The Chronic Cholestasis Enigma in Adults

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Chronic cholestasis may result from diverse etiologies. Patients with clinical and laboratory features of chronic cholestasis present a diagnostic challenge. Recent advances in laboratory and serologic tests, together with the expanded use of endoscopic retrograde pancreatography and more recently computerized tomographic cholangiography, endoscopic ultrasound and magnetic resonance cholangiopancreatography, allow us to classify the different disorders. Classification is difficult due to the presence of common symptoms and overlapping findings, indicating the possibility of common pathogenic processes and the need for more knowledge on the etiology and pathogenesis of these diseases. In this review we discuss chronic cholestasis involving intrahepatic bile ducts in the adult population. The clinical, laboratory, histologic and imaging findings of various patients are presented, reflecting the variability of the entity, the clinical challenges and the therapeutic difficulties.

Case 1

A 50 year old woman was admitted for evaluation of elevated alkaline phosphatase. Her previous medical history was remarkable for diabetes mellitus and breast lumpectomy. Physical examination was normal. Laboratory values showed alanine aminotransferase 35 U/L, aspartate aminotransferase 35 U/L, alkaline phosphatase 843 U/L, gamma-glutamyltransferase 490 U/L, bilirubin 0.6 mg/dl, and positive antimitochondrial antibody. Hepatitis B surface antigen (Australian antigen), anti-hepatitis C virus antibody, antinuclear antibody, and anti-smooth muscle antibody were negative. Needle liver biopsy revealed inflammation of the portal tracts and biliary ducts, with granulomas. Doppler ultrasound showed patent vessels and no evidence of portal hypertension. ERCP was normal except for mild irregularities of some small bile ducts in the right lobe.

The patient was treated with ursodeoxycholic acid 900 mg daily with normalization of her liver function tests, which remained stable for 4 years of follow-up.

Case 2

A 33 year old man presented with bloody diarrhea and abdominal pain of 3 months duration. Physical examination showed mild jaundice and hepatosplenomegaly. Laboratory tests revealed negative titers of ALP 1,513 U/L, GGT 260 U/L, ALT 89 U/L, AST 112 U/L, albumin 2.9 g/dl, globulin 3.8 g/dl, serum amylase 4,000 U/L. HBsAg, anti-HCV antibody, anti-HIV antibody, AMA, and ASMA. Ceruloplasmin and antitrypsin values were normal. Liver scan was consistent with chronic hepatocellular disease with a shift of the colloid to the spleen. Colonoscopy demonstrated moderate to severe pancolitis (ulcerative colitis by histology). Gastroscopy showed esophageal varices grade II. ERCP revealed a classic pattern of sclerosing cholangitis, and a biliary stent was introduced for drainage. The serum amylase returned to normal.

The patient was treated with prednisone, ursodeoxycholic acid and mesalamine. The ALT, AST, bilirubin, and GGT returned to normal, and ALP decreased to 257 U/L. A second ERCP showed improvement of the biliary tree patency with less narrowing areas. Ursodeoxycholic acid, propanolol and 5-ASA were prescribed.

Case 3

A 40 year old man was hospitalized for sudden right abdominal pain, fever, rigor and jaundice. His physical examination demonstrated jaundice and tenderness in the right upper abdomen. Relevant laboratory analysis revealed cholestatic features: ALP 370 U/L, AST 33 U/L, ALT 57 U/L, and bilirubin 9.3 mg/dl. HBsAg, anti-HCV antibody, AMA and ASMA were negative. ERCP showed a characteristic finding of extra- and intrahepatic sclerosing cholangitis. Papillotomy and stent ameliorated the jaundice and the septic condition. A liver biopsy confirmed the diagnosis of sclerosing cholangitis. On colonoscopy an "atrophic" mucosa of the left colon was seen and the biopsy showed chronic inflammation, fibrosis, and atrophic glands. During a detailed history-taking the patient remembered an episode of diarrhea and a brief course of medical therapy 15 years previously. His files contained a rectoscopy and rectal biopsy report consistent with colitis.

During 6 years of follow-up his treatment included ursodeoxycholic acid, calcium and vitamin D, and sulfasalazine. On follow-up, his physical condition had deteriorated, with recurrent episodes of cholangitis, colitis exacerbation, and laboratory features of persistent cholestasis. He is a potential candidate for liver transplantation.

ERCP = endoscopic retrograde pancreatography
ALP = alkaline phosphatase
GGT= gamma-glutamyltransferase
ALT = alanine aminotransferase
AST = aspartate aminotransferase

HBsAg = hepatitis B surface antigen
anti-HCV = anti-hepatitis C virus
anti-HIV = anti-human immunodeficiency virus
AMA = antimitochondrial antibody
ASMA = anti-smooth muscle antibody

Case 4

A 21 year old woman in her 12th week of pregnancy was admitted to hospital because of abnormal liver function tests during the preceding 2 years. A year previously she had undergone a cholecystectomy at which time an intraoperative cholangiogram was normal. The gallbladder showed cholesterolosis without evidence of inflammation, and a small cholesterol stone was found. The liver enzyme tests remained abnormal despite the absence of clinical complaints. On admission, physical examination was normal. Laboratory examinations showed AST 225 U/L, ALT 226 U/L, ALP 171 U/L, GGT 38 U/L, bilirubin 1.0 mg/dl, and normal parathyroid. HBsAg, anti-HCV antibody, antinuclear antibody, AMA, ASMA, and anti-liver-kidney microsomal antibody were negative; serum ceruloplasmin and urine copper were normal. Abdominal ultrasound was normal. MRCP showed a normal biliary tract. Liver biopsy disclosed chronic cholestasis with mild bile duct damage and cholangiolar proliferation, portal and lobular mild hepatitis, portal fibrosis and early septal formation.

She delivered a normal healthy baby. A colonoscopy showed normal mucosa, as did the biopsies. The liver enzymes continued to be abnormal, with pronounced cholestatic features; a second liver biopsy 5 months later showed chronic hepatitis with more advanced portal fibrosis, septal formation, chronic cholestasis, chronic bile duct damage, cholangiolar proliferation, and loss of bile ducts in the portal tracts. A tentative diagnosis of small bile duct primary sclerosing cholangitis was made, and she was treated with colchicine 1.5 mg/day and ursodeoxycholic acid 900 mg/day. Within one month all liver enzyme tests returned to normal.

Case 5

A 52 year old woman was admitted due to left upper abdominal pain. Her physical examination revealed palmar erythema and enlarged spleen. Relevant laboratory studies showed mild leukopenia and thrombocytopenia, ALT 38 U/L, AST 41 U/L, ALP 906 U/L, GGT 202 U/L, albumin 4.1 g/dl, globulin 4 g/dl, and elevated immunoglobulin M. Thyroid-stimulating hormone was 9.53 μg/ml, vitamin B12 25 pg/ml. HBsAg, anti-HCV antibody, and AMA were negative. ANA, antithyroid antibody, antimicrosomal antibody, and antiparietal cell antibody were positive. Doppler ultrasound and gastroscopy revealed portal hypertension. Liver biopsy demonstrated widened portal spaces, inflammation with piecemeal necrosis, proliferation of bile ducts, fibrosis and nodular formation, without granulomas.

The findings were interpreted as consistent with AMA-negative primary biliary cirrhosis or autoimmune cholangitis. A course of corticosteroids was initially given, followed by ursodeoxycholic acid with improvement in liver function.

Case 6

A 23 year old woman was admitted to hospital because of pruritus, dryness of mouth and eyes, arthralgia, and abnormal liver function tests during the previous 2 years. Her physical examination indicated skin excoriation and an enlarged liver. Laboratory analyses showed ALP 1,494 U/L, AST 67 U/L, ALT 73 U/L, GGT 22 U/L, bilirubin 0.4 mg/dl, albumin 3.6 g/dl, globulin 3.2 g/dl, and positive ANA and ASMA; negative HBsAg, anti-HCV antibody, AMA, anti-LKM antibody, antiparietal antibody, anti-sclerodema antibody, and anti-Ro; and normal ceruloplasmin and urinary cooper excretion. Schirmer's test and lower lip biopsy confirmed the diagnosis of Sjogren syndrome. MRCP demonstrated normal bile ducts. A liver biopsy showed mild mononuclear infiltration of the portal tracts as well as lobular inflammation without fibrosis. The portal tracts showed paucity and absence of bile ducts, with no evidence of inflammation of the bile ducts or of granulomas. Discrete copper staining was demonstrated.

Treatment with ursodeoxycholic acid 900 mg was initiated with improvement in liver functions; high steroid dose only partially relieved her severe pruritus and naltrexone was given successfully. Liver transplant should have been considered because of the alarming features of ductopenia.

Discussion

Cholestasis in adults is considered chronic if it has persisted for 6 months or more [1], Several entities should be considered, ranging from the more common, such as biliary and pancreatic tumors or stones, and alcoholism (usually with a more acute presentation), to chronic parenchymal diseases with cholestatic features. The clinical presentation can be diverse: dramatic (as ascending cholangitis or esophageal bleeding), gradual, or even insidious. A detailed medical history – including ingestion of drugs, herbs or alcohol, as well as personal habits – and a careful physical examination are mandatory. An algorithmic workup will help to design a logical pathway of investigation. Exclusion of biliary obstruction with available imaging studies should be the first step, and once viral hepatitis and drug-induced cholestasis are also ruled out [2] a more detailed workup should be planned.

Primary biliary cirrhosis

PBC is a chronic uncommon cholestatic disease, with a prevalence of 40–150 cases per million. It involves the interlobular and septal bile inflammatory ducts and is characterized by progressive non-suppurative inflammation and destruction of these bile ducts with the development of portal and periportal inflammation, subsequent fibrosis and eventually cirrhosis [3–5]. It occurs predominantly in middle-aged women (female-male ratio 9:1) usually between the ages of 40 and 60. It may be discovered incidentally in the setting of elevated alkaline phosphatase levels and hypercholesterolemia, or diagnosed on the basis of complaints of pruritus and fatigue. The pathogenesis of PBC appears to be related to abnormalities in the immune system. CD4 and CD8 lymphocytes have been described in areas of bile duct destruction and periportal inflammation [6]. The hallmark of PBC is the presence of AMA in the serum in 90–95% of patients [7–9]. These antibodies have been shown to be directed against the E2 component of the pyruvate dehydrogenase complex,

MRCP = magnetic resonance cholangiopancreatography

ANA = antinuclear antibody
LKM = liver-kidney microsomal
PBC = primary biliary cirrhosis

which is located on the inner mitochondrial membranes [10]. While granulomatous cholangitis on liver biopsy is diagnostic, it has been suggested that in a middle-aged woman with cholestasis features and positive AMA a liver biopsy may not be necessary [2].

Patient no. 1 described above represents the classical features of PBC: positive AMA test, characteristic liver biopsy findings, and diminished symptoms and improved liver function resulting from appropriate treatment, namely ursodeoxycholic acid. This drug has been shown to be very safe and well tolerated. Early studies demonstrated improvement in long-term survival with use of the drug [11,12], however a recent meta-analysis did not show evidence of it having therapeutic benefit for PBC [13].

Primary sclerosing cholangitis

Diffuse inflammation and fibrosis of the biliary system resulting in irregular, often patchy structuring characterize PSC. Its natural history is one of progression to bile duct obliteration, biliary cirrhosis and liver failure. Approximately 70% of patients have inflammatory bowel disease, most commonly chronic ulcerative colitis [14]. The prevalence is 2.4–4% in inflammatory bowel disease patients, while the population prevalence is 2–7 cases per 100,000 in western countries. The etiology of PSC remains unknown. Portal bacteremia, toxins absorbed from the diseased colon in inflammatory bowel disease, cytomegalovirus and reovirus infections have been implicated by various investigators, but there is little evidence to support these hypotheses. The close association between PSC and various human leukocyte antigen haplotypes is now well established and lends support to the theory that immunologic and genetic mechanisms may be involved in its pathogenesis. Patients with PSC may have elevated levels of circulating immune complexes, immunoglobulins and non-organ-specific autoantibodies [15,16]. The association between ulcerative colitis and PSC remains unexplained and both groups of patients have a high prevalence of antibodies to the perinuclear cytoplasmic antigen [15,17]. ANA and ASMA may be present in low titers but AMA is absent [18]. The male to female ratio is 2:1, and onset is usually between the ages of 25 and 45. The diagnosis of PSC involving large bile ducts is made by MRCP and ERCP. The typical abnormalities are multifocal strictures, which are diffusely distributed, short and annular, with intervening segments of normal or dilated ducts. PSC usually involves large bile ducts, but in a minority of patients only small bile ducts or both are afflicted [19–22]. Liver histology in early stages may show mild portal inflammation, proliferation of ducts and ductules, and non-suppurative cholangitis; later, periductal concentric fibrosis and progressive damage of the liver parenchyma and eventually a biliary pattern of cirrhosis can be observed. Patients with PSC and ulcerative colitis are at increased risk for malignancies of the colon and biliary system and have a particular poor prognosis [23].

Patients 2 and 3 represent different expressions of the disease; the first had an abrupt presentation of the two disorders in the colon and the biliary system. The second patient expressed a different facet: the hidden development of sclerosing cholangitis after a short and forgotten burned-out limited colitis. The acute presentation dictated an urgent therapeutic approach, and the findings raised the suspicion of an underlying disease that was confirmed by the patient's history, a review of old files, and colonoscopy. Patient number 4, who presented with cholestasis in early pregnancy and had undergone a cholecystectomy in the past, represents a real challenge. The possibility of cholestasis in pregnancy should be ruled out, but choledocholithiasis or damage to the bile ducts during the cholecystectomy should also be considered. The long-standing cholestatic features, the imaging procedures, the histologic features of the liver biopsies and the normal biliary tree support the tentative diagnosis of small bile duct primary sclerosing cholangitis, which has only microscopically identifiable features without cholangiographic abnormalities. In retrospect, the presence of the stone in the gallbladder was probably an incidental finding and the abnormal liver function tests were erroneously attributed to the stone.

Autoimmune cholangitis

The term autoimmune cholangitis is a recently proposed entity that describes a specific group of patients presenting overlapping features of primary biliary cirrhosis and autoimmune hepatitis, i.e., histologic findings of PBC coexisting with varying degrees of parenchymal inflammation but with negative AMA and positive ANA. [24,25]. The first patients described were treated successfully with prednisolone and azathioprine [24,25]. When sera from a group of patients thought to have PBC but with negative AMA were analyzed, IgM concentration was lower in these AMA-negative patients and all had high serum levels of ANA; and more were also positive to SMA compared to the AMA-positive patients. Aside from the ANA tests and IgM concentrations, these AMA-positive and negative patients could not be distinguished especially since the liver histology was also non-contributory [26,27]. An early study [28] reported no apparent benefit of ursodeoxycholic acid in four of five patients, but in a recent report the beneficial biochemical effect of ursodeoxycholic acid therapy given to eight patients with AMA-negative PBC (autoimmune cholangitis) was thought to be comparable to that in patients with AMA-positive PBC [29]. It is probable that autoimmune hepatitis is a cholestatic liver disease with a natural history similar to AMA-positive PBC and should be treated with ursodeoxycholic acid.

In patient no. 5, the clinical setting of chronic liver disease, the liver biopsy findings and serology tests support the diagnosis of autoimmune cholangitis. The protean manifestation of autoimmune diseases in different systems (pernicious anemia, hypothyroidism) suggests that the basic etiopathogenesis of the disease is not confined to the liver only, and is rather an expression of underlying derangements of the immune system. Banal complaints of vague abdominal pain revealed severe underlying disease that developed without clinical manifestations over a long period. A short course of prednisone and long-term treatment with urso-

PSC = primary sclerosing cholangitis

IgM = immunoglobulin M

deoxycholic acid 900 mg/day led to amelioration of the cholestatic features. Vitamin B12, thyroxine and propanolol were added.

Idiopathic adult ductopenia

First described in 1988 [30], IAD affects predominantly young adults with clinical and biochemical evidence of cholestasis. The hallmark of the disease is the loss of interlobular and septal bile ducts observed in liver biopsy [31–33]. In the original description of the syndrome, ductopenia was morphologically defined as the absence of interlobular bile ducts in >50% of small portal tracts. Two types are recognized. Type 1 patients are asymptomatic or manifest symptoms of cholestatic liver disease, they tend to have less destruction on the intrahepatic bile ducts, and the clinical course ranges from spontaneous improvement to progression to biliary cirrhosis. Type 2 patients have extensive destruction of the biliary ducts and advanced cholestatic features, and frequently require liver transplantation [34,35]. The pathogenesis is unknown and IAD remains a condition of exclusion.

Four possible etiologies are under discussion. a) late-onset non-syndromic paucity of intrahepatic bile ducts, b) viral cholangitis, c) small bile duct PSC, and d) AMA-negative PBC [36]. Other cholestatic syndromes such as PBC, as well as drug reactions and viral infections must also be ruled out before IAD can be diagnosed [30,31,37]. A follow-up of 23 patients revealed that 7 died from liver failure after a medium of 6.5 years following the diagnosis, 4 underwent liver transplantation, D-penicillamine was administered to 2 patients (no effect), corticosteroids to 2 (improvement in one), and ursodeoxycholic acid to 2 (improvement). With or without treatment the disease was either unchanged or slowly progressive during a mean follow up of 4 years in 10 patients [2].

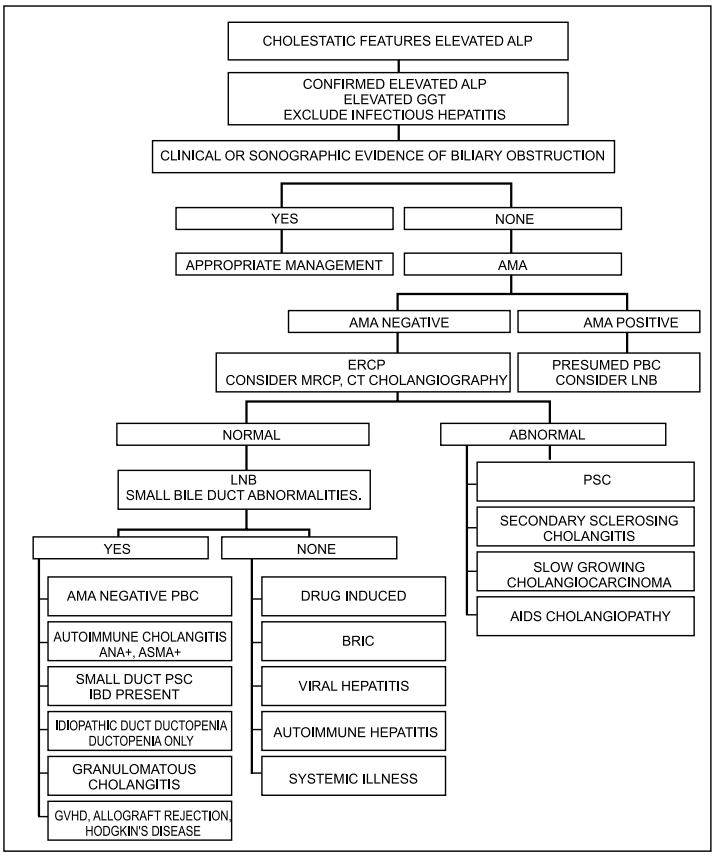

Figure 1. Algorithm for cholestatic disease. BRIC = benign recurrent intrahepatic cholestasis

Conclusions

The clinical presentation of these patients and this review illustrate the diversity and complexity of cholestatic diseases. When confronting a patient with cholestasis, the first steps in the diagnostic evaluation are: a) an assessment of the past medical history, drug therapy, herb use and alcohol ingestion; b) the family history; and c) abdominal ultrasonography to exclude extrahepatic biliary obstruction. Initial laboratory investigations should include liver biochemistry, viral serology, and screening for antimichondrial, antinuclear and anti-smooth muscle antibodies. The combination of the clinical, radiologic and laboratory data may enable us to identify the possible etiology and offer a suitable treatment and follow-up.

An algorithmic approach [Figure 1] guides us to a logical process. The first step encompasses clinical and sonographic assessment of biliary obstruction, the absence of which leads to checking for AMA, ANA, and ASMA. A positive AMA with a titer greater than 1:80 in a female over 40 years old points to PBC, and a liver biopsy will be considered. If AMA tests negative, with positive or negative ANA and/or ASMA, then ERCP is indicated; but MRCP and CT cholangiography, if available, should be considered. MRCP is a promising non-invasive technique that was recently introduced as an alternative to diagnostic ERCP, but a recent study reached the conclusion that the value of MRCP may be limited if patient selection is inappropriate [38]. Oral CT cholangiography is also a feasible non-invasive technique, but the visualization of the biliary tree is suboptimal in 36% of patients, which is a major limitation of this technique [39]. CT cholangiography with the administration of intravenous cholangiographic contrast agent was associated with a high incidence of adverse reactions, including anaphylaxis and occasionally death, which limit their use [40]. Further studies will clarify the role of these promising techniques. If the cholangiography is abnormal, PSC and less common entities – including secondary sclerosing cholangitis, slow growing cholangiocarcinoma or AIDS cholangiopathy – could be diagnosed in the proper clinical and laboratory setting. A normal ERCP indicates the need for liver biopsy. The presence of small bile duct abnormalities enables us to narrow the differential diagnosis: AMA-negative patients with normal cholangiogram are considered to have AMA-negative PBC, or autoimmune cholangitis in the presence of ANA and/or ASMA. The features of the liver biopsy also lead to the possibility of small duct PSC, idiopathic adult ductopenia, granulomatous cholangitis, Hodgkin's lymphoma, graft versus host disease, or allograft

IAD = idiopathic adult ductopenia

rejection in the appropriate clinical setting. In the absence of small bile duct abnormalities, the differential diagnosis includes drug-induced cholestasis, benign recurrent intrahepatic cholestasis, viral hepatitis, autoimmune hepatitis and systemic illnesses.

Science has yet to elucidate the precise and entire mechanism involved in the pathogenesis of cholestatic diseases in which overlapping findings are frequent. Common pathophysiologic mechanisms are probably involved, targeting the same part of the liver with different pathologic and clinical expressions. Immune or even genetic factors are also likely involved. Further studies and research will allow us to better understand and classify these conditions and to establish adequate treatment and management.

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