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Effect of cytomegalovirus infection on moderate and severe ulcerative colitis

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ABSTRACT *AIM: to evaluate the effect of cytomegalovirus (CMV) infection on the course of moderate and severe flare ups of ulcerative colitis (UC).*

PATIENTS AND METHODS: a prospective cohort single-center study was done in September 2018 — December 2020. The study included patients with moderate and severe flare ups of UC. All patients underwent colonoscopy with biopsy to quantify CMV DNA by polymerase chain reaction (PCR). Subsequently, the patients were divided into subgroups: with the presence of CMV (CMV+) and its absence (CMV–). In the CMV+ subgroup, antiviral therapy was carried out with an assessment of virological, clinical and endoscopic results on the 19th day of therapy, one month after and after 6 months. In the CMV– subgroup these results were evaluated after 6 months only.

RESULTS: the study included 126 patients. CMV was detected in 51 (40.5%). At the same time, its presence was not influenced by gender, age, or previous therapy. Laboratory indicators in both subgroups were comparable, as well as the severity of UC. A significant increase in the risk of steroid resistance was revealed in CMV+ patients with severe UC attack (OR 1.33, 95% CI: 1.059–19.4). The effectiveness of antiviral therapy was 60.8%. All patients who did not respond to antiviral therapy underwent surgery. At the same time, among patients in whom antiviral therapy was effective (virus eradication was achieved), there was no need for surgery.

CONCLUSION: CMV infection significantly increases the likelihood of steroid resistance in patients with severe flare up of UC, while all patients who responded to antiviral therapy did not require surgery. Further multicenter randomized trials are needed.

KEYWORDS: *ulcerative colitis, cytomegalovirus infection, antiviral therapy*

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INTRODUCTION

Ulcerative colitis (UC) is a chronic autoimmune disease of the colon, characterized by inflammation of its mucous membrane [1]. The prevalence of ulcerative colitis in the world is about 505 per 100,000 people, while severe and moderate flare-ups occur in 45% of cases [2]. The incidence and prevalence of UC, along with Crohn's disease (CD), is highest in the industrialized countries of Western Europe and North America. In recent years, there has also been an increase in these indicators in developing countries, probably due to changes in environmental factors, such as a refined diet, changes in the intestinal microbiota, uncontrolled use of antibiotics, environmental pollution, etc. [3-9]. The UC etiology has not established yet. The most important risk factors for developing UC that are currently known include smoking cancel [10-12], uncontrolled use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, vaccination and heredity [13-15]. The choice of treatment is determined by the severity of the

Table 1. *Predictors of CMVI risk*

Factor	Regression coefficient	OR	95% CI	*p*
Disease duration	–0.007	0.99	0.99–0.10	0.027
Partial Mayo Index	0.312	1.37	1.09–1.72	0.008
GCS > 20 mg/day	0.887	2.43	1.44–4.03	0.001
TNF-α blockers	2.41	11.13	3.31-37.44	0.001
The extent of the lesion	0.668	1.95	0.77–4.96	0.160

current flare-up, the extent of the bowel lesion, the presence of extraintestinal manifestations, the duration of the disease, the effectiveness and safety of previous therapy, as well as the presence of UC complications [16].

In the treatment of moderate and severe flare-ups of ulcerative colitis, systemic steroids traditionally used to stop the inflammatory process quickly. However, 10-15% of patients have steroid resistance [17-19]. Concomitant active CMV infection, which occurs in 43% of patients with steroid resistance, plays an important role in its development [20,21]. First, the occurrence of CMV infection is facilitated by a decrease in immunity, which is typical for patients suffering from IBD and receiving immunosuppressive therapy. In the latent form, lifelong persistence of the virus is possible, which observed in 45-85% of cases. In this group of patients, CMVI is a serious threat to life, since during the generalization of infection, any organ, including vital, can be affected [22]. In addition, the relationship between CMVI and the severity of IBD, as well as the refractoriness to anti-inflammatory therapy, has now been proven [23,24].

Clinical manifestations characteristic of IBD (such as diarrhea, blood in the stool, fever, etc.) are non-specific and can occur in some infectious diseases. In addition, in IBD, there may be an association of IBD flare-ups with various infectious agents. The addition of these agents, as a rule, aggravates the underlying disease. Gecse K.B. and Vermeire S. (2018) emphasize the importance of accurately determining the cause that aggravates the IBD course [25]. A group of Chinese scientists led by Li Y. conducted a retrospective study of cases of IBD associated with Cl. difficile in patients hospitalized from January 2010 to December 2015, and concluded that with mixed infection (CMV and Cl. Difficile), the course of IBD is associated with worse outcomes [26]. Rowan C. with co-authors (2018) recommend to make diagnostic tests for the detection of CMVI markers in all patients with IBD with fever [23]. In 2015, the National Center for Children's Health of the Russian Academy of Sciences checked up 43 children with IBD for the presence of viral infection. In 88.4% of patients, active forms of herpes virus infection were confirmed, and in 16.3% of cases, active CMVI was detected, the presence of which caused a more severe course of the disease [27].

The study of Nowacki T.M. et al. also confirms the pathogenetic significance of CMV in ulcerative colitis. Cytomegalovirus colitis is often found in patients with severe UC forms.

It was found that the clinical activity of UC, the duration of the disease, the prevalence of the lesion, as well as the use of steroids and anti-TNF-α drugs are risk factors for the development of CMV colitis ($p < 0.05$). Based on five predictors, a CMV-colitis risk scale was developed. A strong correlation was found between some predictors and the incidence of CMV colitis (AUC: 0.855; 95% CI 0.79–0.92; $p < 0.0001$) (Table 1) [28]. The predictor scale determines the risk of developing CMV-colitis and can help to conduct a timely diagnosis of CMV, as well as the choice of treatment approach, especially if timely optimization of therapy is necessary in the absence of reliable diagnostic tests [28].

In a number of patients with the IBD remission, the presence of CMV in the large bowel mucosa persists, despite the absence of endoscopic activity [29]. This fact indicates that CMV does not always cause a recurrence of the disease or aggravates it. Now, there is no clear understanding of how the presence of CMV affects the severity of

Table 2. *Patients' demographics and clinical features*

Indicators	Indicator values
Gender (m/f), *n* (%)	78/48 (61.9/37.1)
Median age, years (M ± m)	37.8 ± 12.7
Assessment on the general Mayo scale, *n* (%)	
3-6 scores	0 (0)
7-9 scores	92 (73)
10-12 scores	34 (27)
Severity of the disease, *n* (%)	
Medium-severe	91 (72.2)
Severe	35 (37.8)
Acute flare ups, *n* (%)	12 (9.5)
Albumin, g/l (M ± m)	35.5 ± 5.6
Hemoglobin, g/l (M ± m)	112.2 ± 24.3
C-reactive protein, mg/l	43.3
Total protein, g/l (M ± m)	63.2 ± 8.5
Leukocytes, $*10^9$/l (M ± m)	8.4 ± 3.5
Steroid resistance, *n* (%)	32 (25.4)
Steroid dependence, *n* (%)	41 (32.5)
Endoscopic activity, Schroeder scores (%)	
Minimum (1)	9 (7.1)
Moderate (2)	57 (45.2)
Expressed (3)	60 (47.6)

Table 3. *Previous treatment for UC in patients with CMVI+ and CMVI–*

	Group CMV+	Group CMV–
Without therapy, *n* (%)	8 (15.7)	12 (16.0)
5-ASA, *n* (%)	29 (56.9)	45 (60)
Thiopurines, *n* (%)	10 (19.6)	14 (18.7)
Infliximab, *n* (%)	4 (7.8)	3 (4.0)
Adalimumab, *n* (%)	1 (2.0)	0 (0.0)
Golimumab, *n* (%)	1 (2.0)	5 (6.7)
Vedolizumab, *n* (%)	2 (3.9)	2 (2.7)
Tofacitinib, *n* (%)	1 (2.0)	3 (4.0)

the IBD course, its refractoriness to therapy and how necessary it is for specific antiviral therapy. However, this is only one side of the problem.

The second, no less important aspect is associated with the widespread use of immunosuppressors in the treatment of patients with UC and CD with a high risk of infectious complications against the background of ongoing therapy. When treating patients with immunosuppressive drugs, there is a high probability of an association of UC with opportunistic infections, which sometimes, with the generalization of these infections, can lead to a fatal outcome [23]. It should also be noted that antiviral therapy reduce the risk of complications and the incidence of colectomy [24]. At the same time, antiviral therapy is not mandatory for all UC patients with CMVI [25].

In this regard, we started our own study, the purpose of which was to clarify the role of cytomegalovirus infection during ulcerative colitis in patients with severe and moderate flare-ups.

PATIENTS AND METHODS

The study included 126 patients with severe and moderate UC flare-ups, from September 2018 to December 2020. The main demographic and laboratory data of patients presented in Table 2.

The severity of the UC flare-up was estimated based on the Mayo index. In addition to the severity of the UC flare up, the concepts of steroid resistance and steroid dependence were important. According to the existing clinical guidelines, the steroid resistance is the lack of improvement in clinical and laboratory indicators during therapy with systemic steroids at the rate of 2 mg/kg of body weight per day in prednisone terms for 7 days with a severe flare-up, and the absence of such a response during therapy with steroids at a dose of 1 mg/kg per day in prednisone terms for 2 weeks with a moderate flare up. Steroid dependence is an increase in the activity of the disease with a decrease in the dose of steroids with an initial improvement or within 3 months after complete withdrawal of steroids [1]. All the patients (n = 126) underwent colonoscopy with biopsies from the sigmoid colon with a size of about 2 mm. The biopsies were placed in a sterile container with 10 ml of 0.9% sodium chloride solution. The CMV DNA was determined in the biopsies by quantitative PCR on an automatic Light Cycler-96 amplifier (Roshe, Germany).

Table 4. *Laboratory data in the groups*

Indicator	Group CMV+ (*n* = 51)	Group CMV– (*n* = 75)
Albumin, g/l Me (5%; 95%)	35 (32; 36.1)	35.8 (33.7; 36.4)
Hemoglobin, g/l Me (5%; 9%)	111.6 (109.7; 113.6)	114.1 (110.7; 114.8)
C-reactive protein, mg/l M ± m	32.8 ± 38.7	49.7 ± 58.4
Total protein, g/l Me (5%; 95%)	62.3 (61; 63.8)	61.3 (61; 63.9)
Leukocytes, $*10^9$/l M ± m	8.6 ± 3.9	8.3 ± 3.9

After determining the CMV DNA, the patients were divided into two groups depending on the presence or absence of CMV in the biopsy: "CMV-positive" (CMV+) and "CMV-negative" (CMV–). The CMV+ patients, along with the therapy, were prescribed ganciclovir at the rate of 5 mg/kg twice a day for 21 days. The clinical and endoscopic response in patients, and in the CMV+ patients the results of antiviral therapy, were evaluated in 6 months after discharge from the hospital.

The level of hemoglobin, albumin, total protein, C-reactive protein, the number of leukocytes, erythrocytes were evaluated in all the patients on the day of admission to the hospital.

The statistical analysis was carried out using the software IBM SPSS Statistics 24.0. and STASTICA 7.0. The analysis of qualitative parameters was carried out by occurrence rate. To describe the quantitative variables, the methods of descriptive statistics were used: mean, standard deviation (M ± m). The Spearman correlation test was considered significant at $p < 0.05$. When using the rank correlation test, the relationship between the signs was evaluated on the Cheddock scale, considering the values of the coefficient less than 0.3 — a sign of weak relationship; values of more than 0.3, but less than 0.7 are a sign of moderate correlation, and values of 0.7 or more are a sign of high correlation. The odds ratio (OR) was calculated as events in one group to the risks of events in the other group, with 95% coincidence intervals (CI) were calculated with the conjugacy tables using logistic regression analysis.

RESULTS

The CMV DNA in biopsies was detected in 51 (40.5%) of 126 patients. The average age of the CMV+ patients (*n* = 51) was 35.0 years, the CMV– patients (*n* = 75) — 35.6 years. In both groups, the males prevailed: in the CMV+ group — 72.5%, in the CMV– group — 54.7%. In the CMV+ subgroup of the patients, a severe UC flare-up was registered in 14 (27.5%) cases, and among the CMV– patients — in 21 (28.0%) cases ($p > 0.05$). Acute UC flare up among the CMV+ patients was noted in 8 (15.7%) cases, among the CMV-negative — in 4 (5.3%) cases ($p > 0.05$). Accordingly, high endoscopic activity in the bowel was detected in 22 (41.3%) and 38 (50.7%) patients ($p > 0.05$). The results obtained demonstrate that the nature and severity of the flare-up has no correlation with the CMV infection. There are no clinical signs that could more or less likely predict the presence/absence of this infection. It should also be noted that there are no differences in the previous UC therapy in the CMV+ and CMV– patients (Table 3).

Eleven (21.6%) CMV-positive patients and 9 (12.0%) CMV-negative patients ($p > 0.05$) received steroids before the UC flare-up. It is important to emphasize that among the CMV-positive patients, steroid dependence revealed in 16 (31.4%) cases, and among CMV-negative patients — in 33.3%. Accordingly, steroid resistance was detected in 17 (33.3%) and 15 (20.0%) cases. CMVI did not significantly affect the rate of steroid resistance or steroid dependence. However, the analysis revealed a significant increase in the risk of steroid resistance in the CMV+ patients among patients with severe UC flare-ups (OR-1.33; 95% CI-1.059-19.4). The average number of copies of the CMV DNA in a biopsy of the bowel mucosa 12939 +/– $5675*10^5$cells. There was no significant difference in the main laboratory indicators characterizing the severity and activity of the inflammation between the groups ($p > 0.05$) (Table 4).

Table 5. *Distribution of the prospective group according to clinical and endoscopic changes*

Indicator	CMV+ (*n* = 51)	CMV– (*n* = 75)	*p*
Clinical improvement after 6 months, n (%)	18 (35.3)	21 (28.0)	0.39
Endoscopic improvement after 6 months, n (%)	28 (54.9)	25 (33.3)	0.13
Clinical and endoscopic remission after 6 months, n (%)	14 (27.5)	23 (30.7)	0.77

It should be emphasized that among the CMV-positive patients receiving antiviral therapy, colectomy was performed in 8 (15.8%) of 51 patients, among the CMV-negative patients — in 9 (12.0%) of 75 patients ($p > 0.05$). This fact indicates that the results of the therapy in the CMV-positive patients are comparable to the results of the standard therapy in the CMV-negative patients. All the patients from the CMV+ subgroup who underwent colectomy had no response to the antiviral therapy. The changes of the patients' condition according to the main clinical indicators is presented in Table 5.

The effectiveness of the antiviral therapy, according to the data obtained, was 60.8% with respect to the elimination of the virus from the mucosa. Thus, in the diagnosis and treatment of severe and moderate UC flare-ups, information is needed about the presence of concomitant CMV infection in the mucosa in the patient. As follows from the study, about 50% of severe and moderate UC flare-ups go together with the CMV infection. At the same time, neither gender, nor age, nor previous steroids, immunosuppressors, biologic therapy nor the onset of the disease with a severe or moderate flare-up are risk factors for the CMV infection. The data obtained differ somewhat from the results of German authors, who attributed male gender, age over 60 years and previous steroid therapy to the risk factors for the CMVI against the background of UC [28]. According to the results obtained, CMV infection increases the risk of developing resistance to therapy in severe UC flare-ups. If antiviral therapy is effective in patients with concomitant active CMV infection, the risk of colectomy significantly reduced.

CONCLUSION

We found that the prevalence of CMV infection among patients with severe and moderate UC flare-ups is 40.5%. CMV infection significantly affects the steroid resistance in patients with severe UC flare-ups. The effectiveness of antiviral therapy is 60.8% and clinical and endoscopic improvement detected in all patients who responded to antiviral therapy. The lack of response to antiviral therapy is a unfavorable factor in relation to the risk of a colectomy.

The association of CMVI and IBD is an insufficiently studied problem that presents serious difficulties for gastroenterologists and coloproctologists. It should not be forgotten that the issue of antiviral therapy in patients with IBD should be decided individually in each case. According to the majority of specialists involved in the treatment of inflammatory bowel diseases, it is necessary to conduct multicenter controlled studies to assess the need and effectiveness of antiviral therapy for CMVI [29].

AUTHORS CONTRIBUTION

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