Primary Cytomegalovirus Peritonitis Following Unrelated Hematopoietic Stem Cell Transplantation

Seong Kyu Park
Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea

Cytomegalovirus (CMV) has emerged as a significant opportunistic pathogen in the era of immunosuppression. Among patients with hematopoietic stem cell transplantation (HSCT), CMV has become an increasingly important cause of gastrointestinal disease. Almost cases of CMV peritonitis are due to CMV colitis with or without bowel perforation. However, primary CMV peritonitis combined without CMV colitis is very rare. We report the first case of primary CMV peritonitis not accompanied by CMV colitis or bowel perforation in a patient who underwent allogeneic HSCT from unrelated donor. Diagnosis of primary CMV peritonitis was made by computed tomography of abdomen, colonoscopy, peritoneal biopsy, and real time reverse transcription-polymerase chain reaction for CMV. Thereafter, he was treated successfully with intravenous ganciclovir.

Keywords: Cytomegalovirus; Peritonitis; Stem cell transplantation

INTRODUCTION

Cytomegalovirus (CMV) seroprevalence in general population is high at 60% to 100% and has showed geographic variation [1]. CMV seroprevalence tended to be highest in South America, Africa and Asia and lowest in Western Europe and United States. In Korea, the thorough surveillance of CMV infection and the development of an effective CMV therapeutic strategy may be especially important, because CMV seroprevalence exceeds 90% [2]. Reactivation of latent CMV, or reinfection with a novel strain, commonly occurs in immunocompromised patients [3]. CMV infection and disease were associated with significant morbidity in the early period after allogeneic hematopoietic stem cell transplantation (HSCT) and led to mortality. The clinical manifestations of CMV disease vary. The most common disease manifestation is gastrointestinal disease, which can escape blood-based surveillance by polymerase chain reaction (PCR) and the pp65 antigenemia assay in approximately 25% of patients [4]. CMV pneumonia is clearly the most serious complication, but has become infrequent with current prevention strategies [5]. CMV usually affects the colon and common manifestation of CMV colitis is diarrhea [6]. Within the colon, CMV colitis is generally characterized by mucosal ulceration, often associated with bleeding. CMV colitis can induce perforation and peritonitis. However, primary CMV peritonitis combined without CMV colitis is very rare. We present the first case of primary CMV peritonitis not accompanied by CMV colitis or bowel perforation in a patient who underwent allogeneic HSCT.

CASE REPORT

A 59-year-old man who had done allogeneic HSCT 51 days ago complained diffuse abdominal pain for three days and had diffuse tenderness of abdomen. He had been diagnosed with acute myeloid leukemia with myelodysplasia-related changes seven months earlier. Complete remission was achieved after administration of remission induction chemotherapy with idarubicin and cytarabine. He underwent allogeneic HSCT from full matched unrelated donor who was CMV-seronegative after administering two cycles of consolidation. His CMV serological status was positive (anti-
CMV immunoglobin-G, positive; anti-CMV immunoglobin-M, negative) before transplantation. Tacrolimus and sirolimus were initially used for the prophylaxis of acute graft versus host disease. However, sirolimus was discontinued after the event of viral hemorrhagic cystitis. He complained dysuria and hematuria day +21 after transplantation. Urine microscopic examination, urine cultures, cytological examination of urine specimens, and molecular studies for viruses including polyomavirus were performed. Reverse transcription-PCR (RT-PCR) of urine samples yielded results positive for BK virus and negative for JC virus and adenovirus. We administered three times of weekly infusions of 5 mg/kg cidofovir to the patient. Symptoms and signs of cystitis were improved three weeks later without nephrotoxicity and RT-PCR status for BK virus was converted to negative.

On day +51 after transplantation, the patient complained mild to moderate fever, and diffuse abdominal pain for three days, which were different from those of BK virus associated cystitis. He didn’t have diarrhea, or hematochezia. On physical examination, the abdomen was distended due to mild ileus and there were diffuse abdominal tenderness, wall rigidity, and guarding. Anemia, jaundice, skin lesions, and enlarged lymph nodes in neck and groin were not detected.

In laboratory findings, blood cell count was subnormal (white blood cell count, 2,810/µL; absolute neutrophil count, 2,200/µL; hemoglobin, 8.6 gm/dL; hematocrit, 24.8%; and platelet 75,000/µL). Liver and kidney function test were normal. Lactate dehydrogenase was slightly increased (492 IU/L; normal, 219 to 480 IU/L) and C-reactive protein was also increased (14.66 mg/dL; normal, 0 to 0.5 mg/dL). Routine cultures of blood and urine sample were all negative for bacteria and fungi. The follow-up study for BK virus by RT-PCR was negative. CMV titer determined by real-time RT-PCR was rapidly increased (376,045 copies/mL) comparing with that of a week before the event (650 copies/mL) (Fig. 1). And CMV antigenemia using pp65 antigen assay was also detected (8 positive cells on $2 \times 10^5$ leukocytes). However, it took some time to confirm the result of pp65 antigen assay due to requested test and labor-intensive procedure.

A computed tomography (CT) scan of the abdomen showed the diffuse fat infiltration of omentum and mesentery with no evidence of bowel perforation (Fig. 2). And a CT scan of the chest was performed to rule out any infiltrative lung disease and the result was normal. Colonoscopic examination revealed only small ulcer

**Fig. 1.** (A) Clinical course including changes of hematologic parameters and (B) results of real time reverse transcription-polymerase chain reaction (RT-PCR) for cytomegalovirus. WBC, white blood cell; Allo-SCT, allogeneic stem cell transplantation; CMV, cytomegalovirus.
without edematous wall thickening and hemorrhage (Fig. 3). The biopsy of colonic ulcer showed non-specific inflammation with lymphoid follicle. To make a definite diagnosis, the biopsy of peritoneal lesions was performed using ultrasonography guided gun-biopsy and the result showed the findings of chronic granulomatous peritonitis, including lipid vacuoles surrounded by a dense red fibrin ring and epithelioid macrophages which are consistent with fibrin ring granulomas (Fig. 4). Evaluations of nested PCR for mycobacterium tuberculosis and non-tuberculosis mycobacteria were all negative. In addition, RT-PCR for CMV on paraffin-embedded tissue was experimentally performed to confirm CMV disease and the result was positive.

Based on the above findings, he was diagnosed with primary CMV peritonitis without colitis and perforation. To treatment, intravenous gancyclovir (5 mg/kg/day) therapy was started. After the therapy for 3 weeks, he was over the CMV disease and the CMV titer returned to normal (Fig. 1). Oral feeding was initiated on day +61 after transplantation and the patient’s oral intake increased successfully.

**DISCUSSION**

Regardless of currently available antiviral strategies, HSCT recipients remain at risk for CMV infection not only during the early post-transplantation period (<100 days), but also later (>100 days) in the post-transplantation course. Whereas the prevalence of early CMV disease has declined to 3% to 6% with intense antiviral drug use, the risk of late CMV disease has increased over the past few years, with up to 18% of recipients developing disease even when no prevention is administered [7].

Here, we report a case of primary CMV peritonitis after unrelated HSCT. As CMV peritonitis is usually due to CMV colitis, primary CMV peritonitis not accompanied by CMV colitis is very rare. Disease can occur anywhere in the gastrointestinal tract, but colitis is most frequent, followed by gastritis, and it may range from asymptomatic to perforation or hemorrhage. Among transplant patients with gastrointestinal CMV disease, Fica et al. [8] found that over half reported ‘esophagitis-gastritis’ symptoms, 41% reported diarrhea, and 32% reported epigastric or thoracic pain. Gastrointestinal hemorrhage or perforation occurred in less than 10%. Fever and malaise as a general symptom accompany most cases. Gastrointestinal CMV disease should be differentiated from gastrointestinal complications after allogeneic HSCT. Transplant patients can present with signs and symptoms of graft rejection or graft-versus host disease. Other common complications include mucositis (90%), vomiting (85%), and abdominal pain (71%) [9]. Laboratory findings associated with CMV disease include thrombocytopenia, leukopenia, and elevated liver enzymes. However, in
tissue-invasive disease of CMV, many of these markers may be within normal ranges. Fica et al. [8] evaluated 31 patients with tissue-invasive disease (71% with gastrointestinal manifestations) and found thrombocytopenia in 50% and leukopenia in 35.5%.

In our patient, the risk of CMV disease was increased due to allogeneic HSCT from unrelated donor, the intense immunosuppressive therapy including tacrolimus and sirolimus, and poor performance status complicated by previous viral cystitis of BK virus. Abdominal pain was initially considered to be associated with acute graft versus host disease or colitis, because the interruption of cidofovir that has been commonly employed to treat CMV disease was of short duration and cytopenias may be observed with graft versus host disease. In addition, the last titer of CMV before the event was less than 1,000 copies/mL. However, peritoneal disease without perforation was suggested based on the

Fig. 3. (A) Colonoscopic examination reveals only small ulcer of ascending colon without edematous wall thickening and multiple ulcers. (B-D) Others are normal finding.

Fig. 4. The section from the peritoneum shows lipid vacuoles surrounded by a dense red fibrin ring and epithelioid macrophages, which are consistent with fibrin ring granulomas. (H&E, ×200).
result of computed tomography and colonoscopic findings. And then we performed peritoneal biopsy. We couldn’t find intra-nuclear inclusion or cytoplasmic inclusions in the peritoneal biopsy because of the limitation of blunt biopsy. CMV has been shown to be a causal agent of chronic granulomatous disease [10] and fibrin ring granuloma of the peritoneal tissue may be seen in a variety of infections including CMV. By follow-up study of CMV and no infection evidence on any other sites except peritoneum, CMV disease of peritoneum was strongly suggested. Therefore, we tried to test RT-PCR on paraffin-embedded tissue to confirm CMV disease of peritoneum although it was not routine test. Recently Mills et al. [11] reported the usefulness of PCR method for CMV detection in tissue. The major benefit of this CMV PCR is its use of paraffin-embedded tissue. Prior PCR based investigations of viral load in the biopsies have relied on fresh tissue, which can be difficult to acquire in routine practice. The use of paraffin-embedded tissue allows histologic review before performing PCR, facilitating the selection of the most appropriate block for testing and allowing initial testing by immunohistochemical stain. In addition, other potential advantage of the PCR method is its ability to quantify viral burden.

There have been reported only two cases of primary CMV peritonitis in immunocompromised patients in the world. Wilcox et al. [12] reported a 29-year-old Hispanic bisexual man with AIDS (acquired immune deficiency syndrome) for the first time. He was admitted to hospital for severe abdominal pain, and surgical treatment was done. And then CMV peritonitis could be confirmed by the biopsy of lesions. There was absence of intestinal or colonic perforation. Second case was a renal transplantation patient with CMV peritonitis after administering anti-CD52 antibody alemtuzumab combined with methylprednisolone, followed by a sequential immunosuppressive therapy with tacrolimus [13]. She was admitted because of abdominal pain and persistent leukopenia. In the second case report, CMV peritonitis was diagnosed by performing quantitative RT-PCR of the culture-negative peritoneal fluid and routine CMV monitoring using CMVpp65 antigen initially failed to identify CMV peritonitis. Therefore, authors suggested complications of CMV disease might be under-diagnosed in immunocompromised patients due to the sensitivity of CMV monitoring method. Cases of CMV peritonitis including our case were successfully treated with intravenous ganciclovir treatment.

In conclusion, we here report primary CMV peritonitis without colitis or bowel perforation after allogeneic HSCT from unrelated donor. Meticulous monitoring for CMV by high quantitative RT-PCR is mandatory in patients of allogeneic HSCT.

REFERENCES