Review on hepatobiliary disorders and complications of ulcerative colitis

N.S.Nurmukhamedova
Z.A.Sharopov
A.A.Xudoynazarov
Tashkent Medical Academy

Abstract: Inflammatory bowel diseases (IBD) are a group of chronic relapsing diseases of an autoimmune nature that affect various parts of the gastrointestinal tract. According to the European Organization for Research on Crohn's Disease (CD) and Ulcerative Colitis (UC), about 2.2 million people in Europe (and 5 million worldwide) suffer from these diseases. In recent years, there has been a tendency towards an increase in the number of severe, treatment-resistant forms of UC, complications and surgical interventions leading to disability in patients of young, working age, which determines medical -social relevance of the problem of these diseases. In more than a third of patients with UC, in addition to intestinal symptoms, extraintestinal manifestations are observed, which sometimes appear long before the manifestation of the classic clinical picture of UC, which significantly complicates and prolongs the diagnosis and prescription of adequate therapy for UC and UC. On the other hand, a number of systemic (extraintestinal) manifestations of UC are essentially complications of these diseases or a consequence of drug exposure. One of the most vulnerable in UC is the hepatobiliary system. More than 30% of patients with IBD have abnormal liver function tests, which prompts additional diagnostics.

Keywords: inflammatory bowel diseases, ulcerative colitis, hepatobiliary disorders, hepatobiliary complications

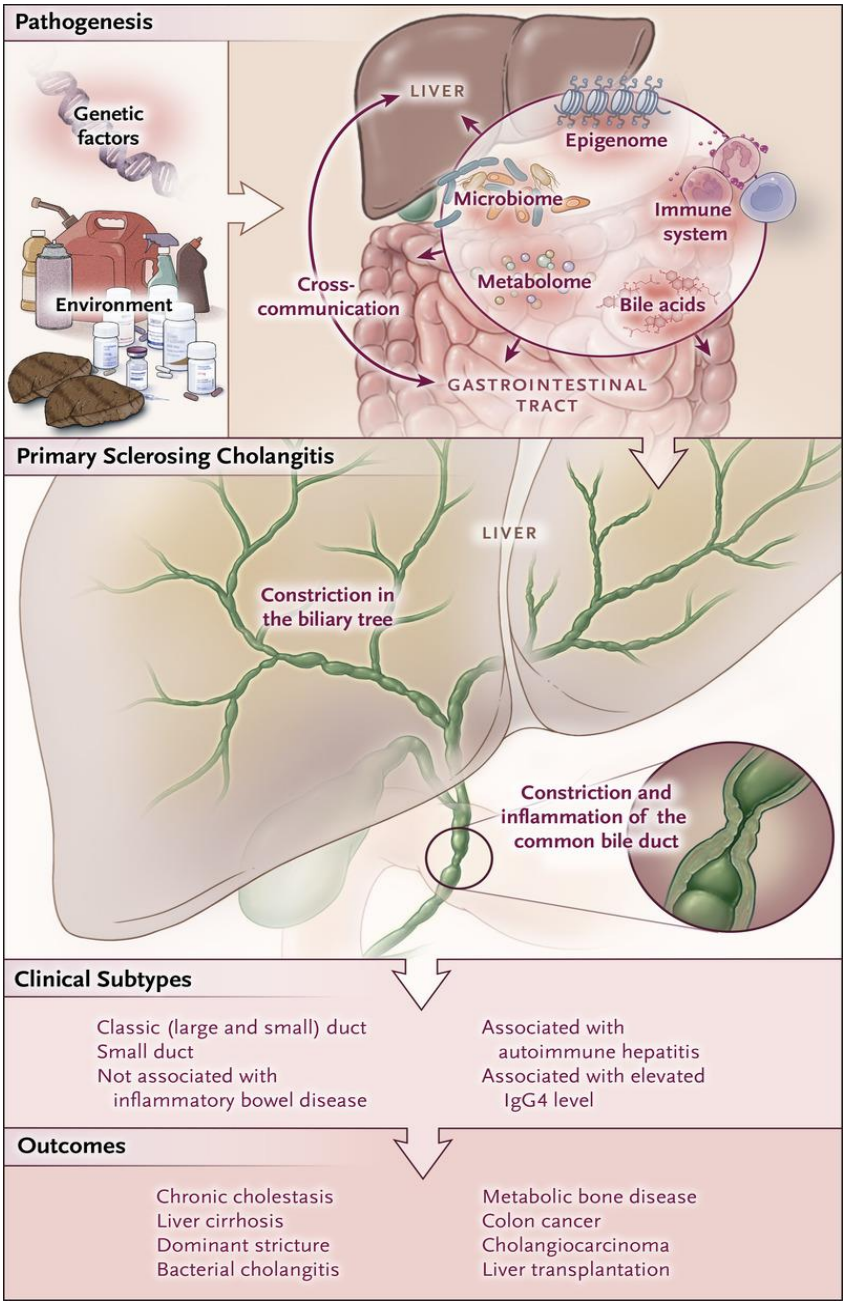
Liver and biliary tract diseases are common extraintestinal manifestations of both UC and CD. Some of these hepatobiliary diseases are benign and require only observation, while others can lead to liver failure and eventual liver transplantation.Liver lesions in IBD are conventionally divided into three main groups: diseases caused by a pathogenetic mechanism common to IBD (primary sclerosing cholangitis (PSC), overlap syndromes: small duct PSC/pericholangitis and autoimmune hepatitis/PSC, IgG4-associated cholangitis, primary biliary cirrhosis); diseases arising as a result of structural and physiological changes against the background of UC (cholelithiasis, portal vein thrombosis, liver abscess,granulomatous hepatitis, amyloidosis), diseases associated with adverse effects of drug therapy for

IBD(drug-induced hepatitis and liver cirrhosis, reactivation of hepatitis B and C viral infection, liver lymphoma (associated with biological therapy).

Primary sclerosing cholangitis (PSC) is the most common hepatobiliary disorder associated with UC. Approximately 70-80% of patients with PSC have concomitant UC and on average 1.4-7.5% of patients with UC develop PSC [33]. PSC is typically characterized by progressive inflammation, obliterative fibrosis, and destruction of intra- and extrahepatic bile ducts, leading to liver failure, portal hypertension, and ultimately, if untreated, death. PSC occurs more often in non-smoking young and middle-aged male patients suffering from UC. In more than 90% of patients, intestinal damage is total. On average, PSC is diagnosed at the age of 40 years. The diagnosis of PSC usually precedes UC. In a study by Faubion et al. (2001) 11% of pediatric patients with PSC had asymptomatic UC at the time of diagnosis. The opposite situation is also possible, when PSC is diagnosed in patients with established IBD. In a study examining the natural history of PSC and IBD in pediatric patients, the mean age at diagnosis of IBD and PSC was 13 and 14 years, respectively. This study also showed that the time from the development of IBD symptoms to the diagnosis of PSC was 2.3 months [2]. With an active process in the liver, a mild course of IBD is observed; the outcome of hepatobiliary damage does not depend on the activity and severity of inflammation in the intestine, as well as on proctocolectomy for UC. The etiology and pathogenesis of PSC still remain unclear. The role of genetic, immunological and environmental factors in the development of this pathology is discussed (1-pic.). There is an increased risk of PSC and UC in first-degree relatives of patients with PSC. Several genetic factors have been identified that are associated with susceptibility to these disorders, in particular HLA-B8, HLA-DRB1*0301 (DR3), HLA-DRB3*0101 (DRw52a) and HLA-DRB1*0401 (DR4). In addition, three common loci (REL, IL2 and CARD9) of candidate genes predisposing to the development of UC and PSC have been identified [1,18].

The autoimmune nature of liver damage in UC is confirmed by the detection of a number of autoantigens in patients with PSC. Antinuclear (ANA) antibodies are detected in 24-53% of patients, anti-smooth muscle antibodies (SMA) in 13-20%, and antinuclear cytoplasmic (p-ANCA) antibodies in 65-88% of patients. Other autoantibodies, including those to cardiolipin, thyroid peroxidase, and rheumatoid factor, may also be present but are of uncertain clinical significance. In a study by P. Angulo et al. (2000) 97% of PSC cases were positive for at least one autoantibody, while 81% were positive for three or more. There is an assumption about the special role of bacterial infection in the pathogenesis of PSC in patients with IBD. Increased permeability of the intestinal epithelium in UC facilitates the penetration of endotoxin and toxic waste products of bacteria into the portal vein and further into the liver.

Enterotoxins can cause pericholangitis, impaired bile excretion and damage to the bile ducts.



1-pic. Pathogenesis of PSC

The clinical manifestations of PSC are variable. Most patients are asymptomatic at the time of diagnosis, and only the detection of abnormal values of liver biochemical parameters allows one to suspect this pathology. Patients complain of fatigue, heaviness in the right hypochondrium, periodic low-grade fever, weight loss, jaundice and itching of the skin. Biochemical parameters correlate with cholestasis and are characterized by a marked increase in serum levels of alkaline phosphatase and hepatic transaminases. Magnetic resonance cholangiopancreatography (MRCP), which has a high degree of sensitivity (85-88%) and specificity (92-97%) and ensures non-invasiveness of the study, is of decisive importance in the diagnosis of PSC. Identification of a diffuse, multifocal stricture involving medium- and large-caliber

intra- and extrahepatic ductal systems forms the basis for establishing a diagnosis. Endoscopic retrograde cholangiopancreatography (ERCP) is superior in diagnostic accuracy but has an increased risk of procedure-related complications [8]. The role of liver biopsy in the diagnosis of PSC is limited, and is probably of greater relevance in the diagnosis of conditions such as small duct PSC and pericholangitis, when PSC is combined with autoimmune hepatitis, as well as in patients with suspected PSC and normal cholangiography.

Patients with PSC typically develop complications of end-stage liver disease with portal hypertension, such as esophageal varices, ascites, and hepatic encephalopathy. Other complications include steatorrhea and fat-soluble vitamin deficiency, secondary chronic cholestasis, secondary amyloidosis with tissue deposition of amyloid protein A due to progressive inflammation, severe biliary stricture, cholangiocarcinoma and colorectal cancer [2]. Risk factors include the presence of IBD, liver cirrhosis, variceal bleeding, severe bile duct stricture, and alcohol consumption [21,37]. Increased jaundice, weight loss, and abdominal discomfort may suggest cholangiocarcinoma. Patients with PSC have an increased risk of developing gallbladder, pancreatic, and hepatocellular carcinoma [19]. A higher risk of developing colorectal dysplasia/cancer has also been described in patients with UC and PSC [7], even after liver transplantation. The severity and duration of PSC were not significantly associated with the risk of developing colon cancer [4]. The prognosis of the disease is poor, with a survival rate of 10% within two years of diagnosis and a recurrence rate in transplanted livers of approximately 20-25% of patients [33].

Treatment of PSC in the setting of UC remains a significant challenge. Pharmacological agents used to treat PSC (colchicine, D-penicillamine, corticosteroids, methotrexate, azathioprine-AZA, cyclosporine A, tacrolimus) have no effect on slowing the progression of the disease. The use of ursodeoxycholic acid (UDCA) helps normalize the activity of liver enzymes without significantly improving the histological structure of the liver and increasing the survival rate of patients without liver transplantation [30]. The use of UDCA in the treatment of patients with PSC has some benefit in the primary prevention of colon cancer. The treatment of choice for end-stage PSC or PSC with cholangiocarcinoma is orthotopic liver transplantation (OLT). The 5- and 10-year survival rates after OLT in patients with PSC are 85 and 70%, respectively [24].

Small duct PSC is characterized by laboratory and histological features similar to PSC in the absence of changes on the cholangiogram. The presence of concomitant IBD is necessary for the diagnosis of this condition. According to a large multicenter study, 80% of patients with small duct PSC had concomitant IBD (78% UC and 21% CD) [3]. CD is more often associated with small duct PSC than with PSC. Progression of small duct PSC was observed in 12-23% of cases. Small duct PSC has a more

favorable long-term prognosis compared to PSC. There are no cases of cholangiocarcinoma described in the literature. Some patients may require OLT to treat end-stage liver disease, and small duct PSC may recur after liver transplantation. In patients with IBD with cholestatic syndrome and a normal cholangiogram according to ERCP/MRCP, liver biopsy is recommended after excluding other hepatobiliary disorders.

Autoimmune hepatitis (AIH)/PSC overlap syndrome is most often observed in children, adolescents and young adults suffering from IBD, mainly UC (35-60%). In 6% of patients with AIH, signs of PSC are detected, and in 2-8% of patients with PSC there are signs of AIH. To diagnose overlap syndrome AIH/PSC, a specific set of criteria is used, including demographic, histological and laboratory markers developed by the International AIH Study Group: signs of AIH on a diagnostic scale of ≥15 points; detection of ANA or SMA antibodies in a titer ≥1:40; changes in the bile ducts, typical for PSC, detected by ERCP/MRCP; detection of stepwise necrosis, lymphocytic rosettes, moderate or severe periportal or periseptal inflammation [11].

For the treatment of AIH/PSC overlap syndrome, it is recommended to focus on alkaline phosphatase (ALP) levels. When the ALP level is ≤2 norms, preference is given to corticosteroids or a combination of corticosteroids and AZA. When the ALP level is ≥2 norms, corticosteroids and UDCA are used at a dose of 13-15 mg/kg/day. A positive effect in the treatment of AIH/PSC from the use of budesonide at a dose of 6-9 mg/day, cyclosporine, mycophenolate mofetil and tacrolimus in some patients has been described. The effectiveness of immunosuppressive therapy in patients with PSC/AIH may lead to a better prognosis compared with patients with isolated PSC [28]. IgG4-associated cholangiopathy, one of many IgG4-associated systemic diseases of the biliary system with unknown immunopathogenesis, has been described in patients with UC. The disease is characterized by a cholangiographic picture similar to PSC and differs in histological features. Diagnostic criteria for IgG4-related cholangiopathy include the presence of systemic organ involvement, elevated serum IgG4 levels (≥135 mg/dL), and histopathological features of infiltration of IgG4 plasma cells into the bile ducts and other organs [10]. Often IgG4-associated cholangiopathy is combined with autoimmune pancreatitis. At the time of diagnosis, the average age of patients with IgG4-associated cholangiopathy is 50-60 years, while in patients with PSC the onset of the disease is observed at a younger age (30-40 years). The first symptom of this pathology may be intense jaundice, while it is not typical for PSC and is observed at a late stage of the disease [31]. The first-line treatment for IgG4-associated cholangiopathy is steroids. They lead to resolution of jaundice, improve liver laboratory parameters, and also provide a decrease in serum IgG4 levels and reversal of strictures on cholangiograms. AZA should be considered as an alternative

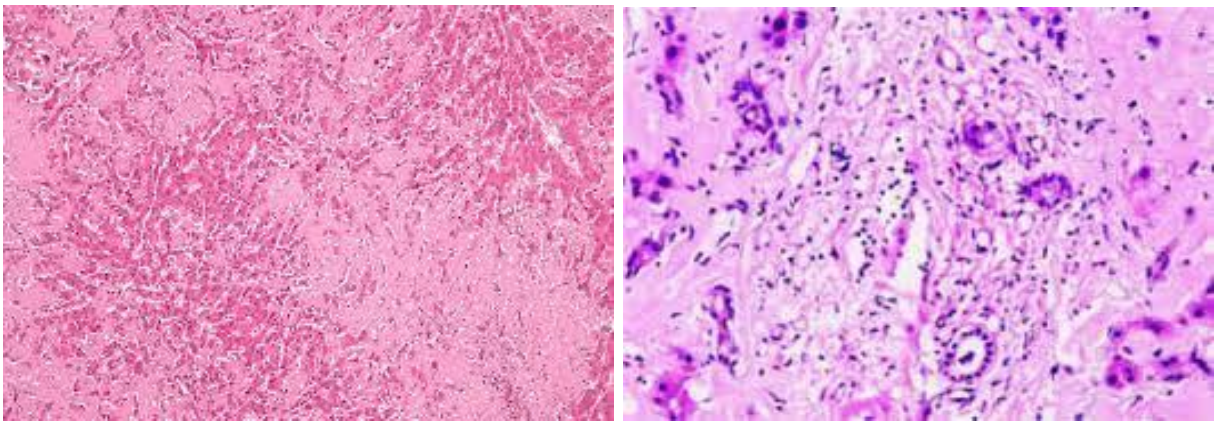
treatment in cases of proximal and intrahepatic stenosis, as well as in cases of relapse of symptoms during and/or after corticosteroid therapy [31].

Primary biliary cirrhosis (PBC) is extremely rare in UC. The foreign literature describes about two dozen clinical cases in which the course of PBC was complicated by UC [34, 39]. The clinical picture of PBC in UC does not differ from the classical one. Patients are concerned about skin itching, abdominal pain and general weakness, accompanied by biochemical signs of cholestatic syndrome (increased levels of alkaline phosphatase, gamma-glutamyltransferase-GGT, total bilirubin), positive autoimmune markers (increased titer of antimitochondrial antibodies). Unlike classic PBC, which predominantly affects women, IBD more often develops in younger men at earlier stages of PBC. The course of UC is usually mild, limited to left-sided lesions of the colon. In 13 cases, PBC developed against the background of previously diagnosed UC. According to the authors, the prevalence of PBC in patients with UC was almost 30 times higher than in the general population. In a patient with UC on the background of PBC, genetic markers (HLA-DRB1*1502 and HLA-DRB1*0802) characteristic of both diseases were identified, which presumably may indicate a genetically determined susceptibility to these diseases. The drug of choice for the treatment of PBC in combination with UC is a combination of UDCA at a daily dose of 13-15 mg/kg and budesonide 9 mg/day.

Cholelithiasis is a fairly common complication of UC. According to F. Parente et al. (2007), the presence of CD increases the risk of gallstone formation by 2 times compared to the general population of patients without IBD, while the presence of UC is not associated with an increased risk of stone formation [26]. The incidence of cholelithiasis in patients with CD is 13-34% [16]. Predictors of the development of this complication in patients with CD include the localization of the inflammatory process (elitis), the presence of a history of surgical interventions, and the degree of ileal resection. The age of the patient (not observed in children), the frequency of clinical relapses, length of hospital stay, and the use of total parenteral nutrition are essential. The pathophysiology of cholelithiasis in CD has not been fully studied. Studies have shown that patients with CD experience a decrease in biliary motility, which can lead to the development of gallstone disease [21]. Increased saturation of bile with cholesterol, acceleration of enterohepatic circulation of bile acids and impaired resorption of bile from the affected ileum increases the risk of developing cholelithiasis in patients with CD.

Hepatic amyloidosis is a rare complication of UC. Its frequency in CD is 0.9%, in UC - 0.07% [37]. The presence of a chronic active autoimmune inflammatory process in the intestine contributes to the deposition of amyloid in the walls of blood vessels and sinusoids of almost any organ, including the liver. Clinically, secondary liver amyloidosis can manifest itself as asymptomatic hepatomegaly and is more common

in men with colonic localization of CD and UC. Treatment is based on controlling the activity of the inflammatory process in the intestine, which leads to a decrease in the release of acute phase protein—serum amyloid A. Colchicine 1.2-1.8 mg/day is recommended as an additional therapy for amyloidosis.

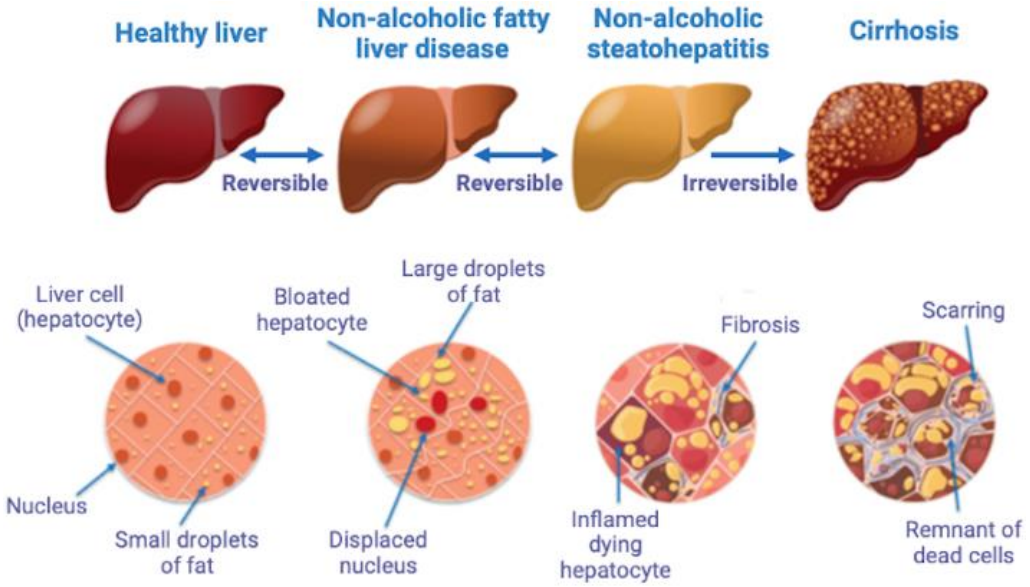


2-pic. Microscopic view of hepatic amyloidosis

Granulomatous hepatitis is a rare complication of UC and occurs in less than 1% of patients [23]. It is characterized by an increase in serum markers of cholestasis, in particular ALP and GGT. Granulomatous hepatitis develops in patients taking sulfasalazine. Other causes of granulomatous hepatitis include malignancy or infection. This complication is diagnosed by liver biopsy, which reveals specific granulomas. Corticosteroids and immunosuppressants are used to treat granulomatous hepatitis.

Vascular complications of IBD include thrombosis of the portal and hepatic veins (Budd-Chiari syndrome). Patients with IBD are significantly more likely to develop thromboembolic complications than the general population. Portal vein thrombosis and mesenteric thrombosis, according to Mayo Clinic research, occurs in 1.3% of patients with IBD, and the mortality rate from this complication reaches 50%. A higher incidence of portal thrombosis is observed in the early postoperative period in young women. The causes of portal vein thrombosis are varied. Increased platelet counts, fibrinogen, coagulation factors V and VIII, along with decreased antithrombin III levels in patients with IBD are risk factors for thrombus formation. Additional procoagulant risk factors include chronic inflammation, immobilization, extent of colonic disease, abdominal surgery, central catheter placement, corticosteroid use, and smoking [32]. Hepatic vein thrombosis often complicates the course of UC. In conditions of acute inflammation, the risk of developing Budd-Chiari syndrome increases 8 times. There is also a significant risk of thromboembolism in the perioperative period. The basis of conservative treatment of thromboembolic complications of IBD, even in conditions of gastrointestinal bleeding, are anticoagulants such as low molecular weight heparins and warfarin [21]. The duration of prescription of anticoagulants for six months allows obtaining an adequate therapeutic effect.

Non-alcoholic fatty liver disease (NAFLD) develops significantly less often in patients suffering from UC than in the general population of the United States (8.3% versus 33.6%) [22]. When conducting ultrasonographic studies of patients with IBD and analysis of liver biopsies, steatosis is observed quite often (35-50%). As a rule, patients with NAFLD do not have liver complaints, but at the same time, the degree of fatty infiltration is associated with the severity of colitis, in particular UC. The reasons for the development of NAFLD in UC are malnutrition, hypoproteinemia, and the use of corticosteroids, which are primarily responsible for the formation of hepatic steatosis. Among the metabolic risk factors for the development of NAFLD in patients with UC, arterial hypertension (OR=3.5), obesity (OR=2.1), small intestinal surgery (OR=3.7), and steroid therapy (OR= 3.7) [33]. NAFLD is less common in patients who have received tumor necrosis factor antagonist (anti-TNF) biologic therapy. Modern therapy aims to treat the intestinal disease and improve the patient's overall nutritional status (3-pic.).



3-pic. Formation of NAFLD, NASH and cirrhosis

Viral hepatitis B. Patients with UC receiving immunosuppressive therapy with thiopurines and anti-TNF are at high risk of reactivation of hepatitis B viral infection. Research data suggest that AZA in combination with corticosteroids, as well as infliximab, lead to replication of the hepatitis B virus [25]. No cases of reactivation of hepatitis B viral infection have been reported with adalimumab and certolizumab, but should be expected as these new drugs continue to be used more widely.

The European consensus on the prevention, diagnosis and treatment of opportunistic infections in IBD (2009) recommends the prevention of reactivation of hepatitis B viral infection in patients with UC and CD receiving immunosuppressive therapy. Before starting immunosuppression, it is necessary to screen patients for the presence of markers of the hepatitis B virus (HBsAg, anti-HBc and anti-HBs). Subsequent patient management tactics are as follows [5,21]: HBV serology-negative

patients should be vaccinated;patients with positive HBsAg and HBV-DNA >2000 IU/ml are recommended to be treated with tenofovir or entecavir as in patients with chronic viral hepatitis B;HBsAg-positive patients and HBV-DNA <2000 IU/mL or undetectable, as well as HBsAg-negative and HBV-DNA-positive patients, should be treated with tenofovir or entecavir for 6-12 months after the end of immunosuppressive therapy. In this case, it is necessary to monitor the level of alanine aminotransferase and the HBV-DNA titer every three months during treatment; HBsAg-negative and anti-HBc-positive patients with or without anti-HBs should be closely monitored every 1-3 months by measuring alanine aminotransferase levels and HBV-DNA titers for 6-12 months after the end of therapy. For patients with an increase in viral load, antiviral therapy with entecavir or tenofovir should be started immediately.

Viral hepatitis C. Data on the effect of immunosuppressive therapy for UC on hepatitis C are contradictory. However, the results of recent studies indicate that antiviral therapy for hepatitis C does not affect the natural course of UC, and immunosuppressive therapy for UC and CD does not contribute to the reactivation of hepatitis C viral infection [29]. Currently, there are no options for both primary and secondary prevention of viral hepatitis C, but in the near future the use of interferon-free treatment regimens using a combination of inhibitors of the viral protease NS3/4A (asunaprevir), NS5B polymerase (sofosbuvir) and NS5A protein (daclatasvir) may be promising in the treatment of hepatitis C in UC [17].

Drug-induced liver damage often develops due to the use of all groups of drugs used to treat UC. The aminosalicylic acid derivatives sulfasalazine and mesalazine are highly safe drugs and rarely lead to serious adverse effects such as bone marrow aplasia, acute pancreatitis, nephropathy or hepatotoxicity. Sulfasalazine was the first drug used in the treatment of UC and was 5-aminosalicylic acid combined with sulfapyridine. It was the presence of the sulfapyridine component that caused the development of side effects in the form of increased liver aminotransferases, hyperbilirubinemia, hepatomegaly, lymphadenopathy and increased body temperature. In clinical trials, liver function abnormalities based on biochemical tests were observed in 2% of patients with UC receiving mesalazine [15]. The United Kingdom Committee on the Safety of Medicines noted that in the period 1991-1998. The incidence of toxic hepatitis was 3.2 and 6 cases per million prescriptions filled for mesalazine and sulfasalazine, respectively, with the presence of rheumatoid arthritis being a more significant risk factor than IBD. Aminosalicylates can develop hepatotoxicity at any time from the start of therapy - from 6 days to 1 year, both acute and chronic [20].

Thiopurines (AZA and 6-mercaptopurine) are immunomodulators used in the treatment of IBD. Their mechanism of action is based on conversion to the active metabolite 6-thioguanine. The hepatotoxicity of this group of drugs is due to the effect of another metabolite, 6-methylmercaptopurine (6-MMP), and occurs due to its

intracellular accumulation due to a decrease in the activity of the enzyme thiopurine-S-methyl-transferase (TPMT). The effectiveness of thiopurines is limited due to the need to interrupt treatment due to intolerance in 15% of patients with IBD. The most common dose-independent side effects are allergic reactions (fever, skin rash, myalgia and arthralgia) and acute pancreatitis. Dose-dependent adverse reactions are observed in 2-5% of patients in the form of leukopenia, thrombocytopenia, anemia, megaloblastic erythropoiesis, macrocytosis, as well as symptoms from the digestive system (nausea, loss of appetite, vomiting, diarrhea, abdominal pain). AZA and mercaptopurine can damage the vascular endothelium, especially the sinusoids and terminal veins, which contributes to the development of veno-obliterating diseases, regenerative hyperplasia of the lymph nodes and peliosis of the liver. These complications can be detected between 3 months and 3 years from the start of treatment [15]. Before prescribing immunosuppressants from the thiopurine group, it is necessary to determine the level of TPMT and regularly conduct biochemical blood tests to determine liver function, especially during the first months of treatment, to identify myelotoxicity and/or hepatotoxicity. Clinically insignificant deviations in biochemical parameters of the liver and hemogram allow continued treatment with AZA at a lower dose. However, persistent jaundice or lack of positive dynamics in biochemical parameters, despite a dose reduction, require immediate cessation of treatment.

Side effects of methotrexate use in the form of myelosuppression and drug-induced hepatitis are dose-dependent. A number of risk factors for hepatotoxicity have been identified, including alcohol consumption, obesity, diabetes mellitus, and an initial increase in cytolytic liver enzymes, which also includes the use of methotrexate, especially in an accumulated dose of more than 15 g [6]. Patients taking methotrexate require regular biochemical tests to assess basic liver functions [27]. In the case of a persistent increase in transaminase levels, especially if they do not decrease after reducing the dose of the drug, as well as in patients with high accumulated doses, along with other risk factors, a liver biopsy or elastography is recommended to diagnose liver fibrosis. In cases of liver fibrosis or cirrhosis, treatment should be discontinued. In order to reduce the number of side effects associated with taking methotrexate and prevent fibrosis and cirrhosis of the liver, which can develop as a result of the progression of drug-induced hepatitis, it is recommended to take folic acid in a dose of 5-10 mg once a week the next day after taking methotrexate.

The biological therapies infliximab and adalimumab are anti-TNF, which plays a role in hepatocyte regeneration, hence a possible connection with the development of hepatotoxicity. The main side effects of these drugs are lymphoproliferative diseases, reactivation of hepatitis B viral infection, opportunistic infections, and neurological complications. An autoimmune nature of liver damage is often observed, both by serological and histological markers, the pathogenesis of which remains not entirely

clear, but probably depends on the characteristics of the drugs and the genetic determination of the patients [12]. In most cases, cholestatic and hepatocellular variants of toxic drug-induced hepatitis were observed while taking infliximab, while the spectrum of side effects in patients taking adalimumab was comparable to placebo. Discontinuation of infliximab led to an improvement in laboratory parameters of liver function tests [13].

T-cell lymphoma with hepatosplenomegaly develops predominantly in young men with CD receiving combination therapy with AZA and anti-TNF. Clinical manifestations of the disease are characterized by the appearance of fever, hepatosplenomegaly, increased liver function tests and pancytopenia. Effective therapy has not yet been developed [21].

Thus, extraintestinal lesions of the liver and biliary system in IBD require increased attention from gastroenterologists, therapists and surgeons. Timely diagnosis of complications from the hepatobiliary system and their adequate treatment will certainly help improve the prognosis and quality of life of patients with UC and CD.

References

1. Bambha K., Kim W.R., Talwalkar J. et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. Gastroenterology. 2003; 125: 1364-1369

2. Bjo..rnsson E., Olsson R., Bergquist A., Lindgren S., Braden B., Chapman R.W., Boberg K.M., Angulo P. The natural history of small-duct primary sclerosing cholangitis. Gastroenterology. 2008; 134: 975-980.

3.Broome U., Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. Semin Liver Dis. 2006; 26: 31-41.

4. Buti M., García-Samaniego J., Prieto M. et al. [Consensus document of the Spanish Association for the Study of the Liver on the treatment of hepatitis B infection (2012)]. Gastroenterol Hepatol. 2012; 35: 512-528.

5. Chande N., Abdelgadir I., Gregor J. The safety and tolerability of methotrexate for treating patients with Crohn's disease. J Clin Gastroenterol. 2011; 45: 599-601.

6. Chaparro M., Trapero-Marugan M., Guijarro M., Lopez C., Moreno-Otero R., Gisbert J.P. Dysplasia and colorectal cancer in a patient with ulcerative colitis and primary sclerosing cholangitis: a case report and a short review of the literature. J Crohns Colitis. 2013; 7: e61-e65.

7. Chapman R., Fevery J., Kalloo A., Nagorney D.M., Boberg K.M., Shneider B., Gores G.J. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010; 51: 660-678.

8. Chevaux J.B., Bigard M.A., Bensenane M. et al. Inflammatory bowel disease and hepatitis B and C. Gastroenterol Clin Biol. 2009; 33: 1082-1093.

9. Culver E.L., Chapman R.W. Systematic review: management options for primary sclerosing cholangitis and its variant forms - IgG4-associated cholangitis and overlap with autoimmune hepatitis. Aliment Pharmacol Ther. 2011; 33: 1273-1291.

10. Czaja A.J. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013; 58: 326-343.

11. French J.B., Bonacini M., Ghabril M., Foureau D., Bonkovsky H.L. Hepatotoxicity Associated with the Use of Anti-TNF-α Agents. Drug Saf. 2016; Mar; 39 (3): 199-208.

12. Ghabril M., Bonkovsky H.L., Kum C. et al. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol. 2013; 11: 558-564.e3.

13. Gisbert J.P., Gonzalez-Lama Y., Mate J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol. 2007; 102: 1518-1527.

14. Gisbert J.P., Luna M., Gonzalez-Lama Y., Pousa I.D., Velasco M., Moreno-Otero R., Mate J. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. Inflamm Bowel Dis. 2007; 13: 1106-1114.

15. Gizard E., Ford A.C., Bronowicki J.P., Peyrin-Biroulet L. Systematic review: The epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2014; Jul; 40 (1): 3-15. Epub 2014, May 11.

16. Horn T.L., Reynolds J., de Villiers W., Pe~na L.R. Hepatitis C virus and inflammatory bowel disease. Dig Dis Sci. 2009 (25).

17. Janse M., Lamberts L.E., Franke L., Raychaudhuri S., Ellinghaus E., Muri Boberg K., Melum E., Folseraas T., Schrumpf E., Bergquist A. Three ulcerative colitis susceptibility loci are associated with primary sclerosing cholangitis and indicate a role for IL2, REL and CARD9. Hepatology. 2011; 53: 1977-1985.

18. Joo M., Abreu-e-Lima P., Farraye F., Smith T., Swaroop P., Gardner L., Lauwers G.Y., Odze R.D. Pathologic features of ulcerative colitis in patients with primary sclerosing cholangitis: a case-control study. Am J Surg Pathol. 2009; 33: 854-862.

19. Loftus E.V., Kane S.V., Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2004; 19: 179-189.

20. Rojas-Feria M., CastroM., Suarez E. Hepatobiliary manifestations in inflammatory bowel disease: The gut, the drugs and the liver. World J Gastroenterol. 2013; Nov 14; 19 (42): 7327-7340.

21. McGowan C.E., Jones P., Long M.D., Barritt A.S. Changing shape of disease: nonalcoholic fatty liver disease in Crohn's disease-a case series and review of the literature. Inflamm Bowel Dis. 2012; 18: 49-54.

22. Navaneethan U., Shen B. Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease.Inflamm Bowel Dis. 2010; 16: 1598-1619.

23. Navaneethan U., Venkatesh P.G., Lashner B.A., Shen B., Kiran R.P. The Impact of ulcerative colitis on the long-term outcome of patients with primary sclerosing cholangitis. Aliment Pharmacol Ther. 2012; Epub ahead of print.

24. Ojiro K. Naganuma M., Ebinuma H., Kunimoto H., Tada S., Ogata H., Iwao Y., Saito H., Hibi T. Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. J Gastroenterol. 2008; 43: 397-401.

25. Parente F., Pastore L., Bargiggia S., Cucino C., Greco S., Molteni M., Ardizzone S., Porro G.B., Sampietro G.M., Giorgi R. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study.Hepatology. 2007; 45: 1267-1274.

26. Saibeni S., Bollani S., Losco A., Michielan A., Sostegni R., Devani M., Lupinacci G., Pirola L., Cucino C., Meucci G. The use of methotrexate for treatment of inflammatory bowel disease in clinical practice. Dig Liver Dis. 2012; 44: 123-127.

27. Santos O.M., Mu~noz Ortiz E., Perez C., Restrepo J.C. [Autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome in adults: report of three cases]. Gastroenterol Hepatol. 2012; 35: 254-258.

28. Scherzer T.M., Staufer K., Novacek G., Steindl-Munda P., Schumacher S., Hofer H., Ferenci P., Vogelsang H. Efficacy and safety of antiviral therapy in patients with Crohn's disease and chronic hepatitis C. Aliment Pharmacol Ther. 2008; 28: 742-748.

29. Shi J., Li Z., Zeng X., Lin Y., Xie W.F. Ursodeoxycholic acid in primary sclerosing cholangitis: meta-analysis of randomized controlled trials. Hepatol Res. 2009; 39: 865-873.

30. Silveira M.G. IgG4-associated cholangitis. Clin Liver Dis. 2013; 17: 255-268.

31. Sinagra E., Aragona E., Romano C., Maisano S., Orlando A., Virdone R., Tese L., Modesto I., Criscuoli V., Cottone M. The role of portal vein thrombosis in the clinical course of inflammatory bowel diseases: report on three cases and review of the literature. Gastroenterol Res Pract. 2012; 2012: 916428.

32. Sourianarayanane A., Garg G., Smith T.H., Butt M.I., McCullough A.J., Shen B. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease. J Crohns Colitis. 2013; 7: e279-e285.

33. Tada F., Abe M., Nunoi H. et al. Ulcerative colitis complicated with primary biliary cirrhosis // Intern med 2011; 50 (20): 2323-7. Epub 2011; Oct 15.

34. Titos Arcos J.C., Hallal H., Robles M., Andrade R.J. Recurrent hepatotoxicity associated with etanercept and adalimumab but not with infliximab in a patient with rheumatoid arthritis. Rev Esp Enferm Dig. 2012; 104: 282-284.

35. Uko V., Thangada S., Radhakrishnan K. Liver disorders in inflammatory bowel disease. Gastroenterol Res Pract. 2012; 2012: 642923.

36. Venkatesh P.G., Navaneethan U., Shen B. Hepatobiliary disorders and complications of inflammatory bowel disease. J Dig Dis. 2011; 12: 245-256.

37. Wester A.L., Vatn M.H., Fausa O. Secondary amyloidosis in inflammatory bowel disease: a study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962 to 1998. Inflamm Bowel Dis. 2001; 7: 295-300.