Case Report

Cytomegalovirus Esophagitis and Colitis, Esophageal Candidasis and Colon Amebiasis in an HIV Patient with More than 200/μl CD4-positive T Lymphocytes

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Case : A 24-year-old Japanese man with HIV infection (a man who has sex with men) was referred to our hospital because of diarrhea, abdominal pain and high-grade fever. Endoscopic examination revealed colon and esophageal ulcers, which were histologically found to be caused by cytomegalovirus (CMV) infection. Esophageal candidasis and amebic colitis were concurrent with CMV infection. CMV pp65 antigenemia value was 18 positive cells per 50,000 cells. At the time of the CMV diagnosis, a CD4-positive (CD4+) T lymphocyte count was 259/μl. Fever and diarrhea gradually improved after treatment with ganciclovir and foscarnet for CMV infection and metronidazole for amebiasis followed by anti-retroviral therapy.

Discussion : The risk of opportunistic infections in patients with HIV has long been known to depend on the degree of immunodeficiency as measured by CD4+ T cells. In the antiretroviral-naïve patient, CMV infection usually occurs only when CD4+ T cells are less than 100/μl. However, our case demonstrates that even at a higher CD4+ T cell count, the complication of CMV infection may occur in HIV infection.

Introduction

Cytomegalovirus (CMV) infection is one of the most common opportunistic infections in people with human immunodeficiency virus (HIV), with clinical CMV disease seen in up to 40% of patients with advanced immunodeficiency, most often with CD4-positive (CD4+) T lymphocytes less than 100/μl[1]. We describe a patient with HIV infection and a CD4+ lymphocyte count greater than 200/μl who developed CMV colitis and esophagitis, as well as esophageal candidasis and amebic colitis.

Case Report

The patient was a 24-year-old Japanese man with HIV infection (a man who had sex with men). He was diagnosed with HIV infection after presenting with oral and esophageal candidiasis and an esophageal ulcer in September 2000. At the time of diagnosis, his CD4+ T lymphocyte count was 316/μl, and viral load was 220,000 copies/ml. He was admitted to our hospital with complaints of fever, watery diarrhea, and weight loss in December 2000. On physical examination, his blood pressure was 103/44 mmHg, heart rate was 96/minute, and body temperature was 39.6℃. His conjunctivae were slightly anemic. Numerous cervical, axillary and inguinal lymph nodes were observed—0.5 to 1.5 cm in size, elastic, soft and movable. Liver was palpable 3 cm below the right costal margin, and spleen was palpable 1 cm below the left costal margin.

On admission, CD4+ T lymphocyte count was 259/

μl, and viral load was 150,000 copies/ml. CMV pp65 antigenemia value[2] was 18 positive cells per 50,000 cells, which demonstrated a possibility of CMV infection as the cause of fever, lymphadenopathy, and hepatosplenomegaly. Ganciclovir (500 mg/day) was started, but was stopped 6 days later because of neutropenia, thrombocytopenia, fever, and liver dysfunction. On his 12th hospital day, he had sudden massive hematochezia. Emergent colonoscopic examination showed multiple punched-out ulcers in the rectum and ascending colon (Figure 1 A). Biopsy specimen revealed CMV infection by immunostaining methods using anti-CMV antibody (Figure 1 B) ; however inclusion bodies were not observed. Many amoebas with phagocytosis were also observed (Figure 1 C, 1 D). The cause of the colon ulcers in this case, as
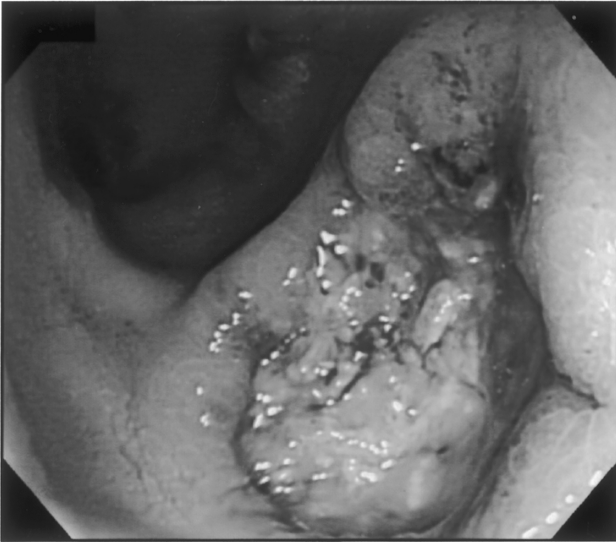

Figure 1 A. Colon ulcers observerd by colonoscopy. Multiple ulcers like craters were found at the sigmoid colon, and the bottoms of the ulcers exhibited hemorrhaging.
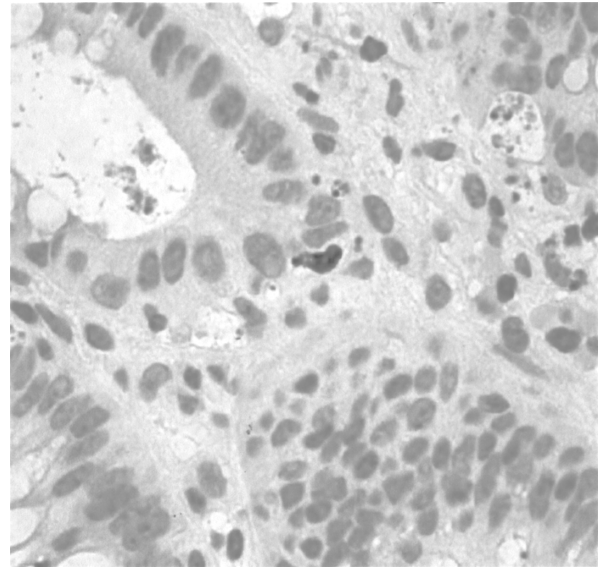

Figure 1 B. Biopsy specimen of a colon ulcer that shows positive immunostaining against anti-CMV antibody.
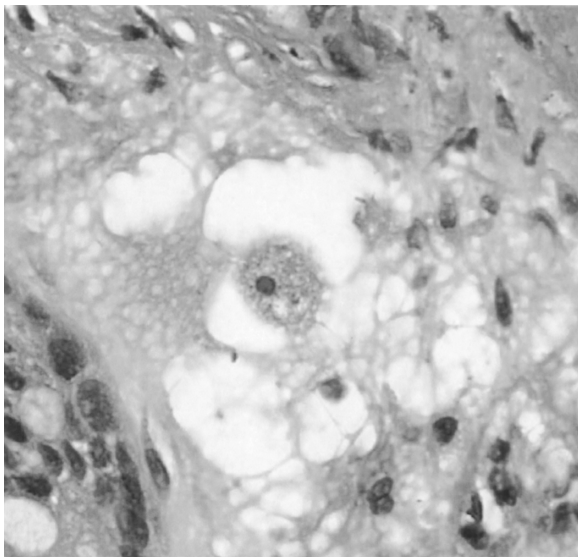

Figure 1 C. Biopsy specimen of a colon ulcer with amoebas in the epithelial cells and interstitial cells. Hematoxylin-Eosin stain.
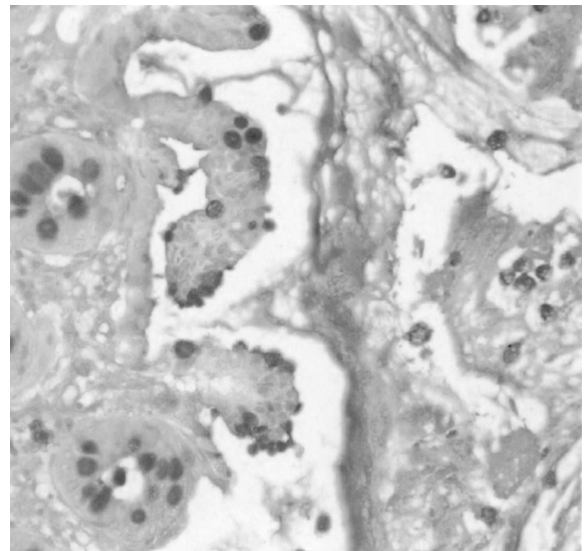

Figure 1 D. Biopsy specimen of a colon ulcer with amoebas in the epithelial cells and interstitial cells. PAS stain.

confirmed by histological examination, was CMV with amebiasis.   Foscarnet was administered at 160 mg/kg as initial therapy for 9 days, then 80 mg/kg as maintenance dose thereafter.   It was reduced earlier than the standard 14 days because newly appeared leukocytopenia seemed to be a side effect.   Metronidazole (1,000 mg/day) was also administered.

Esophagogastroduodenoscopy showed extensive, large, shallow mucosal ulcers in the esophagus, which is a classical sign of CMV esophagitis (Figure 2 A).   The biopsy specimens revealed typical intranuclear inclusion bodies in the epithelial cells (Figure 2 B).

His clinical course is summarized in Figure 3. Antiretroviral therapy with stavudine, lamivudine, and nelfinavir was started on his 65th hospital day ; however, the treatment was stopped after a week because of fever and diarrhea.   The CMV pp65 antigenemia level had decreased to 0 positive cells per 50,000 cells at this stage, but later increased to as high as 813 positive cells on his 102nd hospital day.   We assumed that the CMV became resistant to foscarnet.   We replaced this with ganciclovir at a half dose (250 mg/day).   Fever and diarrhea gradually improved, and CMV pp65 antigenemia level again returned to 0 positive cells.   Fever and diarrhea were relieved after treatment for both CMV and HIV.   He was discharged on his 249th hospital day on a regime of stavudine, lamivudine and indinavir.   His viral load has remained at undetectable levels for 9 months since discharge.

Discussion

CMV esophagitis occurs in approximately 10% of persons with AIDS.   The most common symptom is odynophagia[3].   CMV colitis can occur in up to 7.3% of persons with AIDS[4].   According to a report by Wilcox et al., chronic diarrhea and abdominal pain are the most frequent clinical manifestations, seen in 80% and 50%, respectively, with 9% of the patients presenting with lower gastrointestinal hemorrhage[5].

For the treatment of gastrointestinal CMV disease, ganciclovir 5 mg/kg twice daily or foscarnet 90 mg/kg twice daily are usually recommended[6].   However, the dosage used was a little less than the standard dose. This might be the reason why foscarnet was not effective and CMV became resistant to foscarnet after the long administration in this case.

The risk of opportunistic infections in patients with HIV has been known to depend on the degree of immunodeficiency as measured by CD4+ T cells. Ulcers and erosions caused in the gastrointestinal tract by CMV infection are observed usually when the number of CD4+ T lymphocytes decreases to less than $100/\mu$l, and especially when less than $50/\mu$l.   Mentec et al. have reported that CMV colitis occurs late in the course of HIV infection, on average 4 months before death[7].   Wilcox et al. have done a prospective study of fifty-six patients with HIV infection and CMV colitis.

Figure 2 A.   Esophageal ulcers observed by esophagogastroduodenoscopy.   Dye sprayed esophagoscopy revealed a punched out ulcer at the squamocolumnar junction.
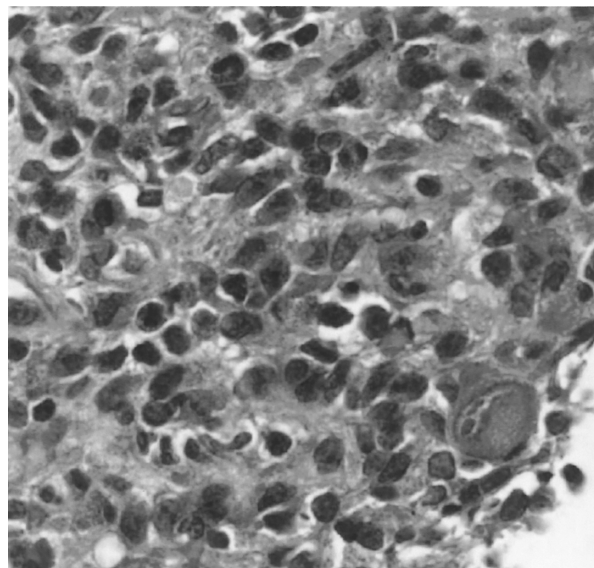

Figure 2 B.   Biopsy specimen of an esophageal ulcer with intranuclear inclusion body.   Hematoxylin-Eosin stain.
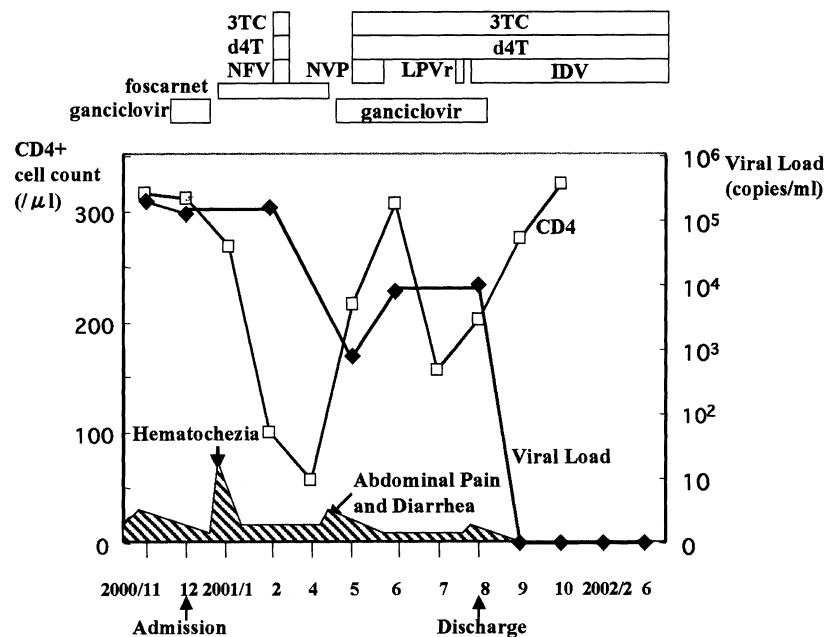
Figure 3. Clinical course of the case.

The majority of the patients were homosexual men with severe immunodeficiency with a median CD4$+$ lymphocyte count of 15/μl[5].

We present here an antiviral-naïve patient diagnosed with CMV esophagitis and colitis at a relatively early stage of HIV infection with a CD4$+$ T cell count ranging from 250 to 350/μl. Several reasons can explain this. One possibility is that the function of each CD4$+$ T lymphocyte might be deteriorated by HIV infection. It was, however, difficult to demonstrate this. The second is that the impairment of immunity could have been caused by the patient's general condition. We assume nutritional factors may have contributed to this man's immunosuppression status. Clinical and experimental studies have demonstrated that excessive alcohol consumption can result in impairment of the immune system, including immune tolerance and host defense against opportunistic infections. Barve *et al.* have recently reported that depletion of helper CD4$+$ T lymphocytes is a major contributing factor in ethanol-induced immune dysfunction and exacerbation of HIV and/or HCV pathogenesis[8]. Latif *et al.* have reported that alcohol impairs Th1-regulated cell-mediated immune responses[9]. Our patient had abused alcohol and maintained a poor diet prior to presenting with diarrhea and fever. Diabetes mellitus is well known in compromised immunity, but the patient did not have diabetes. The third possibility might be damage of the local immunological defense system. We assume combined infections of candidasis and

amebiasis may alter focal mucosal barriers in the esophagus and colon, leading to the development of a local CMV infection. Smith *et al.* have previously reported a case of a patient with CMV colitis and a CD4$+$ T cell count at 800/μl[10]. They concluded that recent attacks of *C. trachomatis, N. gonorrhoeae,* and non-specific urethritis may have increased CMV shedding, with recent cases of rectal warts and *C. difficile* infection also contributing to the development of CMV disease.

Our patient is a man who has sex with men, so there is also a possibility of mucosal damage related to receptive anal intercourse. Surawicz *et al.* have reported CMV colitis in immunocompetent individuals as a consequence of receptive anal intercourse (2 cases) or rectal manipulation with an enema (1 case)[11]. They concluded that self-limited CMV colitis could occur in immunocompetent individuals in a manner that mimics inflammatory bowel disease, so careful histological evaluation of the mucosa is essential for diagnosis.

The incidence of CMV disease has decreased by more than 80% since the advent of highly active antiretroviral therapy (HAART). Most cases now seen in Western countries are in profoundly immunosuppressed patients who have failed to respond to HAART[12], though CMV retinitis has also been reported in patients with relatively high CD4$+$ T cell counts[13,14]. Benson and Johnson have previously discussed three forms of CMV-associated ocular inflammation in HIV-infected patients receiving potent antiretroviral therapy[15]. The first form has been ascribed to the evolution of retinitis

lesions present before the initiation of therapy. The second has been ascribed to a reconstituted vigorous immune response to CMV antigens localized in the eye. The third is CMV developing despite the patient receiving antiretroviral therapy and having apparent immune reconstitution as evidenced by CD4＋ T cell counts of ＞200 cells/μl[16-18]. Our case differs from all three, as this patient was antiviral-naïve when he presented with CMV esophagitis and colitis, despite having more than 200/μl CD4＋ T cells.

In conclusion, the occurrence of CMV esophagitis and colitis can be multifactorial. Clinicians should be aware that this complication of HIV disease may occur at a higher CD4＋ T cell level than usual, particularly when concurrent risk factors exist.

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