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ORIGINAL ARTICLE

Endoscopic and Clinical Features of Cytomegalovirus Colitis in Critically Ill Patients: A Retrospective Review

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Background: Patients with cytomegalovirus (CMV) colitis have increasingly been recognized among critically ill patients, yet few specific clinical and endoscopic features are known. In this study, we investigated the common clinical and endoscopic features of CMV colitis in critically ill patients.
Methods: From January 1, 2000 to February 28, 2014, patients with a histopathological diagnosis of CMV colitis were retrospectively reviewed. We reviewed and analyzed the clinical presentation, primary diseases, serum CMV antibody, treatment, mortality, and endoscopic features of these patients.
Results: Eighteen patients were diagnosed as having CMV colitis and 15 CMV colitis patients were included in this study. The mean age was 65.7 years (range 42–92 years). Bloody diarrhea and persistent diarrhea were the most common initial presentations of CMV, and sepsis was the most common co-morbidity found. CMV-IgM was positive in three (17%) patients, and CMV-IgG was positive in 14 (93.3%) patients. All patients received ganciclovir and 11 patients clinically improved. Four (26.6%) patients died and two patients had colon perforation. According to the severity of the diseases, endoscopic presentation of CMV colitis ranged from colonic mucosa edema, loss of vasculature, subepithelial hemorrhage, and circular or geographic ulcers to perforation. Ten (66.7%) patients had multiple ulcers and five (33.3%) patients had a single ulcer. Eleven (73.3%) patients had colitis involving distal to splenic flexure, and four (26.6%) patients had colitis involving the whole colon.
Conclusion: Critically ill patients who present with bloody stool or persistent diarrhea should be considered for the diagnosis of CMV colitis. The endoscopic presentation of CMV colitis is highly variable. We suggest that the endoscopic manifestation of CMV colitis can be divided into three stages: non-ulcerative inflammatory stage, simple ulcerative stage, and complicated ulcerative stage.

1. Introduction

A high incidence of active cytomegalovirus (CMV) infection (36%) has been found among critically ill patients.[1] The most commonly involved organ is the gastrointestinal tract, especially the colon.[2] Critically ill patients with active CMV infection are associated with higher morbidity and mortality.[3,4] Diagnosing CMV colitis relies largely on colonoscopic and pathological studies. Early detection and prompt treatment of CMV colitis can lessen the morbidity and mortality rates. Endoscopic features of CMV colitis among patients with human immunodeficiency virus (HIV), post-transplantation, or with inflammatory bowel disease have been reported previously.[5] However, well-recognized clinical and endoscopic features of CMV colitis among critically ill patients are lacking. In this study, we investigated the clinical and endoscopic features of CMV colitis of patients at our center, to facilitate early detection and treatment with an antiviral agent.

2. Methods

From January 1, 2000 to February 28, 2014, we retrospectively reviewed the medical records of patients with a histopathological diagnosis of CMV colitis. We used the keywords “cytomegalovirus” and “CMV” to search for cases with a histological diagnosis of CMV colitis in the electronic medical records of the pathology laboratory. CMV colitis was diagnosed histologically using the identification of true cytomegalic viral inclusion on hematoxylin and eosin staining, and subsequently confirmed immunohistochemically using a specific antibody against CMV antigen and by noting the presence of

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focal owl-eye intranuclear inclusions. We identified 18 patients that were diagnosed as having CMV colitis in the study period. Three patients were excluded because one patient was infected with HIV, and two patients did not have colonoscopic images. We eventually selected 15 patients with CMV colitis.

Endoscopic images and descriptions were documented in 15 CMV colitis patients. We recorded and analyzed the clinical history, primary diagnosis, laboratory data, treatment, and mortality of these patients. The Taipei Medical University-joint institutional review board approved the protocol of this study without the need to obtain consent from the patients.

3. Results

Table 1 shows the demographic and clinical information of these 15 patients.

The mean age of the patients was 65.7 years (range 42–92 years). The most common primary diseases included cerebral vascular accident on bed-ridden status (47%), followed by end stage renal disease (35%) and type 2 diabetes mellitus (35%). Fourteen (93.3%) patients had a history of sepsis treated with extended (>10 days) broad-spectrum antibiotics, and eight patients developed septic shock. The most common indications for colonoscopy were bloody stool (60%) and persistent diarrhea (40%). Clinically, none of the above were diagnosed as having CMV colitis before receiving their endoscopic examination. All patients received testing for CMV antibody status; CMV-IgM was positive in three (17%) patients, and CMV-IgG was positive in 14 (93.3%) patients. All patients received treatment with ganciclovir, and colitis clinically improved in 11 (73.3%) patients. Four (26.6%) patients died, of whom, one patient died of colon perforation and three patients died of their comorbidities.

Cecal intubation was successful in 10 (66.6%) patients, and terminal ileum had been examined in three patients. One patient was intubated up to the ascending colon, two patients up to the transverse colon, and two patients up to the sigmoid colon. Table 2 describes the endoscopic features of the 15 patients. Colitis involved distal to splenic flexure in 11 (73.3%) patients, and involved the whole colon in four (26.6%) patients. Two of three patients with successful terminal ileum intubation had proven CMV involvement of the ileum. Only one patient had CMV colitis involving solely the proximal to transverse colon without the involvement of the distal part of the colon. Two patients had colon perforation occurring at the sigmoid colon.

Ten (66.7%) patients had multiple ulcers and these ulcerative lesions were skipping lesions. Five (33.3%) patients had a single ulcer, which was predominantly located at the rectum or sigmoid colon. The earliest endoscopic features of CMV colitis presented as colonic mucosa edema, loss of vasculature, and scattered subepithelial hemorrhage (Figure 1A). Twelve (80%) patients had scattering subepithelial ecchymosis at the base or adjacent to the ulcers (Figure 1B). Extended subepithelial hemorrhage turned purplish in color, and was followed by mucosa necrosis leading to necrotic mucosa debris and ulcer formation (Figure 1C and D). Ulcer morphology was either circular (Figure 1E) or geographic (Figure 1F) in shape, and no longitudinal ulcers were found in our series. Eleven (73.3%) patients had an ulcer greater than 2 cm in diameter or exceeding one-third of the circumference (Figure 1G). Giant and deep ulcers were mostly observed in advanced disease with polypoid lesion formation and the presence of necrotic tissue (Figure 1H).

Table 2 Endoscopic features of cytomegalovirus (CMV) colitis

Patient no.	Location	No. of lesions	Size (cm)	Ulcer morphology	Subepithelial ecchymosis	Perforation
1	R to A	Multiple	>2	C and G	Yes	+ sigmoid
2	R to ileum	Multiple	>2	C and G	Yes	—
3	R	Single	>2	C	Yes	—
4	R	Single	>2	C	Yes	—
5	S to D	Multiple	1–2	G	Yes	—
6	R to S	Multiple	1–2	G	No	—
7	T to Ileum	Multiple	1–2	C	Yes	—
8	S	Multiple	>2	G	No	—
9	R to A	Multiple	>2	C and G	Yes	—
10	R	Single	>2	G	Yes	—
11	R	Single	>2	G	No	—
12	R to S	Multiple	>2	G	Yes	—
13	S to D	Multiple	<1	G	Yes	—
14	S	Single	>2	C	Yes	+ sigmoid
15	R to D	Multiple	>2	C and G	Yes	—

A = ascending; C = circular; D = descending; G = geographic; R = rectum; S = sigmoid; T = transverse.

4. Discussion

In this study, we described the clinical and endoscopic features of CMV colitis in 15 critically ill patients from January 1, 2001 to February 28, 2014 at Wan Fang Medical Center. Of all 15 patients, we found that both bloody stool and persistent diarrhea were the most common clinical presentations (Table 1), with an increased rate among critically ill patients with extended intensive care unit stays. We also found that most of our patients had severe sepsis or septic shock and were treated with extended broad-spectrum antibiotics

Table 1 Demographic data of the patients

Patient no.	Age (y)	Sex (M/F)	Comorbidity			Initial presentation	Serum CMV Ab (IgM/IgG)	Survival
1	42	M	ICH	CRF	Sepsis	Diarrhea	+/−	+
2	72	M	Amyloidosis	ESRD	Sepsis	Bloody stool	+/+	Expired
3	81	M	CVA	CRF	Sepsis	Bloody stool	−/+	+
4	81	M	COPD	CRF	Sepsis	Bloody stool	−/+	Expired
5	75	F	C-S injury	CRF	Sepsis	Bloody stool	−/+	+
6	85	M	CVA	sepsis		Diarrhea	−/+	+
7	55	M	ESRD	ICH	Sepsis	Diarrhea	−/+	+
8	64	F	ESRD	CAD	Sepsis	Bloody stool	−/+	+
9	65	M	ESRD	T2DM	Sepsis	Diarrhea	−/+	+
10	78	M	Prostate cancer	ICH	Sepsis	Bloody stool	−/+	+
11	92	M	CVA	T2DM	Sepsis	Bloody stool	−/+	+
12	69	M	ESRD	T2DM	Sepsis	Diarrhea	−/+	+
13	43	F	ESRD			Diarrhea	−/+	+
14	81	F	COPD	T2DM	Sepsis	Bloody stool	−/+	Expired
15	86	F	Lung cancer	CAD	Sepsis	Bloody stool	+/+	Expired

C-S = cervical spine; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRF = chronic respiratory failure; CVA = cerebrovascular accident; ESRD = end stage renal disease; ICH = intracranial hemorrage; T2DM = type 2 diabetes mellitus; F = female; M = male.

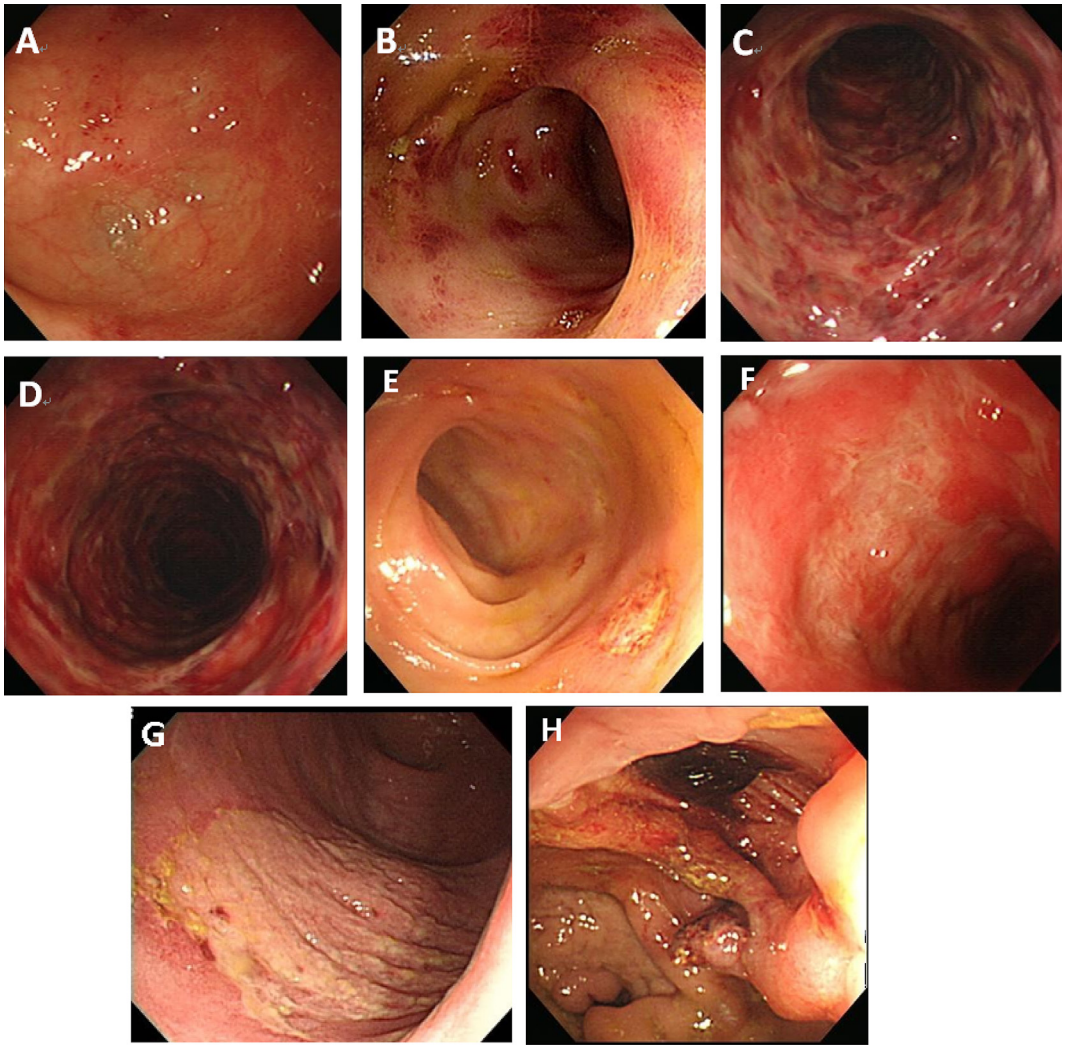

Figure 1 Colonoscopic characteristics of cytomegalovirus (CMV) colitis. (A) Edematous change of colonic mucosa with loss of vascularity and scattering subepithelial hemorrhage on the sigmoid colon; (B) submucosa vasculitis progressed, vasculitis related thrombosis caused mucosal ischemic change and turned purplish on the sigmoid colon; (C) extensive vasculitis related thrombosis leading to necrotic mucosa debris without shallow ulcer formation on the descending colon; (D) mucosa necrosis leading to necrotic mucosa debris with shallow ulcer formation on the descending colon; (E) small shallow, round ulcer on the sigmoid; (F) geographic shallow ulcer with polypoid lesion formation on the sigmoid; (G) large circular shallow ulcer with scattered subepithelial hemorrhage on the sigmoid; (H) major necrosis leading to deep ulcer formation on the rectum.

(Table 1). Sepsis has been identified as a risk factor for reactivating human CMV in critically ill patients,[6] and its occurrence has increasingly been recognized.[7] CMV-IgM antibody has shown as a weak predictive value among our patients (17%), where CMV reactivation is mostly favored in this circumstance.[8] All of our patients received ganciclovir and 11 patients clinically improved. Four patients did not respond well to antiviral treatment; this might be attributed to a severe underlying clinical condition with multiorgan dysfunction or severe CMV colitis with advanced complications.

The common differential diagnoses of CMV colitis include pseudomembranous colitis, inflammatory bowel disease, and ischemic colitis. *Clostridium difficile* colitis and CMV colitis had overlapping risk factors, especially in patients with severe sepsis who received broad-spectrum antibiotic coverage. Endoscopic diagnosis of both diseases can be challenging for an endoscopist. Typical endoscopic features of *Clostridium difficile* colitis include patchy circular subepithelial hemorrhage with raised white plaque-like lesions.[8,9] In fact, CMV colitis resembling pseudomembranous colitis has been reported earlier.[9] Meanwhile, *Clostridium difficile* and CMV coinfection are increasingly recognized, particularly when patients are refractory to treatment.[10]

Contrariwise, endoscopic features of inflammatory bowel disease with or without CMV infection are almost indistinguishable,[11] and it is being increasingly recognized in patients with refractory inflammatory bowel disease or acute flares. Patients with shock confront an increased risk of ischemic colitis, where the classic features of ischemic colitis are distinct demarcation (focal subepithelial hemorrhage) with abrupt termination. In fact, typical features are not usually presented.

In our series, we found that patients' endoscopic presentation of CMV colitis was highly variable (Table 2). However, the hypothetic pathogenesis could be correlated with our endoscopic findings. CMV reactivations can cause submucosa vasculitis, resulting in a colonoscopic picture of colonic mucosa edema, loss of vasculature, and scattered subepithelial hemorrhage. As submucosa vasculitis progressed, vasculitis related thrombosis caused mucosal ischemic change, and colonoscopy in this stage revealed subepithelial hemorrhage turned purplish in color, and was followed by mucosa necrosis leading to necrotic mucosa debris and ulcer formation.[11] Furthermore, local mucosa barrier defect can complicate the clinical pictures with secondary infection or major necrosis leading to gangrene, and hence, colon perforation eventually developed.

Therefore, we suggest that endoscopic presentation of CMV colitis can be divided into three stages: (1) nonulcerative inflammatory stage (early stage) manifests as colonic edema, loss of vasculature, scattering subepithelial hemorrhage, and easy contact bleeding (Figure 1A and B); (2) simple ulcerative stage (progression stage) manifests as well demarcated flat ulcers with more condense subepithelial hemorrhage with or without necrotic debris coating and stigmata of bleeding (Figure 1C–G); and (3) complicated ulcerative stage (advanced stage) manifests as extended ulcerations with deep depression, prominent necrotic debris, swollen surrounding tissue, and active oozing (Figure 1H).

In addition, different stages of CMV colitis can be found in a patient at different sites of colon simultaneously. In our series, we saw only one isolated proximal colonic ulcerative lesion. From the endoscopic view, large, circumferential or geographic ulcers with scattering subepithelial ecchymosis were predominantly observed over the rectum and distal part of the colon in our patients. Similar endoscopic descriptions are also mentioned in earlier literature.[12] Rafaillidis et al[13] reported that the rectum and distal colon are the most frequent sites of CMV disease among immunocompetent patients. Patients involved in both proximal and distal colon share the common findings. However, of the four patients with involvement of the whole colon, they tended to have more dense subepithelial hemorrhage, a larger sized colon, and deeper ulcerative lesions in the distal part of the colon compared with those of patients without involvement of the proximal part of colon.

In conclusion, critically ill patients with comorbidities who present with bloody stool or persistent diarrhea should raise a suspicion index of CMV colitis. Endoscopic presentation of CMV colitis is highly variable. We hypothesize that the endoscopic manifestation of CMV colitis can be divided into three stages, and that early recognition of the typical endoscopic features of CMV colitis leads to a prompt diagnosis, helping with more rapid management of the disease.

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D.E.T. and F.M.S. contributed to the conception and design of this project. G.S.L. and T.S.C. were involved in data collection and C.N.C. was involved in the interpretation of the data and editing the manuscript. All authors revised the manuscript together and approved the final version.

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