Liver Disease Associated with Inflammatory Bowel Disease

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a chronic condition characterized by persistent inflammation of the gastrointestinal tract, comprising ulcerative colitis (UC) and Crohn's disease (CD). While the current global incidence of IBD exceeds 0.3% in Western nations, Indonesia reports a comparatively lower prevalence however projections indicate a potential rise in incidence from 2020 to 2050. Hepatobiliary manifestation is one of the most common extraintestinal manifestations of IBD. Some of the liver diseases associated with IBD had similar background immune responses, inflammatory reactions, similar risk factors, or due to the treatment of IBD. Primary sclerosing cholangitis (PSC) has a close association with IBD and both affect the prognostic and disease progression of each other. Non-alcoholic fatty liver disease (NAFLD) shares common metabolic risk factors. Several drugs used as the treatment of IBD might cause hepatic injury especially due to the long treatment duration of IBD. Hepatitis B reactivation is another concerning event found after prolonged use of immunosuppressive drugs for IBD. Therefore, close monitoring of liver function tests periodically is a mandatory test to screen for liver disease in IBD patients.

Keyword: *autoimmune hepatitis, drug-induced liver injury, inflammatory bowel disease, liver disease*

INTRODUCTION

Inflammatory bowel disease (IBD) is a condition caused by chronic inflammation of the gastrointestinal tract. The manifestation of IBD consists of ulcerative colitis (UC) and Crohn's disease (CD). Currently, the incidence of IBD is rapidly increasing worldwide with an estimated prevalence of >0.3% in the western countries.[1] The incidence of IBD in Indonesia is still less than 20 per 100,000 people.[2]

However, this figure is predicted to increase from 2020 to 2050, possibly due to advancements in diagnosis and the risk factors that trigger IBD. The increase in IBD incidence has been explained through two reasons; with the first one being an advancement in diagnosis of IBD which in turn reveals more of the previously undiagnosed cases and the second one is the true rise of incidence due to lifestyle changes thus genuinely increasing the number of incidences.[3] Currently, there are no definitive cure to IBD and cases of relapse or complications are not uncommon. Therefore IBD has substantially led to a socioeconomic burden.[4]

PATHOPHYSIOLOGY OF IBD

There are two main disease manifestations of IBD: Crohn's disease and ulcerative colitis. Commonly Crohn's disease would be found in the terminal ileum, colon, caecum, and perianal area. However, it could also be found throughout all the gastrointestinal tracts. Crohn's disease is a Th1 cell-mediated disease as exhibited by increased levels of inflammatory cytokines, for example, interferon-gamma and IL-

17A. Crohn's disease is characterized by an increased cellular intake of intestinal microflora, which stimulates antigen-presenting cells (APCs) to induce the differentiation of CD4 cells into Th1 cells.[5]

In contrast to Crohn's disease, in ulcerative colitis inflammatory reaction would affect all the layers of mucosal tissue and could be found in the rectum, left semicolon, or the entire colon.[6] Ulcerative colitis is caused by disruptions in the mucosal barrier and tight junctions between cells, leading to increased exposure to luminal antigens. T helper 2 cells play a role by producing interleukin-13, which will disturb the membrane integrity by increasing apoptosis and changing the composition of tight junctions.[7] These changes will increase gut permeability thus allowing more luminal antigens to pass through. These antigens stimulate APCs to induce the differentiation of CD4 T cells into Th2 effectors.[5]

RISK FACTORS OF IBD

Some of the risk factors that can lead to IBD include dietary patterns, sleep, stress levels, medications, lack of physical activity, history of appendectomy, smoking, genetic factors, and environmental factors.[5] The clinical manifestations of IBD encompass a wide spectrum, with most patients complaining of fatigue, abdominal pain, anxiety, depression, bloating, and the presence of blood in the stool. Approximately 30% of IBD patients also report extraintestinal symptoms. Extraintestinal symptoms commonly found may involve the dermatological, diarrhea, joint, pancreatic, and hepatobiliary systems.[8] Hepatobiliary manifestations are common extraintestinal manifestations of IBD. Around 30% of patients with IBD have an increase in liver transaminase with 5% developing chronic liver disease.[9] These hepatobiliary alterations initially had no symptoms with some of them will develop severe liver failure.[10,11]

EXTRAINTESTINAL MANIFESTATION OF IBD

Extraintestinal manifestations of IBD were determined by immunological factors, gut microflora, environmental factors, and genetics of the host.[12] Gut microflora play an important role in activating the immune system through cross-reactivity between bacterial antigen and colonic mucosa.[13] The leaky intestine enabled bacteria to cross the intestinal barrier and trigger adaptive immune response which were unable to distinguish between epitopes found in joints, skin, liver, and the antigen within the bacteria.[14]

Genetic risk of both IBD and extraintestinal manifestation has an extensive overlap with association studies that revealed a concordance in extraintestinal manifestation present in 70% of parent-child pairs and 84% between sibling pairs.[15] These findings could indicate a notable role of genotype or early environmental factors. The genetic makeup of the host especially in human leukocyte antigen (HLA) genes, could trigger autoimmune response found in IBD. CD complications were observed in patients with a mutation of HLA-DR1, HLA-A2, and HLA-DQw5. On the other hand, CD complications were observed in patients with the HLA-DR103 genotype.[16]

Dysbiosis of gut microfloral has been linked to the development of extraintestinal manifestation of IBD. Patients with low fecal microbial diversity have been associated with primary sclerosing cholangitis.[17] The diversity of gut microflora might play a significant role through molecular mimicry, the microenvironment of the microflora could trigger extraintestinal manifestations, microbial translocation, metabolite of the microfloral, and interaction between gut microfloral and immune system.[18]

IBD ASSOCIATED LIVER DISEASE

The relationship between IBD and liver disease can be attributed to diseases with a similar autoimmune background to IBD, conditions associated with intestinal inflammation, diseases related to malabsorption or metabolic disorders, and IBD therapies that can lead to liver damage. Based on the disease entities, ulcerative colitis is associated with primary sclerosing cholangitis (PSC), autoimmune hepatitis, primary biliary cholangitis, portal vein thrombosis, and non-alcoholic fatty liver disease (NAFLD). In contrast, Crohn's disease is associated with granulomatous hepatitis, liver abscess, cholelithiasis, hepatic amyloidosis, and NAFLD.[19]

PRIMARY SCLEROSING CHOLANGITIS

PSC is a condition that often occurs in patients with IBD, with 70% of PSC patients having ulcerative colitis. PSC is characterized by the narrowing of the bile ducts due to inflammation induced by autoimmune reactions. It is usually diagnosed in males aged 30 to 40 years.[20] Factors that may contribute to PSC in IBD include enterohepatic flow, immunopathogenic factors, genetic risk, and gut microbiota.

Diagnostic workup for PSC includes radiological, histological, and laboratory examinations. PSC can also lead to complications such as cholelithiasis, cholecystitis, gallbladder cancer, cholangiocarcinoma, cholangitis, and colorectal cancer.[19,21] Unexplained cholestasis in IBD patients warrants further investigation by MRCP and on the other hand, those with PSC should undergo routine examination of colonoscopy with biopsy. Commonly the diagnosis of IBD precedes the diagnosis of PSC, although either of them could occur at different times.[22]

IBD which occurs along with PSC has different manifestations most frequently presenting with extensive disease, rectal sparing, backwash ileitis, mild intestinal activity, and right colonic involvement, respectively.[23] However, the effect of IBD in PSC is not well established with some of the studies showing higher rates of intrahepatic and extrahepatic involvement.[24] Patients with PSC and IBD are much more likely to have a greater risk of colon cancer and similarly, patients with IBD have a higher risk of cholangiocarcinoma with 33% higher risk every 10 years.[25]

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is found in up to 33.6% in patients with IBD. This finding is often independent of metabolic risk factors. However, those with IBD who developed NAFLD were older, diabetic, and more often had diabetes compared to those who did not develop NAFLD.[26] Measurement of liver steatosis reveals more severe steatosis in NAFLD patients with severe IBD with no significant difference in stiffness measurement nor the APRI score.[27]

The pathogenesis of NAFLD is related to disruptions in intestinal metabolism, gut microbiota, and elevated inflammatory markers that can lead to hepatic steatosis and inflammation. A meta-analysis by Zamani et al. demonstrated a twofold increased risk of developing NAFLD in patients with IBD.[28,29] However, with the recognition that the majority of IBD patients had NAFLD in the absence of metabolic syndrome, inflammatory load might be a significant cause of NAFLD in IBD patients compared to metabolic risk factors.[27]

HEPATIC INJURY DUE TO IBD MEDICATIONS

Hepatic damage due to IBD medications can also occur since most of the drugs used for IBD are hepatotoxic. Although the incidence of serious complications is low.[30] Sulfasalazine and 5-ASA are commonly used drugs to treat mild-to-moderate IBD. These drugs might induce hypersensitivity reactions which manifest as fever, hepatomegaly, rash, lymphadenopathy, eosinophilia, and atypical lymphocytosis. The hypersensitivity usually occurs within 2 months of therapy initiation.[31] Sulfasalazine might also induce sulfasalazine-induced granulomatous hepatitis which manifests as fever, malaise, and right upper quadrant pain. Increased serum alkaline phosphatase, ALT, and bilirubin can be found through laboratory tests. Biopsy of the liver might reveal noncaseating granuloma.[30] The 5-ASA/Mesalamine rarely causes liver injury, although some have reported cholestatic injury and some hypersensitivity reactions.[32]

Thiopurine is one of the drugs used in the treatment of IBD with up to 25% of the patients were not able to tolerate the side effects. Thiopurine concludes drugs like AZA and 6-MP with the incidence of hepatotoxicity ranging from 0% to 32%. Some laboratory findings include an increase in ALT, conjugated bilirubin, ALT, and ALP. This reaction is frequently observed within 1 month of treatment initiation.[30] Liver function tests should be measured before starting thiopurines and routinely at weeks 2, 4, and 8 and every 3 months.[33]

Methotrexate is a dihydrofolate reductase inhibitor and is used in the treatment of Crohn's disease.[34] Methotrexate can cause increased levels of AST and ALT. Aside from liver toxicity, myelosuppression is one of the most common side effects.[35] Folic acid supplementation can be beneficial in preventing the liver toxicity and myelosuppressive effects of methotrexate.[34]

Tumor necrosis factor alpha (TNF-α) inhibitors is a commonly used drug for induction and maintenance of remission in moderate-severe IBD. The side effects of TNF-α are myelosuppression, opportunistic infections, and liver injury. Some cases of hepatic injury reported increased levels of ALT, autoimmune pattern of liver injury, and rarely cholestatic liver injury.[36,37]

VIRAL HEPATITIS REACTIVATION

Hepatitis B is a chronic hepatitis with reactivation being one of the concerns during treatment of IBD. HBV reactivation has been found in the usage of high-dose steroids, infliximab, and thiopurine. Before starting treatment using immunosuppressants, measurement of HbsAg, anti-HBs, and anti-HBc antibodies should be done. Those without a history of

previous vaccination should be vaccinated and assessed for serological response. Patients with HBsAg positive should receive prophylactic treatment using nucleotide/nucleoside analogs during the time of treatment and for at least 1 year after stopping immunosuppressants.

DETECTION OF LIVER DISEASE ASSOCIATED WITH IBD

The approach to liver diseases associated with IBD should be initiated with the identification of abnormal liver function test results. Basic characteristics such as sex, ethnicity, age, duration, extension of disease, and history of medication are crucial parts in the early detection of liver disease associated with IBD.[18] The patient's surgical history or flares of IBD should also be considered for the elevated liver enzymes. If the elevation is persistent, further examinations such as bilirubin levels, GGT, and ALP can be conducted to discern the pattern of the disease. Subsequently, additional diagnostic tests like imaging, autoantibodies, or serology may be considered as per the established diagnosis.[2] Therefore, it is crucial to regularly monitor liver function in patients with IBD to identify and treat IBD-related liver diseases.

PROGNOSIS OF LIVER DISEASE ASSOCIATED WITH IBD

Association between liver disease and IBD has been described within several liver diseases. Autoimmune liver disease like PSC has been associated closely with IBD with 64.8% of patients having IBD/PSC association. PSC is the most specific liver disease in IBD patients with 4-5% cases of IBD patients having PSC. On the other hand, 70% patients of with PSC have associated IBD with ulcerative colitis being the most common.[24] Some studies suggested an increased need for colectomy in autoimmune liver disease associated with IBD compared to patients with IBD alone. The recurrence of ulcerative colitis is 30% and Crohn's disease is 80% in patients with PSC.[38] Patients with PSC associated with ulcerative colitis had a higher risk of developing colorectal cancer compared to patients with ulcerative colitis alone.[39] The risk of *de novo* IBD is also much higher in transplant patients who die of PSC or autoimmune hepatitis.[40] The mortality rate of patients with PSC associated with IBD was higher compared to IBD alone with retrospective studies pointing out four times higher mortality rate in these patients.[41]

CONCLUSION

IBD has some close associations with several liver diseases. With the rise of IBD cases, it is important for early detection of liver disease especially those with close associations with IBD. Management of these liver diseases along with the IBD would reduce the risk of complications and the disease burden.

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