Tuberculosis-immune reconstitution inflammatory syndrome in HIV-infected patient: A case report

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ABSTRACT

We describe a case of immune reconstitution inflammatory syndrome (IRIS) secondary to reactivation of Mycobacterium tuberculosis in an HIV-infected patient with a high CD4+ cell count, who presented with a generalized seizure 6 weeks after starting antiretroviral therapy (ART). In our patient, the inflammatory response resulted in radiological features of neurological, pulmonary, and lymph node (LN) tuberculosis (TB) IRIS, without the typical symptoms. Diagnosis was confirmed by LN biopsy and acid-fast bacilli (AFB) culture of LN and sputum. Treatment with isoniazid, rifabutin, ethambutol, and pyrazinamide was started in addition to continuation of ART.

To our knowledge, we describe the first case of an atypical clinical presentation of an unmasking reaction of disseminated TB-IRIS in an HIV infected patient without acquired immune deficiency syndrome (AIDS), with restoring immunity during ART. Clinical and radiological predictors of TB-IRIS in co-infected patients starting ART are therefore essential in anticipating complications and facilitating expedient management and prompt therapy.

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Introduction

Tuberculosis- (TB) associated immune reconstitution inflammatory syndrome (IRIS) refers to an abnormally exaggerated immune response against alive or dead Mycobacterium tuberculosis infection [1]. This phenomenon occurs mostly in HIV-infected patients, most often within two months of the initiation of ART [1]. Risk factors for TB-IRIS include advanced HIV, rapid rise in CD4+ cell count or rapid drop in HIV RNA following initiation of ART, and high pathogen or antigen burden [1].

There are two distinct temporal versions of TB-IRIS: paradoxical and unmasking. Paradoxical refers to clinical deterioration after initiation of ART in a patient previously diagnosed with TB who has responded to antituberculosis treatment. Unmasking refers to a patient with asymptomatic TB disease prior to starting ART, which presents after initiating ART, as in our patient [2]. Lymph nodes (68%) and lungs (16%) are the principal sites involved in TB-IRIS. Typically, patients present with fever, abdominal pain, cough and lymphadenopathy [1]. Neurological involvement occurs in 12–31% of TB-IRIS patients [3]. Most reported cases were paradoxical TB-IRIS, which is the best studied of the two forms [2].

There is no specific diagnostic test that can establish or rule out the diagnosis of TB-IRIS [1]. Although there is no standard optimal treatment for TB-IRIS, antituberculosis therapy should be initiated as soon as possible [1].

In this unique case report, we describe a patient who presents with an atypical presentation of disseminated TB-IRIS, which is rarely seen in non-advanced HIV patients with restoring immunity during ART. Given this entity, it is important to ensure timely initiation of treatment.

Case report

A 42-year-old Chinese man was admitted to the hospital with a generalized seizure, which was witnessed. He recalled feeling twitching of his eyes and mouth prior to a brief period of loss of consciousness. The patient felt well after the episode, with the exception of fatigue. There was no fever, chills, headache, or visual disturbances.

The patient is from China, and has resided in the United States for 8 years. He has used intravenous heroin and alcohol but stopped 10 years previously. He smoked 1 package of cigarettes daily for 20 years.

Past medical history is significant for HIV, hepatitis B and C (HCV), all diagnosed 3 months prior to this admission when he presented with progressive swelling of the lower extremities and elevated blood pressure. A renal biopsy showed membranoproliferative
glomerulonephritis. The initial CD4+ cell count was 389/mm³, quantitative HIV RNA 58,254 copies/ml and HCV viral load 202,489 IU/mL.

Treatment with dolutegravir and emtricitabine/tenofovir alafenamide was started 6 weeks previously, followed by sofosbuvir/velpatasvir.

On admission, the oral temperature was 99.3°F, pulse 100 beats/minute, respiratory rate 16 breaths/min, blood pressure 155/104 mmHg and oxygen saturation 99% on room air.

Physical examination showed a laceration on the lateral aspect of the tongue and bilateral axillary lymphadenopathy. Neurological assessment revealed an alert and oriented patient with normal speech. No motor deficits were noted, and sensation was intact bilaterally. There was no facial weakness, and the tongue was midline. Cranial nerves were intact, with normal visual fields. Deep tendon reflexes were normal and symmetrical. No gait abnormalities were appreciated, and cerebellar function was intact.

The leukocyte count was 7900/UL, hemoglobin 10.2 g/dL, and platelet count 177,000/UL. Blood urea nitrogen was 16 mg/dL, and creatinine was 1.2 mg/dL. The erythrocyte sedimentation rate was greater than 145 mm/h. Cerebrospinal fluid (CSF) analysis showed 10 leukocytes/mm³, glucose of 45 mg/dL (serum glucose 90 mg/dL) and protein of 48 mg/dL. CSF cryptococcal antigen, VDRL and bacterial cultures were negative. Absolute CD4+ count was 343/mm³ and HIV RNA was undetectable. Hepatitis B viral DNA and hepatitis C RNA were undetectable.

Blood cultures, urine culture, urine toxicology and an echocardiogram were normal. Chest radiograph (CXR) was also normal. Parasitological investigation of stool samples did not reveal pathogens. The initial brain computed tomography (CT) showed numerous areas of white matter edema at the gray-white junction within the bilateral hemispheres, as well as in the left cerebellum (Fig. 1). Gadolinium-enhanced magnetic resonance imaging (MRI) revealed numerous small ring-enhancing masses with targetoid appearance and moderate surrounding vasogenic edema (Fig. 2). Serum cysticercus IgG and toxoplasma IgM and IgG antibodies were negative. Although the CXR was normal, the CT of the chest (Fig. 3) showed extensive lymphadenopathy, with bilateral apical airspace disease with tree-in-bud like appearance. Initial sputum acid-fast smears were negative.

An axillary lymph node biopsy showed granulomatous inflammation with necrosis. Acid fast and fungal stains were negative.

Treatment with isoniazid, rifabutin, ethambutol, and pyrazinamide was started. In addition, dexamethasone 0.3 mg/kg/day was given together with anti-tuberculous medication and gradually tapered over six weeks. The patient was discharged on hospital day 23. Three weeks later, the axillary lymph node and sputum cultures grew Mycobacterium tuberculosis.

Follow-up brain MRI with gadolinium five months later showed that nearly all of the previously demonstrated ring enhancing masses had decreased in size and markedly decreased surrounding vasogenic edema (Fig. 4). In addition, follow-up CT of the chest 2 weeks after initiation of treatment revealed partial resolution of the previously seen bronchial and bronchiolar inspissation in both upper lobes (Fig. 5).
Fig. 5. Post-treatment computed tomography of the chest revealing partial resolution of the previously seen bronchial and bronchiolar inspissation in both upper lobes.

Discussion

Our patient, who is a former injecting drug user, presented with a generalized seizure six weeks after starting ART.

The differential diagnosis of brain lesions in HIV infected patients includes cryptococcosis, neurocysticercosis, toxoplasmosis, progressive multifocal leukoencephalopathy-IRIS, syphilitic gumma, septic emboli and malignant lymphoma [1]. Because our patient had a CD4+ cell count over 300, opportunistic pathogens were less likely. We made a presumptive diagnosis of unmasking disseminated TB-IRIS based on the following: ART was initiated six weeks earlier; the presence of multiple small intracerebral space-occupying lesions; coexistent bilateral upper lung infiltrates; extensive lymphadenopathy throughout the chest, abdomen and pelvis; and granulomatous inflammation with necrosis in a lymph node.

Interestingly, our patient did not present with any systemic or pulmonary manifestations.

In contrast to existing reports and case series, our patient presented with an unmasking pattern of disseminated TB-IRIS six weeks after initiation of ART. In addition, our patient’s nadir CD4+ cell count was 389 cells/mm³ and viral load was not high.

There is no specific diagnostic test that can establish or rule out the diagnosis of TB-IRIS [1]. It is difficult to differentiate this syndrome from the development of new occult opportunistic bacterial infections or malignancy. These diagnostic challenges often delay diagnosis and treatment. Clinicians should take into consideration a combination of clinical presentation and timing of initiation of antiretroviral therapy in making the correct diagnosis [1]. Although there is no standard optimal treatment for TB-IRIS, antituberculosis therapy should be initiated as soon as possible [1]. Furthermore, ART should be continued during the management of IRIS unless the disease is life threatening [2]. In severe forms of TB, use of anti-inflammatory medications such as corticosteroids improved symptoms, and reduced hospital days and morbidity [4].

To conclude, unmasking TB-IRIS should be included in the differential diagnosis in an HIV-infected patient with a high CD4+ cell count, even with an atypical presentation, to ensure timely initiation of treatment.

Conflict of interest

On behalf of all authors the corresponding author states that there is no conflict of interest.

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Consent

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

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