Immune reconstitution inflammatory syndrome in treatment-experienced HIV-infected patients

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ABSTRACT

We described two cases of treatment-experienced HIV-infected patients who presented with cytomegalovirus uveitis and *Cryptococcus neoformans* adenitis as a manifestation of immune reconstitution inflammatory syndrome (IRIS) during salvage treatment. Little is known about IRIS in highly experienced patients, and this report suggests that IRIS should be considered in this setting if there is a favorable response to salvage therapy.

Keywords: AIDS; HAART; immune reconstitution syndrome; immune reconstitution inflammatory syndrome; immune reconstitution disease; salvage therapy

The immune reconstitution inflammatory syndrome (IRIS) is characterized by an otherwise unexplained paradoxical onset of clinical and laboratorial manifestations of an opportunistic infection or inflammatory condition after recovery of CD4 T cells levels and function and virologic suppression of >1 log 10 copies/mL in HIV RNA viral load following highly active antiretroviral therapy (HAART) initiation[1]. Proposed definitions for IRIS are usually limited to patients who are initiating HAART[1-3]. However, little is known about IRIS in treatment-experienced patients. In this report, we aimed to describe two recent cases of heavily pretreated patients who develop IRIS following salvage therapy, emphasizing that this syndrome is not limited to treatment-naïve patients who start HAART.

CASE 1

The first case was a 44-year-old male HIV patient who had started HAART in 1997. This scheme was changed twice by July 2004, when his CD4 count was 98 cells/mm^3 and the HIV load was 341,269 (log 5.53). His highest CD4 count had been 174 cells/mL in 2000, and his viral load had never been undetectable. In March 2005, the therapeutic scheme was as follows: tenofovir 300 mg once a day, lamivudine 150 mg twice a day, saquinavir 1000 mg twice a day, and lopinavir/ritonavir 400/100 mg twice a day, according to a viral resistance genotyping test. Three months latter, he complained of floaters and decreased visual acuity in the right eye. Indirect ophthalmoscopy revealed a cystoid macular edema and severe vitritis in the right eye. Signs of inactive cytomegalovirus retinitis were also observed. The left eye examination was unremarkable. The CD4 count was 247 cells/mm^3 and the HIV load was 1,492 copies/mL (log 3.17). The patient was initially

treated with ganciclovir 5mg/kg twice a day (three weeks), despite the absence of active cytomegalovirus retinitis, and with prednisone 60mg/a day for two weeks, followed by a gradual reduction to 10mg/a day for 8 weeks. At the end of the treatment, vitritis was mild to moderate, and the patient still complained of blurred vision. A three-month follow-up examination did not reveal any sign of vitritis nor of macular edema, but the patient remained with minimal visual complaints (slight blurred vision). The CD4 count was 187 cells/mm^3, and the HIV load was undetectable.

CASE 2

The second case was a 33-year-old female patient who had been diagnosed with AIDS in 2000. The CD4 cell count was unknown. The patient started HAART at the moment of diagnosis, but due to therapeutic failure the scheme was modified three times by September 2005, when she was admitted to the hospital with a diagnosis of disseminated cryptococcosis (*Cryptococcus neoformans* was recovered from the cerebrospinal fluid, cervical lymph nodes, and blood). The patient was then started on zidovudine 300 mg twice a day + lamivudine 150 mg twice a day + lopinavir/ritonavir 400/100 mg twice a day. She was successfully treated with 15 days of amphotericin B 1mg/kg/a day, followed by 8 weeks of fluconazole 400 mg/a day orally, and then kept on suppressive therapy with fluconazole 200 mg/a day. In February 2006, she was once again admitted to the hospital with cryptococcal lymphadenitis. Compliance to both HAART and suppressive fluconazole therapy was ensured. Meningeal involvement was ruled out. The hallmark of this presentation was the exuberant granulomatous reaction and the few encapsulated fungi found at histopathological examination of the lymph node, which contrasted with her first biopsy in September 2005, in which abundant fungal structures and minimal inflammatory reaction were observed. Her CD4 count and viral load were 91 cells/mL and 582 copies/mL (log 2.76). The patient was treated with amphotericin B and prednisone 0.5 mg/kg a day for 16 days and recovered well.

DISCUSSION

It is estimated that IRD may occur in 10-25% of patients who start HAART and reach immune restoration[1-3]. The current report presents distinct features that must be highlighted, since it supports that immune reconstitution, although less frequently and less potently[4,5], occurs with advanced disease and in HAART-experienced patients, even in those who have experienced multiple failures, and this immune recovery can be strong enough to trigger IRIS.

In a recent cohort, being drug-naïve was an independent risk factor for IRIS[6]. This association is probably related to a more robust virological and immunological response to therapy by this group of subjects, when compared with those who had been on prior therapy[4-6]. Only four of 57 patients who had developed IRIS were HAART-experienced, compared with 38 of 123 patients who had not developed this syndrome[6]. Previous HAART experiences were not described for these four patients, and it is not known whether they presented multiple failures.

In both cases, many features support the diagnosis of IRIS, particularly the exuberant inflammatory responses. In the second case, notably, the CD4 count, which may be low in IRIS[3], was below 100 cells/ml, but an increase is likely to have occurred, although the CD4 count prior to the latter treatment was unknown and this hypothesis could not be confirmed.

In summary, IRIS should be considered even in the setting of multiple previous failures if there is favorable response to salvage therapy.

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