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

Ying Wen¹, Meng-chan Wang², Ying Zhou¹, Xu-yong Lin³, Gang Hou²,* and Yan Yin²,*

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

Date received: 3 February 2020; accepted: 10 July 2020

¹Department of Infectious Disease, First Hospital of China Medical University, Shenyang, China
²Department of Pulmonary and Critical Care Medicine, First Hospital of China Medical University, Shenyang, China
³Department of Pathology, First Affiliated Hospital and College of Basic Medical Sciences, Shenyang, China

*These authors contributed equally to this work.

Corresponding author:
Yan Yin, Department of Pulmonary and Critical Care Medicine, First Hospital of China Medical University, No. 155 Nanjing Street, Shenyang, Liaoning 110001, China. Email: yinyan1b@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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). IRIS is associated with considerable morbidity and mortality. 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) 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 CO₂ (PaCO₂) 34 mmHg; and arterial partial pressure of O₂ (PaO₂) 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; PaCO₂ 27.9 mmHg; and PaO₂ 54.7 mmHg), elevated white blood cell count (14.51 × 10⁹/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
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 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.
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. 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. As a result, a rapid onset of pulmonary inflammation and respiratory distress is followed by immune recovery, which is called IRIS.

IRIS comprises two distinct syndromes: paradoxical IRIS and unmasking IRIS. 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. In adults, IRIS has most frequently been observed in persons with nontuberculous mycobacteria, PJP, and cryptococcal infections. 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. 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.

Notably, IRIS should be considered when relapse is associated with a short time between the diagnosis of an OI and the initiation of HAART. The history, worsening clinical manifestations, and chest CT all indicated that our patient might have IRIS. 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.

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

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.
then withdrawing the mini-probe after lesion detection, leaving the guide sheath in situ as a working channel for obtaining lesion samples. It can increase the ability to diagnose peripheral pulmonary lesions endoscopically, even lesions that are predominantly ground-glass opacities, with a diagnostic yield of 58% for benign peripheral disease. 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. 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.

Funding
The work was supported by the science and technology foundation of Shenyang (China) of Ying Wen (18-014-4-30) in the First Affiliated Hospital of China Medical University.

ORCID iD
Gang Hou https://orcid.org/0000-0003-3438-1764

References
1. Achenbach CJ, Harrington RD, Dhanireddy S, et al. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination
antiretroviral therapy after AIDS-defining opportunistic infection. *Clin Infect Dis* 2012; 54: 424–433. DOI: 10.1093/cid/cir802.

2. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep* 2009; 58: 1–166.

3. Da Cunha Colombo ER, Mora DJ and Silva-Vergara ML. Immune reconstitution inflammatory syndrome (IRIS) associated with *Cryptococcus neoformans* infection in AIDS patients. *Mycoses* 2011; 54: e178–e182. DOI: 10.1111/j.1439-0507.2010.01870.x.

4. Manzardo C, Guardo AC, Letang E, et al. Opportunistic infections and immune reconstitution inflammatory syndrome in HIV-1-infected adults in the combined antiretroviral therapy era: a comprehensive review. *Expert Rev Anti Infect Ther* 2015; 13: 751–767. DOI: 10.1586/14787210.2015.1029917.

5. Bhagwat SP, Wright TW and Gigliotti F. Anti-CD3 antibody decreases inflammation and improves outcome in a murine model of *Pneumocystis* pneumonia. *J Immunol* 2010; 184: 497–502. DOI: 10.4049/jimmunol.0901864.

6. Curic K, Poljak M, Ihan A, et al. Very recent HIV infection accompanied by *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium* complex immune reconstitution inflammatory syndrome: a case report. *Acta Dermatovenerol Alp Pannonica Adriat* 2016; 25: 57–58.

7. Wang J, Gigliotti F, Bhagwat SP, et al. Immune modulation with sulfasalazine attenuates immunopathogenesis but enhances macrophage-mediated fungal clearance during *Pneumocystis* pneumonia. *PLoS Pathog* 2010; 6: e1001058. DOI: 10.1371/journal.ppat.1001058.

8. Zhang ZQ, Wang J, Hoy Z, et al. Neither classical nor alternative macrophage activation is required for *Pneumocystis* clearance during immune reconstitution inflammatory syndrome. *Infect Immun* 2015; 83: 4594–4603. DOI: 10.1128/IAI.00763-15.

9. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; 58:1–207; quiz CE1-4.

10. Ikezawa Y, Shinagawa N, Sukoh N, et al. Usefulness of endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation for ground-glass opacity lesions. *Ann Thorac Surg* 2017; 103: 470–475. DOI: 10.1016/j.athoracsur.2016.09.001.

11. Kurimoto N, Miyazawa T, Okimasa S, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. *Chest* 2004; 126: 959–965. DOI: 10.1378/chest.126.3.959.

12. Ikezawa Y, Sukoh N, Shinagawa N, et al. Endobronchial ultrasonography with a guide sheath for pure or mixed ground-glass opacity lesions. *Respiration* 2014; 88: 137–143. DOI: 10.1159/000362885.

13. Shinagawa N, Nakano K, Asahina H, et al. Endobronchial ultrasonography with a guide sheath in the diagnosis of benign peripheral diseases. *Ann Thorac Surg* 2012; 93: 951–957. DOI: 10.1016/j.athoracsur.2011.11.073.