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SEPSIS LIKE A SEVERE COMPLICATION OF AUTOIMMUNE LIVER DISEASE IN GASTROENTEROLOGICAL PATIENTS

Abstract

In the article, we present features of clinical pattern and treatment of patients with ulcerative colitis associated with primary sclerosing cholangitis and autoimmune hepatitis. Course of disease was complicated by bacterial cholangitis, sepsis, and multiple organ failure. Pathogenetic features of autoimmune disorder in liver and bowel diseases are described. The role of bacterial translocation in primary immune disorder development and in inflammatory syndrome maintenance is described. Differential diagnosis challenges in primary and secondary cholangitis are described. Features of management of patients in critical condition are reviewed in the article. The role of glucocorticosteroids in sepsis treatment is sketched. Modern guidelines for the management of patients with overlap syndrome are highlighted. Patient D. was admitted to the intensive care unit of the hospital with a clinical pattern of shock and systemic inflammatory response syndrome. Exacerbation of ulcerative colitis complicated by infection on the background of primary sclerosing cholangitis and autoimmune hepatitis was diagnosed. This condition led to sepsis and multiple organ failure. Despite intensive care treatment, there was a progressive worsening of the patient's state until clinical death. Resuscitation procedures within 6 minutes were successful. Multiple areas of necrosis have developed on the limbs because of multiple organ failure and intensive treatment with vasopressors. Glucocorticosteroids in combination with antibacterial agents were prescribed despite sepsis with ulcerative colitis exacerbation and cytolysis syndrome. On the thirtieth day of hospital stay, patient D. was transferred from the intensive care unit to the gastroenterology department, where the treatment was continued. Because of the treatment provided, signs of multiple organ failure, infectious complications, exacerbation of ulcerative colitis and primary sclerosing cholangitis regressed. The patient was regularly followed-up.

Key words: *ulcerative colitis, primary sclerosing cholangitis, autoimmune hepatitis, sepsis, glucocorticosteroids*

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BP — blood pressure, AIH — autoimmune hepatitis, 5-ASA — 5-aminosalicylic acid, BT — bacterial translocation, IBD — inflammatory bowel disease, GCS — glucocorticosteroids, BMI — body mass index, ABS — acid-base status, CT — computed tomography, MRCPG — magnetic resonance cholangiopancreatography, MOF — multiple organ failure, PSC — primary sclerosing cholangitis, RGA — Russian Gastroenterological Association, BOS — bacterial overgrowth syndrome, CRP — C-reactive protein, SIRS — systemic inflammatory response syndrome, UDCA — ursodeoxycholic acid, HR — heart rate, UC — ulcerative colitis, CLIF-C ACLF — Chronic liver failure consortium Acute on chronic liver failure

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Introduction

Currently, there is a steady increase in the number of patients with ulcerative colitis (UC) and, as a consequence, with associated conditions. According to available epidemiological data, the prevalence of the disease is 505 per 100,000 people [4]. The social and economic significance of this pathology is also determined by the presence of a morbidity peak attributable to persons of working age from 20 to 30 years.

UC is a chronic disease of the colon, characterized by immune inflammation of its mucous membrane [2]. In addition, there are many extra-intestinal manifestations of the disease, aggravating the course and prognosis. Among them, liver diseases play a special role.

The proven association of UC and primary sclerosing cholangitis (PSC) is demonstrated in the phenotypic classification of the latter. The study of UC confirmed that the variant with liver damage differs from the isolated form of the disease [3]. In 5% of patients with autoimmune bowel disease, there are signs of liver disorder. UC associated with PSC is characterized by a milder course, a pronounced lesion of the proximal colon and the remaining almost intact rectum [3]. In turn, liver damage sometimes manifests itself before the onset of the clinical picture of UC in the form of a moderate increase in serum cholestasis enzymes.

Another variant of association of UC with liver damage is autoimmune hepatitis (AIH), which is detected in 1–5% of patients. Increase of cytolysis enzymes, detection of autoantibodies, hypergammaglobulinemia in patients can serve as evidence of this disease.

In some cases, clinical and laboratory signs of the above-described liver diseases are combined, in which case this condition is called autoimmune overlap: PSC with signs of AIH.

Clinical case

On 04.08.18, patient D., 34 years old, was urgently delivered by ambulance service to the Moscow City Clinical Hospital after V. M. Buyanov with a referral diagnosis of hypotension of unknown origin. He was admitted to the intensive care unit with

complaints of fever up to 39 °C, jaundice of the skin and sclera, pronounced weakness.

He considers himself sick since December 2014, when he first noticed signs of weakness, reduced tolerance to the usual physical activity (playing football and fighting without rules), pulling pain in the right hypochondrium, liquid blood-streaked stool up to 4 times a day. In outpatient settings, increased activity of enzymes of cytolysis and cholestasis, which was the reason for hospitalization in the Central Research Institute of Gastroenterology, Moscow, was revealed. According to the results of the examination, the patient was diagnosed with: PSC with signs of autoimmune hepatitis (AIH), moderate biochemical activity. UC with total involvement, of minimal activity. Therapy with ursodeoxycholic acid (UDCA) 1,500 mg/day, 5-aminosalicylates (5-ASA) 3 g/day, glucocorticosteroids (GCS) 40 mg/day was started, during which a positive change was noted. After discharge, patient D. continued to engage in heavy physical activity, diet was not followed; the recommended therapy was not adhered to.

Subsequently, the patient was repeatedly hospitalized at the Loginov Moscow Clinical Scientific Center due to UC attacks caused by non-compliance with the diet, recommended therapy and exercise regimen. There was a progression of the disease and deterioration of the clinical picture with each subsequent hospitalization. The patient noted current deterioration from August 2018, which was the reason for hospitalization.

In the intensive care unit, the patient's condition was regarded as severe. Fever was up to 39 °C. Position of the body due to severe weakness was forced lying on a gurney. The patient was conscious, euphoric, sluggish, inhibited, oriented in space, time and person. Skin was intensely jaundiced, dry, distal limbs were cold, cyanotic. Lymph nodes were not palpable. There were phenomena of respiratory failure — tachypnea at rest with respiratory rate of 30 per minute. Auscultatory breathing was bronchial, heard symmetrically throughout all lung fields, weakened in the lower parts, rales were not heard. Hypotension (BP — 60/40 mm Hg), tachycardia (HR — up to 100 beats/min), heart tones were rhythmic, muffled; heart murmurs during auscultation were not heard. Tongue was dry, covered

with a coat. Abdomen was soft and painless during palpation. The liver was 10×10×9 cm according to Kurlov's method, indurated, non-tender; its lower edge was sharp. The lower pole of the spleen was located in the depth of the hypochondrium on the left side. Peritoneal signs were not observed. Peristalsis was heard. The rate of diuresis is reduced, Pasternatsky's symptom is negative on both sides. The dynamics of analyses for the period of hospitalization is presented in Table 1. Because of the auscultatory picture, right-sided community-acquired lower lobe pneumonia was suspected. High levels of hepatic enzymes and creatinine were evidence of severe hepatic and renal failure. Taking into account tachypnea, tachycardia, hypotension, fever, as well as an elevated level of C-reactive protein (CRP) and procalcitonin, the development of sepsis was not excluded. According to the integrated scale Chronic liver failure consortium — acute on chronic liver failure (CLIF-C ACLF) — 39 points. Infusion, antibacterial, anticoagulant therapy was started; hemodynamics was supported by administration of vasopressors, and humidified oxygen was injected through nasal cannulas. Rectosigmoidoscopy with biopsy was conducted, and its results identified a UC attack (Mayo index — 10 points) [4]. In a day spent in the intensive care unit, the patient's condition deteriorated sharply. There

was a progression of the phenomena of multiple organ failure (MOF): cardiovascular — requiring vasopressor support with a tendency to escalate dosages; respiratory — with the development of decompensated shifts of acid-base state (ABS), low oxygen saturation; hepatic — with an increase in the level of bilirubin, enzymes of cholestasis and cytolysis; renal — clinically manifested by decreased rate of diuresis to oliguria and increased azotemia parameters (Table 1). Due to the increase in MOF phenomena and metabolic disorders, the patient was put on mechanical ventilation.

The patient's condition on 06.08.18 was regarded as extremely severe. Due to the lack of efficacy of antibiotic therapy, the drugs were repeatedly changed, including macrolides, semi-synthetic penicillins and cephalosporins protected by sulbactam, oxazolidones, glycopeptides, antifungal agents. Vasopressor, infusion, sedative, gastroprotective therapy, correction of metabolic disorders and prevention of thromboembolic complications were also carried out.

Despite intensive therapy, on 08.08.18 the patient's condition is regarded as agonal with transition to clinical death. Extended resuscitation was carried out, after 6 minutes of which sinus rhythm was restored, BP — 80/40 mm Hg, HR — 160 beats/min.

Table 1. Dynamics of the main laboratory parameters in patient D.

Показатели	04.08.18	05.08.18	08.08.18	10.08.18	16.08.18	26.08.18	17.09.18
Hemoglobin (130-170 г/л)	116	118	88	107	118	101	114
Erythrocytes (4.28-5.78*10 ¹² /л)	3.47	3.36	2.50	2.89	3.43	3.06	3.13
Leukocytes (3.9 — 10.9*10 ⁹ /л)	10.70	47.20	30.20	49.50	21.60	28.60	21.60
Platelets (150-340*10 ⁹ /л)	444	203	24	59	35	305	562
AST (5-34Е/л)	354	562	814	559	379	270	119
ALT (0-32Е/л)	324	376	429	412	258	214	248
GGTP (9-39Е/л)	2259	1975	820	1239	420	716	745
Alkaline phosphatase (64-306Е/л)	2502	1346	1205	753	1688	1509	1402
Total bilirubin/Conjugated bilirubin (0.86-5.0мкмоль/л) 1.7-20.5 мкмоль/л	82/47	112/79	205/100	233/197	274/161	292/178	146
Creatinine (71-115мкмоль/л)	196	176	121	133	72	73	70
CRP 0.1-7.0	-	-	325.9	124,8	-	-	-
Procalcitonin (0.05-0.50 нг/мл)	13.38	33.04	-	7.59	-	-	-



Figure 1. Condition of the lower and upper extremities of patient D. on the 12th day of stay in the intensive care unit



Figure 2. The condition of the lower and upper extremities of patient D. at discharge

With further observation, the patient's condition was regarded as stable and severe. On chest CT from 10.08.18 — pattern of bilateral polysegmental pneumonia. A bronchoscopy with airway hygiene was performed with further microbiological examination of washings (in bronchial washings — *Enterococcus faecium*, *Klebsiella pneumoniae*).

On the 12th day of staying in the intensive care unit, the patient's condition was severe, without negative change; the patient was conscious, available to limited contact. On the distal phalanges of the fingers of the lower and upper extremities, multiple areas of necrosis were determined (Photo 1). The high level of cholestasis enzymes, CRP, conjugated bilirubin and insufficient efficacy of antibiotic therapy did not allow to exclude bacterial cholangitis, which was the reason for selective

cannulation of the large duodenal papilla for bile sampling. In a bacteriological study, *Acinetobacter* species and *Klebsiella pneumoniae* were determined in bile, and therapy with tigecycline, meropenem was prescribed taking into account sensitivity. During treatment, positive changes were noted: normalization of body temperature, regression of respiratory failure (pneumonia at resolution phase), reduction of cholestasis in the blood (Table 1).

On the 22nd day, due to the continuing activity of UC (diarrhea up to 5 times a day, blood admixture in feces, leukocytosis), the Medical Council decided to prescribe to patient D. GCS-prednisolone at a dose of 140 mg/day by intravenous bolus. Two days later, the patient was transferred to self-breathing with minimal support with humidified oxygen.

From Day 30, patient D. continued treatment in the Department of Gastroenterology, intravenous GCS was replaced by oral one (Metypred) at a dose of 24 mg/day; positive changes in laboratory parameters were noted (Table 1). In addition, signs of MOF, infectious complications, exacerbation of UC and PSC regressed. The Mayo index was 2 points.

At discharge, the patient was limited in activity, as trophic changes on the skin of the limbs were preserved (Photo 2). A recommendation was made to continue taking UDCA, 5-ASA, GCS (with tapering course), additional enteral nutrition, and protective diet. The patient continued dynamic follow-up; after 2 months the condition was apparently improved.

Discussion

A clear relationship between UC and PSC is shown by high frequency (70–90%) of association [5]. At the genetic level, UC susceptibility loci were identified, that may be associated with PSC [5]. The latter is characterized by a number of specific complications (bacterial cholangitis, cholelithiasis, bile duct strictures, cholangiocarcinoma).

The phenomenon of bacterial translocation (BT), which provides the key to understanding the relationship between these states, deserves attention. There are two ways of bacteria migration through the intestinal wall: transcellular pathway and directly through the intercellular space of enterocytes [6].

The primary link in the mechanism of bacterial translocation is bacterial overgrowth syndrome (BOS). However, there is a need for a second, but no less important, element of the pathological process — disturbed immune response of the macroorganism. Patients with UC showed changes in the phagocytic immunity [7] and elevated levels of pro-inflammatory cytokines [8].

The research results do not allow to eliminate the etiological role of microbiota as one of the factors of induction and maintenance of inflammatory process in the intestine and liver.

There are microorganisms that are more predisposed to translocation, perhaps due to their better ability to adhere to the intestinal epithelium. These are, first of all, gram-negative bacteria — *Escherichia coli*, *Klebsiella pneumoniae*, and enterococci. In our observation, the association of *Acinetobacter* species and *Klebsiella pneumoniae* was found in the bile of the patient, which does not contradict well-known ideas about the etiological role of microorganisms in the formation of bacterial cholangitis.

It should be noted that there are difficulties in diagnosing bacterial cholangitis in patients with IBD/PSC. A classic sign of acute cholangitis is the Charcot triad — pain in the upper right quadrant of the abdomen and epigastrium, accompanied by chills and rapidly developing mechanical jaundice. However, the clinical picture of PSC can mask the signs of bacterial cholangitis. So abdominal pain occurs in 35% of cases, jaundice — in

30%; fever — only in 17% of cases [9, 10]. Manifestations of general intoxication syndrome may be due to exacerbation of UC, as well as the development of cholangiocarcinoma [11]. The increase in cholestasis is also possible due to the development of morphofunctional changes in hepatocytes in sepsis [12].

Among the instrumental methods of examination, ultrasonography and endoscopy play an important role. Signs of biliary hypertension in the form of bile duct dilation above the level of the obstacle always reliably indicate the mechanical nature of cholestasis, but thickening and/or focal expansion was also noted in PSC. A mandatory element of instrumental diagnosis in patients with jaundice and cholangitis is endoscopic examination. The absence of bile in the intestine and signs of papillitis may indicate the mechanical nature of jaundice. Endoscopic retrograde cholangiopancreatography has long been the gold standard of diagnosis [13, 14]. However, this procedure has a number of complications — the development of pancreatitis and sepsis [15]. According to the recommendations of both the European and Russian society for liver research, as well as of American College of Gastroenterology, the first line method is MRCPG [13–15].

Currently, the role of invasive methods of examination remains important during the diagnostic and treatment procedures. Our patient underwent selective cannulation of the large duodenal papilla for bile collection for bacteriological study, the results of which diagnosed the bacterial nature of cholangitis, which confirms the difficulties of diagnosis between primary and secondary cholangitis in real clinical practice.

Reduced compensatory capacity of the body due to UC, autoimmune liver disease, severe hypoproteinemia led to the aggravation of the cascade of pathological reactions — activation of macrophages, neutrophils, vascular endothelium, and, as a consequence, to the hyperproduction of cytokines with the development of organ dysfunction (MOF, sepsis). An important role is given to the definition of strategy for the management of such conditions, the detection of MOF syndrome, the diagnosis of severe sepsis and septic shock. The CLIF-C scale is a more accurate tool for dynamically

assessing the degree of organ dysfunction, as well as the estimated survival rate in patients with liver disease [16].

An extremely important role in the management of patient D. was played by GCS administration under the cover of antibacterial drugs. Only on Day 22 of staying in the intensive care unit GCS allowed to achieve stabilization of the patient.

According to international recommendations for the treatment of patients with sepsis, GCS may be used in cases of absence of stabilization of the disease, but with adequate water load and vasopressor therapy (the third-line therapy) [17]. The authors of the recommendations refer to publications with proposals to consider GCS, in particular hydrocortisone, in moderate doses (200 mg/day) in patients with refractory septic shock [18].

In the present clinical observation, endotoxemia in patient D. was primarily due to the activity of UC — increased permeability of the intestinal wall. However, despite adequate antibiotic therapy, the symptoms of BT persisted. We do not exclude that due to the etiological therapy in combination with GCS, it was possible to reduce SIRS and suppress the growth of bacterial flora.

The difficulties in management of patient D. lay not only in the features of long-term therapy of critical conditions, but also in the need to continue treatment in gastroenterological department, as well as in the choice of further tactics after discharge.

According to clinical guidelines for the management of patients with PSC, UDCA (at a dose of 15-20 mg/day) plays a major role. However, its use does not have a proven effect on the life expectancy of patients, but only improves the results of surrogate prognostic markers [13].

The second important aspect is the use of glucocorticosteroids, recommended for patients with UC/PSC and AIH signs. During GCS therapy at a dose of 40 mg/day with subsequent replacement with 5-ASA (mesalazine) at a dose of 2.4 g/day, the patient showed significant positive changes. An important role was played by spasmolytic therapy, correction of trophic insufficiency, as well as long-term psychological support with an explanation of the principles of diet therapy and the promotion of a positive attitude towards such a serious disease.

It is also necessary to mention the problem of compliance of patients with UC/PSC. Their average life expectancy is 25 years from the time of diagnosis, provided there is compliance with all the doctor's recommendations [19], and in the absence of treatment, the UC acquires an uncontrolled course with frequent exacerbations or attacks of the disease.

Some authors believe that a lack of adherence to treatment regimens is a major problem in patients with any chronic disease, and about half of them do not follow the prescribed regimen to such an extent that they do not receive optimal clinical benefit [20]. The most effective strategy for increasing patient adherence today is the so-called compliance therapy based on a motivational interview [20].

Today, the problem of UC/PSC and their combination with other autoimmune conditions remains insufficiently studied. Etiological treatment does not exist; however, the use of pathogenetic therapy, UDCA, GCS, 5-ASA, in adequate doses can help to achieve longer and improved quality of life of patients.

Conflict of interests

The authors declare no conflict of interests.

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