

## Case report

# Refractory acute respiratory failure due to *Pneumocystis jiroveci* (PCP) and Cytomegalovirus (CMV) pneumonitis: A case report and review of literature



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## ABSTRACT

**Background:** Opportunistic infections with *Pneumocystis jiroveci* pneumonia (PCP) are common in patients with HIV (human immunodeficiency virus) and are encountered once the CD4 count decreases below 200 cells/mm<sup>3</sup>. Cytomegalovirus (CMV) tends to cause disease once the CD4 count drops below 50 cells/mm<sup>3</sup>. CMV pneumonitis is not common in this population. However, detecting its presence in broncho-alveolar lavage (BAL) fluid has been associated with increased morbidity and mortality. The role of antiviral therapy against CMV remains unclear.

**Case presentation:** We report a newly diagnosed HIV patient with a CD4 count of 44 cells/mm<sup>3</sup> presenting with acute respiratory failure secondary to PCP that failed to respond to 3 weeks of standard therapy with trimethoprim-sulfamethoxazole and corticosteroids. He was later diagnosed to have a CMV co-infection causing pneumonitis with BAL cytology findings showing CMV cytopathic effects and PCP. Plasma CMV DNA PCR was 17,424 copies/mL. He responded well after introduction of intravenous ganciclovir.

**Conclusion:** The presence of histopathologic changes demonstrating viral cytopathic effects on BAL cytology along with a high plasma CMV DNA PCR should raise the specificity for diagnosing CMV pneumonitis. True PCP and CMV pneumonitis can occur, and the addition of antiviral therapy with ganciclovir may benefit such patients in the right clinical scenario.

## Background

*Pneumocystis jiroveci* pneumonitis, formerly *carinii* (PCP), is the most frequently encountered pulmonary infection in immunocompromised patients, especially patients with human immunodeficiency virus (HIV). Coinfection with Cytomegalovirus (CMV) has been associated with worse outcomes, but is often a marker of severe immunosuppression. Antiviral therapy targeting CMV in such a setting remains controversial.

## Case presentation

A 53 year old man with a history of substance abuse initially presented to an emergency room with complaints of progressive dyspnea. He was diagnosed with an acute exacerbation of chronic obstructive pulmonary disease (COPD) and discharged home. With worsening dyspnea, dry cough, and weight loss, he was hospitalized and started on

levofloxacin along with corticosteroids. Due to a history of high risk behaviour, an HIV test was obtained which returned positive. Given the patient's hypoxia and demonstration of diffuse ground glass opacities on computed tomography (CT) of the chest [Fig. 1], a clinical diagnosis of PCP was made, and the patient was switched to intravenous (IV) trimethoprim-sulfamethoxazole (TMP-SMX) and corticosteroids. He remained in the hospital for about 3 weeks, continuing to require supplemental oxygen as well as non-invasive ventilation in the form of BiPAP (Bilevel Positive Airway Pressure). This prompted transfer to our institution, a tertiary care university hospital, for a possible need for an open lung biopsy.

Upon presentation at our institution, he had no fever or hemodynamic instability. He appeared to be in moderate respiratory distress requiring BiPAP support. He had diffuse, coarse crackles on lung auscultation bilaterally. The rest of his examination was unremarkable except for the presence of skin tattoos and oral thrush.

**Abbreviations:** HIV, human immunodeficiency virus; PCP, *Pneumocystis jiroveci* pneumonia; CMV, Cytomegalovirus; BAL, broncho-alveolar lavage; PCR, polymerase chain reaction; COPD, chronic obstructive pulmonary disease; CT, computed tomography; IV, intravenous; TMP-SMX, trimethoprim-sulfamethoxazole; BiPAP, bilevel positive airway pressure; AB, arterial blood gas; AFB, acid fast bacilli; RPR, rapid plasma reagin; GMS, Gömöri methenamine silver; DPHS, dihydropteroate synthetase

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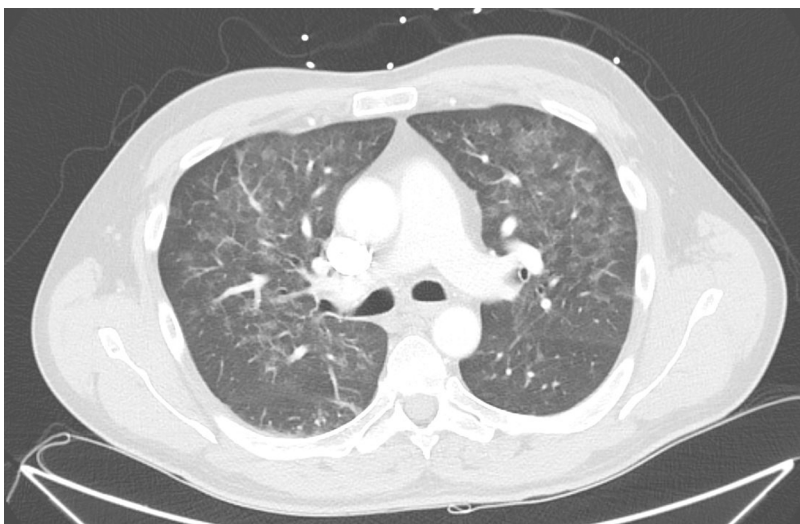


Fig. 1. CT chest showing diffuse bilateral ground glass opacities.

He reported a 37-pack-year smoking history and denied any alcohol abuse. He denied international travel or known exposure to anyone with tuberculosis. He reported that he had sex with men and prior history of IV methamphetamine use. He denied any known exposure to chemicals or toxic fumes.

#### Differential diagnoses

Differential diagnoses in this case included atypical infections such as *Mycoplasma*, *Legionella*, mycobacteria such as *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis*, fungal etiology such as *Cryptococcus* or *Histoplasma*, and viral pneumonia including CMV, adenovirus, respiratory syncytial virus, or influenza virus. Drug-resistant *Pneumocystis* was also possible given the non-response to treatment. Non-infectious causes such as acute eosinophilic pneumonia, acute interstitial pneumonia, cryptogenic organizing pneumonia as well as immune reconstitution syndrome were possibilities. Considering the patient's immunocompromised status, infectious causes were, however, more likely.

#### Investigations

A complete blood count revealed a normal white count of 6500/mm<sup>3</sup> (normal: 4000–10,000/mm<sup>3</sup>). Hemoglobin was 10.5 g/dL (normal: 13.0–16.5 g/dL) with a normal platelet count. Chemistry panel showed normal renal and hepatic function with a low albumin of 2.9 g/dL (normal: 3.5–5.0 g/dL). Arterial blood gases (ABG) analyses showed a PaO<sub>2</sub> of 64.7 mmHg on supplemental oxygen. HIV RNA PCR showed a viral load of 194,901 copies/mL. His CD4 count was 44 cells/mm<sup>3</sup> with CD4% of 8.5%.

1,3-beta-D-glucan assay was strongly positive with a value > 500 pg/mL (> 80 pg/mL is considered positive). Routine blood cultures showed no growth at 5 days, fungal and AFB (acid fast bacilli) blood cultures also remained negative. Urinary *Histoplasma* antigen and serum *Cryptococcal* antigen were both negative. Serum rapid plasma reagin (RPR) was non-reactive.

A repeat CT scan of the chest showed progression of bilateral ground glass opacities with development of mild interlobular septal thickening resulting in a characteristic “crazy-paving” pattern [Fig. 2].

On day 3 of admission, he underwent a bronchoscopy and bronchoalveolar lavage (BAL). BAL Gram stain and culture showed no organisms. BAL fungal and AFB stains along with cultures remained no growth. BAL galactomannan was negative. BAL cytology showed enlarged cells with a large intranuclear inclusion surrounded by a halo, creating an “owl’s eye” appearance which is characteristic for

Cytomegalovirus. Also present were alveolar casts which stained weakly with Gömöri methenamine silver (GMS) and revealed structures morphologically consistent with *Pneumocystis* organisms [Fig. 3].

Plasma CMV DNA PCR was also positive with 17,424 copies/mL.

#### Treatment

Intravenous ganciclovir was initiated at 5 mg/kg every 12 h. He also received IV TMP-SMX 20 mg/kg/day for continued treatment of PCP, along with once weekly azithromycin for MAC prophylaxis. Repeat CMV DNA PCR decreased to 2497 copies/mL after 7 days of treatment.

After 16 days of hospitalization, the patient was discharged home to complete 4 weeks of oral valganciclovir 900 mg twice daily, 3 weeks of TMP-SMX (20 mg/kg/day in three divided doses) and then switch to prophylactic doses of valganciclovir and TMP-SMX until CD4 count recovery. His oxygen requirement continued to decrease throughout his hospital stay and was titrated down to 3 L/min by nasal cannula at discharge. He was also set up with an outpatient HIV clinic to initiate antiretroviral therapy.

#### Discussion

Even with the introduction of antiretroviral therapy against HIV, PCP is the commonest opportunistic infection in patients with CD4 counts below 200 cells/mm<sup>3</sup> [1]. It often presents with worsening dyspnea, dry cough, with or without the presence of fever which progresses over days to weeks [2]. Certain findings such as hypoxia, diffuse bilateral interstitial infiltrates on chest x-ray, elevated serum lactate dehydrogenase point toward the diagnosis. CT findings of ground glass opacities, alveolar consolidations, bronchial dilation and interlobular septal thickening, while seen with PCP [3], are non-specific. TMP-SMX is the preferred treatment unless the patient has a sulfa allergy, in which case alternatives such as pentamidine, TMP-dapsone, clindamycin-primaquine or atovaquone could be used [4]. Drug resistance resulting from mutations in the dihydropteroate synthetase (DHPS) gene has been reported in patients on TMP-SMX prophylaxis [5]. Its presence, however, does not seem to affect response to treatment [6]. The benefit of concomitant corticosteroids in patients with moderate to severe disease (PaO<sub>2</sub> < 70 mmHg on room air) has been demonstrated by several randomized trials [7] and has also been illustrated in a Cochrane meta-analysis [8].

The morbidity and mortality associated with CMV infections in immunocompromised patients is quite substantial, especially in transplant recipients and patients with advanced HIV. Common manifestations of CMV disease in the HIV population are chorioretinitis, while

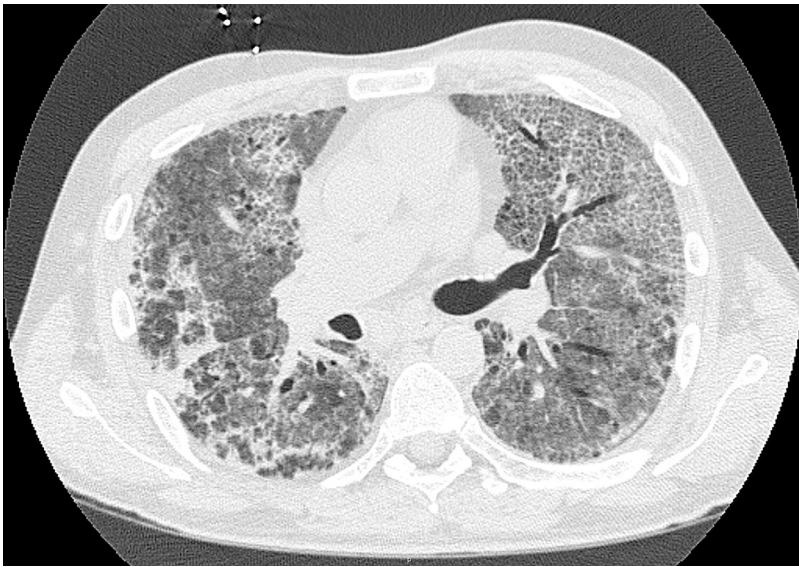


Fig. 2. CT chest 3 weeks later showing “crazy-paving pattern”.

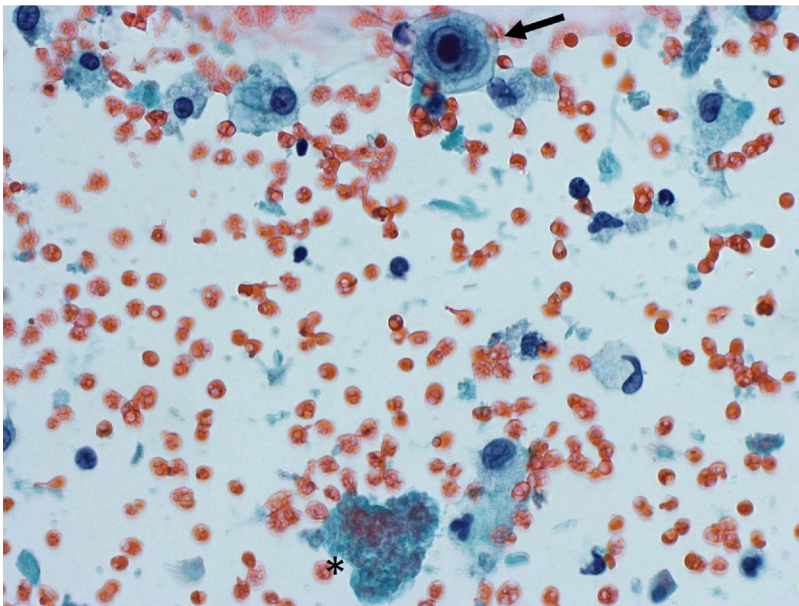


Fig. 3. A pap-stained cytology slide of the bronchoalveolar lavage showed enlarged cells with a large intranuclear inclusion which is surrounded by a halo, creating an “owl’s eye” appearance characteristic of Cytomegalovirus (arrow, top). Alveolar casts which are consistent with pneumocystis (asterisk, bottom) are also seen. Papanicolaou stain, original magnification  $\times 500$ .

other manifestations include esophagitis, gastritis, colitis, pneumonitis, and neurologic disease such as encephalitis, myelitis and peripheral neuropathy [9]. These are more likely when the CD4 count drops below 50 cells/mm<sup>3</sup>. Differentiation between CMV infection and invasive disease remains challenging. Its mere presence on culture, antigen detection assays, DNA PCR implies infection. However, infection in the presence of specific end organ dysfunction, often in conjunction with the overall clinical picture, is considered invasive CMV disease. Quantitative PCR with estimation of CMV viral load has been investigated for use as a marker of invasive CMV disease, although mainly in transplant recipients [10]. Viral loads in the range of 2000 to 5000 copies/mL are generally considered as the cut-off for predicting invasive disease, with sensitivity of 86% and specificity of 87% when the cut-off is applied at > 5000 copies/ml [11].

In patients with PCP, the co-presence of CMV in BAL fluid has traditionally been presumed to be non-invasive and is often not treated. Previous reports also found no difference in outcome between CMV-treated and CMV-untreated groups [12]. However, these studies were prior to corticosteroids becoming standard of care in patients with moderate to severe PCP. Several recent reports have highlighted a poor

outcome among HIV patients that are co-infected with PCP and CMV [13,14]. A Danish study reported a two-fold higher mortality at 3 months in patients with PCP treated with adjunctive corticosteroids who also had CMV cultured from BAL [15]. Whether this is reflective of deteriorating immune function or is a direct effect of CMV disease is unclear.

Our patient was previously treated at an outside institution with TMP-SMX and corticosteroids without improvement. It remains plausible that given the patient’s pre-existing immunosuppression, the addition of corticosteroids further lowered his immunosuppression, causing CMV reactivation and end-organ disease in the form of pneumonitis. The presence of histopathologic changes demonstrating viral cytopathic effects on BAL cytology along with a high CMV DNA PCR should raise the specificity for diagnosing CMV pneumonitis. Our patient in a way served as his own control, as the addition of antiviral therapy targeting CMV seemed to contribute to the favourable outcome.

In conclusion, this case demonstrates that true co-infection with PCP and CMV pneumonitis can occur, and that the addition of antiviral therapy with ganciclovir may benefit such patients in the right clinical scenario.

**Ethics approval and consent to participate**

N/A. Patient identifying data de-identified.

**Informed consent to publish**

Obtained from patient.

**Availability of data and materials**

N/A.

**Conflicts of interest**

None.

**Funding source**

None.

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