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ORIGINAL ARTICLE

Acute Cytomegalovirus Infection Is a Risk Factor in Refractory and Complicated Inflammatory Bowel Disease

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Abstract The role of cytomegalovirus (CMV) infection in patients with inflammatory bowel disease (IBD) is controversial. Although CMV has been specifically associated with refractory disease, the strength and nature of this association have been a subject of debate. The aim of this study was to evaluate the prevalence and outcome of acute cytomegalovirus infection in patients with severe refractory and complicated inflammatory bowel disease. Seventy-two patients with active IBD (both ulcerative colitis [UC] and Crohn's diseases [CD]) were included in this study. Thorough history taking and physical examination of all patients was made with special emphasis on symptoms and signs of CMV disease. Colonoscopic assessment was made for the extent and activity of IBD and collection of specimen. Prevalence of CMV infection was estimated by serology; anti-CMV IgM and IgG antibodies, and pathologic studies of colonic biopsies used conventional haematoxylin and eosin (H & E) and immunohistochemistry (IHC) with monoclonal antibodies. Complete blood count and liver function tests were done for all patients. Among 72 patients with active inflammatory bowel disease, 23 (31.9%) were resistant to intravenous steroids. CMV was detected in eight (six with UC and two with CD) of the 23 (34.8%) steroid-resistant patients and in only one (3.2%) patient in the remaining 31 patients under steroid treatment and was not detected in 18 IBD patients not using steroids. Among nine CMV-positive IBD patients, six (66.6%) were female and six had fever; cervical lymphadenopathy was found in five patients and splenomegaly in two, compared to no patients in the CMV-negative group ($P = 0.01$ and 0.03, respectively). Leucopenia and thrombocytopenia were predominantly seen in the CMV-positive versus CMV-negative patients (2.1 ± 0.3 vs. 5.9 ± 3.4 and 98 ± 34 vs. 165 ± 101, respectively). Pancolitis was found in five of nine CMV-positive IBD patients whereas in only two patients out of 63 in the CMV-negative group ($P = 0.005$). Acute CMV infection in patients with IBD is not rare and is often underestimated. CMV infection in patients with refractory or complicated IBD should be ruled out before aggressive immunosuppressive therapy. High clinical index of suspicion for the association of CMV infection with IBD should be directed towards female IBD patients presenting with fever, lymphadenopathy, splenomegaly, leucopenia, and mild hepatitis. CMV IHC is significantly more sensitive than routine H & E stain and should be considered as part of the routine evaluation of IBD patients with severe exacerbation or steroid-refractory disease before proceeding with other medical or surgical therapy that may not be necessary once the CMV is treated.

Keywords Inflammatory bowel disease · Ulcerative colitis · Crohn's · Cytomegalovirus

Introduction

Cytomegalovirus (CMV) is a member of the herpes-virus family and is a common viral infection in humans, occurring in 40–100% of adults. Clinically significant gastrointestinal CMV disease usually occurs in the immunocompromised [1].

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Approximately one-third of bone marrow or organ transplant patients experience CMV disease [2]. It also affects cancer patients receiving chemotherapy, patients treated with steroids, and elderly patients. Cyclosporine and high-dose steroids have especially potent amplifying effects on CMV [3].

Inflammatory bowel disease (IBD) patients are usually immunosuppressed due to immunosuppressive medications and poor nutrition, as well as possible impairment of natural killer function [1, 4]. These factors, as well as CMV tropism for sites of inflammation, leave IBD patients at increased risk for active CMV infection and disease [1].

Another theory was that CMV was an innocent bystander in IBD colitis; this was based on experimental studies that showed that rapidly proliferating cells in granulation tissue are susceptible to CMV infection [5]. Many previous cases, however, have shown that some severe, refractory IBD colitis flares have been associated with documented CMV inclusion bodies and, in some instances, a 15% toxic dilation rate, a 62% colectomy rate, and a 44% mortality rate [5, 6].

The current most widely held theory is that CMV infects areas of active IBD and causes colonic injury in most cases [7]. Data on the prevalence of CMV colitis complicating IBD are sparse. A systematic review was published in 2004 that identified 33 case reports and nine case series [6]. The majority of case reports described patients with severe ulcerative colitis (UC) who had received steroids prior to CMV diagnosis [8]. Authors of one systematic review concluded that "critical appraisal of the available studies does not allow any firm conclusions about CMV seroprevalence in IBD" and that the strongest evidence is to be expected in a prospective case series of consecutive IBD patients [6].

The aim of this study was to evaluate the prevalence and outcome of acute CMV infection in patients with severe refractory and complicated inflammatory bowel disease.

Methods

Patients

The study was conducted over a 2-year period (September 2005–July 2007). Seventy-two patients with active IBD (both UC and Crohn's disease CD) attending the Gastroenterology Clinic or admitted to King Fahd Hospital, Hofuf, KSA were included in this study. Of these, 49 patients had UC (33 were females and 16 were males with age range 28–58 years) and 23 had CD (15 were males and eight were females with age range 17–43 years). Diagnosis of UC and CD was based on clinical, endoscopic, radiologic, and histologic parameters. Informed consent was obtained from each patient.

All patients were admitted and investigated as inpatients. UC patients had moderate or severe disease according to the Truelove–Witts scale [9], and all patients with CD had scores over 220 according to the CD activity index [10]. Thorough history taking and physical examination of all patients was made with special emphasis on symptoms and signs of CMV disease including high fever, lymphadenopathy and splenomegaly. Also, attention was paid as well to drugs used in the treatment for IBD prior to collection of the specimens for study of CMV infection, with particular attention to treatment with systemic steroids, azathioprine, methotrexate, and cyclosporine. The dose of these drugs and duration of administration were recorded. Demographic, clinical, and laboratory characteristics of IBD are shown in Table 1.

Colonoscopic Assessment for the Extent and Activity of IBD and Collection of Specimens

Colonoscopy was performed using a video colonoscope (Pentax EG- 3840 L) in all UC patients and 17 CD patients (in the remaining six CD patients, four had small intestinal lesions and two presented complications). Because patients with severe attacks of IBD are at increased risk of perforation during full-length colonoscopy [11], we tried to minimize air inflation during the procedure. Multiple biopsies were obtained during colonoscopy for histologic examination of inflammatory activity and CMV inclusion body. Biopsies were taken from active lesions and ulcer margins only.

Histopathology

Colonic biopsies, fixed in buffered neutral formalin, were paraffinized, sectioned, and stained with conventional haematoxylin and eosin (H & E). These sections were evaluated under a microscope for characteristic cytomegalic cells that are often two- to four-fold larger than surrounding cells, usually with large eosinophilic intranuclear inclusions, sometimes surrounded by a clear halo and smaller cytoplasmic inclusions [2, 4, 12]. Immunohistochemistry (IHC) with monoclonal antibodies directed against CMV immediate early antigen increases diagnostic yield of CMV compared to routine H & E staining [13, 14].

Histologically, activity of IBD was classified according to a standard system described previously [4, 15]. Briefly, absence of any significant inflammation was considered as remission, heavy inflammatory infiltrate with epithelial ulceration was considered active disease, while some degree of inflammatory infiltrate without epithelial ulceration was considered as moderately active disease.

Table 1 Demographic, clinical, and laboratory characteristics of inflammatory bowel disease (IBD)

Variable	Ulcerative colitis ($n = 49$)	Crohn's disease ($n = 23$)
Gender (male/female)	16/33	15/8
Age range, years (mean)	28–58 (41)	17–43 (30)
Duration of disease, months (mean)	18–70 (43)	16–55 (30)
Clinical findings		
Fever	8	44
Myalgias	23	17
Cervical	6	3
Lymphadenopathy		
Splenic enlargement	5	3
Disease presentation		
Moderate	16	6
Severe	17	7
Refractory	16	7
Complicated	–	3
Extent of disease	Left-side colitis (22)	Ileocecal (16)
	Pancolitis (7)	Small intestinal (4)
	Ulcerative proctitis (20)	Colonic (3)
Treatment		
Salazopyrine	39	14
Oral steroids	16	7
IV steroids	19	12
Azathioprine	11	5
Metronidazole	–	9
None	–	–

Serology

Anti-CMV IgM antibodies were tested in all sera by μ-capture ELISA using a commercially available kit (Organon Teknika) using the positive and negative controls provided with the kit.

Complete blood count and liver function tests were done for all patients.

Statistical Analyses

Data were compared using the Mann–Whitney U test. Parameters found to be associated with infection with CMV were entered into a multivariate setting, where the independent effect of each factor was adjusted for the contributions of each of the other factors with infection with CMV. P values below 0.05 were considered significant. Statistical tests were done using a computerized model for repeated measures (SPSS version 12.0; SPSS, Inc., Chicago, IL, USA).

Results

Patients with UC and CD had clinically moderate or severe inflammatory bowel disease during the time of their assessment in the study. UC location was proctitis (40.8%), left-side colitis (44.9%), and pancolitis (14.3%). CD location was small bowel (17.4%), colon (13%), and ileocecal (69.6%).

Fifty-three (73.6%) of the IBD patients were treated with salazopyrine, 16 (22.2%) were treated with azathioprine, and 54 (75%) were treated with steroids. Thirty-one (57.4%) of the steroid-treated group of patients were given high-dose steroids (receiving glucocorticoids $\geq$0.5 mg/kg body weight) during the 14 days before inclusion.

The average period from onset of IBD symptoms to entrance in the study was 41.3 $\pm$ 22.9 months, whereas the average duration of treatment was 31.6 $\pm$ 21.1 months. Eight UC and four CD patients had fever at onset of admission, nine IBD had cervical lymphadenopathy, and eight had splenomegaly. Eleven were leuckopenic, seven had low platelets, and 17 had hypertransaminases.

Among 72 patients with active inflammatory bowel disease, 23 (31.9%) were resistant to intravenous steroids (16 were UC and seven were CD; three of them were admitted with complications, two cases had intestinal obstruction, and one had ileocecal inflammatory mass with abscess formation). In eight (six with UC and two with CD) of these 23 (34.8%) steroid-resistant patients, CMV was detected by anti-CMV IgM alone in three patients, histologic specimens stained with conventional haematoxylin and eosin alone in one, by IHC in three (43.5%), and by all methods in one patient. CMV was detected in only one (3.2%) patient of the remaining 31 under steroid treatment, and CMV was not detected in 18 IBD patients not using steroids.

In one of these CD patients, CMV was detected in the surgical specimen because the patient was operated on the day 3 due to intestinal obstruction.

Among nine CMV-positive IBD patients, six (66.6%) were female, with 27 out of 63 (42.8%) females in the CMV-negative group ($P = 0.01$). No significant statistical difference was found between both groups regarding disease duration ($P > 0.67$).

Six out of nine CMV-positive IBD patients had fever (38°C $\pm$ 2.9°C) compared to no fever in CMV-negative patients (36.4°C $\pm$ 0.8°C; $P = 0.0001$). There was significant statistical difference regarding presence of cervical lymphadenopathy and splenomegaly which was found to be five and two patients, respectively, in the CMV-positive

Table 2 Demographic, clinical and laboratory characteristics of inflammatory bowel disease (IBD) with and without cytomegalovirus (CMV)

Variable	CMV-positive ($N = 9$)	CMV-negative ($N = 63$)	P value
Age (years)	41.3 ± 13	44 ± 11	0.64
Female gender	6 (66.6%)	27 (42.8%)	0.01
Duration of disease (months)	33.4 ± 12.1	40 ± 15.4	0.67
Myalgia	6/9	34/63	0.71
Fever (°C)	38 ± 2.9	36.4 ± 0.8	0.0001
Cervical lymphadenopathy (*n*)	5/9	0/63	0.01
Splenomegaly	2/9	0/63	0.03
WBC count (10^9/l)	2.1 (±0.3)	5.9 (±3.4)	0.007
Platelet count (10^9/l)	98 (±34)	165 (±101)	0.03
Transaminases (ALT & AST)	80 (±163)	43 (±28)	0.001
Pancolitis at colonoscopy	5/9	2/63	0.005
Corticosteroid refractory	8/9	1/63	
Complicated cases	2/9	1/63	
Azathioprine	2/9	10/63	
Requirement of surgery	1/9	0/63	

Table 3 Clinical data of refractory and nonrefractory inflammatory bowel disease (IBD) patients

Variable	Steroid-refractory ($N = 23$)	Steroid responsive ($N = 31$)	No steroid ($N = 18$)
CMV-positive	8/23	1/31	0/18
Age (years)	38.1 ± 15	40 ± 6	41 ± 12
Female/male	16/23	15/31	10/18
Disease duration (months)	32.5 ± 16.1	41 ± 11.6	36 ± 12.7
Duration of steroids (months)	16 ± 2.7	11 ± 13	–
Extent of disease pancolitis/left-sided/proctitis	5/10/6	2/5/6	3/5/0

CMV, cytomegalovirus

group compared to no patients having either lymphadenopathy or splenomegaly in the CMV-negative group ($P = 0.01$ and 0.03, respectively).

Leucopenia and thrombocytopenia were predominantly seen in CMV-positive versus CMV-negative patients (2.1 ± 0.3 vs. 5.9 ± 3.4 and 98 ± 34 vs. 165 ± 101, respectively). Two- to four-fold elevations in transaminases were found in CMV-positive patients compared to the CMV-negative group (80 ± 163 vs. 43 ± 28, $P = 0.001$).

Total colonic involvement (pancolitis) was found in five of nine CMV-positive IBD patients vs. only two patients out of 63 CMV-negative ($P = 0.005$). Eight out of nine were steroid-resistant patients, two of them were CD admitted by intestinal obstruction, while only two patients who were receiving azathioprine had positive CMV. A comparison of demographic, clinical and laboratory characteristics of IBD with and without CMV is shown in Table 2.

CMV-positive IBD patients found in the steroid-refractory group numbered 8 out of 23, with only one patient of 31 in the steroid responsive group, and no CMV-positive patients in the rest of the IBD patients (0/18). There was no statistical significant difference between steroid-resistant, responsive, and IBD patients who did not use steroid with regard to age, gender, and disease duration. Clinical data of refractory and nonrefractory IBD patients are shown in Table 3.

Discussion

CMV infection is a well recognized cause of colitis in immunodepression such as in AIDS, transplant-recipient patients, malignancies, or during treatment with chemotherapy or corticosteroids [16]. In contrast, this infection has been seldom reported in immunocompetent hosts [17].

Patients with IBD could be considered a group at risk for acquiring CMV infection for several reasons. First, these patients are frequently treated with immunosuppressive agents such as corticosteroids, azathioprine, 6-mercaptopurine, cyclosporine A, or methotrexate. Moreover, inflammation itself seems to be a predisposing factor because of the demonstrated tropism of CMV for proliferating cells of granulation tissues [1]. In recent years,

cases of inflammatory bowel disease (IBD) associated with CMV infection have occasionally been reported [18–20]. In these patients and especially those with refractory disease, CMV has been recognized in colonoscopic biopsy specimens obtained during evaluation and management of IBD or diagnosed after pathologic examination of resected colon [18, 19].

In this study, 72 patients diagnosed as active IBD were included, among which were three cases of CD admitted with complications. Fifty-three (73.6%) of the IBD patients were treated with salazopyrine, 16 were treated with azathioprine, and 54 (75%) were treated with steroids. CMV was detected in nine out of 72 patients (12.5%). Six out of nine (66.6%) IBD patients with CMV were females. Female preponderance in the CMV-infected group, as observed in our study, has already been described [21].

Criscuoli et al. [12], in a prospective study of an Italian population, examined the prevalence rate of CMV infection among a population of consecutive IBD patients admitted with severe acute colitis; the prevalence of CMV infection among all admitted IBD patients with severe acute colitis was 21%.

Twenty-three out of 72 (31.9%; 16 UC and seven CD) were resistant to intravenous steroids defined as persistent active disease despite high-dose systemic corticosteroid therapy. In eight (six with UC and two with CD) of these 23 (34.8%) steroid-resistant patients, CMV was detected, while 9 of 54 (20%) patients were CMV-positive in all patients under steroid treatment.

Our results were in agreement with a study by Cottone et al. [19] which examined the prevalence rate of CMV in a group of severe steroid-refractory IBD patients and found it to be 36%. Criscuoli et al. [12], in another prospective study of the same Italian group, showed that the prevalence rate of CMV infection in the steroid-refractory group was 33%, which approximates the previous estimate.

Detection of CMV-specific IgM antibodies has a sensitivity of 100% and specificity of 99% for documenting recent viral infection [22]. In our study anti-CMV IgM was detected in three patients, all in the steroid-resistant group, but immunocompromised patients sometimes may not mount an IgM response at all [2], which may give an explanation as to why anti-CMV IgM was not detected in all our positive cases.

As it was suggested that CMV inclusion bodies are more often found in the right colon than in the left [23], multiple biopsies were taken from the colon, particularly from the inflamed and ulcerated areas since CMV has tropism for the inflamed sites [4, 24]. Since we had to consider risk of perforation during full-length colonoscopy, we tried to minimize air inflation during the procedure.

Therefore, it is less likely that false-negative results in our study were related to sampling error.

Histologic examination of colonic biopsies had the lowest sensitivity, probably because the characteristic inclusion bodies are not readily visible in routinely performed H & E stain and because CMV-infected cells are not always cytomegalic [13]. In our study CMV was detected in only one histologic specimen stained with conventional haematoxylin and eosin.

IHC with monoclonal antibodies directed against CMV immediate early antigen increases diagnostic yield of CMV compared to routine H & E staining [13, 14]. Sensitivity of IHC for detecting CMV infection can approximate 93% [25]. Our study revealed three (43.5%) cases positive for CMV by IHC. It is also of interest that the association was more evident in intestinal tissue than in blood samples.

CMV infection must be distinguished from CMV disease. CMV disease is the presence of CMV infection and the presence of clinical signs and symptoms, such as fever, leukopenia, or end organ involvement [26]. Some also consider the presence of typical CMV inclusions within cell preparations or end organ tissue, or positive viral cultures, crucial for the diagnosis of CMV disease [2].

Because we study CMV in an active state and its implications on IBD patients, we evaluated all patients for clinical and laboratory parameters, and endoscopic extension of CMV disease.

In our study, IBD patients suffering from high temperature, cervical lymphadenopathy, and splenomegaly were found to be related to the CMV-positive group, a presentation that increased clinical suspension about CMV disease. Also, significant leucopenia ($P = 0.007$), thrombocytopenia ($P = 0.03$), and mild hepatitis reflected slight liver function test abnormalities ($P = 0.001$) and five out of nine CMV-positive endoscopically showed pancolitis. All previously mentioned clinically, laboratory and endoscopic extension give more documents of acute CMV presentation rather than only severe IBD.

Previous results have linked CMV infection with ulcerative colitis, whereas a less strong association has been proposed with this viral infection and CD [6, 27, 28]. In our study, a significant association was detected between CMV intestinal infection and either ulcerative colitis or CD, although the association was even stronger for patients with UC. We reported that two cases of CD positive for CMV were presented by complications.

However, immunosuppressive agents for treatment of IBD patients might predispose them for acquiring CMV infection [29, 30]. Also, inflammation itself appears to be a predisposing factor because of the demonstrated tropism of CMV for proliferated cells of granulation tissues [16]. Also, a statistically significant association between clinically severe or endoscopically active IBD and CMV infection was detected here.

In conclusion, acute CMV infection in patients with IBD is not rare and is often underestimated. This has definite clinical significance and therefore should not be ignored.

CMV infection in patients with refractory or complicated IBD should be ruled out before aggressive immunosuppressive therapy for treatment-resistant disease to decrease morbidity and mortality.

High clinical index of suspension for the association of CMV infection with IBD should be directed towards female patients presenting with fever, lymphadenopathy, splenomegaly, leucopenia, and mild hepatitis.

The identification of typical viral inclusions on routine H & E stain continues to be a key screening test in the initial evaluation of biopsy specimens from patients with severe or refractory disease, but viral inclusions can be difficult to detect when they are present in low density or atypical in appearance. CMV IHC is significantly more sensitive than routine H & E stain and should be considered as part of the routine evaluation of IBD patients with severe exacerbation or steroid-refractory disease before proceeding with other medical or surgical therapy that may not be necessary once the CMV is treated. To further improve the generalizability of our findings we recommend a multicenter study, to be applied on larger numbers of UC and CD patients as separate groups.

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