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Translation of the article

CYTOMEGALOVIRUS INFECTION IN PATIENTS WITH MODERATE AND SEVERE ULCERATIVE COLITIS

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AIM: to determine the incidence of accompanying cytomegalovirus infection (CMVI) in patients with moderate and severe ulcerative colitis, and also to determine the value of diagnosis and treatment of this infection in that category of patients.

PATIENTS AND METHODS: the study included 67 patients with severe or moderate ulcerative colitis. The colonoscopy with biopsy with definition of cytomegalovirus DNA by polymerase chain reaction (PCR) was done in all the patients. The patients without virus (CMV negative group) received therapy according to the current clinical recommendations. The patients with virus (CMV positive group) had antiviral therapy by ganciclovir in addition to the standard therapy. The viral load in colonic biopsy of those patients was evaluated before the treatment and on the 19-21st therapy days. In case of patient state deterioration and inability to continue the conservative treatment, colectomy was done. The success of therapy in both groups was assessed by the colectomy rate during hospitalization.

RESULTS: the incidence of severe and moderate ulcerative colitis combination with cytomegalovirus infection was 43.2%. The previous treatment did not influence on the probability of virus detection. Acute attacks of ulcerative colitis were found significantly more often in the CMV-positive group than in the CMV-negative group (20% vs 2.6%, respectively) (p=0.02). The efficacy of the antiviral therapy was 69%. All the patients who responded to the antiviral therapy did not undergo surgery. Failure of the antiviral therapy in the patients with associated cytomegalovirus infection significantly increased the colectomy rate (0 – in the patients who responded to the antiviral therapy vs. 22.2% of those who did not respond).

CONCLUSION: the study showed 43% of cases moderate and ulcerative colitis goes with CMVI persistence. CMVI is the resistance factor for conservative treatment. The specific antiviral therapy in addition to the conservative treatment for this category of patients ameliorates the treatment results and prognosis.

[Key words: cytomegalovirus infection (CMVI), inflammatory bowel disease (IBD), ulcerative colitis (UC)]

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease characterized by immune inflammation of the mucosa [1]. In the treatment of ulcerative colitis, drugs with immunosuppressive effects are used [2].

Cytomegalovirus infection (CMVI) is an important factor that aggravates the course of UC and leads to hormonal resistance and resistance to immunosuppressive therapy.

A special danger of this infection is the possibility of its generalization, which can lead to a heavier course of the main disease [3].

Active CMVI traditionally refers to opportunistic infections, since the detailed clinical picture of the disease develops, as a rule, in individuals with immunosuppression.

The prevalence of active CMVI in UC patients is high: 40-57% in patients with severe UC attack and 31-36% in patients with hormone resistance [4].

Cytomegalovirus infection (CMVI) is an anthroponotic infectious disease caused by cytomegalovirus (CMV),

with various transmission routes, characterized by damage to any organs and tissues [5].
CMVI occurs in 40-100% of adults [2]. The share of seropositive persons in relation to CMV in the Russian Federation is 77-90%. CMVI is often asymptomatic and does not lead to serious consequences. However, in patients with immunosuppression, CMV infection can lead to severe organ damage [6].
Traditionally, patients with UC are treated with systemic immunosuppressors (glucocorticosteroids, azathioprine, antibodies to the tumor necrosis factor-alpha), which increases the risk of CMV infection [9, 10].
The difficulty in diagnosing CMVI in patients with ulcerative colitis is that there are no characteristic endoscopic signs of such an association [9,10].
Serological methods of investigation have low sensitivity, as well as the determination of CMV DNA by polymerase chain reaction (PCR) in blood [11-13].
An informative method for diagnosing the association of UC with CMVI is the determination of CMV DNA by PCR in a bowel mucosa biopsy [13,15-17].
CMVI treatment in patients with UC is performed with ganciclovir at the rate of 5 mg/kg twice a day for 14-21 days [18].

AIM

To reveal the rate and significance of diagnosis and treatment of concomitant cytomegalovirus infection (CMVI) in patients with moderate and severe attacks of ulcerative colitis (UC), as well as to reveal colectomy rate depending on the presence of CMVI and on the conducted therapy.

PATIENTS AND METHODS

The study included 67 patients with severe and moderate UC attacks, who were hospitalized in the gastroenterology department from September 2018 to December 2019.
The severity of the patients' status was assessed by the Mayo index [19]. A moderate attack was detected at the Mayo index value of 6-9, a severe attack – at the Mayo index value of 10-12 points.
All the patients underwent total colonoscopy with biopsies taken from the sigmoid colon.
The colonoscopy was done with the Olympus CF-H190L endoscope (Olympus Corporation, Japan). Biopsies were taken with biopsy forceps.
The size of the biopsies was about 2 mm. The biopsies were placed in a sterile container with 10 ml of 0.9% sodium chloride solution. In biopsies, CMV DNA was determined by quantitative PCR using the Light Cycler-96 automatic amplifier (Roshe, Germany).
After determining the CMV DNA, the patients were divided into two groups depending on the presence or absence of CMV in the biopsy: the patients with a positive CMV, regardless of the number of copies, were assigned to the «CMV-pos.» group, the patients with a negative study result – to the «CMV-neg.» group.
All the patients were treated according to the severity of the attack according to the national clinical guidelines (2019) [2].
The patients in the CMV-pos. group were additionally treated with ganciclovir at the rate of 5 mg/kg 2 times a day for 21 days, followed by monitoring of the endoscopic picture on the 19-21st days of the antiviral therapy and repeated test for CMV by quantitative PCR.
In the absence of the effect of the conservative treatment and progressive deterioration of the patients' condition, colectomy was performed.
The patients in the CMV-pos. group were additionally treated with ganciclovir at the rate of 5 mg/kg 2 times a day for 21 days, followed by endoscopic monitoring on the 19-21st days of the antiviral therapy and repeated examination of the biopsy by quantitative PCR to detect CMV DNA.
In case of progressive deterioration of the patients' condition and the lack of effect from the conservative treatment, the patients underwent colectomy.
The success of therapy in both groups was assessed by the colectomy rate during hospital stay. Such indicators as hemoglobin, albumin, C-reactive protein were also analyzed; the endoscopic picture was evaluated.
In the CMV-pos. group, the viral load was monitored after the antiviral therapy.
Statistical data processing was performed using the Statistica 13 software package. The descriptive part of the study was performed with the definition of the mean and standard deviation. Nonparametric indicators were calculated using the Mann-Whitney test.

RESULTS

Among the 67 patients included in the study, there were 28 (41.8%) females and 39 (58.2%) males (Fig. 1). CMV was detected in 29 (43.2%) patients, including 9 females (Fig. 2). CMV was not detected in 38 (66.8%) patients, including 19 females (Fig. 3). So, both groups were homogeneous for gender (p=0.14)
Patients were aged 18-74 years, the age median in both groups was 37 (31;47) years. In the CMV-pos. group age median was 38 (31;47) years. In the CMV-neg. group, the age median was 31 (27;47). Thus, it was possible to compare these groups, since the groups were comparable in age (p=0.25) and gender (p=0.14).

The number of copies of the virus in the colon mucosa biopsy in the patients we observed was 15,287/10*5 cells (10,000;20500).

In the CMV-pos. group, there were 6 (20.0%) acute attacks, in the CMV-neg. group – 1 (2.6%) (p=0.02).

An acute UC attack was considered to have a disease history of less than 6 months from the debut to inclusion in the study. The UC severity was assessed using the Mayo index. When the Mayo index was 9 or higher, the patient was diagnosed with a severe attack. In the group of the patients with diagnosed CMV infection, severe UC attacks were 11 (37.9%), in the group of the patients with a negative CMV result – 18 (48.6%). Thus, the groups were comparable in terms of attack severity (p=0.64).

The condition of patients at admission was also assessed by metabolic indicators, such as the level of albumin, hemoglobin, and C-reactive protein (CRP) (Fig. 4).

Both groups were comparable in terms of albumin, hemoglobin and CRP levels, as shown in fig. 4, no significant differences were found (for albumin p=0.26, for hemoglobin p=0.69, for CRP p=0.12).

Data on the previously received treatment by the patients are presented in table 1.

The analysis did not reveal a relationship between the type of therapy and the presence or absence of CMV (Table 1). In the patients who did not receive any specific UC therapy, the rate of CMV detection did not significantly increase. The CMV incidence did not increase either in the patients treated with 5-aminosalicylic acid.

This also applied to azathioprine, infliximab, adalimumab, golimumab, and tofacitinib therapy.

The colectomy rate was evaluated as early outcome. In the group of patients without concomitant CMVI, colectomies were performed in 6/38 (15.8%) patients, and in the group with CMVI, colectomies were performed in 6/29 (20.7%) patients. There was no significant difference in the colectomy rate in the CMV-pos. and CMV-neg. groups (p=0.2).

Previous therapy did not affect the severity of the disease (CMV-pos., p=0.12 vs CMV-neg., p=0.36) and the outcome (p=0.12 for the CMV-pos. group, p=0.45 for the CMV-neg. group). In neither group the level of albumin affect the colectomy rate (for the CMV-positive group p=0.49, for the CMV-negative group p=1.0).

In the group without CMV, the colectomy rate did not depend on the level of albumin (p=0.06), hemoglobin (p=0.18), and CRP (p=0.17).

In the CMV-pos. group, the colectomy rate did not depend on the level of albumin (p=0.9) and CRP (p=0.66) either, but had a direct relationship with the level of hemoglobin (p=0.04). The severity of the attack did not affect the colectomy rate (for the group with CMVI p=0.33, for the group without CMVI p=1.0).

Twenty-nine patients of the CMVI group received ganciclovir therapy (5 mg/kg twice a day for 21 days).

In the control PCR study of bowel mucosal biopsies on the 19-21st days of the therapy, the viral load was maintained in 7 patients, with the number of CMV copies decreased in 4 patients and increased in 3 ones.

Two patients were not given a follow-up study of CMV

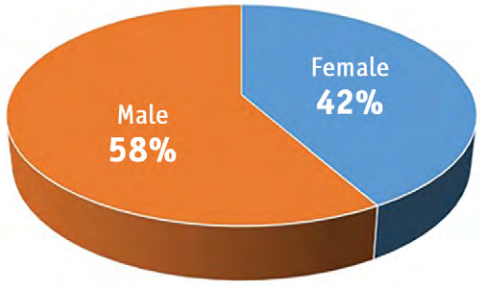

Figure 1. *Gender distribution*

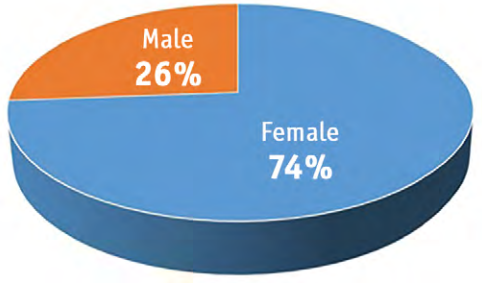

Figure 2. *CMV+Group*

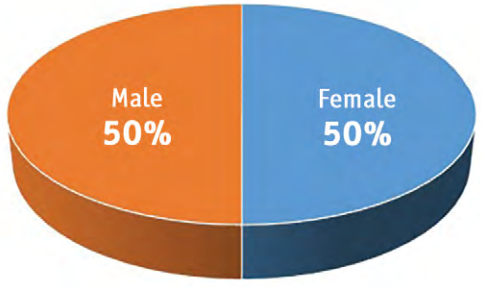

Figure3. *CMV-Group*

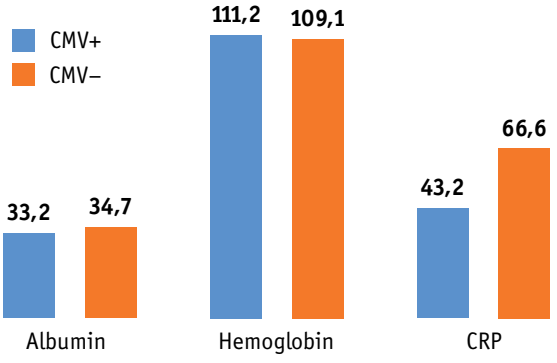

Figure 4. *Metabolic indicators in the groups*

Table 1. *Distribution of patients in groups by previously received therapy*

Medications received by patients	CMV-neg. *N*=38	CMV-pos. *N*=29	*P*-value
Without therapy	7 (18.4%)	3 (10.3%)	0.86
Drugsof 5-aminosalicylic acid	15 (39.5%)	14 (46.7%)	0.69
Azathioprine	8 (21.1%)	5 (16.7%)	0.3
Infliximab	2 (5.3%)	4 (13.3%)	0.09
Adalimumab	0	1 (3.3%)	–
Golimumab	2 (5.3%)	1 (3.3%)	0.72
Vedolizumab	0	0	–
Tofacitinib	2 (5.3%)	0	–

due to progressive deterioration of the condition and inability to postpone surgery for vital indications.
The failure of antiviral therapy significantly affected the colectomy rate (p=0.018).

DISCUSSION

According to Ciccocioppo R, et al., 47% of severe UC attacks are CMV-associated [6]. CMVI makes the UC more severe and makes it impossible to conduct immunosuppressant therapy. According to our study, CMV-associated UC was diagnosed in 43.2% of patients, which corresponds to the literature data.
However, we did not find a relationship between the severity of the UC attack and the CMV presence, since the incidence of severe UC forms in the group with and without CMV did not significantly differ. It was found, that the majority of patients with acute form of the disease were included in the group of CMV-associated UC (20.0% vs. 2.6% without CMV), and these patients have not yet received immunosuppressant's or biological therapy.
At the same time, literature data indicate that the association with CMV infection is more common in patients who have long received immunosuppressors or anti-TNF [6,8,9].
Thus, it can be assumed that not only immunosuppressive therapy, but also the severity of the attack can affect the development of CMVI.
However, our study does not yet have enough data to confirm this position. At the moment, we have not found a reliable influence of biological therapy in the anamnesis on the incidence of the CMVI, which can be explained by a small number of cases.
According to the literature, the presence of concomitant CMVI in a patient with UC makes the disease more severe and makes it resistant to intensive anti-inflammatory therapy [5,8].
Our assumption was the likely positive effect of specific antiviral therapy on the course of the disease and prognosis.
In the study, we found that treating patients with UC and CMVI with specific antiviral drugs allowed us to obtain comparable results in the colectomy rate, as in patients without CMVI.
At the same time, the success of antiviral therapy in patients with CMVI had a projective effect on colectomy.

CONCLUSIONS

Based on our research, we can draw the following conclusions:

1. The incidence of CMVI in severe and moderate UC attacks is 42.3%.
2. CMVI in men with UC develops significantly more often (50% vs. 26% p=0.01).
3. The CMVI in a patient with UC is affected not only by long-term immunosuppressive therapy, but also by acute UC.
4. In patients with UC and CMVI the probability of colectomy is higher than in patients without CMVI [5,8,20].

When performing specific antiviral therapy in patients with CMV-associated UC attack, the frequency of colectomies decreases and does not significantly differ from the group of patients without CMVI.

THE PARTICIPATION OF THE AUTHORS:
Concept and design of the study: *Alexandrov T.L., Shapina M.V., Kisteneva L.B.*
Collection and processing of the material: *Alexandrov T.L., Sukhina M.A., Kuznetsov A.N.*
Statistical processing: *Alexandrov T.L., Shapina M.V.*
Writing of the text: *Александров Т.Л.*
Editing: *Shapina M.V.*

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