Hepatobiliary Manifestations of Inflammatory Bowel Disease

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Hepatobiliary manifestations occur quite frequently in patients suffering from chronic ulcerative colitis and Crohn's disease and carry with them considerable morbidity and mortality. Although the true incidence is difficult to determine, clinically significant hepatobiliary disease occurs in 5%–10% of patients. At the present moment, the aetiology and pathogenesis of inflammatory bowel disease and its systemic manifestations remains speculative. For those hepatobiliary manifestations that respond to therapy of the underlying bowel disease, medical and/or surgical therapy must be aggressively pursued. More urgent research is required towards understanding the underlying cause(s) of the primary bowel disease and its systemic manifestations in order to improve the overall management of this condition.

Keywords: Inflammatory bowel disease, chronic ulcerative colitis, Crohn's disease, extraintestinal manifestations

INTRODUCTION

Chronic ulcerative colitis (CUC) and Crohn's disease (CD), though chiefly effect the gastrointestinal tract, are frequently associated with a wide array of extraintestinal manifestations

(EIM), the incidence of which varies between 25% and 36% [1–3]. Hepatobiliary manifestations are amongst the most common EIM associated with inflammatory bowel disease (IBD). They not only complicate the management of the primary disease but also contribute significantly to mortality and morbidity. Even before CUC was recognized as a clinical entity, fatty liver changes with diffuse colonic ulceration were described as early as 1874 by Thomas [4] which were confirmed by Lister in 1889 [5] who reported a patient with CUC and secondary diffuse hepatitis. Further evidence of association between CUC and hepatic involvement emerged from an autopsy study [6]. Although initial studies failed to show any association between CD and hepatobiliary disease, it soon became apparent that liver and biliary tract involvement occurs with equal frequency in patients with CD and CUC [7].

Although the prevalence of hepatobiliary disease in patients with IBD varies widely in different series from 2%–95%, clinically significant liver disease occurs in only 5%–10% of patients

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[8] (Tab. I). Such a discrepancy between the various series occurs because of a number of factors which include (a) on how aggressively diagnostic studies are pursued; (b) the number of patients included with mild, moderate and severe disease; (c) whether the disease was active or in remission and (d) the type of bowel involvement *i.e.*, extensive or limited. There is no consistent temporal relationship between the onset of symptoms and hepatobiliary abnormalities [7]. On average, CUC is present for approximately 8 years before the hepatic abnormalities become apparent [7]. The onset of symptoms may precede, follow or occur at the time of exacerbation of bowel disease. Associated hepatic conditions range from those which are little more than laboratory abnormalities, to those that are life-threatening. An interesting observation noted in patients with CD is, if the disease is restricted to the small bowel, hepatic involvement is rare.

Because the etiology and pathogenesis of IBD and the associated hepatobiliary complications remain elusive and speculative in the large part, it remains unresolved if these manifestations represent the systemic nature of the IBD or whether they truly are complications of the colitis.

FATTY LIVER (HEPATIC STEATOSIS)

Fatty liver occurs in 15%–80% of patients with IBD [9]. Patients with severe colitis, fulminant

first attack of colitis and those requiring colectomy over the age of 50 have the highest risk of developing this condition [8]. The incidence, however, falls to approximately 5% with mild disease [10]. Numerous factors may contribute towards this condition including malnutrition, bacterial metabolites, anemia, protein loss, drugs such as corticosteroids and tetracycline, chronic debilitating illness and total parental nutrition. Histological analysis reveals large fat droplets within hepatocytes with minimum surrounding inflammation. Fortunately, fatty liver does not progress to debilitating liver disease. This is an asymptomatic condition, although abdominal examination may reveal hepatomegaly. Treatment of the underlying bowel pathology and improving general health of the patients is all that is required. With advances in the treatment of IBD, the incidence of this condition may be far less than previously reported.

CHOLELITHIASIS

Cholelithiasis occurs in 4%–34% of patients with IBD [2, 8, 11–13]. It occurs more frequently in CD than in CUC, and is perhaps more a secondary complication rather than a systemic manifestation. In CD, there is a positive correlation between stone formation and location, extent, and duration of ileal involvement as well as ileal resection and increased patient age [2, 13–15]. For CUC, total colitis extending to the caecum poses the greatest risk for gallstones

TABLE I Hepatobiliary manifestations of IBD

	Chronic ulcerative colitis	Crohn's disease
More commonly associated (>5%)	<ul style="list-style-type: none"> • Hepatic steatosis • Small duct primary sclerosing cholangitis (Pericholangitis) 	<ul style="list-style-type: none"> • Hepatic steatosis • Cholelithiasis • Hepatic amyloidosis
Less commonly associated (≤5%)	<ul style="list-style-type: none"> • Primary sclerosing cholangitis • Bile duct carcinoma • Cryptogenic cirrhosis • Cholelithiasis 	<ul style="list-style-type: none"> • Primary sclerosing cholangitis • Autoimmune chronic active hepatitis • Cryptogenic cirrhosis
Rare associations(<1%)	<ul style="list-style-type: none"> • Hepatic amyloidosis • Hepatic granuloma • Pancreatitis • Herpes simple hepatitis 	<ul style="list-style-type: none"> • Hepatic granuloma • Liver abscess • Bile duct carcinoma

[16]. The formation of cholesterol gallstones stems from the interruption of the normal enterohepatic circulation of bile acids. Disruption of the normal enterohepatic circulation results in depletion of the bile salt pool and the subsequent secretion of lithogenic bile [17,18]. The mechanism involved in the formation of radiopaque pigmented stones is not completely understood. If the gallstones becomes symptomatic, laparoscopic or open cholecystectomy is the treatment of choice.

CHOLANGIOCARCINOMA/ HEPATOCELLULAR CARCINOMA

Cholangiocarcinoma in association with CUC was first recognized by Parker and Kendall in 1954 [19]. Since then this relationship between biliary tract tumors and CUC has been well established. The reported incidence of cholangiocarcinoma in patients with IBD is between 0.4%–1.4%, which is 10–100 times greater than reported for the general population [9,20–24]. On the other hand, the incidence of CUC in patients with bile duct cancer is between 6% and 14% [24]. It is more common in men and occurs in the fourth and fifth decades, about 20 years earlier than in the general population [8,10,14]. It occurs predominantly in patients with CUC, but has also been reported in patients with CD. Most cholangiocarcinomas develop in patients with preexisting PSC [25]. The greatest risk appears to be for those CUC patients with pancolitis and for those with an average duration of 15 years of disease [9]. There is no apparent relationship between the development of cholangiocarcinoma and the activity of bowel disease as it may develop during prolonged remission and even following proctocolectomy [21,22,26,27]. The clinical presentation of cholangiocarcinoma is that of progressive cholestatic jaundice. Radiographically, these tumors may present as polypoid or papillary masses, as rapidly progressive strictures, or as annular constricting lesions with proximal bile duct

dilatation. Common sites of involvement are large biliary ducts or the bifurcation of the intrahepatic ducts. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) will demonstrate the majority of these lesions, while laparotomy may be reserved where diagnosis is in doubt. A retrospective study suggests that the measurement of tumor associated antigen CA 19–9, may be promising for the detection of cholangiocarcinoma complicating PSC [28]. The tumour usually pursues a progressive course and prognosis is very poor, with a median survival of 5 months [29]. Palliative surgery is the most effective treatment but has little impact on prolonging the survival [8]. Similarly the results of orthotopic liver transplantation has been disappointing due to early recurrences [30].

Fibrolamellar hepatocellular carcinoma has recently been diagnosed in two patients with CUC and PSC [31,32]. Both of these patients were free of cirrhosis. One of these patients received liver transplantation but died of tumor recurrence [32].

LIVER CIRRHOSIS

Cryptogenic liver cirrhosis occurs in approximately 1–5% of patients with hepatic abnormalities and IBD [33,34]. It is more frequently seen in extensive ulcerative colitis or Crohn's colitis as compared to Crohn's ileitis. Autoimmune Chronic Active Hepatitis (AICAH), pericholangitis and PSC are important risk factors [9]. In some patients who have received multiple blood transfusions, hepatitis C may be a causative agent. The treatment of choice for end stage liver disease is liver transplantation. Central portosystemic shunts must be avoided as not only do they increase perioperative mortality rates but they also make liver transplantation technically more challenging [8]. Patients may present with signs and symptoms of end-stage liver disease such as jaundice, ascites, encephalopathy, spontaneous bacterial peritonitis and gastric and oesophageal

bleeding. Oesophageal variceal bleeding can easily be treated using endoscopic banding, sclerotherapy or transjugular intrahepatic portosystemic shunting (TIPS). The majority of authors report that neither medical or surgical treatment of IBD has any effect on the natural history of cirrhosis [35]. Eade *et al.* [36] nonetheless did show arrest or regression of fibrosis in the majority of patients after colectomy.

AUTOIMMUNE CHRONIC ACTIVE HEPATITIS (AICAH)

Autoimmune chronic active hepatitis occurs in 1% of cases of IBD, mainly in CUC [3,37]. Conversely, the incidence of IBD in patients with AICAH varies between 4% and 30% [35]. There is no relation between the activity of the hepatitis and the severity or activity of colitis. Olsson and Hulten [38], however, have reported significant improvement in AICAH following colectomy. Factors implicated in the causation of AICAH include blood transfusion, ethanol abuse, PSC and autoimmune phenomenon with genetic predisposition [9]. Progression to post-necrotic cirrhosis may occur. There is some evidence that patients with severe AICAH with CUC respond less favourably to treatment compared to their counterparts without CUC [39].

HEPATIC AMYLOIDOSIS

Hepatic amyloidosis occurs in less than 1% of patients with IBD, and the majority of these patients have CD [8,10,14]. There is no relationship between the site of bowel involvement and occurrence of amyloidosis [40]. It usually involves the media of the branches of the hepatic artery in the portal triad and, to a lesser extent, the portal venules and bile ductules [40,41]. Clinically patients may present with hepatomegaly. Regression has been reported following the resection of inflamed bowel [42,43]. These

patients may also develop renal amyloidosis resulting in renal impairment which may culminate into renal failure in the post-operative period [9]. The prognosis of these patients is generally poor.

HEPATIC ABSCESS

Pyogenic liver abscess occurs in 0.3% of patients with CD. The abscesses are frequently multiple and carry a high mortality [2]. A number of mechanisms have been proposed including (a) seeding from the portal vein; (b) direct extension from intra-abdominal abscesses; (c) indirect complications from CD such as acalculous cholecystitis or enteric fistulas; and (d) from sepsis occurring in malignancies metastasizing to the liver [8,9]. Patients may present with right upper quadrant pain, pyrexia, nausea, vomiting, hepatomegaly, jaundice, and right subcostal tenderness. The diagnosis can be made on the basis of history, clinical examination, cultures, ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI) and radionuclide scanning [9]. Streptococcus, Klebsiella, and E. Coli are the three most common organisms identified and treatment includes broad spectrum antibiotics combined with percutaneous drainage under ultrasound or CT guidance. Surgical drainage is reserved for patients who deteriorate or who do not respond to the above regimen within two weeks.

HEPATIC GRANULOMAS

Hepatic granulomas are rare findings occurring commonly in patients with CD, although they have been described in patients with CUC. Usually asymptomatic, they may present with fever, hepatomegaly and jaundice. They may cause modest elevation in serum alkaline phosphatase (50% of cases) and may resolve when the diseased bowel is resected [33,44,45].

PRIMARY SCLEROSING CHOLANGITIS

Primary Sclerosing Cholangitis (PSC) is a chronic, slowly progressive, cholestatic liver disease of unknown pathology, most commonly occurring in young men between the ages of 20 and 40 years [46,47]. It is characterized by progressive chronic stenosing and fibrosing inflammation of both the intrahepatic and extrahepatic biliary tree. Generally accepted diagnostic criteria for PSC are outlined in Table II. Primary sclerosing cholangitis occurs in 4%–10% of patients with CUC [9,48,49] and 3.4% of patients with CD [50]. However, when CD involves the large bowel, the incidence of PSC increases to 9%, a rate similar to CUC [51]. On the other hand between 54% and 100% of PSC patients have IBD [47,52–56].

Currently the etiopathogenesis of both PSC and IBD remains speculative. Present evidence however suggests that PSC is an autoimmune disorder, where immunologic factors triggered by a virus or bacteria in genetically susceptible individuals are thought to damage bile duct epithelial cells [57]. Other factors that have been implicated in the etiology of PSC include environmental toxins, hepatic copper, viral infections (hepatitis A,B,C,D, cytomegalovirus, and reovirus), portal bacteremia, absorbed colonic toxins, toxic bile acids, genetic predisposition (HLA-B8, HLA-DR2, HLA-DR3 and HLA-DRw52A), ischemic arteriolar injury and altered cellular and humoral immunological responses [47,58–66].

There is no relationship between PSC and the onset, duration, activity, or extent of CUC [2,67–69]. It can even present years after proctocolectomy [67–70]. Although most patients have no

hepatobiliary symptoms or signs during the early phase of the disease, others will present with malaise, fatigue, jaundice, weight loss, right upper quadrant abdominal pain, hepatomegaly, pruritus, acute cholangitis and/or portal hypertension. Diagnosis is based on history, laboratory investigations, ERCP or PTC and liver biopsy. To date there is no effective treatment available which can reverse or halt the progression of PSC. In desperation there has been a surge of interest in the use of ursodeoxycholic acid in PSC [47,71]. Ursodeoxycholic acid (UDCA) has been investigated on the grounds that it: (a) is minimally toxic, (b) replaces the bile acid pool with a less toxic bile (compared to lithocholic acid), (c) decreases the expression of class I antigens on the biliary epithelium, thereby modifying immunological responses and (d) improves biochemical indices as well as histopathological features. In two randomized trials [72,73], however, the use of UDCA failed to show any improvement in clinical parameters, histology, or time to treatment failure or liver transplantation. Symptomatic treatments for PSC include cholestyramine, UDCA or/and antihistamines for pruritus, replacement of fat soluble vitamins (A,D,E,K), calcium and vitamin D for metabolic bone disease, ERCP, endoscopic sphincterotomy and stone extraction for obstructed jaundice and cholangitis secondary to choledocholithiasis, antibiotics for bacterial cholangitis, endoscopic dilatations and stents for bile duct strictures, and cholecystectomy for gallstones.

A number of other therapies and strategies are also relevant to IBD complicated by PSC. First of all, the mainstay for end stage liver disease in a selected group of patients is liver transplantation. In the event of variceal bleeding, most

TABLE II Criteria for diagnosing PSC

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- Cholestatic biochemical profile *i.e.*, alkaline phosphatase level greater than 1.5 fold over the normal limits for 6 months or more
 - Generalized beading, stricturing or irregularity of the biliary system based on cholangiography
 - Interlobular and septal bile duct fibrosis and obliteration on liver biopsy in the absence of other causes of chronic liver disease
 - Exclude other cause of liver disease such as biliary calculi, biliary tract surgery, congenital biliary conditions, AIDS associated cholangiopathy, ischaemic stricturing, biliary neoplasms, chemical hepatitis, PBS or CAH
-

surgeons do not recommend hepatobiliary shunt surgery because it increases the risk of bacterial cholangitis and may increase the perioperative mortality of a potential liver transplantation [37]. Sclerotherapy is considered a treatment of choice in these patients. If variceal sclerotherapy fails to control the bleeding, transjugular intrahepatic portosystemic shunt (TIPS) should be considered as a bridge to liver transplantation [8]. Liver transplantation is ultimately recommended for patients with variceal bleeding or known varices with hypersplenism, rising serum bilirubin levels, decreased synthetic liver function, recurrent cholangitis, repeated radiological or endoscopic procedures to maintain the ductal patency or spontaneous bacterial peritonitis. Parastomal bleeding can be another troublesome source of problems in these patients after colectomy and ileostomy [74]. The complication of parastomal bleeding can be prevented by performing an ileoanal anastomosis, or ileal pouch anal anastomosis rather than fashioning an ileal stoma, in patients undergoing panproctocolectomy for IBD in the presence of PSC [74–76]. Primary sclerosing cholangitis seems to be an additional risk factor for the development of colon cancer in those with long standing CUC [72,77]. If carcinoma or precancerous lesions develop in the colon, a proctocolectomy is indicated.

PERICHOLANGITIS OR SMALL DUCT PRIMARY SCLEROSING CHOLANGITIS

Pericholangitis or small duct primary sclerosing cholangitis is a subset of PSC which is diagnosed

on the basis of liver biopsy in the presence of a normal cholangiogram. It occurs in 30% of patients with IBD, is usually benign, and its course often parallels the bowel disease activity and severity [33,78]. It is now believed that pericholangitis represents a continuum in the spectrum of PSC [79]. The majority of cases resolve with residual mild periductal fibrosis, some may progress to a chronic phase or to PSC or to cirrhosis [7,79,80].

CONCLUSION

Hepatobiliary manifestations are an important cause of morbidity and mortality in patients with IBD. On one hand the presence of some of these manifestations may provide a justification for bowel resection, but on the other hand their presence may predict a complex and complicated perioperative recovery. Although some hepatobiliary complications are obviously directly related to local disease complications, such as stone formation or liver abscesses, or related to therapeutic side-effects, such as drug-induced liver steatosis, others appear to be systemically-mediated. Frustratingly, the aetiology and pathogenesis of IBD and its systemic manifestations including hepatobiliary disease remains mysterious. For now, we must settle for a more practical approach to understanding the relationship between hepatobiliary manifestations and bowel disease activity if and when it exists (Tab. III). For those hepatobiliary manifestations that respond to therapy of the underlying bowel disease, medical and/or surgical

TABLE III Hepatobiliary manifestations of IBD and their relationship to bowel activity and bowel surgery

Hepatobiliary manifestations	Relationship to bowel activity	Relationship to bowel surgery
Hepatic Steatosis	Usually parallels*	May resolve*
Cholelithiasis	Unrelated	May deteriorate*
Pericholangitis	Unrelated	No change
Primary sclerosing cholangitis	Unrelated	No change
Autoimmune chronic active hepatitis	Unrelated	May improve*
Cryptogenic cirrhosis	Unrelated	No change
Adenocarcinoma of bile ducts	Unrelated	No change
Hepatic amyloidosis	Unrelated	May resolve*
Hepatic granulomas	Unrelated	May resolve*

therapy must be aggressively pursued. The response of a given hepatobiliary manifestation to surgery at least provides a framework for considering the role of the surgeon in the management of these often difficult clinical problems.

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