

# Neurotuberculosis immune reconstitution inflammatory syndrome in the setting of HIV infection: A case report and review of literature

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## Abstract

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated immune response which can occur with various coinfections in human immunodeficiency virus (HIV) infected patients, of which the most commonly implicated in central nervous system (CNS)-IRIS are progressive multifocal leukoencephalopathy (PML), cryptococcosis, and tuberculosis (TB). TB-IRIS is a known complication of pulmonary TB or TB lymphadenitis coinfection in HIV infected patients who are on antituberculosis treatment (ATT) after the initiation of antiretroviral therapy (ART). However, development of IRIS in extrapulmonary TB such as CNS TB is very rare. Our case is that of an isolated CNS-TB-IRIS, presenting as increase in the size and perilesional edema of the ring enhancing lesions in the brain, which was observed in two sequential magnetic resonance imaging done over a period of 2 months in a retropositive patient who presented with clinical deterioration after commencement of ART. As prompt diagnosis was made and specific management aimed at IRIS was started without delay, the patient improved symptomatically.

**Key words:** Anti-retroviral therapy; Anti-tubercular treatment; CNS-TB-IRIS; human immunodeficiency virus; immune reconstitution inflammatory syndrome

## Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an intense inflammatory response to dead or latent organisms or to self-antigens due to exaggerated but dysregulated immune response in human immunodeficiency virus (HIV) infected individuals after initiation of antiretroviral therapy.<sup>[1]</sup> IRIS can occur with various coinfections in HIV patients. Central nervous system (CNS)-IRIS is commonly

reported in association with progressive multifocal leukoencephalopathy (PML), cryptococcosis, and rarely tuberculosis (TB).<sup>[2]</sup> Though TB IRIS occurs in 8–43% of HIV patients receiving antitubercular treatment (ATT) after antiretroviral treatment (ART) initiation, the reported incidence of CNS-TB-IRIS is only 0.9 to 1.5%.<sup>[3-5]</sup> Here, we report the case of an 18-year-old retropositive patient coinfecting with TB of CNS and put on ATT presenting with CNS-TB-IRIS after the commencement of ART.

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**Cite this article as:** Jaganmohan D, Chakkalakkoombil SV, Beena AA, Krishnan N. Neurotuberculosis immune reconstitution inflammatory syndrome in the setting of HIV infection: A case report and review of literature. Indian J Radiol Imaging 2016;26:446-50.

### Access this article online

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**Website:**  
www.ijri.org

**DOI:**  
10.4103/0971-3026.195782

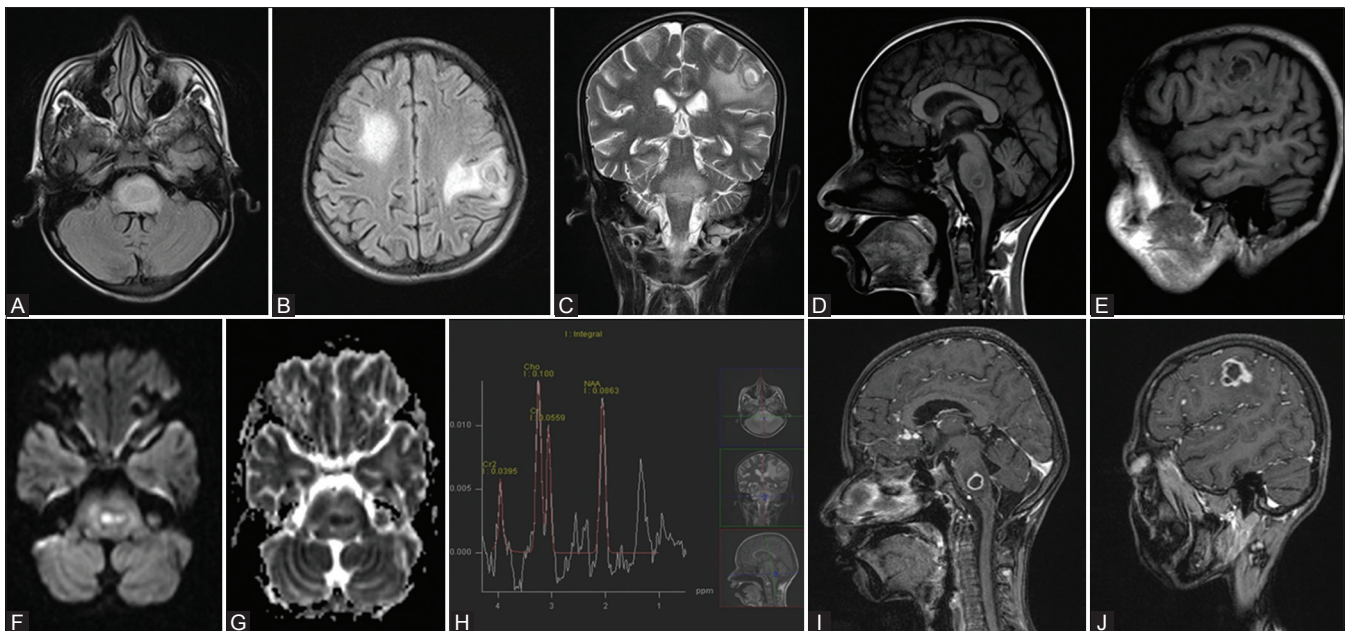
## Case History

An 18-year-old man, recently tested positive for HIV, presented with fever and altered sensorium of 5 days duration and 2 episodes of generalized tonic-clonic seizures (GTCS) with no focal neurological deficits. His CD4<sup>+</sup> count was 14 at the time of presentation. The patient was evaluated initially with contrast enhanced computed tomography (CT) of the brain, which showed multiple ring enhancing lesions with perilesional edema in the brainstem and left cerebral hemisphere. Subsequently, contrast enhanced magnetic resonance imaging (MRI) of the brain was performed for further characterization of the lesions [Figure 1A-J]. MRI showed multiple ring enhancing lesions in the gray-white matter junction in the cerebral hemispheres, brainstem, and cerebellum, as well as extra-axially in the left Sylvian fissure [Figure 1I and J]. The lesions were predominantly hypointense with a hyperintense rim in T1 weighted images [Figure 1D and E], hyperintense with a hypointense rim on T2 weighted images [Figure 1C], and showed restricted diffusion of the central area [Figure 1F and G]. A few of the lesions were conglomerated and showed nodular enhancement. The lesions showed perilesional hyperintensities in T2 weighted and fluid-attenuated inversion recovery images and hypointensities in T1 weighted images consistent with perilesional edema. There was associated leptomeningeal enhancement adjacent to the lesions. MR spectroscopy showed a prominent lipid-lactate peak, reduced N acetyl aspartate (NAA), mild choline elevation, and increased choline/creatinine ratio in

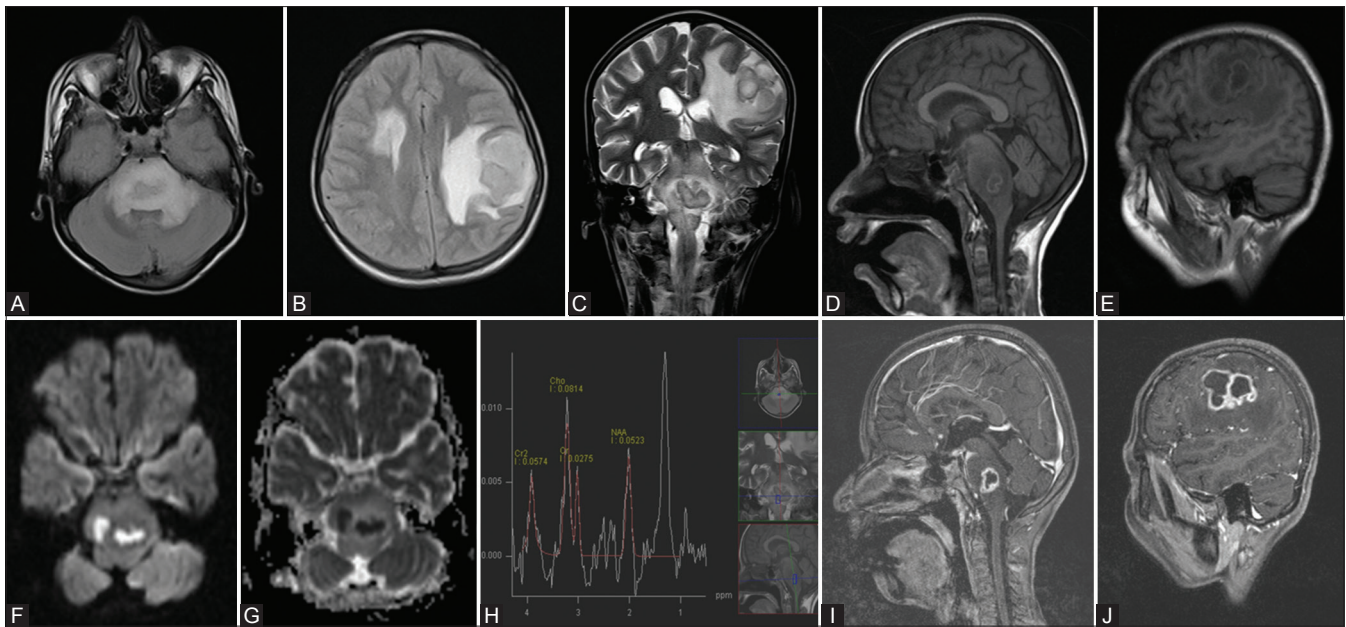
the central part of a few lesions [Figure 1H]. Cerebrospinal fluid (CSF) analysis was done which showed lymphocytic predominance and elevated proteins. CSF adenosine deaminase (ADA) level was significantly elevated (58 IU/L). Sputum was negative for acid fast bacilli (AFB).

The following entities were considered as the possible differentials for multiple ring enhancing lesions in brain in the background of HIV infection: Tuberculous abscess, toxoplasmosis, primary CNS lymphoma, and fungal abscesses. However, the typical conglomerated appearance, ring as well as solid enhancement, extra-axial lesions, and leptomeningeal enhancement correlated with the CSF analysis report favoring the diagnosis of tubercular meningitis with tuberculomata. Based on this, the patient was treated as a case of HIV-TB coinfection. The patient was put on category I ATT, and at discharge after 2 weeks, was complemented with antiretroviral drugs.

Two months later, the patient presented with acute onset altered sensorium, seizures, bilateral 3<sup>rd</sup> and 6<sup>th</sup> cranial nerve palsies, respiratory difficulty, and aspiration pneumonia. On fundus examination, there was established papilledema. There was no significant cervical lymphadenopathy. A repeat MRI was done in view of worsening symptoms which showed increase in the size of some of the lesions, especially the one in the left parietal lobe and there was increase in the perilesional edema [Figure 2A-J]. However, there was an overall reduction in the number of lesions, more so of the smaller lesions with solid enhancement.



**Figure 1 (A-J):** Pretreatment magnetic resonance imaging. Fluid-attenuated inversion recovery images show hyperintensity in pons (A), right frontal and left frontoparietal lobes (B). T2 weighted image shows hyperintense lesions with perilesional edema in pons and left frontal lobe (C). T1 weighted images show lesions in pons (D) and left frontal lobe (E). Diffusion weighted image (F) and apparent diffusion coefficient mapping (G) show restricted diffusion in pontine lesion. Magnetic resonance spectroscopy within pontine lesion shows elevated choline, reduced N acetyl aspartate, and lipid-lactate peak (H). Postcontrast T1 weighted images show rim enhancing lesion in pons (I) and left frontal lobe (J)



**Figure 2 (A-J):** (A-J) Magnetic resonance images taken 2 months after the initiation of ATT and ART, at same levels, and of same sequences as the pretreatment images shown in Figure 1 reveal marked increase in the size of the lesions and perilesional edema compared to the pretreatment images

MR spectroscopy showed similar findings as before. In view of the increase in the size of the lesions and clinical deterioration while on ATT, an alternative diagnosis was sought. The CD4<sup>+</sup> count at current admission was 53, which was higher compared to the pretreatment count of 14. HIV-RNA titres also showed a decreased viral load compared to pre-ART. Hence, a clinicoradiological diagnosis of IRIS was made. Patient clinically improved with steroids and was continued on ART and ATT.

## Discussion

Paradoxical deterioration can occur in an immunocompetent patient with TB on starting ATT as either an increase in the size or the number of lesions. This phenomenon has been termed as "paradoxical reaction."<sup>[6]</sup> IRIS is a T-cell-mediated reaction that occurs in the setting of treated HIV or multiple sclerosis when restored immunity causes an exaggerated immune response to infectious or noninfectious antigens. It is of two types, namely, unmasking IRIS and paradoxical IRIS.<sup>[2]</sup> Unmasking IRIS occurs when ART reveals a subclinical, previously undiagnosed opportunistic infection. Paradoxical IRIS occurs when a patient who has been successfully treated for a recent opportunistic infection unexpectedly deteriorates after initiation of ART. As per Colebunders *et al.*,<sup>[7]</sup> for the diagnosis of TB-associated IRIS, the following three criteria should be met:

- Radiological examinations showing worsening or emergence of pulmonary infiltrates intrathoracic lymphadenopathy, pleural effusions, abdominal lymph nodes, hepatosplenomegaly
- A good virological response and/or increase in

CD4<sup>+</sup> lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment

- Exclusion of other conditions that could explain the patient's clinical manifestations, such as ATT failure, or other concomitant infections, tumors, or allergic reactions.

The consensus definition for paradoxical TB-IRIS is summarized by a confirmed diagnosis of TB with a positive initial response to antimycobacterial therapy, onset of defined inflammatory clinical manifestations within 3 months of subsequently commencing highly active anti-retroviral therapy (HAART), with exclusion of plausible alternative explanations for this clinical deterioration.<sup>[8]</sup> Low CD4<sup>+</sup> cell count on ART initiation and short time interval between starting TB therapy and ART were the best predictors of paradoxical TB-associated IRIS.<sup>[3,9]</sup> This is because the bacterial/antigen load is significantly higher in the initial phase of ATT, which triggers the inflammatory response. The consensus definition for the diagnosis of unmasking TB-IRIS is based on heightened clinical inflammatory manifestations in a primary presentation of TB occurring within 3 months of commencing HAART.<sup>[8]</sup> Our case is a paradoxical type of TB-IRIS because the patient was already diagnosed with CNS tuberculosis, was on ATT, and his symptoms worsened within 2 months of starting ART.

The common antigens associated with IRIS are John Cunningham (JC) virus (PML-IRIS), fungal infections, especially *Cryptococcus* (crypto-IRIS), TB (TB-IRIS), with

PML-IRIS being the most common.<sup>[10]</sup> Rarely, Varicella zoster virus (VZV) IRIS, *Candida* IRIS have also been reported in literature.<sup>[11]</sup> Various studies have concluded that a CD4+ count of <50, high pretreatment viral load, and starting ART before control of the opportunistic infection are the predisposing factors for the development of IRIS.<sup>[12,13]</sup> Imaging features of CNS-IRIS varies with the provoking pathogen. CNS-TB-IRIS presents with increasing number and/or size of the parenchymal enhancing lesions and greater enhancement in T1-weighted images post-gadolinium administration.<sup>[2]</sup> The typical imaging findings in HIV-associated CNS TB may differ slightly from those in immunocompetent patients. The common imaging findings are that of meningitis, multiple parenchymal granulomas, and abscesses.

Tuberculosis is one of the most common coinfection in immunocompromised patients afflicted with HIV acquired immunodeficiency syndrome. TB-IRIS occurs in 15% of patients who are coinfecting with TB if ART is initiated before TB is adequately treated. Navas E *et al.*<sup>[14]</sup> suggested that IRIS occurred in patients on ART within 2 months of TB therapy initiation. IRIS is commonly encountered in TB patients with pulmonary involvement and cervical lymphadenitis. The development of IRIS in extrapulmonary TB, such as CNS TB rarely occurs. In a retrospective study by Pepper *et al.*,<sup>[15]</sup> neuro TB-IRIS was reported in 12% of 190 cases of proven paradoxical TB IRIS (patients in whom ATT preceded ART). Meningitis and tuberculomas were the most common presentations in neuro TB-IRIS similar to our case.

Similarly, in a study conducted by Marais *et al.*,<sup>[16]</sup> 47% of TB meningitis patients developed TB meningitis-IRIS. The combination of high CSF tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and low interferon (IFN)- $\gamma$  in TB meningitis was found to be a good predictor of development of TB-IRIS.<sup>[17]</sup> However, the availability of CSF analysis for the levels of TNF- $\alpha$  and interferon (IFN)- $\gamma$  are limited in resource-poor settings, and hence, IRIS should be suspected when clinical and imaging deterioration occurs despite an increasing CD4+ T-lymphocyte count and decreasing plasma viral loads of HIV. In a retrospective study conducted by Rajeswaran G *et al.*,<sup>[18]</sup> among 11 patients who developed TB-IRIS, the cases presented as worsening or new lesions in the form of cervical, mediastinal, or intraabdominal lymphadenopathy, pulmonary nodules, and abscesses. None of the cases had worsening of CNS lesions. Treatment of TB-IRIS depends on the severity of the clinical manifestations. Various studies have shown symptomatic improvement with steroids and non-steroidal anti-inflammatory drugs.<sup>[19,20]</sup>

Hence, symptomatic worsening corroborated with accentuation of imaging findings (such as increased edema, enhancement, and increased size and number

of lesions in the brain) in a retropositive patient with opportunistic infection on ART and on specific therapy for the opportunistic infection may lead the clinician and radiologist to seek an alternative imaging diagnosis quite often. However, there is a need to be aware of the clinical entity IRIS and the radiologist can alert the treating physician of this possibility, even though it is a diagnosis of exclusion supported by the laboratory data of increase in CD4+ cell count and reduction in the viral load compared to pretreatment values. All enlarging lesions are not due to nonresponse to therapy and immune mechanisms may lead to such atypical presentations.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

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