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Rapid development of unmasking disseminated tuberculosis-related immune reconstitution inflammatory syndrome in a young HIV-infected patient after starting combination antiretroviral therapy

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ABSTRACT: Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical worsening of a known condition, or the appearance of a new one, after initiating combination antiretroviral treatment (cART) in HIV-infected patients. A young Moroccan man was referred to our hospital after newly diagnosed HIV infection. After ruling out any active opportunistic infection, cART was started, but two weeks later the patient developed high fever unresponsive to medication. With clinical, imaging and laboratory tests, we noticed a rapid dissemination of tuberculosis (TB) with multiple organ involvement. These features were compatible with unmasking TB-IRIS. During hospitalization the patient received the TB treatment with poor improvement.

Keywords: Tuberculosis, Immune reconstitution inflammatory syndrome, HIV, Antiretroviral therapy, Mycobacterium tuberculosis.

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical worsening of a known condition, or the appearance of a new one, after initiating combination Anti-Retroviral Treatment (cART) in HIV patients. There are two recognized forms of tuberculosis: the first one, called *paradoxical*, is defined by recurrent or new tuberculosis (TB) symptoms developing after cART initiation in patients who are receiving anti-TB treatment. The second one is called *unmasking* TB-IRIS, and is diagnosed when any sign of active TB appears within the first 2-8 weeks after start of cART in patients who are not receiving anti-TB treatment before the start of an antiretroviral therapy. In Europe and the United States, the reported incidence of TB-IRIS went from 11% to 45% from 1995 to 2005. There is no diagnostic test for IRIS, and its diagnosis relies on clinical, laboratory, and imaging data together with the clinicians' expertise[1-5].

CASE REPORT

We report the case of a man referred to the Infectious Disease Department of "Santissima Trinità Hospital" of Cagliari (Italy) in March 2016.

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RESULTS

A 39 years old Moroccan man was admitted in a peripheral hospital of Sardinia (Italy) with a diagnosis of community acquired pneumonia (CAP). He was treated with an intravenous (IV) 10 days ceftriaxone course (2 g once-daily) together with 6 days of orally azithromycin (500 mg once-daily). Due to poor improvement and persistent leukopenia (WBC 3500 cells/mmc), a HIV test was performed, resulting positive. The patient was then referred to the Infectious Disease Department at "Santissima Trinità Hospital" of Cagliari, for specialist management.

At the admission the patient's conditions were stable. There was no cough or fever, and the chest X-Ray only showed a small left posterior basal thickening. White blood cell count (WBC) showed leukopenia with a low absolute lymphocyte cell count (800 cells/mm). CD4+ T-cell count was 51 cells/μL (7.33%) and HIV-RNA was 144,599 cps/mL. We performed a lumbar puncture that revealed normal glycorrhachia, normal protidorrachia and a normal white cell count in the cerebrospinal fluid (CSF), negative cryptococcal antigen (CrAg) and a HIV-RNA of 34,583 cps/ml. CrAg was also negative in the serum.

Since the patient's clinical conditions were stable and there was no evidence of any active opportunistic infection, we decided to start cART with tenofovir/emtricitabine (TDF/FTC) and boosted darunavir (DRV/r), for its high barrier to resistance.

Two weeks after the beginning of the treatment, the patient developed high fever unresponsive to paracetamol and other non-steroid anti-inflammatory drugs (NSAIDs), so we decided to start an IV steroid (methylprednisolone 20 mg once-daily). Suspecting a pneumonia recrudescence, we performed a chest computed tomography (CT) scan, which showed swelling with center colliquation of the lymph nodes localized in the left lung ilum, mediastinum and para-tracheal area (Figure 1).

The Interferon-Gamma Release Assays (IGRA) test (Quantiferon-TB) resulted positive, so we sent three samples of sputum smear for alcohol-acid fast bacilli (AAFB) identification to the microbiologist.

As soon as the microbiology laboratory reported the positivity of the smear to the Ziehl-Neelsen coloration and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* complex, we started anti-tubercular therapy with once-daily rifampin 600 mg, once-daily isoniazid 300 mg, pyrazinamide 500 mg every 8 hours, ethambutol 400 mg every 8 hours. At the same time, DRV/r was switched to double dose (800 mg every 12 hours) raltegravir (RAL), to avoid drug interactions with rifampin.

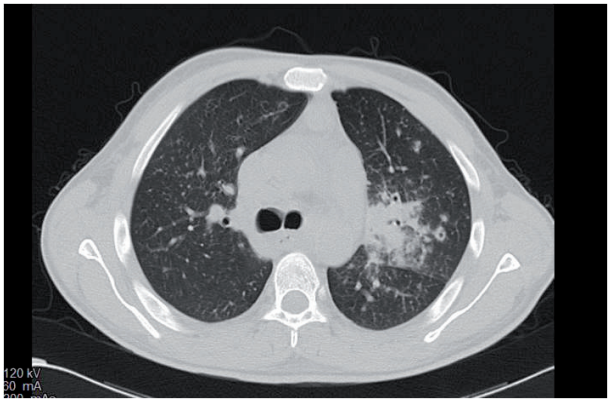

Figure 1. Computed tomography (CT) scan of the chest showing left lung ilum colliquation and thickening.

Diagnostic staging was completed with a contrast-enhanced total body CT scan, resulting suggestive for disseminated TB. Multiple diffuse lymphnode enlargement and multiple spleen hypodensities were highlighted (Figure 2).

As the patient's conditions did not improve, with a persistent high-body temperature, steroid dosage was increased, still with poor symptoms control.

The isolated *Mycobacterium tuberculosis* was sensitive to first-line anti-TB drugs, and the antimicrobial treatment was continued.

A contrast-enhanced Total-body CT scan, performed after a month of treatment, showed a general worsening of the conditions, with diffuse increased lymph node enlargement, mainly in the neck and parahilar area of the left lung with minute aerial formations compatible with small cavitations, diffused dishomogeneity of the bone tissue due to presence of multiple hypodense areas some with erosion of the cortical bone due to localization of tubercular disease, compatible with Pott disease. A bone marrow biopsy was performed, which showed mycobacterial presence, confirming the diagnosis of disseminated TB (Figure 3).

Seriated sputum smear test for AAFBs was done every two weeks until negativization at the Ziehl Neelsen coloration that occurred after 43 days of anti-TB treatment.

The patient continued intensive phase of anti-TB treatment for four months with very poor improvement, then pyrazinamide and ethambutol were suspended, beginning the continuation phase with only two anti-TB drugs. By that time, the leucocytes were 4,900/μL with normalization of lymphocytes. CD4+ T-cells raised up to 181/μL and HIV-RNA were undetectable in the blood. Imaging examinations showed no signs of improvement of the tubercular disease still with disseminated involvement.

After six months of hospitalization with stable but still poor clinical conditions, the patient suddenly developed acute respiratory distress (probably due to a respiratory virus) unresponsive to oxygen and high-dose steroids. He was referred to the Intensive Care Unit (ICU) where, despite prompt intubation and mechanical ventilation, he died.

DISCUSSION

In this case we experienced a dissemination of TB disease following the immune recostitution given by effective antiretroviral treatment, this is called "unmasking TB-IRIS"[6]. When the patient was admitted, he was in good clinical conditions with no sign of active TB, either pulmonary or extrapulmonary. Toghether with the

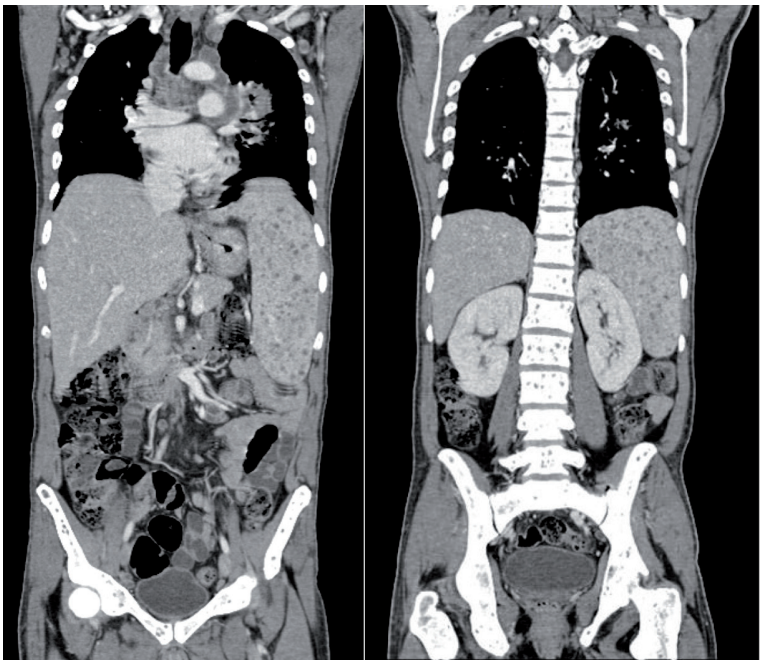

Figure 2. Coronal sections of Total Body CT scan showing multiple diffuse lymphnode enlargement and multiple spleen hypodensities.

raise of CD4+ count and the drop of HIV-RNA, we assisted to a dissemination of tuberculosis with multiple involvement and worsening of general clinical condition with fever, loss of weight, night sweats. Despite the antitubercular drugs, we failed to control the disseminated disease during the long-standing admission time.

Nowadays we are encouraged to start cART as soon as possible, sometimes even on the same day of diagnosis of a new HIV infection. Nevertheless, even in the era of an early start of cART, many patients are diagnosed as late-presenter and IRIS still constitutes a difficult condition to diagnose and manage[7-9]. Recent studies suggest increased risk for developing IRIS in late presenter patients who are starting cART with integrase strand inhibitors (INSTIs), especially raltegravir. Probably the cART regimen we adopted had a role in accelerating the process of tuberculosis dissemination that occurred with quick HIV viral load drop and CD4+ cell raise[10].

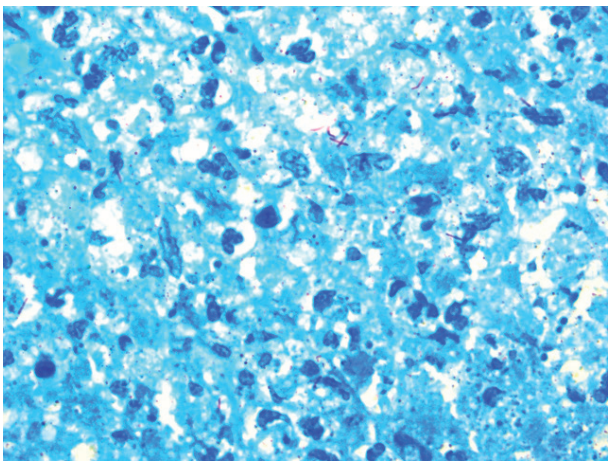

Figure 3. Bone marrow biopsy showing AAFBs at the Ziehl Neelsen coloration.

CONCLUSIONS

Clinicians managing a newly diagnosed HIV-infected patient (especially those who have an advanced disease stage) should identify and actively search for all the possible underlying opportunistic infections, especially latent TB. A careful choice of the right time of cART initiation is crucial to prevent or reduce the risk of a potentially life-threatening IRIS[11].

Conflict of Interest:
The authors declare no conflict of interest.

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