Received: 30 June 2022 | Accepted: 24 July 2022

DOI: 10.1002/rcr2.1014

CASE REPORT

Respirology Case Reports | WILEY

The IRIS paradox: Imaging findings in a case of PJP-IRIS

Taryn Reddy[1] | Ramey Bajwa[2] | Andrew Burke[2]

[1]Department of Medical Imaging, The Prince Charles Hospital, Brisbane, Queensland, Australia

[2]Department of Thoracic Medicine, The Prince Charles Hospital, Brisbane, Queensland, Australia

Correspondence
Taryn Reddy, Department of Medical Imaging, The Prince Charles Hospital, 627 Rode Rd, Chermside 4032, QLD, Australia.
Email: taryn.reddy@health.qld.gov.au

Associate Editor: Yet Hong Khor

Abstract

Immune reconstitution inflammatory syndrome (IRIS) in patients with human immunodeficiency virus (HIV) and *Pneumocystis jirovecii* pneumonia infection reflects an exaggerated inflammatory response of the host immune system to an antigen, which is temporally related to recovery of the immune system. Clinical manifestations include fever, cough, dyspnoea and hypoxia following the commencement of antiretroviral therapy. Diagnosis is made on clinical and radiological criteria with exclusion of other infective and non-infective causes. Unrecognized, IRIS may be associated with significant morbidity and mortality. Treatment with corticosteroids often results in prompt recovery. There is limited literature on radiological findings of *Pneumocystis jirovecii* pneumonia-associated IRIS. Here we describe cross-sectional imaging findings of PJP-IRIS in a patient following commencement of antiretroviral therapy.

KEYWORDS

computed tomography, HIV, immune reconstitution syndrome, IRIS, *Pneumocystis jiroveci*

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) can be associated with both infectious and non-infectious aetiologies. Of infections associated with IRIS, tuberculosis (TB)-IRIS is the most common world-wide. *Pneumocystis jirovecii* pneumonia-associated IRIS (PJP-IRIS) is less common, with retrospective studies demonstrating that *Pneumocystis jirovecii* only accounts for approximately 2.7%–4% of IRIS cases. Risk factors for development of PJP-IRIS include high-viral load at baseline, low CD4 count and rapid reduction of viral load following initiation of ART.

Achieving a diagnosis of PJP-IRIS requires the integration of clinical, radiological and pathological data. Radiological recognition is often hindered by an apparently normal radiograph in a high percentage of cases, as well as relative sparsity of comparative radiographic and cross-sectional descriptors of PJP-IRIS in the literature.

CASE REPORT

A 57-year-old female, with a known history of HIV who had self-ceased anti-retroviral medications 2 years prior, presented with a two-week history of progressive dyspnoea, cough, an oxygen saturation of 90% on room air and temperature of 37.6°C. Computed tomography pulmonary angiogram demonstrated diffuse ground glass change with relatively well demarcated peripheral sparing (Figure 1A). Subsequent testing revealed a HIV viral load of 4.2×10^6 copies/ml, CD4 count 50 cells/mm^3 and induced sputum *Pneumocystis jirovecii* PCR had 2.8×10^8 copies/ml.

Treatment for PJP with intravenous trimethoprim-sulfamethoxazole for 2 days before changing to oral dosing at 320/1600 mg three times daily and prednisolone 40 mg twice daily was commenced with complete clinical recovery. After 3 weeks high dose oral trimethoprim-sulfamethoxazole, she was changed to prophylactic dosing at 160/800 mg daily. Bictegravir-emtricitabine-tenofovir alafenamide was commenced on day 16 of the admission and the patient was

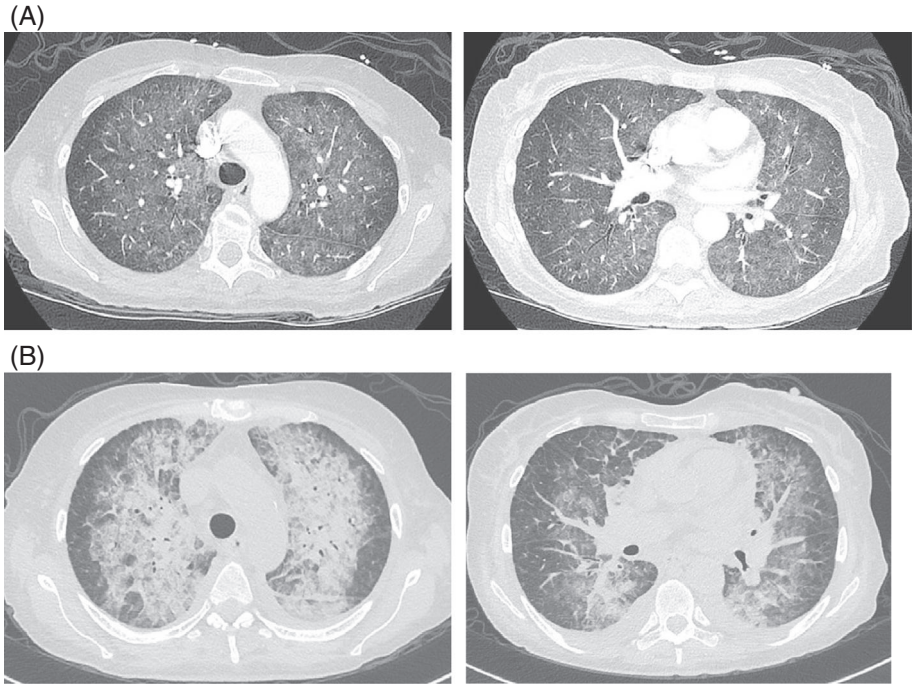

FIGURE 1 (A) Extensive bilateral ground glass change with peripheral sparing at initial presentation and (B) deterioration at re-presentation, with development of marked bilateral consolidation where ground glass change was previously demonstrated, and persistent peripheral sparing. New interlobular septal thickening and bilateral pleural effusions attributed to marked inflammatory response.

discharged on day 18. Oral prednisone was ceased after 20 days.

The patient represented to hospital 21 days after commencing anti-retroviral therapy with a 5-day history of cough and post-tussive emesis, with no history of dyspnoea. Vital signs revealed a temperature of 38.1°C and oxygen saturation was 96% on room air. The patient reported rigours on day two of the hospital admission. High resolution computed tomography at this time demonstrated new consolidation where ground glass changes were previously seen, maintaining boundaries of these earlier changes, as well as new interlobular septal thickening and pleural effusions (Figure 1B).

A bronchoscopy was performed and bronchoalveolar lavage analysis revealed 9.3×10^5 copies/ml *Pneumocystis jirovecii* with a lymphocyte predominance of 23%. Viral cytopathic changes or fungal hyphae were not seen on microscopy. Cytomegalovirus (CMV), Herpes simplex virus and full respiratory virus nucleic acid amplification tests were negative. Fluorescence microscopy did not reveal acid-fast bacilli. Mycobacterial and fungal culture was later confirmed to be negative.

Repeat HIV viral load measurement showed a significant reduction to 43 copies/ml reflective of prompt response to ART. A review of the medication list revealed no drugs associated with drug induced pneumonitis. Based upon the exclusion of alternative infective and non-infective causes, IRIS due to PJP in the context of ART initiation was considered the most likely diagnosis.

There was rapid clinical improvement after recommencing corticosteroid therapy with intravenous hydrocortisone 100 mg QID for 3 days before changing to oral prednisone 50 mg daily. The patient was discharged on day eight with a gradual prednisolone weaning regimen, completing 10 weeks of treatment with a full clinical and radiologic recovery (Figure 2B).

DISCUSSION

IRIS refers to dysregulation of the inflammatory response to an antigen following reconstitution of the immune system, typically following commencement of ART.[1] Pulmonary IRIS is characterized by paradoxical worsening of clinical signs (e.g., tachypnoea, hypoxia) and radiological findings despite improvement in HIV surrogate markers such as viral load and CD4 count.[2] The interval between the start of ART and the onset of IRIS is variable, ranging from less than 1 week to several months. The majority of events occur within the first 8 weeks after ART initiation in those with HIV characterized by a high baseline viral load and CD4 < 200 cells/mm^3.[2] IRIS can occur with a decrease in viral load and no accompanying large increase in CD4 count.[5]

Typical imaging findings of HIV-PJP manifest as fine bilateral, perihilar or diffuse infiltrates that may progress to consolidation over 3–5 days.[3] On computed tomography, extensive ground glass attenuation is often distributed in a

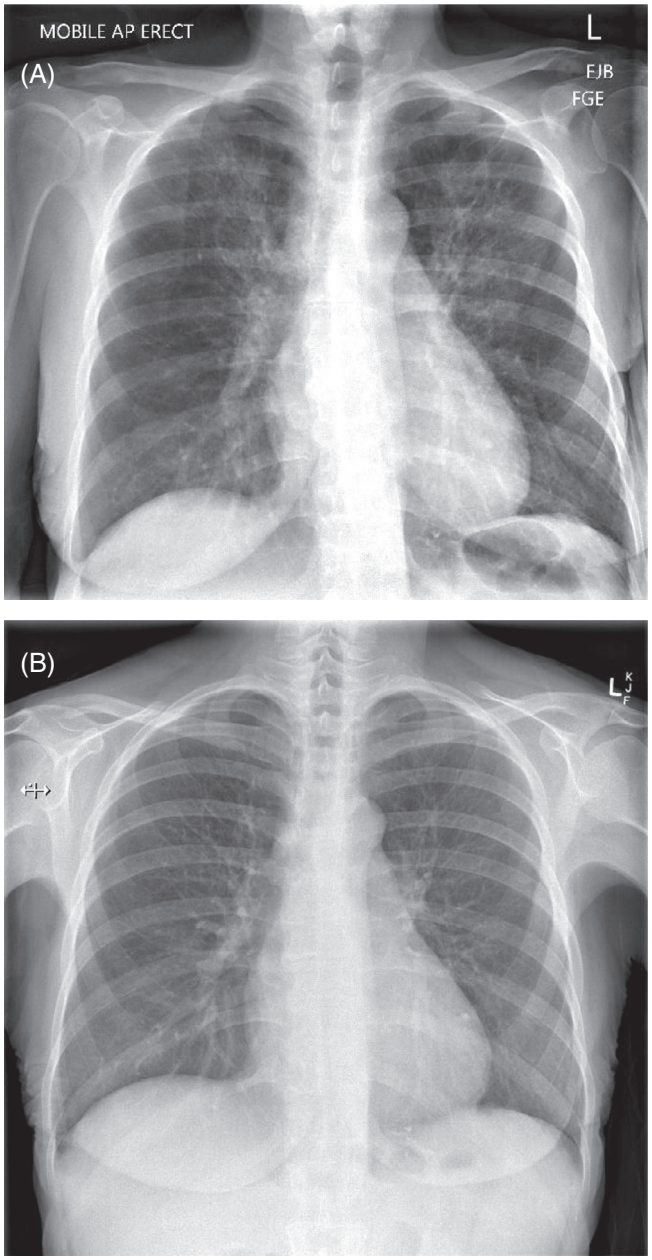

FIGURE 2 Comparative radiographs taken at (A) time of PJP-IRIS diagnosis with bilateral perihilar consolidation and (B) 5 weeks post treatment, with resolution of changes following corticosteroid treatment.

patchy or geographic fashion, with a predilection for the central, perihilar regions of the lungs and peripheral sparing.[4] Interlobular septal thickening may also be present.[4] Cystic lung disease may occur in 10%–34% of PJP cases and is associated with an increased risk of spontaneous pneumothorax.[4] Lobar consolidation, nodules, mediastinal adenopathy and pleural effusions are uncommonly reported and these findings should prompt a search for an alternative pathology. Imaging findings of PJP-IRIS are not widely published but worsening infiltrates, organizing pneumonia and granulomatous changes with nodules or masses have been described.[5] Imaging in this case was notable for development of consolidation within regions where ground glass abnormality had previously been demonstrated, with "respect" for boundaries of the earlier changes and unchanged well marginated peripheral sparing.

PJP diagnosis currently often relies on quantitative PCR performed on bronchoalveolar lavage or induced sputum.[1] The lack of consensus on molecular threshold values for fungal load can make PCR results difficult to interpret.[1] Further diagnostic difficulty is created by lack of a culture technique for PJP. There are no specific diagnostic criteria for PJP-IRIS. Diagnosis requires consideration of other infective and non-infective diagnoses such as CMV and pulmonary oedema, respectively. Drug-induced pneumonitis is an important differential diagnosis. All of these factors can make a definitive diagnosis of PJP-IRIS challenging to make.

IRIS can be associated with significant morbidity and mortality, with mainstay of treatment comprising corticosteroids and continuation of ART. As respiratory failure may be rapidly progressive, prompt diagnosis and initiation of steroids is vital.[2]

When the clinical picture does not fit with more common pathologies such as worsening infection, a second opportunistic infection such as CMV or drug toxicity, IRIS should be considered, particularly in the setting of immunosuppressed patients on recently commenced ART.

AUTHOR CONTRIBUTION

Taryn Reddy: conception and design, acquisition of data, draft of manuscript. Ramey Bajwa: acquisition of data, draft of manuscript. Andrew Burke: draft and revision of manuscript.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

ORCID

Taryn Reddy https://orcid.org/0000-0003-4932-3065

REFERENCES

1. Dellière S, Guery R, Candon S, Rammaert B, Aguilar C, Lanternier F, et al. Understanding pathogenesis and care challenges of immune reconstitution inflammatory syndrome in fungal infections. J Fungi. 2018;4(4):139
2. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. Clin Infect Dis. 2004;38(8):1159–66.
3. Fishman JA. *Pneumocystis jiroveci*. Semin Respir Crit Care Med. 2020; 41(1):141–57.

4. Ketai L, Jordan K, Busby KH. Imaging infection. Clin Chest Med. 2015;36(2):197–217. viii.
5. Roade Tato L, Burgos Cibrian J, Curran Fábregas A, Navarro Mercadé J, Willekens R, Martín Gómez MT, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients with *Pneumocystis jirovecii* pneumonia. Enfermed Infec Microbiol Clin. 2018; 36(10):621–6.

How to cite this article: Reddy T, Bajwa R, Burke A. The IRIS paradox: Imaging findings in a case of PJP-IRIS. Respirology Case Reports. 2022;10:e01014. https://doi.org/10.1002/rcr2.1014