Case Report

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Immune reconstitution inflammatory syndrome associated with *Pneumocystis* pneumonia in a patient with AIDS

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Abstract

Immune reconstitution inflammatory syndrome (IRIS) after starting antiretroviral treatment for human immunodeficiency virus (HIV) infection has a wide variety of causes. Delayed diagnosis and treatment of IRIS is fatal. We report a case of a 21-year-old man with HIV infection and *Pneumocystis jirovecii* pneumonia. The patient presented with fever and dyspnea with deterioration of pulmonary infiltrations 5 days after starting antiretroviral treatment. We reached the diagnosis of IRIS based on radial endobronchial ultrasound (EBUS)-guided lung biopsy. In conclusion, radial EBUS-guided lung biopsy via bronchoscopy is a valuable and minimally invasive technique for the rapid diagnosis of IRIS-associated *Pneumocystis jirovecii* pneumonia.

Keywords

Human immunodeficiency virus, immune reconstitution inflammatory syndrome, endobronchial ultrasound, transbronchial lung biopsy, *Pneumocystis jirovecii* pneumonia, highly active antiretroviral therapy

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Introduction

Patients with acquired immunodeficiency syndrome (AIDS) suffer from opportunistic infections (OIs). When such patients start highly active antiretroviral therapy (HAART), they may experience a paradoxical worsening or recurrence of OIs, termed "immune reconstitution inflammatory syndrome" (IRIS).[1] IRIS is associated with considerable morbidity and mortality.[2] Thus, rapid definite diagnosis and targeted treatment of IRIS are urgently needed. Sampling with bronchoscopy is an important method of obtaining a definite diagnosis. Here, we report a case of IRIS-associated *Pneumocystis jirovecii* pneumonia (PJP)[3] in a patient with AIDS that was confirmed by bronchoscopy and radial endobronchial ultrasound (EBUS)-guided lung biopsy. The patient recovered rapidly after treatment with trimethoprim/sulfamethoxazole (TMP/SMX) and methylprednisolone.

Case report

A 21-year-old man was referred to our hospital with a 20-day history of dyspnea and productive cough. He started empirical antibiotic treatment but the symptoms were not relieved. On admission, his vital signs were normal: temperature 36.5°C; respiration rate 15 breaths/minute; pulse 70 beats/minute; and blood pressure 105/60 mmHg. Breath sounds in the bilateral lungs were rough without rales. Chest computed tomography (CT) on the day of admission showed ground-glass opacities in the bilateral lungs (Figure 1a). Blood gas analysis showed type I respiratory failure [pH 7.41; arterial partial pressure of CO_2 ($PaCO_2$) 34 mmHg; and arterial partial pressure of O_2 (PaO_2) 52 mmHg], and a combination human immunodeficiency virus (HIV) antigen/antibody test was positive. The $CD4^+$ T cell count was 81 cells/μL. The lactate dehydrogenase (LDH) level was 471 U/L, and C-reactive protein (CRP) level was 8.40 mg/L. Renal and liver function were normal. The patient was diagnosed with "possible PJP," and treatment with TMP/SMX (TMP 15 mg and SMX 75 mg)/kg orally daily and levofloxacin 500 mg intravenously daily was initiated. After 8 days of treatment, the patient recovered. He was discharged from our hospital with a plan to complete a 21-day course of TMP/SMX and a 1-week course of levofloxacin.

After 3 weeks of treatment of PJP with TMP/SMX, the chest CT showed obvious resolution (Figure 1b), so the dosage of TMP/SMX was reduced to a prophylactic dose, and antiretroviral treatment with efavirenz, tenofovir ester, and lamivudine was initiated. Five days later, the patient presented with a high fever lasting 3 days, with 39.6°C as the highest temperature. He also suffered from chills and nausea, accompanied by productive cough and dyspnea. At presentation, the patient was afebrile (36.7°C) with an oxygen saturation level of 87.2% on room air, a respiration rate of 20 breaths/minute, a heart rate of 116 beats/minute, and blood pressure of 105/70 mmHg. Thoracic auscultation revealed a "Velcro sound" in the bilateral lower lobes. Blood tests revealed type I respiratory failure (pH 7.423; $PaCO_2$ 27.9 mmHg; and PaO_2 54.7 mmHg), elevated white blood cell count (14.51×10^9/L), CRP level (90.50 mg/L), and LDH level (554 U/L); and a $CD4^+$ count of 189 cells/μL. A chest CT demonstrated bilateral diffuse patches with the air bronchogram sign (Figure 1c), revealing that the pulmonary infiltrations had worsened compared with the previous chest CT. Empirical antibiotic therapy was started with meropenem, levofloxacin, caspofungin, oseltamivir phosphate, and clarithromycin. However, the patient did not respond to treatment. To obtain a definite diagnosis and select a targeted treatment, we performed bronchoscopy with EBUS-guided lung biopsy (Figure 2). The EBUS image revealed heterogeneous internal

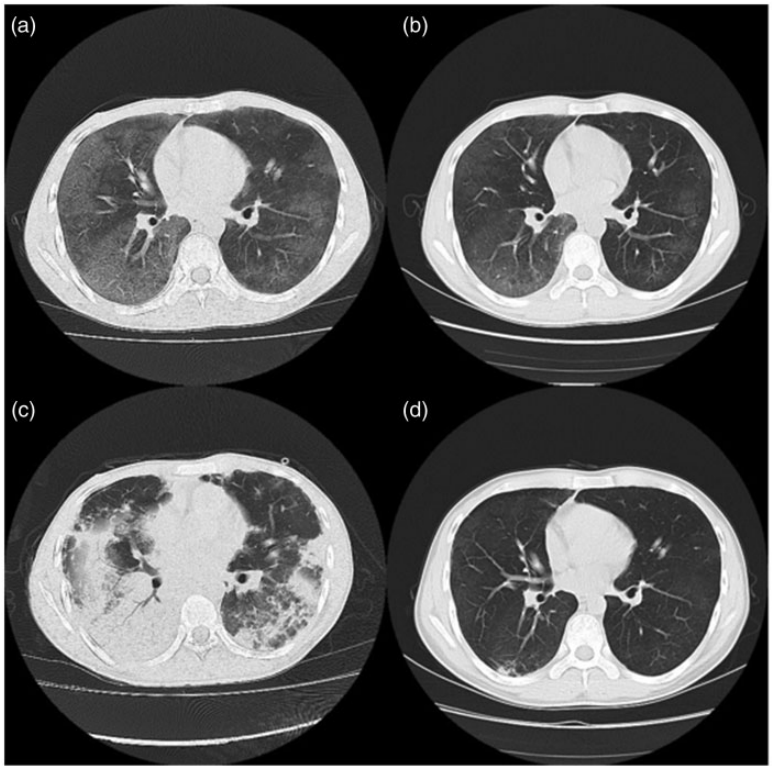

Figure 1. Chest CT findings. (a) Chest CT at first admission showed characteristic GGOs in the bilateral lungs. (b) A repeated CT performed after 21 days of TMP/SMX treatment demonstrated that the GGO in bilateral lungs were obviously resolved. (c) Chest CT at second admission showed deterioration of pulmonary infiltration mostly in the right lung. (d) Follow-up CT after 28 days of methylprednisolone and TMP/SMX treatment showed resolution of the GGOs and consolidation. CT, computed tomography; GGOs, ground-glass opacities; TMP/SMX, trimethoprim/sulfamethoxazole.

echoes and an irregular margin of the lesion within the lumen of right bronchus 6 (RB6), with almost no vessels or bronchi within the lesion (Figure 2c and d). We obtained six biopsies with forceps for histopathological examination. We also performed bronchoalveolar lavage to identify potential pathogens. Hematoxylin and eosin staining showed consolidation of the lung tissue, proliferated fibrous tissue with inflammatory cell infiltration, and a local pink-stained substance (Figure 3a). Histopathologic evaluation of the tissue showed the presence of pneumonitis. One diagnostic criterion for IRIS is progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary *Mycobacterium tuberculosis* or PJP.[1,4] PJP was subsequently confirmed with a positive result following Gomori's methanamine silver nitrate staining for *P. jirovecii* in the biopsied specimens (Figure 3b) and detection of *P. jirovecii* DNA in the bronchoalveolar lavage fluid. We diagnosed the patient with IRIS-associated PJP. Then, antibiotic treatment for PJP was initiated, with methylprednisolone 40 mg orally daily and TMP/SMX (TMP 20 mg and SMX 100 mg)/kg orally daily. After 7 days of therapy, the patient's condition was significantly improved, and a

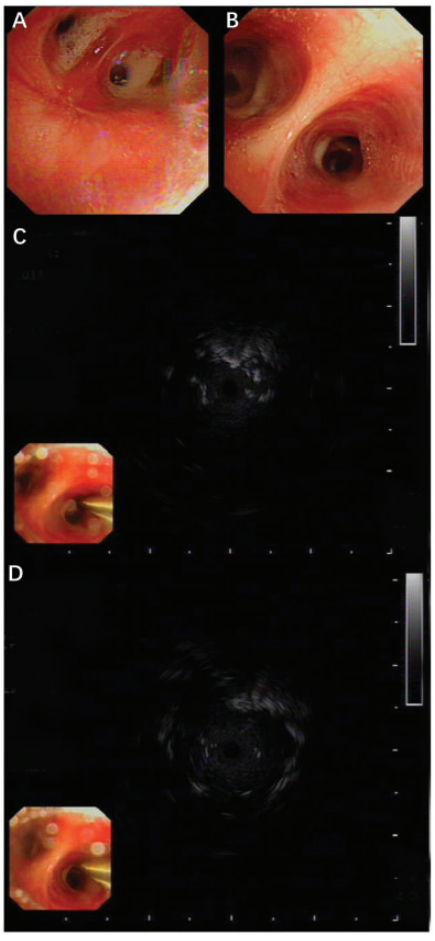

Figure 2. Manifestations on bronchoscopy and EBUS images. (a, b) Bronchoscopy revealed increased secretions from different bronchi. (c, d) The EBUS image revealed heterogeneous internal echoes and an irregular margin of the lesion within the lumen of RB6, with almost no vessels or bronchi within the lesion. EBUS, radial endobronchial ultrasound; RB6, right bronchus 6.

chest CT revealed recovery of the infiltrations (Figure 1d).

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent for the patient's information and images to be published was provided by the patient.

Discussion

Current HAART regimens suppress HIV replication and provide significant immune reconstitution.[2] However, for patients with AIDS who develop OIs and then initiate HAART, an intense inflammatory reaction to foreign antigens may occur due to the recovery of T cell-mediated immunity.[1] As a result, a rapid onset of pulmonary inflammation and respiratory distress is followed by immune recovery, which is called IRIS.[5]

IRIS comprises two distinct syndromes: paradoxical IRIS and unmasking IRIS.[6] The clinical presentation of IRIS is nonspecific and mainly consists of fever and the deterioration of primary OIs; therefore, similar clinical conditions and treatment failures must be ruled out before diagnosing IRIS.[4] In adults, IRIS has most frequently been observed in persons with nontuberculous mycobacteria, PJP, and cryptococcal infections.[2] *P. jirovecii* is an opportunistic fungal respiratory pathogen that causes life-threatening pneumonia in patients suffering from defects in cell-mediated immunity, including those with AIDS.[7] Despite major advances in health care, PJP remains a leading cause of death among HIV-infected patients and a significant cause of AIDS-related mortality and morbidity.[8] Notably, IRIS should be considered when relapse is associated with a short time between the diagnosis of an OI and the initiation of HAART.[1] The history, worsening clinical manifestations, and chest CT all indicated that our patient might have IRIS.[1] However, progression of the initial infection and development of a new OI should be ruled out before diagnosing IRIS. Thus, histopathologic or cytologic evaluation of tissue, fluid, bronchoalveolar lavage fluid, or induced sputum samples is required to reach a definitive diagnosis.[1,9]

EBUS-guided lung biopsy is performed by introducing a guide sheath-covered mini-probe into the target bronchus and

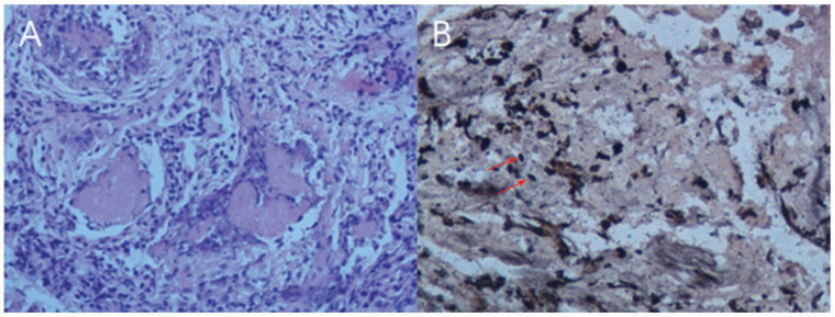

Figure 3. Histopathology of the transbronchial lung biopsy. (a) Hematoxylin and eosin staining showed frothy eosinophilic exudates and obvious consolidation of lung tissue with inflammatory cell infiltration. (b) Gomori's methanamine silver nitrate staining showing a cluster of *Pneumocystis* cysts.

then withdrawing the mini-probe after lesion detection, leaving the guide sheath in situ as a working channel for obtaining lesion samples.[10] It can increase the ability to diagnose peripheral pulmonary lesions endoscopically,[11] even lesions that are predominantly ground-glass opacities,[12] with a diagnostic yield of 58% for benign peripheral disease.[13] In our case, we performed bronchoscopy and radial EBUS-guided lung biopsy to obtain a definite diagnosis.

For the treatment of patients who develop IRIS soon after initiation of HAART, HAART should be continued and OI-related treatment should be initiated.[2] A short course of corticosteroids is recommended for acute respiratory failure.

Conclusion

Patients with AIDS who develop OIs and then initiate HAART may experience IRIS, which is characterized by a paradoxical worsening or recurrence of OI symptoms. Radial EBUS-guided lung biopsy via bronchoscopy is a valuable and less invasive technique for the rapid diagnosis of IRIS-associated PJP.

Authors' contributions

HG and YY made substantial contributions to the conception or design of the work. All authors contributed to the acquisition of data for the work. WY and YY helped collect the data. YY and W-MC wrote the manuscript. HG, YY and WY interpreted the data. HG performed the bronchoscopy. All authors revised the paper critically for important intellectual content. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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