Commentary: A challenge of paradoxical worsening and immune reconstitution uveitis

Immune reconstitution inflammatory syndrome (IRIS) is characterized by paradoxical worsening of treated opportunistic infection or the unmasking of previously subclinical, untreated infection in patients with HIV after initiation of antiretroviral therapy.[1]

The current definition of IRIS includes five fundamental criteria: (1) confirmed case of HIV, (2) temporal association between the development of IRIS and initiation of highly active antiretroviral therapy (HAART), (3) specific host responses to HAART, such as a decrease in HIV-viral RNA load and an increase in CD4+ cell count (over 100 cells/mm^3), (4) clinical deterioration characterized by an inflammatory process, and (5) exclusion of other causes that may lead to a similar clinical presentation.[2]

Ocular IRIS is referred to as immune recovery uveitis (IRU). It remains a leading cause of ocular morbidity. The interval between the initiation of HAART and manifestation of IRIS is highly variable (from 1 week to more than 1 year), but a majority of cases occur during the first 2 months of HAART.[3] The risk of IRU increases many fold with increasing CD4+ T-cell count to a level of ≥100 cells per microliter.[4] TB-IRIS is an acute inflammatory condition that presents with worsening, or development of new, tuberculosis disease in a patient already on TB treatment after starting ART (paradoxical TB-IRIS), or a new diagnosis of TB with a particularly acute, inflammatory presentation after starting HAART (unmasking TB-IRIS).[5]

In the context of TB-IRU, authors[6] have presented a striking case of chronic ocular tuberculosis with granulomatous panuveitis progressing to panophthalmitis. The index case was on HAART for 1 year until presentation, and CD4 count 1 month before antitubercular therapy (ATT) initiation was 324. Repeat testing after 3 months showed a mild increment in the level of CD4 to 410. Conventionally, IRIS follows introduction of HAART, but the present case report presents a contrasting clinical picture, wherein the disease process worsened after introduction of ATT, while the patient was already on HAART for a year. Sudharshan *et al.* noted that interval between the start of HAART and onset of IRU was from 4 months to 2.5 years.[7] Hence, the temporal association between development of IRIS and initiation of HAART could be established (criteria 2) and present case may be placed under "unmasking TB-IRIS" subset where paradoxical reaction secondary to ATT might have occurred simultaneously. It is noteworthy that the criticality of drug-resistant tuberculosis was astutely addressed by the authors while managing this case.

However, other factors involved in the management of the index case could also lead to similar clinical presentation (criterion 5), i.e., disease progression despite ATT. First, this entails the use of topical corticosteroids that could have contributed to the development of scleral abscess. Second, disease progression from chronic tubercular endophthalmitis to panophthalmitis, likely presents a natural course of intraocular multi-bacillary tuberculosis in an immunocompromised setting (HIV), wherein the ocular Minimum Inhibitory Concentration (MIC) of systemically administered ATT might not have been achieved.

The absence of a systemic focus of tuberculosis and unilateral ocular involvement in the absence of apparent Cytomegalovirus (CMV) infection make this a unique case presentation. Since IRU in non-CMV retinitis eyes is not common, the ocular inflammation is postulated to be due to CMV infection itself, which brings about breakdown in the blood ocular barrier. Although the pathologic immune reaction in IRU occurs in the eye, some kind of immune dysregulation is likely caused by faulty systemic immune cell reconstitution.[8]

Though systemic tuberculosis is quite common among HIV patients, ocular TB is relatively rare, as compared to more common CMV retinitis. Ocular TB most commonly occurs due to secondary spread of bacterium to the eye via hematogenous route. HIV patients with ocular TB may present with choroidal tubercle, subretinal abscess, conjunctival mass, or panophthalmitis. The pathogenesis of IRU remains largely speculative. Current theories involve a combination of underlying antigenic burden, the degree of immune restoration following HAART, and host genetic susceptibility.[9]

Treatment of IRU should follow a tailored approach, as in, an isolated case with mild vitritis without CME may be observed, since the vitreous inflammation can be transient. More severe vitreous inflammation and/or CME typically is treated with periocular corticosteroids, short courses of oral corticosteroids, or intravitreal steroid implants. Formation of epiretinal membrane or development of vitreomacular traction syndrome may necessitate surgical intervention.

As an increasing number of HIV-infected individuals present with treatment failure in developing countries, the risk of ophthalmic complications may increase. TB-IRIS causes significant morbidity in resource-limited settings. With the increasing longevity of these patients due to the use of HAART, treatment of IRU may pose an issue in times to come. Therefore, future research should focus on improving diagnosis and investigating novel therapeutic interventions.

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