The Egyptian Journal of Internal Medicine

CASE REPORT Open Access

Fatal form of immune reconstitution inflammatory syndrome (IRIS) developed post pneumonia in a solid organ transplant recipient

Hussain Hussain[1*], Aya Fadel[2], Ekaterina Casmartino[1], John Sullivan[1], Amanda Fernandes[1], Samantha Garcia[1] and Efrain Garcia[1]

Abstract

Background Immune reconstitution inflammatory syndrome (IRIS) is a complex phenomenon commonly diagnosed with human immunodeficiency virus (HIV). However, rarely, IRIS can develop with other diseases outside of HIV. We are discussing a rare presentation of IRIS following a pseudomonal infection.

Case presentation We present a 79-year-old Hispanic male who completed a course of cefepime for *Pseudomonas aeruginosa* hospital-acquired pneumonia. The patient had a 21-year history of solid organ transplant and immunosuppressive therapy, and he developed a fatal form of IRIS post-*Pseudomonas aeruginosa*.

Conclusions IRIS may occur in any immunocompromised patient who develops an insidious onset of unexplained clinical and serological deterioration.

Keywords Immune reconstitution inflammatory syndrome, Pneumonia, Solid organ transplant, HIV, *Pseudomonas aeruginosa*

Introduction

Immune reconstitution inflammatory syndrome (IRIS) represents a clinical and serological phenomenon often linked with human immunodeficiency virus (HIV) [1–3]. The non-HIV form of IRIS is seen in various contexts, including solid organ transplant, postpartum, neutropenia, tumor necrosis factor antagonist, and malignancy [2–6]. There are two classic forms of IRIS: unmasking and paradoxical. Both conditions are associated with a severe immunological surge in response to pathogens that could be concomitantly associated with the current HIV infection or postinfection (unknown residual pathogen), respectively [1, 5, 6].

Case description

A 79-year-old Hispanic male presented to the hospital with evidence of a lower respiratory tract infection. The patient developed a high-grade fever (38.9 °C), cough, and worsening psychological capacity. According to his wife, his mental status declined over 2 weeks with noted aggression, agitation, and episodes of visual and auditory hallucinations. He had multiple admissions to different area hospitals secondary to recurrent urinary tract infections that were treated successfully. The patient had a history of renal transplant in 2004, dementia, atrial fibrillation, dyslipidemia, diabetes mellitus type

*Correspondence:
Hussain Hussain
hussainhussainmd77@gmail.com
[1] Department of Internal Medicine/Infectious Disease, Larkin Community Hospital, Miami, FL 33143, USA
[2] Hackensack Meridian Ocean University Medical Center, Department of Internal Medicine, Brick Township, NJ, USA

II, hypertension, and chronic kidney disease. Additionally, the patient had surgery for a subdural hematoma occurring after a fall in 2022. The patient has been on immunosuppressive therapy (tacrolimus 360-mg qd po, mycophenolate 500-mg q12h po, and methylprednisolone 20-mg qd) since 2004. Notably, there was no prior history of HIV or hepatitis.

The laboratory investigation disclosed leukocytosis of 15,000 with neutrophil left shift (normal range 4000–10,000), an elevated erythrocyte sedimentation rate (ESR) at 35 mmHg, creatinine level of 0.88 mg/dL, glucose level of 253 mg/dl, and BUN of 42 mg/dl; the rest of the laboratory results were unremarkable. The patient was diagnosed with hospital-acquired pneumonia for which broad-spectrum antibiotics, cefepime (2g q12h), and vancomycin (1g q12h) were started. The chest computed tomography scan (CT) revealed bilateral consolidations (Fig. 1 A and B). CT scans of the brain, abdomen, and pelvis were unremarkable. Sputum culture was positive for *Pseudomonas*, while nasal swab for methicillin-resistant *Staphylococcus aureus* (MRSA) was negative. Therefore, we discontinued vancomycin, and the patient was continued on cefepime as per protocol.

Strict observation through clinical, serological, and radiographical imaging was continued over the course of the antibiotic regimen, and significant improvement was noted. The repeated chest X-ray (Fig. 1C) showed resolution of pneumonia after the patient completed cefepime. However, the patient unexpectedly deteriorated in the subsequent 36 h while undergoing a workup for his mild normochromic anemia and underlying dementia. At that time, vital signs revealed a temperature of 38.7 °C, elevated blood pressure (160/91 mmHg), respiratory rate of 28, and pulse rate of 110. We suspected IRIS; as our investigation showed elevated C-reactive protein (CRP) to 61 from 5, ESR increased to more than 100 from 39 mmHg, as well as leukocytosis to 20,000 with a neutrophil percentage of 95% from 8000. Moreover, D-dimer was steadily elevated during the hospitalization at 2.1 g/L (normally, < 0.5), creatinine level increased to 3.8 mg/dL (normal range 0.7–1.2) and sodium at 130 mEq/L (137–145), and PaCO2 level was elevated (49 mmHg, normally 35–45). Given his worsening kidney function, the transplant specialist and nephrologist recommended holding tacrolimus, reducing the mycophenolate dose from 360 to 180 mg and increasing the dose of methylprednisolone to 3-g qd. See the graphical timeline (Fig. 2). There were no other clinical features indicative of *Mycobacterium* species infection, and blood/urine cultures were negative. The rest of the investigations were unremarkable, including *Cytomegalovirus*, *Cryptococcus*, galactomannan, D-glucan, urinalysis, and liver function tests. Therefore, cefepime (2-g q12h) was reinitiated at a renally adjusted dose along with clindamycin (600-mg TID). Anticoagulation and chronic medications were continued during hospitalization. The chest X-ray showed severe pulmonary changes (Fig. 1D). Despite extensive management (respiratory support, steroids, antibiotics, anticoagulation, and

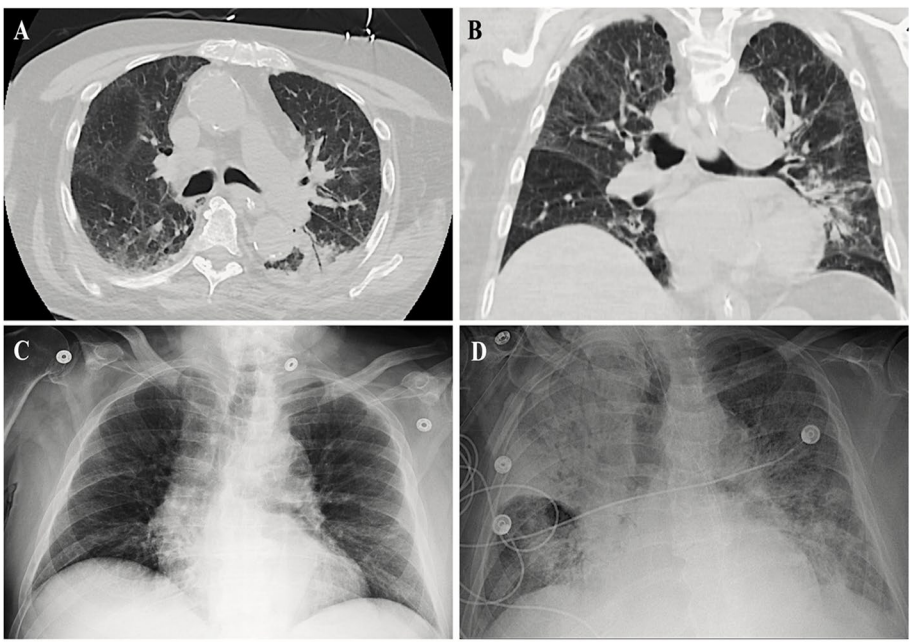

Fig. 1 Radiographical findings of the chest. **A** and **B** showed bilateral consolidation. **C** Resolution of the condition post antibiotics and pre-IRIS. **D** is the development of IRIS

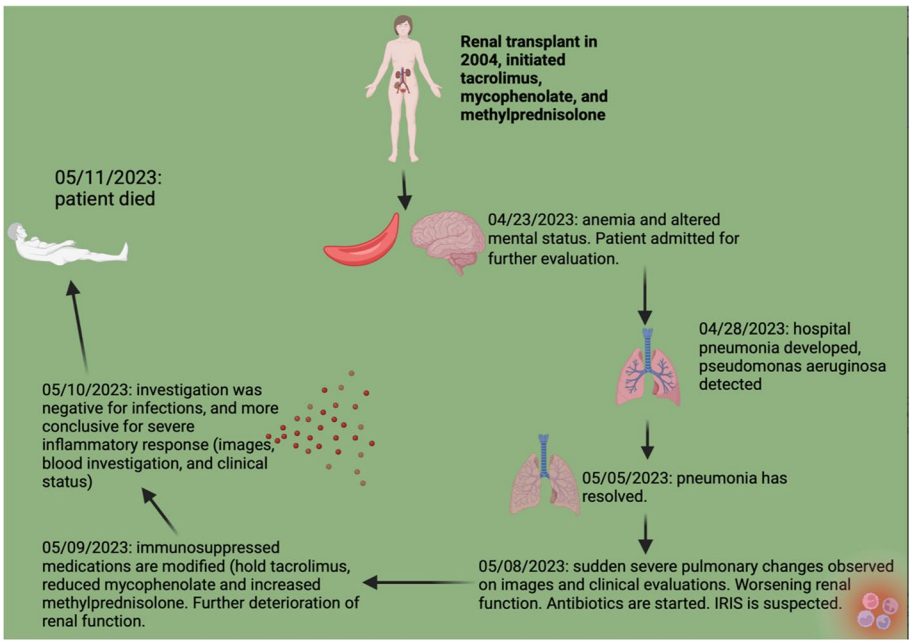

Fig. 2 Graphical timeline

immunosuppressive therapy), the patient died 24 h after the onset of the disease.

Discussion

Immune reconstitution inflammatory syndrome is a complex disorder [1]. The pathogenesis of IRIS is due to the activation of cytokines/cellular pathways in response to pathogen(s) [6, 7]. CD4 T cells (Th0) differentiate into either T helper 1 (Th1) or 2 in the presence of interleukin (IL)-2 or IL-4, respectively [7]. Th1 initiates the pro-inflammatory response, while Th2 produces anti-inflammatory activity through IL-4 and IL-10 [7]. Additionally, Th0 differentiates into either Th17 to stimulate IL-17A, IL-17F, and IL-22 to initiate proinflammation or Treg to release tumor growth factor beta and IL-10 that regulate the immune system [7]. An imbalance in the activation of the above T-cell pathways can ultimately lead to the development of IRIS in the presence of different conditions/pathogens [7].

The incidence of IRIS in solid organ transplant, infection, autoimmune diseases, and medications is rare [1–9]. However, the most common microorganisms reported with IRIS are *Mycobacterium* species, *Cryptococcus*, herpes simplex virus, hepatitis B/C, *Pneumocystis jirovecii* pneumonia, histoplasmosis, and toxoplasma, parvovirus, *Strongyloides*, smallpox virus, and *Cytomegalovirus* [7, 10] (see Table 1). To the best of our knowledge, this is the first case of the development of IRIS posthospital-acquired pneumonia due to *Pseudomonas aeruginosa*. Our patient successfully completed a course of antibiotics for pneumonia, leading to the resolution of his condition. However, the patient's clinical, radiographical, and laboratory status deteriorated severely within less than 36 h upon the resolution of pneumonia.

Several factors and criteria in this case support a diagnosis of IRIS triggered post-infection. First, the patient was immunocompromised due to multiple immunosuppressive therapies (tacrolimus, mycophenolate, and steroids). Second, the patient had undergone a solid organ transplant. Third, multiple organ involvement in an insidious presentation that significantly impacted the patient's clinical status. Fourth, the radiographical evidence in Fig. 1 showed severe bilateral interstitial lung infiltrates. Lastly, classic IRIS biomarkers were elevated, including CRP, interferon-gamma, tumor necrosis factor-alpha, and D-dimer.

There is no specific test to recognize IRIS, and the diagnosis relies on clinical, radiographical, and laboratory findings [2, 6, 7, 10]. The treatment depends on the underlying etiology, and reorchestrating the cytokines and T cells pathways is considered the gold standard method to halt the progression of the disease [6, 7, 10]. Therefore, corticosteroids should be the main treatment regimen when IRIS is diagnosed [6, 7, 10]. While nonsteroidal anti-inflammatory drugs can aid in management, they are generally less effective than corticosteroids [6, 7, 10].

Table 1 Common bacterial infection associated with immune reconstitution inflammatory syndrome

Authors	Title
Legris T. et al.	Immune reconstitution inflammatory syndrome mimicking relapsing cryptococcal meningitis in a renal transplant recipient
Iglesias J. et al.	Immune reconstitution inflammatory syndrome occurring in a kidney transplant patient with extrapulmonary tuberculosis
Jackowiak E. et al.	A case of immune reconstitution syndrome complicating progressive multifocal leukoencephalopathy after kidney transplant: clinical, pathological, and radiographic features
Lemoine M. et al.	Immune reconstitution inflammatory syndrome secondary to *Mycobacterium kansasii* infection in a kidney transplant recipient
Deshayes S. et al.	Severe cryptococcal-associated neurological immune reconstitution inflammatory syndrome in a renal transplant recipient treated with adalimumab
Scemla A. et al.	Dramatic improvement of severe cryptococcosis-induced immune reconstitution syndrome with adalimumab in a renal transplant recipient
Lanternier F. et al.	Cellulitis revealing a cryptococcosis-related immune reconstitution inflammatory syndrome in a renal allograft recipient
Guenette A. et al.	Blastomycosis in a renal transplant recipient: case of immune reconstitution inflammatory syndrome
Kuwahara M. et al.	A case of cryptococcal necrotizing fasciitis and immune reconstitution inflammatory syndrome in a renal transplantation recipient

Conclusions

We are presenting a case of fatal IRIS in the context of posthospital-acquired pneumonia. Given that IRIS is rarely diagnosed with infection, especially bacterial infections, this may be the first reported case of this condition developing insidiously in a patient with posthospital-acquired pneumonia due to *Pseudomonas aeruginosa*.

Abbreviations

IRIS Immune reconstitution inflammatory syndrome
HIV Human immunodeficiency virus
CT Computed tomography scan
ESR Erythrocyte sedimentation rate
CRP C-reactive protein

Acknowledgements

We thank Dr. Lamia Naseer for her assistance and organization of the images.

Authors' contributions

HH, EG, and AF conceived the study and wrote the paper, and HH, JS, AF, EC, AF, and SG wrote the paper. All authors have read and approved the manuscript.

Funding

No funding

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This research has received all the required approvals. The patient has provided written informed consent and had no objections or comments regarding the publication of this case report and its content.

Consent for publication

A written informed consent to publish this information was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

Received: 22 June 2023 Accepted: 31 January 2024
Published online: 13 February 2024

References

1. McLin VA, Belli DC, Posfay-Barbe KM (2010) Immune reconstitution inflammatory syndrome and solid organ transplant recipients are children protected. Pediatr Transplant. 14(1):19–22. https://pubmed.ncbi.nlm.nih.gov/20078839/
2. Tappuni AR (2011) Immune reconstitution inflammatory syndrome. Adv Dent Res 23(1):90–96. https://pubmed.ncbi.nlm.nih.gov/21441488/
3. Sueki H, Mizukawa Y, Aoyama Y (2018) Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients. J Dermatol. 45(1):3–9. https://pubmed.ncbi.nlm.nih.gov/28944502/
4. Miller C, Daugherty R, McCulloch M, Stephens I, Williamson PR (2022) Immune reconstitution inflammatory syndrome complicating cryptococcal meningitis in a pediatric heart transplant patient. Pediatr Infect Dis J. 41(2):145–147. https://pubmed.ncbi.nlm.nih.gov/34609105/
5. Sueki H, Watanabe Y, Sugiyama S, Mizukawa Y (2022) Drug allergy and non-HIV immune reconstitution inflammatory syndrome. Allergol Int. 71(2):185–192. https://pubmed.ncbi.nlm.nih.gov/35236619/
6. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M; IeDEA Southern and Central Africa. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(4):251-261. https://pubmed.ncbi.nlm.nih.gov/20334848/
7. Sun HY, Singh N (2009) Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 22(4):394–402. https://pubmed.ncbi.nlm.nih.gov/19483618/
8. Gopal R, Rapaka RR, Kolls JK (2017) Immune reconstitution inflammatory syndrome associated with pulmonary pathogens. Eur Respir Rev. 26(143):160042 (https://pubmed.ncbi.nlm.nih.gov/28049128/)
9. Kuwahara M, Yurugi S, Ando J, Takeuchi M, Miyata R, Harada M, Masuda Y, Kanagawa S, Yoneda T, Fukumori T, Ogawa T, Nakamura-Uchiyama F, Kasahara K (2021) A case of cryptococcal necrotizing fasciitis and immune reconstitution inflammatory syndrome in a renal transplantation recipient. Int J Surg Case Rep. 85:106199 (https://pubmed.ncbi.nlm.nih.gov/34280874/)
10. Marais S, Wilkinson RJ, Pepper DJ, Meintjes G (2009) Management of patients with immune reconstitution inflammatory syndrome. Curr Hiv/AIDS Rep. 6:162–171. https://pubmed.ncbi.nlm.nih.gov/19589302/

Publisher's Note