Seymour Katz, M.D., Series Editor

Hepatobiliary Complications of Inflammatory Bowel Disease

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INTRODUCTION

Extraintestinal complications are frequent in patients with inflammatory bowel disease (IBD). Although clinical liver disease is unusual, elevations of liver enzymes are common and often lead to additional evaluation and testing in an effort to uncover its cause. The reported prevalence of hepatobiliary abnormalities in IBD range from 5% to 95% (1), however, a more realistic estimate is 5% to 15% (2).

Early reports included chronic active hepatitis, cirrhosis and steatosis as common hepatobiliary manifestations of IBD. These studies predated the availability of hepatitis C serologic tests and most likely included a number of patients with undiagnosed chronic viral hepatitis that showed evidence of chronic active hepatitis or cirrhosis on liver biopsy. Indeed, the prevalence of chronic hepatitis B and C has been found to be increased among patients with Crohn's disease (3). Macrovesicular steatosis is a common, nonspecific and reversible liver lesion that is often related to malabsorption, malnutrition and protein loss, medication effect or the metabolic syndrome and is not likely a direct complication of IBD.

Before the availability of endoscopic retrograde cholangiopancreatography (ERCP), liver biopsy series of IBD patients with abnormal liver tests emphasized the presence of "portal triaditis" or "pericholangitis" as lesions typically associated with IBD. With the advent of ERCP it became clear that most of these patients had classical primary sclerosing cholangitis (PSC), which can affect up to 10% of IBD patients and is usually associated with ulcerative colitis. Other hepatobiliary complications that can be seen in association with IBD include cholelithiasis, drug-induced liver disease, autoimmune hepatitis, liver abscess and portal or hepatic vein thrombosis. In general, patients with IBD should be monitored with liver enzymes tests at least once a year to detect hepatobiliary com-

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Table 1
Differential Diagnosis of IBD-Related Liver Dysfunction Based on The Pattern of Liver Enzyme Elevation

Cholestatic (AP >> ALT/AST)	*Hepatocellular (ALT/AST >> AP)*
Primary sclerosing cholangitis	Autoimmune hepatitis
Drug-related	Drug-related
Granulomatous hepatitis	Autoimmune-PSC overlap
Autoimmune-PSC overlap	Viral hepatitis
Pericholangitis	Fatty liver disease
Hepatic abscess	
Cholelithiasis/choledocolithiasis	
Amyloidosis	

AP = alkaline phosphatase, AST = aspartate aminotransferase, ALT = alanine aminotrasferase, PSC = primary sclerosing cholangitis.

plications at an early stage. This paper will present a practical approach to the patient with IBD and abnormal liver tests.

INITIAL APPROACH TO THE PATIENT

Hepatobiliary complications of IBD are not the most common cause of abnormal liver tests in patients with IBD, particularly when the liver enzyme elevation is in a hepatocellular pattern (ALT and AST elevated out of proportion to the alkaline phosphatase). Thus, a systematic approach to exclude common causes of liver disease, unrelated to IBD, should be undertaken in all patients (4). Appropriate serologic testing to exclude viral hepatitis and hemochromatosis should be performed. Fatty liver should be considered among patients with features of the metabolic syndrome. Medication-related liver test abnormalities should be excluded and additional evaluation should be performed depending on the patient's associated symptoms, medical and family history and age.

Hepatobiliary complications of IBD typically present with a cholestatic pattern of liver enzyme elevation (alkaline phosphatase elevated out of proportion to AST and ALT), an early manifestation of PSC. A right upper quadrant ultrasound should be obtained to exclude biliary obstruction or liver masses. When other causes of liver dysfunction are not apparent, IBD-related hepatobiliary dysfunction should be suspected (Table 1). Of these, PSC is the most specific hepatobiliary complication of IBD.

PRIMARY SCLEROSING CHOLANGITIS

PSC, a chronic cholestatic syndrome of unknown cause, has a prevalence of 2.4% to 7.5% among patients with ulcerative colitis (5). There is a 2:1 male predominance and the average age at diagnosis is 39 years (6). Although PSC can develop in patients with Crohn's disease, it occurs for the most part in patients with extensive colonic involvement (7). It is estimated that between 70% to 80% of patients with PSC have IBD.

The diagnosis of PSC should be suspected in any patient with IBD who presents with asymptomatic elevation of the liver tests in a cholestatic pattern with or without hyperbilirubinemia. In more advanced cases, clinical symptoms include fatigue and pruritus followed by the development of jaundice. Ascending cholangitis with jaundice, fever, right upper quadrant pain and rigors, although a common complication of advanced PSC, is not a common presenting feature in previously asymptomatic patients. Physical exam frequently uncovers hepatomegaly, which is painless in the absence of cholangitis. While there are no diagnostic serologic tests for PSC, up to 70% of patients test positive for p-ANCA. Anti-nuclear and anti-smooth muscle antibodies are present in less than 20% of patients. Although in 70% to 80% of patients the diagnosis of IBD predates the discovery of PSC, there is no relationship between the activity of the bowel disease and progression of PSC. In some cases, PSC has developed years after total colectomy for ulcerative colitis. Treatment of the IBD does not have an effect on the clinical course of PSC.

Magnetic resonance cholangiopancreatography (MRCP) is the initial diagnostic test of choice when PSC is suspected.The presence of strictures and beading affecting both the intrahepatic and extrahepatic biliary system is classical for PSC and in the absence of

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atypical clinical or biochemical features usually requires no further diagnostic evaluation. In early cases of PSC, MRCP may be normal or inconclusive. In such cases an ERCP may show the typical cholangiographic changes of early PSC (Figure 1).

The role of liver biopsy in PSC has recently been re-evaluated (8). In cases with classical changes on cholangiography, liver biopsy rarely contributes additional information that affects the management of patients with PSC. In the past, a liver biopsy was recommended to "stage the disease" and help determine the possible need for liver transplantation in the future. However, studies with paired biopsies have shown a high degree of sampling variability, thus a liver biopsy is rarely helpful in patients with typical PSC and may be associated with an increased risk of complications including bile leak.

In contrast, for patients with cholestatic elevation of liver tests and normal cholangiography, a liver biopsy may uncover the presence of small duct primary sclerosing cholangitis (previously known as pericholangitis). The natural history of small duct PSC is controversial. Two recent series (9,10) found progression to classical PSC to be uncommon, and no cases of cholangiocarcinoma, suggesting a much better prognosis for patients with small duct PSC compared to classical PSC.

The pathogenesis of PSC is not well understood but there appears to be a genetic susceptibility with a known association between PSC and certain HLA haplotypes (11). Other factors such as portal bacteremia, accumulation of cytotoxic bile acids, deconjugation of bile salts by bacteria, viral infections and toxins have all been implicated in the pathogenesis of PSC. An abnormality in mucosal lymphocyte homing to the liver leading to the immune mediated hepatic complications of IBD has recently been proposed as a possible mechanism (12).

The natural history of PSC is variable. In general, the median survival time from diagnosis to death or liver transplant is 10 to 12 years. Older age, elevated serum bilirubin, low serum albumin, variceal bleeding, and advanced fibrosis on liver biopsy predict a poor prognosis (13). There is an increased incidence of cholangiocarcinoma in patients with PSC, with a frequency of 6% to 30% (14). Patients with long standing ulcerative colitis and cirrhosis are at the highest risk. The diagnosis is very difficult to establish as cholangiographic findings of PSC with cholangiocarcinoma are similar to PSC alone and brush cytology is rarely diagnostic. Serologic markers such as CEA and cancer antigen 19-9 levels have not been found to be uniformly helpful and routine screening for cholangiocarcinoma is not recommended.

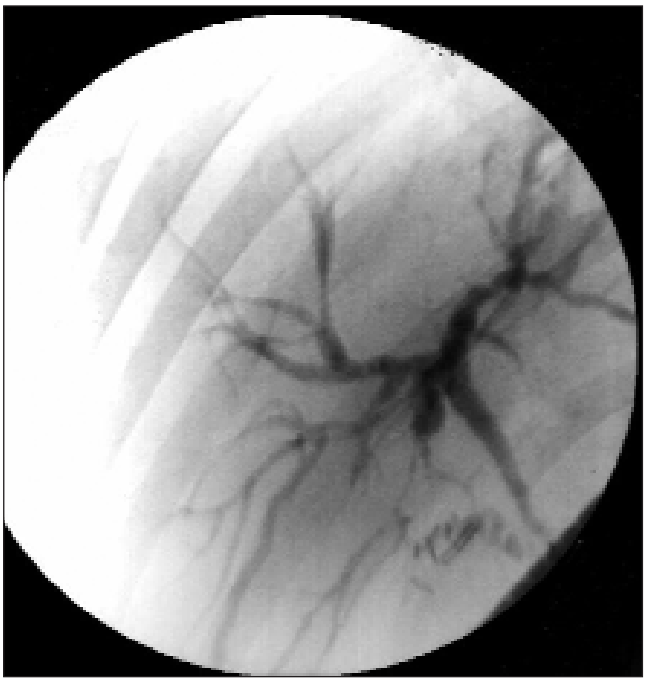

Figure 1. Endoscopic retrograde cholangiography demonstrating early changes of primary sclerosing cholangitis including beading with areas of narrowing in the intra- and extra-hepatic biliary system.

There is no specific therapy for PSC, and no drug has been found to alter its natural history. Ursodeoxycholic acid (UDCA) has been widely used to treat PSC, but recent trials have failed to show a benefit in improving the natural history of PSC. UDCA, however, is useful as a chemopreventive agent in patients with ulcerative colitis and PSC, decreasing the incidence of colon carcinoma (15,16).

Patients with PSC develop various complications that need to be addressed. Pruritus is a common symptom and usually responds to bile salt binders such as cholestyramine. Patients should be cautioned to separate cholestyramine from the other medications by at

least 3 hours to prevent intraluminal binding of medications by the bile salt binder. Steatorrhea and fat-soluble vitamin deficiencies may occur as a result of the cholestasis and can be aggravated by therapy with cholestyramine. Fat soluble vitamins should be prescribed and levels monitored as needed. Metabolic bone disease is a common complication, monitoring with bone densitometry and treatment with calcium, vitamin D and biphosphonates on an individual basis is recommended.

Bacterial cholangitis usually develops after endoscopic procedures to retrieve stones or dilate biliary strictures. In some cases, recurrent cholangitis may develop without prior endoscopic procedures, particularly in patients with dominant strictures. Antibiotic therapy, and occasionally chronic antibiotic use, may be needed to treat and prevent cholangitis.

Liver transplantation is the only definitive therapy for patients with PSC. Transplantation in these patients is often difficult because of the presence of cholangitis or cholangiocarcinoma which are common contraindications to transplant. For those patients who still have a colon in place, careful surveillance for colorectal carcinoma must be followed after transplant, as the immune suppression may allow colon carcinoma to spread rapidly.

AUTOIMMUNE HEPATITIS AND AUTOIMMUNE-PSC OVERLAP

Marked elevation of ALT and AST, hypergammablobulinemia and the presence of high titer anti-nuclear antibodies or anti-smooth muscle antibodies raise the possibility of autoimmune hepatitis (AIH). Up to 16% of adults with AIH have ulcerative colitis (17). These patients are clinically and biochemically indistinguishable from those with AIH and no ulcerative colitis. In up to 40% of patients with UC and AIH, cholangiography will reveal changes typical of sclerosing cholangitis (17). Patients with ulcerative colitis and AIH who do not respond well to prednisone therapy should undergo cholangiography as co-existent sclerosing cholangitis may be the cause of refractoriness to treatment. In a small group of patients with AIH and normal cholangiography, liver biopsy may show evidence of pericholangitis or small-duct PSC.

An overlap syndrome of AIH and PSC is well documented. These patients present with clinical and biochemical features typical for both diseases. In a recent series, approximately 7% of patients with cholangiographically confirmed PSC met histologic criteria for AIH as well (18). The treatment of patients with the overlap syndrome is controversial. While the hepatic component tends to improve with immunosuppession, response becomes less prominent as the cholestatic features advance. Treatment with ursodeoxycholic acid alone or in combination with prednisone may be of benefit for those with predominantly cholestatic features or those who do not respond well to prednisone.

CHOLELITHIASIS

There is an increased incidence of gallstones among patients with Crohn's disease, an association that has not been noted with UC. Among patients with CD incidence of cholelithiasis ranges from 13% to 34%, higher than in the general population (19).

The pathogenesis of gallstones in CD is felt to be related to altered bile salt metabolism in patients with ileal involvement or after surgical resection of the ileum. The decrease reabsorption of bile salts by a diseased or shortened ileum results in cholesterol supersaturated bile increasing the risk of gallstones. Other series have shown an increase in conjugated and unconjugated bilirubin in the gallbladder bile of CD patients with ileal disease or resection, increasing the risk of bilirubin stones (20). The management of gallstone disease in IBD patients does not differ from that in the general population.

CHRONIC VIRAL HEPATITIS

Theoretically, patients with inflammatory bowel disease are at increased risk of contracting viral hepatitis due to multiple hospitalizations, invasive procedures and transfusions of blood and blood products, particularly before 1992 when the risk of transmission of hepatitis C was high. In a study from Italy, patients with Crohn's disease were found to have a higher prevalence of hepatitis C antibody (7.4%) compared to ulcerative colitis patients (0.6%) (3).

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A pertinent issue when treating patients with viral hepatitis and IBD is whether immunomodulatory drugs for IBD can affect the course of the liver disease. Prednisone may allow levels of HBV and HCV to rise during therapy with the potential for a symptomatic flare of the disease upon withdrawal of the steroid therapy. This phenomenon is more of a concern in hepatitis B rather than hepatitis C infection. In general, it is believed that corticosteroid therapy has little effect on the natural course of hepatitis C infection despite rising levels of viremia. Because of the concern of hepatitis B flare after withdrawal of immunosuppression, most experts would consider either close monitoring of HBV viral levels and liver enzymes during and after treatment with corticosteroids or using an oral nucleoside or nucleotide analogue as a prophylactic measure during and for at least 6-8 weeks after completion of prednisone therapy.

The safety of infliximab in chronic hepatitis C infection has been demonstrated in retrospective studies of rheumatoid arthritis patients (21). Among 16 viremic patients with HCV, no significant changes in liver enzymes or viral load measurements were noted during a median 9-month follow up of infliximab therapy. Additional isolated case reports and small case series also demonstrate that infliximab can be safely used in patients with hepatitis C infection and Crohn's disease (22).

Infliximab should be used with great caution in patients with chronic hepatitis B infection. Immune control of viremia is pivotal in controlling the activity of the disease in hepatitis B infection. Immune modulating therapies that alter the immune balance can easily trigger a flare in patients with stable chronic hepatitis B; these flares can at times be severe. While there are isolated case reports of patients with HBV who were safely treated with infliximab (23), there are several case reports and case series of hepatitis B virus flares during infliximab therapy (24). Patients at risk for viral hepatitis should be tested for hepatitis B surface antigen in serum prior to therapy with infliximab. For those with known chronic hepatitis B infection, strong consideration should be given to prophylactic therapy with an oral nucleoside or nucleotide analogue to control the hepatitis B viremia during and for 6 to 8 weeks after completion of infliximab therapy.

Table 2
Hepatotoxicty of IBD-Related Medications

Medication	*Type of Liver Toxicity*
5-ASA	Acute hepatitis (classical) Cholestasis Granulomatous hepatitis
Thiopurines	Asymptomatic liver enzyme elevation Acute hepatocellular injury Cholestasis Nodular regenerative hyperplasia
Methotrexate	Asymptomatic liver enzyme elevation Steatosis Fibrosis
Infliximab	Cholestasis (rare) Flare of pre-existing hepatitis B

MEDICATION-INDUCED HEPATOTOXICITY

Patients with inflammatory bowel disease are exposed to multiple medications that can be associated with hepatotoxicity. The pattern of liver enzyme elevation is sometimes helpful in elucidating the culprit (Table 2). Although drug hepatotoxicity is uncommon, most IBD medications have been identified as potential culprits.

5-ASA Drugs

Sulfasalzine hepatotoxicity can manifest in various ways. Classically it presents as an acute hepatitis picture with marked elevations of ALT and AST. Cases of cholestatic hepatitis, granulomatous hepatitis and a mixed picture have been described as well. Systemic manifestations such as fever and rash are also commonly seen. Hepatotoxicity is much less common with the newer 5-ASA compounds. As with sulfasalazine, cases of hepatocellular liver injury, cholestasis and granulomatous hepatitis have been reported (25). The mechanism for the toxicity of 5-ASA compounds is unknown but interaction with iron to yield oxygen-derived free radicals may be the cause in susceptible individuals.

Thiopurines

Hepatotoxicity from thiopurine use is usually a dose-dependent effect and can be reversible with dose reduction or discontinuation. Both acute hepatocellular and cholestatic presentations have been described, and the occurrence of hepatotoxicity appears to be greatest among patients co-treated with corticosteroids (26). Approximately 10% of patients treated with thiopurines develop abnormalities of the liver tests, although only a minority develop symptomatic hepatitis. Elevated levels of 6-methylmercaptopurine (6-MMP) have been shown to be associated with an increased frequency of hepatotoxicity as defined by elevations in transaminase levels greater than two times normal. These findings suggest that the accumulation of 6-MMP could play an important role in the pathogenesis of thiopurine–induced hepatic toxicity; however, even patients with low levels of 6-MMP can develop thiopurine-related hepatotoxicity.

Nodular regenerative hyperplasia (NRH), a condition associated with portal hypertension, was first described as a complication of thiopurine therapy among patients with leukemia. Several documented cases of NRH in IBD patients treated with thiopurines are well described. This complication appears to be idiosyncratic rather than dose related and should be suspected in patients presenting with complications related to portal hypertension in the absence of cirrhosis.

Infliximab

Concerns regarding the use of infliximab in patients with co-existent viral hepatitis have been previously discussed. A case of reversible cholestatic liver disease has been described in a patient with Crohn's disease and no underlying liver disease who received infliximab (27). In a review of 500 patients receiving infliximab, drug-hepatotoxicity was not described (28).

Methotrexate

Methotrexate use has been associated with hepatotoxicity primarily among patients with psoriasis and psoriatic arthritis. A small series of 32 patients with IBD who received cumulative doses of methotrexate >1,500 mg has been described (29). Abnormal liver chemistries were present in 30% of patients and did not correlate with histologic findings of methotrexate hepatotoxicity. Among 20 patients who underwent liver biopsy, 95% had mild histologic findings and only one patient had fibrosis.

MISCELLANEOUS HEPATIC COMPLICATIONS OF IBD

Liver abscess is increased in frequency among patients with IBD (30). Bacterial translocation through a diseased small bowel or colon, or local or arterial seeding from intra-abdominal abscesses can lead to the formation of pyogenic liver abscess. Portal pyelophlebitis can lead to portal vein thrombosis, a condition that is also increased in prevalence among IBD patients even in the absence of intra-abdominal infections. Thromboembolic complications are well described in patients with IBD (31), even in the absence of intra-abdominal infections. Portal and hepatic vein thrombosis are recognized hepatic complications of patients with IBD.

Other rare hepatic complications include hepatic amyloidosis, which is more common in Crohn's disease than in ulcerative colitis (32). A granulomatous hepatitis can develop in patients with Crohn's disease (33), typically presenting as a cholestatic hepatitis with predominant elevation of the alkaline phosphatase. On histologic examination, the hepatic granulomata are identical to those classically seen in the intestinal biopsies from patients with Crohn's disease. Inflammatory pseudotumor of the liver, a rare benign lesion characterized by proliferating fibrous tissue infiltrated by inflammatory cells, has been described in patients with Crohn's disease (34). These lesions can mimic malignancy on radiologic examination, but have classical histologic findings and a good prognosis in most cases.

CONCLUSIONS

Inflammatory bowel disease is a systemic illness that can present with multiple extra-intestinal manifestations. Primary sclerosing cholangitis is the classical IBD-related liver disorder and occurs most often in patients with ulcerative colitis. It is important to remember that patients with IBD are as likely as other

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patients to develop non-IBD related liver disorders and a diligent search for common causes of hepatobiliary disease should be performed. ■

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