A successfully cured case of cytomegalovirus multiple organ infection after hematopoietic stem cell transplantation: A case report

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Abstract. Cytomegalovirus (CMV) infection is one of the most common infectious complications following hematopoietic stem cell transplantation (HSCT); however, cases involving multiple organs at the same time are rare. The present study describes a case of CMV pneumonia combined with CMV DNAemia and CMV cystitis after HSCT. A 33-year-old male patient with acute myeloid leukemia was treated with HSCT. The first month after HSCT, the patient developed a cough and shortness of breath. At 2 months post-HSCT, the patient developed hematuria. The CMV DNA levels in the blood and urine were elevated; bronchoalveolar lavage fluid (BALF) was also positive for CMV DNA. Heterotypic cells exhibiting a large nuclear morphology were observed in the BALF and bronchial brushes. Recurrent and progressive ground-glass opacities were evident on chest computed tomography. The patient was diagnosed with CMV pneumonia complicated by CMV DNAemia and CMV cystitis, and was treated with a combination of ganciclovir and foscarnet, along with immunoglobulin therapy. The patient was cured and discharged. It was determined that the CMV DNA in the blood was inconsistent with that in the BALF, which delayed the early diagnosis of CMV pneumonia. The association between T-cell immune function and the therapeutic efficacy for CMV multi-organ infection following HSCT is known to be significant. Moreover, the timely administration of ganciclovir and foscarnet in combination with immunoglobulin therapy demonstrated favorable clinical outcomes.

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Abbreviations: BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation

Key words: CMV pneumonia, HSCT, CMV DNAemia, CMV cystitis

Introduction

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for hematological tumors. With the development of transplantation technology, an increasing number of patients with hematological tumors are undergoing HSCT (1). Cytomegalovirus (CMV) is an opportunistic virus, and patients after HSCT are the most susceptible population (2). CMV infection is one of the most common infectious complications following HSCT, with an incidence of 5-10% (3). Although great progress has been made in early diagnosis and treatment, CMV seropositivity is still a risk factor for non-relapse mortality (4). The spectrum of CMV infection is quite broad, ranging from asymptomatic viremia to CMV end-organ disease, such as esophagitis, gastroenteritis, hepatitis, retinitis, pneumonia and encephalitis (5). CMV pneumonia represents a severe manifestation of CMV disease, with a 6-month survival rate of only 30% in patients with HSCT (6). The treatment of refractory CMV infection and CMV multiple organ infection remains a major therapeutic challenge. The current study presents a case of a patient with CMV infection involving the lung, blood and bladder after HSCT, with a good subsequent therapeutic effect. The aim of the study was to report a diagnostic and treatment experience for the benefit of clinicians managing similar cases, with the ultimate goal of enhancing the early detection, diagnosis and treatment of CMV infection after HSCT, so as to reduce organ damage and improve the survival rate of affected patients.

Case report

A 33-year-old male patient was admitted to The First Affiliated Hospital of Guangxi Medical University (Nanning, China) in April 2018 due to a recurrent cough, with sputum, and shortness of breath after activity for >6 months following HSCT. The patient had undergone HSCT for acute myeloid

leukemia in September 2017. On day 40 after HSCT, the patient developed the aforementioned symptoms. The recorded arterial oxygen partial pressure was 82.8 mmHg (normal range, 80-100 mmHg). Treatments using antibacterial agents (cefoperazone sulbactam, levofloxacin and meropenem) and antifungal agents (voriconazole and caspofungin) were ineffective. Chest computed tomography (CT) showed a ground-glass shadow in the lower lung fields of both lungs (Fig. 1A). The blood CMV DNA count was $7.4x10^4$ copies/ml (normal range, <500 copies/ml) according to fluorescence quantitative PCR performed by the Clinical Laboratory of The First Affiliated Hospital of Guangxi Medical University (Fig. 2); thus, the diagnosis of CMV DNAemia was reached. Immediate treatment with foscarnet (intravenous drip, 6 g every 12 h) and γ-globulin (intravenous drip, 2.5 g every 12 h) was initiated. However, the symptoms were not improved after 2 weeks of treatment.

On day 55 after HSCT, the blood CMV DNA level further increased to $1.61x10^5$ copies/ml and the respiratory symptoms were not relieved. On day 62 after HSCT, the patient developed hematuria, and frequent and painful urination. The CMV DNA level in the urine was $1.8x10^3$ copies/ml (Fig. 2), and the patient was diagnosed with CMV cystitis. The aforementioned treatment was ineffective; therefore, the patient was treated with ganciclovir (intravenous drip, 0.3 g every 12 h) for 1 month to strengthen the anti-CMV treatment. On day 98 after HSCT, the urinary symptoms had improved, but the cough with sputum, and the shortness of breath after physical activity remained, even though the blood and urine analyses were now negative for CMV DNA.

On day 107 after HSCT, the patient presented with multiple rashes on the face and extremities, leading to a diagnosis of mild graft-versus-host disease of the skin; tacrolimus (oral, 1 mg every 12 h) and mycophenolate mofetil (oral, 0.25 g three times a day) treatment was administered. On day 120 after HSCT, chest CT revealed scattered ground-glass and patchy shadow lesions in the lower lungs, which had progressed compared with the findings on previous scans (Fig. 1B). Additionally, bronchoscopy showed mucosal congestion (Fig. 3). BALF culture, (1,3)-β-D-glucan test and galactomannan test results on BALF samples were normal, with no signs of bacterial or fungal infection. However, the BALF exhibited CMV DNA levels of $1.12x10^4$ copies/ml (Fig. 2), but was negative for CMV IgM. Under a microscope, gian T cells could be observed in the BALF and bronchial brushes, and their nuclei were enlarged, dark-colored and rich in cytoplasm (H&E staining; light microscopy; Fig. 4A and B). The clinical diagnosis was therefore CMV pneumonia and a treatment was again initiated consisting of a combination of ganciclovir (intravenous drip, 0.3 g every 12 h) and foscarnet (intravenous drip, 6 g every 12 h), with the addition of γ-globulin (intravenous drip, 2.5 g every 12 h) to augment immune function. After 1 month of treatment, although the patient experienced some relief from the cough with sputum and from the shortness of breath after activity, these symptoms persisted and recurred.

On day 233 after HSCT, the patient presented with a fever and dry cough. Bone marrow examination revealed active hyperplasia and no evidence of a relapse of the leukemia. The total T-cell count was 1,774/μl, with $CD4^+$ T cells at 98/μl and $CD8^+$ T cells at 1,654/μl according to flow cytometry performed by the Clinical Laboratory of The First Affiliated Hospital of Guangxi Medical University (Fig. 5). The BALF CMV DNA level was $1.87x10^5$ copies/ml (Fig. 2), and the gian T cells had disappeared from the BALF (Fig. 4C) but were still apparent in the bronchial brushes (Fig. 4D). Chest CT showed that the ground-glass and patchy shadows of both lungs were visible (Fig. 1C). Given the patient's compromised immune system and subsequent inadequate infection control, the tacrolimus treatment was discontinued and ganciclovir (intravenous drip, 0.3 g every 12 h) and foscarnet (intravenous drip, 6 g every 12 h), plus γ-globulin (intravenous drip, 2.5 g every 12 h) therapy was administered. After 1 month of treatment, the patient exhibited improvement in the fever and cough symptoms, and subsequently the number of T lymphocytes increased significantly (Fig. 5).

On day 272 after HSCT, chest CT showed that the lesion had more lesions (Fig. 1D) and the BALF CMV DNA level was $5.96x10^3$ copies/ml. On day 300 after HSCT, after 1 month of intensive antiviral therapy with ganciclovir, the BALF was negative for CMV DNA, the gian T cells had disappeared from the BALF (Fig. 4E) and the bronchial brushes (Fig. 4F), and chest CT revealed that the lung lesions in both lower lungs had been absorbed (Fig. 1E). The patient was discharged from the hospital. At 7 months post-discharge, the patient had no cough with sputum or shortness of breath, the blood CMV DNA results were still negative, and there was further lung lesion uptake on chest CT (Fig. 1F). The patient will be followed up by re-examination every 3 months, and the prognosis is good with no recurrence.

Discussion

Early diagnosis of the present case was challenging due to the patient's atypical symptoms and multiple organ CMV infection. The patient in the present study first experienced shortness of breath, a cough and hypoxemia. Blood CMV DNA testing was positive, and the patient's lung changes on a chest CT scan were mild, leading to the diagnosis of CMV DNAemia. As the disease progressed, hematuria, and frequent and painful urination were brought on by the CMV infection that had progressed to the bladder. Additionally, blood and urine tests revealed the presence of CMV DNA, which is a sign of CMV cystitis. After receiving therapy, the patient continued to have frequent coughing fits, expectoration and post-exercise breathlessness. CT showed ground-glass and patchy shadows in the lungs, and the BALF CMV DNA test was positive. The condition was clinically determined to be CMV pneumonia in accordance with the diagnostic standards for CMV pneumonia following organ donation (7). Finally, the patient was diagnosed with CMV pneumonia complicated by CMV DNAemia and CMV cystitis.

During diagnosis and treatment, a notable phenomenon was found in the present report: The CMV DNA in the blood was not consistent with that in the BALF. After the patient was treated with anti-CMV drugs, the blood CMV DNA result became negative. However, the patient's BALF CMV DNA result was positive. It has previously been reported that the CMV DNA level in the blood of patients with CMV pneumonia is inconsistent with that in the BALF, and that the positive CMV DNA detection rate in the BALF is greater than

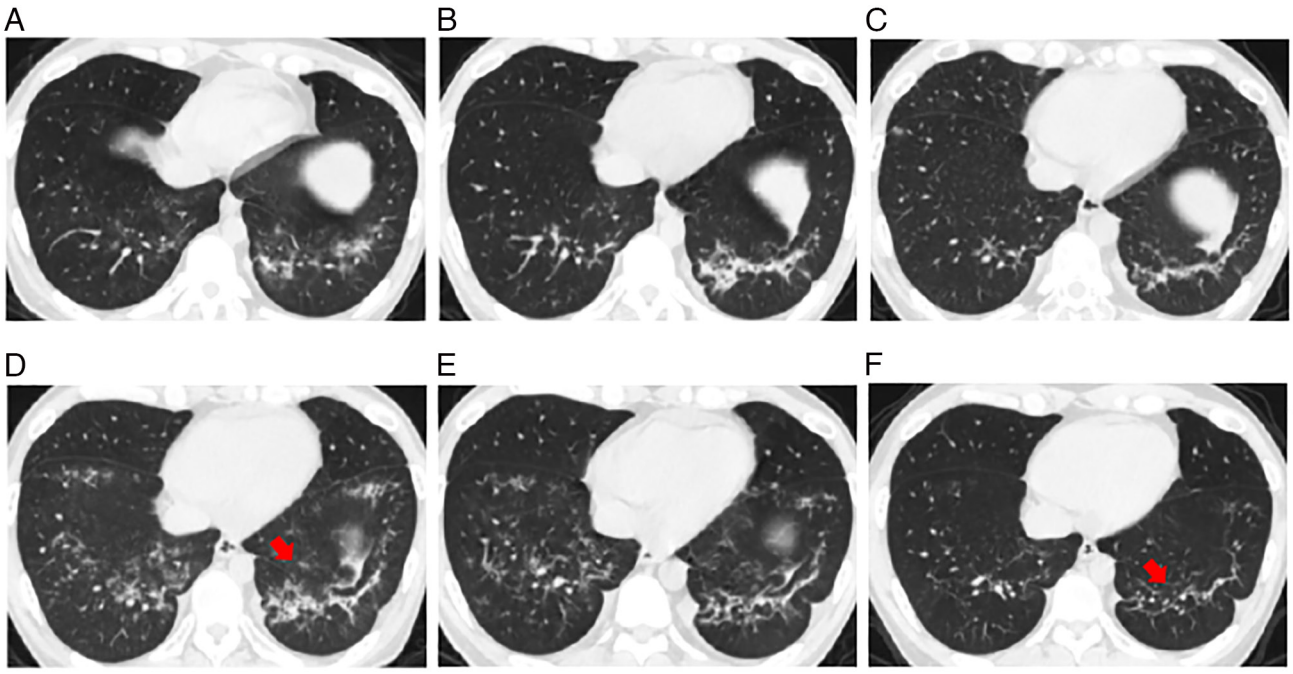

Figure 1. Thoracic computed tomography. (A) At 40 days post-HSCT, a small exudation and ground-glass shadow was present in both lower lungs. (B) At 120 days post-HSCT, scattered ground-glass shadows, and streak-like and patchy high-density shadows were still found in both lungs. (C) On 233 days post-HSCT, the ground-glass, strip-like and patchy shadows of the two lungs were obvious. (D) At 272 days post-HSCT, the number of ground-glass and patchy high-density shadows (arrow) of both lungs increased markedly. (E) At 309 days post-HSCT, the number of ground-glass and patchy shadows of both lungs decreased. (F) At 535 days post-HSCT, the lesions in the lower lobe of both lungs (arrow) were obviously absorbed and decreased. HSCT, hematopoietic stem cell transplantation.

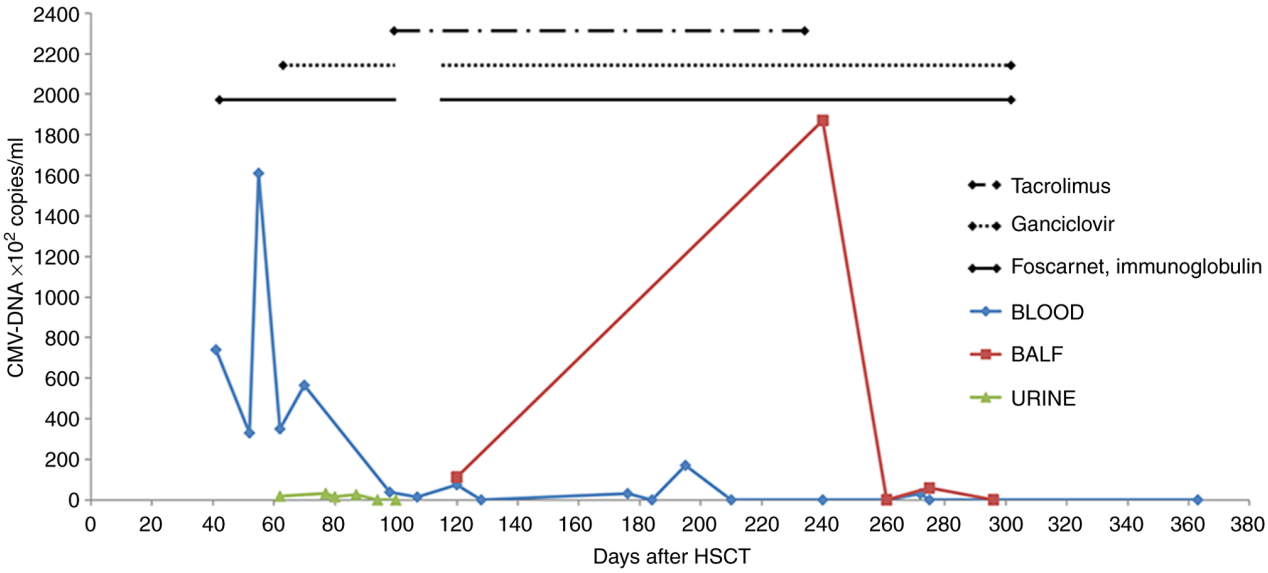

Figure 2. Number of copies of CMV DNA in blood, BALF and urine, and the timeline for using different drugs. Blood CMV DNA count was elevated and peaked on the early period after HSCT, before decreasing to normal on day 103 post-HSCT. BALF CMV DNA count was positive on day 120 post-HSCT, reached the peak on day 240 post-HSCT, and finally returned a negative result after anti-CMV therapy. Urine CMV DNA count was elevated on day 60 post-HSCT, fluctuated and became negative on day 100 post-HSCT. The treatment time of tacrolimus was from 107 days to 233 days post-HSCT, and was stopped at 233 days post-HSCT. The treatment time of ganciclovir was from 62 days to 92 days post-HSCT, was stopped after a negative result was returned for hematuria CMV DNA, and the was used again from 102 days to 302 days post-HSCT. The treatment time of foscarnet and immunoglobulin therapy was from 40 days to 92 days post-HSCT. Treatment stopped after a negative result was returned for hematuria CMV DNA, and then was used again from 102 days to 302 days post-HSCT. BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation.

that in the blood (8). In the present case, the patient's blood was negative for CMV DNA after anti-CMV therapy. However, at that time, the patient still had respiratory symptoms (cough, expectoration and shortness of breath), and chest CT showed a small number of ground-glass shadow in the lungs twice. Since the symptoms and CT findings were atypical, it was easy to diagnose as a pulmonary bacterial infection in the clinic. However, there was no significant improvement after aggressive

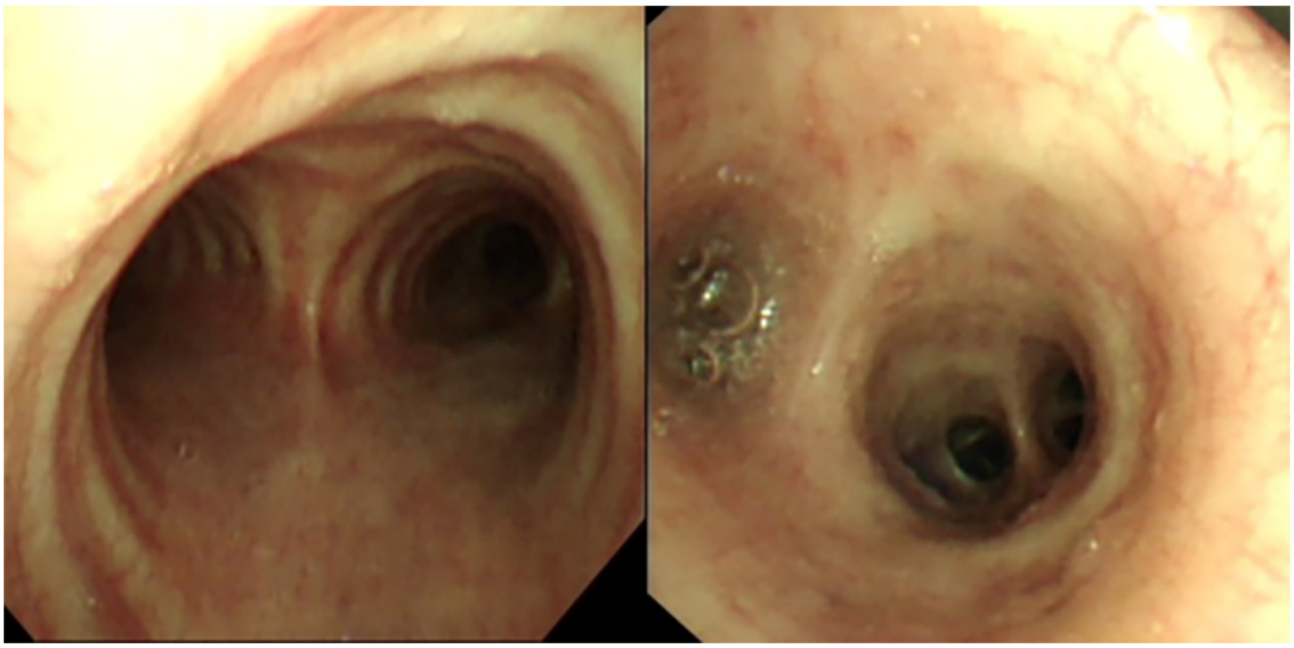

Figure 3. Bronchoscopy manifestations. On day 120 post-HSCT, the lumen was clear, the mucosa was slightly congested and serous secretions were observed at the left lower lobe opening.

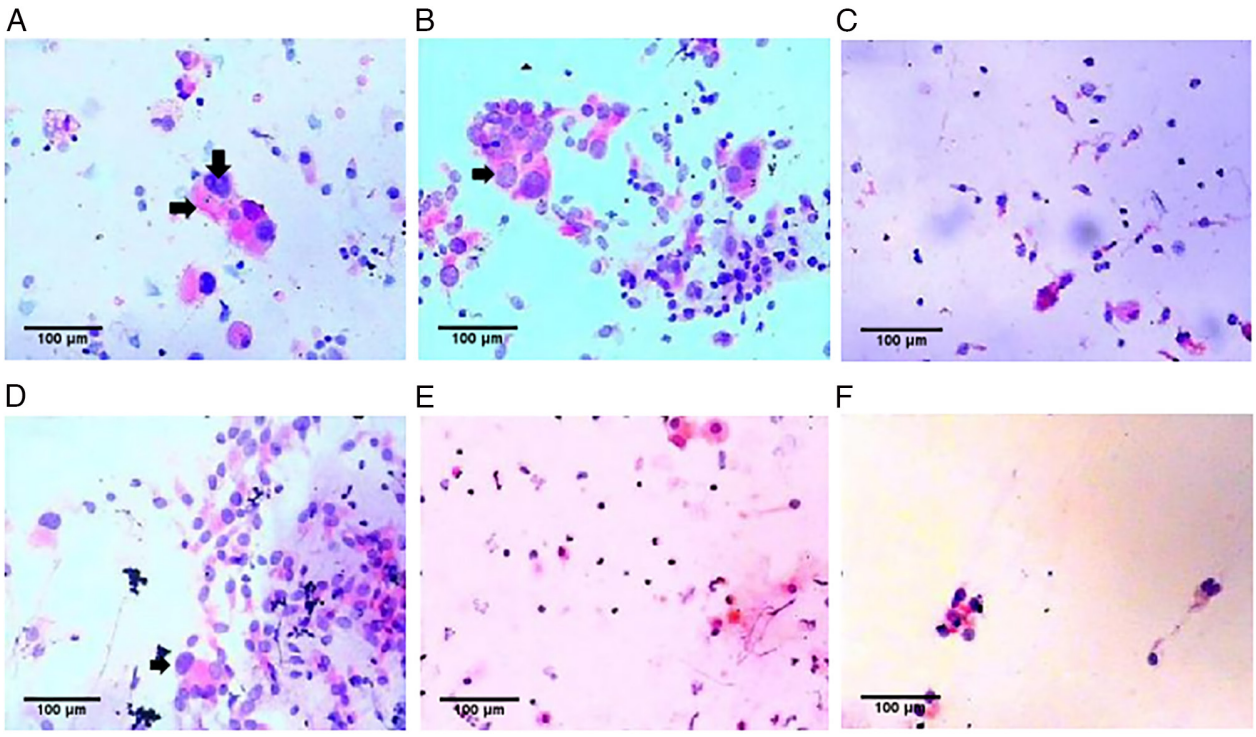

Figure 4. Cytological pathology of BALF and bronchial brushes. Large allotypic cells with enlarged and dark stained nuclei, and with abundant cytoplasm (black arrows) were found in (A) the BALF and (B) bronchial brushes on 120 days post-HSCT. These cells disappeared in (C) the BALF, but were still seen in (D) the bronchial brushes on 250 days post-HSCT, and had disappeared totally in (E) the BALF and (F) the bronchial brushes after treatments on day 275. All images are stained with hematoxylin and eosin at x100 magnification. BALF, bronchoalveolar lavage fluid; HSCT, hematopoietic stem cell transplantation.

anti-inflammatory treatment. Meanwhile, the patient was suffering from CMV cystitis. It was considered that the CMV had involved the organs and that the lung anti-inflammation treatment was ineffective, indicating that this patient may have CMV pneumonia. A bronchoscopy, CMV DNA testing of the BALF and cytological analyses of the bronchus brushes were promptly conducted, and CMV pneumonia was finally diagnosed. Therefore, even if the blood CMV DNA positivity of patients with HSCT becomes negative after treatment, doctors should be alert to the possibility of CMV pneumonia when patients have respiratory symptoms such as a cough, expectoration, shortness of breath and/or ground-glass shadows on

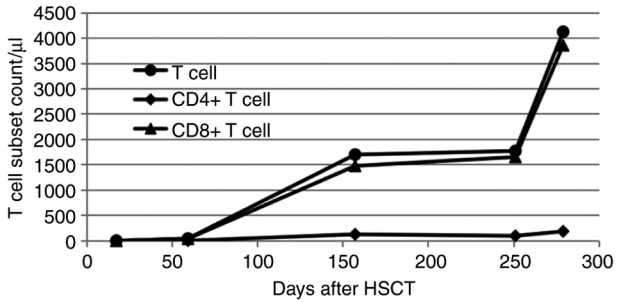

Figure 5. T-cell subset count. The number of total T cells and CD8+ T cells increased gradually at 62 days after HSCT, and increased significantly at 253 days after HSCT. The number of CD4+ T cells was at a low level at 0-252 days after HSCT, and increased significantly at 253 days after HSCT. HSCT, hematopoietic stem cell transplantation.

chest CT. In particular, fiberoptic bronchoscopy, BALF CMV DNA detection and brush cytological examination should be completed as soon as possible to eliminate CMV infection. In addition, the present study found that gian T cell degeneration in the BALF and bronchial brushes could be used as an index for diagnosis and treatment. It has been reported that compared with normal cells, bronchial brush cells that are infected with CMV morphologically undergo gian T cell degeneration, and in particular, the size of the nucleus increases by 2.61-4.25 times (9). No CMV inclusion bodies were found in the present study, but the cells were enlarged, the heteromorphic cells had large nuclei and the nuclear-cytoplasmic ratio was increased. Bone marrow examination showed no recurrence of leukemia. It was considered that the change in cells was caused by CMV infection. After treatment, reexamination of the BALF and brush cytology revealed that the gian T cells were gradually disappearing, whereas chest CT findings and clinical manifestations were improved.

After the patient was diagnosed, the effect of treatment was still not good. The following two reasons should be considered: First, the patient's CMV infection status included CMV viremia, CMV pneumonia and CMV cystitis. The patient's condition was complicated, and it was necessary to treat not only the CMV infection but also the associated complications. The patient developed CMV anemia 40 days after HSCT. Anti-CMV therapy failed to treat the CMV in time, which led to CMV pneumonia and CMV cystitis. The patient had recurrent pneumonia, which was considered to be a bacterial or fungal infection according to clinical experience; however, the anti-bacterial and fungal treatment was not effective, thus CMV infection was considered and relevant examinations were performed to finally confirm the diagnosis of CMV pneumonia. Second, after HSCT, the T-cell immune function of the patient had not fully recovered, and the antiviral treatment effect was of slow onset. HSCT CMV pneumonia is more likely to occur within 100 days after HSCT. This is the immune reconstruction period following HSCT; it takes between 3 months and 1 year for the $CD8^+$ T-cell count to return normal, whereas it takes longer for the $CD4^+$ T-cell count to return to normal, and even several years before a low $CD4^+/CD8^+$ ratio is maintained (10). In the present case, the patient had recurrent episodes of CMV pneumonia and a long treatment time during antiviral therapy, which was considered to be related to the decrease of T lymphocyte subsets and low immunity. It has been reported that the median number of $CD8^+$ T cells in refractory CMV-infected patients after HSCT is 371 cells/μl at 1 month after HSCT, and that the median number of $CD4^+$ T cells is still <100 cells/μl at 4 months post-HSCT (11). Anti-CMV therapy relies mainly on T-cell immunity, and tacrolimus inhibits the proliferation of $CD4^+$ T cells and $CD8^+$ T cells (12). In the present case, the patient was administered tacrolimus as anti-rejection treatment after HSCT. Meanwhile, the early immunity did not fully recover, and the number of $CD4^+$ T cells and $CD8^+$ T cells was low, resulting in CMV pneumonia and CMV cystitis. After stopping the tacrolimus, the patient's T cell count, especially the $CD8^+$ T cell count, increased markedly, and immunity gradually recovered. The effect of the antiviral treatment on the CMV pneumonia was significantly improved.

It is difficult to treat CMV pneumonia complicated with CMV hematuria and CMV cystitis after HSCT. According to the therapeutic effect on the current patient, a suitable treatment plan was proffered. The guidelines for the management of CMV infection after SCT from the 2017 European Leukemia Infection Conference indicated that the first-line treatment for CMV infection after HSCT is intravenous injections of ganciclovir or foscarnet (3). Immunoglobulin can be added in the treatment of CMV pneumonia, although it is not recommended to add immunoglobulin in the treatment of any other CMV diseases except pneumonia. The indicated second-line therapy is cidofovir or ganciclovir and foscarnet (3). When the current patient was diagnosed with CMV anemia and CMV cystitis, foscarnet sodium was chosen as the first-line drug according to the guidelines. Furthermore, immunoglobulin was added. Intravenous propionic immunoglobulin contains a high dose of anti-CMV IgG antibodies that specifically bind and kill CMV, and enhance immune persistence with a median half-life of 51.2 days (13). The role of immunoglobulin in preventing CMV infection is controversial. A study previously showed that immunoglobulin not only had no preventive function in CMV diseases, but that it also led to interstitial pneumonia (14). In addition, it was also reported that immunoglobulin had a good clinical therapeutic effect in the treatment of CMV diseases (15). In the present study, after 1 month of treatment with ganciclovir and foscarnet combined with immunoglobulin, the patient's blood and urine were negative for CMV DNA. The notable feature of this patient's treatment was that when a diagnosis of CMV pneumonia was made, ganciclovir and foscarnet combined with immunoglobulin were chosen for treatment, but the treatment effect was poor. This may be due to two main reasons: First, the patient developed graft-versus-host disease after HSCT and had been treated with tacrolimus; tacrolimus can inhibit T-cell proliferation and reconstruction (16). Second, the T-cell immune function of the patient after HSCT had not been fully recovered. The patient was diagnosed with CMV pneumonia 120 days after HSCT. At this time, the patient's immunity was being rebuilt, the number of T cells was small and the immune function was compromised. This led to the poor anti-CMV efficacy of ganciclovir and foscarnet sodium combined with immunoglobulin. It was observed that the number of T cells in the patient increased markedly 250 days after transplantation once tacrolimus was stopped. At this time, the immune

function recovered, and the anti-CMV effect of the ganciclovir and foscarnet sodium combined with immunoglobulin was notable. The patient's CMV DNA test was negative, and chest CT showed that the lung lesions had been absorbed; therefore, the patient was considered cured and discharged.

When the patient was diagnosed with CMV infection, treatment with foscarnet and immunoglobulin was implemented, but the symptoms were still apparent. After adding ganciclovir, the antiviral effect was marked. We suggest that ganciclovir combined with foscarnet should be used as soon as possible to strengthen the anti-CMV treatment and immunoglobulin to improve immunity when the anti-CMV effect is not good. Therefore, we recommend that ganciclovir and foscarnet combined with immunoglobulin should be used as the first-line treatment for HSCT CMV multi-organ infection.

In summary, it took a long time to diagnose and treat the current patient, although he was eventually cured. The CMV DNA in the blood was inconsistent with that in the BALF, which delayed the early diagnosis of CMV pneumonia. Attention should be focused on the early diagnosis of CMV infection. When CMV pneumonia cannot be completely ruled out in patients with HSCT, it is crucial to conduct a pathogenic examination, CMV DNA detection and cytological examination of the BALF. After treatment in the present case, the gian T cells in the alveolar lavage fluid gradually disappeared and the brush cytology returned to normal, suggesting that gian T cell degeneration can serve as a diagnostic and therapeutic index. In this case, the course of the disease was long, and the anti-CMV treatment effect was not good. It was considered that the immune function of the T cells after transplantation had not been fully recovered, and that the immunosuppression was caused by the use of tacrolimus. Therefore, we propose a plan for treatment standardization. In the treatment of patients with CMV multiple organ infection after HSCT, attention should be focused on the side effects of tacrolimus, and ganciclovir and foscarnet combined with immunoglobulin should be used as soon as possible.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QiL and QuL made important contributions in designing this study, acquiring and analyzing the data, and writing the manuscript. RM, QX and YZ participated in the interpretation of the data. CW, YW and KH participated in collecting the data and analyzing patient data. ML made substantial contributions in conceptualizing and designing the study, in acquiring and analyzing the data, and in critically revising the manuscript. All authors contributed to the writing of the final manuscript. QiL, QuL, RM, QX, YZ, CW, YW, KH and ML confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee associated with the Faculty of Medicine at the First Affiliated Hospital of Guangxi Medical University (approval no. 2023-E379-01; Nanning, China).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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