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Immune Reconstitution Inflammatory Syndrome

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Introduction

Immune reconstitution inflammatory syndrome (IRIS) is a collection of inflammatory disorders associated with paradoxical worsening of preexisting infectious processes after the initiation of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected individuals. At the initial stage of the disease, the imaging findings can be misdiagnosed as pneumonia resulting from bacterial, viral, or fungal causes. However, IRIS should be suspected when the onset correlates more closely with the initiation of HAART rather than with the treatment for an opportunistic infection.

Case Summary

A 27-year-old HIV-infected man was admitted because of a 7-day history of fever, cough, and progressive dyspnea. *Pneumocystis jiroveci* pneumonia (PJP) had been diagnosed 2 months earlier, and he had completed a 3-week course of antibiotics. Secondary prophylaxis for PJP was then given. At initial presentation, his viral load and CD4 counts were 98,200 copies/mL and 8 cells/μL, respectively. Hence, HAART regimen with efavirenz, tenofovir, and lamivudine had been initiated 40 d prior to this admission. His viral load had declined to 316 copies/mL, and CD4 counts increased to 76 cells/μL 1-month later. On arrival, his body temperature was 38.0°C, and breathing frequency was 30 breaths/min. Physical examination revealed bilateral inspiratory crackles. Laboratory studies showed the following values: white blood cell count, 4010/μL; neutrophils, 32%; lymphocytes, 57%; hemoglobin, 5.6 g/dL; platelet count, $43 \times 10^3/\mu$L; and C-reactive protein, 0.62 mg/dL. Chest radiography showed diffuse opacities in both lungs, more prominent on the left side (Fig. 1, Left). We performed isolation of the virus from the sputum, polymerase chain reaction for *P. jiroveci* and cytomegalovirus, fungal stain and culture, acid-fast stain, Gram stain, and sputum culture. Cefepime (2.0 g) was administered intravenously every 8 h. Trimethoprim (80 mg) plus sulfamethoxazole (400 mg) was orally administered as a single tablet per day. One week later, microbiological cultures were negative for viruses, fungi, and bacteria.

Paradoxical IRIS was diagnosed based on the following three reasons: (1) The findings of progressive dyspnea and cough were consistent with the symptoms of pneumonia caused by *P. jiroveci*; (2) medication toxicity or other disease entity was excluded as the cause of the clinical event; and (3) the chest radiograph showed a remarkable pulmonary infiltrate. Thus, we prescribed prednisolone at a dose of 10 mg/d for 2 weeks. Subsequently, his chest radiograph showed significant resolution of the pulmonary infiltrate (Fig. 1, Right) and clinical improvement.

Discussion

Paradoxical IRIS, an unbalanced restoration of the immune system, occurs in association with worsening of preexisting infectious processes after the initiation of HAART in HIV-infected individuals.[1] Two IRIS categories have been described as follows: paradoxical IRIS, a clinical deterioration of a known and treated condition; and unmasking IRIS, a condition stemming from an underlying opportunistic infection that is diagnosed as IRIS.[2] We excluded other causes of drug-induced lung toxicity by performing a detailed review of medications. We performed a series of examinations, and no pathogen was identified. Thus, we confirmed that our patient had paradoxical IRIS based on clinical symptoms, physical examinations, laboratory results, and treatment response.

IRIS is quite common in HIV-infected persons co-infected with *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, or *Cryptococcus neoformans*.[3] The cumulative 1-year rate of incidence of IRIS is 16% for individ-

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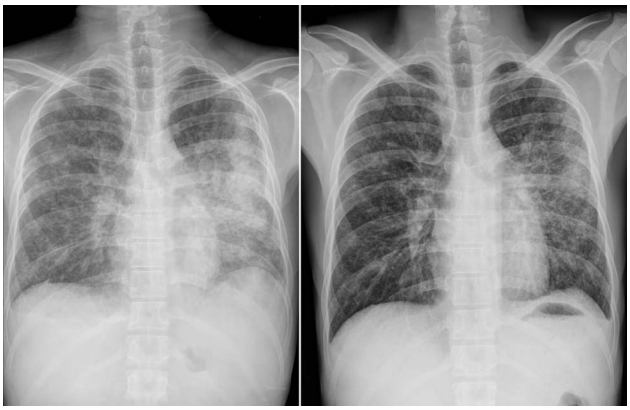

Fig. 1. Left: Chest radiograph taken at admission showing diffuse nodular opacities in both lungs (more prominent on the left side). Right: Chest radiograph taken 2 weeks later showing resolution of the ground-glass opacities in both lungs.

uals infected with *M. tuberculosis*, 10% for those with *M. avium* complex infection, and 14% for those with *C. neoformans* infection.[1] Conversely, IRIS is not commonly observed after PJP as an opportunistic infection, and the estimated cumulative 1-y incidence rate of this condition is 4%.[1] While the majority of patients develop IRIS within the first 60 d of initiation of HAART, IRIS may occur up to 2 y after the initiation of HAART.[3] In addition, antiretroviral drug-naïve patients who begin HAART immediately after the diagnosis of an opportunistic infection and who have a significant decrease in the viral load are more prone to develop this disorder.[3]

Reversal of immunosuppression caused by HIV infection is suggested to be involved in the immunopathogenesis of IRIS.[4] This condition is characterized by innate and adaptive immune responses to dead or live pathogens that result in the release of cytokines and chemokines, which may differ for different types of pathogens. Determination of the levels of inflammatory markers such as C-reactive protein, interferon-inducible protein 10, or interferon gamma may be helpful in prediction of IRIS events, especially in patients with *M. tuberculosis* infection.[4] However, large prospective studies are still required to elucidate the predictive and diagnostic value of IRIS biomarkers.

HAART regimen usually combines 3 or more different drugs such as two nucleoside reverse transcriptase inhibitors and a protease inhibitor or 2 nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor that can inhibit HIV replication, induce a marked decrease in the plasma HIV viral load, and increase CD4 counts even in patients in the advanced stages of the disease.[5] Early initiation of HAART during treatment for an opportunistic infection, high antigen load in those with advanced opportunistic infection, low baseline CD4 cell counts, high baseline viral load, and marked immunological and virological responses to HAART are the well-established risk factors for paradoxical IRIS.[6] Development of unmasking and paradoxical IRIS can be prevented by decreasing the risk of an opportunistic infection through early diagnosis of HIV infection and initiation of HAART when the CD4 cell counts are > 200 cells/μL.[6] Furthermore, the risk of paradoxical IRIS could be reduced by delaying the timing of HAART during treatment for certain opportunistic infections such as pulmonary tuberculosis.[5] However, several randomized controlled trials indicate that early initiation of HAART has an overall benefit on the survival of patients. Moreover, decreasing the mortality by early initiation of HAART is very important.[5] Therefore, clinicians should modify the timing of initiation of HAART individually.

The general therapeutic approach for IRIS involves continuation of HAART and treatment of the concomitant infection.[7] Corticosteroids, the only agents that have been proven to be effective by clinical trials (for treating paradoxical tuberculosis-associated IRIS), are the most frequently used therapeutic agents for IRIS. Limited information is available about the efficacy of other agents, including the non-steroidal anti-inflammatory drugs pentoxifylline, montelukast, thalidomide, and hydroxychloroquine. Interruption of HAART may be considered in lethal forms of IRIS.[8] The majority of patients with PJP-related paradoxical IRIS are treated with steroids and continue anti-PJP therapy and show a complete recovery within a few weeks.[9]

In conclusion, we report a case of paradoxical IRIS after PJP mimicking acute pneumonia. This case is a reminder to clinicians that paradoxical IRIS should be considered in the differential diagnosis of HIV-infected patients with respiratory symptoms and pulmonary infiltrates when HAART is initiated.

Teaching Points

- Paradoxical IRIS should be considered in the differential diagnosis of HIV patients (receiving HAART) with respiratory symptoms and pulmonary opacities.
- The diagnosis of IRIS is generally one of exclusion. Investigations to rule out the possibility of drug reaction, patient noncompliance, and persistently active infection are usually warranted before concluding that IRIS is present.
- Most patients with IRIS develop symptoms within 1 week to a few months after the initiation of HAART. With later onset, other diagnoses are more likely.
- Initiation of HAART at CD4 cell counts > 200 cells/μL could reduce the risk of paradoxical IRIS, and delaying initiation of HAART may be helpful in reduction of the risk of pulmonary tuberculosis-related IRIS. However, mortality reduction by early initiation of HAART is very

important. Therefore, clinicians should modify the timing of initiation of HAART individually.

- The general therapeutic approach for IRIS involves continuation of HAART and treatment of the concomitant infection.
- Corticosteroids may help decrease the inflammatory response in some patients with IRIS. The timing to use corticosteroids should be individualized, and the adverse effects of steroid therapy should be taken into account.

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