

Clinical significance of cytomegalovirus and other herpes virus infections in ulcerative colitis

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KEY WORDS

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ABSTRACT

Herpes virus infection leads to severe and fatal disease in individuals with suppressed immunity. In patients with inflammatory bowel disease (IBD), particularly those with ulcerative colitis (UC), those undergoing immunosuppressive therapy, or those unresponsive to medical therapy, cytomegalovirus (CMV) has been found to be associated with significant clinical morbidity. In addition, other herpes viruses, particularly human herpes virus 6 (HHV-6) and Epstein–Barr virus (EBV), have been identified recently in the colonic mucosa of individuals with IBD, although the relationship between herpes virus infection other than CMV and exacerbation of IBD remains unknown. In this review, we discuss herpes virus infection in patients with UC, focusing on the prevalence and diagnosis of CMV infection as well as the prevalence of single or mixed infection with herpes virus (HHV-6 and EBV) in addition to CMV. Moreover, significance of genotyping of CMV in UC is discussed.

Introduction Ulcerative colitis (UC) and Crohn disease (CD), which are clinically and pathologically 2 distinct medical conditions, are both inflammatory bowel diseases (IBDs). In UC, continuous inflammation limited to the colonic mucosa is a typical feature, while CD is characterized by transmural inflammation and skin lesions limited to the mucosal and submucosal layer and involving any part of the gastrointestinal tract from the mouth to the perianal region.¹ Therapeutic options include the use of glucocorticoids, thiopurines, or tumor necrosis factor (TNF) inhibitors as monotherapy or the use of glucocorticoids in combination with immunosuppressive drugs such as azathioprine, cyclosporine A, and biological drugs. Recently, an anti- $\alpha 4\beta 7$ integrin antibody, such as vedolizumab, and Janus kinase inhibitors, such as tofacitinib, have been approved as novel immunosuppressant agents in UC.²

The use of different biologics and immunosuppressive agents as monotherapy or in combination has been reported as a risk factor for serious infections in patients with UC. A recent systematic review and meta-analysis compared the risk of

infections between TNF inhibitors, vedolizumab, and immunosuppressive agents in patients with IBD.³ It showed that the risk of serious infections is higher in combination therapies of TNF inhibitors and corticosteroids than in monotherapy with TNF inhibitors. On the other hand, it revealed that the risk of infections was higher for monotherapy with TNF inhibitors than for combined therapies of TNF inhibitors and immunosuppressive agents other than corticosteroids. Furthermore, thiopurines were shown to be primarily responsible for viral infections, which sometimes become serious and, in some cases, may even require hospitalization.³ Moreover, few data are available regarding the effect of vedolizumab and tofacitinib on the risk of serious infection. Several clinical trials of vedolizumab have not reported any significant risk of serious infections, particularly in the intestines.³ However, tofacitinib-treated patients with UC had a higher prevalence of infections with herpes zoster virus and cytomegalovirus (CMV) than patients receiving placebo.⁴ Finally, patients with IBD have been reported as a high-risk group for

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serious infection due to poor nutritional status, inflamed mucosa, and, most importantly, due to the use of immunosuppressive drugs as an effective therapeutic option. The most frequently reported infection in IBD is CMV.⁵

Cytomegalovirus is a double-stranded DNA virus belonging to the β -herpesviridae family. It commonly affects people of all ages and establishes lifelong latency like other herpes viruses. Endothelial cells as well as blood mononuclear cells have been reported as reservoirs for CMV following primary infection. In a quiescent stage, CMV usually does not manifest significant clinical signs and symptoms except mononucleosis. However, latent CMV becomes reactivated due to an immunodeficiency disease⁶ and prescribed drugs, such as corticosteroids, which cause considerable immunosuppression. Patients diagnosed with IBD are often put on long-term prednisolone and/or other immunosuppressive drugs and may develop iatrogenic immunosuppression. Therefore, immunosuppressive drugs have been reported as one of the most important stimuli to reactivate CMV in IBD.^{7,8} Previous epidemiological data regarding IBD coexistent with CMV infection revealed that patients with UC have a higher risk of CMV infection than those with CD (in whom the risk is lower than 5%).⁹ In UC, CMV infection may present with 2 coexisting conditions: CMV colitis (where CMV itself causes colitis) or CMV infection.¹⁰ In this paper, we focus on CMV infection in UC, with particular emphasis on a diagnostic strategy, by reviewing our own research and other studies. We discuss differences between CMV-induced colitis and CMV infection in UC patients (FIGURE 1). We also briefly refer to colonic infection by herpes viruses other than CMV, such as human herpes virus 6 (HHV-6) and Epstein-Barr virus (EBV).

Prevalence of cytomegalovirus infection in ulcerative colitis Cytomegalovirus infection is diagnosed on the basis of positive serology or polymerase chain reaction (PCR) results for CMV DNA in relevant clinical samples such as blood, stool, or intestinal fluid. The analysis of feces by PCR seems to be more specific for diagnosing a colonic CMV infection in UC.

There are scarce data on the exact prevalence of CMV in UC. A review of published data revealed variations in the prevalence of CMV infection in UC due to the use of different diagnostic techniques by different laboratories. Therefore, the actual prevalence of CMV infection in UC is unclear.

An association between UC and CMV infection was first reported in 1961.¹¹ Since then, numerous studies have investigated the role of CMV in UC. Recently, a prospective study reported that a significantly higher CMV DNA level was detected in 8 of the 17 patients (47%) with IBD refractory to conventional therapies compared with 5 of the 23 patients (21.7%) with nonrefractory IBD and 2 of the 40 controls (5%).¹² Studies suggested that the rates of CMV infection

appear to be higher in UC, particularly in steroid-refractory cases. Iida et al¹³ analyzed the prevalence of CMV infection in 105 corticosteroid- and thiopurine-free patients with UC and in 82 patients with UC refractory to corticosteroid treatment, using serology testing, CMV antigenemia assay, CMV-DNA PCR, and histology. They reported the prevalence of 75.2% and 69.5% in corticosteroid-free patients with UC, assessed by serology and CMV antigenemia, respectively. In the refractory group, the prevalence was 81.7%, 32.9%, 77.6%, and 25.9% for serology, CMV antigenemia, PCR, and histologic examination, respectively.¹³ Another study reported that 75% of patients with steroid-refractory UC tested positive in a CMV antigenemia assay.¹⁴ Kim et al¹⁵ reported the prevalence of CMV in active UC of 10% (12 of the 122 patients), using the immunohistochemical method. The prevalence of CMV was 29.4% in patients with active UC who did not undergo any immunosuppressive therapies in a study by Fukuchi et al¹⁶ and 56.7% in patients with active UC refractory to immunosuppressive therapies who tested positive for CMV DNA in the colonic mucosa by PCR in a study by Yoshino et al.¹⁷

Endoscopic evaluation Studies suggest that the diagnosis of CMV infection in UC on the basis of colonoscopic findings is challenging.¹⁰ After a retrospective analysis of colonoscopic images, the authors differentiated 2 types of colonic lesions: mucosal defects and ulcerative changes. Mucosal defects include the lack of visible blood vessels under the mucosa, erythematous lesions, fragile mucosa that is prone to bleeding on minimal contact with an endoscope, mucosal edema, as well as blood and pus exudates. Some studies have indicated several forms of ulceration, for example, widespread mucosal defect, a clearly demarcated round ulcer, ulcer along the colon, irregular ulceration, and cobblestone-like appearance, to explain ulcerative changes (FIGURE 2). Punched-out, longitudinal, and irregular ulceration has been suggested as a characteristic colonoscopic finding in patients with UC complicated by CMV infection.^{18,19} However, most studies reported that endoscopic features of UC and CMV infection or colitis overlap in patients with active UC who were considered susceptible to CMV infection.²⁰⁻²³ Thus, endoscopic evaluation might have a less significant role in establishing an accurate diagnosis of CMV in UC patients.

Diagnostic strategy Cytomegalovirus infection adversely affects the clinical course of UC. Therefore, an appropriate diagnosis of the infection in these patients is necessary. There are numerous methods available to identify a colonic infection, for example, assessing the presence of CMV-specific antibodies or CMV and CMV DNA in peripheral blood and colonic tissue, fluid, or feces, which helps determine an association of the infection with concomitant clinical symptoms of UC.

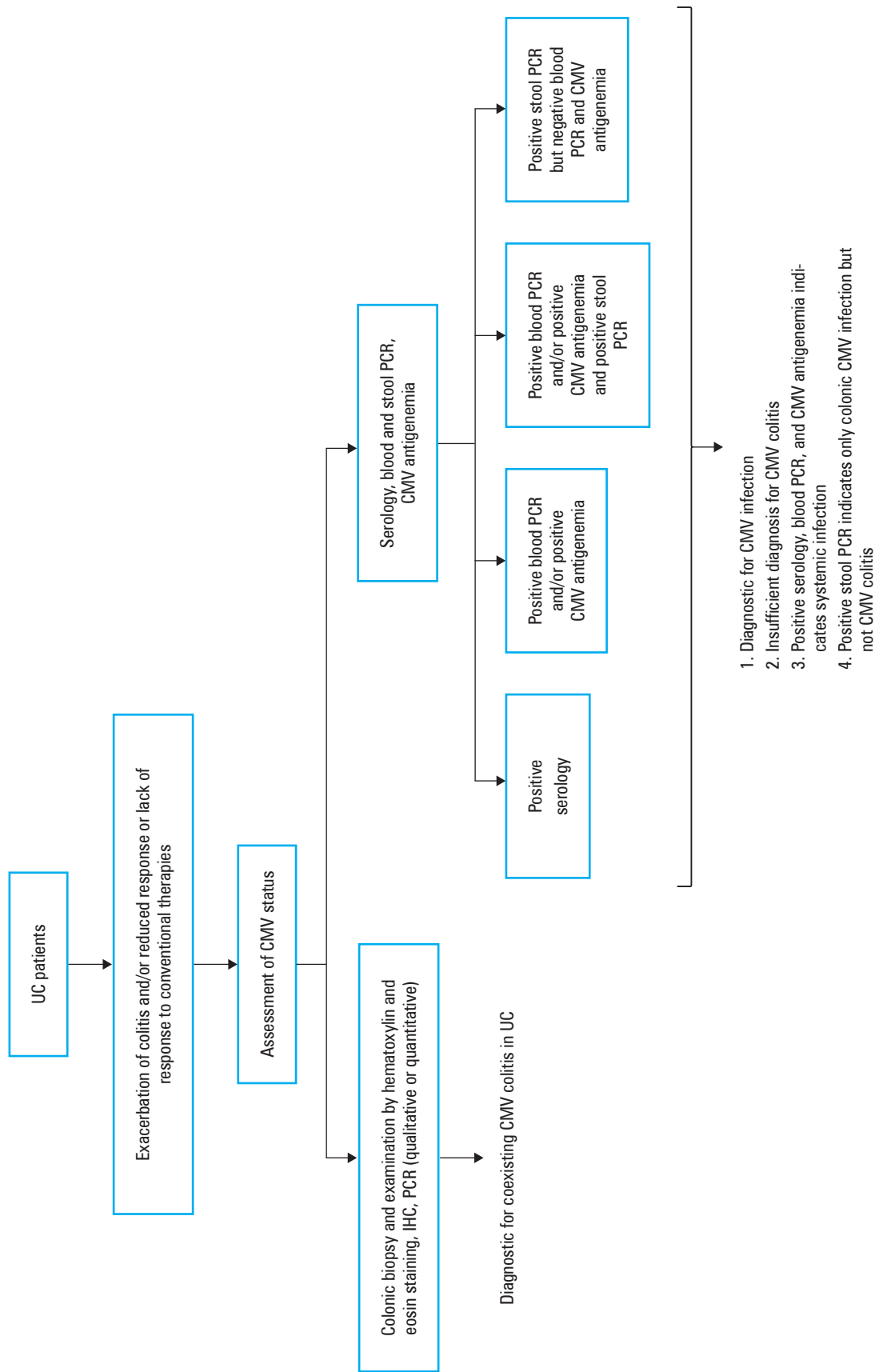
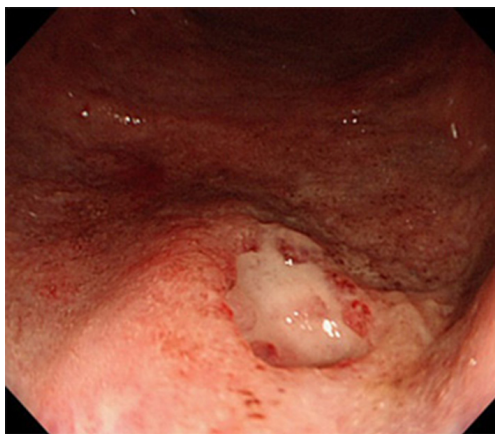


FIGURE 1 A diagram for differentiating cytomegalovirus (CMV) colitis from CMV infection in patients with ulcerative colitis (UC) based on literature data.^{42-46,48,49,54,64} Exacerbation of clinical symptoms (excessive watery/bloody diarrhea, fever, fatigue, abdominal pain), presence of endoscopic features of CMV colitis, lack of response to conventional therapy of UC, as well as positive results of immunohistochemistry (IHC) and/or polymerase chain reaction (PCR) of colonic tissue reveal CMV colitis, while the presence or absence of exacerbating symptoms, negative IHC but positive blood or stool PCR results indicate CMV infection.

FIGURE 2

Colonoscopic image of a cytomegalovirus-associated punched-out round ulcer in the rectum of a patient with active ulcerative colitis



The currently used techniques to diagnose colonic CMV infection are discussed below.

Detection of immunoglobulin IgM and IgG antibodies to cytomegalovirus

Serology testing helps determine a previous exposure to a virus. Serological analysis is usually performed by an enzyme-linked immunosorbent assay using a serum sample. Both IgM and IgG antibody titers are necessary to diagnose CMV infection. An increased IgM antibody titer indicates primary infection, takes 2 years to disappear from serum, and is rarely increased during reactivation of CMV (0.2%–1% of cases). Cytomegalovirus-specific IgG antibody titer is analyzed in 2 different serum samples collected at an interval of 2 to 4 weeks. A 4-fold increase in IgG antibody titers is used as one of the criteria to diagnose CMV. However, a serological analysis is considered a nonspecific test for diagnosing colonic CMV infection.²⁴

PP⁶⁵ antigenemia Detection of the PP⁶⁵ antigen in peripheral blood mononuclear leukocytes using immunofluorescence generally indicates an active infection or reactivation of CMV, with a sensitivity of 60% to 100% and a specificity of 83% to 100%.^{25,26} However, similar to serology, positive results in blood samples do not reflect the concurrent CMV infection in the colon.²⁷ If there is neutropenia, a CMV antigenemia test may reveal a false negative result.⁸ Positive results of CMV antigenemia reflect a systemic infection, but they do not always correlate with colonic infection in UC.²⁸

Histologic detection of cytomegalovirus in colonic tissue

A histologic analysis of a colonic biopsy specimen is performed mainly by hematoxylin and eosin staining followed by microscopy. Cytomegalovirus induces the production of inclusion bodies in the nucleus and cytoplasm. Large-sized cells (approximately 25 to 50 μm in diameter) containing intranuclear and cytoplasmic inclusion bodies visible under a microscope as an owl's-like eye are defined as cytomegalic cells, which are a typical feature of CMV infection in tissue. Cytomegalic inclusion bodies are found very rarely, and a histologic analysis is considered to

have a low sensitivity for detecting CMV in intestinal tissue. Importantly, the collection of biopsy specimens from the deep mucosal layer is difficult for endoscopists due to inflamed mucosa in UC. The superficial mucosal layer is collected for biopsy to prevent the risk of bleeding and mucosal damage. Therefore, epithelial cells, rarely infected by CMV, can be visible under a microscope following hematoxylin and eosin staining. That is why, a histologic analysis provides false negative results.²⁹⁻³²

The area for collecting a tissue specimen from the colon and the amount of a tissue specimen required to identify CMV infection have not been fully elucidated. Zidar et al³² showed that the density of CMV-positive cells was higher in the base and edge of the ulcer, whereas CMV-positive cells were not found in the uninvolved portion of the colon using immunohistochemistry. McCurdy et al³³ recommended collecting 11 biopsies to assess CMV in UC. Although CMV is heterogeneously distributed along the colon, the region shown to be the most affected by CMV was the rectum. As the rectal region is more prone to the infection and usually shows the most severe inflammation in UC, CMV may be more likely to be accumulated at this site.³⁴ The ulcer bed seems to be the reservoir of CMV^{35,36}; however, this area cannot be accessed due to the risk of bleeding and intestinal perforation. To improve the sensitivity of histologic examination, an immunohistochemical study has been used, and this combination is considered the gold standard for the detection of CMV.^{37,38} A recent study has shown that patients with 2 or more CMV-positive cells on immunohistochemistry per biopsy had a higher risk for colectomy.³⁹ Jones et al⁴⁰ recommended that 5 positive cells per biopsy should be considered as immunohistochemistry positive for CMV. Finally, Kredel et al⁴¹ have recently studied the diagnostic accuracy of immunohistochemistry and considered it to be positive when only 1 positive cell was detected. However, they performed immunohistochemistry in UC patients with clinical and endoscopic suspicion of CMV colitis.⁴¹ Despite its advantages, histologic analysis is a time-consuming and technically demanding method.

Diagnosis of intestinal cytomegalovirus infection by polymerase chain reaction

Amplification of CMV DNA by a qualitative and quantitative PCR assay is used to detect CMV in blood, urine, colonic tissue, and feces. Colonic samples such as colonic mucosa and feces are more specific to identify colonic CMV infection than blood or urinary PCR. Similar to a CMV antigenemia test, a blood sample positive for CMV DNA does not indicate a colonic infection.⁴²⁻⁴⁵ Recently, Okahara et al⁴⁶ analyzed mucosal tissue for the detection of CMV infection by PCR. Among UC patients with CMV-DNA positivity determined by mucosal PCR, 56% showed negative results in a CMV antigenemia assay.

It was reported that the use of noninvasive tests such as stool PCR is beneficial for patients with UC. Qualitative or quantitative PCR analysis has also been introduced to detect CMV DNA in feces.⁴⁷⁻⁵⁰ Fecal analysis may have considerable advantages in patients with UC, because physicians often face difficulties in obtaining endoscopic tissue specimens, particularly in patients with flare-ups due to the risk of bleeding. Moreover, patients sometimes refuse an endoscopic examination, especially in severe cases. Thus, stool analysis may prove as an easy, noninvasive, and convenient tool. The European Crohn's and Colitis Organisation has recommended the use of fresh stool samples for PCR.⁵¹ In our previous article, a qualitative multiplex PCR assay using fresh stool samples was suggested as a rapid and feasible screening tool for the detection of CMV DNA in patients with UC.⁵² Although only qualitative tests can detect CMV infection, they are not useful for diagnosing CMV colitis, in which a histologic analysis or PCR of colonic tissue is recommended. Positive results of PCR for CMV DNA were defined as reactivation by previous study.¹⁷ A PCR assay indicates the presence of colonic CMV infection rather than CMV colitis. Furthermore, if colonic PCR results are positive for the presence of CMV DNA, patients with UC should be monitored or treated for CMV infection. Particular attention should be paid to patients with UC who are refractory to immunosuppressive therapies.⁵³

Risk factors for cytomegalovirus infection in ulcerative colitis Three major risk factors for CMV infection have been identified in experimental studies: 1) inflamed colonic tissue with ulcer, which acts as a reservoir of CMV; 2) impaired immunity in patients with UC; and 3) the use of immunosuppressive drugs such as corticosteroids or cyclosporine, or their combination. Several lines of evidence have indicated that a monotherapy with corticosteroids or the combined use of corticosteroids and immunosuppressive drugs constituted a major risk factor for CMV infection in UC.⁵⁴⁻⁵⁶ Moreover, a recent retrospective study indicated old age, high endoscopic score, and a higher corticosteroid dose as risk factors for CMV infection in patients with UC.⁵² Suzuki et al¹⁹ reported that all patients who were positive for CMV in a CMV antigenemia assay received corticosteroid therapy, in contrast to CMV-negative patients. Other authors showed that after starting ganciclovir therapy and discontinuing steroids, steroid-resistant symptoms of UC improved.²¹ Our experimental data revealed that immunosuppressive drugs increased the risk of CMV infection in UC patients.⁵⁶ Similarly, a large retrospective observational study demonstrated that all UC patients positive for CMV infection had a history of corticosteroid therapy. It was shown that symptoms of CMV colitis develop due to immunosuppressive states, particularly in organ transplant recipients, patients with HIV infection, and in those on immunosuppressive therapy.⁵⁷ A systemic review

of case series reported that all UC patients had CMV infection after a long-term corticosteroid therapy. Patients with UC receiving azathioprine and steroids were found to be at increased risk of CMV infection in a prospective study.⁵⁸ Finally, a recent meta-analysis revealed that the use of corticosteroids and thiopurines was associated with CMV reactivation in UC.⁵⁹

Mixed infection with herpes viruses in ulcerative colitis There is limited evidence on mixed infection with CMV, EBV, and/or HHV-6 in patients with UC. In our study, a multiplex PCR analysis of herpes virus DNA using stool samples demonstrated the prevalence of CMV, EBV, and HHV-6 of 36.6%, 36.6%, and 11.3%, respectively, and the simultaneous presence of CMV and EBV, and/or HHV-6 was significantly higher in patients with active UC (24.1%). Our study also suggested the possible synergistic role of these 3 viruses in the pathogenesis of UC.⁵² Our findings are in line with a study by Wakefield et al,⁶⁰ who examined herpes virus DNA in colonic tissue and peripheral blood samples collected from patients with UC. They demonstrated a higher prevalence of CMV (81%), EBV (76%), and HHV-6 (76%) in patients with UC than in controls. They also showed that the simultaneous presence of HHV-6 and CMV and/or EBV was more common in the colonic tissue of UC patients than in controls (76% vs 29%; $P < 0.05$), which also suggests the synergistic role of these viruses in the pathogenesis of UC.⁶⁰

The role of HHV-6 in the development of CMV infection was reported in solid organ transplant recipients.^{61,62} Similarly, EBV reactivation was also demonstrated in a large study of patients with primary CMV infection.⁶³ Several studies have reported a mixed infection with herpes virus in patients with UC. Hosomi et al⁶⁴ enrolled 66 patients with UC in whom herpes virus DNA was detected using the multiplex PCR of colonic tissue. The simultaneous presence of different herpes viruses (CMV, EBV, and/or HHV-6) was shown in 10.6% patients with UC. Further analysis demonstrated the association of a mixed infection (CMV with concurrent EBV or HHV-6) with the clinical course of UC. The authors showed that EBV or HHV-6 could synergistically exacerbate the intestinal inflammation or increase the risk of CMV reactivation, which increased the risk of surgery.⁶⁴ Shimada et al⁶⁵ reported the prevalence of EBV, CMV, and HHV-6 infection of 53.7%, 24.4%, and 39%, respectively, in patients with UC, using mucosal PCR. However, they did not report on a mixed infection.

Based on these findings, it is likely that the prevalence of mucosal infection of EBV and HHV-6 is higher in UC coexisting with CMV infection, which may imply the role of mixed herpes virus infection (CMV, EBV, and HHV-6) in the pathogenesis of UC.

Cytomegalovirus is frequently reactivated in UC, particularly in individuals taking corticosteroids, thiopurines, or TNF inhibitors.^{66,67} Also

a significant association was reported between CMV infection and clinical morbidity, including toxic megacolon or increased risk of colectomy.⁶⁸ However, there has been no clear evidence regarding the association between other herpes viruses or a combined presence of human herpes viruses and the risk of CMV in patients with UC, although a few cases of colitis associated with herpes simplex virus have been reported in patients with UC.⁶⁹⁻⁷¹ It was also reported that patients with UC who take immunosuppressive drugs are at high risk for varicella zoster virus reactivation.⁷² However, infection with herpes simplex virus 1 and 2 or varicella zoster virus is not common in colonic tissue.⁷³

Genotyping of cytomegalovirus in ulcerative colitis

Despite the availability of extensive results on the distribution of pathogenic CMV strains in patients with congenital infection, solid organ transplant recipients, patients after hematopoietic stem cell transplantation, and those with AIDS, there are few data regarding the genotypic distribution of CMV in patients with UC. Our previous study revealed that glycoproteins B1, N3, and H2 were the most frequent genotypes in UC. A correlation between the gB1 and gH2 genes and symptoms of UC was reported.⁷⁴ However, due to the lack of sufficient data, it was impossible to draw firm conclusions. Similarly, gB1 was shown as the most prevalent genotype of CMV in UC.⁷⁵ A genotypic analysis in a large population is needed to differentiate between the pathogenic and nonpathogenic strains of CMV to elucidate the role of CMV in the pathogenesis of UC.⁷⁶

Conclusions As there is growing evidence for a considerable prevalence of herpes virus infection, particularly with CMV, in patients with UC, future research should focus on several crucial issues such as establishing the exact prevalence of CMV infection in UC, the effect of CMV infection on the exacerbations of colitis, the best diagnostic and preventive strategies, accurate timing for starting antiviral therapy, the exact mechanism of reactivation or enhancing the pathogenicity of CMV, as well as the impact of infection depending on whether there is 1 or more herpes viruses.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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