliary elements are integral in this regard. Bile ducts are found parallel to hepatic artery branches of similar size, whereas ductules tend to appear near the limiting plate or within lobules [8].

Causes and clinical associations

Ductopenia is an end result associated with multiple insults (Box 1) As previously mentioned, ductopenia is a well-recognized complication of neonatal jaundice and plays an important role in many forms of adult cholestasis. Loosely, this collection of disorders resulting in progressive loss of intrahepatic bile ducts is coined VBDS.

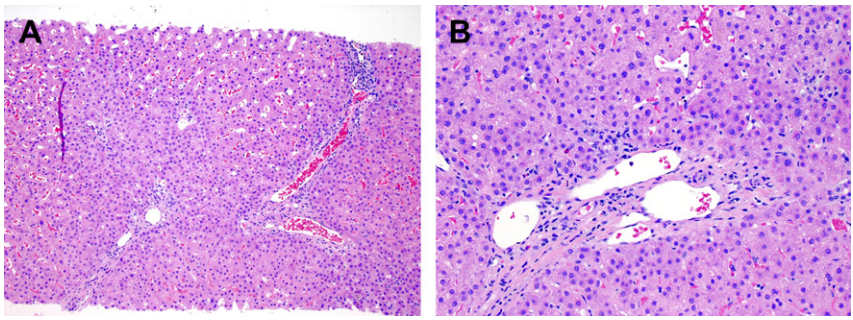

Fig. 2. Ductopenia. Hemolysin and eosin stain of portal tract without bile duct. (*A*) Low power. (*B*) High power.

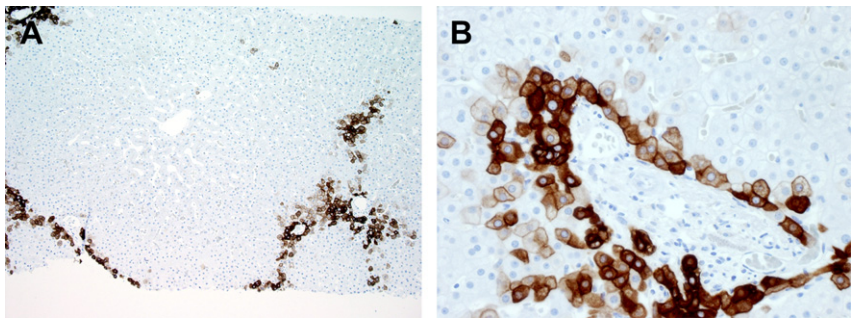

Fig. 3. Portal tract without bile duct. Cytokeratin immunostaining. (*A*) Low power (magnification ×100). (*B*) High power (magnification ×200). (*Courtesy of* J. Hart, MD, Chicago, IL).

Congenital, developmental, and genetic diseases

Ductal plate formation is integral to intrahepatic bile duct development. These plates are remodeled throughout fetal and neonatal development, making the histologic diagnosis of bile duct paucity difficult during the evaluation of a jaundiced premature infant [9]. Embryonic bile duct patterns or ductal plate malformations may reflect aberrant remodeling. Ductal plate malformations generally are atretic, as in extrahepatic bile duct atresia, or fibrocystic, as in autosomal recessive polycystic kidney disease, congenital hepatic fibrosis, Caroli's disease, and Von Meyenburg complexes. More typically, pediatric bile duct paucity is categorized as syndromic or nonsyndromic bile duct loss. The syndromic form originally was considered synonymous with Alagille syndrome [10]. In 1997, however, mutations in the *Jagged1* gene were identified as the cause of Alagille syndrome, facilitating the characterization of other forms of early bile duct loss, such as Williams syndrome, that are not associated with the *Jagged1* gene [11,12]. Ductopenia also has been well described in association with perinatal infections; chromosomal anomalies such as trisomies 17,18,21; abnormalities in bile metabolism and transport; and multiple genetic diseases including cystic fibrosis, alpha-1 antitrypsin deficiency, trihydroxycoprostanic acidemia, and Byler's disease (see Box 1) [13].

Immunologic associations

Immune injury to the biliary system was an early-recognized link involved in several diseases that resulted in bile duct loss. Injury to either the biliary epithelial cells or to the endothelial cells of the peribiliary capillary plexus can result in bile duct destruction. It is thought that immunologic cells, generally T cells, recognize antigens on biliary epithelial cells. Antigen is processed and presented by specialized antigen-presenting cells, ultimately resulting in immune cell infiltration into the intraepithelial layer of the bile ducts, apoptosis, and T-cell cytotoxicity leading to bile duct injury and loss [2].

Box 1. Causes of ductopenia

- Congenital diseases
  - Atretic
    - Extrahepatic bile duct atresia
    - Paucity of interlobular bile ducts
  - Fibrocystic
    - Autosomal recessive polycystic kidney disease
    - Congenital hepatic fibrosis
    - Caroli's disease
    - Von Meyenburg complexes
- Developmental and genetic diseases
  - Syndromic
    - Alagille's syndrome
    - Williams syndrome
  - Nonsyndromic
    - Cystic fibrosis
    - Alpha-1 antitrypsin deficiency
    - Trihydroxycoprostanic acidemia
    - Trisomies 17,18,21
    - Byler's disease
    - Niemann-Pick type C
    - Peroxisomal disease (Zellweger syndrome)
- Idiopathic
- Immunologic
  - Primary biliary cirrhosis
  - Immune cholangitis
  - Primary sclerosing cholangitis
  - Sarcoidosis
  - Chronic graft versus host disease
  - Acute hepatic cellular rejection
  - Chronic hepatic cellular rejection
- Infectious
  - Neonatal exposure to cytomegalovirus, syphilis, reovirus 3, and rubella
  - Enteric organisms
  - Viral infections
    - Cytomegalovirus
    - Reovirus type 3
    - Hepatis C virus
    - Hepatitis B virus
    - Epstein-Barr virus
    - Cryptosporidium
- Ischemic
- Neoplastic disorders
  - Hodgkin's disease
  - Histiocytosis X
- Toxins and drugs

Primary biliary cirrhosis

PBC is the most widely recognized cause of ductopenia in adults [1]. Examination of the portal triads of patients who have PBC demonstrates large numbers of CD4+ and CD8+ T lymphocytes, some of which can be identified infiltrating injured bile ducts, easily validating an immune cause [14,15].

Immune cholangitis and anti-mitochondrial antibody–negative primary biliary cirrhosis

Patients who clinically, histologically, and biochemically seem to have PBC but are anti-mitochondrial antibody (AMA) negative, are referred to as having autoimmune cholangitis. Frequently anti-nuclear antibodies are present [16].

Primary sclerosing cholangitis

Although the exact cause of PSC is unknown, immune activation seems to play a prominent role. It is strongly associated with ulcerative colitis, another immune-mediated disease; autoantibodies frequently are present in afflicted patients, and evidence points to T-cell–mediated injury of biliary epithelial cells [13,17]. PSC typically results in gross injury to both the intra- and extrahepatic biliary systems. Because cholangiography confirms the diagnosis, PSC is not typically considered predominantly a disease of duct paucity, but small duct PSC is an exception. Cholangiography is normal in this mild form of PSC, which affects predominantly small-caliber bile ducts, and biopsy often is obtained during evaluation. Biopsy findings resemble classic large duct PSC [18] or, as the disease progresses, biliary cirrhosis and PBC [19].

Sarcoidosis is a systemic disease characterized by noncaseating granulomas. Although clinical liver disease is uncommon, most patients have hepatic granulomas. Rarely, portal tract granulomas result in adjacent bile duct injury and subsequent ductopenia [17,20]. Although the cause is unknown, immunohistochemical staining confirms that the granulomas are comprised of lymphocytes. Centrally, most are CD4+ T cells, but the periphery of the granuloma is composed of CD8+ as well as CD4+ T cells [21].

Chronic graft-versus-host-disease, acute hepatic cellular rejection, and chronic hepatic cellular rejection have been associated with interlobular bile duct injury and bile duct disappearance. T-cell recognition of alloantigen is the initiating event, ultimately leading rejection and tissue injury.

Neoplastic disorders

Hodgkin's disease is a well-established cause of hepatic ductopenia, but occasionally other malignancies such as histiocytosis X or Langerhans' cell histiocytosis may present with periductal fibrosis and duct loss [22,23].

Hepatic involvement in Hodgkin's disease is common. It is seen in up to 50% of autopsy cases and increases in frequency as the disease advances

[24–26]. Conversely, cholestasis with bile duct loss is an established but rare presentation of Hodgkin's disease [26]. Portal inflammation with atypical lymphoid cells and eosinophils, even without typical Reed-Sternberg cells, should trigger a search for malignancy [27]. Although the cause remains obscure, malignancy-induced cytokines, chemotherapy-associated toxins, and occult lymphoma infiltration have all been postulated [28].

Infections

Multiple infectious etiologies, including both bacteria and viruses, have been associated with ductopenia, especially in neonates. Early exposure to cytomegalovirus, syphilis, reovirus 3, and rubella has been implicated in biliary paucity [2,23]. *Cryptosporidium parvum* is a well-recognized cause of AIDS cholangiopathy. Bile duct obstruction may result in colonization of the bile duct with enteric organisms, especially *Escherichia coli*. The subsequent ascending cholangitis and bile duct damage can lead to bile duct loss [1,23]. Infections also may play a role in the triggering or progression of immune-mediated biliary disease [2].

Viral infections

Several viral infections have been linked to cholestasis and small duct loss. Both hepatitis B and C may cause bile duct damage, but predominantly cholestatic injury with severe bile duct loss is best recognized after liver or kidney transplantation. This aggressive form is termed "fibrosing cholestatic hepatitis" and is a particularly virulent disorder, generally resulting in rapid hepatic failure [29,30]. This rapidly progressive disease may recur with subsequent liver replacement. Cholestasis is a common but generally reversible manifestation of Epstein-Barr virus infection. Associated small bile duct loss has been reported [31].

Toxins, drugs

Cholestasis is a common result of drug toxicity, explaining 2% to 5% of hospitalizations for jaundice and up to 20% of cases of jaundice in the geriatric population [3,32]. In a minority of cases, cholestasis persists longer than 6 months and is associated with an increasing risk of progression to the rare occurrence of VBDS. Although uncommon, several medications have been reported to cause VBDS (Box 2), and VBDS may occur despite discontinuation of the offending medication [33–38]. Liver chemistries and jaundice generally demonstrate gradual improvement and may normalize over the ensuing months despite the persistence of duct loss. In some patients, however, progressive bile duct loss may lead to secondary biliary cirrhosis, liver failure, and transplantation or death [39].

Ischemic causes

The biliary epithelium receives its blood supply exclusively from the hepatic artery, and thus any disruption in this blood flow may result in

Box 2. Drugs reported to cause chronic cholestasis and ductopenia

Acepromazine
Ajmaline
Amineptine
Amitriptyline
Amoxicillin/clavulanic acid
Ampicillin
Androgenic anabolic steroids
Azathioprine
Barbiturates
Carbamazepine
Carbutamide
Chlorothiazide
Chlorpromazine
Cimetidine
Clindamycin
Co-trimoxazole
Cromolyn sodium
Cyamemazine
Cyclohexyl propionate
Cyproheptadine
Diazepam
Erythromycin
Estradiol
Flucloxacillin
Glibenclamide
Glycyrrhizin
Haloperidol
Ibuprofen
Imipramine
Methyltestosterone
Norandrostenolone
Phenylbutazone
Phenytoin
Prochlorperazine
Tetracyclines
Thiabendazole
Tiopronin
Trifluoperazine
Tolbutamide
Trimethoprim-sulfamethoxazole
Troleandomycin
Xenalamine

ischemic necrosis and resultant ductopenia. This condition can be a serious complication, especially after liver transplantation, often leading to the need for retransplantation or to the development of chronic biliary strictures and abscesses.

Idiopathic adulthood ductopenia

IAD, a rare condition was first described by Ludwig [8] in 1988 as a case series of three patients. Since that time, numerous reports have reinforced its importance. A retrospective evaluation of 2082 cases of intrahepatic bile duct injury at a single center identified 1.2% that could not be otherwise classified and were termed "IAD." By definition, IAD is a syndrome of chronic cholestasis without inflammatory bowel disease and with biopsy proven ductopenia, for which no cause for bile duct loss can be determined by imaging, biopsy or serology. The florid duct lesion, pathognomonic for PBC, rarely is demonstrated in IAD. More often, PBC is characterized by periductular granulomas with bile duct injury, a finding not seen in IAD. Thus, IAD is excluded if granulomas are present on a biopsy specimen. It has been hypothesized that IAD comprises several disorders, some with atypical features, including (1) late-onset nonsyndromic paucity of intrahepatic bile ducts, (2) small duct PSC without large duct involvement and without evidence of inflammatory bowel disease, (3) nonsuppurative viral cholangitis, and (4) autoimmune disorders (AMA-negative PBC, autoimmune cholangitis, or cholangitis in autoimmune hepatitis) in the absence of the typical autoantibodies [8,28]. Some patients may have genetic factors, because familial clustering of IAD has been described [40].

Pathophysiology of bile duct loss

The disappearance of bile ducts is a pathologic manifestation of multiple different diseases and thus multiple different mechanisms. As in most tissues, in the healthy liver the biliary epithelial layer is maintained through a balance between cell death and regeneration. Apoptosis is a common and well-studied mechanism for cell death, and the proteins involved in the regulation of apoptosis are diffusely expressed throughout the biliary tree [2]. BCL2-Associated X Protein (Bax), an apoptosis promoter, and B cell lymphoma/leukemia 2 (Bcl-2), which counteracts apoptosis, are both expressed on bile duct cells. Bax is expressed along the entire biliary tree, however, whereas Bcl-2 seems to be limited strategically to bile ductules and interlobular bile ducts. Activation of cell death receptors by various insults may lead to biliary epithelial apoptosis. The cell death receptor CD95 (Fas) and its ligand (FasL), perforin and granzyme B, tumor necrosis factor-alpha, oxidative stress leading to DNA damage, and down-regulation of Bcl-2 have all been implicated in bile duct injury [2]. Immune-mediated injury occurs in more than just the established immune

diseases. Recognition of allo- or autoantigens on biliary epithelial cells by immunologic cells initiates a cascade ultimately ending in biliary injury. CD3-positive T cells generally predominate; the dominant T cell (CD4+ or CD8+) varies with disease state. Antigen is processed and presented, and in the presence of an appropriate costimulatory signal, proinflammatory cytokines are released, leading to proliferation of cytotoxic T lymphocytes, more efficient antigen presentation, and immune cell recruitment. Eventually, apoptosis and T-cell cytotoxicity predominate, leading to bile duct injury and loss. Irreversible ductopenia occurs when apoptosis exceeds the proliferative response [2].

Bile duct regeneration also may influence ductopenia. Successful biliary regeneration seems to involve a regenerative compartment composed of progenitor cells in the smallest branches of the biliary tree [41]. This compartment has been defined as the finer branches of the biliary tree (FBBT) and includes bile ductules and canals of Hering [42]. The integral involvement of the FBBT in biliary regeneration has been demonstrated in multiple liver diseases. ''Ductular reaction'' refers to the expanded population of cells with ductular phenotype at the interface of the biliary tree and the hepatocyte [42]. This phenomenon reflects the activation of the FBBT regenerative cells and is common in chronic cholestasis [43]. The loss of the FBBT also has been associated with bile duct loss in chronic liver rejection, whereas preservation of the FBBT prevented progression to ductopenia in patients experiencing acute rejection [44]. Hepatic arterial ischemia is a well-established cause for biliary injury. This injury is mirrored on the microscopic scale, because the integrity of the microvasculature supplying the FBBT is vital for the preservation of these minute biliary structures. After biliary damage, both in patients who have PBC and in patients experiencing acute hepatic rejection after liver transplantation, an initial decrease of canals of Hering is followed by a biliary proliferative response [44,45]. This response presumably reflects activation of the progenitor cell compartment after biliary damage. Further studies demonstrated that the biliary proliferation consisted first of bile ductules without escorting microvessels, followed by an increase in ductules with microvasculature. A lack of microvessel proliferation was associated with chronic ductopenic rejection [46]. Thus, successful biliary regeneration seems to depend on both the preservation of the FBBT and a compensatory increase in its supporting blood supply.

Clinical manifestations

As expected in a group of heterogeneous diseases, the clinical presentation and course are highly variable and depend on available therapies. Disease onset can be rapid, as in acute cellular rejection, or gradual, as is typical for primary biliary cirrhosis. Symptoms are highly disease specific, although constitutional complaints are common and include fatigue, anorexia, abdominal pain, and weight loss. Patients frequently complain of

pruritus and may experience typical manifestations of cholestasis such as gallstone formation, hyperlipidemia, malabsorption, xanthelasmas, and fat-soluble vitamin deficiencies. Most patients are identified by chemistries consistent with cholestasis. Typically, the alkaline phosphatase and gamma-glutamyltransferase levels are markedly elevated. A predominantly conjugated or direct hyperbilirubinemia and a mild transaminase elevation may be present also. Because this disease is characterized by small duct injury, imaging generally is nondiagnostic, but extrahepatic biliary obstruction must be excluded. Liver biopsy is necessary to confirm ductopenia and may reveal the underlying cause. Generally there are two potential outcomes: progressive, irreversible bile duct loss leading to extensive ductopenia and biliary cirrhosis, or gradual biliary epithelial regeneration and clinical recovery.

Idiopathic adulthood ductopenia

IAD is a protean disease. A literature review identified 39 reported cases of IAD. The median age at diagnosis was 27 years (range, 15–67 years), and there was a nearly 2:1 male-to-female distribution. One third presented with episodic jaundice and pruritus [28]. In both the pediatric and the adult populations, idiopathic ductopenia is thought to have a poor prognosis. Although hepatic decompensation tends to be slow, the end result is progressive biliary obstruction and the development of secondary biliary cirrhosis [8,40]. Consistent with this prognosis, 50% of the patients for whom there was follow-up information experienced slowly progressive disease leading to transplantation or death [28].

On the other hand, a cohort of 24 asymptomatic patients who had abnormal liver biochemistries and mild ductopenia (less than 50% of portal tracts lacked bile ducts) failed to develop disease progression or symptoms of liver disease during 12 years of follow-up [47], confirming the lack of understanding of this disease process. Coincidently, age may be a key diagnostic clue toward cause. The average age in the asymptomatic cohort was 41 years (range, 27–57 years); 71% were women. Cases studies suggest a breakdown of prognosis by age, with a more favorable clinical course for patients older than 40 years. It is hypothesized that younger patients who have IAD do poorly because they actually may have late-onset nonsyndromic pediatric bile duct paucity [1].

Treatment

Successful therapy may depend on identifying the underlying cause of ductopenia. Drug withdrawal, use of choleretic agents, and immunosuppression have been used with varying effects. Unfortunately, there is no treatment to induce biliary regrowth after duct loss, and thus treatment

frequently centers on supportive care and symptom control. Chronic cholestasis may result in fat-soluble vitamin deficiencies, osteoporosis, cholelithiasis, and hyperlipidemia, as well as cirrhosis with complications of portal hypertension. Pruritus is perhaps the most frequent and debilitating complication. Medical management often is less than satisfactory.

As a result of cholestasis, the liver undergoes adaptive responses in all three phases of bile production in attempts to minimize injury. The hepatic uptake of bile acids and organic solutes is decreased, bile acid synthesis is reduced, bile acid detoxification is accelerated, and alternative pathways for bile salt excretion are up-regulated [48]. Although none of these reactions fully prevent disease progression, current attempts to augment these responses are ongoing.

Ursodiol

Ursodeoxycholic acid (UDCA) is a hydrophilic dihydroxy bile acid found in high concentrations in the bile of the Chinese black bear [49]. Originally used in Chinese herbal therapies, it subsequently has been used for multiple cholestatic syndromes. It seems to confer benefit through multiple effects including choleresis, antiapoptosis, anti-inflammation, immune modulation, alteration of the bile acid pool, changes in cell signaling, and cytoprotective mechanisms. UDCA stimulates hepatobiliary secretion by increasing the expression of transporter proteins that determine hepatocyte secretory capacity, thus enhancing the elimination of toxins from the hepatocytes [50]. UDCA also has been shown to interrupt the classic pathways of apoptosis by blocking proapoptotic events and by activating intracellular survival signals [50]. In models of cholestasis, intracellular accumulation of hydrophobic bile acids leads to apoptosis and necrosis [51]. High-dose UDCA therapy changes the composition of bile, rendering it less hydrophobic and possibly displacing hepatotoxic biliary components. Although not universally beneficial for bile duct loss, UDCA has proven utility in PBC [51]. Well-established as a therapy for PSC, most studies have not demonstrated a significant, long-term benefit. Reports also suggest improvement in other forms of cholestasis including graft-versus-host disease and drug-induced cholestasis [51]. One case series found recuperation with very high dose (45 mg/kg/d) UDCA for amoxicillin clavulanate-induced VBDS [52]. Multiple case reports also attest to improvement in liver biochemistry in IAD, but the impact on disease progression is unknown [40,52,53].

Immunosuppression

Immune modulation is prominent in multiple causes of ductopenia; thus, immune suppression seems a logical treatment option. In PBC, however, immune modulation may not be the optimal strategy. Anecdotal reports of improvement in IAD with immune suppression exist (Alfrod Baker,

personal communication, 2006). Nonetheless, controlled trials are needed before immune modulation can be adopted as an effective treatment approach, especially given the toxicity associated with many of these agents.

Transplantation

Any patient as having decompensated cirrhosis or debilitating symptoms should be considered for liver replacement. Transplantation for chronic cholestasis is well established, with excellent postoperative organ and patient outcomes. Transplantation without posttransplantation disease recurrence also has been described in patients who had IAD [40].

Summary

Multiple hepatic insults lead to chronic cholestasis and bile duct loss. The term ''VBDS'' refers loosely to this entire group of acquired disorders, whereas IAD represents the small, probably heterogeneous, population in whom no obvious insult can be identified. As transitional research provides more genetic insight into diseases of cholestasis, the understanding of this disorder is certain to improve, allowing earlier identification of patients at risk for disease progression. Basic science also is shedding light on the effects of nuclear receptor ligands and activators of bile acid metabolism. Someday this information will translate into an educated therapeutic approach to drug treatment.

References

[1] Ludwig J, Wiesner RH, LaRusso NF. Idiopathic adulthood ductopenia. J Hepatol 1988;7:193–9.
[2] Nakanuma Y, Tsuneyama K, Harada K. Pathology and pathogenesis of intrahepatic bile duct loss. J Hepatobiliary Pancreat Surg 2001;8(4):303–15.
[3] Guebel AP, Sempoux CL. Drug and toxin-induced bile disorders. J Gastroenterol Hepatol 2000;15:1232–8.
[4] Moore KL. The digestive system in the developing human. Clinically oriented embryology. 4th edition. Philadelphia: WB Saunders; 1988.
[5] Clotman F, Libbrecht L, Gresh L, et al. Hepatic artery malformations associated with a primary defect in intrahepatic bile duct development. J Hepatol 2003;39(5):686–92.
[6] Holund B, Poulsen H, Schlichting P. Reproducibility of liver biopsy diagnosis in relation to the size of the specimen. Scand J Gastroenterol 1980;15:329–35.
[7] Ludwig J, Wiesner RH, Batts KP, et al. The acute vanishing bile duct syndrome (acute irreversible rejection) after orthotopic liver transplantation. Hepatology 1987;7:476–83.
[8] Ludwig J. Idiopathic adulthood ductopenia: an update. Mayo Clin Proc 1998;73:285–91.
[9] Kahn E, Markowitz J, Aiges H, et al. Human ontogeny of the bile duct to portal space ration: clinical and laboratory findings in 10 cases. J Pediatr Gastroenterol Nutr 1997;24:44–8.
[10] Alagille D, Estrada A, Hadchouel M, et al. Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. J Pediatr 1987;110:195–200.
[11] Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human Jagged1, which encodes a ligand for Notch1. Nat Genet 1997;16:243–51.

[12] O'Reilly K, Ahmed SF, Murday V, et al. Biliary hypoplasia in Williams syndrome. Arch Dis Child 2006;91:420–1.
[13] Woolf GM, Vierling JM. Disappearing intrahepatic bile ducts: the syndromes and their mechanisms. Semin Liver Dis 1993;13:261–75.
[14] Kita H, Matsumura S, He XS, et al. Quantitative and functional analysis of PDC-E2-specific autoreactive cytotoxic T lymphocytes in primary biliary cirrhosis. J Clin Invest 2002;109:1231–40.
[15] Colucci G, Schaffner F, Paronetto F. In situ characterization of the cell-surface antigens of the mononuclear cell infiltrate and bile duct epithelium in primary biliary cirrhosis. Clin Immunol Immunopathol 1986;41:35–42.
[16] Lacerda MA, Ludwig J, Dickson ER, et al. Antimitochondrial antibody-negative primary biliary cirrhosis. Am J Gastroenterol 1995;90:247–9.
[17] Vierling JM, Howell CD. Disappearing bile ducts: immunologic mechanisms. Hosp Pract 1990;141–50.
[18] Wee A, Ludwig J. Pericholangitis in chronic ulcerative colitis: primary sclerosing cholangitis of the small bile ducts? Ann Intern Med 1985;102:581–7.
[19] Ludwig J. Small-duct primary sclerosing cholangitis. Semin Liver Dis 1991;11:11–7.
[20] Murphy JR, Sjogren MH, Kikendall JW, et al. Small bile duct abnormalities in sarcoidosis. J Clin Gastroenterol 1990;12:555–61.
[21] Agostini C, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma. Curr Opin Rheumatol 2000;12:71–6.
[22] Thompson PPP, Pitt HA, Lewin KJ, et al. Sclerosing cholangitis and histiocytosis X. Gut 1984;25:526–30.
[23] Sherlock S. The syndrome of disappearing intrahepatic bile ducts. Lancet 1987;493–6.
[24] Liangpunsakul S, Kwo P, Koukoulis GK. Hodgkin's diseases presenting as cholestatic hepatitis with prominent ductal injury. Eur J Gastroenterol Hepatol 2002;14:323–7.
[25] Ozkan A, Yoruk A, Celkan T, et al. The vanishing bile duct syndrome in a child with Hodgkin disease. Med Pediatr Oncol 2001;36(3):398–9.
[26] Hubscher SG, Lumley MA, Elias E. Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. Hepatology 1993;17:70–7.
[27] Dich NH, Goodman ZD, Klein MA. Hepatic involvement in Hodgkin's disease. Cancer 1989;64:2121–6.
[28] Kim WR, Ludwig J, Lindor KD. Variant forms of cholestatic diseases involving small bile ducts in adults. Am J Gastroenterol 2000;95:1130–8.
[29] Lefkowitch JH, Schiff ER, Davis GL, et al, (Hepatitis Interventional Therapy Group). Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. Gastroenterology 1993;104:595–603.
[30] Delladetsima JK, Makris F, Psichogiou M, et al. Cholestatic syndrome with bile duct damage and loss in renal transplant recipients with HCV infection. Liver 2001;21(2):81–8.
[31] Kikuchi K, Miyakawa H, Abe K, et al. Vanishing bile duct syndrome associated with chronic EBV infection. Dig Dis Sci 2000;45:160–5.
[32] Levy C, Lindor K. Drug-induced cholestasis. Clin Liver Dis 2003;7:311–30.
[33] Velayudham LS, Farrell GC. Drug-induced cholestasis. Expert Opin Drug Saf 2003;2(3):287–304.
[34] Choi SH, Yang SH, Song YB, et al. [A case of vanishing bile duct syndrome associated with hypersensitivity to allopurinol]. Korean J Hepatol 2005;11:80–5 [in Korean].
[35] Capra F, Nicolini N, Morana G, et al. Vanishing bile duct syndrome and inflammatory pseudotumor associated with a case of anabolic steroid abuse. Dig Dis Sci 2005;50(8):1535–7.
[36] Srivastava M, Perez-Atayde A, Jonas M. Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. Gastroenterology 1998;115:743–6.
[37] Taghian M, Tran TA, Bresson-Hadni S, et al. Acute vanishing bile duct syndrome after ibuprofen therapy in a child. J Pediatr 2004;145(2):273–6.
[38] Hautekeete ML, Horsmans Y, Van Waeyenberge C, et al. HLA association of amoxicillin-clavulanate-induced hepatitis. Gastroenterology 1999;117:1181–6.

[39] Desmet VJ. Vanishing bile duct syndrome in drug-induced liver disease. J Hepatol 1997;26S: 31–5.
[40] Burak KW, Pearson DC, Swain MG, et al. Familial idiopathic adulthood ductopenia: a report of five cases in three generations. J Hepatol 2000;32:159–63.
[41] Theise ND, Saxena R, Portmann BC, et al. The canals of Hering and hepatic stem cells in humans. Hepatology 1999;30:1425–33.
[42] Roskams T, Theise ND, Balabaud C, et al. Nomenclature of the finer branches of the biliary tree: canals, ductules and ductular reaction in human livers. Hepatology 2004;39:1739–45.
[43] Van den Heuven MC, de Jong KP, Boot M, et al. Preservation of bile ductules mitigates bile duct loss. Am J Transplant 2006;6:2660–71.
[44] Van den Heuvel MC, De Jong KP, van der Horts ML, et al. Impaired regeneration of biliary cells in human chronic liver allograft rejection. Special emphasis on the role of the finest branches of the biliary tree. Liver Transpl 2004;10:28–35.
[45] Saxena R, Hytiroglou P, Thung SN, et al. Destruction of canals of Hering in primary biliary cirrhosis. Hum Pathol 2002;33:983–8.
[46] Van dn Heuvel MC, Gouw ASH, Boot M, et al. The finest branches of the biliary tree might induce biliary vascularization necessary for biliary regeneration. J Hepatol 2006;44:947–55.
[47] Moreno A, Carreno V, Cano A, et al. Idiopathic biliary ductopenia in adults without symptoms of liver disease. N Engl J Med 1997;336:835–8.
[48] Boyer JL. New perspectives for the treatment of cholestasis: lessons from basic science applied clinically. J Hepatol 2007;46:365–71.
[49] Hagey LR, Crombie DL, Espinosa E, et al. Ursodeoxycholic acid in the Ursidae: biliary bile acids of bears, pandas, and related carnivores. J Lipid Res 1993;34:1911–7.
[50] Pusl T, Beuers U. Ursodeoxycholic acid treatment of vanishing bile duct syndromes. World J Gastroenterol 2006;12:3487–95.
[51] Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid mechanisms of action and clinical use in hepatobiliary disorders. J Hepatol 2001;35:134–46.
[52] Smith LA, Ignacio JR, Winesett MP, et al. Vanishing bile duct syndrome: amoxicillin-clavulanic acid associated intra-hepatic cholestasis responsive to ursodeoxycholic acid. J Pediatr Gastroenterol Nutr 2005;41(4):469–73.
[53] O'Brien CB, Shields DS, Saul SH, et al. Drug-induced vanishing bile duct syndrome: response to ursodiol. Am J Gastroenterol 1996;91(7):1456–7.