

Acute Human Immunodeficiency Virus (HIV) Infection Presenting With Bilateral Interstitial Pneumonia: Case Report and Discussion of Potential HIV-Induced Interstitial Pneumonia

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A 50-year-old man was admitted to intensive care unit because of acute respiratory failure due interstitial pneumonia; after admission, a diagnosis of acute human immunodeficiency virus (HIV)-1 infection was made. Clinical and radiological improvement was observed only after introduction of antiretroviral treatment. We discuss the hypothesis of interstitial pneumonia induced by the acute HIV-1 infection.

Keywords. acute HIV infection; interstitial pneumonia.

CASE REPORT

A 50-year-old patient with unremarkable medical history was admitted to the emergency department (ED) with fever and acute respiratory failure. The patient had been febrile for 5 days and developed rapidly worsening shortness of breath and dry cough in the last 24 hours. A chest x-ray performed in the ED showed bilateral multifocal involvement of the lungs with marked diffuse interstitial pattern and blood tests showed mildly elevated white blood cells ($10\,240/\text{mm}^3$ with normal differential count) and increased C-reactive protein (CRP) (27 mg/dL) with low procalcitonin (2 ng/mL). The patient denied recent travel history, close contacts with animals or contacts with sick people and intravenous drugs use; he reported cigarette smoke and frequent unprotected heterosexual intercourse.

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Physical examination revealed tachypnea (28 breaths/minute), fever (101°F), hypotension (90/60 mmHg) and tachycardia (110 bpm). Lungs showed diminished vesicular breath sounds. Physical examination was otherwise unremarkable.

The high risk for sexually transmitted infections and the clinical and radiological presentation raised the suspicion of *Pneumocystis jirovecii* pneumonia. Results from a human immunodeficiency virus (HIV-1) antibody-antigen test (fourth-generation chemiluminescence assay; Roche Diagnostics) were positive. In addition, a weak positivity for pneumococcal urinary antigen (immune-chromatographic method) was detected. Arterial blood gas analysis showed severe hypoxemia (pH 7.46, pO₂ 50 mmHg, pCO₂ 27 mmHg, SatO₂ 84%) that could not be corrected by high oxygen supply with reservoir bag (pH 7.42, pO₂ 58 mmHg, pCO₂ 33 mmHg, SatO₂ 88%). After collection of blood cultures, empirical therapy with piperacillin-tazobactam, levofloxacin, and cotrimoxazole was started. The patient was transferred to the intensive care unit and placed on mechanical ventilation.

On hospital day 4 the patient underwent bronchoscopy: Gram stain of bronchoalveolar lavage (BAL) was negative and no bacterial or fungal growth was observed on BAL cultures, including aerobic bacteria, *Legionella*, molds, and yeasts. Bronchoalveolar lavage also tested negative for *P jirovecii* (immunofluorescence assay [IFA]), consequently, cotrimoxazole was ceased. No acid-fast bacteria were detected through Ziehl-Neelsen staining and *Mycobacterium tuberculosis*-complex polymerase chain reaction (PCR) tested negative, as did *cytomegalovirus*, *Epstein-Barr virus*, *herpes simplex virus 1/2*, *adenovirus*, *influenza A/B* nucleic acid amplification, and *Aspergillus galactomannan* antigen. BAL cytology showed the following cellularity: macrophages (32%), neutrophils (63%), and lymphocytes (5%) and excluded the presence of neoplastic cells. On the same day, a pneumococcal urinary antigen test was repeated and the result was negative. Blood cultures performed before antibiotics as well as *Legionella* urinary antigen and serology for intracellular bacteria (*Mycoplasma*, *Chlamydia*, *Legionella*) were negative.

On hospital day 6 bronchoscopy was repeated. Again, Gram stain and Ziehl-Neelsen stain were negative and no bacterial or fungal growth was observed on BAL cultures. *Pneumocystis jirovecii* IFA and PCR-mediated tests for viruses were repeatedly negative. Procalcitonin was repeated twice and was found to be between 0.5 and 0.6 ng/mL.

No substantial clinical or radiological improvement was observed during the first week of antibiotic therapy. The patient was persistently febrile and in severe respiratory distress. Control chest x-rays persistently showed a marked interstitial

bilateral pattern with overlapping acute respiratory distress syndrome radiological signs (Figure 1A).

A confirmatory HIV Western blot (from blood collected on day 1) was negative. It was then repeated on day 5 and showed positivity only for gp41, confirming the diagnosis of acute HIV-1 infection (Fiebig stage IV). Plasma HIV-ribonucleic acid (RNA) was above 10 000 000 copies cps/mL, CD4⁺ T-cell count was 571 cells/mm³ (57%), whereas CD8⁺ T-cell count was 234 cells/mm³ (23%), with CD4⁺/CD8⁺ ratio of 2.44 (Figure 1B). The patient reported a previous negative HIV test approximately 6 months before admission.

HIV-RNA on the last BAL was performed and quantified 206 647 cps/mL. Antiretroviral treatment (ART) was introduced on day 8 containing tenofovir disoproxil fumarate/emtricitabine + darunavir/ritonavir 800/100 mg + raltegravir 400 mg bid.

On the same day (day 8) the patient experienced worsening respiratory failure and onset of septic shock requiring noradrenaline. Laboratory tests showed neutrophilia and increased CRP. Although the chest x-ray was unchanged, cultures of bronchoaspirate (taken on day 8) were found to be positive for *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-Kp) (1 000 000 colony-forming units [cfu]/mL). Hence, on day 9 (when preliminary results of bronchoaspirate cultures became available) high-dose meropenem, gentamicin, and

tygeclicine were started. Blood cultures taken on days 8 and 9 gave negative results. Upon introduction of ART and the new antibacterial regimen, the patient became hemodynamically stable and showed progressive improvement of respiratory distress. Control chest x-rays showed radiological improvement on day 14, after 7 days of ART and 6 days of anti-KPC antibiotics.

On day 14 the patient was extubated and transferred to the pneumology ward and, on day 18, he was transferred to the infectious diseases unit. Here, oxygen supply was rapidly de-escalated as the patient experienced remarkable clinical improvement.

On day 27 follow-up bronchoscopy was performed: BAL cultures were still positive for KPC-Kp (100 000 cfu/mL), whereas HIV-RNA on BAL was diminished to 177 cps/mL. Antiretroviral treatment was well tolerated and on day 34, after complete clinical recovery, the patient was discharged. Plasma HIV-RNA after 8 and 12 weeks of ART decreased to 97 cps/mL and <40 cps/mL, respectively (Figure 1B).

DISCUSSION

We reported a case of acute HIV-1 infection presenting with bilateral multifocal interstitial pneumonia. A BAL tested negative for all pathogens possibly involved in the aetiology of the pneumonia.

The initial weak positivity of the pneumococcal urinary antigen was not confirmed at a second test performed a few days later, and it was not associated with the isolation of *Streptococcus pneumoniae* from either BAL or blood. This discrepancy lowers the likelihood of a pneumococcal aetiology, because several studies demonstrated that, in cases of proven pneumococcal pneumonia, the urinary antigen remains positive for several weeks and sometimes even months [1, 2]. Furthermore, the radiologic findings were unusual for a pneumococcal form, considering the marked interstitial pattern.

As we looked for alternative causative agents, the only positive result that was found on BAL was an elevated HIV-RNA (206.647 cps/mL), compatible with viral dissemination during acute HIV infection (AHI).

It is well known that HIV-1 impacts the pulmonary immune system through macrophage and lymphocyte activation, secretion of proinflammatory cytokines and chemokines, and accumulation of CD8⁺ T cells [3]. Antiretroviral treatment, by controlling viral replication, is able to reduce the pulmonary inflammatory state [4, 5]. Evidence exists regarding the role of HIV-1 in causing pulmonary disease during chronic infection, with a much higher incidence of chronic respiratory diseases in HIV-infected patients compared with noninfected individuals, despite effective ART [6, 7]. Less is known about the role of HIV on the pulmonary system during AHI.

AHI can range from asymptomatic to a severe illness. Symptoms of AHI are described in 40%–90% of patients [8] and may reflect the immune response to the virus, particularly the

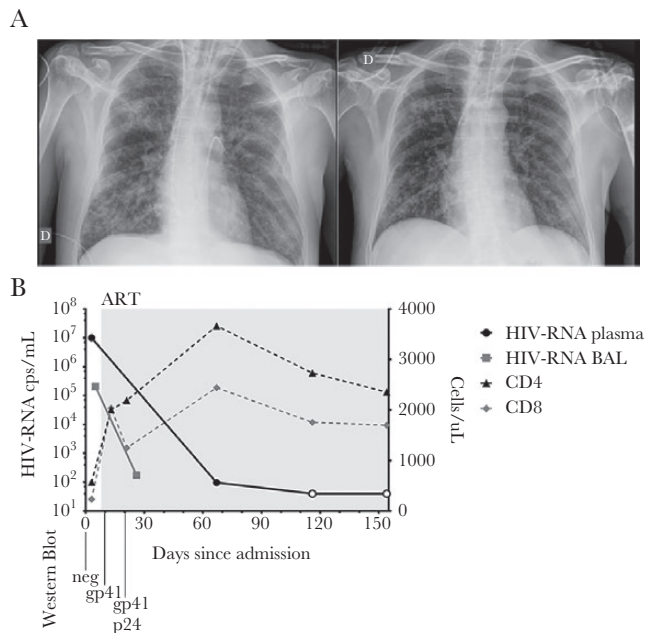


Figure 1. (A) Chest x-ray during the first days of intensive care unit stay (left) and 1 week after introduction of antiretroviral treatment ([ART] right). (B) Graph showing plasma and bronchial lavage (BAL) human immunodeficiency virus-ribonucleic acid (HIV-RNA) (cps/mL, on the left y axis) and CD4⁺ and CD8⁺ T-cell count (cells/mm³ on the right y axis) over time (the horizontal axis represent days from admission). Open circles indicate values below the limit of detection. HIV Western blot results are shown below the graph.

cytokine storm that follows infection, with resolution upon the partial control of viral replication [9] by the adaptive immune response, or by early initiation of antiretroviral therapy.

The most common symptoms of AHI are fever, rash, lymphadenopathy, pharyngitis, and, sometimes, aseptic meningitis [9]. Respiratory involvement during AHI is rarely reported [10]. Occasionally, AHI can present with classic opportunistic infections, and few cases of *P jirovecii* pneumonia during AHI are reported in the literature [11–13]. A recent study on the frequency and spectrum of unexpected clinical manifestations during AHI reported respiratory tract involvement in 5 of 290 patients with AHI (0.017%): in particular, 3 of 290 patients (0.010 %) had viral pneumonia as the main clinical finding, and 2 of them were hospitalized due to severe respiratory distress. The remaining 3 of 5 patients with respiratory tract involvement presented with an upper respiratory tract infection [14].

Given the characteristics of the case report presented here, we wonder whether high HIV replication during AHI and the associated immune response could possibly be involved in the pathogenesis of the pneumonia. No clinical nor radiological improvement was observed during the first week of hospitalization, when only antibiotic therapy was administered to the patient.

The clinical deterioration on day 8 was associated with the isolation of KPC-Kp from BAL. We may consider the KPC as a nosocomial superinfection, and we speculate that the anti-KPC regimen led to the resolution of the septic shock, whereas ART therapy contributed to the progressive resolution of the pre-existing interstitial pneumonia.

CONCLUSIONS

Our hypothesis of an HIV-induced pneumonia represents a clinical diagnosis of exclusion. Additional analyses could support this hypothesis such as the characterization of HIV tropism, genetic compartmentalization analysis in the lung versus plasma, HIV-specific CD8⁺ T cells on BAL and plasma as well as the study of proinflammatory cytokines on BAL [15].

Unfortunately, we could not perform any additional immunological or molecular investigation on our patient's BAL and we can only speculate about the role of HIV in the

pathogenesis of this unusual case of pneumonia during acute infection. However, this clinical observation may encourage clinicians to perform HIV testing and also look for acute infection, especially in cases of lower respiratory tract infection with no alternative explanation.

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