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Cytomegalovirus Pneumonia with Progressive Lung Volume Loss

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Case series

Patients: Male, 65 • Male, 63 • Female, 35
Final Diagnosis: CMV pneumonia
Symptoms: Respiratory failure
Medication: —
Clinical Procedure: Excepting diagnosis
Specialty: Pulmonology

Objective: Unusual clinical course

Background: Cytomegalovirus (CMV) pneumonia is common in immunocompromised patients with hematological malignancies. Although the spectrum of illness caused by CMV is well-documented in immunocompromised patients, the clinical course and evolution of lung changes after initiation of antiviral therapy remain unclear.

Case Report: We present the cases of 3 patients with leukemia who developed CMV pneumonia following cord blood transplantation and who presented with distinctive features on chest computed tomography (CT). In all patients, chest CT showed central peribronchial changes with severe lung volume loss. Furthermore, the patients were refractory to high-dose steroids, and the lung volume loss rapidly progressed, leading to death from respiratory failure.

Conclusions: We observed central peribronchial changes with severe lung volume loss after the acute phase in 3 cases of CMV pneumonia. While our diagnosis was made on the basis of exclusion, it is important to bear in mind that lung involvement in CMV pneumonia may be refractory to various treatment modalities and can lead to a fatal clinical course.

MeSH Keywords: Cryptogenic Organizing Pneumonia • Cytomegalovirus • Fatal Outcome • Leukemia

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/911708>

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Background

Cytomegalovirus (CMV) pneumonia is common in immunocompromised patients with hematological malignancy and can be life-threatening at times. In the acute phase, CMV pneumonia presents with ground-glass attenuation, areas of consolidation, and small nodules on chest computed tomography (CT) [1]. Secondary organizing pneumonia (SOP) is occasionally associated with various diseases, including infections, connective tissue diseases, malignancies, and even the intake of certain drugs [2]. A central peribronchial pattern of organizing pneumonia after CMV pneumonia with an atypical clinical course was previously reported, showing significant clinical improvement following treatment with systemic corticosteroids [3]. However, it is unclear whether central peribronchial changes, such as in organizing pneumonia, indicate a favorable clinical outcome. Herein, we present 3 patients with CMV pneumonia who had central peribronchial changes, such as organizing pneumonia and lung volume loss, which led to a fatal clinical course.

Case Report

Case 1

A 65-year-old male patient received cord blood transplantation (CBT) for acute myelogenous leukemia that recurred after the first complete response (CR), but failed to achieve second CR. Antibody titers carried out prior to CBT suggested previous CMV infection. He continued taking acyclovir as a prophylaxis against herpes simplex virus (HSV) infection. He achieved engraftment on day 21 after CBT. On day 33, CMV antigenemia was confirmed by an assay using C10/C11 monoclonal antibodies, followed by administration of foscarnet. The patient developed severe melena, leading to anemia and hypovolemic shock. He underwent mechanical ventilation and blood transfusion. On day 44, a chest radiograph showed consolidation in the right mid zone. Although antibacterial drugs – doripenem (500 mg IV q12h), teicoplanin (600 mg IV q24h), and daptomycin (350 mg IV q24h) – were administered, his respiratory status worsened. On day 47, computed tomography (CT) of the chest showed bilateral ground-glass attenuation accompanied by mild traction bronchiectasis and thickening of the interlobular septa (Figure 1A). Bronchoalveolar lavage (BAL) was performed and the BAL fluid (BALF) showed a neutrophil differential count of 45%. Considering the possibility of interstitial pneumonia, he was started on 120 mg of prednisolone daily; however, the pneumonia did not improve. The levels of CMV DNA were significantly elevated in the quantitative CMV-polymerase chain reaction (PCR) assay of the BALF and the patient was diagnosed with CMV pneumonia. Foscarnet was continued, followed by the disappearance of CMV antigenemia. CMV antigenemia disappeared on day 51. On day 62, diffuse,

central, peribronchial, organizing pneumonia-like changes with severe lung volume loss were observed on chest CT scan (Figure 1B). SOP or acute respiratory distress syndrome (ARDS) with CMV pneumonia were considered. Although the patient was treated 3 times with pulse steroid therapy, bilateral shadowing and lung volume loss did not improve, and he died of respiratory failure on day 78.

Case 2

A 63-year-old male patient underwent CBT for acute lymphatic leukemia and achieved second CR. Antibody titers carried out before CBT suggested previous CMV infection. He continued taking acyclovir as a prophylaxis against HSV infection. He achieved engraftment on day 22 after engraftment. On day 29, a chest CT scan, performed as a follow-up for the previous infection, showed widespread and peribronchial ground-glass attenuation (Figure 1C). However, on day 31, he developed a fever of 39°C; bacterial pneumonia was suspected and antibacterial drugs, specifically, doripenem (500 mg IV q12h), teicoplanin (600 mg IV q24h), and levofloxacin (500 mg IV q24h), were administered. On day 35, a chest CT scan showed bilateral ground-glass attenuation of the lungs accompanied by patchy consolidation (Figure 1D). CMV antigenemia was confirmed by assay using C10/C11 monoclonal antibodies; ganciclovir was administered, suspecting CMV pneumonia. On day 38, BAL was performed; the BALF showed a neutrophil differential count of 63.1%. On day 54, his respiratory condition drastically worsened; a repeat chest CT scan showed central, peribronchial, organizing pneumonia-like changes accompanied by lung volume loss (Figure 1E). CMV antigenemia disappeared on day 45. Based on this clinical picture, we suspected SOP or CMV pneumonia with ARDS. Although he was treated 3 times with pulse steroid therapy and immunoglobulin, his respiratory status did not improve and he died of respiratory failure on day 60.

Case 3

A 35-year-old female patient received a third CBT for treatment of acute lymphatic leukemia. She had achieved CR on the first occasion and subsequently received CBT twice. Antibody titers for CMV suggested a past infection before CBT. She continued taking acyclovir as prophylaxis against HSV infection. She developed a dry cough on day 24 following CBT. Engraftment was achieved on day 28. On day 31, she presented with frothy, blood-stained sputum and decreased oxygen saturation. A chest CT scan showed widespread bilateral ground-glass attenuation and reticular shadowing (Figure 1F). CMV antigenemia was confirmed by assay using C10/C11 monoclonal antibodies. Ganciclovir was administered, suspecting CMV pneumonia. On day 33, BAL was performed; the BALF showed a neutrophil differential count of 75.7%. Her respiratory status gradually worsened, and on day 36, a repeat chest CT scan showed peripheral

Figure 1. Findings on chest computed tomography (CT). (**A, B**) A 65-year-old male patient: chest CT scan showing bilateral ground-glass attenuation accompanied by mild bronchial traction and thickening of the interlobular septa (**A**). Organizing pneumonia-like changes with severe lung volume loss were observed in a diffuse central peribronchial area on the chest CT scan (**B**). (**C–E**) A 63-year-old male patient: chest CT scan showing widespread, peribronchial ground-glass attenuation (**C**). Ground-glass attenuation spread across bilateral lung fields, partially accompanied by consolidation (**D**). Progression of organizing pneumonia-like changes and lung volume loss in the diffuse central peribronchial area (**E**). (**F–H**) A 35-year-old female patient: chest CT scan showing widespread bilateral ground-glass attenuation and reticular shadows (**F**). Central organized change spread peripherally with traction bronchiectasis (**G**). Progression of lung volume loss (**H**).

lung changes with traction bronchiectasis and central, peribronchial lung volume loss (Figure 1G). Other possibilities considered included graft-versus-host disease, SOP, and CMV pneumonia complicated by ARDS. On day 37, prednisolone 60 mg daily was commenced. However, on day 42, her chest CT scan showed progressive loss of lung volume (Figure 1H). On day 45, she started receiving mechanical ventilation; CMV antigenemia disappeared on day 53. Although she was treated 7 times with pulse steroids besides immunoglobulin, cyclosporine, pirfenidone, and etanercept, her respiratory status did not improve. She died of respiratory failure on day 76.

Discussion

The 3 cases described above reveal several noteworthy findings. The patients had CMV pneumonia characterized by central peribronchial changes with severe lung volume loss. These changes in the lungs can be refractory to various treatment modalities, including antiviral drugs and steroids and can lead to a fatal clinical course.

We considered SOP and ARDS as possible differential diagnoses, with persistent abnormal findings on the chest radiograph and CT scan after the acute phase of illness. There is no difference

Table 1. Critical characteristics of 3 cases.

Parameter	Case 1 65-year-old male	Case 2 63-year-old male	Case 3 35-year-old female
Underlying disease	Acute myelogenous leukemia	Acute lymphatic leukemia	Acute lymphatic leukemia
Transplantation	Cord blood	Cord blood	Cord blood
Date from transplant to onset of pneumonia (day)	44	21	28
Prior chemotherapy	Flu, Busulfan	Flu, Busulfan	Flu, L-PAM, ATG
Smoking	Never	Never	Never
Underlying lung disease	None	None	None
Date until CMV antigenemia becomes negative (day)	18	20	22
Peak KL-6 (U/ml)	1386	206	2356
SP-D, SP-A (ng/ml)	2226, 79.7	N/A	N/A
BALF			
Total cell count	N/A	318000	321000
Cell fraction	Mφ 33.5% Lym 19.0% Neu 45.0%	Mφ 11.9% Lym 24.9% Neu 63.1%	Mφ 23.6% Lym 0.6% Neu 75.7%
CD4/CD8	N/A	1.76	2.07
Treatment for pneumonitis			
Antiviral drug	FCN	GCV, FCN	GCV, FCN
Steroid	mPSL pulse ×3	mPSL pulse ×3	mPSL pulse ×7
Other	Methotrexate ×3	Immune globulin ×6	Immune globulin ×15 Pirfenidone
Outcome	Death on day 85 after transplantation	Death on day 57 after transplantation	Death on day 75 after transplantation

L-PAM – L-phenylalanine mustard; ATG – antithymocyte globulin; CMV – cytomegalovirus; BALF – bronchial alveolar lavage fluid; FCN – foscarnet; Flu – fludarabine; GCV – ganciclovir; mPSL – methylprednisolone; N/A – not available.

between SOP and cryptogenic OP (COP) with regard to the clinical course and chest CT findings including bilateral, multiple alveolar opacities in the peripheral lung fields [2]. In contrast, in diffuse alveolar damage, which is the pathological finding in ARDS, CT changes progress with time: 1) in the acute phase, non-homogeneous infiltrates are seen with a ventro-dorsal gradient of density; denser consolidations are seen in the dependent regions, with widespread ground-glass opacities; 2) in the intermediate phase, reticular opacities and bronchiectasis are observed; and 3) in the chronic phase, lung volume loss and coarse reticulations are sometimes observed [4]. In addition, the typical ARDS distribution may be predominantly peripheral, and a gravitational gradient is usually present. In all 3 of our patients, the CT findings were distinct from SOP and ARDS in terms of a predominantly central distribution. CT findings in our patients suggest that central peribronchial changes with

severe lung volume loss are characteristic features of CMV pneumonia. In fact, Cuadrado et al. reported 5 cases of a central peribronchial pattern of organizing pneumonia complicating CMV infection that resulted in chronic lung damage [3]; our cases showed similar findings on chest CT scans.

The international guidelines on the management of CMV in solid-organ transplantation (2018) suggest that serology has no role in the diagnosis of active CMV replication and disease after transplantation. Quantitative nucleic acid amplification testing is the preferred method for diagnosis of CMV infection, guiding preemptive strategies, and monitoring response to therapy. This testing is preferred on BAL specimens and increased DNA levels may better correlate with symptomatic CMV disease [5]. All our patients received broad-spectrum antibacterial and antifungal agents; blood cultures and

serological tests were negative, and the patients' symptoms did not improve; thus, we excluded bacterial or mycotic pneumonia, such as pneumocystis pneumonia. In case 1, quantitative CMV-PCR was significantly elevated, but in cases 2 and 3, quantitative CMV-PCR could not be evaluated. CMV antigen was positive in the BALF in all 3 cases. Although it was not sufficient for a confirmed diagnosis of CMV pneumonia, we made a clinical diagnosis of the condition. Moreover, there was no heart failure based on echocardiography findings and the values of brain natriuretic peptide.

These patients followed a fatal clinical course refractory to steroid therapy. SOP generally responds well to systemic steroid administration and carries a good prognosis [2,6]. Although 5 patients in a report by Cuadrado et al. showed chronic lung damage, organizing pneumonia was controlled with steroids [3]. However, our patients were refractory to regular steroid therapy of >1 mg/kg/day and several courses of pulse steroid therapy, immunosuppressants, and anti-fibrosis agents. The course of the disease progressively worsened, with a fatal outcome.

Table 1 shows the clinical characteristics of our patients. We observed a predominance of neutrophils in the BALF. There were 2 differences between our cases and previous reports in terms of an autologous stem cell transplantation for treatment and prognosis. CMV infection represents a pathological pattern characterized by diffuse alveolar damage (DAD) with changes

on the alveolar surface, in the alveolar space, and in the alveolar wall [7]. We speculate that the central peribronchial change with severe lung volume loss and resistance to steroids seen in our patients was associated with DAD, similar to ARDS. We could not perform transbronchial lung biopsy in our patients because of severe respiratory failure; pathological autopsies were not performed as the families declined consent. Collectively, CMV pneumonia may be characterized by central peribronchial changes and severe, progressive lung volume loss, as evident on the chest CT scan, with a variable prognosis. Therefore, further clinical research, including pathological examination, is necessary to elucidate the pathology of CMV.

Conclusions

We observed central peribronchial changes with severe lung volume loss after the acute phase in 3 cases of CMV pneumonia. While our diagnosis was made on the basis of exclusion, it is important to bear in mind that lung involvement in CMV pneumonia may be refractory to steroids and other treatment modalities and can lead to a progressively worsening course and death.

Conflict of interest

None.

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