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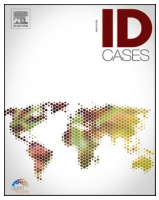

Letter to the Editor

Coccidioides immitis immune reconstitution inflammatory syndrome (IRIS) in advanced HIV – An evidence-based summary

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Dear Editor,

We read the case report titled "A case of disseminated coccidioidomycosis and immune reconstitution inflammatory syndrome (IRIS) in a patient with HIV/AIDS" with great interest [1]. The authors treated a case of disseminated *coccidioidomycosis* with simultaneous initiation of antifungals and combination anti-retroviral therapy (ART). We would like to highlight a few important aspects of the timing of ART initiation based on the available evidence.

The pathogenesis of IRIS is not clearly understood as a whole. It is believed that CD4 recovery post-ART initiation is the key to developing this inflammatory reaction. Better antigen presentation and competent immune cells are all that happen behind the scenes. There are two types of IRIS described to happen in immunocompromised individuals. Unmasking IRIS occurs in those with hidden opportunistic infections (OI). They do not have inflammatory organ-specific symptoms and signs. Very low numbers and functional impairment of immune cells are responsible for this immune anergy. Once ART is initiated, improved numbers and function of lymphocytes will start reacting against those hidden organisms. The second one also known as paradoxical IRIS is characterized by worsening signs and symptoms of pre-existing infection. Paradoxical IRIS is most commonly seen with *Mycobacterium tuberculosis* [2].

A low pre-ART CD4 count (12 cells/microliter in this case) and higher viral load (99,300 copies/ml here) have been associated with a higher risk of developing IRIS as per the scientific literature available. The lower the CD4 count the greater the chance of hidden OI. The antigenic burden will also be higher in very low CD4 as the disease will become disseminated involving multiple organs. Lower CD4 (< 50 cells/microliter) will not react with the microbial antigens even those that are abundant [3–6].

The patient was initiated on ART quite early. Duration of treatment of the underlying opportunistic infection before ART initiation is another important determinant of the development of IRIS. The principle is to reduce the antigenic burden as low as possible before starting the ART. Delayed initiation of ART post antifungal therapy commencement up to 3–4 weeks has been shown to decrease IRIS-associated mortality in *cryptococcal* meningitis [7]. Similar recommendations were made for those with tubercular meningitis with HIV as well [8]. Based on the mortality seen in the largest case series on *coccidioidomycosis*-related IRIS in patients with AIDS; where ART was initiated after 21 days of antifungal therapy (median 28 days), delaying ART to complete a longer duration of antifungal treatment, similar to cryptococcal meningitis, can potentially reduce the risk of severe IRIS [9]. The optimal timing of ART initiation in patients with AIDS and *coccidioidomycosis* is yet to be defined. The onset of IRIS varies from 1 week to 1 month. Hence, judicial and shared decisions should be taken on a case-to-case basis on ART initiation for those with disseminated *coccidioidomycosis in HIV*. Some degree of caution would be prudent to adhere to despite IDSA's current recommendations for the treatment of *coccidioidomycosis* in HIV-infected patients [10].

Our conclusion

Those with advanced AIDS with a CD4 count of < 50 cells/microliter and disseminated disease having a higher organism burden at baseline should receive a longer duration of effective *anti-coccidioides* therapy before starting ART to reduce the incidence of life-threatening paradoxical IRIS.

CRediT authorship contribution statement

Priscilla Rupali: Conceptualization. **DIPANKAR PAL:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Ethical approval

Received.

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

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Conflict of interest

There is no conflict of interest.

Declaration of Competing Interest

The authors have no competing interest in anyone else or any organization.

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