Immune reconstitution inflammatory syndrome in central nervous system tuberculosis

Sindromul de reconstructie imună inflamatorie în tuberculoza sistemului nervos central

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Abstract

Background. *Immune reconstitution inflammatory syndrome (IRIS) related to tuberculosis (TB) is an exacerbation of an inflammatory response that most often occurs in HIV-infected patients but it has also been observed in non-HIV immunocompromised hosts. We describe two cases of TB associated IRIS with CNS involvement, one in a patient diagnosed with HIV infection and the other in a patient with immunosuppression due to anti tumor necrosis factor treatment.*

Case report. *The first case was a 40-year-old man, newly diagnosed with HIV infection, who developed right hemiplegia and expressive aphasia. Lumbar puncture and MRI sustained the diagnosis of TB meningoencephalitis. He initially improved under standard antituberculous therapy (ATT). After 6 weeks of ATT antiretroviral treatment (ART) was initiated and one week later the patient experienced worsening of his symptoms (left hemiparesis and mixed aphasia), of CSF and MRI changes. He improved after he was starting on corticosteroids in tapering doses, with clinical deterioration at lower doses over a 5-month period. The second case was a 56-year-old male, treated for 3 years with Infliximab for ankylosing spondylitis. He was diagnosed with disseminated TB (CNS tuberculomas and pulmonary TB), histological and bacteriological confirmed the diagnosis. His neurological symptoms improved after starting ATT, but after 2 weeks of therapy he presented with diplopia and generalized tonic-clonic seizures. These symptoms improved only after corticosteroids were added (tapering doses during the next 6 months).*

Conclusion. *TB-associated IRIS with CNS involvement is potentially life threatening. Corticosteroids should be used to control the IRIS symptoms in those patients. The dosing and duration should be tailored to each patient.*

Keywords: *tuberculosis, immune reconstruction, corticosteroid treatment*

Rezumat

Introducere: *Sindromul de reconstrucție imună inflamatorie (IRIS) corelat cu tuberculoza (TB) reprezintă o exacerbare a răspunsului inflamator ce apare frecvent în pacienții HIV pozitivi, dar a fost raportat și la pacienții imunocompromiși de alte cauze.*

Caz clinic. *Prezentăm 2 cazuri de TB asociate cu IRIS cu afectarea sistemului nervos central. Primul caz este un pacient infectat HIV, iar al doilea caz un pacient imunocompromis secundar tratamentului cu anti factor de necroză tumorală. Primul caz este un bărbat de 40 de ani, recent diagnosticat cu HIV ce a prezentat hemiplegie dreaptă și afazie expresivă. Puncția lombară și RMN-ul au susținut diagnosticul de meningoencefalită TB. Pacientul a prezentat o ameliorare inițială sub tratament antituberculos. După 6 săptămâni a fost inițiat și tratamentul antiretroviral. La 7 săptămâni de la diagnostic pacientul prezintă agravarea simptomelor, motiv pentru care se inițiază corticoterapia orală. Evoluția clinică a fost favorabilă, cu scăderea progresivă a dozelor pe o perioadă de 5 luni. Al doilea caz este un pacient de 56 de ani, tratat de 3 ani cu Infliximab pentru spondilită anchilopoietică. A fost diagnosticat cu TB diseminat confirmat bacteriologic și histopatologic (la nivel pulmonar și al sistemului nervos central). După inițierea tratamentului antituberculos pacientul a prezentat diplopie și crize tonico-clonice generalizate. Se inițiază corticoterapia cu ameliorarea simptomelor.*

Concluzii: *TB asociată IRIS cu afectarea sistemului nervos central este o patologie gravă. Corticoterapia este utilă în controlul IRIS la acești pacienți. Dozele și durata tratamentului trebuie adaptate funcție de caz.*

Cuvinte-cheie: *tuberculoză, reconstrucție imună, corticoterapie*

Introduction

Tuberculosis (TB) - associated immune reconstitution inflammatory syndrome (IRIS) continues to be a poorly understood entity and also a clinical challenge for care providers. IRIS refers to an exacerbation of inflammatory response in HIV-infected patients, after starting antiretroviral therapy. All over the world, TB-IRIS is an important complication of antiretroviral therapy (ART) in patients with HIV infection. In addition to HIV-infected patients, IRIS has also been observed in non-HIV immunocompromised hosts, like transplant recipients, women during the postpartum period, neutropenic patients, and tumor necrosis factor (TNF) antagonist recipients. There are no specific diagnostic tests for IRIS, and confirmation of the disease relies on case definition based on clinical and laboratory data.

Studies performed in Europe and in the USA reported an incidence of TB-associated IRIS varying between 11% and 45% in HIV-infected patients. Paradoxical worsening of TB after initiation of antituberculous treatment (ATT) has been reported in 2–23% of treated TB patients without HIV infection[1].

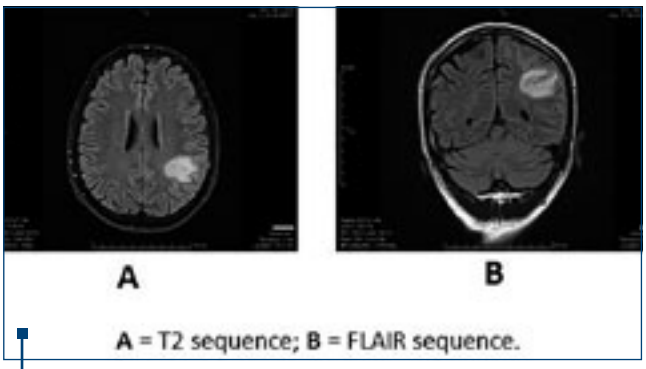

Figure 1. *MRI of the brain revealing hyperintense T2 and FLAIR left subcortical temporal and parietal inhomogeneous areas with unrestricted diffusion*

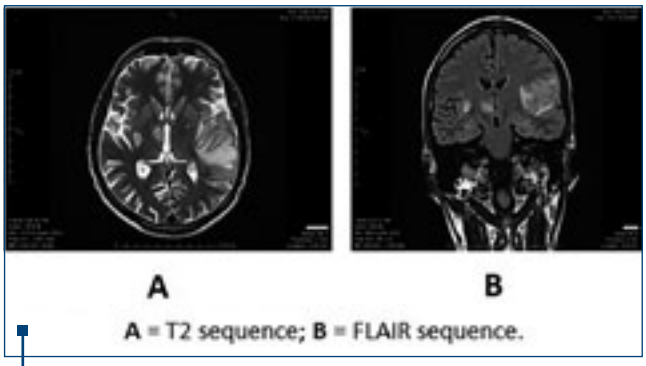

Figure 2. *MRI revealing hyperintense T2 and FLAIR left subcortical temporal and frontoparietal inhomogeneous areas, with adjacent pachymeningitis, and infracentrimetric abscess in the right lentiform nucleus*

TB-associated IRIS with central nervous system (CNS) involvement manifests with more severe symptoms and with potential life threatening complications. Thus the addition of corticosteroids is required, although there are not clearly defined criteria for initiating corticosteroids.

Case 1

We report a case of a 40-year-old man, diagnosed in August 2013 with HIV infection with a CD4 cell count of 271 cells/mm3 and a viral load of 270.316 copies/ml. The patient had no history suggestive for previous/actual tuberculosis and no contact with active tuberculosis. In December 2013 he developed right haemiplegia and expressive aphasia and was admitted to our unit. Magnetic resonance imaging (MRI) of the brain revealed hyperintense T2 and FLAIR left subcortical temporal and parietal inhomogeneous areas of 35/28mm, respectively 12/8 mm, with unrestricted diffusion (Figure 1). Cerebrospinal fluid (CSF) analysis showed 210 elements, lymphocytic predominance, with a high level of protein (210 mg/dl) and a low level of glucose (26 mg/dl); Gram and Ziehl–Neelsen staining were negative, as were tests for usual bacteria, syphilis and cryptococcosis. His CD4 cell count was 200 cells/mm3. The chest X-ray was normal. Since the CSF was suggestive for tuberculous meningitis, standard ATT, with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol (HRZE) was initiated, along with intravenous steroids (Dexamethasone 24 mg/day) and the patient was discharged after ten days, with an improved neurological status. He continued to receive Methylprednisolone in doses of 48mg/day, decreasing 16mg every three days. After four weeks, CSF culture yielded a *Mycobacterium tuberculosis* isolate susceptible to all antituberculous agents.

In February 2014, seven days after ART initiation with Lamivudine, Abacavir and Efavirenz, the patient was readmitted with intense headache, left haemiparesis and mixed aphasia. A lumbar puncture was performed that showed 750 nucleated cells with polymorphonuclear predominance, a high level of protein (310 mg/dl) and a low level of glucose (31mg/dl). The patient was started on Ampicilin 3g/6h and Ceftriaxone 2g/12h, but there was no evidence of *Listeria monocytogenes* or usual bacterial pathogens in the CSF cultures and this treatment was stopped. MRI revealed hyperintense T2 and FLAIR left subcortical temporal and frontoparietal inhomogeneous areas, with adjacent pachymeningitis, and infracentrimetric abscess in the right lentiform nucleus (Figure 2). The patient continued ATT and ART, along with intravenous steroids (Dexamethasone 24 mg/day), and was discharged after 14 days, with tapering doses of corticosteroids. HRZE was continued for two months, followed by Isoniazid and Rifampin.

In March 2014, ten days after discharge, the patient was readmitted with recurrence of the left haemiparesis and worsening aphasia. The worsening symptoms occurred when reducing the steroid dose to 8 mg of Methylprednisolone. CSF analysis revealed 34 nucleated cells, protein level of 70 mg/dl and a low level of glucose (44 mg/dl). The patient was maintained on ATT (with Isoniazid and Rifampicin), ART and the steroid dose was increased (Dexamethasone 16 mg/day), with gradual improvement. The patient was discharged on a slow steroid taper (5 mg of Prednisone every three days).

In July 2014, at the six month evaluation, the patient was presenting a low degree of dysarthria, without haemiparesis. The follow-up lumbar puncture showed 21 nucleated cells, a protein level of 80 mg/dl and a glucose level of 48 mg/dl. His CD4 count was 177 cells/mm^3 and his viral load was 125 copies/ml.

The ATT was maintained for a total duration of 12 months and corticosteroids for 6 months. At one year follow-up all signs and symptoms of CNS-TB resolved.

Case 2

We report the case of a 56-year-old male, HIV negative, with a history of HLA-B27 positive Ankylosing spondylitis, treated between 2010 to 2013 with Infliximab, who in November 2013 developed diplopia, vertigo and intermittent fever.

The MRI scan performed in December 2013, on admission to our unit, showed multiple intraaxial nodes, the majority of which supratentorial, predominantly located in the cortico-subcortical region, with a maximum diameter of 3-10mm (the largest one located in the pontine area, adjacent to the fourth ventricle); the nodes were hypointense in T2 and hypointense overall in T1, with a discrete mass border-

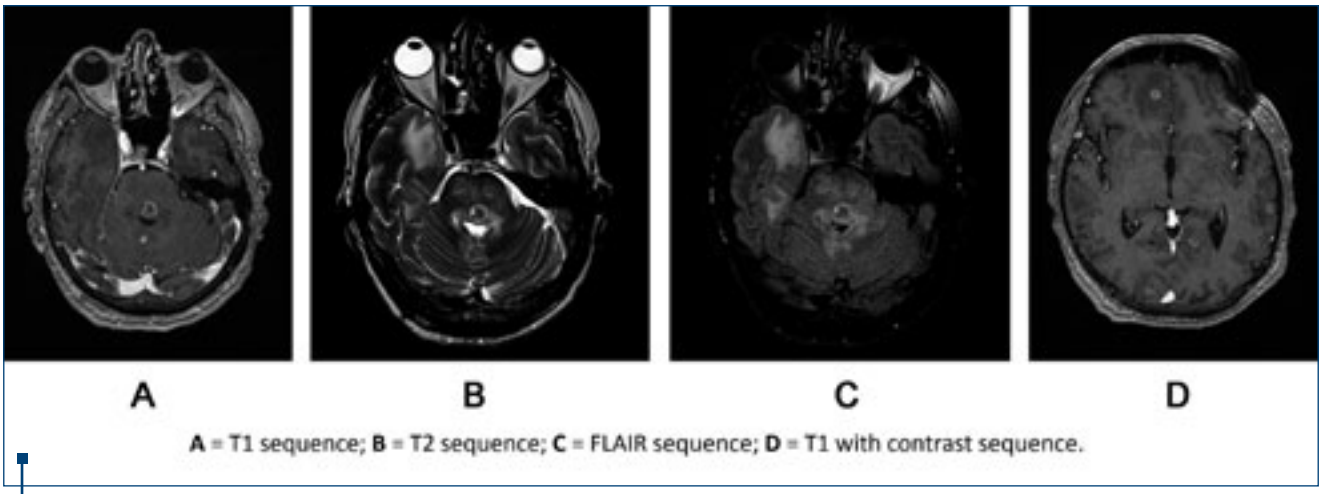

Figure 3. *Multiple intraaxial nodes, the majority of which supratentorial, predominantly located in the cortico-subcortical region*

line T1 hyperintensity, with no restricted diffusion; some lesions had perilesional edema, with the majority having peripheral contrast enhancement, giving an annular appearance (Figure 3). The CSF analysis was normal, with a PCR assay negative for *M. tuberculosis* and positive for *Toxocara canis*. The blood anti-*Toxocara canis* IgG antibodies were also positive. The chest X-ray at the admission was normal. The patient was started on Albendazole and corticotherapy for two months (Dexamethasone 16mg/day, followed by an 80mg dose of Methylprednisolone, gradually tapered thereafter), with improvement of his symptoms.

In February 2014, one week after stopping Albendazole while the patient was on Methylprednisolone (4mg/day), he developed fever, chills, productive cough and four days later diplopia reappeared. The chest X-ray was highly suggestive for miliary TB and from sputum we obtained positive PCR assays and cultures for *M. tuberculosis* susceptible to Rifampin and Isoniazid. The patient was diagnosed with miliary tuberculosis and was started on HRZE therapy, with cessation of corticotherapy and due to diplopia reappearance Albendazol was restarted. Ten days later the patient developed hepatic toxicity related to Pyrazinamide administration, leading to its replacement with Streptomycin (S) and addition of Moxifloxacin, to increase ATT CNS penetrability.

Despite correct ATT and antihelmintic therapy the patient had persistent fever and worsening of the neurological symptoms: persistent diplopia, divergent strabismus, vertigo and generalized tonic-clonic seizures. A new MRI examination showed the same intracerebral masses with increased perilesional edema. Levetiracetam was added to the therapy and a brain biopsy was performed in April 2014. After the biopsy we added Dexamethasone 16mg/day with resolution of the fever and neurological improvement. The cerebral biopsy revealed epithelioid and giant cell granuloma formation and a histological PCR assay positive for *M. tuberculosis*.

The patient received daily HRES plus Moxifloxacin for three months, followed by HRE plus Moxifloxacin for another three months, and then another six months of HR, to be continued until full recovery. Corticotherapy was continued, with gradually decreasing doses up to a total of six months, with no recurrence of neurological symptoms. The MRI scan performed after ten months of therapy showed lowering numbers of intraaxial nodes, the majority of which were supratentorial, predominantly in the cortico-subcortical region - masses already described in the previous examination; no new lesions and resolving cerebral edema. The following masses could be identified: left paramedian medullary mass (3mm), medial posterior pontine mass (11/9mm), left occipital mass (6mm), right occipital mass (5mm), right parietal mass (4mm), left parietal mass (6mm). (Figure 4)

At one year follow-up the patient was feeling well, with no signs and symptoms of CNS-TB and Infliximab therapy was not restarted.

Discussion

Mycobacterium tuberculosis is among the most frequently reported pathogens associated with IRIS[2]. IRIS is most commonly associated with pulmonary TB followed by tuberculous lymphadenitis and central nervous system manifestations[1,3].

The use of consensus case-definition is helpful in establishing the diagnosis of TB-associated IRIS, allowing a better prevention and management strategies. A case definition for IRIS was published by French and collaborators in 2004. This definition proposed major criteria, including a 1 log HIV-RNA copy decrease and atypical presentation of opportunistic infections or tumors in patients responding to ART. The minor criteria proposed refer to an increased CD4 count after ART initiation, increased specific immune response to relevant pathogens and spontaneous resolution of disease without antimicrobials or chemotherapy with continuation of ART[4]. In 2006, other researchers proposed case definitions also including clinical, immunological, virological and radiological parameters[5,6]. Also, Robertson et al proposed a score based on the use of protease inhibitors, in addition to clinico-biological data[7]. However, clinical management and research on IRIS were impeded by the lack of a consensus case definition. To provide a consensus IRIS case

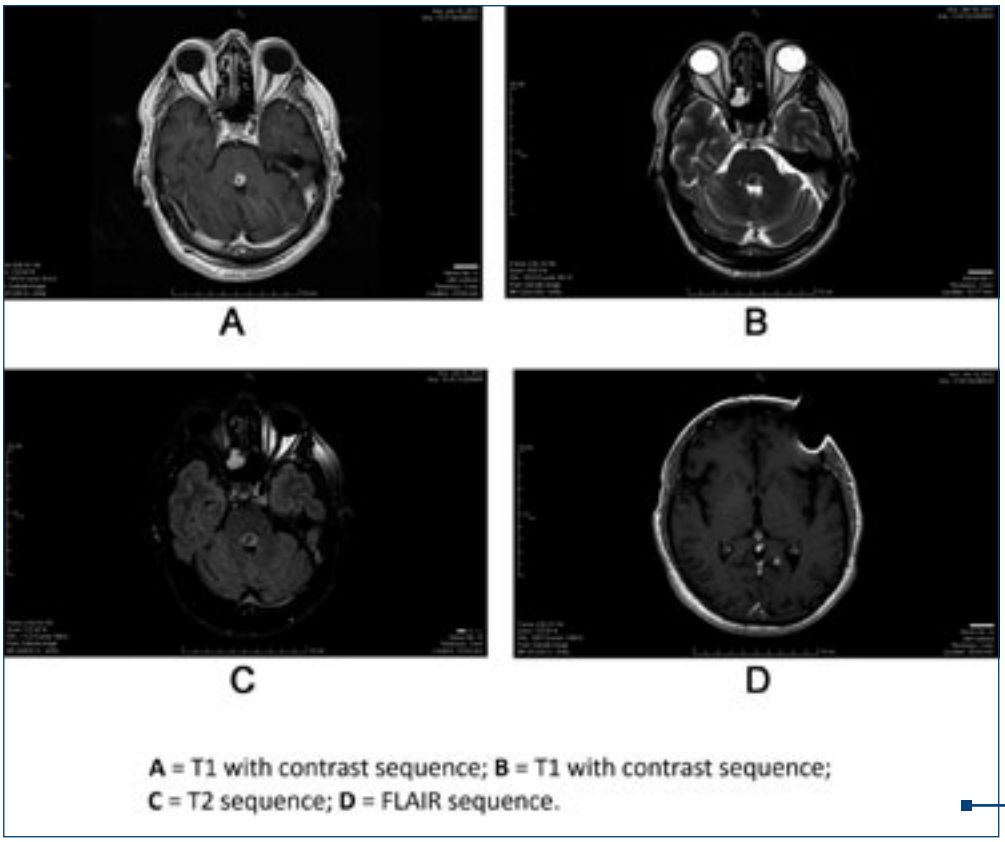

Figure 4. *Masses identified on MRI: left paramedian medullary, medial posterior pontine, left occipital, right occipital, right parietal left parietal*

definition suitable for high-income and low-resource countries, the International Network for the Study of HIV-associated IRIS (INSHI) invited around 100 researchers from 16 countries to Kampala, Uganda, in November 2006[8]. In 2008, INSHI published criteria for two different types of IRIS: "paradoxical" TB-IRIS and "unmasking" TB-IRIS diagnosis. Paradoxical deterioration or recurrence of symptoms in patients previously diagnosed with opportunistic infection and on antimicrobial treatment prior to starting ART is defined as *paradoxical IRIS*. In order to sustain the diagnosis of paradoxical IRIS, other worsening conditions should be excluded (bacterial or fungal infections, lymphoma, Kaposi sarcoma, anti-tuberculous drug resistance or poor adherence to treatment). If the opportunistic infection was unknown at the start of ART because the patient was either asymptomatic or minimally symptomatic but manifests in the first three months after therapy initiation, the IRIS response is described as *unmasking*[9].

Our first patient fulfilled the INSHI criteria for a ,,paradoxical" TB-IRIS since the diagnosis of TB, based on a positive CSF culture for *Mycobacterium tuberculosis,* was made before the initiation of ART. The CNS symptoms of IRIS occurred within 1 week of initiation of ART, the patient being already on ATT. The worsening of CNS symptoms and the extension of lesions on the second MRI are strongly suggestive of IRIS in a patient started on ART, in which other conditions associated with worsening of the neurological symptoms were excluded: resistant *M. tuberculosis,* poor adherence to ATT and presence of another opportunistic infection or neoplasm[10].

The correct diagnosis of active TB before ART initiation should represent a priority. In our patient, TB meningitis was strongly suggested by laboratory characteristics of CSF (210 elements, lymphocytic predominance, with a high level of protein (2,1g/l) and a low level of glucose (26mg/dl) and negative test for Cryptococcus spp. The diagnosis was subsequently microbiologically confirmed. ART in our patient was started after six weeks from the initiation of ATT. A short time interval between initiation of ATT and starting ART is the most frequent risk factor for TB-IRIS development mentioned by the majority of studies together with a low baseline CD4 T-cell count and a high viral load[11]. In some studies, lower levels of hemoglobin were associated with an increased risk of IRIS[7,12]. Also, higher plasma levels of IL-6 and CRP prior to ART initiation could be used to identify patients that would develop IRIS[12,13].

The second case met the criteria for TB associated IRIS (,,paradoxical reaction") in a non-HIV immunocompromised host treated with Infliximab. He experienced a clinical deterioration during correct ATT, after initial improving of simptomatology, which is known as a "paradoxical reaction". Infliximab, a TNF-α antagonist, binds TNF-α and impedes phagocytosis of mycobacteria by the macrophages, which supports dissemination of the infection.

This case also ilustrates the diagnostic difficulties in patients with cerebral tuberculoma. The initial diagnosis of neurotoxocariasis was based on the positive IgG antibodies in peripheral blood and the positive PCR for

toxocara canis in the CSF, in a patient with multiple cerebral masses, owner of several dogs. Nevertheless we could not determine specific IgG antibodies in the CSF and a direct examination of the CSF for larva detection was not available to support our diagnosis. In addition, there are studies evaluating the role of PCR techniques for the diagnosis of toxocariasis showing some benefit only when these methods were used on histological samples, ocular fluids and broncho-alveolar lavage. However molecular diagnosis of neurotoxocariasis is not used in daily clinical practice[14-16]. Retrospectively, we consider that the cerebral masses were cerebral tuberculomas and in this case molecular methods only delayed correct diagnostic and treatment.

To date, the incidence of TB-associated IRIS in patients receiving TNF-α antagonist is not known. In one study including 284 patients treated with Infliximab, active TB occurred after a median duration of 3.5 months of Infliximab use and 67% of the patients with active tuberculosis developed a paradoxical response to ATT[17]. Our patient received Infliximab for a time span of three years before starting to have symptoms of TB.

Paradoxical reaction among patients who have been treated with Infliximab and who develop active TB infection is not well described in studies[17].

Corticosteroids are commonly used in addition to antituberculous drugs for the treatment of TB meningitis. Cochrane review showed that the use of corticosteroids reduces the risk of death and is associated with a lower rate of residual neurological deficit[18].

Treatment for mycobacterial-associated IRIS depends on the presentation and disease severity. The management of mild IRIS presentation is based on nonsteroidal anti-inflammatory agents and continuation of ART in HIV positive patients. TB-IRIS associated neurological complications are defined as a severe form of IRIS, which may threaten the patient's functional status or may cause permanent disability and corticosteroid therapy should be considered in order to suppress inflammatory response[19]. Our HIV-infected patient's neurological symptoms improved with continuation of ART in association with corticosteroids. In both patients steroid treatment was difficult to taper because the patients experienced worsening of neurological symptoms at lower doses of corticosteroids. The first patient received corticosteroid therapy for a total of five months and the second one for six months.

In studies where therapy for IRIS was mentioned, the use of corticosteroids was variable. Some of them recommend 1-2 mg/kg prednisone, or the equivalent, for 1-2 weeks, then taper. ATT should be continued unless there is a reason to suspect that the current regimen is inadequate. HIV positive patients with TB-IRIS should remain on ART. Temporary interruption of ART should be considered in the presence of life-threatening central nervous system complications of IRIS[2,19,20].

Conclusions

TB-associated IRIS known as "paradoxical reaction" occurs under ATT, regardless of the nature of the immunosuppression. TB-associated IRIS with CNS involvement (either meningo-encephalitis or multiple tuberculomas) is potentially life threatening. Although the role of corticosteroids is controversial in the management of TB-associated IRIS and there are not any clearly defined criteria for initiating corticosteroids, they should be used in all patients presenting with neurological symptoms. The dosing and duration of corticosteroids should be tailored to the clinical circumstances of each patient. ■

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