Cytomegalovirus Infection in Ulcerative Colitis: An Ambispective Study from a Single Center

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Abstract

Background and Objectives Cytomegalovirus (CMV) is often detected in colonic tissue of patients with inflammatory bowel disease. Its role as a "bystander" or "culprit" in ulcerative colitis (UC) flares is unclear. The aim of the study is to detect the prevalence and outcomes of CMV infection in UC

Materials and Methods All adult patients (both retrospective and prospective), diagnosed with UC in a tertiary care center, were included. Patients underwent colonic biopsies for histopathological examination for CMV. CMV immunoglobulin G (IgG) was also tested to ascertain seroprevalence in this population. CMV infection was defined as presence of CMV inclusions in histopathology. Treatment outcomes were defined as remission, clinical improvement, and partial response. The number of flares and outcomes of disease activity in terms of flare of disease, hospitalization, need of colectomy, and mortality was noted at follow-up.

Results A total of 58 patients of UC were included (mean age was 37.3 years, males—66%). Serum CMV IgG was positive in all patients. Twelve patients (20.6%, 9 males) with active UC were found to have CMV infection in histopathology specimens with hematoxylin and eosin staining. Two-third of patients (8/12) had severe disease, while the remaining (4/12) had moderate disease activity. Nine patients (9/12) with CMV colitis achieved complete remission with standard treatment without antiviral therapy. Of the three patients who needed antiviral therapy, two underwent colectomy in follow-up. CMV-positive patients to be predominantly male ($p = 0.58$) had more frequent relapses ($p = 0.08$) and were hospitalized for their flares ($p = 0.06$) when compared with CMV-negative patients. None of these factors were found to be statistically significant.

Conclusion CMV infection was found in one-fifth of patients of UC with flare. All patients with CMV infection had moderate-to-severe disease. Majority achieved remission without the need of antiviral therapy.

Keywords
- inflammatory bowel disease
- ganciclovir
- colectomy
- cytomegalovirus
- ulcerative colitis

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Introduction

Cytomegalovirus (CMV) is a linear double-stranded DNA virus of the herpes family.[1] Infection with CMV is a common phenomenon seen in humans leading to a lifelong latent phase. Immunocompromised state may cause reactivation leading to CMV disease. Immunocompromised patients include patients on immunosuppressive drugs, cancer patients on chemotherapeutic agents, posttransplant patients, and patients with human immunodeficiency virus infection.[2] Ulcerative colitis (UC) being a chronic inflammatory colonic disease requires long-term immunosuppression. They are prone for CMV reactivation. The first association of CMV infection in UC was described in 1964.[3] The prevalence of CMV infection in steroid refractory colitis was seen in 33 to 36% patients of UC.[4,5] In the setting of acute severe colitis, the prevalence ranged from 21 to 34%.[4] The impact of CMV infection in disease severity, outcomes, and response to therapy is unclear despite multiple studies.

The relationship of CMV infection and UC has always been a matter of debate. There has been a tag of "innocent bystander," while others consider it as "pathogenic." The European Crohns and Colitis Organization guidelines recommend ruling out CMV infection in immunosuppressive refractory UC.[6] The aim of the study was to study the prevalence and outcomes of CMV infection in patients of UC.

Methods

The study was conducted at the department of gastroenterology at a tertiary care center over 2 years. All patients (age $\geq$18 years), diagnosed with UC, were included. The study adheres to the guidelines of the Declaration of Helsinki, 1975. Institutional ethical clearance was obtained prior to the start of the study. The study was also done in compliance with Good Clinical Practice guidelines and Indian Council for Medical Research guidelines. All patients who were not on regular follow-up, who were on irregular treatment, and those who did not give consent were excluded from the study. Patients were included both from retrospective databases and prospective enrolment. UC was diagnosed based on clinical features, endoscopic and histological findings. Disease activity was classified as mild/moderate/severe based on Truelove and Witt's classification.[7] The treatment principles were kept uniform with respect to induction and maintenance therapy as per standard guidelines.[8] All patients underwent clinical, endoscopic, laboratory, and radiological investigations as per their disease status. Endoscopic severity of disease was defined as Baron scoring (grade 0—normal mucosa, grade 1—loss of vascular pattern, grade 2—granular, nonfriable mucosa, grade 3—friability on rubbing, and grade 4—spontaneous bleeding, ulceration).[9]

For CMV serology, CMV-IgG (immunoglobulin G) antibodies (Novalisa CMV IgG enzyme-linked immunosorbent assay, Novatec, Germany) were sent for all patients to study prevalence of CMV infection in UC patients. Patients underwent colonic biopsies for histopathological examination (HPE). Patients with positive HPE were studied regarding the course of disease, need for antivirals, and treatment outcomes. CMV positivity was diagnosed based on histopathology. CMV infection was diagnosed based on positive hematoxylin and eosin (H & E) staining (cytomegalic cells with large eosinophilic intranuclear inclusions, and smaller cytoplasmic inclusions) on colonic biopsy specimens. The slides were re-examined by two independent pathologists before being taken as positive for CMV.

Treatment outcomes were defined as follows: (i) remission—defined as complete resolution of symptoms and endoscopic mucosal healing, (ii) clinical improvement—with absence of symptoms of active disease (no rectal bleeding, reduced stool frequency $\leq$ 3 stools /day, no abdominal pain; and (iii) partial response—clinical improvement with stool frequency still more but $<$50% of previous, and sigmoidoscopy showing downgrading of endoscopic severity.[10]

All enrolled patients were followed up till 1 year. The number of flares and outcomes of disease activity in terms of flare of disease, hospitalization, need of colectomy, and mortality was noted.

Statistical Analysis

All data were represented as mean $\pm$ standard deviation in case of normally distributed data or median and interquartile range, if it had a nonparametric distribution. The demographic and clinical parameters of CMV-positive patients treated with antivirals were compared with those of patients who did not require antiviral therapy. Continuous variables were analyzed by student *t*-test for continuous variables and Fisher's exact test for categorical variables. Kolmogorov Smirnov test was used for normal distribution. Univariate followed by multivariate analysis was done for the prediction of risk of CMV infection in UC. *p*-Value less than 0.05 was considered significant.

Results

A total of 65 patients of UC were enrolled. Seven patients were excluded due to noncompliance or irregular follow-up. There were 58 patients in this study. The mean age of the cohort was 37.3 years and males constituted 66%. The age of onset of disease was 17 to 64 years. All patients were on 5-aminosalicylic acid (5-ASA), while 36 (62.1%) patients were on thiopurines. The number of patients on steroids was 31 (53.4%). Moderate disease activity was seen in 35 patients (60.3%), while 15 patients (25.9%) had severe disease. Seven patients had a mild disease, while one patient was in remission. Fifty-three (53/58, 91.3%) patients had high endoscopic severity scores (Baron grade ¾) at presentation.

Prevalence of CMV Infection

Serum CMV IgG was positive in all 58 (100%) patients. Twelve patients (12/58 [20.6%], 9 males) with active UC were found to have CMV infection on histopathology specimens with H & E staining. The mean age of the CMV-positive patients (12/58) was 37.5 years (range: 20–54 years). Ten patients with CMV were already diagnosed cases of UC on follow-up, whereas only two patients were newly diagnosed. At

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presentation, two-third of patients (8/12) had severe disease, while the remaining (4/12) had moderate disease activity as per Truelove and Witt's criteria. Endoscopic severity scores at presentation were of Baron grade 4 in nine (9/12) patients, while remaining patients (3/12) patients had Baron grade 3.

At the time of diagnosis of CMV colitis—six (6/12) patients were receiving immunosuppression (5 were on azathioprine and 1 on steroids) along with 5-ASA. Three patients were only on 5-ASA, while three patients were not on any treatment.

Eleven (11/12) patients received corticosteroids along with 5-ASA as standard treatment for their flare. Intravenous ganciclovir was given to three patients in addition to standard treatment owing to inadequate treatment response with standard medical therapy of 5 to 7 days. Hence, antiviral therapy was not used in the remaining nine patients. Steroids were tapered at 5 mg per week after 2 weeks of 0.75 mg/kg therapy.

Outcome of CMV Infection

Nine patients (9/12) with CMV colitis, including five patients who received azathioprine, achieved complete remission with standard treatment without antiviral therapy. Three patients (3/12) received antivirals in which one achieved complete remission, one had partial response, and one patient did not respond to medical treatment and underwent colectomy ►**Fig 1**.

On follow-up, one patient treated with ganciclovir who responded to treatment underwent colectomy 3 months later due to severe relapse. However, the colectomy specimen was negative for CMV. The second patient on antiviral treatment achieved remission over 6 weeks, but died 3 months later due to progressive radiculoneuropathy of unknown etiology. The third patient did not respond to medical treatment in spite of addition of antivirals and underwent colectomy. Patient was asymptomatic on follow-up after colectomy. Nine patients who did not receive antivirals were on regular follow-up (range: 9–60 months), did not have any adverse outcomes, and remained in remission during study period.

Predictors of CMV Infection in UC

CMV-positive patients were found be predominantly male (72.7 vs. 63.8%, $p = 0.58$), had more frequent relapses (more than two) (63.6 vs. 34%, $p = 0.08$), and were hospitalized for their flares (72.7 vs. 40.4%, $p = 0.06$) when compared with CMV-negative patients. None of these factors were found to be statistically significant ►**Table 1**.

Discussion

CMV infection was found in 20.6% patients of UC in this study. All the patients with CMV infection had moderate-to-severe disease activity. Antiviral therapy was given only to three patients. On follow-up, two of three patients, who required antiviral therapy, underwent colectomy. The remaining nine patients did not necessitate antiviral therapy and the underlying inflammatory bowel disease was treated with standard medical therapy. They did not have any adverse outcomes on follow-up. Numerically patients with CMV infection were more often males, had more frequent relapses, and were more hospitalized for flare of disease. However, none of these factors was statistically significant.

The prevalence of CMV in patients of UC has been variable (2–38%).[4] We found the prevalence of CMV infection in

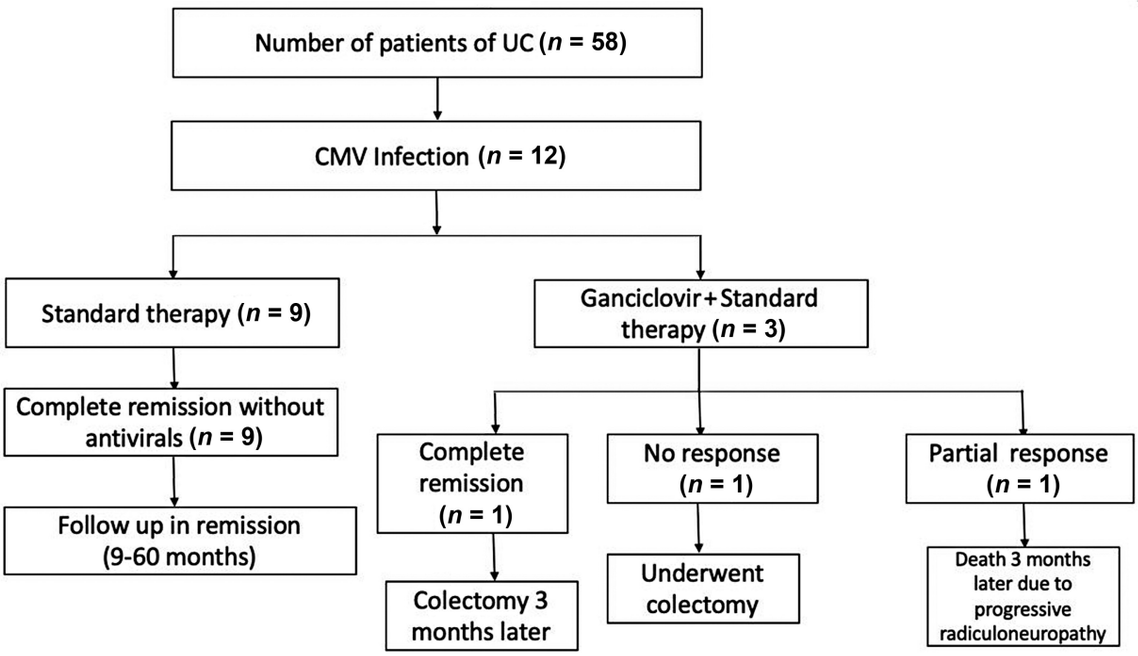


Fig. 1 Outcomes of cytomegalovirus (CMV) infection in patients of ulcerative colitis (UC).

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Table 1 Risk factors of CMV infection in patients with UC

Parameters	CMV-positive group ($n = 12$)	CMV-negative group ($n = 47$)	OR (95% CI)	*p*-Value
Age >40 years ***n* (%)**	4 (36.4)	17 (36.2)	1.008 (0.25,3.94)	0.99
Male gender ***n* (%)**	8 (72.7)	30 (63.8)	0.662 (0.15,2.80)	0.58
Newly diagnosed UC ***n* (%)**	2 (18.2)	10 (21.3)	1.21 (0.22,6.55)	0.82
Number of patients who received less than 2 courses of steroid ***n* (%)**	5 (45.5)	12 (25.5)	2.43 (0.62,9.43)	0.19
Number of patients with more than two flares ***n* (%)**	7 (63.6)	16 (34)	3.3 (0.86,13.32)	0.08
Number of patients on azathioprine, ***n* (%)**	9 (81.8)	27 (57.4)	3.33 (0.64,17.14)	0.15
Hospitalization	8 (72.7)	19 (40.4)	3.93 (0.92,16.73)	0.06

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio.

patients with active UC was 20.6%. The prevalence of CMV infection depends largely on the method of detection. The method for detection used in this study was histopathological analysis that is the gold standard of diagnosis. Owl eye appearance of inclusion bodies is specific for CMV infection. Blood based tests were found to aid in prediction of CMV reactivation but were insensitive tests. IgG test was done to look for seroprevalence of past/present CMV infection in this population. Tissue polymerase chain reaction (PCR) and IgM studies have poor sensitivities and ill-defined cutoff values and hence were not used in this study.[11] On the other hand, HPE examination although had very low sensitivity, it performed marginally better in specificity. Tissue HPE examination along with immunohistochemistry is the gold standard for diagnosis.

All the patients with CMV infection in this study had moderate-to-severe disease. In patients with active UC, proinflammatory cytokines (interferon gamma, interleukin 6, tumor necrosis factor alpha) stimulate immune responses for the activation of nuclear factor kappa B and protein kinase C pathways.[12] These help in replication of viruses by transcription of immediate early genes of CMV virus. Along with immunosuppression, this leads to CMV reactivation.

The exact clinical impact of CMV infection in outcomes of UC is difficult to evaluate. CMV infection was found to be associated with increased steroid resistance as compared with patients of UC without CMV.[13] There was an association of increase in the rate of colectomy as well as severe disease in patients of UC with CMV.[14–17] In previous studies, one meta-analysis revealed that use of antiviral therapy had limited value in the management of CMV infection in UC.[18] It was contradicted by another meta-analysis and showed antivirals to be beneficial in the small subset of steroid refractory disease.[19] We found around two-third of patients of CMV infection achieved remission of disease in UC without requiring antiviral therapy. Of the three patients who needed antivirals, two of them underwent colectomy later. Antivirals did have a transient response in two patients of three who received it, but this was in addition to standard immunosuppressive therapy. Hence, it is difficult to conclude that the clinical response was entirely due to antiviral treatment. This untoward outcome of colectomy in two patients with antiviral therapy is perplexing and should drive further larger studies to find the subset that would actually benefit from antiviral therapy.

The strength of the study includes its prospective follow-up of patients of UC on a long term for outcomes of CMV infection. The study showed patients could be managed with standard therapy for UC despite being diagnosed with CMV infection. There are certain limitations of the study. First, it was a small single-center study. Second, immunohistochemistry and tissue PCR for CMV could not be performed for patients due to cost concerns. At the time of this study, CMV immunohistochemistry markers were not available at our center. None of the patients were on biologicals; hence, we could not evaluate the outcome in this subset. We did not use histological scores for the assessment of severity. Lastly, we could not do endoscopic evaluation in follow-up of all patients.

To conclude, CMV infection was found in one-fifth of patients of UC in this cohort. All patients with CMV infection had moderate-to-severe disease. Majority achieved remission without the need of antiviral therapy. Future trials should look into the benefit of antiviral therapy in UC.

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Ethical Statement
Informed consent prior to participation was taken. Ethics committee approval (no. 435/2012) was obtained from institutional committee.

Author Contributions
S.B. - Data collection, writing manuscript and review and editing of final manuscript; A.J. - writing manuscript, data review, editing of final manuscript; R.K. - histopathology support, review of data; C.G.P. - conception of study, review of study, review of manuscript.

Data Availability Statement
There is no data associated with this work.

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Conflict of Interest
None declared.

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