

Case Report

Brain tuberculosis-associated immune reconstitution inflammatory syndrome in an HIV-positive patient: a biopsy-proven case

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Abstract

The case of an HIV-infected man from Eritrea previously diagnosed with tuberculosis, who presented neurological impairment and cerebral lesion after having voluntarily stopped anti-tubercular and antiretroviral therapies, is here reported. Treatments associated with steroids and mannitol were administered. The patient's condition improved, but neuroimaging showed a continuous worsening of the lesion, while a great immunological reconstitution was observed. Brain microsurgery was performed. A tuberculosis diagnosis was supported by pathological and microbiological examinations. Tuberculosis arising during immune reconstitution inflammatory syndrome is a complication of antiretroviral treatment and is considered to be an emerging disorder, especially in countries highly endemic for tuberculosis.

Key words: HIV; tuberculosis; tuberculoma; immune reconstitution inflammatory syndrome (IRIS); antiretroviral therapy; central nervous system.

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Introduction

Tuberculosis (TB) involving the central nervous system (CNS) in human immunodeficiency virus (HIV) patients is an uncommon but severe disorder [1]. CNS tuberculosis accounts for approximately 1% of all cases of TB, and causes high mortality and morbidity, with severe neurological sequelae. Some issues about pathogenesis, diagnosis, treatment, and management of CNS TB still remain unclear. There are various clinical presentations, and the diagnosis is not easy in all cases [1,2]. Meningitis is the most frequent clinical feature; patients present with fever, headache and stiff neck, and sometimes with focal neurological deficits such as cranial nerve palsies, behavioral changes, and alterations in consciousness. Tuberculoma and tuberculous brain abscesses are less frequent. Magnetic resonance imaging (MRI) of tuberculoma shows low or high density, round or lobulated, single or multiple lesions with irregular walls and homogenous or ring enhancement after contrast, typically in frontal and parietal lobes. CNS TB in HIV-infected patients requires differential diagnosis to exclude other causes of mass lesions. Mass algorithms in the pre-highly active antiretroviral

therapy (HAART) era were well defined [3], but in the HAART era, when the epidemiology of opportunistic infections have been modified, mass algorithms are lacking.

TB arising during immune reconstitution inflammatory syndrome (TB-IRIS) is a complication of potent antiretroviral treatment. Based on the initiation of antiretroviral therapy, it causes a paradoxical or an unmasking disorder before or after the TB diagnosis, respectively [4]. To promote standardization, a general consensus on case definition for TB-associated IRIS was defined in 2006, to be used in high-income and resource-limited settings [4]. TB-IRIS is an emerging disorder, especially in countries highly endemic for TB [4,5]. It evokes diagnostic and therapeutic problems. The mortality rate in paradoxical TB is considerable [5]. Steroid treatment is often required [6], but the treatment is not yet definitively established.

The case of an HIV-infected man who developed a CNS TB-IRIS is here described in detail.

Case presentation

A 31-year-old man from Eritrea, affected by HIV since 2000, was admitted for the first time to our hospital in February 2010 and discharged one month later with a diagnosis of disseminated tuberculosis (TB) involving the lungs, spleen, and nodes, and oral thrush. TB diagnosis was based on the positive result of *M. tuberculosis* RNA on bronchoalveolar lavage (BAL), later confirmed by *M. tuberculosis*-positive culture. *M. tuberculosis* did not show resistance to isoniazid, rifampin, ethambutol, or streptomycin in the antibiogram; acid-fast bacilli (AFB) were found in the blood culture. At that time, CD4 count was $59/\text{mm}^3$, HIV-RNA was 480,537 copies/mL, and hepatitis B virus (HBV) markers and hepatitis C virus (HCV) antibodies were negative. During hospitalization, antitubercular treatment with isoniazid, rifampin, ethambutol, and pyrazinamide was started.

On April 2010, HAART with a regimen including efavirenz, tenofovir, and emtricitabine was started on an outpatient basis; the patient took antitubercular and antiretroviral therapy for the following month, and then he stopped therapy and clinical controls. On 3 September 2010, the patient was taken to the emergency department of another hospital, presenting with headache and fever, and then was transferred to our institute. On admission to our hospital, the patient was in critical condition and presented mental confusion. At examination, he presented neck stiffness, but no focal neurological deficits. No node enlargement was observed.

MRI showed a multiloculated necrotic lesion in the left tempo-parietal-occipital region, with ring contrast enhancement. The lesion had perilesional edema and showed a significant mass effect against ventricular system, midbrain, and subaracnoidal space, with shift of the median line (Figure 1). Diffusion-weighted imaging showed inhomogeneously restricted diffusion (avg $0.793 \times 10^{-3} \text{ mm}^2/\text{s}$). Spectroscopy, performed using a short echo time (TE) (35 ms), showed a large lipid peak inside the lesion with reduced N-acetylaspartate (NAA)/creatinine (CR) and elevated choline (Cho)/CR ratio. Total body computed tomography (CT) showed minute spleen lesions in the absence of node enlargement or lung involvement.

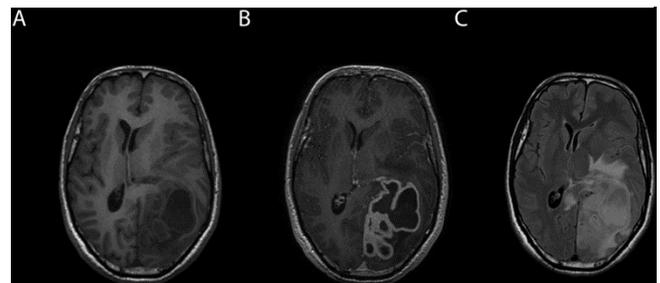
From 4 September, antitubercular therapy with isoniazid, rifampin, ethambutol, pyrazinamide, and anti-toxoplasmic therapy with sulfadiazine and pyrimethamine, and antibiotic therapy with ceftriaxone and metronidazole were started. Dexamethasone (8 mg every eight hours) and mannitol were added, and the antiretroviral therapy previously stopped was started

again. A few days later, a lumbar puncture was performed. Limpid cerebrospinal fluid (CSF) was obtained, showing an increased level of proteins (136 mg/dL) and an increased number of cells ($280/\text{mm}^3$, mainly lymphocytes). The glucose in CSF was 0.39 g/L, and in the blood was 1.09 g/L. Cryptococcal antigens were negative; *M. tuberculosis* complex, *Toxoplasma gondii*, Epstein-Barr virus, Varicella Zoster virus, human herpesvirus 6, herpes simplex virus 1 and 2, and John Cunningham (JC) virus by polymerase chain reaction (PCR) in CSF were negative. Culture of CSF was sterile. HIV-RNA was 11,288 copies/mL in CSF, and 2,577 copies/mL in a concomitant plasma sample. All the other microbiological examinations performed, which included cryptococcal antigenemia, seric antibodies against *Tenia solium*, RPR for syphilis (<1:2), antigens for *Aspergillus* (galattomannan), antibodies against *Aspergillus fumigatus* and *Entamoeba histolytica*, PCR and blood antigens for cytomegalovirus, and blood cultures and PCR for yeast yielded negative results. IgG against *Toxoplasma gondii* were positive, while IgM were negative. Three sputum direct examinations failed to reveal AFB.

Dexamethasone and mannitol, which had been slowly decreased and then stopped, were started again at the same doses, to treat edema around the cerebral lesion and the worsening of cranial hypertension, which were associated with vomiting and headache. The patient showed a great immunological reconstitution, starting from a level of CD4 of $163/\text{mm}^3$ (14.2%) in September 2010 to $445/\text{mm}^3$ (29.7%) in October, while the HIV-RNA load decreased from 16,334 copies/mL at hospital admission, to 2,577 copies/mL at lumbar puncture after a few days, to 687 copies/mL one month later, in October.

The patient's health was improving, his headache disappeared, and his neurological examination was normal, but neuroimaging showed a continuous

Figure 1. Brain magnetic resonance imaging of the study patient before surgery.



worsening of the cerebral lesions in several controls.

On 15 November, microsurgery with craniotomy, the evacuation and removal of the multiple cerebral lesions, was performed. Neurosurgery revealed a non-vascular tissue with a highly increased consistency; at the opening of the capsule around the lesions, a dense, creamy, purulent fluid was extracted by aspiration. Fluid direct examination for AFB was negative, and *M. tuberculosis* PCR yielded a positive result. Fluid culture for bacteria was negative, as were PCR for *Entamoeba dispar* and *Entamoeba histolytica* and for *Toxoplasma gondii*. The histologic examination of the cerebral lesion capsule showed a granulomatous chronic inflammation with evidence of AFB.

The anti-toxoplasmic therapy was promptly stopped. The antitubercular therapy was continued for 18 months (isoniazid, rifampin, ethambutol, and pyrazinamide for three months, then only isoniazid and rifampin for a further 15 months, discontinued on March 2012). Steroids were gradually reduced and then stopped after four months of administration. The patient showed a complete recovery of his health status; he was discharged from hospital in December, three months after his admission, one month after surgery, and continued follow-up as an outpatient.

Discussion

The case demonstrates unusual features of cerebral tuberculosis. The clinical evolution of the patient was characterized by paradoxical neuroradiological worsening despite great improvement of general conditions, in the absence of findings supporting a tubercular diagnosis, while a good virological response and restoration of the immune function subsequent the start of HAART were observed. In fact, the first suspicion was that the patient had had a relapse of tuberculosis after the voluntary interruption of the specific therapy. However, the site primarily affected TB seemed not to be affected by TB at present (negative chest X-ray, negative sputum for AFB, no lymph node enlargement). At the beginning, the patient was not investigated with neuroimaging; at that time, there was no reason to suspect cerebral involvement. Taking antiretrovirals for a month was apparently enough to control the systemic TB symptoms, but not brain involvement. After discontinuation of therapy, TB progressed, involving mainly cerebral sites. As the patient was admitted to the hospital, an evidence-based diagnosis of TB neurological disorders was not easy. In fact, cerebral toxoplasmosis should be considered in every HIV-positive patient with a low immunity and cerebral

focal lesions. We therefore initiated antitubercular and anti-toxoplasmic therapy, and also an antibacterial therapy. During therapy, the patient improved, while his cerebral lesion continued to worsen. It may be assumed that, when the patient reached a good immunological response with HAART, the neurological compartment showed a paradoxical worsening despite the improvement of systemic conditions and the disappearance of fever. MRI is the most advanced method for examining the brain; the use of spectroscopy (MRS) adds further information. In our case, MRI and MRS were compatible with TB diagnosis, but diffusion imaging did not support the tubercular diagnostic hypothesis because it showed a restricted pattern in all the observed sites. In the absence of microbiological diagnostic findings and because of the progression of the cerebral lesion, neurosurgery was necessary. In the HAART era, a brain biopsy is no longer mandatory for the diagnosis of mass lesions in HIV patients [7]; however, in selected cases, it is still the only way to make a diagnosis, and it is worth carrying it out when HIV patients have a good prognosis even in severe immunodepression. In contrast with recent literature concerning neuroradiological features of TB during IRIS [8], our diagnosis was supported by biopsy.

Another point to consider is drugs crossing the blood-brain barrier. The first antitubercular drugs perhaps were not sufficient to control cerebral TB. On the other hand, the antiretrovirals prescribed (efavirenz, emtricitabine, tenofovir) showed good CSF penetration [9] and could explain the great brain inflammation and the paradoxical cerebral lesion enlargement.

After worsening, a prolonged steroid therapy was prescribed; the patient improved and is now in stable condition.

The case here reported showed neurological TB-IRIS. TB-IRIS is a severe complication during antiretroviral treatment, and it is a relevant problem especially in countries highly endemic for TB [4,5]; our patient came from Africa. Pepper *et al.* reported a large case series of neurological manifestations of paradoxical TB-IRIS in a prospective observational study in South Africa [5]. They reviewed 279 patients with suspected TB-IRIS; 19% of them had suspected neurological TB-IRIS, according to the consensus clinical case definition [4], and 23 patients (12%) had a diagnosis of neurological TB-IRIS (8 had meningitis, 7 tuberculoma, 5 both meningitis and tuberculoma, and 3 had a radiculomyelopathy). Most of those patients had a good prognosis, but the mortality rate

was considerable (13%). In their case series, 17 out of 23 HIV-infected patients without apparent neurological TB before antiretroviral therapy presented neurological TB-IRIS after HAART initiation [5], as occurred in our case. The case definition of TB-IRIS, besides a worsening of the signs and symptoms, included the exclusion of alternative explanations for clinical deterioration. In our case, brain biopsy provided a definite diagnosis. Marais *et al.* [8] described the neuroradiological features of the TB-IRIS patients previously reported. Sixteen patients were reviewed (CT in 13 patients and MRI in 3 patients). Of these patients, four had meningitis; five had intracranial space occupying lesions, mainly multiple and with perilesional edema; five had both meningitis and space occupying lesions; one had radiculomyelitis; and one had spondylitis [8]. A recent prospective observational cohort study by Asselman *et al.* [10] in South Africa found CNS tuberculosis in 36% of CNS diseases diagnosed during the first year of HAART; paradoxical neurological IRIS comprised 21% of the diagnoses. In 2012, Guevara-Silva *et al.* reported their experience at a Mexican neurological center, where they found that 9.3% of patients developed cerebral IRIS, two of whom had tuberculosis, and those patients showed a good prognosis [11]. A review of the CNS-IRIS from 2002 to 2007 was reported in that paper, including a case of TB previously reported separately. In 1998, Crump *et al.* reported a biopsy-proven tuberculoma during IRIS after HAART was initiated [12]. Later, other cases of paradoxical worsening of brain tuberculoma or tuberculous meningitis were reported [13-15].

The best management of paradoxical neurological TB-IRIS is not yet defined. In the case here described, corticosteroids were added to the specific therapy. The benefit of the use of prednisone for paradoxical TB-IRIS is evidenced in a randomized placebo-controlled trial [6], and in the case series described by Pepper *et al.* [5], in which 18 out of 19 (91%) patients with initial improvement received corticosteroids.

Conclusions

The case here reported describes an unusual MR imaging and unusual immune reconstitution features, and underlines the opportunity of brain screening in HIV patients and the need for neurosurgery in selected cases. The findings illustrate a severe emerging complication of antiretroviral therapy.

References

1. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK (2008) Central nervous system tuberculosis: pathogenesis and clinical aspects. *Clin Microbiol Rev* 21: 243-261.
2. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J (2009) British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 59: 167-187.
3. Antinori A, Ammassari A, De Luca A, Cingolani A, Murri R, Scoppettuolo G, Fortini M, Tartaglione T, Larocca LM, Zannoni G, Cattani P, Grillo R, Roselli R, Iacoangeli M, Scerrati M, Ortona L (1997) Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology* 48: 687-694.
4. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Wordria W, Elliott JH, Murdoch D, Wilkinson RJ, Seyler C, John L, van der Loeff MS, Reiss P, Lynen L, Janoff EN, Gilks C, Colebunders R; International Network for the Study of HIV-associated IRIS (2008) Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 8: 516-523.
5. Pepper DJ, Marais S, Maartens G, Rebe K, Morrioni C, Rangaka MX, Oni T, Wilkinson RJ, Meintjes G (2009) Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis* 48: e96-e107.
6. Meintjes G, Wilkinson RJ, Morrioni C, Pepper DJ, Rebe K, Rangaka MX, Oni T, Maartens G (2010) Randomized placebo-controlled trial of prednisone for paradoxical TB-associated immune reconstitution inflammatory syndrome. *AIDS* 24: 2381-2390.
7. Antinori A, Ammassari A, Luzzati R, Castagna A, Maserati R, Rizzardini G, Ridolfo A, Fasan M, Vaccher E, Landonio G, Scerrati M, Rocca A, Butti G, Nicolato A, Lazzarin A, Tirelli U (2000) Role of brain biopsy in the management of focal brain lesions in HIV-infected patients. Gruppo Italiano Cooperativo AIDS & Tumori. *Neurology* 54: 993-997.
8. Marais S, Scholtz P, Pepper DJ, Meintjes G, Wilkinson RJ, Candy S (2010) Neuroradiological features of the tuberculosis-associated immune reconstitution inflammatory syndrome. *Int J Tuberc Lung Dis* 14: 188-196.
9. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I, Ellis RJ; CHARTER Group (2008) Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol* 65: 65-70.
10. Asselman V, Thienemann F, Pepper DJ, Boule A, Wilkinson RJ, Meintjes G, Marais S (2010) Central nervous system disorders after starting antiretroviral therapy in South Africa. *AIDS* 24: 2871-2876.
11. Guevara-Silva EA, Ramirez-Crescencio MA, Soto-Hernandez JL, Cardenas G (2012) Central nervous system immune reconstitution inflammatory syndrome in AIDS: experience of a Mexican neurological centre. *Clin Neurol Neurosurg* 114: 852-861.
12. Crump JA, Tyrer MJ, Lloyd-Owen SJ, Han LY, Lipman MC, Johnson MA (1998) Miliary tuberculosis with paradoxical expansion of intracranial tuberculomas complicating human immunodeficiency virus infection in a patient receiving

- highly active antiretroviral therapy. *Clin Infect Dis* 26: 1008-1009.
13. Vidal JE, Cimerman S, Schiavon Nogueira R, Bonasser Filho F, Sztainbok J, da Silva PR, Lins DL, Coelho JF (2003) Paradoxical reaction during treatment of tuberculous brain abscess in a patient with AIDS. *Rev Inst Med Trop Sao Paulo* 45: 177-178.
 14. Lee CH, Lui CC, Liu JW (2007) Immune reconstitution syndrome in a patient with AIDS with paradoxically deteriorating brain tuberculoma. *AIDS Patient Care STDS* 21: 234-239.
 15. Dautremer J, Pacanowski J, Girard PM, Lalande V, Sivignon F, Meynard JL (2007) A new presentation of immune reconstitution inflammatory syndrome followed by a severe

paradoxical reaction in an HIV-1-infected patient with tuberculous meningitis. *AIDS* 21: 381-382.

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