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Review Article

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A review of liver disorders in inflammatory bowel disease (IBD)

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Abstract

Disorders of the liver and the biliary tract are frequently the extraintestinal manifestations of inflammatory bowel disease (IBD). The etiology of these hepato-biliary conditions is deemed secondary to their shared pathogenesis, the chronic effects of a long term, ongoing inflammation of the bowels, along with the medications used to manage IBD. For up to 30% of patients with IBD, abnormal liver biochemical tests are present. Other, selected patients with IBD are followed for reactivation of hepatitis B, through guidelines only relatively recently in place. The vast realm of related clinical conditions does not always correspond well with IBD severity, which can range from mild hepatic insult to end-stage liver disease, necessitating liver transplantation. Hence it is critical to follow its presence, clinical course and long term consequences. Moreover, the management of these disorders is necessarily individualized, with some patients requiring frequent monitoring and others a more multi-disciplinary approach. Studies aimed at improving the outcomes of patients with IBD who experience associated liver and biliary tract disorders are now needed to assess early identification, possible screening approaches and more effective systems of referral. This article covers the evidence-based literature on topics detailing the co-existence of liver conditions in inflammatory bowel disease with a focus on its epidemiology, clinical manifestations, diagnosis and management.

Introduction

Although it would lack biopsy confirmation until the mid-20th century, published accounts of inflammatory bowel disease (IBD) were in circulation in the early 19th century suggesting evidence for an association between hepatobiliary disorders and IBD. This evidence has now immensely expanded, with hepatobiliary disease in IBD now known to constitute some of the disorder's most common extra-intestinal manifestations [1-8]. Also, these hepatobiliary manifestations do not always parallel IBD disease activity, but instead may follow an independent natural course [5].

The most specific hepatobiliary complication associated with IBD is primary sclerosing cholangitis (PSC). Nonalcoholic fatty liver disease (NAFLD), however, is its most common manifestation. Liver toxicity arising from IBD-related medications is also common [9-15], as is hepatitis B reactivation, secondary to the use of immunosuppressive agents, including biologics. Given the high risk implicated for these agents, regular hepatitis B screening has been suggested for this sub-group. Relatively recent studies have also suggested that the emergence of obesity has changed the phenotype of the IBD population [16,17], with greater numbers of patients with IBD having NAFLD. Other, less common, hepatobiliary manifestations of IBD include cholelithiasis, autoimmune hepatitis, hepatic abscess, IgG4-associated cholangitis, portal vein thrombosis, granulomatous hepatitis and primary biliary cholangitis. Finally, comparative studies of the prevalence of cholelithiasis, PSC and fatty liver in the general population (1.8%-22.4%, not applicable, 6%-35%) indicate a higher prevalence in Ulcerative Colitis (4.6%-36.4%, 0.76%-5.4%, 1.5%-55%) and Crohn's Disease (11%-34%, 1.2%-3.4%, 1.5%-39.5%) [18].

Materials and methods

Literature search

We conducted online electronic searches of manuscripts published by PubMed and the Cochrane Library. We also conducted manual searches of selected specialty journals to identify any pertinent literature. The search was conducted using the key words 'inflammatory bowel disease',' liver diseases', 'ulcerative colitis', 'crohn's disease', 'primary sclerosing cholangitis', 'drug induced liver injury', and 'hepatitis B'. The references of articles were reviewed to identify additional articles. Studies not published in English were excluded.

Abnormal liver test in IBD

As about 30% of patients with IBD are reported to have an abnormal liver biochemical profile, either transient (due to IBD activity) or persistent [19], a systematic approach to excluding common liver conditions unrelated to IBD should be considered [20]. At a minimum, all patients with IBD should be screened for viral

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hepatitis, substance abuse and alcohol abuse. Further, an etiology-based approach to an abnormal liver test should examine the pattern of liver injury, whether cholestatic or hepatocellular, and clinicians should inquire about the patient's use of over-the-counter medications, NSAIDs, and any other drugs.

In a *cholestatic pattern* of liver injury, the *elevation of alkaline phosphatase* is out of proportion to the transaminases. This pattern of injury includes primary sclerosing cholangitis (PSC), drug-related liver injury from drugs used to manage IBD or others, cholestasis, autoimmune hepatitis, PSC overlap syndrome, granulomatous hepatitis, hepatic abscess or, rarely, hepatic amyloidosis.

A *hepatocellular pattern* of liver injury presents with an *elevated transaminitis* out of proportion to *alkaline phosphatase*. This too can occur through drug related liver injury, stemming either from drugs used for the management of IBD or others, NAFLD (with ALT > AST), autoimmune hepatitis, as well as PSC overlap syndrome, viral hepatitis or autoimmune hepatitis.

Below we discuss our findings from the literature on the a few of the overarching types of hepatobiliary complications associated with IBD, possible subtypes, and evidence-based recommendations for clinical work-up and therapeutic approaches.

Non-alcoholic Fatty Liver Disease (NAFLD)

Physicians have long been trained to recognize the association of fatty liver with IBD. However, only with the past decade's growing concerns about obesity has fatty liver's astounding prevalence of 50% to 60% of patients with IBD, been recognized. Globally, fatty liver is both on the rise and well on its way to be the leading cause of liver transplant, given that excessive fat deposition and its associated oxidative stress, in turn leads to fibrosis, cirrhosis and even liver cancer. Nevertheless, NAFLD has one important, positive attribute: with early recognition and such decisive interventions as a 10% reduction in body weight, exercise and adherence to a balanced diet, reversal is possible. That said, fatty liver is multi-factorial and seen in non-obese, as well as the obese, populations. Hence, an extensive workup is required to ascertain the true etiology of fatty liver in specific patients. During this workup, it important to avoid assumptions about any specific etiologies, including its association with IBD [21,22].

Hepatic steatosis in IBD was first reported on an autopsy finding by C. H. Thomas in 1873; it was described as "a much enlarged fatty liver" in a young patient with "ulceration of the colon" [23]. Numerous case series, including studies well before the current obesity epidemic, depicted steatosis in patients with IBD. However, the obesity epidemic, coupled with effective pharmacotherapy for the management of IBD, has altered the phenotype of a malnourished, under-weight IBD patient to one identified as having NAFLD. NAFLD, moreover, has an increasing incidence and prevalence in the general population, and it is likely to be more prevalent in future in patients with IBD.

The etiology of NAFLD in IBD is poorly understood, but considered to be multi-factorial and influence by such factors as age, gender, alcohol use, presence of metabolic syndrome (insulin resistance), IBD disease activity, duration of disease, gut dysbiosis, history of IBD related surgical intervention, medications used (corticosteroids, anti-TNF agents) and parenteral nutrition playing a role. The prevalence of NAFLD in IBD populations ranges from 6.2% to 40% [24-30], with the obvious discrepancy observed in this range attributed to varied definitions for describing NALFD, as well as to the different tools used for diagnosis. Ultrasonography for the diagnosis of NAFLD has a sensitivity and specificity of 85% (95% CI: 79.5-88.9%) and 94% (95% CI: 87.2-97%), respectively [31].

NAFLD is the leading cause of elevated transaminases (ALT>AST, except in cirrhosis). Limited data exists on liver fibrosis and IBD, but they are respectively reported to be between 6.4% and 10 [32]. The degree of steatosis, a reflection of IBD disease activity, may be reversed with the treatment of IBD [25]. The prevalence of metabolic syndrome in IBD patients has geographical variation. Nagahori *et al. in 2010 in J Gastroent* reported that, in Japan, its prevalence was 18.6%, and thus comparable with the general population. However, a 2013 study conducted by Sourianarayanane *et al. in J Crohn's colitis* in 2013 demonstrated a lower prevalence of metabolic syndrome in the IBD population as compared to the general American population.

Dysbiosis with alteration of gut microbiota has been associated with IBD disease activity and NAFLD [33,34], with the duration of IBD identified as an independent risk factor for NAFLD [30]. The topic on IBD related medications and liver toxicity including NAFLD has been covered later in this review article. NAFLD can lead to cirrhosis and its complications, yielding increased morbidity and mortality with co-existing IBD.

At present no specific guidelines exist for screening or assessing patients with IBD for NAFLD. However, patients are usually asymptomatic and may present with hepatomegaly. Biochemical and histological improvements in NAFLD patients have been achieved with >7% weight loss [35]. Obese patients with CD may have increased anoperineal disease, require earlier surgical intervention and experience greater surgical complications than their non-obese counterparts [36-38]. Elevated liver enzymes with NAFLD can limit the use of Azathioprine and Methotrexate. Patients should be advised to monitor for excessive weight and to maintain healthy dietary and exercise habits.

Primary Sclerosing Cholangitis (PSC)

PSC is a chronic progressive cholestatic liver disease characterized by gradual inflammation and fibrosis of intrahepatic and/or extrahepatic bile ducts leading to chronic cholestasis and elevated alkaline phosphatase. PSC is the most specific hepatobiliary manifestation of IBD [1,39,40]. It is likely the most well-known condition almost all physicians associate with IBD. It may have a characteristic presentation while its diagnosis requires a high index of suspicion. Recurrent cholangitis is one of the most serious complications associated with PSC. Its management involves the use of ursodeoxycholic acid aimed to reduce the progression of PSC; while a liver transplant remains the sole long term treatment hope. A host of other medications including anti-inflammatory agents or biologics, none have shown to alter the natural course of progression of the disease. PSC's incidence ranges from 0 to 1.3 per 100,000 person/year, its prevalence is 0 to 16.2 per 100,000 people [41], and it usually affects young and middle aged patients, especially those with underlying IBD [39,42], with median age of onset between 30 and 40 years. From 0.4 % to 7.5% of patients with IBD develop PSC [1,42]; however, among patients with an established PSC diagnosis, 70% to 80% have UC and 15% to 20% have CD [43,44]. Of note, IBD is associated with poorer outcomes in patients with PSC with increased risk for malignant complications and hence requirement for liver transplantation [45]. The natural course of PSC, though varied, is usually progressive and can lead to liver cirrhosis and failure [39,46].

PSC: Etiology and pathogenesis

PSC's exact etiology is unknown. Genetic susceptibility, autoimmune mechanism, intestinal dysbiosis with toxin production

from the gut microbiota, chronic portal bacteremia, unrecognized viral infections, as well as abnormal metabolism, transport and immunoregulation of bile acids have all been proposed [47-49]. However, multiple HLA haplotypes have been associated with PSC [50], and at the genome level, about 16 risk loci, accounting for 7.3% of overall liability [51], have been identified for PSC. These risk loci for PSC overlap with risk loci for UC and/or CD [52,53].

The pathogenesis of pathogenesis of PSC has been proposed to arise through increased intestinal permeability during bacterial translocation, as well as activation of innate immune response [54,55]. This view suggests that the ectopic aberrant expression of mucosal address in cell adhesion to molecule 1, expressed in the liver and usually in PSC and other liver inflammatory states, along with those T-helper cells responsible for liver fibrosis, are primed in the intestine, circulate via entero-hepatic circulation and linger as memory cells, triggering in a portal inflammation that results in biliary destruction [56-58].

PSC-diagnosis

PSC is an uncommon medical condition, with as many as half the patients affected by it asymptomatic. A diagnosis of PSC must be considered when cholestasis occurs, especially in the setting of colitis. Patients with a history of colitis, recurrent cholangitis, and symptoms of pruritus and jaundice may be more likely to have sclerosing cholangitis. Note that patients may have ascending cholangitis characterized by fevers, chills, or both, right upper quadrant pain, and jaundice. Physical findings may be nonspecific; however, icterus, excoriation, or hepatosplenomegaly, especially in a male, may suggest the diagnosis [59]. Presenting symptoms for PSC are often fatigue (75%), pruritus (50%), weight loss (40%), and fever (35%) [54,59]. Mean survival after diagnosis of PSC is 10-12 years [39,60-62], with survival much shorter for patients who are symptomatic at the time of diagnosis.

Laboratory testing for PSC will reveal a cholestatic pattern, with elevated alkaline phosphatase and mild elevations in transaminases, hypergammaglobulinemia and IgM. A low albumin is indicative of active IBD and poor prognosis [63]. To establish the diagnosis of PSC, intrahepatic and/or extrahepatic strictures must be demonstrated, either by magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or percutaneous transhepatic cholangiography [63].

MRCP provides the test of choice for PSC, as it is readily available, less invasive and a cost effective option for the initial diagnosis; however, MRCP does not provide access to the biliary tree for tissue diagnosis or therapeutic manipulation [64,65]. Also, MRCP can miss early PSC changes and large duct involvement for which an ERCP is more helpful [63]. ERCP allows for an easy identification of fibrotic annular strictures that alternate with normal or dilated segments to produce the characteristic beaded pattern of the biliary tree. It also provides histologic/cytological sampling and therapeutic maneuvers.

A liver biopsy is not always indicated. We should, however, obtain a liver biopsy if the MRCP and ERCP are non-diagnostic, as well as a cholestatic biochemical profile to rule out small duct PSC or, if we suspect an overlap syndrome of PSC, with autoimmune hepatitis [63]. The classical biopsy finding for PSC includes the fibrous obliteration of the small duct, with periductal concentric fibrosis in an "onion skin" fashion. However, periductal fibrosis, seen in secondary forms of sclerosing cholangitis [66,67], is not pathognomic for PSC, and is seldom seen.

Management of PSC

With no current medical management available to decrease PSC progression, the currently available aim is to halt its progression with UDCA (Ursodeoxycholic acid) and to manage its complications. UDCA enhances hepatobiliary secretion and protects cholangiocytes and hepatocytes from apoptosis [68,69].

Trials suggests a dose of 13 to 15 mg/kg/day of UDCA as appropriate [70,71]. Higher doses of UCDA (20-30 mg/kg/day) have been shown to be detrimental, rather than to have any substantial clinical benefit [72-76]. UCDA does not improve liver histology or liver transplant free survival, nor does it prevent the development of cholangiocarcinoma, colonic adenomas, colon cancer or incidence of death [73,77-79]. Corticosteroids have not been proven effective either as single agents or when used with colchicine or ursodeoxycholic acid [80], nor have methotrexate, colchicine, pentoxifylline, etanercept, or mycophenolate mofetil proved useful in PSC [81-86]. Preliminary studies suggest that selected antibiotics may be beneficial but evidence for their routine clinical use is lacking [87-89].

Pruritus in PSC is common; its initial management consists of cholestyramine or colespitol (bile acid sequestrants). Where prurities is refractory to bile acid sequestrants, patients should be treated with either Rifaximin (150-300 mg twice daily), Naltrexone (50 mg daily) or Sertraline (75-100 mg daily) [90].

Advice against alcohol consumption, smoking and marijuana use. A review of hepatitis A and B status (to assess any exposure) and recommendation of vaccinations is vital. Warn patients to avoid high-risk behaviors for hepatitis C, such as intravenous drug use and sexual promiscuity.

Patients with decompensated advanced liver disease, hepatocellular carcinoma or refractory bacterial cholangitis should be evaluated for liver transplant. The outcome from liver transplantation for PSC is substantially better than would be predicted from natural history models [91,92]. The possibility of recurrent PSC in the transplanted liver exists, however, and may affect graft and patient survival [93-95].

IgG4-associated cholangiopathy (IAC)

The pathogenesis of IAC is largely unknown. IAC has been described in patients with UC and is a IgG4-related systemic disease causing biliary destruction similar to PSC [96]. Although 9% to 36% of patients with PSC may have elevated IgG4; these levels are lower than in patients with IAC [97,98] and hence the tissue diagnosis of IgG4 plasma cell infiltration in the bile duct has greater diagnostic utility [96,99].

Primary biliary cholangitis (PBC)

Several case reports of PBC in UC have been published [100,101]. Though PBC and UC share some common HLA haplotypes [101,102], the prevalence of PBC in UC patients have been reported to occur only by chance [103]. These IBD patients with PBC were generally young with a male preponderance. Also, the UC was mild with limited colitis [100,101].

Medication associated liver injury in IBD

Most drugs used for the suppression of IBD activity has potential for liver toxicity; though serious complications are relatively low [24,104]. The mechanism of hepatoxicity for these drugs is complex and ranges from immune mediated, metabolic, direct toxic effects to induction or worsening of intrinsic liver disease. The laboratory finding of hepatocellular versus cholestatic pattern of injury helps clinician's decipher the etiology of the injury (Table 1).

Table 1. Medications and hepatotoxicity

Medication	Mechanism of injury	Liver toxicity
Corticosteroids	Oxidative hepatotoxicity	Worsening of NASH, steatosis Chronic hepatitis B reactivation
Aminosalicylates	1. Hypersensitivity 2. 5-ASA components toxicity	Drug induced hepatitis Cholestasis Granulomatous hepatitis Drug induced pancreatitis
Thiopurines	1. Direct toxicity from intracellular accumulation 2. Damage to the vascular endothelium	Asymptomatic transaminitis Drug induced hepatitis cholestasis Nodular regenerative hyperplasia Drug induced pancreatitis
Methotrexate	Is stored in the liver as a polyglutamate metabolite which is hepatotoxic with long term use [105]	Asymptomatic transaminitis Steatosis Fibrosis Drug induced pancreatitis
Infliximab and Adalimumab (Monoclonal antibodies against TNF α)	Interfere with the activity of TNF α –leads to precipitation of "denovo autoimmune hepatitis", cholestasis and direct hepatocellular necrosis [13,106]	Chronic hepatitis B reactivation or hepatitis C reactivation Cholestasis
Combination of anti-TNF and immunosuppressive therapy	Interfere with the activity of TNF α –leads to precipitation of "denovo autoimmune hepatitis", cholestasis and direct hepatocellular necrosis [13,106]	Hepatosplenic T-cell lymphoma

Aminosalicylates: Sulfasalazine and mesalamine

The mechanism of the anti-inflammatory properties of Aminosalicylates are not entirely understood but is attributed to inhibition of both prostaglandins and leukotrienes. Sulfasalazine is largely replaced (due to adverse effects) by Mesalamine and is indicated in the induction and maintenance of mild to moderate Ulcerative Colitis. The mechanism of injury is by the following [105,106]:

Hypersensitivity to Sulfasalazine: This can in rare cases lead to acute liver failure presenting with fever, tender hepatomegaly, lymphadenopathy, transaminitis and hyperbilirubinemia [107,108].

Directly toxicity from the 5-ASA component: This can lead to both acute or chronic hepatitis and has been shown to occur mostly between 6 days to 1 year of starting the drug

Both 5-ASA and Sulfasalazine are equally responsible for the number of cases of drug induced hepatitis from Aminosalicylates [109-113]. Studies have reported liver enzyme abnormalities in up to 2% of patients on Mesalamine [114]. Most of these abnormalities have no clinical significance. The use of Mesalamine and 5-ASA are considered low risk as an etiology for the development of toxic hepatitis (3.2 and 6 cases per million prescriptions for Mesalamine and sulfasalazine respectively) [115] and hence close liver enzyme monitoring is not deemed necessary. Cholestasis, granulomatous hepatitis and drug induced pancreatitis have also been reported in patients on Aminosalicylates.

Corticosteroids

Corticosteroids when used for a short duration for induction therapy causes minimal liver injury. When used at higher doses for extended periods corticosteroids can enhance NASH and oxidative hepatotoxicity in high risk patients with obesity, insulin resistance, uncontrolled diabetes and hypertriglyceridemia [116].

Thiopurines

Thiopurines are immunomodulators indicated for the maintenance of clinical remission in CD and UC. Azathioprine (the pro-drug) and 6 mercaptopurine (6-MP) convert to the metabolite 6 –MMP (6-methylmercaptopurine) and 6-TG (6-Thioguanine); the levels of which relates to the therapeutic efficacy and the drug [117] (Figure 1).

6-MMP levels relates to therapeutic efficacy and in very high levels relates to liver toxicity. 6-TG levels also relates to therapeutic efficacy and in high levels relates to bone marrow toxicity.

TPMT Genotype is measure before initiating AZA or 6-MP to reduce hepatic toxicity. Those with homozygous mutant alleles should not receive azathioprine or 6-MP. Those with normal/heterozygous-should be started on low dose and then increase the dose every 2-4 weeks. Routine liver enzyme monitoring is advised. The medication can be continued with mild abnormalities without clinical symptoms; but should be discontinued when patient develops jaundice or abnormalities persists despite lowering the dose of Azathioprine or 6-MP [118].

The measurement of the TPMT enzyme activity (phenotype) helps guide the Azathioprine or 6-MP dose and detect possible non-adherence. Undetectable TPMT levels may be due to altered metabolism or non-adherence. High TPMT-levels may suggest toxicity (Table 2).

Hepatotoxicity secondary to the use of Thiopurines ranges from 3% (in retrospective trials) to 10% (in prospective trials) [119]. The occurrence of hepatotoxicity increases with concomitant use of corticosteroids [119]. Pancreatitis and veno-occlusive disease caused by Thiopurines is an example of the dose independent side event while hepatotoxicity is dose dependent (and hence is reversible with discontinuation).

The mechanism of injury of Thiopurines is believed to be by:

1. Intracellular accumulation of 6-MMP and 6-TG: which is a direct result of reduced TPMT enzymatic activity
2. Damage to the sinusoidal vascular endothelium: It's rare and patients present with veno-occlusive disease and NRH (nodular regenerative hyperplasia). These patients usually present with non-cirrhotic portal hypertension.

Methotrexate

Methotrexate impairs DNA synthesis via inhibition of dihydrofolate reductase and also blocks T cell activation and expression

Table 2. TPMT: Its genotype and phenotype and its significance

TPMT Genotype	TPMT Phenotype	% population	Significance
wild type	Normal/high enzyme activity	89%	6-MP works well
Heterozygous mutations	low TPMT enzyme activity	11%	May require higher doses of 6-MP
Homozygous mutations	negligible activity	0.3%	6-MP is ineffective Also causes 6-MP to be preferentially metabolized to produce higher levels of 6-TG

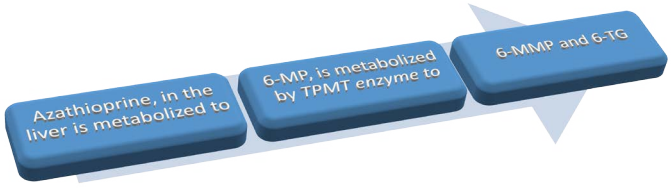

Figure 1. Thiopurine metabolism

of intercellular adhesion molecules [120]. It is indicated for use in the maintenance of the clinical remission of steroid dependent CD patients [121]. A meta-analysis of the use of methotrexate in IBD patients published in *IBD in 2012* revealed elevation of transaminases (was seen in 10.5% of the patients) to be usually < 2 fold the upper limit of normal. This transaminitis reduced without any intervention with only 2.68% requiring discontinuation [9].

The careful selection of patients (avoidance of use of Methotrexate in patients with obesity, alcohol related health problems, diabetes) and close monitoring combined with use of folic acid or folinic acid has reduced the incidence of hepatotoxicity associated with Methotrexate [9,122]. Methotrexate should be discontinued if the patient develops fibrosis or cirrhosis [123].

Earlier when the cumulative dose of methotrexate exceeded 1.5 grams a liver biopsy was warranted [124]; but this is no longer the case. Recent guidelines suggests closer monitoring of transaminases and albumin every 4-8 weeks and later every 8-12 weeks upon stabilization of the dose. A liver biopsy should be performed only if 6 out of the 12 tests within a year is abnormal [125]. The future role of fibroscan in monitoring of patients on Methotrexate is yet to be ascertained [123].

Biologic agents

Infliximab and Adalimumab are monoclonal antibodies directed against TNFα (which usually plays a role in hepatic regeneration) and is indicated for the induction and remission of steroid resistant and steroid dependent CD and UC [126,127]. Upon withdrawal of viral suppression as a result of immunosuppression with biologics; patients with chronic hepatitis B and hepatitis C are prone for reactivation with viral replication. The mechanism of injury with use of biologics is detailed in the table above. HSTCL (Hepatosplenic T-cell lymphoma) is a rare and fatal complication (seen mostly in young males) described with use of combination of anti-TNF and immunosuppressive therapy [12,128,129].

Natalizumab is a α4-integrin monoclonal antibody was used for the management of IBD (in Europe) and has been associated with severe liver injury, liver failure and progressive multifocal leukoencephalopathy (PML) [130,131].

Vedolizumab is a gut specific anti-integrin therapeutic antibody. Evidence collected from pre-licensure controlled trials reveal <2% of patients with Vedolizumab demonstrating > 5 times the upper limit of normal ALT elevation; which was similar to the placebo group [132]. No cases of significant liver toxicity has been reported till date.

Hepatitis B and IBD

Hepatitis B is a DNA virus that permanently leaves its genetic imprint, the ccc DNA (covalently closed circular DNA), which is embedded in the nucleus of the hepatocytes. The ccc DNA serves as a persistent viral reservoir and is responsible for hepatitis B re-activation following host immunosuppression. Nucleos(t)ides such as Tenofovir or Entecavir achieve sufficient viral suppression via blocking HBV DNA synthesis in the hepatocyte cytoplasm, but do not affect the ccc DNA in the nucleus of the hepatocytes. Immunosuppressive agents used for the management of IBD can result in the cessation of viral suppression resulting in HBV reactivation. This ccc DNA serves as the template for HBV transcription and subsequent replication.

The HBV reactivation is of various types as detailed below (Table 3).

Various recommendations exists for the screening of HBV reactivation especially before initiation of immunosuppressive medications. The AASLD recommends screening of hepatitis B reactivation with HBsAg and anti-HBC while the USPSTF recommends only HBsAg. Before initiating any patients on immunosuppressive agents we have to perform a risk stratification for the reactivation of HBV infection. This risk stratification is based on the presence of hepatitis B surface antigen and the medication been used.

Table 3. Types of HBV reactivation

HBV reactivation types	HBV DNA	ALT	Symptoms of liver injury: jaundice/fatigue	Liver failure: Coagulopathy, hepatic encephalopathy, ascites
Silent	detectable	Normal	No	No
Mild	detectable	High	No	No
Moderate	detectable	High	Yes	No
Severe	detectable	High	Yes	Yes

HBV reactivation is an underappreciated challenge and we should screen everyone as all patients face the risk of reactivation. It is not uncommon, can be lethal and is preventable. All HBsAg positive should be treated. For patients that are HBsAg negative with anti-HBc positive indicating a past infection we need to determine they risk status and start anti-virals accordingly. Tenofovir or Entecavir is used for at least the duration of the immunosuppression. Further studies need to be carried out to ascertain the cost of routine screening and monitoring of laboratory parameters in the diagnosis and follow up of hepatitis B reactivation.

Hepatitis C and IBD

Contrary to a study by Hou *et al.* [134] it has been reported that the prevalence of hepatitis C infection in IBD sub-group is comparable to the general population [135,136]. Corticosteroids are considered to flare hepatitis C viral replication especially after a liver transplant but no prospective studies exists. Also Azathioprine, Methotrexate, cyclosporine and mycophenolate mofetil has been shown to be safe for use in transplanted patients without any hepatitis C reactivation [137-139]. Thus, immunosuppressive agents used in IBD do not result in HCV reactivation.

Till the advent of directly acting anti-virals for the management of hepatitis C the IBD subgroup with hepatitis C infection were always excluded and hence not many trials exists to decipher whether hepatitis C medications affected the natural course of IBD. Several case reports of use of interferon in patients with IBD and hepatitis C concluded interferon not to adversely affect the IBD course [14-144]. Zein *et al.* demonstrated improved SVR (sustained virological response) rates when etanercept (an anti-TNF agent) was used in conjunction with interferon and ribavirin. This shows that anti-TNF agents are safe to use in IBD patients with hepatitis C infection [145]. Thus, anti-virals for hepatitis C does not have any adverse outcome on the IBD course.

Granulomatous hepatitis

Granulomatous hepatitis is a rare complication of Crohn disease. It's usually benign and not progressive. The patients are mostly asymptomatic; but may have symptoms secondary to Crohn's disease. The main laboratory abnormality is that of an elevated alkaline phosphate. Some have a mild degree of transaminitis while hyperbilirubinemia is rare. Granulomatous hepatitis and its association with the use of Sulfasalazine for the management of Crohn's disease has also been well documented [104]. Ultrasound and CT scan is usually normal while lesions > 5 mm are identified on an MRI. A complete workup for any hepatic granuloma depends on the positive history and exam findings while a liver biopsy for its diagnosis

is not indicated. When a biopsy is performed (for other indications); a non caseating granuloma with epithelioid cells, giant cells and lymphocytes. Granulomatous hepatitis secondary to inflammatory bowel disease rarely requires treatment (which includes corticosteroids and immunosuppressive drugs) (Table 4).

Secondary Amyloidosis

Secondary or reactive amyloidosis in IBD is associated with chronic inflammation of the gut leading to extracellular (vasculature and sinusoids) amyloid deposition in the liver. The prevalence of amyloidosis in IBD has been estimated to be around 3% [146]. The incidence is higher in male individuals with colonic involvement and more common in Crohn's disease when compared to Ulcerative colitis [146,147]. Patients present with asymptomatic hepatomegaly and rarely the diagnosis of hepatic amyloidosis precedes that of IBD [146]. Suppression of gut inflammation in Crohn's disease reduces the oxidative burden thereby reducing precursors of amyloid fibrils and progression of hepatic amyloidosis [147,148]. Though medical management has limited success; colchicine, budesonide and infliximab been tried with varied results [149-151].

Cholelithiasis

The incidence of cholelithiasis in CD is doubled when compared to IBD-free controls and has been reported to be between 13% and 34% [6,152]. UC (which does not involve the small bowel) is not considered a risk factor for cholelithiasis. Patients with ileo-colonic CD are at increased risk of cholelithiasis when compared to CD patients with only the ileal involvement [153-155]. Past history of intestinal resections and the number of resections have also been implicated as risk for the development of cholelithiasis [26,152-155]. Ileal involvement (either resection or inflammation) with decreased bile salt absorption leading to lithogenic super saturated bile is considered the main mechanism for the development of cholelithiasis in this sub-group [156,157]. Also, patients undergoing ileoanal anastomosis have been identified to have increased gallstone cholesterol concentration leading to cholelithiasis [158].

Portal vein thrombosis

This is a relatively rare yet significant complication observed in patients with IBD secondary to a consequence of an inflammatory hypercoagulable state [159-161]. 1% to 2% of patients with IBD have been found to have thrombosis of the portal and the mesenteric veins [162]. IBD patients are hypercoagulable with elevated platelets, fibrinogen, factor V and VIII levels and reduced anti-thrombin III levels [163,164]. Portal vein thrombosis is most likely to occur in patients with UC undergoing restorative protocolectomy [165-168]. Landman *et al.* published their incidental finding of 40% of the patients with inactive IBD with portomesenteric vein thrombosis [169]. Some single center studies have elucidated the course of portal vein thrombosis to be benign [170,171]. Patients with IBD do not have a higher incidence of genetic clotting abnormalities but may develop acquired prothrombotic disorder secondary to disease activity [172,173]. A six month course of anticoagulation has been instituted at various centers. However lifelong systemic anticoagulation is indicated in known congenital hypercoagulable states [162].

Table 4. Medications associated with granulomatous liver lesions

Allopurinol	Gold	Nitrofurantoin
BCG	Hydralazine	Phenytoin
Carbamazepine	Interferon	Procainamide
Chlorpropramide	Mebendazole	Quinidine
Diltiazem	Methyldopa	Sulfa drugs

Budd Chiari Syndrome

Several case reports of IBD patients with Budd Chiari syndrome has been published [174,175]. Due to the hypercoagulable state spontaneous thrombolic embolism can occur; the risk of which is eight times higher during an acute flare [164]. Also, patients during any perioperative period are considered to be at increased risk for the development of thromboembolism.

Hepatic abscess

Liver abscess is a rare complication of CD that has been elucidated in case reports and cohort studies [176,177]. Hepatic abscess could be an initial manifestation of CD [178,179]. A typical presentation is that of a young patient with fever, abdominal pain, jaundice, diarrhea or hepatomegaly. Presence of abdominal abscess, malnutrition, fistulizing CD and corticosteroid therapy are known risk factors for the development of hepatic abscesses [179]. The mechanism of the formation of the abscess is not fully understood and is thought to be either secondary to the extension of the pre-existing abdominal abscess, portal pyemia with seeding of the hepatic parenchyma or due to increased intestinal mucosal permeability with the involvement of the tight junctions. Management of hepatic abscess includes surgical drainage [180] and lowering of the IBD activity.

Pancreatitis

Pancreatitis is rare and usually results in patients with IBD due to ampullary CD, cholelithiasis, PSC or medications (including 6-mercaptopurine and Azathioprine). In a study the use of Azathioprine and 6-mercaptopurine in IBD population resulted in increased risk of pancreatitis when compared to patients treated with these drugs for other causes [181].

Autoimmune pancreatitis (AIP) resembles IBD-associated pancreatitis [182,183]. When compared to the general population the prevalence of IBD in patients with AIP was 10-fold, hence indicating that AIP could be contributing to the clinical finding of IBD-associated pancreatitis [184,185]. Data from a single prospective study of IBD patients with pancreatitis with high serum IgG4 is available and this needs to be further incorporated and validated in future studies.

IBD and liver transplantation

Development of *De novo IBD* after liver transplantation is infrequent; and has been described in various case series [186-189]. The exact etiology is unknown; though a damage-associated or pathogen-associated molecular pattern has been implicated [188]. Presence of a positive CMV donor with a negative recipient [189,190] and use of Tacrolimus post-liver transplant [191] has been identified as risk factors for the development of *de novo IBD*. It is believed that CMV and Tacrolimus can affect the mucosal immune system (via altering the epithelial barrier system [189] or reducing the interleukin-2 dependent generation of regulatory T cells [192,193] respectively) increasing IBD activity. The diagnosis and management is often challenging. Steroids, Azathioprine and anti-TNF therapy have a good therapeutic response [189].

Conflicting reports of IBD activity have been published regarding the impact of a liver transplant on patients with preexisting IBD [192-196]. Risk factors for worsening of preexisting IBD after liver transplant includes active bowel inflammation at the time of transplantation [193], short interval between diagnosis of IBD and transplant [193],

cigarette smoking [197], *Clostridium difficile* infection [198] and use of Tacrolimus after transplant [191,193,199,200]. The use of steroid or immunosuppressive agents prior to transplant does not predict post-transplant IBD activity [194,195]. Steroids, Azathioprine and Cyclosporine should be preferred in these subgroup of patients [94,193,199-201]. The therapeutic response and outcome is usually poor when compared to the *de novo IBD* patients; requiring colectomy for refractory bowel disease [197,199,200]. Conflicting evidence suggesting for and against the association of use of immunosuppressive agents and CRC have been published [202,203].

PSC patients with IBD who have undergone a liver transplantation usually present with prolonged subclinical IBD activity and hence may underestimate the colorectal cancer (CRC) risk [204]. However, there are at increased risk for CRC (even when adjusted for the diagnosis of PSC and IBD in similar populations) [205,206] and should be monitored with annual colonoscopy [199,207].

Conclusion

Hepatobiliary manifestations associated with IBD are common and underdiagnosed. In conclusion, physicians managing IBD patients should be critically aware of these manifestations. Also, important to note is that these disorders may present differently and at times be asymptomatic. It is possible to improve the management and outcome with careful anticipation, screening and identifying complications early. Complex cases require a multidisciplinary approach including gastroenterology, general surgery, colorectal surgery and transplant surgery.

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