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REVIEW PAPER

Autoimmune hepatitis and primary sclerosing cholangitis overlap syndrome in inflammatory bowel diseases

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ABSTRACT

A close relationship between inflammatory bowel diseases (IBD) and hepatobiliary disorders, such as autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC), is well established. Hepatobiliary manifestations occur in 30% of patients with IBD, and 5% develop chronic liver disease. The spectrum of symptoms of the overlap syndrome ranges from asymptomatic elevated liver function tests to serious diseases. The pathogenesis of liver complications in IBD is not fully recognized. It may either have an autoimmune background or be caused by intestinal inflammation, metabolic impairment, or drug toxicity. The aim of this review is to summarize AIH and PSC overlap syndrome in IBD.

KEY WORDS:

inflammatory bowel disease, autoimmune hepatitis, overlap syndrome, primary sclerosing cholangitis.

INTRODUCTION

Inflammatory bowel diseases (IBD) represent a group of chronic systemic inflammatory conditions with predilection to the gastrointestinal tract. It includes Crohn's disease (CD), ulcerative colitis (UC), and if the IBD cannot be further specified, unclassified IBD [1]. A close relationship between IBD and liver and biliary tract diseases has been demonstrated. Elevated liver function tests are reported in up to 30% of patients with IBD. Liver and biliary tract conditions are common extraintestinal manifestations for both CD and UC [2]. The most common hepatobiliary disorders are primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and in a small group of patients with IBD, AIH and PSC overlap syndrome (AIH/PSC) [1, 2]. The aim of this paper is to review the available literature describing the coexistence of these diseases in both adult and paediatric populations.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a chronic inflammatory disease characterized by cholestasis and progressive fibrosis followed by destruction of the bile ducts. It can affect both extrahepatic and intrahepatic bile ducts [3]. The distinguishing feature is the presence of concentric obliterans leading to biliary stenosis. In many cases it induces biliary cirrhosis and hepatic failure [4].

Primary sclerosing cholangitis is a very rare disease. In the general population the incidence of PSC is approximately 0.5–1 per 100,000 adults and 0.2 per 100,000 children [5]. Primary sclerosing cholangitis is not a classical autoimmune disease because it occurs with a 2 : 1 male predominance compared with the female predominance found in classical autoimmune diseases such as primary biliary cirrhosis (PBC) and AIH. The median age is in the 4th decade of life for adults and the 2nd decade for children [3, 5, 6].

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The aetiology is unknown. Both genetic and non-genetic factors have been identified to predispose to PSC [5]. Multicentre studies have shown a higher risk of PSC in first-degree relatives of patients with PSC [7]. A close relationship between the occurrence of PSC and the HLA complex was confirmed. The strongest associations were detected for HLA-B*08 and DRB*03 [4, 8]. Moreover, HLA haplotypes specific to PSC or PSC with IBD were shown not to be associated with UC, but HLA haplotypes specific to UC were not related with PSC [8]. Furthermore, among non-genetic factors, the autoimmune basis plays an important role. Studies have shown that about 33–88% of PSC patients have the atypical anti-neutrophil cytoplasmic antibodies (ANCA) in their blood serum. However, they are not specific to PSC, because they are also present in patients with UC (60–87%) or AIH (50–97%) [4]. The importance of these autoantibodies in the development of PSC is unknown. Another non-specific autoantibodies present in PSC patients are antinuclear antibodies (ANA; 20–67%), antimitochondrial antibodies (AMA; < 10%), and antithyroperoxidase antibodies (7–16%) [9].

Although the pathogenesis of PSC remains unclear, many authors emphasize the likely key role of environmental factors, the main one being intestinal microbiota (IM). Intestinal microbiota can be considered as an environmental factor, but it is also affected by other environmental factors such as diet, medication, hygiene, and even mood [10]. The basic hypothesis regarding the influence of IM in the pathogenesis of PSC is the movement of intestinal microorganisms or their metabolites through the leaky (due to inflammation) intestinal barrier into portal circulation. After that, they are transported through the portal circulation to the liver, where chemokines and cytokines are released from the Kupffer cells. This causes displacement of inflammatory cells and fibroblasts, resulting in an active inflammatory process, ultimately resulting in fibrosis [10, 11].

In healthy patients, IM consists of many species of bacteria in appropriate proportions to each other. It has been shown that patients with PSC have a decrease in IM biodiversity. The result of this dysbiosis is an imbalance in the production of protective and harmful metabolites, as well as the facilitation of abnormal immune processes. Disturbances in the composition of IM shape the bile acid pool and modulate the activity of bile acid-activated receptors. It can affect bile acid metabolism disorders, and consequently the initiation and progression of PSC [11]. On the other hand, recent research has demonstrated the antibacterial effects of bile acids by altering essential bacterial proteins. In addition, it is emphasized that bile acids have not only a direct antibacterial effect, but also indirectly affect IM. In obstructed bile ducts, the flow of bile to the intestine is blocked, leading to bacterial overgrowth and bacterial translocation in the small intestine. Moreover, there is another hypothesis suggesting

the cause of the PSC. It has been shown that defects in the hepatobiliary transport system can result in damage to the bile ducts. As a result of transport disorders, "toxic" bile with altered composition is formed, which stimulates the damage of biliary epithelial cells, periportal inflammation, periductal fibrosis, and consequently the development of PSC [4].

The disease symptoms are not specific. They are usually present before diagnosis in approximately 36–70% of cases. The most common symptoms reported by adults are itching and fatigue, while abdominal pain is dominant in children. However, many cases (up to 45%) of this disease are asymptomatic [1, 6, 12–14].

The laboratory abnormalities characteristic of cholestasis are found in the examination results, as well as the presence of anti-neutrophil cytoplasmic antibodies with a pericellular pattern (p-ANCA), which are the most commonly observed antibodies in both children and adults [15]. Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard to diagnose PSC. These studies make it possible to visualize segmental stenoses and dilations located within the bile ducts [16]. In contrast to MRCP, ERCP also has therapeutic relevance. During the examination, it is possible to widen the narrowed ducts and place stents. It also provides more diagnostic information through brush cytology and biopsy. However, in addition, there is a risk of complications such as pancreatitis, abdominal pain, cholangitis, pancreatitis, bleeding, and perforation of the bile ducts [8].

Currently there is no effective pharmacological causal treatment. Ursodeoxycholic acid improves biochemical parameters. It has been shown to have a positive effect on improving biochemical parameters but has no effect on patient survival [17–21]. The only effective therapeutic option is liver transplantation, which is a necessity for many patients [22].

Recent studies indicate that antibiotics may have beneficial effects in patients with PSC. The mechanisms of such action remain unexplained [23, 24]. Tabibian *et al.* conducted a study in which 35 patients with PSC were randomly assigned to 4 groups. Patients were treated for 12 weeks with vancomycin in doses of 125 mg or 250 mg orally 4 times a day (groups 1 and 2) or metronidazole 250 mg or 500 mg orally 3 times a day (groups 3 and 4). Only the vancomycin-treated groups showed a decrease in alkaline phosphatase activity. Normalization of the activity of this enzyme was achieved in 2 patients receiving the lower dose of vancomycin. Pruritus decreased significantly in the group of patients treated with higher doses of metronidazole. In 6 patients, including 4 on metronidazole, treatment had to be discontinued prematurely due to adverse events. The authors found that both antibiotics showed therapeutic efficacy in PSC, but only vancomycin had a significant effect on alkaline phosphatase activity with relatively good drug tolerance [24].

IGG4-ASSOCIATED CHOLANGITIS

IgG4-associated cholangitis is the hepatobiliary manifestation of immunoglobulin G4-related disease (IgG4-RD). It is characterized by infiltration with IgG4+ plasma cells and sclerosing changes in the bile ducts, which can often be confused with PSC or pancreatic cancer. Similarly to PSC, there is a male predominance (80–85%). The median age is in the 7th decade of life. However, in contrast to PSC, many patients respond very well to high or moderate doses of corticosteroids, resulting in a reduction in symptoms, organ enlargement, and a decrease in sIgG4 level. Most of them require long-term maintenance immunosuppressive therapy to prevent relapse [4, 25, 26].

PRIMARY SCLEROSING CHOLANGITIS AND INFLAMMATORY BOWEL DISEASES

Primary sclerosing cholangitis is strongly associated with IBD. In approximately 50–80% of patients with PSC it is concomitant with UC, being more common than CD or unclassified IBD. On the other hand, of all patients with IBD, 0.8–8% of patients with UC and 0.4–9% of those with CD will develop PSC [27, 28].

The potential association of the 2 diseases is immunopathogenic. In this overlapping syndrome, there are some humoral and cellular immune abnormalities. The most common ones are raised IgM levels (in up to 50% of cases), positive anti-smooth muscle antibodies, ANA (in up to 75% individuals), and p-ANCA (in 80% of patients) [29].

Typically, IBD is diagnosed several years before PSC. However, occasionally symptoms of PSC precede IBD by up to 4 years [30]. There is evidence that patients with UC in childhood have a higher prevalence of liver disorders than adults, with up to 60% children having abnormal liver function tests [30]. Therefore, both children and adults are recommended to have a colonoscopy at the time of diagnosis of PSC [5]. Moreover, due to the high incidence of PSC with IBD overlap syndrome, some experts recommend that follow-up endoscopies be performed in patients with PSC without IBD every 3–5 years [16, 31, 32].

The combination of PSC and IBD is associated with a different IBD phenotype. When PSC is accompanied by UC or CD, the course is usually milder than without PSC [27]. Patients with UC and PSC tend to present with extensive colitis, backwash ileitis, and maintain a healthy rectal mucosa (without inflammation), compared to patients with IBD without PSC. Moreover, it has been shown that patients with clinically asymptomatic PSC and UC had greater histological activity in the right colon and less in the rectum [27, 33]. The dominant phenotype in CD is colitis, which may or may not involve the terminal ileum. Stenosis or fistula phenotypes are less common [34].

Primary sclerosing cholangitis is a significant risk factor for the development of colorectal cancer (CRC) in patients with IBD – a 4-fold increase has been reported in UC patients with PSC when compared to UC alone (RR 4.26 95% CI: 2.8–6.48) [35, 36]. Additional risk factors include duration and extent of disease and a family history of CRC [37].

Despite treatment, PSC is progressive with poor prognosis. An important factor influencing the survival of patients with PSC is the increased risk of cholangiocarcinoma, which is even higher in patients with PSC/IBD [38].

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic liver disease caused by loss of tolerance to hepatocyte-specific autoantigens, characterized by a female predilection, elevated transaminase levels, the presence of autoantibodies, elevated γ-globulin or IgG levels, and biopsy-confirmed interfacial hepatitis [39]. If not properly treated, this disease can lead to the development of cirrhosis and then liver failure [40]. Due to the type of autoantibodies, 2 types of AIH are distinguished: type 1 (AIH-1) with the presence of anti-smooth muscle antibodies (SMA) or ANA, and type 2 (AIH-2) with the presence of antibodies against liver and kidney antigens (LKM-1) or anti-cytosol antibodies (LC1) [40].

The disease affects any age and all ethnic groups [41]. The incidence of AIH in the adult population is 0.67–2.0 cases per 100,000 person-years, while in the paediatric population it is estimated at 0.23–0.4 cases per 100,000 person-years; however, a gradual increase in the number of cases is observed [41]. AIH-1 is mainly characteristic of adult and adolescent patients, and AIH-2 is mainly diagnosed in children. Among patients with AIH, the female sex predominates, both in children (60–76%) and adults (71–95%) [41].

The detailed aetiology of AIH is not known. Recent studies suggest the interaction of genetic and non-genetic factors as key in the pathogenesis. Genetic studies have shown that the predisposition to AIH is partly attributable to HLA complex polymorphisms. HLA genotypes differ depending on the type of AIH, the age of the patient at the onset of the disease, and the region of residence [42]. In general, it has been shown that AIH-1 is associated with the presence of (HLA) DRB1*03, while AIH-2 is associated with the presence of DRB1*07 and DRB*03. Moreover, in paediatric patients DRB1*04 does not predispose to the development of AIH, and may even have a protective function, in contrast to adult patients [43, 44]. Recent studies also draw attention to the role of infectious agents and IM. It is believed that this increase in the incidence of autoimmune diseases in developed countries, including AIH, can be attributed to the so-called "hygiene hypothesis", which assumes reduced exposure to microbes in childhood, accompanied by changes in immune function, and which may favour allergic and autoimmune diseases. In addition, environmental factors such as diet and lifestyle can negatively

affect the composition of IM. As a result of dysbiosis, intestinal permeability increases, which may result in the translocation of microorganisms and their metabolites into systemic circulation [42].

Autoimmune hepatitis arises in genetically predisposed patients when a trigger, such as viral exposure, leads to an autoimmune response mediated by autoreactive T cells directed against hepatocyte autoantigens. At the same time, in the absence of effective inhibition of regulatory B cells, autoreactive B cells produce autoantibodies directed against hepatocytes. It confirms that the loss of immunoregulation plays a key role in the pathogenesis of AIH [42, 45].

Clinical manifestations vary depending on the case, from asymptomatic to severe or even in rare cases fulminant hepatitis [40]. In most cases, the symptoms are non-specific. Fatigue is the main complaint in 85% of patients. Jaundice, weight loss, abdominal pain, and menstrual disorders are also common. In 25–34% of patients AIH is asymptomatic or mildly symptomatic. Then the diagnosis is based on random laboratory tests or the presence of symptoms resulting from complications in the form of portal hypertension (splenomegaly, bleeding from oesophageal varices) [40]. Some patients with AIH have other symptoms that may be a manifestation of other autoimmune diseases. These include joint pain, rash, thyroiditis, enterocolitis, pleuritis, pericarditis, or endocarditis. There are reports of isolated cases of lichen planus, mixed connective tissue disease, macroglobulinaemia, or uveitis. For this reason, it is believed that all patients with suspected autoimmune diseases should have liver biochemical tests performed, and those patients with abnormalities should be tested for AIH [46].

Autoimmune hepatitis diagnosis is based on histological abnormalities, characteristic clinical and laboratory findings, and the presence of one or more characteristic autoantibodies. There is no signature diagnostic marker of AIH, and the diagnosis requires characteristic features and the exclusion of other diseases that may resemble it, such as viral hepatitis, drug-induced liver injury, or Wilson's disease [45]. The typical biochemical profile is characterized by elevations of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and increased serum IgG concentration. ANA, SMA, and anti-LKM1 constitute the conventional serological repertoire for the diagnosis of AIH. The first 2 are characteristic of AIH-1, and anti-LKM1 is present in AIH-2. However, the absence of these antibodies cannot exclude the diagnosis of AIH. Therefore, a liver biopsy and histological examination are essential for accurate diagnosis of AIH and are helpful in differential diagnosis, identification of comorbidities, and staging of fibrosis. Interface hepatitis is the characteristic feature of AIH, accompanied by plasma cell infiltration and lobular hepatitis. Centrilobular necrosis is also found, and it occurs with similar frequency in patients with and without cirrhosis. Cirrhosis is present in 28–33% of adults at diagnosis, especially in the elderly as well as in 38% of children [42, 45, 46].

The purposes of the treatment of AIH are to first relieve symptoms, then to achieve a biochemical response, control hepatic inflammation toward histological remission, prevent disease progression, and promote the regression of fibrosis. Biochemical remission is the normalization of the patient's serum AST, ALT, and IgG levels. It is followed by a histological remission of disease activity. Maintaining biochemical remission for a long time (> 1 year from the start of treatment) significantly affects the long-term survival of the patient [47]. Immunosuppression is an effective method of therapy in AIH; therefore, it should be implemented as soon as possible to avoid disease progression [41]. Both corticosteroid monotherapy and a combination of lower doses of corticosteroids and azathioprine (AZA) have been shown to be effective in AIH treatment [48]. The 2019 American Association for the Study of Liver Diseases practice guidance and guidelines updated their recommendations of first-line treatment. Prednisone monotherapy (40–60 mg/day) or a combination of prednisone (20–40 mg/day) or budesonide (9 mg/day) and AZA (50–100 mg/day) is recommended [45]. Similar suggestions are contained in the 2015 European Association for the Study of the Liver guidelines, which proposes prednisone as the initial treatment (0.5–1 mg/kg/day), followed by the addition of AZA (50 mg/day). That addition makes it possible to maintain remission with the maximum reduction of the corticosteroid dose [49]. For the small group of patients who do not respond to these medications or cannot tolerate their side effects, alternative treatments are required. Second-line treatments have been performed with mycophenolate mofetil, calcineurin inhibitors (cyclosporin A, tacrolimus), mercaptopurine, and biologics [47]. If the applied treatment is ineffective and there is a progressive impairment of liver function with decompensated cirrhosis, qualification for liver transplantation (LT) is recommended [41, 47].

AUTOIMMUNE HEPATITIS AND INFLAMMATORY BOWEL DISEASES

The incidence of AIH in patients with IBD (AIH/IBD) ranges from 0.6 to 1.6%, with up to 16% of cases manifesting as UC [50]. In contrast to PSC-IBD, patients with AIH-IBD are likely to have a more severe course of both diseases. They are more resistant to conventional therapies. More often it is necessary to perform a proctocolectomy. Liver disease also has a more severe progression with younger onset, refractory to treatment, higher risk of progression to cirrhosis, resulting in higher risk death and the need for LT compared to people without AIH-IBD overlap syndrome [51, 52].

AUTOIMMUNE HEPATITIS AND PRIMARY SCLEROSING CHOLANGITIS OVERLAP SYNDROME IN INFLAMMATORY BOWEL DISEASES

A small subgroup of patients have AIH and PSC overlap syndrome (AIH/PSC). It has been reported in up to 6% of patients with PSC and in 18% of AIH patients [53]. The main feature of the AIH/PSC is the presence of histologic, serologic, and laboratory features of AIH, with biliary stricture compatible with PSC [54, 55]. It has a strong association with IBD, more common in UC [56]. However, cases of overlap syndrome in CD have also been described [57]. Perdigoto *et al.* described the coexistence of AIH and UC in 16% of patients, and in approximately 42% of these patients, abnormalities of the bile ducts were visualized [50]. Both intrahepatic and extrahepatic bile ducts may be affected [58]. AIH/PSC is more common in children and young adults, PSC features usually develop later, and it has a better prognosis than PSC alone [45, 51].

Ballotin *et al.* published a case report of AIH/PSC with a systemic review. According to their findings there were more male patients, and their mean age of diagnosis was 25 years. More than 40% of those individuals had also IBD, and the majority of these cases (68%) presented with UC, while the most common manifestation of hepatobiliary disorders was jaundice (28.70% of cases), followed by fatigue and abdominal pain (20.37% and 19.44%, respectively) [58]. Diagnosis, treatment, and prognosis of the overlap syndrome are controversial because there are no standardized diagnostic criteria available. Some patients with AIH/PSC in IBD may respond to immunosuppression, but their management depends on liver histology, serum IgM levels, autoantibodies, and the degree of biochemical cholestasis and cholangiography [58]. Clinical treatment with steroids, AZA, and ursodeoxycholic acid seems to be safe and effective, and it seems adequate to consider this association in such cases. If medical treatment fails, liver transplantation may also be considered as a safe method of treatment and should be performed earlier than with isolated PSC or AIH [58, 59].

CONCLUSIONS

Hepatobiliary disorders are common in patients with IBD. The most frequent autoimmune hepatic associations are PSC and AIH. At the current stage of medical knowledge, there is no definitive and highly specific clinical picture of AIH/PSC overlap syndrome in IBD. It seems that it is a distinct entity with specific presentation and prognosis. Therefore, the gastroenterologist should be aware that patients with laboratory data suggestive of both hepatocellular and cholestatic liver injury should undergo liver biopsy to achieve an adequate diagnosis, especially if they have a previous diagnosis of IBD. The direction of future research should be clinical trials to search for new possible treatments for the AIH/PSC, because of the expected increase in the incidence of these syndromes, consistent with the increase in the incidence of IBD in recent decades, both in the paediatric and adult population.

DISCLOSURE

The authors declare no conflict of interest.

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