

Colonoscopic Features of Cytomegalovirus Colitis and Clinical Experience

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ABSTRACT

Cytomegalovirus (CMV) colitis is the most common infection of the CMV gastrointestinal disease. Patients with CMV colitis often manifest with fever, abdominal pain, watery diarrhea, bloody stool, massive bleeding and occasionally with mega colon and perforation. Colonic ulcer bleeding can be self-limited, but may recur intermittently. Massive colonic bleeding and perforation can be life-threatening. CMV colitis could be concurrently with or following the treatment for *Clostridium difficile* infection-associated colitis of the patients. Diagnosis of CMV colitis relies on colonoscopy with biopsies. Endoscopic features are quite variable and include diffuse erythema, hemorrhagic spots, ischemia, erosions, ulcers, strictures, polypoids, pseudo membranes and pseudo tumors. Specific colonoscopic findings of CMV ulcers are irregular ulceration, map-like appearance, wide mucosal defect, punched-out ulceration and longitudinal ulceration. Histological mucosal specimens typically show viral inclusions, referred to as owl's eyes. The immune histochemical staining to detect of CMV antigen is a more sensitive method. The CMV quantitative polymerase chain reaction or the CMV antigenemia assay can be used as an accurate method to predict CMV disease and to monitor effectiveness of treatment. However,

diagnosis of CMV colitis seems difficult in clinical practice, as diagnostic procedures and specific methods are not routinely performed in clinical services. The outcome of CMV colitis generally favorable by the standard treatment consisting of intravenous ganciclovir or oral valganciclovir. Massive bleeding and perforations require surgical colorectal resections.

Keywords: Colonoscopy; Colitis; Cytomegalovirus; Ganciclovir

INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes virus family and infection with CMV is very common. It spreads by saliva, urine, respiratory droplets, sexual contact, and blood transfusions. CMV is an extremely common pathogen worldwide, with prevalence between 60% and 70% of adults in industrialized countries and 50% to 80% of adults in the United States are infected by the age of 40 years [1,2]. Although most healthy people infected by CMV have no symptoms, primary CMV infection typically is manifested by a mononucleosis-like syndrome with a benign, mild and self-limited course. Most clinical diseases occur in previously infected individuals with seropositive IgG anti-CMV antibodies and therefore represent either reactivation of latent infection or re infection with a novel strain. CMV is a major cause of morbidity in the immune compromised hosts with weakened immune containment. CMV can cause disseminated or localized end-organ disease in patients with advanced immune suppression, such as patients with acquired immunodeficiency syndrome (AIDS), solid organ transplant, hematopoietic stem-cell transplantation, cancer with chemotherapy, inflammatory bowel disease, or those receiving immunosuppressive agents. Overall, 80-90% of all transplant patients are infected by the virus; however, the incidence of active CMV disease is 30-40% [3,4].

CMV colitis is the most common infection of the CMV gastrointestinal disease. Diagnosis of CMV colitis relies on colonoscopy with biopsies. However, diagnosis of CMV colitis remains difficult in clinical practice, as diagnostic procedures and specific methods such as mucosal biopsies are not routinely performed in clinical services. Most endoscopists are reluctant to perform invasive procedures as concerning bleeding complication in the hyperemic mucosa. Therefore, specific colonoscopic features might offer import clues to hint diagnosis of CMV colitis. In this chapter, we review the detail about the endoscopic findings of CMV colitis and report some clinical experience.

EPIDEMIOLOGY AND RISK HOSTS OF CMV COLITIS

CMV infection of the gastrointestinal tract is common and occurs in 10% of all transplants involving any part of the gastrointestinal tract [5]. The colon was the most commonly affected site by CMV infection [6]. CMV of the gastrointestinal tract of normal hosts is very rare. However, CMV colitis has been increasingly recognized in the non-immunocompromised patients, mostly elderly or with chronic comorbidity diseases, such as end-stage renal disease, diabetes mellitus, and coronary artery disease, particularly with prolonged stay in the intensive care units [7-10]. The patients stay in the intensive care units are easily neglected by clinicians to survey CMV

colitis when they have watery diarrhea or bloody stool [8]. The stress and debility of an acute uremic state and a long hospital stay may compromise the patient's immune system and allow for CMV viral invasion to the colon [11]. Besides, in a limited case-control study, steroid use and red blood cell transfusion within 1 month of the diagnosis of colitis were independent risk factors for development of CMV colitis in immune competent hosts [12].

CLINICAL MANIFESTATION OF CMV COLITIS

Clinical manifestation of CMV colitis often include mucosal inflammation, erosion and ulcerations, resulting in nonspecific signs as fever, diffuse abdominal pain, cramping pain located in the lower abdominal quadrants, watery diarrhea, intermittent bloody stool, hematochezia, weight loss as well as toxic mega colon and perforation [13]. Lower gastrointestinal bleeding was the most common initial presentation. The signs recorded in the physical examination of these patients include abdominal tenderness or rebound tenderness and abnormal bowel sounds. Sometimes the patient's colonic bleeding could resolve spontaneously. However, bleeding may recur and cause progression of anemia and shock. Recurrence of colonic bleeding is usually due to severe vacuities or steroid ulcer [14]. CMV colitis is potentially life-threatening and could be even fatal due to massive colonic bleeding or perforation.

DIAGNOSTIC PATHOLOGY OF CMV COLITIS

Histological diagnosis of CMV colitis may be obtained by colonoscopy with biopsies. Upon direct visualization by colonoscopy, various patterns of CMV colitis including mucosal inflammation, focal hemorrhage, edematous folds, erosions, well-demarcated solitary or multiple ulcers, diffuse infiltrative ulcers, polypoid, pseudotumors and pseudo membranous patterns can be seen [8,10]. Colonic biopsies should be taken from inflamed mucosa near or within the ulcers.

The most common pathological findings include mucosal injury, ischemia, ulcerations, hemorrhage and rarely granuloma and perforations. Histological specimens typically show viral intra nuclear inclusions, referred to as owl's eye appearance. CMV colitis is diagnosed by the presence of CMV inclusions, using immune histochemistry stain for a higher sensitivity, with mixed inflammatory cell infiltrate into the lamina propria and numerous neutrophils associated with cryptitis as well as focal ulceration [15].

Numerous vascular endothelial cells transformed into cytomegalic cells in the mucosa and the formation of micro-thrombi promoted by CMV play an important role in the pathogenesis of mucosal ischemia and ulcer formation [15]. CMV necrotizing vacuities and ischemic colitis may manifest with prolonged fever of unknown origin followed by progressive lower abdominal pain and development of disseminated intravascular coagulopathy, thus leading to rapid deterioration with internal bleeding despite hemicolectomy and antiviral therapy [16,17].

CMV-DNA is also highly detected by in situ hybridization in CMV-infected intestinal cells in tissue sections [18]. In specimens with few CMV inclusions, however, there was no staining

with in situ hybridization [19]. CMV antigenemia and polymerase chain reaction (PCR) DNA amplification assay in blood and stool sample is a sensitive and easy way to screen CMV viral reactivation, especially while pending pathologic reports [8]. Furthermore, determination of CMV DNA load by PCR in inflamed colon tissue has the greatest accuracy for virus detection and may be used as a qualitative or quantitative method to guide antiviral therapy [20]. The prognosis of CMV colitis is good if diagnosed and treated with ganciclovir therapy early.

ENDOSCOPIC FINDINGS OF CMV COLITIS

Endoscopic examination of CMV colitis showed three typical types: well-demarcated ulcerative type, diffuse infiltrative ulcers, and pseudo membranous patterns [10]. Sometimes, hemorrhagic colitis, ischemic colitis, polypoid or pseudo tumor could be found [8]. In a study of comparing specific colonoscopic findings in patients with ulcerative colitis complicated by CMV infection determined by CMV antigenemia, the sensitivity of irregular ulceration for positive CMV was 100%. The specificity of wide mucosal defect was 95%. Punched-out ulceration and longitudinal ulceration exhibited relatively high sensitivity and specificity (more than 70% for each) [21].

Hemorrhagic colitis

This type refers to multiple punctuate lesions with hemorrhagic spots and normal intervening mucosa along the colon (**Figure 1**). Each punctuate spot might reveal a shallow ulceronanythematosus base. Some ulcers may be around the punctuate lesions or may not be observed in this disease stage.

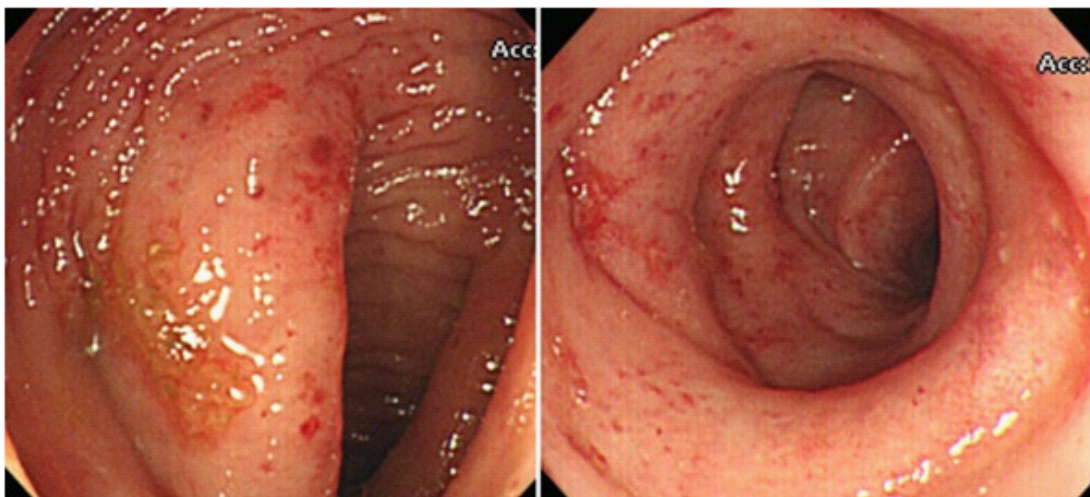


Figure 1: Colonoscopic features show multiple punctuate lesions with hemorrhagic spots and normal intervening mucosa along the colon.

Ischemic colitis

For some patients present with persistent watery diarrhea, fever and abdominal pain, endoscopic finding would describe diffuse ulceration, mimicking or attributed to ischemic colitis [16,22-24]. The colonic ulcers develop following a process of ischemic vasculitis and thus the mucosa and the irregular map-like ulcers appear less erythematous than hemorrhagic ulcers (**Figure 2**). If ischemic stenosis or stricture is present, surgery may be required to remove the colonic obstruction [25].

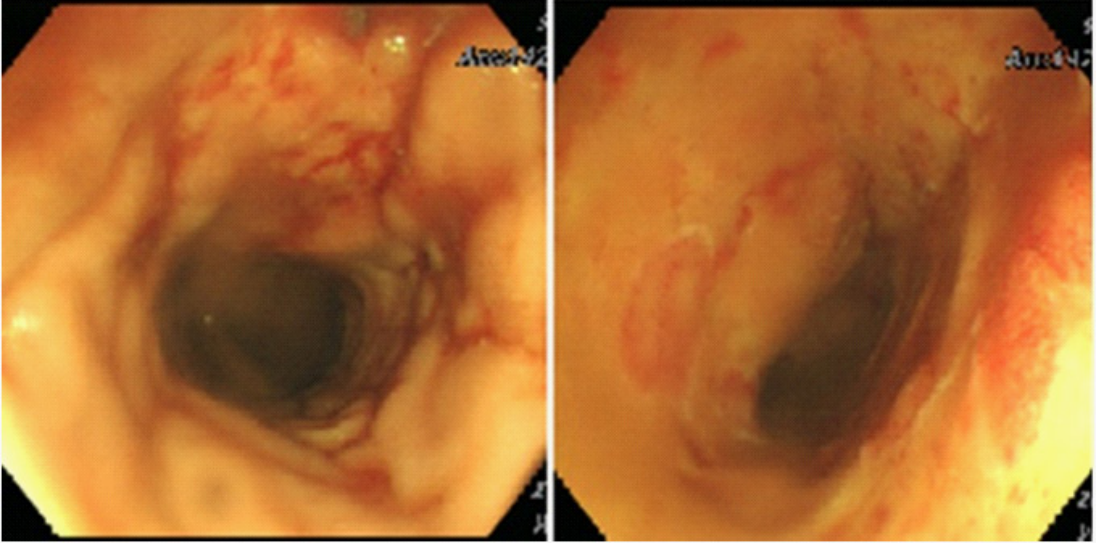


Figure 2: Colonoscopic features show multiple irregular, map-like erosions and ulcers.

Well-demarcated ulcers

The mucosal lesions associated with the CMV infection are typically ulcerative on a background of hemorrhagic erythema (**Figure 3A**). The ulceration shows a characteristic well-defined punched-out appearance [15]. They may be solitary, multiple or longitudinal ulcers (**Figure 3B**). The most common feature is multiple ulcers with at least one large ulcer exceeding 2 centimeters in diameter [26]. Colonoscopy may reveal a giant ulcer with an irregular margin and skip lesions in the colon. Perforation may occur in one of the multiple colon ulcers [27,28]. Even though *Clostridium difficile* is detected from culture of bowel lavage and *C. difficile* antigen in stool sample is positive in some patients, CMV ulcers may occur alone in the colon without evidence of pseudo membranous colitis and response to treatment with metronidazole could not be achieved [29]. A solitary mucosal ulcer in the ascending colon is capable of causing dilatation of the cecum and ascending colon, manifesting toxic mega colon as the initial presentation of the disease [30].

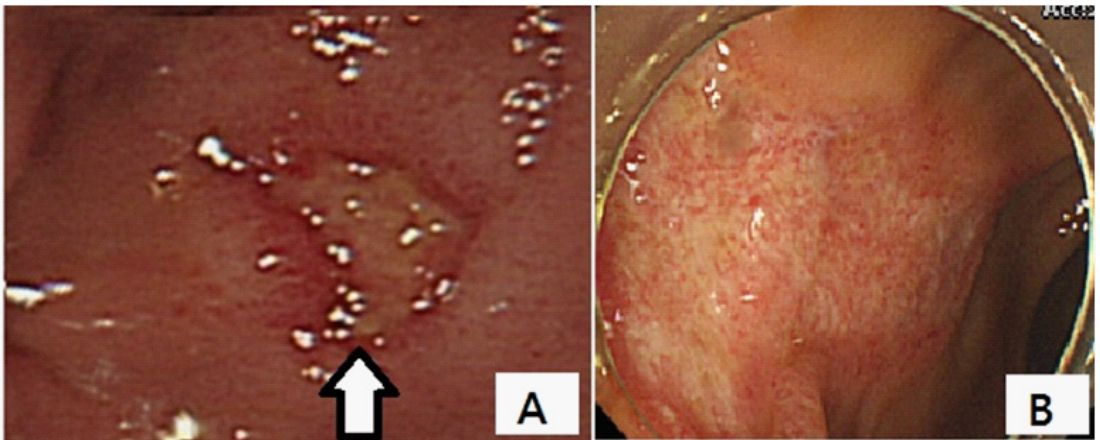


Figure 3: Colonoscopic features show a solitary deep ulcer (arrow) on a background of hemorrhagic erythema (A) and a wide longitudinal ulcer (B).

Diffuse infiltrative ulcers

This type refers to severe and extensive colitis, which is characterized by highly active inflammation with diffuse erythema, sloughing and oozing mucosa or hemorrhage throughout the involved segments or the entire colon (**Figure 4**). The lesions could be deep confluent ulcers [31] or multiple erosions and small ulcers on the diffuse edematous and inflated mucosa [32].

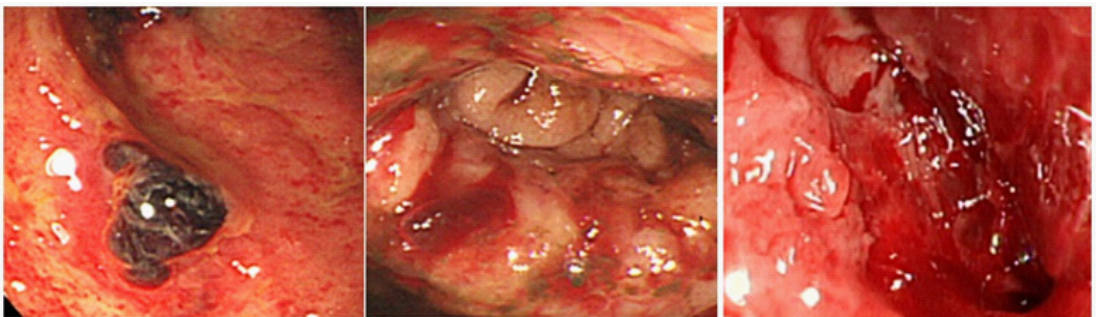


Figure 4: Colonoscopic features show extensive inflammation with diffuse erythema, sloughing mucosa, oozing and hemorrhagic ulceration throughout the involved segments or the entire colon.

Pseudo membranous patterns

CMV colitis can result in ulceration with pseudo membranous formation (**Figure 5**), mimicking *C. difficile* infection-associated pseudo membranous colitis [33-35]. Most patients manifest bloody stool but not watery diarrheal. Colonoscopic findings in some cases may show punctuate hemorrhagic spots and hemorrhage on the hyperemic mucosa covered with white coating sloughs (**Figure 6**). This type refers to negativity of the *C. difficile* antigen in stool sample and stool culture as well as no clinical response to metronidazole and vancomycin. Nevertheless, the CMV-PCR in the stool sample is positive and ganciclovir therapy could achieve therapeutic response.

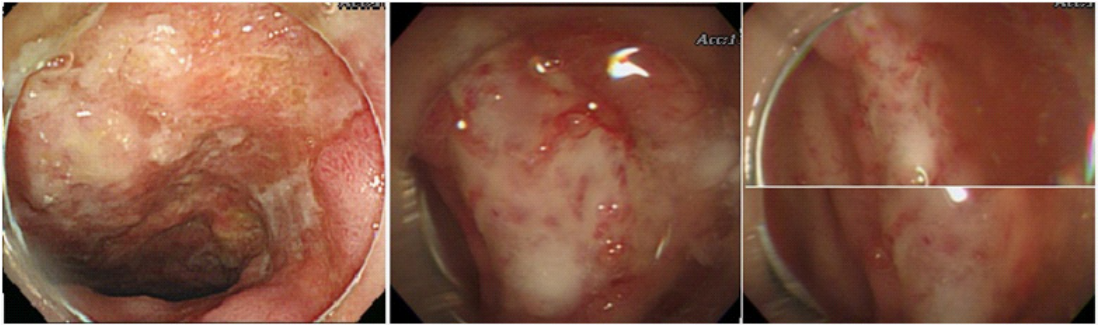


Figure 5: Colonoscopic features show ulceration with pseudo membranous formation, mimicking *Clostridium difficile* infection-associated pseudo membranous colitis.



Figure 6: Colonoscopic features show punctuate hemorrhagic spots and hemorrhage on the hyperemic mucosa covered with white coating sloughs.

Polypoid

A single or multiple, round or linear, polypoidal-like lesions may occur all over the colon (Figure 7). The polypoid lesions may be easy oozing or bleeding on the top or surrounding mucosa. Histopathology reveals consisting of multiple polypoidal, tan brown and inflammatory soft tissue fragments in aggregate measuring 0.3cm to 2.0cm in size. Some lesions may be initially misdiagnosed as inflammatory fibroid polyp [36].

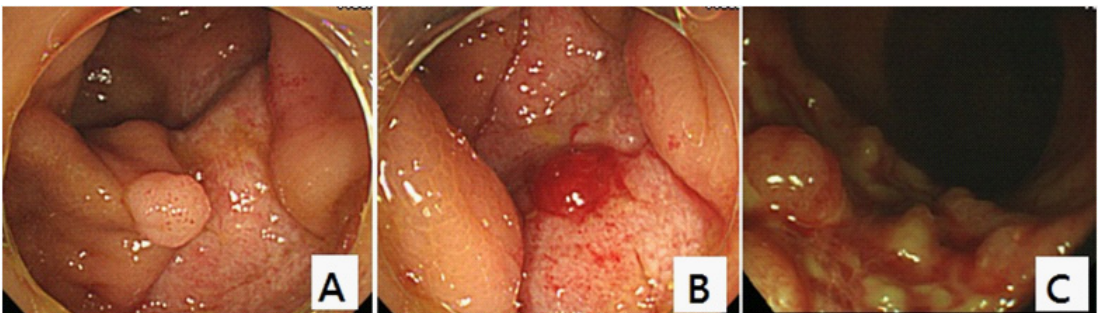


Figure 7: Colonoscopic features show a single or multiple, round polypoidal-like lesions with easy oozing or bleeding on the top or surrounding mucosa.

Pseudo tumors

CMV-induced pseudo tumor is an exceptionally rare presentation, especially in immune competent hosts. Colonoscopic finding usually reveals a polypoidal tumor-like mass or a tumorous lesion with irregular ulceration, mimicking colon cancer [7,37-38]. The tumorous lesions may be large enough to cause bowel obstruction and apparent need of colectomy (Figure 8). However, the tumorous lesion may spontaneously disappear without any specific treatment [38]. Therefore, laparotomy and hemicolectomy could be conducted for suspected neoplastic obstruction, which might potentially be unnecessary procedures [39]. Besides, the presence of CMV in the tumorous lesion would not be able to induce cancer formation. One study demonstrated an absence of CMV proteins and DNA in human colorectal adenocarcinomas, and thus failed to confirm CMV participating in human colorectal tumor genesis [40]. Nevertheless, CMV colitis may coexist with primary colorectal lymphoma [41] or become an important postoperative complication following colectomy for colon cancer [42].

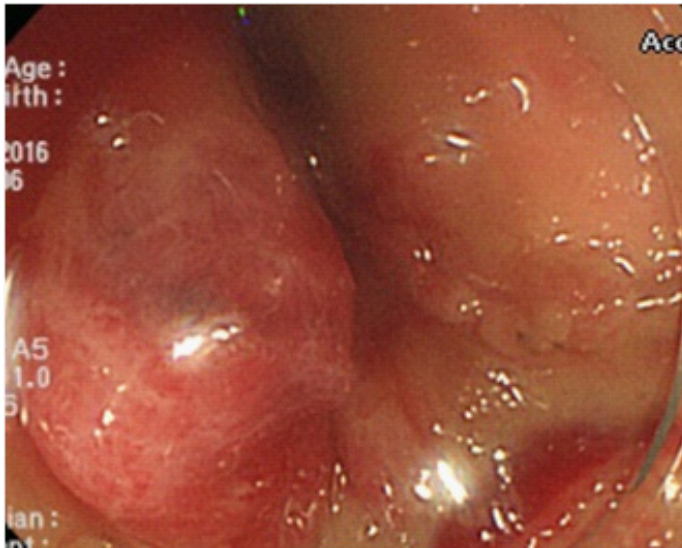


Figure 8: Colonoscopic features reveal polypoidal-like tumors or tumorous lesions with irregular ulceration on the surface, mimicking colon cancer.

COEXISTING CMV AND CLOSTRIDIUM DIFFICILE INFECTION (CDI)

CDI colitis may cause severe diarrhea, mimicking CMV colitis. The CDI colitis usually presents with watery diarrhea, however, CMV colitis commonly presents with bloody stool. In fact, although rare, cases of coexistent CMV with CDI colitis were increasingly reported in the literature [8,29,43,44]. CMV colitis could be concurrently with or following the treatment for CDI colitis of the patients regardless of the immune status [44]. After adequate therapy against CDI colitis, a test for *C. difficile* toxin in the stool would become undetectable, but the pseudo membranous formation may still be persist. In that scenario, nonetheless, it seems warranted to

survey the presence of CMV colitis, which may also contribute concomitantly or independently to the persistent white coating plaques. An important complication of CDI and CMV colitis alone is toxic mega colon [45-47], which could also develop in the patients with pseudo membranous CMV colitis [48] or coexistence of both diseases [49].

THERAPY

CMV colitis can mimic other alternative diagnoses like ischemic colitis, nonspecific colon ulcer, CDI and colon cancer, and pose a significant diagnostic challenge, leading to delayed diagnosis, unnecessary exploratory laparotomy for colorectal surgery and adverse clinical outcomes without specific antiviral therapy. Current evidence suggests that targeted antiviral therapy with ganciclovir or valganciclovir is appropriate for severe CMV colitis, even in immune competent adults, especially if they are elderly or have chronic diseases such as diabetes or chronic kidney disease [50,51].

Patients with intractable diarrhea and abdominal pain may have a dramatic response to ganciclovir therapy without any relapse [52,53]. The clinical and endoscopic improvement could be achieved by ganciclovir therapy within two weeks following onset of main presenting symptom [10]. Likewise, the colonic ulcers disappeared dramatically after 2 weeks of intravenous ganciclovir therapy was reported in a renal transplant recipient [54]. Despite aggressive clinical manifestations, the prognosis of CMV colitis is good if diagnosed by rapid colonoscopy and treated by ganciclovir early [55]. If specific ganciclovir is unresponsive or toxic, in view of severe thrombocytopenia induced by CMV syndrome or by underlying bone marrow disorder, intravenous immunoglobulin is recommended as adjunctive therapy in cases of severe colonic bleeding [56].

There is possibility of spontaneous healing of CMV colitis, even in a patient with human immunodeficiency virus infection receiving antiretroviral therapy alone [57]. However, some experience revealed that the conservative treatment is not enough, and the administration of ganciclovir was essential for improving the disease course, even in an immunocompetent patient [58]. Furthermore, a recurrence of the CMV or poor symptomatic improvement by ganciclovir therapy should consider the occurrence of toxic mega colon [47]. Finally, a colostomy may be indicated for a bowel stricture causing an intestinal outlet obstruction, which made oral intake impossible [59]. Colectomy surgery should be limited to acute complications of CMV colitis such as perforation and to unresponsive disease [11,60].

CLINICAL EXPERIENCE

A 70 year-old woman of diabetes mellitus and old cerebral stroke had vomiting and cold sweating for one day. She has recent hospitalization for urosepsis one month prior to this admission. The diffuse hemorrhagic erosive gastritis with ulcers over whole stomach was ever found by the gastroduodenoscopic examination during last hospitalization.

This time, there was no fever, chills, chest pain, abdominal pain, nor tarry and bloody stool passage. Upon the emergency room, she was intubated due to acute respiratory failure. Vasopressor was given for refractory hypotension, and then she was transferred to the intensive care unit (ICU). Laboratory data revealed pyuria of a urine white blood cell (WBC) > 100/HPF; a blood WBC count of 19,100/ μ L with segment 75% and band form 13%; hemoglobin, 13.5 g/dL; platelet count, 280,000 / μ L; lactic acid, 9.3 mmole/L; procalcitonin, 140.86 ng/mL and C-reactive protein (CRP), 69.9 mg/L. The urine culture yielded *Morganella morganii*. In the ICU, adequate fluid resuscitation and antibiotic therapy for urosepsis were used. As apparent response, the vasopressor could therefore be discontinued.

After 2 weeks of ICU stay, a chest X-ray film revealed ill-defined patchy infiltration in the left lower lung field and sputum culture yielded *Acinetobacter baumannii* resistant to carbapenems. Meanwhile, coffee-ground material was found from the nasogastric tube and gastroduodenoscopic examination showed diffuse gastric ulcer at middle and low gastric body with recent bleeding. However, no mucosal biopsy was performed.

Two weeks later, massive bloody stool was noticed and colonoscopic findings revealed diffuse rectal ulcers with bleeding. The blood platelet count dropped to 55,000/ μ L. Then, CMV-PCR in the blood sample was negative, but was positive in the stool sample and gastric juice. Meanwhile, CMV antigenemia showed two positive cells per 200,000 WBC. A CRP was elevated to more than 250 mg/L. The blood culture yielded *Enterococcus faecium*.

Ten days later, abdominal distension was noticed and the computed tomography scan of the abdomen showed pneumoperitoneum and lobulated fluid accumulation in peritoneal space with peritoneal enhancement, in favor of hollow organ perforation at the site of descending colon, leading to peritonitis and intraperitoneal abscess formation. As high risk of mortality, the family accepted palliative therapy without surgical intervention for the acute abdomen. The clinical condition was deteriorated and she died after 6 weeks of this hospitalization.

Perspective: In this case, the CMV gastritis has probably been neglected for one month since last hospitalization, which subsequently resulted in development of CMV colitis, on the basis of positive CMV-PCR in the gastric juice and the stool sample. Although CMV-PCR in the blood sample was once negative, the CMV antigenemia was positive, suggesting evidence of invasion of CMV into the macrophage. However, the definitive CMV diagnosis could not be made by the endoscopists, who did not perform gastric and colorectal biopsies because of concerning bleeding complication. Persistent inflamed mucosa might contribute to bacterial translocation from the gut. Therefore, we suggest pre-emptive antiviral therapy for CMV colitis based on the evidence of CMV-PCR results, while pending pathologic evaluation, as delayed antiviral therapy would potentially lead to fatal colonic perforation.

CONCLUSION

CMV colitis is frequent in patients with immunodeficiency or receiving immunosuppressive agents, but occur rarely in immunocompetent patients, mostly elderly or those with multiple comorbidities, especially chronic kidney disease and critically ill patients. The stress and debility of an acute on uremic state, frequent steroid use in critically ill patients and a long stay in the intensive care units may have compromised the patients' immune system and allowed for CMV reactivation as well as invasion.

Bleeding stool was the most common initial presentation, which could be intermittent, mild, moderate, massive and life-threatening. Non-invasive testing for CMV is widely available and can facilitate early diagnosis if used appropriately. Endoscopic features are quite variable and include diffuse erythema, ischemia, erosions, ulcers, polypoids, pseudomembranes and pseudotumors. Specific colonoscopic findings of CMV ulcers are irregular ulceration, wide mucosal defect, punched-out ulceration and longitudinal ulceration. CMV colitis can coexist with CDI-associated colitis. Detection of intranuclear inclusions or positive immunohistochemical staining in mucosal biopsy confirms CMV colitis. A positive CMV-PCR result in the stool sample was a useful hint for diagnosis of colonic CMV disease. CMV-PCR DNA load in colon mucosa has the greatest diagnostic accuracy. CMV colitis commonly responds well to ganciclovir therapy and the outcome is favorable if treated early. Massive colonic bleeding and perforations require segmental resections or hemicolectomy surgery.

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