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Cytomegalovirus colitis in intensive care unit patients: Difficulties in clinical diagnosis☆,☆☆

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ABSTRACT

Purpose: Cytomegalovirus (CMV) infection occurs increasingly in critically ill patients in intensive care units (ICUs). We reported CMV colitis which has rarely been recognized in the ICU patients.
Methods: CMV DNA was detected by polymerase chain reaction (PCR) for blood and/or stool samples. Definite diagnosis of CMV colitis required histopathology or CMV immunohistochemical staining of colorectal biopsies. We reviewed ICU patients characterized by positive blood or stool CMV-PCR with colorectal bleeding or water diarrhea.
Results: We identified 18 patients (biopsy-proved, n = 8; probable cases, n = 10). The most common comorbidities were chronic renal disease, diabetes mellitus, and coronary artery disease. Stool CMV-PCR was positive in 7 of 10 patients (2 of 3 biopsy-proved and 5 of 7 probable cases). Colonoscopy was performed for 15 patients, revealing ulcerative or polypoid lesions. The endoscopists obtained colonic biopsies from 9 patients. Yet, the pathologists reported CMV colitis for 4 patients. Additional 4 patients were confirmed using immunohistochemical stain by the request of clinical physicians. Pseudomembranous colitis was found in 4 patients.
Conclusion: Diagnosis of CMV colitis seems difficult in clinical practice and need persistent communication between clinicians. The positive stool CMV-PCR result was a useful hint for adding immunohistochemical stain in mucosal biopsies to make a definite diagnosis of CMV colitis.

1. Introduction

Cytomegalovirus (CMV) is a major human herpes virus pathogen. After primary infections, CMV usually enters a life-long latency in healthy individuals. CMV disease (defined by organ-specific symptoms or signs plus the detection of CMV in organ biopsies by histopathology) occurs particularly in adult patients with immune deficiencies, such as those with AIDS and organ transplant recipients [1]. However, CMV reactivation from latency occurs increasingly in the critically ill patients, mostly between 4 and 12 days after admission to intensive care units (ICUs) [2,3]. Potential risk factors for CMV infection in critically ill patients included use of mechanical ventilation and transfusion, prolonged ICU stay, burns, sepsis, and corticosteroid use [3,4]. Nevertheless, CMV colitis was rarely recognized in the ICU patients [3,4]. Momin et al reported on a 29-year-old young man who developed CMV colitis with large volume diarrhea (>5 L/d) after 2 weeks of admission into ICU due to septicemia [5]. Intriguingly, CMV colitis was associated with refractory diarrhea, thrombocytopenia, massive bleeding, or megacolon, occurring in immunocompetent patients and commonly in elderly patients with comorbidities including diabetes mellitus, chronic renal failure, and ischemic heart disease [6-12].

CMV infection or reactivation is defined as isolation of CMV by viral culture or detection of CMV proteins (pp65) by antigenemia or DNA by polymerase chain reaction (PCR) from blood or other clinical samples. CMV antigenemia is less sensitive in detection of CMV infection than serum CMV-PCR [4]. However, detection of serum CMV DNA by PCR alone is insufficient for the diagnosis of CMV organ disease, which requires histopathological confirmation [4]. CMV colitis can be diagnosed by histopathology of colon mucosal biopsies. Immunohistochemical stain using CMV monoclonal antibodies on biopsies increases the sensitivity of histopathologic CMV diagnosis

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[4,6]. A pilot study demonstrates a high accuracy of the PCR-based stool test for detection of CMV bowel infection in the patients with inflammatory bowel diseases, who presented with worsening gastrointestinal (GI) symptoms [13]. Yet, the role of stool PCR test in the diagnosis of CMV colitis needs to be defined for the ICU patients.

In 2013, Chen et al reported 7 patients with tissue-proved CMV GI diseases in chronic kidney disease (CKD) patients hospitalized at a tertiary hospital during a 20-year period in southern Taiwan [14]. Among them, 4 patients manifested with colitis and one each with esophagitis, perforated duodenal ulcer, and anal necrosis. The diagnostic tissues included 3 from the surgical specimens, 3 from the colonoscopic biopsies, and one from upper GI endoscopic specimen. Two patients died of CMV colitis-related bowel perforations. We believed that the scarcity of the reported CMV GI diseases was due to the diagnostic difficulties but not caused by truly rare incidence of the CMV diseases. The goals of the study were to describe how difficult in diagnosing CMV colitis of the ICU patients in clinical practice and how to prompt motivation of clinicians to diagnose the CMV disease with the aid of using PCR-based methods.

2. Methods

2.1. Patients and methods

This retrospective study was conducted at the ICUs of Chi Mei Medical Center, a tertiary hospital in southern Taiwan. We reviewed the medical records of all adult ICU patients for whom the results of PCR for blood or stool CMV DNA were positive from January 2011 through June 2013. Among them, patients with bloody stool, lower GI bleeding, or watery diarrhea that was refractory to oral metronidazole were selected as having suspicious colitis due to CMV. Patients with mucosal biopsy-proved colitis with inclusion bodies or positive CMV immunohistochemical stain were confirmed as CMV colitis. Probable CMV colitis was defined as symptomatic patients with positive blood CMV-PCR plus either colonoscopic findings of mucosal ulcers or positive CMV-PCR results in the stool samples. Post-transplant recipients and patients with HIV infections were excluded. The reasons for ordering blood or stool CMV-PCR tests were suspicious of CMV syndrome (such as fever, leukopenia, thrombocytopenia, liver function impairment) or CMV organ diseases such as GI diseases [15].

The methods of CMV immunohistochemical stain and CMV PCR assay were performed in the Department of Clinical Pathology of Chi Mei Medical Center. The stool samples were processed through a 0.22-μm filter before performing nucleic acid purification. The purified CMV DNA from blood or stool samples was assayed by a PCR based on real-time detection of accumulated fluorescence (TaqMan, Applied Biosystems, Foster City, CA) [16]. The target gene was UL122. The sequences of PCR primers and probe for CMV PCR were forward, 5′-TCA TCC ACA CTA GGA GAG CAG ACT-3′; reverse, 5′-GCC AAG CGG CCT CTG AT-3′ and probe, 5′- FAM-ACT GGG CAA AGA CCT TCA TGC AGA TCTC-TAMRA-3′. A 137-bp fragment was amplified. The extracted DNA was assayed with the sequence detector system (ABI StepOnePlus System, Applied Biosystems, Foster City, CA) in 50 μL of PCR mixture containing 25 μL TaqMan Universal Master Mix, 15 pmol of each primer and 10 pmol of probe. Thermal cycling conditions were 50°C for 2 minutes, 95°C for 10 minutes and then 40 cycles of 95°C for 15 seconds and 60°C for 1 minutes.

3. Results

3.1. Case identification

During the study period, there were 117 positive blood CMV-PCR samples from adult ICU patients (47.2% of 248 specimens) and 8 positive stool CMV-PCR samples (25.8% of 31 specimens). Six patients had multiple positive blood PCR samples (n = 13). If repetitive samples were excluded, the detection rate of blood CMV-PCR would be 45.6% (110/241). The positive stool PCR results were from non-repetitive samples. One patient with bloody stool and positive for stool CMV-PCR underwent colonoscopy without finding any colon lesion. He did not check the blood CMV-PCR. Therefore, the patient did not conform to our case definition of CMV colitis (defined as false-positive for stool CMV-PCR test). Overall, we identified 18 patients of CMV colitis, including 8 biopsy-confirmed patients and 10 probable cases (Table 1). Among them, the results of CMV-PCR were positive in blood of all 18 patients and positive in 7 stool samples of 10 tested patients (2 of 3 biopsy-proved and 5 of 7 probable cases).

3.2. Reasons for testing blood CMV-PCR

The most common reasons to test CMV-PCR of blood included prolonged or unexplained thrombocytopenia (>2 weeks) and unusual or refractory GI diseases (such as intermittent bloody stool, massive low GI bleeding, colon or rectal ulcers, infectious colitis and pseudomembranous colitis, Table 1). For example, patient 3 had prolonged thrombocytopenia. Hemophagocytosis was evidenced on smears of bone marrow aspiration. However, bone marrow biopsy was not performed, and thus, the causal relation between hemophagocytosis and CMV infection was not established. He received prolonged low-dose steroid therapy for severe sepsis syndrome with relative adrenal insufficiency status before CMV was reactivated. However, no obvious reasons could explain the cause of hemophagocytosis syndrome in the patient, except the presence of CMV colitis.

3.3. Reasons for testing stool CMV-PCR

The most common reasons of 31 patients to test stool CMV-PCR included suspicion of CMV syndrome, CMV reactivation in blood, chronic diarrhea, colorectal ulcers with recurrent bleeding or perforation, infectious colitis and concurrent or relapsed pseudomembranous colitis (data not shown). Among them, 8 samples were positive (one was false-positive) and 23 samples were negative (one was false-negative, 2 were post-treated tests). For example, 10 patients with CMV colitis were tested for stool samples and 7 results were positive (Tables 2 and 3). Two of 3 biopsy-proved cases and 5 of 7 probable cases had positive stool CMV-PCR tests. Patients 11 and 16 had negative results of stool CMV-PCR after 5 days of ganciclovir therapy. Meanwhile, patient 11 had a negative result of CMV immunohistochemical stain on colon mucosal biopsies. Nevertheless, patient 13 had negative results of initial blood and stool CMV-PCR, and the patient died from delayed recurrence of massive colon ulcer bleeding (defined as false-negative).

3.4. Demographic data of patients with CMV colitis

There were 9 men and 9 women. Age ranged from 54 to 84 (mean 66.7) years. All patients have multiple comorbidity diseases (Table 1). The most common comorbidities included CKD or end stage renal disease (n = 12), diabetes mellitus (n = 11), coronary artery disease (n = 9) and peptic ulcers (n = 5). Concurrent infections were also present in all patients (Table 1). Eight patients have interstitial pattern of pneumonia, 6 of whose sputum samples were positive for CMV-PCR. The HIV antibody was not tested for all 18 patients. The main GI manifestations were intermittent bloody stool or massive lower GI bleeding (n = 13) and refractory watery diarrhea (n = 5). The main risk factors for CMV infection were prolonged steroid use (>2 weeks) and cancers. For example, patient 17 had chronic diarrhea. Concurrent sigmoid colon cancer and CMV colitis at transverse colon were simultaneously identified.

3.5. Diagnostic difficulties

Sixteen patients had prolonged stay in the ICUs for >21 days before the diagnosis of CMV colitis (Tables 2 and 3). Colonoscopy was