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A CLINICAL CASE OF DRUG THERAPY COMPLICATIONS IN A PATIENT WITH SEVERE ULCERATIVE COLITIS

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КЛИНИЧЕСКИЙ СЛУЧАЙ ОСЛОЖНЕНИЙ ЛЕКАРСТВЕННОЙ ТЕРАПИИ У ПАЦИЕНТА С ТЯЖЕЛЫМ ТЕЧЕНИЕМ ЯЗВЕННОГО КОЛИТА

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A clinical case of thrombotic complications with a cerebral vascular damage and the development of aplastic anemia against the background of drug therapy for severe ulcerative colitis (UC) in a 34-year-old patient is presented. Treatment of inflammatory bowel diseases (IBD) is currently a complex problem. The main goal of therapy is to achieve stable remission without the use of systemic glucocorticosteroids (GCS). The administration of combined drug therapy, including 5 – aminosalicylic acid preparations, topical and systemic GCS, thiopurines, as well as genetically engineered biological drugs is often required to control an exacerbation. Adverse drug events occur in 40 % of patients and are most frequently associated with the use of GCS, thiopurines and genetically engineered biological drugs. Arterial and venous thrombosis are extra-intestinal manifestations of IBD, the development of which is associated with the activity of the inflammatory process, and may also be caused by taking high doses of systemic GCS. The occurrence of aplastic anemia in IBD is associated with the peculiarities of thiopurine metabolism in some individuals. Thus, the choice of drug therapy option should be carried out considering the course of the disease, the presence of a concomitant pathology, any complications, the effectiveness and safety of drug therapy, as well as the presence of adverse reactions predictors.

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Keywords. Inflammatory bowel diseases, ulcerative colitis, azathioprine, glucocorticosteroids, complications of therapy, thromboembolic complications, aplastic anemia.

Представлен клинический случай тромботических осложнений с поражением сосудов головного мозга и развитием апластической анемии у пациента в возрасте 34 лет на фоне лекарственной терапии тяжелой формы язвенного колита (ЯК). Лечение воспалительных заболеваний кишечника (ВЗК) в настоящее время представляет сложную проблему. Основной целью терапии является достижение стойкой ремиссии без применения системных глюкокортикостероидов (ГКС). Нередко для купирования обострения требуется назначение комбинированной лекарственной терапии, включающей препараты 5-аминосалициловой кислоты, топические и системные ГКС, тиопурины, а также генно-инженерные биологические препараты (ГИБП). Нежелательные лекарственные явления возникают у 40 % пациентов и наиболее часто связаны с применением ГКС, тиопуринов и ГИБП. Артериальные и венозные тромбозы являются внекишечными проявлениями ВЗК, развитие которых связано с активностью воспалительного процесса, а также могут быть обусловлены приемом высоких доз системных ГКС. Возникновение апластической анемии при ВЗК связано с особенностями метаболизма тиопуринов у некоторых лиц. Таким образом, выбор варианта лекарственной терапии должен осуществляться с учетом характера течения заболевания, наличия сопутствующей патологии, осложнений, эффективности и безопасности лекарственной терапии, а также наличия предикторов нежелательных реакций.

Ключевые слова. Воспалительные заболевания кишечника, язвенный колит, азатиоприн, глюкокортикостероиды, осложнения терапии, тромбозэмболические осложнения, апластическая анемия.

INTRODUCTION

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), are a group of immune-mediated gastrointestinal diseases with an unknown etiology. The high incidence rate, young age of patients, progressive course with development of complications and difficulties in choosing therapy define this problem as socially significant. In recent years, there has been an increase in incidence both in Russia and around the world. Despite the fact that large epidemiological studies have not been conducted in our country, according to some published data, the prevalence of ulcerative colitis in Russia is 19.3–29.8 cases per 100 thousand population, and Crohn's disease – 3.0–4.5 per 100 thousand population [1].

As a rule, patients with IBD require long-term, and sometimes lifelong, therapy. Thus, to achieve and maintain stable remission, it is often necessary to prescribe combination drug therapy, including derivatives of 5-aminosalicylic acid (sulfasalazine, mesalazine), topical and systemic glucocorticosteroids (GCS), thiopurines (azathioprine), targeted immunosuppressants (tofacitinib and upadacitinib), as well as genetically engineered biological drugs (GEBD) [2].

In a multicenter cohort study investigating the incidence of adverse drug reactions based on real-world data collected in the IBDREAM registry, 3,080 adverse reactions were reported in 1,179 patients with IBD. One or more adverse reactions occurred in 40.9 % of treated patients, most commonly associated with the use of azathioprine and 6-mercaptopurine [3].

The aim of the study is to present a clinical case of a patient with severe UC and the development of a number of side effects, probably associated with basic drug therapy.

CLINICAL CASE

Patient L, 36 years old, was hospitalized in the gastroenterology department of the regional clinical hospital with complaints of general weakness, numbness of the right hand, increased frequency of stool up to 3 times a day with streaks of scarlet blood and mucus, aching abdominal pain in the left iliac region along the left and right flank, dizziness. It is known that the patient had been under observation since 2012 with a diagnosis of ulcerative colitis, left-sided lesion, and administration of 5-aminosalicylic acid (mesalazine) preparations in a daily dose of 2 g was his basic therapy. A stable remission of the disease was achieved in the course of the treatment, which was maintained over the next ten years. The condition worsened in 2023, when the patient noted an increase in the frequency of stool up to 15 times a day with an admixture of scarlet blood in large quantities, diffuse abdominal pain. He was hospitalized in the gastroenterology department of the city clinical hospital with an exacerbation of UC, where an examination revealed a significant increase in C-reactive protein (CRP) to 75 mg/ml, mild anemia, hypoproteinemia and hypoalbuminemia. Determination of *Clostridioides difficile* toxins A and B in feces showed a negative result. Ultrasound examination of the abdominal organs revealed thickening and inflammatory changes in the colon throughout its entire length, which were most pronounced in the sigmoid colon and

descending colon. Antibacterial and infusion therapy, nutritional support was administered in the hospital, and to stop the attack, a systemic glucocorticosteroid (GCS) prednisolone was prescribed at a dose of 60 mg intravenously by drip, with a transition to oral administration of 55 mg per day. However, on the fifth day from the start of therapy, the patient noted the appearance of intense pain in the right half of the head, nausea, disorientation in place, time and his own identity. A computed tomography (CT) scan of the brain with contrast was performed, which revealed signs of acute cerebrovascular accident (ACVA) in the temporal lobe, thrombosis of the right internal jugular vein, sigmoid, transverse sinuses of the brain on the right, parietal thrombus of the sinus drainage and superior sagittal sinus. The patient was urgently transferred to the neurological department, where prednisolone therapy was continued with a weekly dose reduction, and mesalazine 3.6 g per day was also added to the therapy. A month later, during a control colonoscopy, endoscopic remission of the disease was confirmed.

However, against the background of prednisolone withdrawal, the patient again noted an increase in stool frequency up to 40 times with an admixture of blood, mucus, febrile fever, abdominal pain syndrome. He was again hospitalized, where an examination revealed a high content of leukocytes and erythrocytes in the coprogram, an increased level of CRP up to 16.5 mg/l and hypokalemia. Severe UC was found during rectoromanoscopy. Antispasmodic, antibacterial (ciprofloxacin, metronidazole), infusion therapy was administered, and prednisolone tablets were again prescribed at a daily dose of 105 mg to relieve the exacerbation, which significantly

exceeded the recommended doses. In parallel, azathioprine therapy was started at 150 mg per day. The attack was stopped. But two months after the cancellation of GCS, since November 2023, blood in the stool reappeared. Laboratory data showed thrombocytopenia (platelets $119 \cdot 10^9/l$), an increase in CRP to 15.33 mg/l. Rectomanoscopy shows signs of moderate UC activity. To stop the exacerbation, high-dose prednisolone therapy (up to 115 mg per day) is prescribed, against which the patient develops a repeated ACVA of ischemic genesis in the left middle cerebral artery basin, which was confirmed by CT of the cerebra. The patient was prescribed conservative treatment in a neurological hospital and continued basic UC therapy with azathioprine and mesalazine.

In April 2024, shortness of breath during physical exertion, general weakness, and dizziness were noted. In the general blood test, thrombocytopenia, anemia (Hb 76 g/l), the patient assessed the changes as a side effect of azathioprine therapy, and therefore independently reduced the dose of the drug to 100 mg per day, and completely stopped taking it in June. Since May 2024, a gradual deterioration in health in the form of weakness, unstable stool, and blood in the stool has been noticed. In June 2024, therapy was intensified with prednisolone at a dose of 60 mg per day, against the background of which clinical improvement of UC was noted, but complaints of general weakness and numbness of the right hand appeared. CT of the brain revealed venous thrombosis of the parietal lobe on the left, acute cerebrovascular accident of ischemic genesis in the left MCA basin. The neurologist prescribed a permanent intake of apixaban 5 mg 2 times a day, valproic acid 500 mg

2 times a day. Due to the presence of a severe course of UC, with the ineffectiveness of basic therapy with 5-ASA drugs, intolerance to azathioprine, the development of steroid resistance, as well as an increase in thrombocytopenia (platelets $(83-48) \cdot 10^9/l$) and anemia (Hb 89-61 g/l), the patient was hospitalized in the gastroenterology department of the regional clinical hospital. At the time of hospitalization: the condition is satisfactory. Severe anemia (Hb 79 g/l, erythrocytes $2.67 \cdot 10^{12}/l$), thrombocytopenia (platelets $33 \cdot 10^9/l$), lymphocytosis (76%), increased indicators of systemic inflammation (ESR - 43 mm/h, CRP - 14.4 g/ml, ferritin - 1602 mcg/l), moderate hypoproteinemia (total protein - 62 g/l) were noteworthy). No changes were detected in the coagulogram while taking apixaban, however, a threefold increase in D-dimer was detected (1.28 mg/l). CT of the chest, abdominal cavity and retroperitoneal space with intravenous contrast did not reveal signs of pulmonary artery thromboembolism. A colonoscopy was performed, which showed the presence of catarrhal proctitis, which corresponded to minimally active UC. Given the patient's history of repeated episodes of acute cerebrovascular accident, secondary antiphospholipid syndrome was excluded in the clinic, in connection with this, the presence of antinuclear factor, antibodies to cardiolipin and phospholipids (IgM and IgG), lupus anticoagulant were determined, which were not detected. Taking into account progressive pancytopenia, changes in the leukocyte formula (lymphocytosis), viral infections such as herpes simplex virus, cytomegalovirus and Epstein-Barr virus were excluded using the polymerase chain reaction method and determination of the level of immunoglobulin antibodies

of class M and G. In order to exclude systemic blood pathology, a bone marrow puncture was performed with aspirate collection for immunophenotyping. As a result of the studies, a decrease in bone marrow cellularity with an increase in the number of T-lymphocytes due to CD3+CD8-T-lymphocytes was revealed. The trephine biopsy confirmed a significant decrease in bone marrow cellularity, with the fat component accounting for more than 95 % of the substance, without signs of reticulin fibrosis (MF) and collagen fibrosis (Coll), which indicated aplastic anemia, MF-0, Coll-0. Basic therapy for UC was continued in the clinic with mesalazine 4.8 g per day, and three transfusions of erythrocyte suspension and platelet concentrate were performed. Positive clinical and laboratory dynamics were noted against the background of the therapy: an increase in Hb to 94 g/l, a decrease in CRP to 8 mg/l. The patient was discharged under the supervision of a hematologist and gastroenterologist at the place of residence, and an in-person consultation was also recommended at the Federal State Budgetary Institution "NMIC of Hematology" of the Ministry of Health of Russia with bone marrow trepanoblocks.

RESULTS AND DISCUSSION

The peculiarity of the presented clinical case is the presence of repeated TEC of the cerebral vessels, both venous and arterial, in a patient with a severe course of UC, as well as the development of aplastic anemia. It should be noted that cardiovascular events and hematopoietic aplasia in patients with IBD may be caused by the underlying disease or be a manifestation of an adverse reaction to therapy.

Numerous studies, including large meta-analyses, have found that active IBD is associated with an increased risk of developing cardiovascular diseases (CVD), such as coronary heart disease, myocardial infarction, and thromboembolic complications [4; 5]. The pathogenesis of CVD is based on multiple processes that are activated in patients with UC and Crohn's disease, including: local and systemic inflammation, intestinal microbiome disorders, endothelial dysfunction and thrombosis [4; 6]. The most common vascular events complicating IBD are deep vein thrombosis, pulmonary embolism, and cases of cerebral venous sinus thrombosis have also been described. Arterial thromboembolic complications occur less frequently than venous ones and are in most cases associated with high disease activity, surgical interventions, and hyperhomocysteinemia [4; 7]. The cerebral arteries, retinal arteries, carotid sinus, coronary arteries, arteries of internal organs and extremities are most frequently involved in the process [8; 9]. According to data from the Swedish National Registry, published in 2023, which includes an analysis of more than 85 thousand patients with IBD, patients with UC and Crohn's disease are at increased risk of ischemic stroke (2.5 times more often than in the general population), regardless of the disease phenotype. Moreover, the excess risk persisted even 25 years after diagnosis [10].

Today it is known that CVD in IBD is also caused by side effects of therapy. In particular, the administration of high doses of systemic GCS, which are often used to relieve exacerbations of moderate and severe forms of UC and Crohn's disease, is associated with the development of diabetes mellitus, immunosuppressive conditions, osteoporosis, hypertension,

and hypercoagulation. GCS lead to the development of venous thromboembolism by activating factors VII, VIII, and XI and fibrinogen and blocking anticoagulation mechanisms [11]. A population-based study conducted in the UK found that the risk of developing primary ischemic stroke was several times higher in individuals aged 35–74 years who had been taking prednisolone for a year [12]. A cohort study found that an increase in the frequency of venous TEC occurred in the first month after the start of using GCS at a daily dose of prednisolone of 20 mg or more [13]. It should be noted that the patient was repeatedly prescribed high daily doses of oral prednisolone (more than 100 mg) in the demonstrated clinical case due to high UC activity, and all cases of cerebral vascular TEC occurred within the first 10 days from the start of therapy. This fact, in our opinion, confirms the manifestation of an adverse drug reaction of GCS.

Given the high thromboembolic risk associated with active IBD, patient management should include prevention (primary and secondary) and treatment of TEC. The ECCO guidelines published in 2016 contain data on the principles of primary prevention in patients with high inflammatory activity [14]. However, modern Russian clinical guidelines do not contain clear algorithms for managing patients with TEC in IBD. Treatment for existing thromboses is carried out according to the general standards and protocols for managing patients without IBD, but taking into account the clinical manifestations of the underlying disease, changes in the coagulogram, as well as the presence of previous thromboembolism in the anamnesis. Long-term anticoagulant therapy is

carried out with low-molecular heparins, vitamin K antagonists (warfarin) or direct oral anticoagulants (rivaroxaban, dabigatran, apixaban, etc.) [11].

The literature describes single cases of aplastic anemia in IBD. It is believed that the common pathogenetic mechanisms for the two diseases are immunological disorders, in particular, increased production of proinflammatory cytokines: tumor necrosis factor- α and interferon- γ , changes in the T-cell link of immunity. It is tumor necrosis factor- α and interferon- γ that are capable of blocking the proliferation of bone marrow progenitor cells (stem cells), causing hematopoietic aplasia [15].

It should be noted that the development of the cytopenic state in the patient occurred against the background of taking azathioprine at a daily dose of 150 mg. There is evidence that azathioprine therapy in 43 % of cases is associated with the development of side effects that require a dose reduction or drug withdrawal. Most often, adverse effects are associated with the peculiarities of thiopurine metabolism, namely, with the level of 6-thioguanine nucleotides (6-TH) – the main product of metabolism, its concentration in the blood is due to both the main and myelotoxic effects. It has been proven today that only 20 % of patients metabolize thiopurines to form high concentrations of 6-TH, which is associated with inefficiency and the development of adverse drug reactions. Another important factor that has a direct impact on the concentration of 6-TH is the level of the metabolizing enzyme thiopurine methyltransferase (TPMT). Thus, people with low enzyme activity (0.3 % in the population) may develop severe myelodysplastic reaction [16].

CONCLUSIONS

1. Patients with active IBD may develop thromboembolic complications with damage to the vessels of the brain, the risk of which is associated with the activity of the inflammatory process in the intestine. Also, thromboembolic complications are often associated with complication of the therapy, in particular by high doses of systemic GCS.

2. There are limited data confirming the possibility of a combination of IBD and aplastic

anemia. Most often, hematopoietic aplasia is associated with the use of thiopurines, up to the development of severe forms of hematopoietic aplasia.

3. Treatment of patients with severe forms of IBD is a complex task of modern gastroenterology. It is a personalized approach to treatment taking into account the nature of the disease, the presence of concomitant pathology, complications, based on predicting the effectiveness and safety, as well as searching for predictors of possible complications of drug therapy, that will reduce the risks of developing adverse reactions.

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Stepina Ye.A. – 60 % (collection of material, analysis and interpretation of the stationary map, writing the text, approval of the final text of the article).

Khlynova O.V. – 40 % (editing the article and approving the final text, responsibility for the integrity of all parts of the manuscript).

Limitation of the study. The study complies with the standards of the Helsinki Declaration and was approved by the Ethics Committee of the Ye.A. Vagner Perm State Medical University; Protocol No. 2 dated March 12, 2025. The patient gave written informed voluntary consent for the publication of anonymized data.

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