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CROHN'S DISEASE AND MULTIPLE MYELOMA: A CLINICAL CASE AND LITERATURE REVIEW

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Crohn's disease and multiple myeloma are pathological entities, the development of which, at least in part, is associated with an immune dysregulation. Crohn's disease is often combined with extra-intestinal manifestations from different organs and systems (joints, skin, eyes, etc.). Hematological extra-intestinal manifestations, such as myelodysplastic syndrome, aplastic autoimmune anemia, autoimmune thrombocytopenia, B12-deficiency anemia are less common. The list of extra-intestinal manifestations of Crohn's disease is constantly expanding, including more and more descriptions of the combination of Crohn's disease with diseases of the blood system. The paper presents a rare clinical case of a combination of Crohn's disease and multiple myeloma.

The female patient is 53 years old. In 1993 ulcerative colitis was diagnosed and she received Sulfasalazine 4gr per day. In 2015, with the recurrent attack, the diagnosis was transformed towards Crohn's disease basing on colonoscopy. She received steroid therapy. In 2018 the control examination revealed an increase in the level of total protein to 117gr/l. Patient underwent a sternal biopsy. Multiple myeloma was diagnosed on the basis of a myelogram.

[Key words: inflammatory bowel disease, Crohn's disease, multiple myeloma, aplastic anemia, cobalamin deficiency, extraintestinal manifestation]

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INTRODUCTION

The combination of multiple myeloma (MM) and Crohn's disease (CD) in one patient is an extremely rare clinical situation. Only 11 such cases have been published in the literature to date, and only 16 patients, comorbid in MM and IBD (search for keywords «plasmacytoma», «multiple myeloma», «inflammatory bowel diseases», «ulcerative colitis», «Crohn's disease») [1-13], while none – in Russian (search in the database library for keywords «plasmocytoma», «multiple myeloma», «inflammatory bowel disease», «Crohn's disease», «ulcerative colitis»). Therefore, we found it interesting to publish another such case that took place in our practice.

CLINICAL OBSERVATION

Patient X., female, aged 53, first entered the gastroenterology and hepatology unit in 2015 with complaints of liquid stools up to 5-6 times a day with a mixture of mucus, periodical pain in the left abdomen. From the history it is known that the patient, in 1993 at the place of residence, was diagnosed left-sided ulcerative colitis by colonoscopy. The patient received

Sulfasalazine 4g per day with a positive effect. There after, the patient independently periodically took sulfasalazine 2-3 g per day, was not examined, and did not go to see doctors.

Deterioration was noticed in 2015, when there was a frequent liquid stool up to 10 times a day with a mixture of mucus and blood, abdominal pain, fever up to 37.5 C. The patient was hospitalized at the place of residence. During hospitalization sigmoidoscopy was performed. The identified erosive and ulcerative changes in the mucosa were regarded as an acute ulcerative colitis. Given the clinical and endoscopic picture, the patient was prescribed prednisolone 120 mg /i.v. Then the patient was transferred to our clinic.

At the time of admission, the patient received i.v. steroids for 5 days. During this time, the frequency of the stool decreased twice, almost completely disappeared admixture of blood in the stool, but remained fever and abdominal pain. The examination was continued.

Taking into account the incomplete examination of the colon in the previous endoscopic study, a colonoscopy with an examination of the terminal part of the ileum was performed again (Fig. 1).

The Ileum segment of 15 cm long was examined – mucosal layer was pink, velvety, villi were not thickened.

The dome of the cecum was straightened by insufflation, the lumen was not deformed, the folds were preserved, the mucosal layer was pink, the vascular pattern was clear. In the ascending, transverse, descending colon, sigmoid colon folds were preserved, tone was low, peristalsis was active, mucosal layer was pink, vascular pattern was lubricated. Against the background of virtually unchanged mucosa, multiple slit-like ulcers in the sigmoid, descending colon, transverse colon and ascending colon were determined. There was no contact bleeding. Rectum was intact. The revealed changes in the colon mucosa allowed to reconsider the diagnosis in the direction of CD. **New diagnosis:** active CD with lesions of the colon (ascending, transverse, descending colon and sigmoid), luminal form, moderate severity. The patient continued corticosteroid therapy with a positive effect – all clinical symptoms stopped. The patient was discharged with recommendations to gradually reduce the dose of prednisolone until complete withdrawal. She was prescribed azathioprine 150 mg per day and re-hospitalization for control colonoscopy in a year. However, a year later the patient did not appear for a control examination, because she felt well. Azathioprine was not taken due to the lack of the drug in the pharmacy network. The clinical remission lasted 3 years without maintenance therapy. Another recurrent acute attack with an increase in stool up to 5 times a day with an admixture of mucus took place in March 2018, resulting in re-hospitalization in the clinic. The patient underwent colonoscopy (Fig. 2). The device was entered in the ileum at 20 cm, the lumen of the intestine was not deformed, the folds were well expressed, the mucosal layer was pink, velvety. Dome of

the cecum: the lumen of the dome was not deformed, mucosal layer was pink. The mouth of the appendicular process was closed. Bauhinia lip-shaped valve was pink. Ascending, transverse, descending intestine: the folds were smoothed all the way through, the lumen was slightly narrowed, the vascular pattern was preserved, multiple whitish scars were revealed, in the sigmoid colon, the vascular pattern was rebuilt according to the type of mesh, single afts were visible. Rectum: folds were preserved, mucosal layer was pink, vascular pattern was clear. The general blood analysis revealed anemia (hemoglobin 93.7 g/L, red blood cells $3.02 \times 10^{12}/L$, anisocytosis, poikilocytosis), lymphocytosis (57.7%), ESR 64 mm/h. Of laboratory indicators a dramatically increased level of total protein was noted, which was not at the previous hospitalization. Biochemical blood test in comparison with 2015 is given in table 1. Electrophoresis of serum proteins showed no abnormalities (M-gradient was not detected). No Bens-Jones protein was found in the urine. No significant destructive changes were found on the x-rays of the skull bones. A sternal puncture was performed – a significant increase in the number of plasma cells, a decrease in the number of myelocytes and segmental neutrophils were revealed. Based on the results of sternal puncture (Table 2), multiple myeloma was diagnosed (MM) in the 3d stage. Given the low activity of Crohn's disease, the patient was prescribed only azathioprine 150 mg per day. Further treatment was continued at the department of hematology, where due to the MM the induction chemotherapy with the targeted drug – the proteasome Bortezomib inhibitor – was assigned. Against the

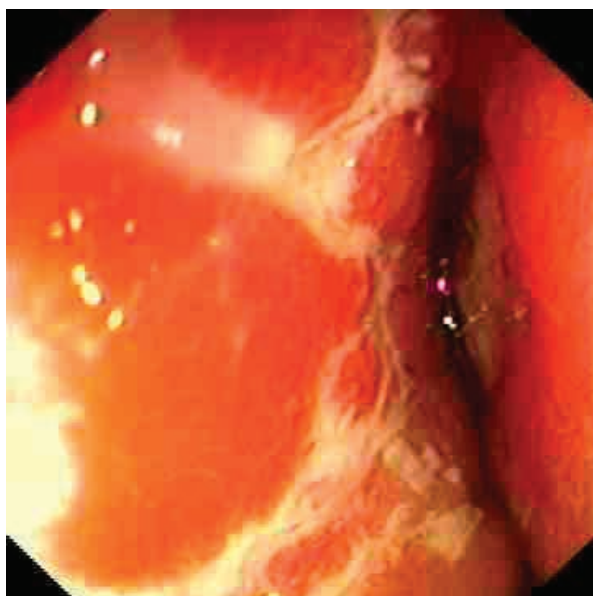


Figure 1. Slit-like ulcers of the mucosa of the sigmoid colon during colonoscopy in a female patient X., 2015



Figure 2. Aphthous lesions of mucosal layer of the sigmoid colon during colonoscopy in patient X., 2018

Table 1. Laboratory parameters of patient X

Indicators	2015	2018	Reference values
Total protein, g/l	68	117	64-83
Albumin, g/l	34	37	35-52
Alanine aminotransferase, U/l	16	15	0-40
Aspartate aminotransferase, U/l	15	12	0-40
Ferrous, $\mu\text{mol/l}$	9,8	15,7	6,6-28,3
CRP, mg/l	6,4	4,4	0,01-4,99
Hemoglobin, g/l	105	93,7	120-140
White blood cells, $\times 10^9/\text{l}$	9,2	10,9	4,0-9,0
Lymphocytes, %	19	57,7	19-37
ESR, mm/h	21	64	2-15

Table 2. Myelogram of patient X

Indicator	Value	Reference values
Blasts, %	1,2	0.4-1.6
Neutrophil Myelocytes, %	2,6	7-12.2
Neutrophil Metamyelocytes, %	7,2	8-15
Stab neutrophils, %	4,0	12.8-23.7
Segmental neutrophils, %	12,0	13.1-24.1
Segmental eosinophils, %	0,6	0.4-2.4
Segmental basophils, %	0,4	0-0.5
Monocytes, %	1,2	0.7-3.1
Lymphocytes, %	9,2	4.3-13.7
Plasma cells, %	57,0	0.1-1.8
Erythroblasts, %	0,2	0.2-1.1
Basophilic normocytes, %	0,4	1.4-4.6
Polychromatophilic normocytes, %	2,0	8.9-16.9
Normocytes, oxyphilic, %	2,0	0.8-5.6
Megakaryocytes in smears, the amount in the preparation	single cells in the preparation	Up to 10 in the preparation

background of this therapy, within 2 months in the patient peripheral blood parameters and the level of total protein of 69 g/l almost completely normalized. The patient continues to receive Bortezomib against the background of anti-relapse therapy of Crohn's disease with azathioprine 150 mg in the complete absence of intestinal symptoms.

DISCUSSION

The etiology of both Crohn's disease and multiple myeloma has not been established to date, but the pathogenesis of both diseases, at least in part, is caused by immune disorders – excessive production of proinflammatory cytokines, primarily interleukin 6 (IL-6) and interleukin 1b (IL-1b) [14,15]. In IBD, the first line of mucosal protection, including secretory IgA or mucus production, is often compromised, leading to a systemic response to antigens that have penetrated the intestinal mucosa barrier, and activation of B-lymphocytes and plasmocytes [5,13,16]. Chronic stimulation of B-lymphocytes promotes PC monoclonal

proliferation and sometimes leads to monoclonal gammopathy of uncertain genesis (MGNG) [17]. It should be borne in mind that the inflammatory infiltrate of the intestinal wall in CD consists not only of lymphocytes, but, to a large extent, of plasma cells. In turn, many MM cases arose from MGNG as a result of a number of genetic disorders [18]. On the other hand, long-term use of the main groups of drugs used in Crohn's disease: glucocorticosteroids, cytostatics and antibodies to tumor necrosis factor- α (TNF- α) – according to a number of reports may increase the risk of malignant tumors, and the development of MM is not an exception. In addition, among the possible risk factors for MM, the effect of ionizing radiation is discussed, and in Crohn's disease, patients are often exposed to relatively large doses of ionizing radiation throughout their disease, which can also be a risk factor for MM. Since there are common mechanisms in the pathogenesis of both diseases, there may be a causal relationship between CD and MM.

For the first time plasmacytosis in a patient with IBD (ulcerative colitis) was described in 1952 by Fadern R.S. [19]. In 1964, Bernstein J.S. and Nixon D. discussed

Table 3. List of published cases of combination of GCS and MM (by G. Reynolds [8] with supplements and clarifications)

Author, year	Basic diagnosis, localization	Age/sex	The treatment of IBD	The duration of IBD before the MM's debut
Haeney M.R., 1977 [1]	ulcerative colitis, proctosigmoiditis	63/M	Sulfasalazine, cyclophosphamide + GCS	6 months
Haeney M.R., 1977 [1]	ulcerative colitis, proctosigmoiditis	61/F	Sulfasalazine, steroid foam	3 years
Robertson E.J., 1986 [2]	CD, terminal ileitis	66/F	Resection	14 years
Nakajima H., 1990 [3]	CD, ileocolitis	36/M	Observation	45 months
Ligato S., 1996 [4]	CD, ileocolitis	45/M	Unspecified	13 years
Minami A., 1999 [5]	Total ulcerative colitis	58/F	Sulfasalazine	5 years
Minami A., 1999 [5]	CD, ileocolitis	59/F	Prednisone, 5-ASA	9 years
Mateja F., 2000 [6]	CD, localization unspecified	63/M	Unspecified	Unspecified
Freeman H.J., 2002 [7]	CD, terminal ileitis	68/M	Sulfasalazine, resection	30 years
Reynolds G.J., 2007 [8]	CD, ileocolitis	50/F	Azathioprine, mercaptopurine, infliximab	5 years
Liu H., 2008 [9]	ulcerative colitis, length unspecified	49/F	Daclizumab, 5-ask	14 years
Liu H., 2008 [9]	CD, localization unspecified	50/M	Resection, infliximab	6 years
Talamo G., 2010 [10]	CD, localization unspecified	57/M	Azathioprine	Unspecified
Yadav S., 2013 [11]	ulcerative colitis, length unspecified	40/M	5-ASA, infliximab	22 years
Schrenk K.G., 2015 [12]	CD, localization unspecified	57/F	Unspecified	Unspecified
Park S.Y., 2017 [13]	CD, localization unspecified	36/M	Azathioprine, 5-ASA, GCS, infliximab, adalimumab	16 years
2018	CD, colon	58/F	glucocorticosteroids	25 years

a patient with ulcerative colitis, in whom MM was diagnosed against the background of bone marrow plasmacytosis of 19.5-21.5% [20]. Since that time, methods and criteria for the diagnosis of both IBD and MM have advanced significantly, but since 1964 up to date, only 16 cases of combination of MM and IBD have been published [1-13], of which eleven patients had Crohn's disease and five-ulcerative colitis (Table 3).

Of the sixteen cases, previously published in the literature, of association of IBD with MM, seven were male and nine were female patients. The duration of IBD before diagnosis of multiple myeloma ranged from 6 months to 30 years, median 9 years. As for the treatment of IBD, only five of these patients received antibodies to TNF- α , (four received infliximab, which in 1 case was replaced by adalimumab, one patient received in the clinical study daclizumab). Treatment of four patients included cytostatic therapy (1 patient received cyclophosphamide, three – azathioprine, which in one female patient was replaced by 6-mercaptopurine), three systematically received steroids, 5 patients did not receive immunomodulatory therapy. Three publications do not contain information on therapy of IBD.

Since the combination of MM and CD is casuistic, there are no epidemiological data on its incidence. However, several population-based studies have been conducted to find the association of inflammatory bowel diseases with lymphoproliferative diseases [7,8,13,21-24]. In 1981, Greenstein et al. described an increase in the incidence of lymphomas in 1,227 CD patients, presumably associated with immunodeficiency and the use of immunosuppressive drugs or with increased exposure to ionizing radiation [25].

However, the 1985 study by the same authors, which included 734 more patients with IBD (1,961 in total), did not reveal a statistically significant increase in the incidence of extra-intestinal neoplasms in patients with ulcerative colitis and CD, with the exception of non-Hodgkin's lymphomas [24]. The tendency to increase the risk of lymphomas in CD in the work of Persson, P. et al. was not statistically significant [22]. In the work of Arseneau K. and co-authors [21], published in 2001, the two-year cumulative incidence of lymphoid/myeloid malignancies in CD was 3.87/1000 versus 2.12/1000 in the control. The authors did not separate lymphoid and myeloid neoplasia and took into account only in-patient cases of CD [21].

Freeman H. of 1,000 patients with CD reported 5 cases of myeloid and lymphoid neoplasia, including 1 MM case, i.e. a significant increase in cumulative age-standardized incidence of these nosologies compared to control [7]. Later large population studies [26, 27] did not reveal an increased risk of lymphoproliferative diseases in Crohn's disease, with the exception of patients treated with thiopurines [28].

CONCLUSION

The case presented in this article demonstrates a rare combination of CD and MM. The question of whether MM is extra-intestinal, i.e. pathogenetically associated with CD, a manifestation or an independent disease, remains open. Our female patient did not have currently

discussed factors that trigger the development of MM: she was not subjected to x-ray examinations with high radiation exposure, the patient began to take immunosuppressants (azathioprine) when the MM had already been revealed. It is likely that both diseases are caused by immunodeficiency and the same cytokines are involved in their development. The relationship between CD and MM requires further in-depth study. The question of treatment of CD in our patient is still problematic, because azathioprine theoretically increases the risk of lymphoproliferative diseases. The drug was prescribed due to the low activity of CD and the need to treat MM with genetically engineered biological drug. In the future, an option with the use of biological drugs for CD may be considered.

The authors declare no conflicts of interest.

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