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Case report

Double trouble: Concomitant unmasking and paradoxical immune reconstitution inflammatory syndrome in a patient with newly diagnosed HIV

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) is a complication encountered in patients with HIV due to immune function recovery following the initiation of antiretroviral therapy. IRIS can be divided into two forms: paradoxical (recurrence of clinical signs of a previously treated opportunistic infection) and unmasking (uncovering of a previously undiagnosed and asymptomatic infection). We present the rare case of a 48-year-old man diagnosed with AIDS after presenting with cryptococcal meningitis who, shortly after initiation of ART, developed both unmasking IRIS due to *Mycobacterium avium complex* (MAC), and subsequently paradoxical IRIS to his prior cryptococcal meningitis infection. To our knowledge, cases in the medical literature describing "double IRIS" remain scarce.

Introduction

Immune reconstitution inflammatory syndrome (IRIS) is a complication seen with recovery of the immune function in HIV-infected patients following initiation of antiretroviral therapy (ART), as evidenced by recovery of the CD4 count [1,2]. IRIS can be classified into two types: paradoxical, which refers to the recurrence of clinical signs of a previously treated opportunistic infection, most commonly seen with mycobacterial [3] and cryptococcal infections [4–6], and unmasking, which refers to the uncovering of a previously undiagnosed and asymptomatic infection [7,8]. We describe a rare case of a man diagnosed with AIDS after presenting with cryptococcal meningitis who, shortly after starting ART, developed both unmasking IRIS due to *Mycobacterium avium complex*, and subsequently paradoxical IRIS to his prior cryptococcal meningitis infection.

Case report

A 48-year-old man with a past medical history of ischemic cardiomyopathy and G6PD deficiency presented to our institution with complaints of headache associated with fevers, chills, neck stiffness and photophobia for one-week's duration. Initial vital signs were significant for a temperature of 37.8 °C with otherwise stable vital signs. Meningismus was noted on physical examination. Lab work was notable for anemia (hemoglobin 10.7 g/dl). A lumbar puncture (LP) was performed and noted an opening pressure of 26 cm H_2O. Analysis of the cerebral spinal fluid (CSF) revealed mild pleocytosis with 8 white blood cells (85% neutrophils, 11% lymphocytes), glucose of 48 mg/dl, and total protein 70 mg/dl. Gram stain of the CSF showed budding yeast, and India Ink was positive. CSF multiplex polymerase chain reaction panel (BioFire Diagnostics, Salt Lake City, Utah) was positive for *Cryptococcus neoformans* and both the CSF and serum cryptococcal antigens (CrAg) were elevated at 1:2560. The patient was started on intravenous liposomal amphotericin B with oral flucytosine. Testing for HIV was reactive. CD4 count was 8 cells/mm^3 with an HIV RNA level of 145,000 copies/mm^3. He was started on atovaquone for prophylaxis against *Pneumocystis jiroveci* pneumonia. After 2 days, the patient developed an acute kidney injury (creatinine 1.9 mg/dL) and flucytosine was discontinued. Both admission blood cultures and CSF cultures grew yeast after 3 days incubation which was identified as *C. neoformans var grubii*. The patient underwent serial LPs which continued to grow *C. neoformans* for 12 days. The patient completed 17 days of induction therapy with liposomal amphotericin B, at which point the serum CrAg had fallen

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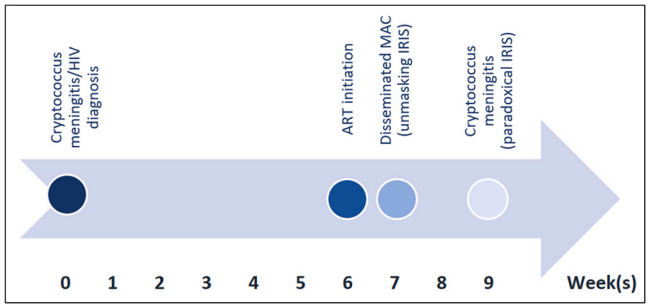

Fig. 1. Clinical timeline since initial diagnosis to double IRIS manifestations.

to 1:1280 and the CSF CrAg had fallen to 1:40, with yeast seen on Gram stain but no growth on culture. The patient was subsequently transitioned to oral fluconazole for consolidation therapy and discharged a month later with outpatient Infectious Diseases (ID) follow up.

The patient was started on bictegravir/emtricitabine/tenofovir alafenamide six weeks after his initial HIV diagnosis (Fig. 1). One week later the patient developed intermittent fevers, chills, night sweats, diarrhea, and abdominal pain which prompted readmission to the hospital. Vital signs were stable on admission. Physical exam was remarkable for diffuse abdominal tenderness without any discreet masses. Blood work showed leukocytosis (white blood cell count 18 $\times 10^3$ cells/μL, 10% immature neutrophils), anemia (hemoglobin 7.4 g/dl), renal insufficiency (creatinine 2.3 mg/dL), and transaminitis (aspartate aminotransferase 102 U/L, alanine aminotransferase 106 U/L, alkaline phosphatase 315 U/L). CD4 count had increased to 186 cells/mm^3 and HIV RNA level had fallen to 650 copies/mm^3. Computed tomography of the chest, abdomen and pelvis revealed mediastinal, thoracic, and mesenteric lymphadenopathy, the largest measuring 2.5 cm × 12 cm. Due to a concern for unmasking IRIS secondary to disseminated *Mycobacterium avium complex* (MAC), mycobacterial blood and bone marrow cultures were sent. Percutaneous lymph node biopsy was deferred due to the location of the mesenteric lymph nodes. Empiric therapy with azithromycin, moxifloxacin and ethambutol was started, the patient clinically improved and was discharged home a week later on MAC therapy. Rifabutin was deferred due to concern for drug-drug interaction with apixaban which the patient had been started on for an acute upper extremity deep venous thrombus related to his peripherally inserted central venous catheter. After 6 weeks incubation the mycobacterial blood cultures grew clarithromycin-sensitive MAC.

Two weeks after his hospital discharge, the patient returned to the outpatient ID clinic complaining of recurrent fevers, dull headache, and photophobia. The patient was readmitted to the hospital and underwent a LP which noted an opening pressure of 34 cm H_2O with 33 white blood cells (32% neutrophils, 43% lymphocytes, 25% monocytes), glucose of 43 mg/dl, and total protein of 79 mg/dl. India Ink and CSF cryptococcal antigen were both negative. HIV RNA level was 160 copies/mm^3. The patient was started on oral prednisone at 1 mg/kg daily for presumed paradoxical IRIS secondary to his previously treated cryptococcal meningitis, with rapid improvement of his symptoms. Prednisone was tapered off over the two months. He completed a 10-week course of consolidation therapy and remains on fluconazole maintenance therapy for his cryptococcal meningitis until his CD4 count goes above 200 cells/mm^3, as well as antimycobacterial therapy for his disseminated MAC. At his most recent outpatient ID visit six months after HIV diagnosis, he was clinically asymptomatic with a CD4 count of 134 cells/mm^3 and HIV RNA level of < 20 copies/mm^3.

Discussion

IRIS is a commonly encountered complication after starting ART in patients with AIDS, with an incidence of 23–27% in some studies [9,10]. It can present as two forms; unmasking or paradoxical, with unmasking occurring more frequently than paradoxical [9]. In this case, our patient developed both forms of IRIS in rapid succession, with unmasking MAC-related IRIS, followed by a paradoxical cryptococcal IRIS. Although there have been reports of both forms of IRIS occurring in patients against a single pathogen [11], the finding of both forms of IRIS occurring in a patient against two distinct opportunistic infections remains rare, with only scarce reports described: Lee et al. presented the case of a 32-year-old man who was diagnosed with CMV retinitis and disseminated MAC due to unmasking IRIS 3 days following initiation of ART, for which appropriate treatment was begun with resolution of symptoms. Seven weeks later, he developed acute abdominal pain with fever and was found to have a jejunal perforation secondary to MAC, which was deemed to be a paradoxical IRIS reaction [12]. While “double” IRIS does not require any specific change in management compared to treating each in isolation, the combined forms of IRIS have the potential to add to the overall morbidity and mortality associated with the underlying advanced HIV.

Current IDSA guidelines [13] recommend that ART be started between four to six weeks after initiation of antifungal therapy in patients with cryptococcal meningitis to reduce the risk of IRIS as delaying ART is associated with improved survival [14,15]. Boulware et al. found that the 26-week mortality with early ART initiation (one to two weeks after diagnosis) was significantly increased when compared to delayed ART initiation (more than five weeks after diagnosis) in patients with cryptococcal meningitis (45% vs. 30%; P = 0.03), particularly those with pauci-inflammatory CSF findings (hazard ratio, 3.87; P = 0.008) [16].

A 2010 meta-analysis showed a 19.5% incidence of IRIS in patients with cryptococcal meningitis (including both paradoxical and unmasking), with an increased incidence noted in patients with lower CD4 counts at the time of ART initiation, particularly CD4 counts below 50 cells/mm^3; the mortality rate from IRIS related to cryptococcal meningitis related IRIS was found to be at 20.8% [17]. Another study showed that pauci-inflammatory CSF findings on initial LP in patients with cryptococcal meningitis was associated with a higher risk of IRIS as this likely represented a more severely immunocompromised state [18]. Our patient had only 8 WBCs in his CSF on initial diagnosis highlighting his advanced immunosuppression, and 33 WBCs in his CSF when subsequently diagnosed with cryptococcal IRIS, reflecting the subsequent immune response as a result of ART initiation [18]. This is evidenced by the higher tendency for IRIS in patients with lower baseline CD4 counts as seen in our patient [18]. Management of cryptococcal IRIS includes serial LPs to reduce intracranial pressure (ICP), as well as continuation of ART and antifungal therapy. Glucocorticoids, usually dosed as 1 mg/kg per day of prednisone equivalent, are added in severe CNS disease manifesting as symptomatic ICP elevation, given the risk for herniation [13].

MAC-related IRIS usually occurs within the first eight weeks following initiation of ART. It remains the most frequently reported atypical mycobacterial infection associated with IRIS. It generally manifests as a localized infection, particularly lymphadenitis [16], but can also have unusual manifestations such as osteomyelitis, granulomatous hepatitis, brain abscess, or mastitis. While disseminated MAC continues to be frequently encountered, the incidence has dramatically decreased in the post-ART era [19]. Similar to cryptococcal IRIS, lower CD4 counts on initiation of ART appears be a risk factor for MAC-related IRIS [20]. The majority of patients with MAC-related IRIS experience favorable outcomes with long-

term antimycobacterial therapy; treatment is pursued for a year and can be safely withdrawn once CD4 count is above 100 cells/mm^3.

In summary, co-infection with cryptococcal meningitis and disseminated MAC in patients with AIDS is exceedingly rare, making our case of particular interest. There is a clear correlation between a patient's baseline immunological status at the time of ART initiation and the likelihood of developing IRIS. IRIS can present either by unmasking an unrecognized infection or paradoxically worsening an infection that has been previously diagnosed and treated. Given that IRIS is associated with worsened patient outcomes and increased death rates, "double" IRIS has the potential to result in increased morbidity and mortality. Our case highlights the importance of remaining vigilant for IRIS-related manifestations of opportunistic infections, as this can alter the therapeutic management, including consideration of initiating glucocorticoid therapy.

Ethical approval

An ethics committee approval was not required as this study did not include any experiments or interventions on participants.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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CRediT authorship contribution statement

Jennifer Makhoul: Data curation, Visualization, Writing – original draft, Writing – review & editing. **Surabhi Uppal:** Writing – original draft. **Marc Siegel:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors have no conflicts of interest to declare.

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