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REVIEW

Clinical Presentation and Outcomes of Autoimmune Hepatitis in Inflammatory Bowel Disease

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Abstract Nearly one-third of patients with inflammatory bowel disease (IBD) have abnormal liver tests, which can be indicative of underlying hepatic disease. Primary sclerosing cholangitis has a clear association with ulcerative colitis, but other autoimmune disorders such as autoimmune hepatitis (AIH) have also been associated with IBD. AIH may also occur in the setting of an overlap syndrome or in the setting of medications, particularly tumor necrosis factor alpha inhibitors. Importantly, some studies have shown that IBD patients with AIH fail treatment more frequently than IBD patients without AIH. This review will focus on the clinical characteristics, diagnosis, and management of autoimmune hepatitis in inflammatory bowel disease patients.

Keywords Autoimmune hepatitis · Overlap syndromes · Primary biliary cirrhosis · Primary sclerosing cholangitis · Abnormal liver function tests

Introduction

Inflammatory bowel disease (IBD) is a systemic disease with a wide array of extraintestinal manifestations, including those hepatic in nature. Up to thirty percent of IBD patients have abnormal liver tests, which can be indicative of underlying hepatic disease [1]. Primary sclerosing cholangitis (PSC) has a clear association with ulcerative colitis, but other autoimmune disorders including autoimmune hepatitis (AIH), IgG4-associated cholangiopathy, and primary biliary cirrhosis (PBC) have also been associated with IBD. In addition, processes such as portal vein thrombosis, granulomatous hepatitis, and nonalcoholic fatty liver disease have been reported [1, 2].

Elevation of aspartate transaminase (AST), alanine transaminase (ALT), and hypergammaglobulinemia and the presence of autoantibodies in the IBD patient raise the suspicion of concurrent autoimmune hepatitis. AIH may also occur as a component of an overlap syndrome or in the setting of medications. In one study, ulcerative colitis was present in 16 % of patients with AIH [3, 4]. It has been suggested that IBD patients with AIH compared to IBD patients without AIH are more likely to relapse and in the case of ulcerative colitis, may be more likely to require proctocolectomy [5]. Additionally, patients with PSC and IBD have a greater frequency of concurrent autoimmunity compared to patients with IBD alone [6]. Therefore, it is important to be aware of the co-existence of AIH and IBD in order to properly direct management. This review highlights the clinical characteristics, diagnosis, and management of autoimmune hepatitis in inflammatory bowel disease patients.

Autoimmune Hepatitis

Autoimmune hepatitis is an immune-mediated condition primarily targeting hepatocytes [6]. Although the exact mechanism of injury remains elusive, pathogenesis is thought to involve a combination of environmental factors such as a triggering infection or toxin, genetic

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predisposition, and other immunocyte activation [7]. AIH affects all ages and ethnicities but with a strong female preference, similar to classic autoimmune diseases [6, 7]. The most common presentation is a mild asymptomatic transaminase elevation, though patients can also present with cirrhosis of unknown etiology and less frequently, acute liver failure [7].

The International Autoimmune Hepatitis Group (AIHG) established criteria for the diagnosis of AIH that include clinical, biochemical, immunological, and histologic parameters [1]. These criteria consist of the presence of autoantibodies, elevated IgG levels, histologic evidence of interface hepatitis, and exclusion of other etiologies of liver disease [6, 8]. Autoantibodies include antinuclear antibody (ANA), anti-smooth muscle antibodies (SMA), anti-liver–kidney microsomal type 1 antibodies (anti-LKM-1), and anti-liver cytosol type 1 antibodies (LC-1) [8, 9] (Table 1). Histologic evaluation is often required for diagnosis, with findings typically including portal-based plasma cell infiltrate, interface hepatitis, and an inflammatory lobular infiltrate [7]. Treatment is with long-term immunosuppression with the goals of normalizing liver biochemistry, eliminating symptoms, and preventing progression of disease.

AIH–IBD: A Separate Phenotype?

Concurrent autoimmune hepatitis and inflammatory bowel disease have been shown to possibly represent unique entities from either process alone. Ordonez et al. [10] compared the clinical course of 28 children with inflammatory colitis associated with autoimmune liver disease, including PSC, celiac disease, and AIH to 27 matched controls with isolated ulcerative colitis. Pancolitis was seen in 18/28 of the patients with associated autoimmune disease compared to 8/27 in the ulcerative colitis alone group [10]. Despite more extensive disease, evolution of disease was less aggressive in the former group. On pathology, differences between the two groups included predominant lesions

Table 1 Diagnostic criteria for diagnosis of autoimmune hepatitis and overlap syndromes

	Diagnostic criteria
AIH (simplified criteria)	ANA or SMA $\geq$ 1:40 (1 pt)
	ANA or SMA $\geq$ 1:80 (1 pt)
	Or LKM $\geq$ 1:40 (2 pt)
	Or SLA positive (2 pt)
	IgG > ULN (1 pt)
	IgG > 1.10 times ULN (2 pt)
	Liver histology compatible with AIH (1 pt)
	Liver histology typical of AIH (2 pts)
	Absence of viral hepatitis (2 pts)
	Probable AIH: $\geq$ 6
	Definite AIH: $\geq$ 7
AIH/PBC (Paris criteria)	*AIH Group (2 of 3)*
	ALT $\geq$ 5 ULN
	IgG $\geq$ 2 ULN or SMA
	Interface hepatitis
	PBC Group (2 of 3)
	Alkaline phosphatase $\geq$ 2 ULN or GGT $\geq$ 5 ULN
	AMA
	florid duct lesions
AIH/PSC	No formal diagnostic criteria but suggested by:
	Predominant AIH
	AMA negative
	Bile duct injury or loss
	Biliary sclerosis
	Concurrent inflammatory bowel disease

AIH autoimmune hepatitis, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *ANA* antinuclear antibodies, *SMA* smooth muscle antibodies, *LKM* liver/kidney microsome, *SLA* soluble liver antigen, *ULN* upper limit of normal, *AMA* antimitochondrial antibodies, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase

located in the right colon, pseudo-villous appearance of mucosa, mild granular lesions, and differing inflammatory infiltrates in those with colitis associated with autoimmunity [10].

Hepatic disease from AIH may also exhibit a distinct course in the IBD patient. Bailey et al. [5] examined 242 patients with inflammatory bowel disease and autoimmune hepatitis confirmed with AIHG scoring and evaluated biochemical response to treatment. In comparison with patients with AIH alone, patients with AIH–IBD developed AIH at a younger age, were more likely to be refractory to treatment, and had a higher frequency of death or liver transplantation. They had similar frequencies of advanced stage fibrosis at presentation [5].

In another study, 105 patients with autoimmune hepatitis were studied to determine the prevalence of chronic ulcerative colitis and/or cholangiographic features of PSC [4]. Seventeen patients had ulcerative colitis, and five of these patients also had features of PSC. The patients with colitis were less likely to enter clinical remission, had increased treatment failure, and progressed to cirrhosis more frequently [4].

Liver inflammation in AIH–IBD may be associated with composition of the microbiome. Microbiota is considered to play an essential role in inflammatory bowel disease, with gut microbial products driving inflammation in colitis [11]. In mouse models of ulcerative colitis, reductions in expression of tight junction proteins increase the permeability of the colon, which leads to bacterial translocation [12]. Low levels of some of these bacterial products have been detected in systemic circulation and the liver [13]. The mouse models have also shown a resulting increase in inflammatory markers, transaminase levels, liver triglycerides, fibrosis, and oxidative stress in the liver [12].

Overlap Syndromes

Individuals with autoimmune hepatitis may exhibit features of other immune-mediated liver diseases. In one study, 7–13 % of patients with AIH also had features of primary biliary cirrhosis, 6–11 % showed signs of PSC, and 5–11 % showed a cholestatic syndrome without other diagnostic features [14]. The commonalities of these syndromes include a cholestatic component and failure to respond consistently to conventional corticosteroid therapy [14]. With the association of ulcerative colitis with PSC, AIH–PSC is the most common overlap syndrome in the IBD patient. The addition of cholangiographic changes showing focal strictures and dilations of the biliary tree characteristic of PSC to a patient meeting AIHG criteria for AIH warrants the diagnosis of AIH-PSC overlap [14]. Likewise, patients with AIH may develop co-existing IBD, cholestasis, or resistance to immunosuppressive therapy. This should prompt work-up for PSC [6]. Autoimmune hepatitis in patients with PSC occurs more frequently in children and adolescents [7, 15–17]. Typically, patients with PSC begin to have elevated transaminases, develop high ANA or AMSA titers and elevated IgG levels. Prominent histologic interface hepatitis, elevated IgG levels, or autoantibodies suggest concurrent AIH [7].

AIH–PBC overlap is the only syndrome for which there are formal proposed criteria, "The Paris Criteria" [18] (Table 1). To qualify for the diagnosis, patients must meet two out of three AIH group criteria (ALT greater than or equal to five times the upper limit of normal, IgG greater than two times the upper limit of normal or SMA positive antibodies, or evidence of interface hepatitis) as well as two out of three criteria for PBC (positive antimitochondrial antibodies, florid duct lesions, and alkaline phosphatase levels greater than two times the upper limit of normal or gamma-glutamyl transferase levels greater than five times the upper limit of normal) [18]. These criteria are thought to be 92 % sensitive and 97 % specific for AIH–PBC overlap syndrome [18]. Patients who lack features of PBC or PSC but have histologic evidence of bile duct injury or loss are described as having autoimmune cholangitis [18]. This term encompasses AMA negative PBC, small duct PSC, autoimmune sclerosing cholangitis, and IgG4-associated cholangitis.

There is debate on whether AIH–PSC or AIH–PBC overlap syndrome is unique pathology [19, 20]. Some argue that they should be considered more as clinical descriptions rather than distinct pathological entities [14]. Overlap syndromes may be variants of a classical autoimmune hepatitis, transitional stages in the evolution of PBC or PSC, or could be two diseases in the same individual [18].

There are no definitive guidelines for treatment of AIH–PSC or AIH–PBC overlap syndromes. Per AIHG guidelines, typically each disease is treated separately according to the predominant features [19]. Treatment of the overlap syndrome in the majority of cases consists of corticosteroids or combination of corticosteroids and azathioprine [4, 21–31].

Clinical outcomes appear to be superior in AIH–PBC overlap than AIH–PSC overlap. Conventional steroid treatment for AIH induces remission in patients with PBC nearly as frequently as in patients with AIH alone (75 vs. 64 %) if cholestatic features of PBC are mild [32]. Comparatively, only 22 versus 75 % respond in those with AIH–PSC compared to AIH alone. Response to therapy is largely determined by the strength of the AIH component of disease and weakness of the cholestatic component [18]. Overall outcomes in either overlap syndrome are worse

when compared to patients with AIH alone. Adults achieve normal liver tests less frequently, fail treatment more often, and have poorer survival [7, 18, 32].

Patients with AIH–PSC overlap syndrome have better long-term survival without transplant when compared to those with PSC alone. Floreani et al. examined the outcomes in seven patients with AIH/PSC overlap syndrome in relation to "classic" PSC patients. Treatment with prednisone and azathioprine in combination with ursodeoxycholic acid was associated with better survival in overlap patients than in adults with classic PSC [14, 21]. However, one study showed that concomitant autoimmune disease such as AIH is an independent risk factor for reduced survival in patients with PSC [33].

In adults with inflammatory bowel disease and AIH, overlap syndromes such as AIH–PBC or AIH–PSC may be more common than IBD with AIH alone. Perdigoto et al. showed 41 % of adults with AIH and chronic ulcerative colitis to also have cholangiographic features of PSC [4]. Detection of AIH–PSC overlap in IBD is typically in the setting of chronic ulcerative colitis with cholestatic features or poor response to treatment [14]. Patients tend to have laboratory markers of both cholestasis and definite AIH with histologic features of both on biopsy [34]. Although most commonly described in ulcerative colitis [1], cases of overlap syndrome in patients with Crohn's disease have also been reported [19]. The frequency of overlap has prompted some to recommend consideration of cholangiography in all adults with AIH and IBD, especially those with prominent cholestatic laboratories, the absence of AMA serologies, and nonresponders to conventional therapies [4, 14, 18]. It is unknown whether these outcomes significantly differ in IBD patients when compared to overlap syndromes in non-IBD patients.

Medication-Induced AIH

Cases of autoimmune hepatitis have also been reported in patients with inflammatory bowel disease receiving therapy [1]. Typical medications used for inflammatory bowel disease include aminosalicylates, methotrexate, and various biologics including antitumor necrosis factor (TNF) alpha drugs. At least eleven cases have been reported to date of autoimmune hepatitis in patients treated with infliximab therapy [35–47]. Etanercept has also been found to exacerbate AIH [48].

In one case, Cravo et al. describe a 38-year-old woman with Crohn's disease who required infliximab [39]. At the start of therapy, liver function tests were normal and antinuclear antibody (ANA) and anti-double-stranded DNA (ds-DNA) were negative. Two years into treatment with infliximab, the patient developed a hypergammaglobulinemia and transaminitis. Serologies for viral infections were negative, and ANA, dsDNA, and antihistone antibodies were positive. Liver biopsy showed "chronic hepatitis with inflammatory plasmocytic infiltrate in the portal tracts, interface hepatitis, and mild periportal fibrosis." The patient met criteria for definitive AIH. Within 3 months after discontinuing infliximab, ANA titers decreased and liver function tests normalized [39].

In most reported cases of infliximab-induced AIH, the hepatitis resolved with withdrawal of the drug and steroid treatment. Other agents used in combination with steroids include azathioprine and ustekinumab [35]. In two of the reported cases, AIH resolved with switching to another biologic agent such as adalimumab suggesting an absence of cross-reactivity [38, 39]. This phenomenon may be attributed to infliximab being a chimeric monoclonal antibody, whereas adalimumab is a fully human antibody [39, 49]. However, there is one case of adalimumab-induced autoimmune hepatitis reported in a patient with Crohn's disease and psoriasis. AIH was diagnosed three months into treatment, requiring discontinuation of adalimumab and initiation of prednisone with azathioprine. Two months later, the hepatitis had resolved and ANA antibodies had disappeared [50]. This reaction may be an isolated incident or may suggest a class-wide effect, but this remains unclear.

Although the pathogenesis of infliximab-induced autoimmune hepatitis remains unclear, it is thought that infliximab triggers the development of autoantibodies that typically include ANA and anti-dsDNA [39]. Studies in the rheumatoid arthritis population show increases in autoantibody formation within 30 days in patients on infliximab [51]. The TNF blockade associated with these agents interferes with the normal suppression of auto-reactive B cell production and apoptosis of CD8 T cells causing an increased lymphocyte presence [42, 51]. Other hypotheses include immune deregulation and dysfunction of liver repair through the proinflammatory and immunoregulatory properties of TNF-alpha [43, 52]. In the liver specifically, it may have dual effects by both promoting liver injury after exposure to toxins and promoting liver regeneration after partial hepatectomy [53]. TNF-alpha mediates increases in reactive oxygen species which can be exploited to evoke a paradoxical proliferative response or increase hepatocyte vulnerability to necrosis [53]. Therefore, in the appropriate setting, TNF-alpha inhibition can lead to both further hepatic damage and regeneration.

Interestingly, infliximab has served as rescue therapy in cases of pediatric autoimmune hepatitis that have been refractory to traditional treatments for AIH such as azathioprine and prednisolone [54–56]. A genetic polymorphism in the TNF-alpha gene has already been described in type 1 autoimmune hepatitis involving a nucleotide

substitution [57]. This polymorphism is associated with high levels of TNF alpha and favors a type 1 cytokine response. Young patients with this polymorphism tend to respond less well to corticosteroid therapy and may explain why children with refractory disease respond to infliximab [57].

Weiler-Normann et al. treated 11 patients with difficult-to-treat AIH with off-label infliximab infusions [56]. All patients showed marked decreased in transaminases, and eight patients experienced normalization of liver enzymes. Six patients achieved full remission. Additionally, Rajanayagam et al. describe the case of a 10-year-old girl with type I autoimmune hepatitis who was unable to achieve sustained biochemical response on azathioprine, mycophenolate mofetil, or tacrolimus [54]. She required persistent corticosteroid therapy. She had no evidence of sclerosing cholangitis overlap on MRCP. Within 3 weeks of beginning infliximab therapy, she experienced biochemical and clinical improvement with steroid-sparing therapy. Apoptotic pathways involving TNF-alpha and TNF receptor I may be involved in the destruction of hepatocytes that characterizes AIH [57]. Therefore, infliximab's impairment of activated lymphocytes may explain its beneficial effects in autoimmune hepatitis [56].

Liver Transplantation

Despite aggressive treatment for autoimmune hepatitis, certain patients are refractory to immunosuppressive therapy and develop decompensated cirrhosis or fulminant liver failure [58]. In these patients, liver transplantation has been shown to be an effective option [58]. AIH is the indication for liver transplant in approximately 4–6 % of transplant cases [59]. Transplant recipients tend to be younger, are more likely to be female, and have a greater likelihood of rejection in the first 3, 6, and 12 months [60].

Recurrent AIH has been seen in patients post-transplant, with rates ranging from 17 to 41 % [60–63]. In one study of 55 patients with autoimmune hepatitis who underwent orthotopic liver transplantation, 11 patients had biopsy-proven recurrence with almost half occurring within the first year after transplant [60]. Proposed diagnostic criteria for recurrent autoimmune hepatitis after transplant include hypergammaglobulinemia, elevated transaminases, presence of autoantibodies, initial liver transplantation for confirmed AIH, compatible histology, response to corticosteroid therapy, and exclusion of other diagnoses [58, 60].

De novo autoimmune hepatitis can also occur following transplant for nonimmune-mediated liver disease. These patients have characteristics similar to recurrent AIH including interface hepatitis, positive autoantibodies, and elevated IgG [58, 61]. Risk factors include repeated cellular rejection, positive HLA DRB1*03, and treatment with cyclosporine [58, 64–66]. Treatment with prednisone and azathioprine added to the post-transplant immunosuppression regimen is comparable in effectiveness to its use in classic AIH patients [58, 61, 67].

Liver transplantation for autoimmune liver disease in patients with known IBD and de novo IBD after transplant has also been reported [68, 69]. In one study, 91 IBD patients were transplanted for PSC or AIH. Forty-nine patients had diagnosed IBD prior to transplant while forty had IBD after transplant (recurrence in 32 cases and de novo IBD in eight cases) [70]. The study found a cumulative 10-year risk of 72 % for IBD recurrence and 10 % for de novo IBD.

Little data exist on appropriate management of IBD in a liver transplant recipient. Corticosteroids are used in liver transplant patients as well as active inflammatory bowel disease, and some data suggest that prednisone tapering may contribute to the development of IBD after liver transplant [71, 72]. There is conflicting evidence regarding the efficacy of cyclosporine or tacrolimus for IBD treatment, but these medications are often used for immunosuppression after liver transplantation [69, 73–75]. Mycophenolate mofetil (MMF) can also be used as long-term immunosuppression but is associated with gastrointestinal side effects, including diarrhea, which may limit its use patients with IBD [76]. One case series examined IBD management in six patients who underwent liver transplantation [69]. Four patients required transplantation for primary sclerosing cholangitis, while one for autoimmune hepatitis. Three patients were diagnosed with IBD prior to transplant, and three were diagnosed afterward. All patients were safely treated for IBD with anti-TNF therapy in addition to other post-transplant immunosuppressants including tacrolimus, MMF, prednisone, and cyclosporine [69]. Anti-TNF therapy was effective in four of the six patients, which is a similar to the effectiveness in patients who have not had liver transplants. In this case series, the addition of anti-TNF medications to standard immunosuppression was thought to be safe and effective. However, combining immunosuppression with anti-TNF medications must be used with caution as this also increases the risk of adverse effects, including cytopenias, opportunistic infections, as well as possible malignancy [69].

Conclusion

Liver test abnormalities from autoimmune liver disease are not uncommon in the IBD patient, and evaluation requires a systematic diagnostic algorithm with work-up including autoimmune serologies as well as imaging of the liver and bile

ducts. Autoimmune hepatitis specifically may occur in various forms in inflammatory bowel disease, including lone autoimmune hepatitis, overlap with PBC or PSC, or as medication-induced autoimmune hepatitis due to treatment of IBD. IBD patients meeting criteria for definite autoimmune hepatitis should also be screened for primary sclerosing cholangitis to determine the presence of overlap syndrome. Although overlap syndromes including AIH–PSC and AIH–PBC lack distinctive clinical, histologic, and serologic identities, characterization of the phenotype of disease helps predict outcomes and response to therapy. Data suggest that IBD patients with AIH may have refractory disease requiring escalation of therapy and providers may wish to consider more aggressive initial treatment. Similarly, AIH may exhibit a poorer response to treatment in the presence of IBD. In refractory cases when autoimmune hepatitis patients require liver transplant, IBD may be an active issue, recur after transplant, or occur de novo. These patients require special treatment considerations in order to balance the benefits and risks of combined immunosuppression.

When IBD patients develop new liver enzyme abnormalities during the course of therapy, medication-induced autoimmune hepatitis should also be considered. Cases are most common in patients on infliximab, though it remains to be seen whether medication-induced AIH is class-wide among the TNF-alpha inhibitors. Liver enzymes and autoimmune serologies should be checked prior to initiation of therapy with such agents to provide a baseline if significant changes occur during the course of treatment.

It is essential for gastroenterologists and hepatologists to appropriately work up liver test abnormalities and understand the phenotypes of AIH in patients with inflammatory bowel disease. When AIH is diagnosed in an IBD patient, overlap syndromes and the role of medications in the appropriate clinical scenarios must be considered, yet further research is still necessary to determine whether these patients require unique therapeutic approaches to achieve remission of either disease.

Conflict of interest None.

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