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Hepatobiliary Disease and Inflammatory Bowel Disease

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Multiple hepatobiliary diseases are associated with inflammatory bowel disease (IBD) with primary sclerosing cholangitis (PSC) being one of these diseases. The majority of patients with PSC also have IBD, more commonly ulcerative colitis (UC) than Crohn's disease (CD).[1-4] PSC manifests as strictures and fibrosis of the intra- and extrahepatic bile ducts and is associated with cholangitis, cholangiocarcinoma and an increased risk of colorectal cancer.[2-4,7,9-11] PSC can also lead to cirrhosis of the liver, which is associated with an increased risk of hepatocellular carcinoma.[4,8] Drug-induced liver disease can be seen in IBD patients. Methotrexate in particular can lead to cirrhosis and patients should be evaluated for liver disease prior to starting methotrexate.[4] Other liver disease manifestations in IBD include amyloidosis, steatosis, and granulomatous hepatitis. Cholelithiasis in patients with IBD occurs in CD with ileal involvement.[4] This review article will discuss the hepatobiliary diseases seen in patients with IBD.

INTRODUCTION

Ten to twenty percent of patients with inflammatory bowel disease (IBD) have liver disease.[1] This article will encompass important inflammatory conditions, such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). We will also discuss drug-induced liver injury, cholelithiasis, steatosis and rare liver diseases associated with IBD, such as amyloidosis and granulomatous hepatitis.

Primary Sclerosing Cholangitis

PSC is a chronic inflammatory condition of the intra- and extrahepatic bile ducts that leads to strictures and fibrosis of the bile ducts (Figure 1).[2-4] The prevalence of PSC is 6-16 cases per 100,000 people in North America and Europe.[2,5,6] The disease is more commonly found in men than in women.[2,4] About 70% of patients with PSC also have IBD, usually ulcerative colitis (UC), but it can also be seen in Crohn's disease (CD).[1-4]

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The pathogenesis of PSC is unknown. There may be a genetic predisposition to PSC as there is an increased risk of PSC in patients having a first-degree relative with the disease.[2]

Patients are often asymptomatic at the time of diagnosis and the most common laboratory abnormality is an elevated alkaline phosphatase.[2,4] Diagnosis can be made with magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) (Figure 1), and percutaneous transhepatic cholangiography (PTC).[2,4,7] When comparing MRCP to the other imaging modalities, the sensitivity and specificity of MRCP for the diagnosis of PSC have been reported at ≥80% and ≥87% respectively.[7] These imaging modalities will demonstrate a "beaded" appearance of the intra- and extrahepatic bile ducts.[4,7] This appearance of the bile ducts represents multiple stricturing areas interspersed with normal or dilated areas.[2,7]

There are a number of adverse outcomes associated with PSC. PSC can lead to cirrhosis and the adverse effects of end-stage liver disease.[4,8] It is also associated with recurrent episodes of cholangitis.[7] There is an increased risk of colorectal cancer in patients with PSC and ulcerative colitis compared to patients with ulcerative colitis alone.[2,9,10] Patients should therefore start screening colonoscopies when they are diagnosed with both diseases.[9] Patients with PSC not only have an increased risk of colorectal cancer, but they also have an increased risk of cholangiocarcinoma, which is seen in 7-15% of patients.[3,7,11] It is important to note that PSC has a course independent of IBD and it is unchanged by colectomy.[2,4,9]

Ursodeoxycholic acid (UDCA) has been studied for the treatment of PSC, but it has not been shown to be beneficial in PSC.[2] High dose UDCA (28-30 mg/kg/day) has demonstrated an increased risk of adverse events in PSC patients.[12,13] Definitive treatment for PSC is a liver transplant, but PSC can recur in patients post-transplant.[2,7]

One type of PSC, small-duct PSC, can only be diagnosed by liver biopsy since it does not have the typical imaging findings seen in large-duct PSC.[2,4,7] Small-duct PSC demonstrates similar laboratory findings and histology to large-duct PSC and it can progress to large-duct PSC.[2,4,7]

An overlap syndrome between autoimmune hepatitis and PSC occurs in IBD patients.[2,4,7] These patients have the classic imaging findings seen in PSC and laboratory findings that suggest autoimmune hepatitis, such as elevated aminotransferase levels, gamma-globulin levels, anti-nuclear antibody levels, and anti-smooth muscle antibody levels.[2,7] Liver biopsy is usually required for this diagnosis.[2]

Primary Biliary Cirrhosis

PBC is characterized by destruction of the intrahepatic bile ducts.[14] It is an autoimmune disease that is seen more often in women, with increased risk in first-degree female relatives.[14,15] Although PBC is not specifically associated with IBD, it should also be suspected in patients with an elevated alkaline phosphatase or cholestasis.[15] PBC can lead to fibrosis and cirrhosis of the liver.[15] 90-95% of patients with PBC have antimitochondrial antibodies.[14] Elevated alkaline phosphatase, mild transaminase elevation, and increased immunoglobulins, usually immunoglobulin M (IgM), are common laboratory abnormalities seen in PBC.[15] The diagnosis of PBC is based on two of the three following criteria: positive antimitochondrial antibodies, elevated alkaline phosphatase and a liver biopsy that demonstrates destruction of bile ducts in the portal triad.[15]

Osteoporosis, hyperlipidemia, and vitamin deficiencies are found in PBC with advanced disease.[14,15]

UDCA is used in the treatment of PBC and it can delay the progression of early stage disease.[14,15] Colchicine and methotrexate have been used as second and third-line agents.[14] When patients have advanced liver disease, the only treatment is orthotopic liver transplantation, but PBC can recur in the transplanted liver.[14,15] A normal or low bilirubin level is the best predictor of survival in PBC.[15]

Cholelithiasis and Choledocholithiais

Cholelithiasis can be seen in patients with IBD, especially in patients with CD with ileal involvement.[4] These patients can have an increased biliary cholesterol saturation and this may increase cholelithiasis.[16] Choledocholithiasis occurs in 15% of patients with cholelithiasis and can lead to cholecystitis, cholangitis and pancreatitis.[17] It is therefore important to evaluate for gallstones in all IBD patients with abnormal liver function tests.

Drug Induced Liver Injury

The most common type of drug-induced liver injury is an idiosyncratic reaction that is not dose-dependent

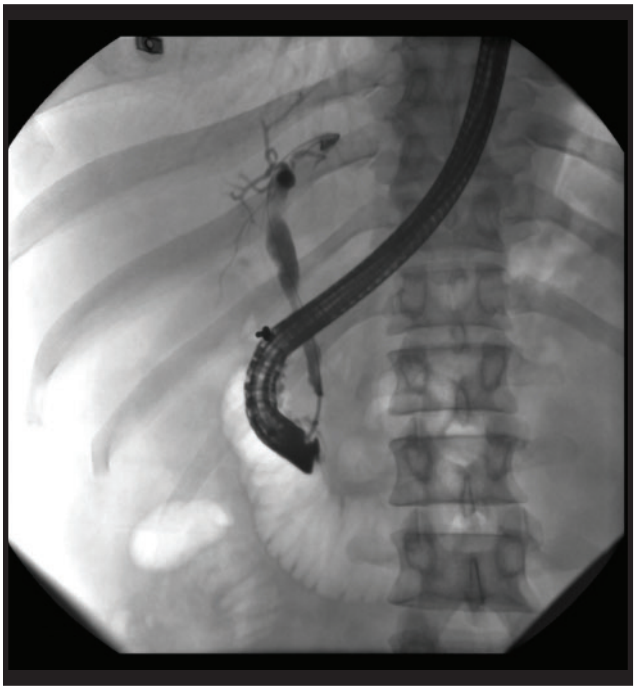

Figure 1. ERCP cholangiogram demonstrating extrahepatic PSC with CBD stricture secondary to cholangiocarcinoma. *Image from author's personal file*

and can occur days after starting the medication.[4] Methotrexate, cyclosporine and azathioprine can cause hepatotoxicity in a dose-dependent method.[4]

5-aminosalicylate (5-ASA) compounds can lead to an elevation in aminotransferase levels.[4] There are case reports of granulomatous hepatitis secondary to sulfasalazine.[18]

Azathioprine and 6-mercaptopurine (6-MP) can cause liver disease in a hepatocellular or cholestatic method, but usually laboratory values improve after stopping the drugs.[1,4,19] Mild transaminase elevation can be managed by lowering the dose of the drugs.[1,4] Azathioprine and 6-MP can also cause nodular regenerative hyperplasia of the liver, which is a rare long-term complication that can lead to portal hypertension.[1,20,21]

Methotrexate can cause a transaminitis.[1] Methotrexate hepatotoxicity can eventually lead to cirrhosis and should be used with caution in patients with pre-existing liver disease.[4,22] Hepatotoxicity occurs in a dose-dependent fashion.[4]

Cyclosporine can also cause hepatotoxicity based on the dosing of the medication.[4] The liver injury is usually a cholestatic pattern.[4]

Infliximab-induced hepatotoxicity is rare and can cause a transaminitis.[1,23,24] Infliximab can also cause an exacerbation of hepatitis B.[25] All patients should be tested for hepatitis B prior to treatment with infliximab.[25]

All Others – Rare Diseases

Steatosis

Steatosis can occur in patients with IBD and often presents as elevated transaminases.[1] Ultrasound, CT and MRI can help diagnose patients with non-alcoholic fatty liver disease (NAFLD).[1,26] Sourianarayanane et al. used imaging techniques and found the prevalence of NAFLD to be 8.2% in IBD patients, which is lower than that seen in the general population. The study also found that IBD patients with NAFLD had a higher BMI, more obesity, and more signs of metabolic syndrome.[26] The patients with NAFLD in this study were more likely to have had previous small intestinal surgery, to take steroids at the time of imaging, and less likely to have received anti-TNF-α medications.[26] The gold standard for diagnosis is liver biopsy and can evaluate for non-alcoholic steatohepatitis (NASH).[1]

Hepatic Amyloidosis

Amyloidosis occurs in 0.9% of patients with CD and 0.07% of patients with ulcerative colitis.[4] Amyloid can deposit in multiple organs, including the liver.[27] Systemic AA amyloidosis is associated with IBD.[27,28] Liver biopsy is needed for diagnosis.[4]

Granulomatous Hepatitis

Granulomatous hepatitis can be seen in patients with CD with an elevated alkaline phosphatase.[4]

Liver Abscess

Liver abscesses can occur in patients with IBD, especially CD, and can present with fever, right upper quadrant pain, leukocytosis and an elevated alkaline phosphatase.[4,29] Diagnosis can be made with imaging studies, such as an abdominal ultrasound or CT scan.[4] Liver abscesses are usually treated via percutaneous drainage.[29]

Cancers – HCC and Cholangiocarcinoma

Patients with PSC are at increased risk of cholangiocarcinoma, with a prevalence of 7-15%.[3,7,11] It is difficult to diagnose cholangiocarcinoma since it

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resembles the strictures seen in PSC and there is often a high mortality rate at the time of diagnosis.[4,7,30] Risk factors for cholangiocarcinoma in PSC include elevated bilirubin, variceal bleeding, proctocolectomy, and ulcerative colitis with colorectal cancer or dysplasia.[11] Cholangiocarcinoma arises in both the intra- and extrahepatic bile ducts and it is divided into intrahepatic, perihilar and distal disease.[30] When imaging the biliary tree in PSC, long strictures may indicate an underlying cholangiocarcinoma.[2,3,11] An elevated CA 19-9 can be helpful; however, patients who are Lewis antigen negative will not be positive for CA 19-9.[3,4]

ERCP with brush cytology may aid in the diagnosis of cholangiocarcinoma, but its sensitivity is low.[2-4] Flourescence in situ hybridization (FISH) increases the sensitivity of ERCP brushings.[2,3]

Cholangiocarcinoma is frequently diagnosed at advanced stages and it is therefore difficult to treat, often palliative.[4,7,31] Liver transplant has been used in treatment of early cholangiocarcinoma.[2,31] The American Association for the Study of Liver Diseases (AASLD) guidelines recommend liver transplant in patients with a single unresectable mass that is ≤ 3cm and no metastatic disease.[2,4,7] Patients are given radiation and chemotherapy prior to transplant.[2,4,7]

Hepatocellular carcinoma (HCC) occurs in patients with PSC when PSC has progressed to cirrhosis.[4,8,32] AASLD recommends surveillance for HCC every 6 months in patients with cirrhosis.[32] The diagnosis of HCC can be made with four-phase CT scans or MRI scans which demonstrate early arterial enhancement and delayed washout of the HCC mass.[32,33] Smaller lesions, usually < 2 cm, often need serial imaging and biopsy to help with diagnosis.[33]

Treatment of HCC is based on the size of the lesion and extent of underlying liver disease.[34] Surgical resection, orthotopic liver transplantation, radiofrequency ablation, transarterial chemoembolization (TACE), and chemotherapy are the treatment modalities used for HCC.[33,34] The Barcelona Clinic Liver Cancer (BCLC) staging helps determine prognosis in patients with HCC.[34,35] The Milan Criteria is used to determine if a patient is eligible for an orthotopic liver transplant.[32-34] Patients with one mass < 5 centimeters or three masses < 3 centimeters are eligible for orthotopic liver transplantation.[32-34] The 5-year survival rate for orthotopic liver transplantation following the Milan Criteria is 70%.[32]

CONCLUSION

IBD is a chronic inflammatory condition that involves the gastrointestinal tract.[9] There are multiple hepatobiliary diseases associated with IBD and these diseases should be investigated when an IBD patient presents with abnormal liver function tests.

PSC is one of the more common manifestations of liver disease in IBD.[1-4] Patients with an elevated alkaline phosphatase and IBD should be evaluated with the appropriate imaging tests for possible PSC.[2,4] Medications used to treat IBD can lead to drug-induced liver injury, which may precipitate discontinuation of these medications. Cholelithiasis and steatosis, similar to the general population, are seen in patients with IBD.[1,4] Rare complications of IBD include amyloidosis and liver abscesses.[27,29] These diseases are associated with systemic symptoms, such as renal and cardiac involvement in amyloidosis and fever and leukocytosis in liver abscesses.[4,27,29] ■

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