Cytomegalovirus Colitis in a Critically Ill Patient Following Severe Legionella Pneumonia with Multiple Organ Failure

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Abstract

A 68-year-old man visited an emergency department complaining of dyspnea. He was diagnosed to have Legionella pneumonia with multiple organ failure. Although his multiple organ failure improved, he suffered from persistent abdominal pain and diarrhea with continuous minor bleeding. Colonoscopy revealed a longitudinal ulcer of the rectum, below the peritoneal reflection. He was diagnosed with cytomegalovirus (CMV) colitis. Antiviral therapy with ganciclovir was initiated. He finally underwent a colostomy after a bowel stricture caused an intestinal outlet obstruction, which made oral intake impossible. Based on the present case, we believe that CMV colitis must be considered as one of the differential diagnoses when critically ill patients develop continuous diarrhea and abdominal pain.

Key words: cytomegalovirus colitis, critically ill patient, Legionella pneumonia, cytomegalovirus antigenemia

(Intern Med 55: 527-531, 2016)
(DOI: 10.2169/internalmedicine.55.4857)

Introduction

Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality among patients with immunosuppression due to organ transplantation, malignant hematologic disease or acquired immune deficiency syndrome (AIDS) (1). The manifestations of CMV infection in immunosuppressed patients range from asymptomatic viral colonization to severe organ disease. Patients without human immunodeficiency virus (HIV) infection and those who are not taking immunosuppressive drugs are not usually considered to be immunocompromised, and are therefore not considered to be at a high risk for CMV infection.

However, some authors have reported that the reactivation of CMV is common in critically ill immunocompetent patients and that the reactivation is associated with prolonged hospitalization and death (2). CMV infection or reactivation is determined by either the isolation of CMV by viral culture, the detection of CMV proteins (pp65) through antigenemia, or the detection of DNA by a polymerase chain reaction (PCR) using blood or other clinical samples. An increase in the levels of CMV antigenemia during the follow-up period is associated with an increased risk of CMV disease and death (3). The real-time PCR detection of CMV reactivation has been shown to be independently associated with continued hospitalization or death within 30 days after intensive care unit (ICU) admission (4).

Nevertheless, CMV colitis is rarely recognized in ICU patients (5, 6). The diagnosis of CMV colitis might be complicated as it may mimic the symptoms of other diseases (7). The reported colonoscopic findings of CMV colitis include various lesions such as a solitary ulcer, multiple ulcers, ischemic colitis, polypoid lesions, and pseudomembranous colitis-associated lesions (8-12). When investigations into the etiology of acute hemorrhagic rectal ulcers are performed, physicians should exclude other diseases such as CMV colitis (13, 14). The definitive diagnosis of CMV colitis is made based on the histological finding of inclusion bodies in enlarged cells of the mucosa and by CMV-specific immunohistochemical staining (6). However, CMV immunohistochemical staining is not routinely performed for patients with mucosal ulcers in which there is no obvious evidence of inclusion bodies in large cells (14). Therefore, it is a great challenge for intensivists and physicians to diagnose CMV colitis in ICU patients in the clinical setting. CMV colitis tends to occur in patients whose ICU stay is prolonged. This mostly includes patients with chronic kidney disease and those who are critically ill.
disease, end-stage renal disease, diabetes mellitus, or coronary artery disease (14). Therefore, CMV colitis is not necessarily limited to immunocompromised patients. The main gastrointestinal manifestations of CMV colitis in intensive care patients are intermittent bloody stool or massive lower gastrointestinal bleeding and refractory watery diarrhea (14). In a previous report, 2 of 18 such ICU patients died due to CMV colitis, while 10 patients died of underlying disorders that were not directly related to CMV colitis (14).

To the best of our knowledge, this is the first report of CMV colitis in a critically ill patient following severe Legionella pneumonia with multiple organ failure.

**Case Report**

A 68-year-old man with a history of lacunar stroke, hypertension and dyslipidemia visited an emergency department complaining of dyspnea and fever. Laboratory tests showed severe inflammation, rhabdomyolysis and acute renal failure with severe hypoxemia (Table). Chest radiography showed an infiltrative shadow, mainly in the left upper lung (Fig. 1). He was intubated and was diagnosed with Legionella pneumonia based on the results of a urinary antigen test. A combination antibiotic therapy with levofloxacin and azithromycin was initiated to treat the Legionella infection. Ceftriaxone was added to the antibiotic combination due to the possible coincidence of other bacterial infections. We chose the airway pressure release ventilation mode of the respirator for managing acute respiratory failure. Noradrenaline and vasopressin were administered to treat septic shock. Renal dialysis was conducted to treat acute renal failure, which arose from rhabdomyolysis. Since a drug eruption was suspected after the first intravenous infusions of levofloxacin, the drug was changed to rifampicin. He showed severe liver dysfunction 2 days after admission, and thus rifampicin and ceftriaxone were changed to ciprofloxacin and ampicillin-sulbactam. The patient presented watery diarrhea after the initiation of enteral tube feeding, although Clostridium difficile tests for toxin A and B were negative. He was extubated 13 days after admission, and received non-invasive positive-pressure ventilation (NPPV) because he showed hypercapnia. The patient’s respiratory failure improved and he was weaned off NPPV; however, his abdominal pain and diarrhea with continuous minor bleeding persisted. Computed tomography (CT) of the abdomen showed wall thickening and the narrowing of the lumen of the sigmoid colon, fluid collection in the oral side of the colon and ascites (Fig. 2). A colonoscopy revealed longitudinal ulcers covered with a uniform white mass from the rectum below the peritoneal reflection to the portion 20 cm from the anal...
CMV colitis. A histological examination of the biopsy specimen showed the granulation of tissue with inflammatory cell infiltration, and a small number of moderate-to-large cells with enlarged cell nuclei (Fig. 4a). An immunohistochemical staining of some of the cells with enlarged nuclei was positive for CMV (Fig. 4b). The laboratory data indicated that the patient was negative for HIV antibody and positive for CMV antigenemia (Table). The creatinine clearance estimated by Cockcroft-Gault equation was 51 mL/min at that time. Thus we administered 150 mg of ganciclovir by infusion every 12 hours for 6 weeks. The patient developed abdominal pain and vomiting and underwent a second colonoscopy, which revealed a large-bowel stricture at the rectum above the peritoneal reflection. An ileus tube was indwelled through his nose to reduce the pressure in the bowel. A third endoscopic study performed 21 days after the second study showed that, although the ulcer from the CMV colitis had improved, a cicatricial stenosis of the colon had developed. The patient finally underwent colostomy because the bowel stricture caused intestinal outlet obstruction which made oral intake impossible. The patient was discharged from hospital 126 days after admission, after he successfully resumed oral intake. He has remained well throughout the follow-up period.

**Discussion**

Human CMV belongs to the family Herpesviridae, which has a seroprevalence of 40-100% in adults (15). Primary infection in immunocompetent hosts seldom results in serious disease and often goes unnoticed, sometimes causing a mononucleosis syndrome resembling primary Epstein-Barr virus infection (1). After the initial infection, the virus remains in a latent state within the host, but can be reactivated and has the potential to affect most organs. It is well recognized that CMV reactivation causes diseases in severely immunosuppressed patients, most notably patients with HIV

**Figure 2.** An abdominal CT scan showing wall thickening and the narrowed lumen of the sigmoid colon (arrow), fluid collection in the oral side of the colon and ascites.

**Figure 3.** A colonoscopy revealed longitudinal ulcers covered with a uniform white mass from the rectum below the peritoneal reflection to the portion 20 cm from the anal verge. The boundary around the ulcers was sharp and the surrounding mucosa was mildly edematous and hemorrhagic.

**Figure 4.** a: A histological study of the biopsy specimen showed the granulation of tissue with inflammatory cell infiltration, and a small number of moderate to large cells with enlarged cell nuclei (arrow) (Hematoxylin and Eosin staining, ×400). b: An immunohistochemistry staining of some of the cells with enlarged nuclei was positive for CMV (arrow) (CMV pp65, ×400).
infection, and those who have undergone solid organ or bone marrow transplantation (1).

Clinically significant CMV-related diseases among immunocompetent hosts are uncommon. However, CMV reactivation is a common occurrence in critically ill patients who are apparently immunocompetent (2, 16). Small observational studies and a systematic review have suggested that CMV reactivation in such patients is linked to an increased length of hospitalization and/or ICU stay (2, 16, 17), an increased duration of mechanical ventilation (2, 16), transfusion (5), corticosteroid use (18) and severe sepsis (17). The studies also suggest that CMV reactivation is associated with high disease severity, and mortality (16, 17). Our patient developed severe Legionella pneumonia with multiple organ failure, and with the exception of corticosteroid use, he had most of the factors that have been linked to CMV reactivation.

CMV has a comparatively long replication cycle. It encodes for a wide variety of gene products, playing an immunomodulatory role in the host. The genome of CMV codes sequentially for three genes, which encode for the immediate-early (IE), early, and late proteins. The activation of the IE region appears to be the first important step for the reactivation of CMV. The IE enhancer/promoter sequences contain various nuclear factor kappa B (NF-κB) consensus sequences, which are regularly inactive (19). Therefore, any mediator that activates NF-κB can trigger the reactivation of CMV. Multiple stimuli are able to activate NF-κB, which can in turn activate CMV. These include proinflammatory cytokines, inflammatory enzymes, chemokines, and receptors that are released in sepsis, burns, surgery, trauma, and multiple organ failure syndrome (19, 20). CMV lies latent in monocytes in which no viral gene is expressed. When these monocytes differentiate into macrophages, as occurs during inflammatory situations such as sepsis, burns, trauma or surgery, the viral genes are expressed and viral replication starts (19, 20). Thus, in patients who are critically ill as a result of sepsis, trauma, burns or other conditions, CMV may be reactivated through the immune mechanisms. According to this hypothesis, the likely cause of the onset of the CMV colitis in our patient would have been severe sepsis and multiple organ failure rather than his Legionella pneumonia infection.

Although the gastrointestinal involvement of CMV is rare in immune competent hosts, it is associated with significant morbidity and mortality (21). Colitis has mainly been reported, but CMV has also been implicated as a cause of symptomatic esophagitis (22), gastritis (23) and ileitis (24) in patients without underlying immunosuppression. While most cases of CMV colitis are secondary to the reactivation of latent infection in immunocompromised patients (7), CMV colitis can occur as a primary infection in immunocompetent patients. That our patient was positive for CMV IgG, indicates that his CMV infection must have been a secondary infection (and not the primary infection), and that reactivation occurred due to his critically ill status. In previous reports, the overall mortality associated with CMV colitis in immunocompetent patients has ranged from 26.7% to 31.8% (25, 26). Patients who are younger than 55 years of age, and who have no other comorbidities tend to show a good prognosis, with a significant rate of spontaneous resolution. In contrast, older age and the existence of comorbidities tend to be associated with poor outcomes (25). The efficacy of antibiotic therapy was unknown, although these reports indicated that antiviral therapy was administered to 34-53.3% of patients (25, 26). Antiviral therapy was initiated in our patient after he developed persistent abdominal pain and diarrhea with continuous bleeding and showed no sign of spontaneous remission.

CMV colitis has not commonly been seen among the ICU patients (5, 6). CMV colitis tends to occur in patients whose ICU stay is prolonged; mostly patients with chronic kidney disease, end-stage renal disease, diabetes mellitus, or coronary artery disease (14). With the exception of a prolonged ICU stay, our patient had none of the other above-mentioned factors. The main gastrointestinal manifestations of CMV colitis in ICU patients are intermittent bloody stool or massive lower gastrointestinal bleeding and refractory watery diarrhea (14). Thus the diagnosis of CMV colitis might be complicated as it may mimic the symptoms of other diseases. CMV colitis can be confused with ischemic colitis when an elderly patient presents with bloody diarrhea and abdominal pain (11). In our patient, other types of colitis (such as ischemic colitis, collagenous colitis or ulcerative colitis) were also suspected. The colonoscopic findings of CMV colitis are various and include various lesions, such as a solitary ulcer, multiple ulcers, ischemic colitis, polypoid lesions, pseudomembranous colitis-associated lesions and rectal ulcer (8-13). A previous case report described an ulcerated stricture caused by CMV colitis (27). Our patient showed multiple longitudinal ulcers, which resulted in a bowel stricture after the ulcers healed. The presence of abnormal mucosal surfaces prior to CMV infection may increase the risk of this infection. This is demonstrated by evidence of gastrointestinal CMV in patients with preexisting inflammatory bowel disease (28). It is unclear whether our patient had preceding colon diseases, but the existence of a preceding bowel disease, such as ischemic rectal ulcer, is possible because such diseases sometimes occur in critically ill patients.

The detection of CMV antigenemia or serum CMV DNA by PCR alone is insufficient for a diagnosis of CMV organ disease. Histological evidence is also required. CMV colitis can be histopathologically diagnosed by a biopsy of the colon mucosa. Immunohistochemical staining with CMV monoclonal antibodies on biopsy specimens raises the sensitivity for the definitive diagnosis of CMV disease (6). In the diagnosis of an ICU patient with bloody stool, positive CMV-PCR results in blood or fecal samples are indirect evidence of CMV colitis, and should encourage intensivists and physicians to ask a pathologist to perform an immunohistochemical staining for CMV using a biopsy specimen (14).
In the recent studies, the detection of CMV by real-time PCR in stool samples was a reliable assay for the non-invasive diagnosis of CMV colitis (29, 30). Since the general status of our patient was relatively stable when he showed the persistent clinical symptoms of colitis, he was able to undergo a colonoscopy and the endoscopic findings showed the possibility of CMV colitis, resulting in a definitive diagnosis. If colonoscopy is not feasible in unstable critically ill patients, the detection of CMV in stool samples by a PCR might be helpful as a non-invasive diagnostic method (30).

In conclusion, we believe that CMV colitis must be considered as one of the differential diagnoses when critically ill patients develop continuous diarrhea and abdominal pain.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We are grateful for the diligent and thorough critical reading of our manuscript by Yoshihiro Ohkuni (Department of Pulmonary Medicine) and John Wocher (Executive Vice President and Director, International Affairs/International Patient Services, Kameda Medical Center).

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