SURGERY

PSEUDOMEMBRANOUS COLITIS COMPLICATED BY TOXIC MEGACOLON IN ONCOLOGICAL PATIENTS

Morikov D.D. [1, 2, 3],
Kartashova V.V. [2],
Shelekhov A.V. [3],
Nikolaeva N.A. [2]

[1] Irkutsk State Medical Academy of Postgraduate Education – Branch Campus of the Russian Medical Academy of Continuous Professional Education (Yubileyniy 100, Irkutsk 664049, Russian Federation)
[2] Irkutsk Regional Cancer Center (Frunze str. 32, Irkutsk 664035, Russian Federation)
[3] Irkutsk State Medical University (Krasnogo Vosstaniya str. 1, Irkutsk 664003, Russian Federation)

Corresponding author:
Dmitry D. Morikov,
e-mail: mdd71@mail.ru

ABSTRACT

In recent years, information on the increase in the incidence of infection associated with Clostridioides difficile (CDI) has appeared in the literature. It is known that C. difficile which causes pseudomembranous colitis (PMC) most often affects debilitated patients who receive treatment for the main pathology for a long time. That is why PMC is most common in cancer patients receiving long-term and aggressive anticancer treatment, which is often accompanied by the use of several courses of antibiotics. The result of the irrational use of antibiotics, incorrect PMC therapy may be the formation of toxic megacolon, intestinal perforation, sepsis, which in turn is fraught with a fatal outcome. It is this state of affairs that aroused our interest in the study of this topic.
The steady increase in the incidence of Clostridioides difficile infection makes it particularly relevant to study CDI problem in relation to cancer patients, since they most often have a wide range of risk factors for developing clostridial infection.
The article presents an overview of domestic and foreign sources describing this pathology, discusses epidemiology, pathogenesis, clinical picture and current understanding of the CDI treatment. At the end of the review, we present a case of successful treatment of pseudomembranous colitis after stoma closure, which was complicated by the development of toxic megacolon. Colproctectomy was performed as part of the complex treatment of this pathology. The patient received respiratory, renal replacement, hepatoprotective, antibiotic and antifungal therapy and other treatments.

Key words: *pseudomembranous colitis, colorectal cancer, toxic megacolon, colectomy, C. difficile*

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ПСЕВДОМЕМБРАНОЗНЫЙ КОЛИТ, ОСЛОЖНЁННЫЙ ТОКСИЧЕСКИМ МЕГАКОЛОНОМ, У ПАЦИЕНТОВ ОНКОЛОГИЧЕСКОГО ПРОФИЛЯ

Мориков Д.Д. [1, 2, 3],
Карташова В.В. [2],
Шелехов А.В. [3],
Николаева Н.А. [2]

[1] Иркутская государственная медицинская академия постдипломного образования – филиал ФГБОУ ВО «Российская медицинская академия непрерывного профессионального образования» Минздрава России (664049, г. Иркутск, Юбилейный, 100, Россия)
[2] ГБУЗ «Областной онкологический диспансер» (664035, г. Иркутск, ул. Фрунзе, 32, Россия)
[3] ФГБОУ ВО «Иркутский государственный медицинский университет» Минздрава России (664003, г. Иркутск, ул. Красного Восстания, 1, Россия)

Автор, ответственный за переписку:
Мориков Дмитрий Дмитриевич,
e-mail: mdd71@mail.ru

РЕЗЮМЕ

В последние годы в литературе появляется информация о росте заболеваемости Clostridioides difficile-ассоциированной инфекции (CDI, Clostridioides difficile infection). Известно, что наиболее часто C. difficile, вызывающая псевдомембранозный колит (ПМК), поражает ослабленных пациентов, долго получающих лечение основной патологии. Именно поэтому ПМК наиболее часто встречается у пациентов онкологического профиля, получающих длительное и агрессивное противоопухолевое лечение, нередко сопровождающееся применением нескольких курсов антибиотиков. Следствием нерационального применения антибиотиков, некорректной терапии ПМК может быть формирование токсического мегаколона, перфорации кишечника, сепсиса, что в свою очередь чревато летальным исходом. Именно такое положение вещей вызвало наш интерес к изучению данной темы.

Неуклонный рост заболеваемости инфекцией Clostridioides difficile повсеместно делает особенно актуальным изучение проблемы CDI в мировом сообществе применительно к больным онкологического профиля, так как именно у них наиболее часто имеется широкий спектр факторов риска развития клостридиальной инфекции.

В статье представлен обзор отечественных и зарубежных источников описывающих данную патологию. Освещаются эпидемиология, патогенез, клиническая картина и современное представление о лечении CDI. По окончании обзора нами представлен случай успешного лечения псевдомембранозного колита после закрытия стомы, осложнившегося развитием токсического мегаколона. В рамках комплексного лечения данной патологии была выполнена операция колпроктэктомии. Пациент получал респираторную, почечно-заместительную, гепатопротективную, антибиотико-и противогрибковую терапию и другое лечение.

Ключевые слова: *псевдомембранозный колит, колоректальный рак, токсический мегаколон, колэктомия, C. difficile*

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LIST OF ABBREVIATIONS

C. difficile	–	*Clostridioides difficile*
CDI	–	*Clostridioides difficile infection*
TcdA	–	*Clostridium difficile* toxin A
TcdB	–	*Clostridium difficile* toxin B
GDH	–	glutamate dehydrogenase
RRT	–	renal replacement therapy
ALV	–	artificial lung ventilation
MIC	–	minimum inhibitory concentration
PMC	–	pseudomembranous colitis
PCR	–	polymerase chain reaction
HSCT	–	hematopoietic stem cell transplantation

INTRODUCTION

Clostridioides difficile infection (CDI) is currently the leading detectable cause of nosocomial diarrhea associated with antibacterial therapy [1]. *C. difficile* toxin B was isolated from stool in more than 95 % of cases of pseudomembranous colitis (PMC) and in 15–25 % of cases of antibiotic-related diarrhea [2]. After the first episode of clostridial colitis, the risk of recurrence may be exponential [3, 4]. Despite modern treatment options for *C. difficile* infection, there is an increase in morbidity and mortality associated with PMC [5]. Mortality from PMC against the background of *C. difficile* ranges from 6 % to 30 % [6]. The observations of K. Neemann et al. [7] show that in patients with malignant neoplasms, the incidence of PMC is 7 %, and about 8 % of these infected people develop a severe form of the disease. Fulminant *C. difficile* leads to toxic megacolon, has a mortality rate of almost 50 %, and in some cases, it is found to be resistant to treatment with drugs such as metronidazole, vancomycin, fidaxomicin [8]. According to R.L. Harries et al., based on an analysis of 13,728 surgical manuals, PMC is a potentially life-threatening complication of ileostomy closure surgery. The frequency of such a complication can reach 4 % [9]. In this article, we would like to review a clinical case demonstrating the successful treatment of PMC, which developed after the closure of the stoma and was complicated by the development of toxic megacolon, which makes the above observation interesting. According to the Department of coloproctology of the Irkutsk Regional Cancer Center (head of the department – Medvednikov A.A., Cand. Sc. (Med)), in 2020–2022, the incidence of PMC developed due to closure of various types of stomas was 3.2 %, sigmoid colectomy – 3.3 %, right hemicolectomy – 2.5 %.

Clostridioides difficile is a toxin–producing spore-forming gram-positive obligate anaerobe found everywhere in nature, most often in soil. Initially, the pathogen was named *Bacillus difficilis* because of its morphology and difficulty of cultivation [10]. Spores protect the microorganism from the damaging effects of temperature, oxygen, chemicals and disinfectants, radiation, which plays an important role in the spread of CDI.

This bacterium was first described by I.C. Hall and E. O'Toole in 1935 as a part of the normal microflora of newborns [11]. In 1970 J.G. Bartlett et al. determined the leading role of toxin A, secreted by *C. difficile,* in the pathogenesis of clindamycin-associated enterocolitis in Syrian hamsters [12]; later, this toxin was isolated from stool samples of patients with diarrhea. By 1978, *C. difficile* was clearly identified as a pathogenic agent of PMC [13].

C. difficile lives in the human intestine and in the environment in the form of spores. The sources of infection are sick people and asymptomatic bacterial carriers. According to the observations of E.J. Kuipers and C.M. Sura-

TABLE 1

RISK FACTORS FOR THE DEVELOPMENT OF PSEUDOMEMBRANOUS COLITIS

Factors affecting the normal intestinal microflora	Contact of patients with *C. difficile*	Patient-related factors
• antibiotic therapy – especially 2nd and 3rd generation cephalosporins, clindamycin, fluoroquinolones, even vancomycin; • antisecretory treatment with proton pump inhibitors and H2 blockers – contributes to a change in the biocenosis of the gastrointestinal tract; • the use of loperamide exacerbates the course of PMC.	• prolonged stay in a medical facility, including hospitals and nursing homes, prolonged contact in the ward with an infected patient; • long-term use of nasogastric tubes and enemas.	• older age – over 60–65 years old; • nutritional status – depletion, low initial albumin level; • immunodeficiency conditions, immunosuppression (glucocorticoid therapy, cytostatics, monoclonal antibodies); • abdominal surgery, organ transplantation; • severe concomitant pathology – CKD, diabetes mellitus, chronic inflammatory bowel diseases, COPD, malignant neoplasms.

Note. CKD is a chronic kidney disease; COPD is a chronic obstructive pulmonary disease.

wicz (2008), it turned out that up to 57 % of elderly people in nursing homes, 84 % of newborns, and 15 % of healthy adults were carriers of the microorganism [14]. *C. difficile* carriage reaches 16–35 % in inpatient patients, and the percentage is proportional to the length of hospital stay and increases when exposed to antibiotics [15]. The main ways of transmission of clostridial infection are fecal-oral transmission from person to person, through environmental pollution, through household items and the hands of medical staff. The risk factors for the development of pseudomembranous colitis are presented in Table 1.

PATHOGENESIS

The pathogenesis of CDI is complex and so far, it has not been sufficiently studied. It is known that the clinical picture of the disease is caused only by toxigenic strains of *C. difficile* [16]. However, pseudomembranous colitis is not formed in all cases. The reason for this is both the protective qualities of the intestinal microbiota and the response of the immune system. With the development of an imbalance of microorganisms and violation of the integrity of the mucous membrane of the colon, *C. difficile* colonizes the intestine, proliferates in it, forming vegetative toxin-producing forms. Their synthesis is encoded by the corresponding genes, and this aspect underlies the molecular biological methods of CDI diagnosis [17].

C. difficile causes multiple changes in the wall of the colon: total neutrophil infiltration; circulatory disorders in the form of dilation, vascular congestion and submucosal edema; obturating thrombi without signs of organization in the vessels of the submucosal layer, including superficial damage to the mucous membrane with the formation of "pseudomembranes" – exudative plaques. In the absence of effective specific therapy directed against *C. difficile*, the infection continues to progress further and contribute to the formation of extensive inflammatory changes [18]. It is generally believed that the combination of chronic diseases and antibiotic therapy in hospital patients affects the normal microbiota of the colon, increases susceptibility to colonization and production of *C. difficile* toxins, which increases the risk of PMC from 2 to 16 times [19].

C. difficile can produce toxins such as A (TcdA), B (TcdB) and binary AB, which contribute to the development of PMC:

- toxin A (enterotoxin) – disrupts the barrier function of the intestinal mucosa, stimulates guanylate cyclase, increases the secretion of fluid into the intestinal lumen and promotes the development of diarrhea, is produced 3–4 times more often than toxin B;
- toxin B (cytotoxin) – stronger than the toxin A by thousands of times, has a pronounced cytopathogenic effect by inhibiting the processes of protein synthesis in enterocytes and colonocytes, determines the severity of infection and the clinical picture of PMC [20];
- binary toxin of the NAP1/BI/027 ribotype (hospital infection in Quebec and clinics in the USA since 2003) – forms a complex on the membrane of an intestinal cell consisting of ADP-ribosyl transferase and a receptor, which subsequently penetrates into the enterocyte by receptor-mediated endocytosis and endosomal exchange and contributes to disruption of cell functioning through ADP-ribosylation of globular actin, which leads to disorganization of the cytoskeleton and subsequent cell death [12, 13]. This toxin also enhances the adhesion and colonization ability of *C. difficile* by inducing the synthesis of microtubules at the base of cell protrusions, which contributes to easier attachment to colonocytes [14, 15, 21].

The appearance of a binary toxin is associated with a mutation in the gene for the regulator-repressor of *C. difficile* toxin production, which leads to increased production of toxins A and B. In this case, toxins A and B are produced 16 and 23 times more, respectively. M.C. McEllistrem et al. show a tendency to a more severe course of the disease in patients whose feces contain a binary toxin [21].

Glutamate dehydrogenase is an enzyme that converts glutamate to α-ketoglutarate, produced by *C. difficile* in relatively large amounts compared to toxins A and B [22]. Although glutamate dehydrogenase (GDH) tests are sensitive, they are not as specific to PMC because this enzyme is produced by both toxigenic and non-toxigenic strains of the microorganism.

The patient's immune status is an important determining factor in the development of the disease. As the observations of J.K. Shim et al. show, bacterial carriers without clinical manifestations have higher concentrations of serum antibodies to toxin A than symptomatic patients and are less prone to the development of PMC [23]. For patients who develop PMC, it is characteristic that a higher level of antibodies to the toxin is associated with a shorter duration of the disease and a reduced risk of recurrence [24].

CLINICAL PICTURE

PMC clinical picture varies from asymptomatic colonization to fulminant toxic megacolon requiring surgical intervention.

In 2013, the classification of PMC by the severity of the disease, proposed by the American Gastroenterological Association (AGA), was published [25]. The classification is presented in Table 2.

With untimely diagnosis and lack of treatment, the disease progresses, that can lead to complications. A rare but life-threatening complication of the disease – toxic megacolon – that is defined as segmental or complete distension of the colon more than 6 cm in the presence of signs of colitis and systemic intoxication. Toxic megacolon syndrome occurs in 0.4–3 % of cases, with concomitant mortality from 38 to 80 % [26, 27]. The development of toxic megacolon in combination with shock, sepsis, and intestinal perforation is characterized as a severe form of clostrid-

TABLE 2

CLASSIFICATION OF PSEUDOMEMBRANOUS COLITIS BY THE GRAVITY OF THE DISEASE

Mild course	Moderate severity course	Severe course	Severe complicated course
• diarrhea* • minor abdominal pain	• diarrhea • body temperature increase up to febrile values	• diarrhea • abdominal pain of a spastic nature • fever to hectic values • hypoalbuminemia < 30 g/l, leukocytosis (over 15×10^9 leukocytes in peripheral blood) • Abdominal tenderness during palpation of the abdomen	• watery diarrhea with blood Plus one of the symptoms: • hypotension with or without vasopressors • fever ≥ 38.5 °C • signs of intestinal obstruction (acute nausea, vomiting, sudden cessation of diarrhea, bloating or radiographic signs of impaired passage through GIT), multiple organ failure • changes in mental status • leukocytes ≥ 35×10^9 or < 2×10^9 cells in peripheral blood, serum lactate level > 2.2 mmol/L

Note. * – according to the definition of the World Health Organization, this is loose stool corresponding to the 5^{th}–7^{th} types of the Bristol stool scale, occurring 3 or more times a day; GIT – gastrointestinal tract.

ial infection. For the first time, toxic dilation of the colon as a complication of PMC was described by C.H. Brown et al. more than forty years ago [28]. According to some data [29], the use of antiperistaltic drugs, for example, loperamide, in patients with PMC is associated with the development of toxic megacolon, probably because these drugs delay the release of the toxin.

PMC recurs after treatment in 3.7 to 64.0 % of cases [30]. A recurrent form of the disease is indicated when the clinical picture occurs less than 8 weeks after the end of therapy. Risk factors for recurrence of infection include: repeated administration of one or more antibiotics; age over 65 years; severity of the underlying disease; low albumin concentration; stay in the intensive care unit or in the hospital for more than two weeks [31, 32]. The recurrence rate of PMC is especially high among cancer patients, as shown by M.S. Chung et al. [33] (20.4 % vs. 9.5 %, respectively; $p = 0.005$), and cancer is an independent risk factor for recurrence. Cases of the occurrence of PMC in *patients with malignant neoplasms* against the background of postoperative chemoradiotherapy without the use of antibiotics in the anamnesis have been described [34, 35].

Studies show that the mortality rate directly associated with PMC in cancer patients was higher than in cancer patients without PMC (9.3 % vs. 7.4 %, respectively; $p < 0.0001$). PMC is also associated with longer hospital stays in cancer patients than in uninfected individuals (9 days vs. 4 days, respectively; $p < 0.0001$) [36].

DIAGNOSTICS

Rapid and accurate diagnosis of PMC is necessary not only for individual patient management, but also for the prevention of nosocomial transmission of infection. According to the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) of 2009, all patients with diarrhea admitted to any hospital should be tested for *C. difficile* regardless of age, previous antibiotic use, concomitant pathology and its treatment [16]. The diagnosis of PMC is based on the clinical picture and laboratory data presented in Table 2, but the detection of toxin A and/or B in feces is fundamental.

Currently, various laboratory tests are available to detect *C. difficile*:

- detection of *C. difficile* products (GDH, toxins A and/or B) – methods of immunochromatographic, enzyme immunoassay, immunochemiluminescence assays, polymerase chain reaction (PCR);
- analysis of cytotoxicity of cell cultures and cultural methods of isolation of toxin-producing strains of *C. difficile* – reference standard methods for the diagnosis of PMC;
- molecular genetic tests – PCR, ribotyping, pulsed-field gel electrophoresis, multilocus assay and determination of the multilocus sequence.

The material for the diagnosis of clostridial infection is samples of fresh lumen feces of patients with diarrhea in an amount of about 10–15 ml. It is also possible to examine smears or tissue of the mucous membrane of the colon obtained during colonoscopy or during surgery.

Fibrocolonoscopy determines diffuse hyperemia and swelling of the mucous membrane of the colon, characteristic yellowish-white fibrinous plaques with a diameter of up to 20 mm or more, pseudomembranes – fused plaques – more often in the left half of the colon (Fig. 1, 2). It should be borne in mind that performing fibrocolonoscopy with a pathological change in the intestine can lead to perforation of the colon.

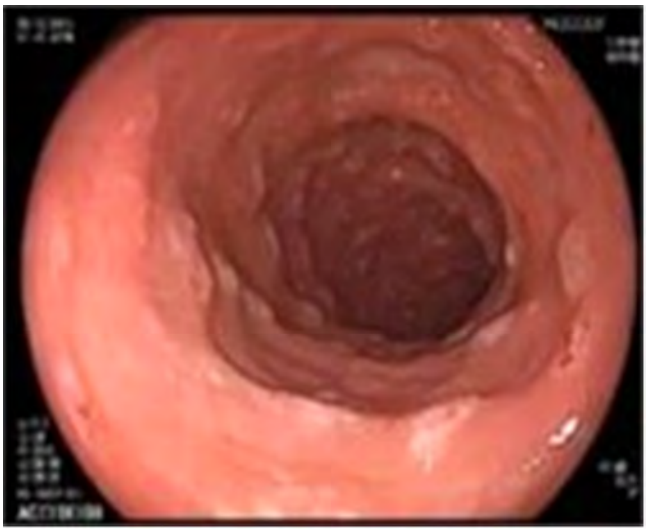

FIG. 1.
Endoscopic picture of pseudomembranous colitis (photo from the Dicom archive of Irkutsk Regional Cancer Center): the folds are smoothed; diffuse hyperemia of the mucosa with thickening of the intestinal wall; vascular pattern is blurred; characteristic whitish yellowish fibrinous plagues 2–5 mm in diameter

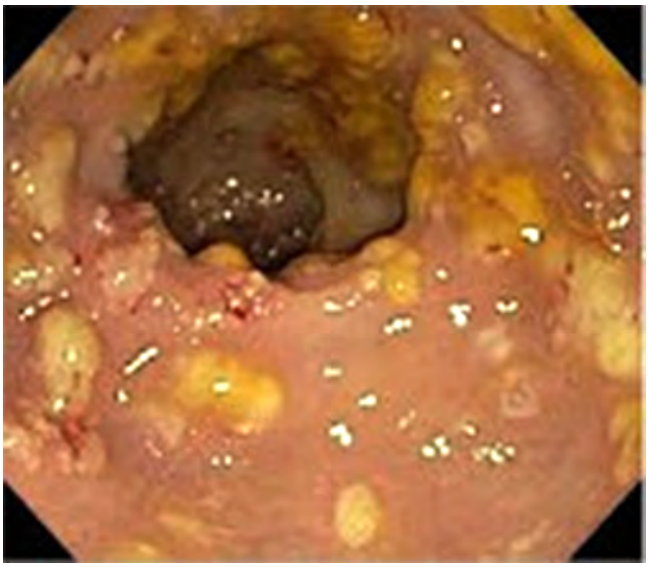

FIG. 2.
Endoscopic picture of pseudomembranous colitis (photo from the Dicom archive of Irkutsk Regional Cancer Center): intestinal mucosa is swollen, loose, hyperemic, capillary pattern is blurred; many yellowish white plagues 3–5 mm in diameter, which are tightly fixed to the mucous membrane

Ultrasound examination shows increased peristalsis of the small intestine and thickening of the colon wall.

Methods of radiological examination used to diagnose CDI:

1. Plain abdominal radiography: edematous colon with areas of thickening of the intestinal wall, haustration disorders are detected. In 30–35 % of patients, radiographic signs of small and large intestinal obstruction are determined.

2. Irrigoradiography: rounded "filling defects" – pseudomembranes – are revealed.

3. Computed tomography of the abdominal cavity can be informative to confirm the diagnosis of PMC. Typical signs are [37] thickening of the intestinal wall, narrowing of the intestinal lumen, effusion in the abdominal cavity, accordion sign (alternating edematous haustral folds separated by transverse mucous ridges filled with oral contrast material imitating an accordion), target sign (alternation of three concentric rings – high, low and high). Also, computed tomography of the abdominal cavity and pelvic organs can be used to determine the severity of the disease, identify toxic megacolon, intestinal obstruction or perforation of the intestinal wall.

TREATMENT

The treatment scheme for PMC, according to the Clinical Guidelines of the National Association of Specialists on Healthcare-Associated Infection Control and the Association of Proctologists of Russia (2017), is presented in Table 3.

Asymptomatic carriers of *C. difficile* have a relatively low risk of developing PMC [23], treatment is not recommended.

Antibiotic therapy is a cornerstone of the treatment of pseudomembranous colitis. R. Morales Chamorro et al. emphasize the importance of early detection of PMC in patients receiving chemotherapy and the initiation of antibacterial therapy immediately after diagnosis [38]. Some studies [39] show that 15–23 % of patients with PMC had spontaneous disappearance of symptoms within 48–72 hours after discontinuation of the antibiotic, as well as continued use of systemic antibiotics was associated with refractory treatment of PMC. However, in practice, it is almost impossible to cancel antibiotic therapy against the background of an infectious process.

The most commonly used antibiotics in PMC are metronidazole and vancomycin, including in cancer patients. These drugs are used either as monotherapy or in combination, depending on the severity of PMC, premorbid background, disease refractoriness and recurrence [40]. The usual dose of metronidazole is 500 mg 3 times a day for 10–14 days. Metronidazole has the same efficacy as vancomycin for the treatment of mild and moderate forms of PMC.

In a retrospective analysis conducted by S.R. Parmar et al. [41] in patients with hematological malignancies, including those who underwent hematopoietic stem cell transplantation (HSCT), patients were divided into 3 groups depending on the treatment received: metronidazole only; vancomycin only; combination therapy. The response rate was 53.7 %, 50 %, 38.5 % with metronidazole monotherapy, vancomycin monotherapy and combination therapy, respectively (p = 0.55). K. Tsuchida et al. [42] report a case involving

a 74-year-old patient with sigmoid colon cancer who received cefepime for the treatment of febrile neutropenia, who subsequently developed pseudomembranous colitis. Against the background of vancomycin enemas, the symptoms of PMC regressed.

The minimum inhibitory concentration (MIC) of vancomycin required to inhibit 90 % of strains (MIC_{90}) is 0.75–2.0 μg/ml. Vancomycin is used orally in the dose of 125 to 500 mg 4 times a day. In *vitro*, the MIC_{90} of metronidazole for *C. difficile* ranges from 0.20 to 2.0 μg/ml (median is 1 μg/ml). After administration by healthy volunteers, metronidazole is completely absorbed from the gastrointestinal tract and is not detected in feces. However, the concentration of this drug in feces is significantly higher if the stool is watery or unformed than if it is solid. This occurs as a result of an increase in the time of passage of the drug through the digestive tube, leading to incomplete absorption or excretion of the drug through the inflamed mucous membrane of the colon [43]. Intravenous administration of metronidazole should reach the luminal surface of the colon in therapeutic concentrations, which depends on the biliary secretion of the drug into the small intestine [43].

Oral vancomycin cannot reach areas of the colon that are not continuous segments of GIT, for example, in ascending ileostomy, obstructive colon resection (Hartmann surgery) or colostomy. If PMC is detected in a disconnected segment of the colon, it is recommended to administer vancomycin with an enema, which guarantees that the drug reaches the affected area [44]. Enemas with vancomycin are used – 500 mg in 100–500 ml of 0.9 % sodium chloride every 6 hours; the volume of the solution depends on the length of the treated segment. The duration of rectal administration of vancomycin is determined by the clinical course of PMC.

Tigecycline is a glycylcycline derivative of tetracycline and has bacteriostatic properties due to inhibition of protein translation in bacteria. It shows broad antimicrobial activity against gram-negative and gram-positive organisms, including *C. difficile*. Due to its properties, it is able to overcome the main mechanisms of resistance of microorganisms to tetracyclines.

Rifaximin is a semi-synthetic derivative of rifampicin and is characterized by a wide range of antimicrobial properties. The drug has a bactericidal effect by inhibiting DNA-dependent RNA polymerase of bacteria. Rifaximin is active against most gram-negative and gram-positive bacteria, anaerobes and aerobes and has in *vitro* activity against *C. difficile* [45].

Fecal microbiota transplantation means that the feces of a healthy person are transplanted into a patient, used in extreme cases when other treatment methods are ineffective [46]. Fecal transplantation has shown its effectiveness in cancer patients with recurrent PMC. Observations describe clinical cases in which two recipient patients underwent fecal microbiota transplantation after HSCT after unsuccessful standard antibacterial therapy. The first patient underwent two fecal transplants within 6 months, and the second patient was cured within 48 hours after one transplant [47, 48].

In recent years, several new specific therapeutic agents against C. difficile have appeared on the market. Fidaxomycin is an antibiotic from the group of macrolides that has a bactericidal effect and inhibits the synthesis of bacterial RNA. The drug is characterized by little or no systemic absorption after oral administration and a narrow spectrum of activity against gram-positive aerobic and anaerobic bacteria, including *C. difficile,* since 2011 it has been approved for the treatment of PMC in the USA. *The* dosage of fidaxomycin is 200 mg 2 times per day for 10 days. In terms of its effectiveness in *in vitro* studies, fidaxomycin was more active than vancomycin in PMC [49]. Human monoclonal antibody – bezlotoxumab – was approved by the U.S. Food and Drug Administration (FDA) in 2016. Bezlotoxumab binds to two very similar sites in the TcdB CROPs domain, thereby blocking the binding of the toxin to carbohydrate receptors. The interaction between the antibody and TcdB prevents intoxication. Given the specificity of these antibodies, it is not surprising that they have minimal adverse effects on the mi-

TABLE 3

TREATMENT SCHEME FOR PSEUDOMEMBRANOSIC COLITIS

Mild and moderate course	Severe course	Severe complicated course
• metronidazole (500 mg orally 3 times a day for 10 days); • in the absence of clinical effect in 5–7 days the drug is replaced with vancomycin (125 mg 4 times a day *per os for* 10 days).	• vancomycin (125 mg orally 4 times a day for 10 days)	• vancomycin orally (500 mg 4 times a day) in combination with metronidazole (500 mg 3 times a day intravenously); • if it is impossible to administer the drug orally, vancomycin is prescribed rectally (500 mg), diluted in 500 ml of 0.9% sodium chloride solution and administered as enemas 4 times a day; • symptomatic therapy

crobiota. Bezlotoxumab is a successful history of monoclonal antibody therapy, but this approach is not without limitations, which is not least due to production difficulties and, as a result, high cost [50, 51].

The development and clinical trials of vaccines against *C. difficile* remain promising. This is evidenced by the large number of registered clinical trials on ClinicalTrials.gov: these include the currently completed studies *NCT01887912, NCT02316470, NCT02561195, NCT040026009*, and those studies still in progress – *NCT05805826*. The studied drugs are based on the action of detoxified recombinant forms of *C. difficile* toxins and enter the body parenterally. It is likely that vaccination can become an effective method of prevention in certain groups of high-risk.

Symptomatic treatment of PMC involves restoration of the water-electrolyte balance with balanced crystalloid solutions, drug prevention of venous thromboembolism (these patients are at high risk), correction of protein-energy deficiency, detoxification therapy, correction of anemia.

If a toxic megacolon is detected in a patient with PMC and there are no signs of improvement in the condition against the background of conservative therapy, surgical intervention is indicated. A number of publications [52–55] investigating the level of postoperative mortality in toxic megacolon against the background of PMC confirm that surgery is indicated in severe cases and that subtotal colectomy is the operation of choice. P.A. Lipsett et al. [52] studied the medical histories of 13 patients in one institution who underwent surgery for PMC, which was only 0.39 % of the total number of patients with PMC who were observed in this hospital over a 6-year period of time. The overall mortality rate in this study was 38 %: 100 % of patients who underwent colon resection died, whereas in the subtotal colectomy group, the mortality rate was only 14 %. Similarly, K. Koss et al. [53] examined the medical histories of 14 patients who underwent surgery for PMC and found that the overall mortality rate was 35 %, with 11 % in the subtotal colectomy group and 80 % in the colon resection group. Patients diagnosed with *C. difficile*-associated colitis before surgery demonstrated a statistically significant survival advantage (85.7 % vs. 33.3 %) [53]. One study demonstrated a tendency to decrease mortality in patients with complicated PMC who underwent colectomy, compared with those who did not undergo the surgery [56]. Postoperative mortality was higher after total colectomy among patients with preoperative acute renal failure, the need for vasopressors and respiratory failure requiring artificial lung ventilation (ALV) [57]. It is worth noting that in recent years, taking into account the development of surgical tactics and perioperative management of patients, the mortality rate in left (right) hemicolectomy has decreased and equaled that of colproctectomy (30.1 % each; $p > 0.99$) [58, 59]. Despite this, the updated recommendations of the World Society of Emergency Surgery (WSES) in 2019 retained colproctectomy as the main choice of surgical intervention [57, 60].

Negative prognostic risk factors for death in patients undergoing colectomy include the development of shock determined by the need for vasopressors, an increase in lactate levels (≥ 5 mmol/L), a change in mental status, multiple organ failure, as well as the need for lung ventilation [61]. This indicates that early surgical treatment before the development of shock and multiple organ dysfunction leads to improved survival. Currently, there are no clear criteria defining the threshold for surgical intervention. However, the more negative prognostic factors a patient has, the earlier the issue of surgical consultation and surgical treatment should be considered.

PREVENTION

The existing primary and secondary prevention of *C. difficile* is multifaceted and includes various measures. Primary prevention is a set of measures aimed at preventing the influence of risk factors on the body: vaccination; optimal work and rest regime; high–quality nutrition; physical activity; environmental protection, etc. Secondary prevention includes a list of measures aimed at eliminating risk factors that, under conditions of stress, decreased immunity, excessive loads on the body, can lead to the onset, exacerbation and recurrence of the disease. The most effective method of secondary prevention is considered to be medical examination as a comprehensive method of early detection of diseases, dynamic monitoring, targeted treatment, as well as rational consistent recovery [62].

Patients with suspected clostridial infection should be placed in a separate room or in a room where patients with already confirmed CDI are located.

A.B. Zafar et al. [63] showed that the strict application of periodic educational measures, environmental disinfection and strict hand washing were associated with a decrease in detected cases of PMC from 155 to 67 per year in medical institutions.

CASE STUDY

In March 2013, patient L. was diagnosed with sigmoid colon cancer pT2aN0M0G2 of the 2nd stage of the 2nd clinical group, confirmed histologically (moderately differentiated adenocarcinoma). Of the concomitant diseases, it should be noted the presence of coronary heart disease, congestive heart failure stage 1, exogenous constitutional obesity 1st degree, cerebral atherosclerosis.

On 25.03.2013, the patient was admitted to Irkutsk Regional Cancer Center for the surgical treatment of the oncological process. On 01.04.2013, left hemicolectomy and anterior rectal resection were performed. In the postoperative period, he received intravenously ceftazidime 1 g 3 times/day. On 04.04.2013, the patient was diagnosed with colorectal anastomosis failure; relaparotomy, resection of colorectal anastomosis, terminal transverse colostomy in the left mesogastric zone were performed. After repeated surgery, ceftazidime was canceled, meropenem was prescribed intravenously 1 g 3 times/day extended in-

fusion for 7 days. The patient was discharged in a satisfactory condition, and did not receive adjuvant chemoradiotherapy for the next six months.

On 18.10.2013, the patient was admitted for inpatient treatment at the coloproctology department of Irkutsk Regional Cancer Center in order to restore intestinal continuity.

On 22.10.2013 (on the 1st day), reconstruction of the colon was performed. During the operation, a pronounced adhesive process was performed in the abdominal cavity, enterolysis was performed. Rectal stump was isolated with pronounced technical difficulties (adhesive process with the back wall of the bladder, contact bleeding of tissues), then hardware descendorectoanastomosis was applied.

In the postoperative period, he received antibiotic therapy: ceftriaxone 2 g 2 times/day, metronidazole 500 mg 3 times/day for 5 days and antimycotics: caspofungin 70 mg on the 1st day, then 50 mg/day. Routine postoperative anesthesia, thromboprophylaxis with early activation, and early enteral feeding were performed.

On the 10th day, due to the appearance of subfebrile fever, spastic abdominal pain and leukocytosis, the patient was prescribed cefoperazone + sulbactam intravenously 2 g 2 times/day, continued administration of antimycotics (caspofungin). Against this background, there was a positive trend, the above symptoms regressed.

On the 16th day, the patient's general condition worsened, nausea, vomiting, febrile fever, frequent loose stools appeared. On examination, the abdomen was noticeably distended and painful on palpation.

The patient was transferred to the intensive care unit; pseudomembranous colitis was suspected and diagnosed (toxins A and B of *C. difficile* were found in the stool), antibacterial therapy was initiated: *per os* vancomycin 250 mg 4 times/day, metronidazole 500 mg 3 times/day, continued administration of antimycotics (caspofungin). Diagnosis of *C. difficile* was carried out by an immunochromatographic rapid test for qualitative detection of the toxin A and toxin B *C. difficile* antigens in feces (DUO TOXIN A+B-CHECK-1).

Fibrocolonoscopy was not performed in the patient due to the severity of the condition and the high probability of iatrogenic perforation of the dilated intestine during manipulation.

Plain abdominal radiography was performed, which revealed radiographic signs of toxic megacolon (Fig. 3).

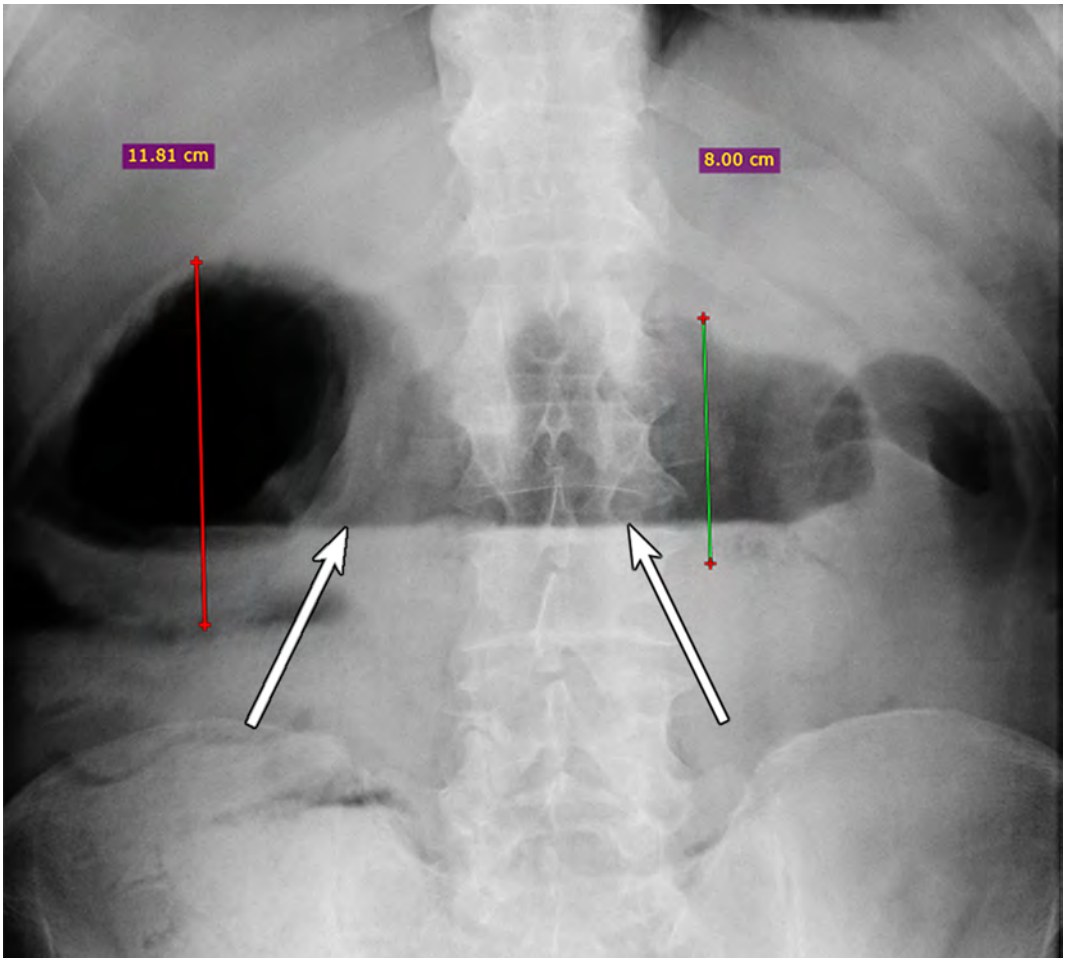

FIG. 3.

Patient L., plain radiograph of the abdominal cavity from 07.11.2013 (photo from the Dicom archive of Irkutsk Regional Cancer Center): pronounced expansion of the colon 11 cm with a wide horizontal level liguid – gas (showed with arrow)

On the 18th day, the patient developed septic shock symptoms, accompanied by a decrease in the level of consciousness to sopor, hypotension, tachycardia, ineffective independent breathing, a decrease in diuresis below 0.5 ml/kg/h, which required prosthesis of vital functions (ALV, infusion of cardiotonics).

It was decided to perform an emergency relaparotomy. During the revision of the abdominal organs, up to 300 ml of odorless light effusion was determined; the colon was swollen to 8–11 cm in diameter throughout; the loops of the small intestine were collapsed to the level of the ileum, increased in diameter at the level of 30 cm from the ileocecal junction due to the accumulation of gases and liquids. A dense infiltrate consisting of a large omentum and retroperitoneal tissue was determined in the left subdiaphragmatic space. Intraoperatively, a toxic megacolon was diagnosed against the background of PMC, a total colectomy and nasointestinal intubation was performed. A colon stump was formed at the level of the upper ampullary rectum with a machine stitch. The preparation is crossed at the level of the terminal part of the ileum. A terminal ileostomy was performed in the right iliac region.

In the postoperative period, the patient's condition remained extremely severe, and prosthesis of vital functions continued: ALV (mandatory ventilation); administration of inotropic drugs (0.5 % dopamine solution 5–10 μg/kg/min).

Due to the development of acute renal damage of prerenal genesis on the 18th day, the patient required renal replacement therapy (RRT), prolonged veno-venous hemofiltration was performed for 96 hours: Aquarius hemoprocessor (Nikkiso Medical, Japan), Aquamax HF-19 hemofilter (Nikkiso Medical, Japan), anticoagulation – unfractionated heparin with the control of blood clotting time and activated partial thromboplastin time. Antibacterial therapy was performed taking into account creatinine clearance and RRT. During the subsequent course of treatment, the patient underwent 4 sessions of prolonged veno-venous hemodiafiltration.

Postoperative anesthesia was sufficient, prolonged epidural anesthesia was performed with a 0.2 % solution of ropivacaine 16–20 mg/hour. Parenteral nutrition was carried out with combined three-component mixtures containing the 3rd generation of fat emulsions with omega-3 fatty acids.

From the 20th day, doripen was prescribed 500 mg 4 times/day by extended infusion, linezolid 600 mg 2 times/day, continued administration of caspofungin 50 mg 1 time/day. Against the background of intensive therapy, the patient's condition stabilized, positive dynamics was noted, tracheal extubation was performed, the nasointestinal tube was removed, enteral nutrition into the nasogastric tube with standard mixtures was started.

The patient underwent daily sanitation tracheobronchoscopy, ultrasound examination of the pleural cavities, if necessary, thoracocentesis (detection of fluid accumulation in the pleural cavities with atelectasis of the lower lobes of the lungs).

On the 22nd day, chest radiography revealed left-sided lower lobe pneumonia. Due to the progression of respiratory failure on the 24th day, the patient repeatedly required prosthesis of lung function.

On the 30th day, caspofungin was discontinued, voriconazole was prescribed (on the 1st day – 600 mg 2 times/day, then 400 mg 2 times/day), clarithromycin 500 mg 2 times/day was added to the prescribing list.

On the 31st day, a tracheostomy was performed due to the predicted prolonged ALV.

From the 37th day, the patient breathed independently through a tracheostomy cannula with insufflation of moistened oxygen.

On the 43rd day, inhalation of sodium colistimethate through a nebulizer 1 million 2 times/day was added to therapy. The radiological dynamics is positive – by 05.12.2013 the infiltration of lung tissue had regressed.

On the 45th day, the patient was transferred from the Department of Anesthesiology and intensive care No. 4 to the specialized department.

On the 55th day, the patient was discharged in satisfactory condition from the coloproctology department of Irkutsk Regional Cancer Center.

The dynamics of the main laboratory parameters, the days of artificial lung ventilation and medications for antibacterial and antifungal therapy are shown in Figure 4.

DISCUSSION OF CLINICAL OBSERVATION

Thus, the clinical example clearly demonstrates that fulminant clostridial colitis is a life-threatening and severe complication. The literature data suggest that performing a total colproctectomy has been a life-saving surgery for many years. The question of the timeliness of its implementation in this pathology is one of the most difficult. A belated decision can lead to further aggravation of the condition, which manifests itself in the form of acute renal damage, respiratory and cardiovascular insufficiency and, in turn, leads to an increase in the percentage of lethal outcomes.

The treatment of complications in the postoperative period also requires a versatile approach in intensive care, highly qualified personnel, and the availability of expensive equipment for prosthesis of vital functions.

Given that total colproctectomy is a complex surgical procedure that not every surgeon is capable of performing, the issue of deciding on timely surgical treatment in small clinics is very difficult. In such cases, we believe that the issue of timely transfer of the patient to a multidisciplinary institution should be addressed. Such a decision can be made after consultations with expert specialists – both face-to-face and using telemedicine.

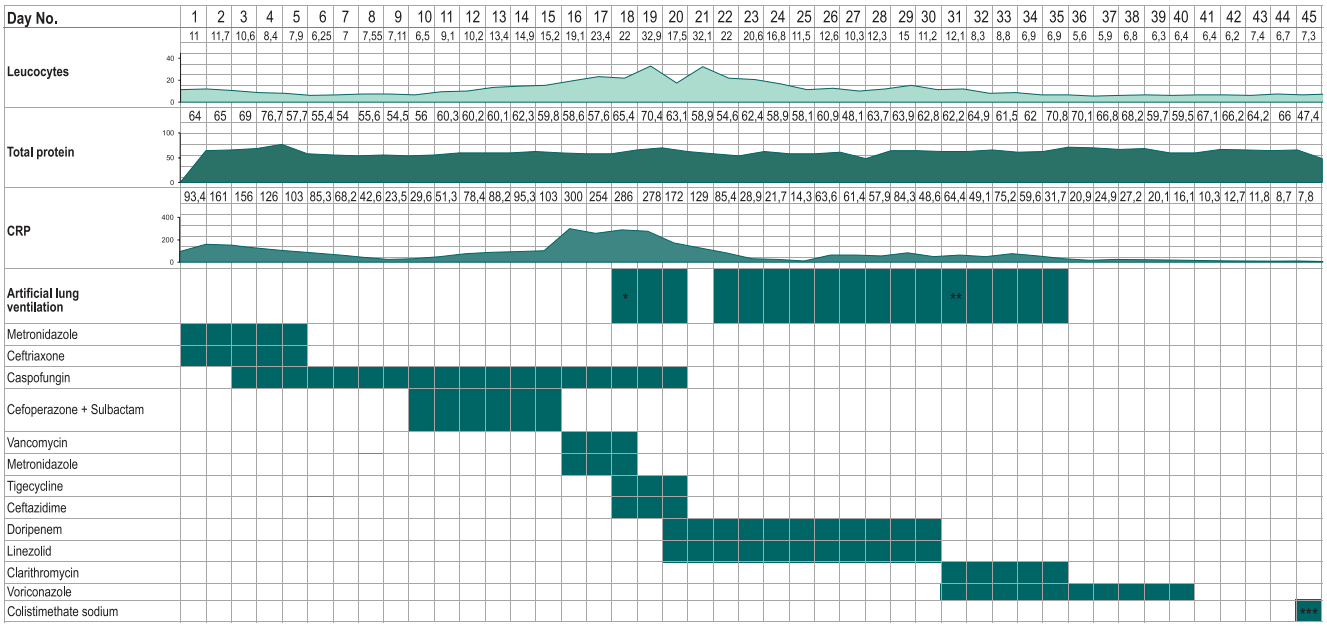

FIG. 4.

*Dynamics of laboratory parameters, days of artificial lung ventilation and medications for antibacterial and antifungal therapy: : * – day of the surgery – colproctectomy; ** – day of the surgery – tracheostomy; *** – administration of sodium colimestate continued until the 55th day*

CONCLUSION

1. In recent years, there has been increased interest in the problem of clostridial infection in clinical practice, in particular, in oncological hospitals. This is due to an exponential increase in morbidity and a high risk of CDI complications.

2. The widespread and uncontrolled use of antibacterial drugs creates prerequisites for the development of resistance of clostridial microorganisms to therapy and the appearance of highly virulent strains of bacteria.

3. The development of pseudomembranous colitis significantly increases the duration of hospitalization, increases treatment costs and can significantly worsen prognosis, increasing the likelihood of death.

4. An important and still unresolved problem is the lack of a unified approach to laboratory microbiological diagnosis of clostridial infection in our country, which leads to a delay in diagnosis, irrational antibiotic therapy and the spread of the pathogen inside the medical institution.

5. To reduce the risk of developing clostridial infection, it is recommended to rationally prescribe antibacterial drugs and reduce, if possible, the duration of hospitalization, especially in people over 65 years of age.

6. When choosing the surgical scope of surgery between total colectomy and hemicolectomy, it is worth remembering that total colectomy is the surgery of choice for patients diagnosed with toxic megacolon. A total colectomy is a potentially life-saving surgery.

7. Postoperative mortality after total colectomy is increased in patients with preoperative acute renal failure, cardiovascular insufficiency requiring vasopressors, and respiratory insufficiency requiring ALV. Therefore, the decision to carry out the surgery should be made before the development of organ failure.

8. A clinical example clearly demonstrates the development of pseudomembranous colitis, complicated by toxic megacolon. The clinical case presented by us represents a late decision on the need for total colproctectomy, which led to the development of multiple organ dysfunction, and only the comprehensive and timely use of respiratory, renal replacement, hepatoprotective, antibiotic and antifungal therapy led to the successful treatment of this patient.

9. In our opinion, the optimal period for surgical intervention was the 16th day. Against the background of deterioration of the general condition, nausea, vomiting, febrile fever, frequent loose stools appeared. During the radiography, a diagnosis of toxic megacolon was made, but at the same time the patient was hemodynamically stable, there were no symptoms of respiratory and renal insufficiency.

Conflict of interest

The authors declare the absence of apparent and potential conflicts of interest related to the publication of this article.

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Information about the authors

Dmitry D. Morikov – Cand. Sc. (Med), Docent, Associate Professor at the Department of Anaesthesiology and Reanimatology, Irkutsk State Medical Academy of Postgraduate Education – Branch Campus of the Russian Medical Academy of Continuous Professional Education; Head of the Intensive Care Unit No. 4, Irkutsk Regional Cancer Center; Teaching Assistant at the Department of Anaesthesiology and Reanimatology, Irkutsk State Medical University, e-mail: mdd71@mail.ru https://orcid.org/0000-0001-7814-511X

Victoria V. Kartashova – Anesthesiologist and Reanimatologist at the Intensive Care Unit No. 4, Irkutsk Regional Cancer Center, e-mail: viktoria3251@rambler.ru, https://orcid.org/0000-0002-9431-8858

Aleksei V. Shelekhov – Dr. Sc. (Med.), Head of the Department of Oncology and Radiation Therapy, Irkutsk State Medical University, e-mail: avshirkru@yandex.ru, https://orcid.org/0000-0001-6666-5951

Nadezhda A. Nikolaeva – Coloproctologist at the Coloproctology Department, Irkutsk Regional Cancer Center, e-mail: Drnikolaeva@bk.ru, https://orcid.org/0000-0002-0475-864X