MAJOR ARTICLE

Clinical Presentation and Risk Factors for Cytomegalovirus Colitis in Immunocompetent Adult Patients

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Background. Cytomegalovirus (CMV) colitis is a common manifestation of CMV end-organ disease, which has typically been described in immunocompromised hosts. Recently, it has been noted that this also occurs in immunocompetent patients. To gather relevant data about clinical presentation, prognosis, and risk factors for development of CMV colitis in immunocompetent hosts, we analyzed all cases that occurred during a 19-year period at our institution.

Methods. A case-control study was performed to identify risk factors for CMV colitis in immunocompetent hosts. Electronic medical records of individuals who were admitted and diagnosed with CMV colitis between January 1995 and February 2014 at a tertiary care university hospital were reviewed. Two non-CMV colitis patients who were age- and sex-matched were selected as controls for each case.

Results. A total of 51 patients with CMV colitis were included in this study along with 102 control patients. Certain conditions including renal disease on hemodialysis, neurologic disease, rheumatologic disease, intensive care unit admission, and exposure to antibiotics, antacids, steroids, or red blood cell (RBC) transfusions within 1 month of diagnosis of colitis were associated with CMV colitis on univariate analysis. Among these, steroid use and RBC transfusion within 1 month were identified as independent risk factors for developing CMV colitis on multivariate analysis. The 30-day mortality rate was 7.8% without any attributable mortality.

Conclusions. Steroid use and RBC transfusion within 1 month of the diagnosis of colitis were independent risk factors for development of CMV colitis in immunocompetent hosts.

Keywords. cytomegalovirus; colitis; blood transfusion; steroids; risk factors.

Cytomegalovirus (CMV) colitis is a common manifestation of CMV end-organ disease, which is associated with significant morbidity, such as abdominal pain, diarrhea, GI bleeding, and colon perforation [1, 2]. Although it has typically been described in immunocompromised patients such as those with human immunodeficiency virus (HIV) infection, solid organ transplant (SOT), ulcerative colitis, or malignancy [3–9], there have been several descriptive case series among immunocompetent hosts [10–12]. One study evaluated outcomes of CMV colitis in 44 immunocompetent patients via literature search [13]. However, data regarding risk factors for development of CMV colitis and clinical characteristics in immunocompetent hosts have not yet been reported. As clinical suspicion and endoscopic examination are essential for the diagnosis of CMV colitis [12], there is a clear need for these data. To this end, all cases of CMV colitis presenting during a 19-year period at our center were analyzed to evaluate risk factors for development of CMV colitis and its clinical presentation in immunocompetent hosts.

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METHODS

Study Design and Patient Selection

A case-control study was designed to identify the clinical presentation and risk factors for development of CMV colitis in adult immunocompetent patients. We reviewed the electronic medical records of individuals who were admitted and diagnosed with CMV colitis between January 1995 and February 2014 at Samsung Medical Center, Seoul, Republic of Korea. This is a 1950-bed tertiary care university hospital and referral center. This study included patients with CMV colitis who were aged >19 years at the time of diagnosis. Patients with HIV infection, ulcerative colitis, or a history of SOT were excluded. Cancer patients were also excluded, with the exception of those who had been in complete remission for >5 years. To establish a control group, we screened all adult patients who were admitted to the hospital with a clinical diagnosis of colitis. Two age- and sex-matched control patients were selected for each case patient. Exclusion criteria were the same as those used for case patients.

Table 1. Clinical Presentation of Cytomegalovirus Colitis

Variables	CMV Colitis (n = 51)
Viral markers	
CMV antigenemia (n = 30), median (IQR)	2 (0–22)
Positive (≥1/200 000 WBCs)	17 (57%)
CMV IgG positive (n = 10)	10 (100%)
CMV IgM positive (n = 12)	1 (8.3%)
Symptoms	
Fever	8 (15.7%)
Abdominal pain	8 (15.7%)
Nausea/vomiting	3 (5.9%)
Diarrhea	23 (45.1%)
Hematochezia	26 (51.0%)
Melena	4 (7.8%)
Time to symptom improvement, d, median (IQR)	4 (3–7)
Endoscopic findings	
Ulcer	45 (88.2%)
Erosion	19 (37.3%)
Mass-like lesion	2 (3.9%)
Endoscopic follow-up performed	17 (33%)
Time to endoscopic improvement, d, median (IQR)	20 (15–25)
Treatment	
Ganciclovir administration	39 (76.5%)
Treatment duration, d, median (IQR)	14 (14–21)
Treatment failure	0 (0%)
Surgical resection	5 (9.8%)
Improved without treatment	9 (17.6%)

Data are expressed as No. (%) of patients unless indicated otherwise.

Abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; WBC, white blood cell.

Data Collection

We collected the following data from the electronic medical records: age, sex, body mass index (BMI), white blood cell (WBC) count with differential, hemoglobin levels, platelet count, albumin, erythrocyte sedimentation rate, C-reactive protein level, CMV antigenemia, CMV serologies, presenting symptoms, endoscopic findings, underlying diseases, comorbid conditions, treatment duration, treatment outcomes, drug administration history, and transfusion history. Laboratory data were collected on the day of diagnosis of colitis. The cumulative dose of steroids administrated within 1 month of the diagnosis of colitis was calculated and converted into an equivalent dose of prednisone. The total amount of transfused blood products within 1 month of the diagnosis of colitis was also calculated. The Charlson weighted index of comorbidity was used to evaluate comorbid conditions.

Definitions

In this study, patients were defined as having CMV colitis if they met both of the following criteria: (1) clinical symptoms and signs compatible with colitis such as diarrhea or hematochezia, and (2) pathologically confirmed CMV tissue involvement. Immunocompetent patients were defined as those who did not have HIV infection, ulcerative colitis, SOT, or active cancer.

Pathologic Confirmation of CMV Infection

Pathologic specimens were obtained by colonoscopy, sigmoidoscopy, or surgery. CMV infection of the involved tissue was confirmed either by immunohistochemistry (IHC) or polymerase chain reaction (PCR), taken together with characteristic histopathologic findings. IHC staining was performed with monoclonal antibodies directed against CMV immediate early nuclear protein and early nuclear protein (Clones CCH2 + DDG9, DAKO, Glostrup, Denmark).

Statistical Analysis

To evaluate risk factors, Student *t* tests and Mann–Whitney *U* tests were used to compare continuous variables, and χ^2 tests and Fisher exact tests were used to compare categorical variables. We used a logistic regression model to control for confounding variables and to identify independent risk factors for the development of CMV colitis. All *P* values were 2-tailed, and those <.05 were considered to be statistically significant. SPSS for Windows (IBM, Armonk, New York), Statistics version 20.0 was used for all statistical analyses.

RESULTS

Clinical Presentation and Prognosis of CMV Colitis

During the study period, we identified 51 immunocompetent patients with CMV colitis, and their clinical presentations are shown in Table 1. The mean age of the patients was 65.2 years, and approximately half were male. CMV immunoglobulin G (IgG) antibody was checked in 10 patients, all of which were positive. CMV antigenemia was tested in 30 patients, and the median titer was 2 per 200 000 WBCs (interquartile range [IQR], 0–22). Hematochezia (51%) was the most frequently observed symptom among patients with CMV colitis, followed by diarrhea (45.1%). Four patients had *Clostridium difficile* colitis concomitantly, and none of the case patients were diagnosed with or treated for other bacterial colitis. Most patients (88.2%) exhibited mucosal ulceration on endoscopic examination, and it took a median of 20 days to show improvement on endoscopic follow-up. A total of 39 patients (76.5%) received ganciclovir treatment for a median duration of 14 days. Five patients (9.8%) underwent surgical resection due to bowel perforation, uncontrolled bleeding, or colon stricture. Nine patients (17.6%) improved without specific treatment. The 30-day mortality was 7.8%, all related to comorbid conditions such as pneumonia, bacterial sepsis, or bowel ischemia. There was no contributable mortality from CMV colitis.

Baseline Characteristics and Comorbid Conditions of Patients With CMV Colitis

A total of 51 immunocompetent CMV colitis patients were age- and sex-matched to 102 control patients with non-CMV colitis. Baseline characteristics of CMV colitis patients were compared to those of control patients (Table 2). The median BMI was lower in the case group ($P = .045$). Patients with CMV colitis had lower WBC counts, hemoglobin levels, and albumin levels (all $P < .05$). Among the various underlying conditions evaluated, renal disease on hemodialysis, neurologic disease, and rheumatologic disease were more frequently observed in the case patients (all $P < .05$). Eleven patients in the case group (21.6%) were receiving care in the intensive care unit (ICU) at the time of diagnosis of colitis, which was significantly higher than that of the control group ($P < .05$).

Table 2. Baseline Characteristics and Comorbid Conditions of Patients With Cytomegalovirus Colitis

Variables	Case Group (n = 51)	Control Group (n = 102)	*P* Value
Age, y, mean ± SD	65.2 ± 14.0	65.1 ± 13.8	.984
Male sex	24 (47.1%)	48 (47.1%)	1.000
BMI, kg/m^2, median (IQR)	20.7 (18.4–22.3)	22.4 (20.1–24.5)	.045
Laboratory tests, median (IQR)			
WBC, cells/μL	6740 (4330–9510)	8830 (6180–11 958)	.003
Hemoglobin, mg/dL	9.7 (8.6–10.7)	12.5 (11.2–14.4)	<.001
Platelets, per μL	209 (107–301)	198 (157–258)	.917
ANC, per μL	4610 (2790–7680)	6610 (3939–10 061)	.005
ALC, per uL	900 (470–1589)	1055 (758–1622)	.100
Albumin, g/dL	2.7 (2.4–3.1)	3.8 (3.2–4.2)	<.001
ESR, mm/h	19 (6–57)	26 (10–53)	.231
C-reactive protein, mg/dL	2.6 (1.1–5.3)	3.9 (1.3–9.5)	.072
Underlying disease, any	44 (86.3%)	62 (60.8%)	.001
Cardiovascular disease	11 (21.6%)	17 (16.7%)	.460
Pulmonary disease	5 (9.8%)	5 (4.9%)	.302
Liver disease	3 (5.9%)	5 (4.9%)	1.000
Renal disease	16 (31.4%)	17 (16.7%)	.037
Renal disease on hemodialysis	10 (19.6%)	4 (3.9%)	.003
Neurologic disease	12 (23.5%)	9 (8.8%)	.013
Diabetes mellitus	15 (29.4%)	23 (22.5%)	.354
Hypertension	22 (43.1%)	37 (36.3%)	.411
Rheumatologic disease	8 (15.7%)	4 (3.9%)	.021
Charlson WIC, median (IQR)	1 (1–2)	0 (0–1)	<.001
ICU care	11 (21.6%)	1 (1.0%)	<.001

Data are expressed as No. (%) of patients, unless indicated otherwise.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BMI, body mass index; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; WBC, white blood cell; WIC, weighted index of comorbidity.

Table 3. Drug Exposure and Transfusion History Within 1 Month of Diagnosis of Cytomegalovirus Colitis

Variables	Case Group (n = 51)	Control Group (n = 102)	*P* Value
Antibiotic use	39 (76.5%)	27 (26.5%)	<.001
H2 blocker/PPI use	35 (68.6%)	11 (10.8%)	<.001
Aspirin/NSAID use	12 (23.5%)	17 (16.7%)	.307
Steroid use	28 (54.9%)	3 (2.9%)	<.001
Cumulative dose of steroid, mg, median (IQR)[a]	448 (155–865)	150 (NA)	.122
RBC transfusion	34 (66.7%)	2 (2.0%)	<.001
Total amount, units, median (IQR)	8 (3–12)	3 (NA)	.198
PLT transfusion	12 (23.5%)	0 (0.0%)	<.001
Total amount, units, median (IQR)	24 (17–83)	NA	
FFP/cryoprecipitate transfusion	15 (29.4%)	0 (0.0%)	<.001
Total amount, units, median (IQR)	6 (2–13)	NA	

Data are expressed as No. (%) of patients unless indicated otherwise.

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; PLT, platelet; PPI, proton pump inhibitor; RBC, red blood cell.

[a] The cumulative dose of steroids was converted into an equivalent dose of prednisone.

Drug Exposure and Transfusion History of Patients With CMV Colitis

Drug exposure and transfusion history within 1 month of the diagnosis of colitis were analyzed and are presented in Table 3. Thirty-nine patients (76.5%) with CMV colitis received antibiotic therapy, and 35 patients (68.6%) received antacid treatment (H2 blocker or proton pump inhibitor), both of which were significantly higher than that of the control group (both $P < .001$). A significantly higher proportion of patients with CMV colitis had a history of steroid use (28 patients [54.9%]) vs 3 patients (2.9%) in the control group ($P < .001$). The median cumulative steroid dose over the course of 1 month prior to diagnosis was 448 mg (as prednisone equivalent) among the CMV colitis patients. Use of aspirin and nonsteroidal anti-inflammatory drugs was not different between groups.

Thirty-four patients with CMV colitis (66.7%) had a history of red blood cell (RBC) transfusion within 1 month of the diagnosis of colitis. In contrast, there were only 2 patients in the control group who had history of RBC transfusion. Five patients in the case group were transfused with leukocyte-depleted RBCs together with non-leukocyte-depleted RBCs. None of the study patients received leukocyte-depleted RBCs only. The median transfusion volume was 7 units among the case patients. In all, 23.5% of the case patients underwent platelet transfusion and 29.4% received fresh frozen plasma (FFP) or cryoprecipitate. None of the control patients had a history of platelet, FFP, or cryoprecipitate transfusion.

Multivariate Analysis for Risk Factors of Development of CMV Colitis

Among the variables analyzed, a history of steroid use (odds ratio [OR], 40.17; 95% confidence interval {CI}, 11.24–143.65) and RBC transfusion (OR, 100; 95% CI, 21.96–255.37) within 1 month of the diagnosis of colitis showed the highest ORs. As the number of total case patients was limited to 51, multivariate analysis to adjust for possible confounding variables was performed separately (Table 4).

The first adjusted analysis was performed with respect to underlying diseases and showed statistical significance on univariate analysis. Renal disease on HD, neurologic disease, rheumatologic disease, history of steroid use, and history of RBC transfusion were included in the multivariate analysis, and only a history of steroid use (OR, 15.38; 95% CI, 2.49–95.08) and RBC transfusion (OR, 46.12; 95% CI, 90.15–232.34) showed statistical significance.

Table 4. Multivariate Analysis of Risk Factors for Development of Cytomegalovirus Colitis

	Adjusted Analysis 1		Adjusted Analysis 2	
Risk Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Renal disease on hemodialysis	1.72 (.24–12.22)	.589		
Neurologic disease	1.28 (.26–6.37)	.766		
Rheumatologic disease	0.807 (.08–8.43)	.858		
Antibiotic use within 1 mo			2.60 (.89–7.64)	.082
H2 blocker/PPI use within 1 mo			2.20 (.61–7.93)	.228
Intensive care unit admission			1.03 (.02–55.12)	.989
Steroid use within 1 mo	15.38 (2.49–95.08)	.003	9.95 (1.95–46.66)	.005
RBC transfusion within 1 mo	46.12 (90.15–232.34)	<.001	30.85 (5.70–167.06)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor; RBC, red blood cell.

The second adjusted analysis was performed with respect to a history of drug use and ICU care. A history of antibiotic use, antacid use, ICU care, steroid use, and RBC transfusion were included in the multivariate analysis. Again, a history of steroid use (OR, 9.95; 95% CI, 1.95–46.66) and RBC transfusion (OR, 30.85; 95% CI, 5.70–167.06) maintained statistical significance.

DISCUSSION

CMV colitis in immunocompetent hosts was first reported in 1988 [14], followed by sporadic case reports and case series [2, 10, 15–18]. Although reports in the early 1990s described CMV colitis in immunocompetent hosts as extremely rare, subsequent case reports suggested that it might be more frequent than previously believed. We also noticed an increasing trend in its occurrence in our data. Among 51 cases of CMV colitis, 36 cases (70.6%) had been diagnosed since 2008. However, the number of orders for CMV IHC or CMV PCR in colonic pathologic specimens also increased, and the rates of positivity of CMV IHC or CMV PCR remained stable throughout the study period (0.09–0.2). Thus, increased reports of CMV colitis in immunocompetent hosts are likely arising from increased clinical suspicion of CMV colitis, rather than true increases in its incidence. Although some reports have suggested that CMV colitis may be related to certain underlying conditions such as chronic renal disease [16, 18], there are no statistical data regarding risk factors for development. This is the first case-control study to evaluate risk factors for development of CMV colitis in immunocompetent hosts.

The prevalence of CMV-specific antibody varies throughout the world [19], and seroprevalence in the Korean population is reported to be high. Although there are no nationwide surveillance data in Korea, some studies have reported 96%–98% CMV IgG seroprevalence in pregnant women (575 women with a mean age of 29.5 years and 744 women with a mean age of 21.9, respectively) [20, 21], and 98%–100% in SOT recipients [22, 23]. As 49 case patients (96%) in this study were at least 40 years old and the younger patients were confirmed as CMV IgG seropositive, we can assume that most patients with CMV colitis in this study were CMV seropositive despite only 10 patients having been tested. Additionally, CMV antigenemia was evaluated in 30 case patients (58.8%), of which 43% were negative. The low sensitivity of CMV antigenemia for predicting CMV gastrointestinal disease was also suggested by previous studies [9, 24–26], and these findings imply that endoscopic testing with pathologic confirmation is essential for the diagnosis of CMV colitis. Among patients who were treated with ganciclovir, none experienced treatment failure. Given the median treatment duration (14 days [IQR, 14–21 days]), we cautiously assume that immunocompetent hosts do not need ganciclovir treatment for as long as HIV patients (21–42 days) for the treatment of CMV colitis [27].

In the 2 separate adjusted analyses, a history of steroid use and RBC transfusion within 1 month of the diagnosis of colitis were found to be independent risk factors for the development of CMV colitis. Steroids have immunosuppressive effect mainly by the derangement of T-lymphocyte and monocyte functions, and blockade of the production of inflammatory cytokines such as tumor necrosis factor α and interleukin 1β [28, 29]. Although direct effect of steroid use on susceptibility of CMV infection is not clearly identified in vitro, many clinical data support their relationship. It is well known that long-term use of systemic steroids may increase the risk of viral infections such as herpes zoster [30, 31], and recent retrospective studies suggest that systemic steroid use is a risk factor for CMV disease among patients with SOT, hematologic malignancies, and rheumatologic diseases [9, 29, 32–35]. To our knowledge, this is the first study to show a statistically significant relationship between steroid use and the development of CMV colitis in immunocompetent hosts.

In the present study, we designed study definition of immunocompetency with broad perspective to include patients with chronic obstructive pulmonary disease, glomerulonephritis, or rheumatologic diseases. As a result, long-term or high-dose steroid users were also included, which may attenuate strict meaning of immunocompetency. There were 5 long-term steroid users (>15 mg prednisone equivalent per day for >1 month) and 5 high-dose steroid users (>1 mg/kg prednisone equivalent per day regardless of duration) in the case group. Two of 5 high-dose steroid users also had history of cyclosporine administration within 1 month. We performed a subgroup analysis excluding these 10 cases. Steroid use within 1 month still showed a statistically significant association in the multivariate analysis (OR, 7.57; 95% CI, 1.18–48.54). This result implicates even low dose of steroid could be a risk factor for development of CMV colitis.

As noted above, most cases in the present study should be considered in the context of reactivation of CMV or acquisition of a new strain, due to the high seropositivity rate of Korean population. In 1972, a hypothesis was proposed that allogeneic blood transfusion may trigger reactivation of latent CMV infections in CMV-seropositive recipients, which was demonstrated in a murine model [36]. Thereafter, several in vitro and murine data supported the hypothesis showing that allogeneic leukocytes may play a role in activating latent CMV [37–39]. Also, a clinical study performed in seropositive cardiac surgery patients showed that similar rates of CMV antibody increase occurred with transfusion form CMV seropositive vs seronegative donors [40]. This indicated that reactivation accounts for most posttransfusion CMV infections in seropositive adults. However, as most studies of transfusion-related CMV infection among

seropositive recipients were designed to find evidence of viral replication in the blood, whether transfusion might result in CMV end-organ disease has not yet been evaluated. The present study provides clinical evidence of a relationship between blood transfusions and CMV end-organ disease.

There are several limitations to our study. Due to its retrospective nature, there may be a bias in the collection of medical information over the 19-year study period. However, all records of laboratory results and medications were fully computerized from the opening of Samsung Medical Center, which minimized possible information bias. Also, there is an inherent limitation in defining immunocompetence. Although we defined immunocompetent hosts as those who do not have HIV infection, ulcerative colitis, SOT, or active cancer, other comorbid conditions such as diabetes mellitus and chronic kidney disease also have negative effects on the host's immune status. Additionally, about half of case patients had history of steroid use within 1 month of the diagnosis with a median cumulative dose of 450 mg, which may have influenced host immunity. However, as most patients with CMV colitis have these comorbid conditions and drug exposure history, we thought it would be more relevant to define immunocompetence from a broader perspective. Last, this study may not provide data that is representative of the general population because it was conducted at a single tertiary care center. Despite these limitations, the present study is the first to identify risk factors for CMV colitis in immunocompetent hosts, and our findings may provide useful information for clinicians regarding their approach to these patients.

In conclusion, this study identified steroid use and RBC transfusion within 1 month of diagnosis as independent risk factors for development of CMV colitis among immunocompetent hosts.

Note

Potential conflicts of interest. All authors: No potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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