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ORIGINAL ARTICLE

Retrospective Study

Characteristic endoscopic findings and risk factors for cytomegalovirus-associated colitis in patients with active ulcerative colitis

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Abstract

AIM: To identify characteristic endoscopic findings and risk factors for cytomegalovirus (CMV)-associated colitis in patients with active ulcerative colitis (UC).

METHODS: A total of 149 UC patients admitted to the Department of Gastroenterology, Nagoya University Hospital, from January 2004 to December 2013 with exacerbation of UC symptoms were enrolled in this retrospective study. All medical records, including colonoscopy results, were reviewed. CMV infection was determined by the presence of CMV antigen, CMV inclusion bodies in biopsy specimens, or positive specific immunohistochemical staining for CMV. Multivariate analysis was used to identify independent risk factors for CMV colitis.

RESULTS: Multivariate analysis indicated independent associations with the extent of disease (pancolitis) and

use of > 400 mg corticosteroids for the previous 4 wk. In contrast, no association was seen with sex, age at UC diagnosis, immunomodulator use, or infliximab use. Punched-out ulceration was also significantly associated with CMV infection in patients with active UC (odds ratio = 12.672, 95%CI: 4.210-38.143).

CONCLUSION: Identification of a total corticosteroid dose > 400 mg for 4 wk, extensive colitis and a specific endoscopic finding of punched-out ulcer might facilitate the more rapid diagnosis and timely initiation of anti-viral therapy for CMV-associated colitis in patients with active UC.

Key words: Colonoscopy; Risk factor; Ulcerative colitis; Antigenemia; Cytomegalovirus

Core tip: It has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC). This paper provides important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC. A total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis. In addition, punched-out ulceration appears predictive of CMV-associated colitis in active UC.

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INTRODUCTION

Cytomegalovirus (CMV), a member of the double-stranded DNA human herpes virus family, is reported to infect between 40% and 100% of the general population[1]. Primary CMV infection is asymptomatic or minimally symptomatic, and is followed by a latent state, similar to other herpes virus infections[2,3]. Most cases of symptomatic CMV infection are therefore caused by reactivation of latent virus[1-3].

Although active CMV infection can occur in immunocompetent individuals, it occurs most frequently in immunocompromised patients, such as those with acquired immunodeficiency syndrome, leukemia patients during chemotherapy, and patients on high-dose immunosuppressants (*e.g.*, recipients of solid organ or bone marrow transplants)[1,4-7].

Powell *et al*[8] reported that CMV infection in patients with ulcerative colitis (UC) was associated with exacerbation of symptoms, while one early retrospective study reported the presence of CMV in surgical specimens of patients who underwent colectomy for the treatment of toxic megacolon or steroid-resistant UC[9]. However, the significance of CMV infection in inflammatory bowel disease (IBD) is still controversial, and the pathogenic role of CMV infection in IBD is debated: Some authors believe that CMV is only an "innocent bystander" and does not significantly impact outcome, whereas many other studies have reported a significant association between CMV infection and IBD[10-13].

Active CMV infection has been observed in UC patients receiving high-dose corticosteroid therapy[13-17]. From 27% to 100% of patients with steroid-refractory UC have been found to harbor CMV, and steroid resistance is one of the central characteristics of CMV infection in UC patients[9,16,18-21]. Moreover, multiple studies have concluded that CMV infection can be an exacerbating factor in UC patients and that UC prognosis is generally poor in patients with CMV if anti-viral therapy is not started at an early stage[2,3,13-15,21-23].

Thus, CMV infection may exacerbate UC and may even cause death if appropriate treatment is not given. Although the development of ganciclovir (GCV) antiviral therapy has improved outcomes of CMV-associated colitis[5,17,20], CMV infection must still be diagnosed early in corticosteroid-resistant UC patients so that antiviral therapy can be initiated as soon as possible. However, it is difficult to distinguish exacerbation of UC by CMV infection from exacerbation not associated with CMV on the basis of symptoms and signs alone. In such cases, UC symptoms, signs, and severity in patients at risk of CMV-associated colitis are routinely evaluated by endoscopy. While a few such studies have reported the absence of any characteristic endoscopic findings in patients with UC complicated by CMV infection[24], others have reported characteristic endoscopic features, including the absence of large single ulcers and the presence of longitudinal ulcers, microerosions, deep ulcers, pseudotumors, punched-out ulcers, mucosal defects, geographic ulcers, and irregular ulcers[1,25-30]. These studies have methodological differences, however, and no consensus on unique endoscopic features that can be used to facilitate early diagnosis of CMV-associated colitis in UC has yet been obtained.

Against this background, we conducted a retrospective review of all clinical and endoscopic findings in a large cohort of patients with moderate to severe UC with symptom exacerbation to identify risk factors and characteristic endoscopic findings of CMV-associated colitis.

MATERIALS AND METHODS

Patients

This study was a retrospective analysis of medical charts and endoscopic images obtained from patients diagnosed with moderate to severe (active) UC. From

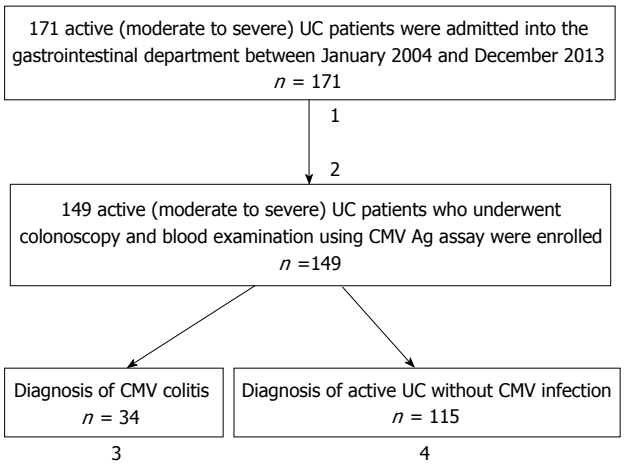


Figure 1 Clinical course of cytomegalovirus-associated colitis in patients with moderate to severe ulcerative colitis. Flow chart of the 171 patients admitted to our department with active UC. [1]Seven patients with a history of CMV-associated colitis or anti-CMV treatment were excluded; [2]Fifteen patients who had not undergone colonoscopy and examination using the CMV antigenemia assay were also excluded; [3]Out of 34 UC patients with CMV-associated colitis, 26 received GCV antiviral therapy. After GCV therapy, 13 patients achieved remission, but 13 required colectomy. Eight patients did not receive GCV antiviral therapy, 4 of whom underwent colectomy; [4]The remaining 115 UC patients not diagnosed with CMV-associated colitis received treatment for active UC, of which 81 achieved remission. Of the remaining patients, some improved but did not fulfill remission criteria, while others required a second treatment, hospitalization, or colectomy. CMV: Cytomegalovirus; UC: Ulcerative colitis; Ag: Antigenemia; GCV: Ganciclovir.

January 2004 to December 2013, a total of 171 UC patients were admitted to the Department of Gastroenterology, Nagoya University Hospital, with exacerbation of UC symptoms (Figure 1). The diagnosis of UC was based on clinical, endoscopic, radiological, and pathological criteria, and the severity of UC was assessed according to Stange *et al*[31], Truelove *et al*[32] and Dignass *et al*[33]. We routinely examine CMV antigenemia in such patients, and almost all undergo colonoscopy or sigmoidoscopy at admission[34-36]. Of the present 171 patients, we excluded 7 patients with a previous history of CMV-associated colitis or anti-CMV treatment, as well as 15 patients who had not undergone colonoscopy or examination using the antigenemia assay. Finally, 149 patients who received both a blood test for CMV antigenemia and endoscopic examination at admission were included in the analysis.

The following demographic and clinical data were obtained at the time of admission and classified according to the Montreal Classification[31,33]: Age at admission, age at diagnosis, sex, familial or spontaneous disease (familial disease was considered when at least one first- or second-degree relative was diagnosed with IBD), and disease localization (proctitis, left sided colitis, or pancolitis) as revealed by colonoscopy.

Endoscopic findings

Disease severity was assessed by colonoscopy. If ulcers were present, the shape and depth were described, and biopsies were obtained at the margin and base for histologic investigation. If no ulcers were detected, biopsies were obtained in the areas with the most severe inflammation. Colonic biopsy specimens were fixed, paraffinized, and stained with hematoxylin and eosin (HE) and specific immunohistochemical (IHC) staining with monoclonal antibody against CMV immediate early antigen[6,37]. Specimens were also evaluated for the presence of characteristic CMV inclusion bodies by experienced pathologists.

Diagnosis of CMV infection/CMV-associated colitis

CMV infection was defined by a positive CMV antigenemia assay, the presence of inclusion bodies in HE stained sections, or positive specific IHC staining for CMV. Diagnosis of CMV-associated colitis in patients with active UC was determined by active UC complicated by CMV infection.

Ethical considerations

The study protocol was approved by the institutional review board of Nagoya University Graduate School of Medicine.

Statistical analysis

Data are presented as mean ± SD or number (%) as appropriate. Categorical data were compared between groups using the χ^2 or Fisher's exact test. Continuous variables were compared using the Mann-Whitney *U* test. To identify candidate risk factors and characteristic endoscopic features for CMV-associated colitis, univariate analyses were conducted using Fisher's exact test. All factors which were significant on univariate analysis were entered into multivariate logistic regression models constructed to identify significant independent risk factors and characteristic endoscopic features of CMV-associated colitis. For continuous variables, we found the best cut-off value with plotting the area under the receiver operating characteristic curve. The results are expressed as odds ratios (ORs) with 95%CIs. *P*-values less than 0.05 were considered statistically significant for all tests. All statistical analyses were performed using SPSS Statistics 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 149 UC patients presenting with UC symptom exacerbation between January 2004 and December 2013 were included in the study. Of these, 34 (22.8%) tested positive on CMV antigenemia assay or had biopsy specimens with indicative of CMV infection. The clinical and demographical parameters of CMV-positive and CMV-negative patients are presented in Table 1. Univariate analysis revealed statistically significant group differences in age at UC diagnosis, age at admission, extent of disease (pancolitis), serum albumin level, systemic steroid dose on the day of admission, total systemic steroid dose for the week before admission, and total systemic steroid dose for 4 wk before admi-

Table 1 Clinical and demographic characteristics of patients with active ulcerative colitis (n = 149)

	CMV (+) n = 34	CMV (-) n = 115	P value
Sex (male/female)	19/15	64/51	0.981
Age at UC diagnosis (yr)	42.3 ± 14.4	29.0 ± 14.4	< 0.001
Age at admission (yr)	46.9 ± 18.1	35.0 ± 15.6	< 0.001
Disease duration (yr)	4.6 ± 4.9	6.0 ± 7.4	0.294
Clinical course			
Relapse	23 (67.6%)	79 (68.7%)	0.908
Chronic active	4 (11.8%)	11 (9.6%)	0.708
First attack	7 (20.6%)	25 (21.7%)	0.886
Disease extent			
Extensive UC (pancolitis)	28 (82%)	52 (45%)	< 0.001
Left-sided UC/proctitis	6 (18%)	63 (55%)	-
BMI at admission	19.5 ± 3.2	18.9 ± 3.1	0.384
Severity			
Severe	11 (32%)	27 (23%)	0.297
Moderate	23 (68%)	88 (77%)	-
Laboratory data at admission			
CRP (mg/dL)	3.4 ± 4.1	3.8 ± 5.4	0.685
WBC (× 10^3/μL)	8.7 ± 3.7	9.9 ± 4.2	0.132
Hemoglobin (g/dL)	11.4 ± 1.8	11.7 ± 1.2	0.387
Platelet (× 10^3/μL)	321.0 ± 118.9	349.9 ± 120.2	0.219
Total cholesterol (mg/dL)	155.3 ± 39.7	155.1 ± 44.3	0.979
Albumin (g/dL)	3.0 ± 0.54	3.4 ± 0.68	0.002
Medication			
Total lifetime systemic steroid dose before admission (g)	4.69 ± 5.80	4.86 ± 8.45	0.892
Total systemic steroid dose for 4 wk before admission (mg)	1083.4 ± 1113.5	245.5 ± 328.4	< 0.001
Total systemic steroid dose for 1 wk before admission (mg)	260.7 ± 103.9	92.3 ± 117.0	< 0.001
Systemic steroid dose on the day at admission (mg)	37.5 ± 15.0	13.9 ± 17.6	< 0.001
5-ASA	29 (85.3%)	82 (71.3%)	0.100
SASP	1 (2.9%)	10 (8.7%)	0.260
Cytapheresis	5 (15%)	11 (9.6%)	0.395
Immunomodulator use	8 (24%)	20 (17%)	0.421
AZA	4 (12%)	16 (14%)	0.747
6-MP	2 (5.9%)	2 (1.7%)	0.177
Tacrolimus	2 (5.9%)	2 (1.7%)	0.177
Infliximab use	5 (15%)	7 (6.1%)	0.105
Family history of IBD	1 (2.9%)	1 (0.87%)	0.356
PSC	0	2 (1.7%)	-
Outcome			
Ganciclovir use	26 (76%)	0	-
Colectomy	17 (50%)	37 (32%)	0.058
Colectomy for cancer or dysplasia	0	4 (3.5%)	-

Values presented as mean ± SD or number (%) as appropriate. CMV: Cytomegalovirus; CRP: C-reactive protein; WBC: White blood count; BMI: Body mass index; 5-ASA: 5-aminosalicylate acid; SASP: Salicylazosulfapyridine; AZA: Azathioprine; 6-MP: 6-mercaptopurine; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis.

Table 2 Risk factors for cytomegalovirus-associated colitis among the 149 patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	P value
Age at UC diagnosis > 30 yr	2.764	0.581-13.152	0.202
Age at admission > 35 yr	1.433	0.295-6.951	0.655
Pancolitis	3.419	1.077-10.856	0.037
Albumin < 3.0 g/dL	1.402	0.480-4.098	0.537
Total systemic steroid dose for 4 wk before admission > 400 mg	26.697	5.848-121.868	< 0.001

UC: Ulcerative colitis; CMV: Cytomegalovirus.

ssion. There were no significant group differences in sex ratio, disease duration, clinical course, total lifetime systemic steroid dose, immunomodulator use, infliximab use, or laboratory data at admission other than serum albumin level.

For multivariate analysis, we selected a total systemic steroid dose for 4 wk before admission as the most important factor among factors regarding steroid dose. This multivariate analysis using a logistic regression model identified pancolitis and a total systemic steroid dose > 400 mg for 4 wk before admission as significant independent risk factors for CMV infection (Table 2). Patients treated with more than 400 mg corticosteroid for UC exacerbation over the 4 wk prior to admission had a 27-fold greater risk of CMV-associated colitis and patients with extensive UC (pancolitis) had about a 3-fold greater risk. The other factors tested (age at UC diagnosis, age at admission, and serum albumin) were not significant risk factors by multivariate analysis.

Table 3 Endoscopic findings in patients with active ulcerative colitis (n = 149)

	CMV (+) n = 34	CMV (-) n = 115	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Deep ulcer	17 (50.0%)	14 (12.2%)	79.2	50.0	87.8	54.8	85.6	< 0.001
Punched-out ulcer	20 (58.8%)	8 (7.0%)	85.2	58.8	93.0	71.4	88.4	< 0.001
Geographical ulcer	14 (41.2%)	25 (21.7%)	76.5	41.2	78.2	35.9	81.8	0.024
Longitudinal ulcer	11 (32.4%)	24 (20.9%)	68.5	32.4	79.1	31.4	79.8	0.165
Mucosal defect	6 (17.6%)	10 (8.7%)	74.5	17.6	91.3	37.5	78.9	0.139
Mucopurulent exudate	24 (70.6%)	66 (57.4%)	49.0	70.6	42.6	26.7	83.1	0.167
Spontaneous bleeding	14 (41.2%)	19 (16.5%)	73.8	41.2	83.5	42.4	82.8	0.002
Cobblestone-like appearance	5 (14.7%)	7 (6.1%)	75.8	14.7	93.9	41.7	78.8	0.105
Post inflammatory polyp	9 (26.5%)	21 (18.3%)	75.8	26.5	81.7	30.0	79.0	0.294

PPV: Positive predictive value; NPV: Negative predictive value; CMV: Cytomegalovirus.

Table 4 Characteristic endoscopic findings for cytomegalovirus-associated colitis in patients with active ulcerative colitis (multivariate analysis)

	Odds ratio	95%CI	P value
Deep ulcer	2.128	0.678-6.680	0.196
Punched-out ulcer	12.672	4.210-38.143	< 0.001
Geographical ulcer	1.919	0.664-5.542	0.229
Spontaneous bleeding	2.106	0.735-6.036	0.166

Endoscopic findings

To identify endoscopic findings characteristic of CMV-associated colitis in patients with active UC, we analyzed ulcerative features (*e.g.*, deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect) and mucosal features (*e.g.*, mucopurulent exudate, spontaneous bleeding, cobblestone-like appearance, and post inflammatory polyp). Characteristic colonoscopic features of CMV-associated colitis included deep ulcer, punched-out ulcer, geographical ulcer, longitudinal ulcer, and mucosal defect (Figure 2). We defined endoscopic findings according to published reports[28,38]. Deep ulcer was defined as deep excavated ulceration near or beyond muscularis propria with or without slightly raised edges. Punched-out ulcer was defined as ulceration with an almost round shape and clear demarcation. Geographical ulcer was defined as ulceration with an irregular pattern and a branched shape. Longitudinal ulcer was defined as ulceration with a longitudinal spread along the lumen of the colon. Mucosal defect was defined as a wide area of defect with a longitudinal and/or transverse spread, indicating that more than one-fourth of the mucosa in the endoscopic field was defective. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for each of these features were determined. Univariate analysis revealed that deep ulcer, punched-out ulcer, geographical ulcer, and spontaneous bleeding were more frequent in CMV-positive patients than in CMV-negative patients (Table 3).

Multivariate analysis showed that only punched-out ulcer was a significant independent predictor of CMV colitis (OR = 12.672, 95%CI: 4.210-38.143) (Table 4).

Patient outcomes

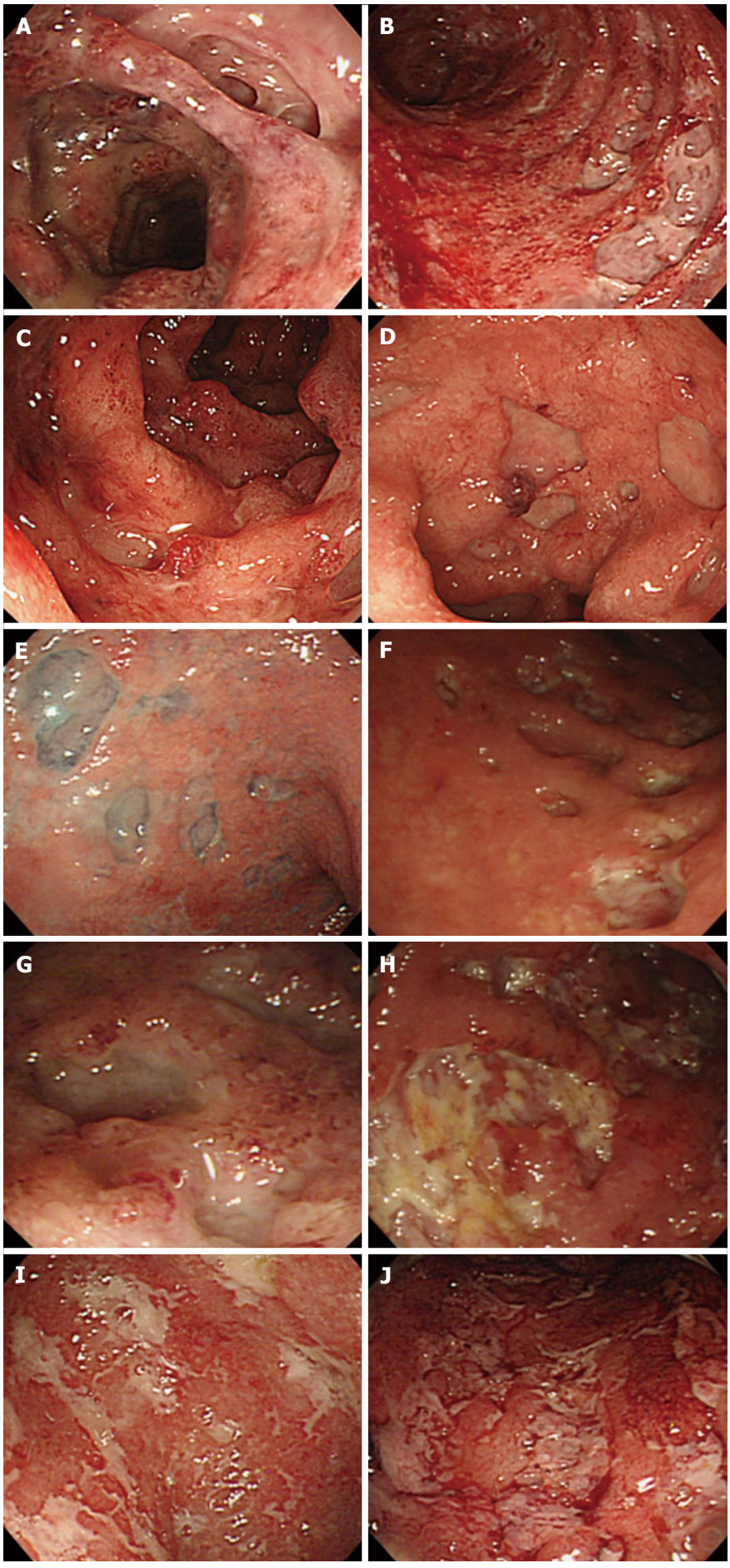
In the CMV-positive (CMV-associated colitis) group, 26 of the 34 patients (76.5%) received antiviral therapy with GCV. After GCV therapy, 13 of these patients achieved remission, while 13 required colectomy because of severe and refractory UC. Of the remaining 8 patients who did not receive GCV antiviral therapy, 4 underwent colectomy because of severe UC.

Among the CMV-negative group, 81 patients (70.4%) achieved remission with anti-inflammatory therapy (including relapse cases), while 37 (32.2%) eventually underwent colectomy during the course of follow-up. Among these 37 patients, 4 underwent colectomy for cancer or dysplasia.

DISCUSSION

In this retrospective study of 149 UC patients presenting with exacerbation of symptoms, we identified extensive UC (pancolitis) and 4 wk of high-dose steroid treatment as independent risk factors for CMV-associated colitis in active UC. The only endoscopic finding indicative of CMV-associated colitis by multivariate analysis was punched-out ulcer. To our knowledge, this is the first study to identify both risk factors and characteristic endoscopic findings for CMV-associated colitis in patients with moderate to severe UC. These factors may help facilitate both the timely diagnosis and treatment of UC complicated by CMV infection.

We evaluated total systemic steroid dose over the patient's lifetime, as well as dose over the 4 wk before admission, over the previous week before admission, and on the day of admission. Between CMV-positive and CMV-negative patients, total systemic steroid dose over the 4 wk prior to admission (total dose > 400 mg) was an independent risk factor for CMV-associated colitis in active UC patients. Furthermore, neither immunomodulator nor infliximab use was associated with CMV-associated colitis. However, this study included only a few cases treated by immunomodulators or infliximab, and additional studies are required to confirm these results. Nonetheless, the finding that immunomodulator and infliximab use did not alter the risk of CMV-associated colitis is important, because it suggests an alternative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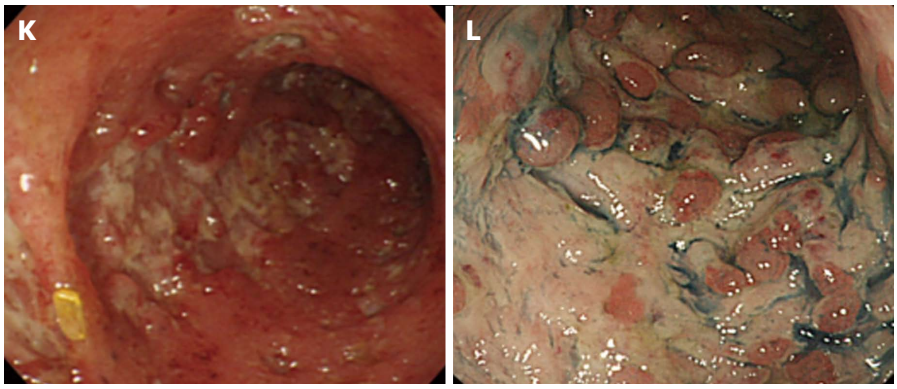

Figure 2 Endoscopic images of cytomegalovirus-associated colitis in patients with active ulcerative colitis. A-C: Deep ulcer; D-G: Punched-out ulcer; H-J: Geographical ulcer; K: Longitudinal ulcer; L: Mucosal defect.

treatment regimen for patients with moderate to severe UC rather than using high-dose corticosteroids for corticosteroid-refractory cases or corticosteroid-resistant cases. Given that tumor necrosis factor (TNF)-α from monocytes and dendritic cells plays an important role in the reactivation of CMV and that infliximab is a potent blocker of TNF-α, we consider that this combination therapy may be particularly effective[7,39]. However, the efficacy of infliximab for UC patients with concomitant CMV infection remains controversial, as there have been few case reports and no controlled clinical trials.

Pancolitis was significantly associated with CMV infection in active UC, consistent with the theory that CMV is prone to proliferate in granulation tissue[9]. Some studies reported that CMV was readily found in granulation tissue and tissue from deep ulcers, suggesting that CMV can penetrate inflamed mucosa *via* mononuclear cells and then proliferate in the mucosa[2,9,40,41]. It is thus possible that a more extensive UC lesion may lead to wider CMV infection.

In general, there is no clear consensus on the diagnostic criteria for CMV infection in active UC. There are several methods of detecting CMV infection, including histology with IHC, serology, CMV culture, polymerase chain reaction (PCR) detection of the CMV genome, and CMV antigenemia[6,34-37,42]. Each method offers advantages and disadvantages in the precise diagnosis of CMV infection. For example, histological examination is a relatively easy method, but its sensitivity is lower (10%-87%) than PCR. In contrast, PCR for CMV genes is highly sensitive, but the method is time-consuming and its selectivity is low given the ubiquity of CMV infection. CMV culture is too slow. In contrast, CMV antigenemia is relatively sensitive (60%-100%) and easy to measure within a short period, and has also been used to monitor CMV infection in heart transplant recipients and for the early diagnosis of CMV infection in renal transplant recipients[43]. Moreover, results of CMV antigenemia are good indication for antiviral therapy[44,45].

Accordingly, we adopted CMV antigenemia and histology, including IHC for CMV, to detect CMV infection in our analysis. Results showed that 33 of the 34 CMV-associated colitis patients (97.1%) were positive for CMV antigenemia. Histology including IHC is considered the objective standard for the diagnosis of CMV infection. In our study, however, among the 34 patients with CMV-associated colitis whose biopsy specimens were stained with HE and a CMV antibody, only 8 patients were positive by histology. Only 7 were positive by both CMV antigenemia and hitology. We therefore suggest that our combination of CMV antigenemia and histology including IHC for CMV is an appropriate strategy for diagnosis of CMV infection/CMV-associated colitis in active UC patients.

Colonoscopy is usually performed in patients with exacerbation of UC symptoms because direct observation of the colonic mucosa provides detailed information on disease status and is useful for judging disease severity and treatment efficacy. The rapid and accurate diagnosis of CMV-associated colitis in UC patients is critical, because its treatment strategy differs markedly from that for UC exacerbation not associated with CMV infection. A few reports have documented the endoscopic findings of CMV-associated colitis, but several failed to find features able to rapidly distinguish CMV-associated colitis from unrelated active UC. Endoscopic findings of UC concomitant with CMV infection can range from normal appearing mucosa to mucosal erosion or ulceration, which can be difficult to distinguish from active UC unrelated to CMV infection. In our study, punched-out ulceration was significantly more frequent in UC patients with CMV infection, consistent with reports that CMV tends to localize to the colon mucosa and granulation tissue in deep ulcers[2,9,40,41]. Regardless of etiology, we suggest that a finding of punched-out ulceration may facilitate the rapid and accurate diagnosis of CMV-associated colitis in UC patients.

The limitations of this study include its retrospective nature and evaluation of patients at a single institution. This study also involved a relatively small number of patients, which limits its statistical power.

In conclusion, this study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of

CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

COMMENTS

Background

Although it has been reported that cytomegalovirus (CMV) infection can be associated with steroid resistance and be an exacerbating factor in ulcerative colitis (UC), the relationship between CMV and UC is not well studied.

Research frontiers

The aim of this study was to identify characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Innovations and breakthroughs

This is one of a few retrospective studies focused on important information regarding characteristic endoscopic findings and risk factors for CMV-associated colitis in patients with active UC.

Applications

This study suggests that a total corticosteroid dose > 400 mg for 4 wk and extensive colitis are associated with an increased risk of CMV-associated colitis in patients with moderate to severe UC. In addition, punched-out ulceration appears predictive of CMV-associated colitis associated with UC. These clinical predictors and specific endoscopic findings may facilitate rapid diagnosis and antiviral treatment.

Peer-review

An interesting article dealing with clinically relevant subject of risk factors in ulcerative colitis. There is a solid number of patients and good experimental and clinical design. Data are good and discussion is a good representation of the problem.

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