Approach for tuberculosis-associated immune reconstitution inflammatory syndrome in an HIV-negative patient

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SUMMARY
A male refugee from the Middle East was diagnosed with pulmonary tuberculosis and Pott’s disease with paravertebral abscess. After starting the standard regimen, the sputum culture converted to negative and the patient’s general condition improved. Six weeks later, the patient presented with clinical worsening of known symptoms, new appearance of focal neurological deficits and progress of radiological features showing progression of the paravertebral abscess. Immune reconstitution inflammatory syndrome with Mycobacterium tuberculosis (TB-IRIS) was presumed, and treatment with high-dose steroids was started. Due to recurrent relapses while tapering, corticosteroids had to be given over a prolonged period. After treatment completion, the patient was in a good general condition, abscesses had decreased and neurological deficits were in complete remission. This case presents the rare manifestation of TB-IRIS in HIV-negative patients and its management in a high-income country.

BACKGROUND
Due to the lack of large prospective cohort studies, there is not much knowledge of disease patterns and outcome of immune reconstitution inflammatory syndrome (IRIS) in patients with Mycobacterium tuberculosis (M. tuberculosis) infection (TB-IRIS) without HIV coinfection. As there is still no consensus case definition for TB-IRIS in this population, diagnosis and treatment remain a challenge. We report the rare presentation of TB-IRIS in a HIV-negative patient in a high-income setting, which implies the disposal of a wide selection of diagnostic tools to ensure a sophisticated approach and a strict follow-up by MRI. It additionally demonstrates the difficulties in diagnosis and treatment even with access to the most advanced medical standard.

CASE PRESENTATION
A male refugee from the Middle East in his mid-20s without significant medical history was diagnosed with smear positive pulmonary TB and Pott’s disease, including multisegmental spondylodiscitis and paravertebral abscess invading the right psoas muscle (figure 1A). He presented with a history of cough, night sweat and weight loss (14 kg) for 3 months, as well as paravertebral back pain for 9 months. Apart from severe paravertebral pain of the lumbar spine on palpation, physical examination was unremarkable. Chest X-ray showed multiple cavities and an opacity in the right upper lobe with bilateral hilar lymphadenopathy. Sputum smear detected acid-fast bacilli, and cultures were positive for M. tuberculosis with neither genotypical nor phenotypical resistance. An HIV test was negative. Laboratory examination revealed an elevated C reactive protein (CRP) of 92 mg/L, and white blood cells (WBC) were in a normal range (8.3 x 10⁹/L).

Standard regimen (isoniazid, rifampicin, ethambutol, pyrazinamide) and vitamin B₆ were initiated, and directly observed treatment (DOT) was established. Clinical symptoms resolved and sputum culture converted to negative within 2 weeks.

Six weeks after the initiation of antituberculosis therapy, the patient presented with persistent back pain and recurrence of B-symptoms. Hypoaesthesia was found in dermatome L3 of the right thigh. Markers of inflammation remained high (CRP 134 mg/L, WBC 10.5 x 10⁹/L), and contrast-enhanced MRI showed progression of the abscess involving the entire cross section of the right psoas muscle (figure 1B). Due to neurological deficits, percutaneous posterior stabilisation from thoracic vertebra (T) 11 to the os ileum was performed. Subsequently, back pain decreased and hypoaesthesia was in complete remission. However, B-symptoms were persistent and hypoaesthesia reoccurred. Postoperative images showed extensive bilateral psoas abscesses (figure 1C). Levels of antituberculosis drugs were in therapeutic range. Hence, TB-IRIS was presumed.

DIFFERENTIAL DIAGNOSIS
As there is neither a specific diagnostic tool nor defined clinical, serological or radiological markers, diagnosis of TB-IRIS is a diagnosis by exclusion. In 2008, the International Network for Study of HIV-associated IRIS (INSHI) elaborated a consensus case definition for TB-IRIS in HIV-positive patients in low-income settings. According to INSHI, infection with M. tuberculosis has to be proven corresponding to WHO definition. In addition, initial response to an appropriate therapy must be observed. Paradoxical TB-IRIS is defined as new or worsening of lymphadenopathy, radiological features, neurological signs or serositis as major criteria and of B-symptoms, respiratory symptoms or abdominal pain as minor criteria. Unmasking TB-IRIS is defined as a new presentation of a TB infection within 3 months after the initiation of antiretroviral therapy (ART).¹ There is no consensus case definition.
in HIV-negative patients. In a review on TB-IRIS, Lanzafame et al suggested that the diagnosis of TB-IRIS in HIV-negative patients has to be taken into consideration if there is worsening of TB-related symptoms and/or radiological findings observed shortly after an initial improvement on an adequate antituberculosis therapy. This deterioration can occur at the primary site of TB infection or at a new location. Other conditions reducing the efficacy of the antituberculosis therapy or explaining clinical worsening such as poor treatment adherence, malabsorption of antituberculosis therapy, drug side effects, drug-resistant TB, malignancies and other infections must be ruled out.2

In our case, non-adherence was ruled out due to reliably performed DOT and sufficient drug levels. Therapeutic drug monitoring allowed excluding altered drug metabolism like rapid metabolism. Clinically, there were no signs for additional infection or malignancies.

TREATMENT

Treatment with 1 mg prednisone per kilogram body weight (60 mg) was initiated. The patient’s health condition improved slowly. A follow-up MRI showed a reduction in Pott’s disease and in bilateral paravertebral abscesses. After tapering steroids to 10 mg over a course of 2 months, B-symptoms reoccurred and a painful swelling on the left side on level T11/T12 was detected corresponding with a new abscess in the autochthonous back musculature in MRI. Dosage of steroids was increased again to the initial dose of 1 mg/kg bodyweight for another 2 months. The patient’s health condition improved, and steroid therapy was slowly tapered to 20 mg over a course of 6 months.

Due to radiologically confirmed progression of Pott’s disease, treatment response was initially unclear, and ethambutol was given for a prolonged duration of 4 months, while pyrazinamide was given for 7 months. Rifampicin and isoniazid were continued for another 5 months. In total, antituberculosis therapy was administrated over an extended duration of 12 months. Steroid therapy was tapered to zero over a 3-month period after completion of antituberculosis therapy.

OUTCOME AND FOLLOW-UP

After completing IRIS treatment, the patient was in a good general condition and nutrition state. B-symptoms and neurological deficits were in complete remission. Percutaneous posterior stabilisation was removed 1 year after completing antituberculosis therapy, and microbiological investigations showed no evidence of a persistent infection with M. tuberculosis. A contrast-enhanced MRI 1 year after treatment completion revealed fibrotic tissue with calcification and no evidence of ongoing infection (figure 1D).

DISCUSSION

IRIS is a severe reaction of the immune system against an infectious or non-infectious antigen, resulting from an immunological recovery after removal of immunosuppression.3,4 Thus, TB-IRIS is an early complication of antituberculosis therapy or ART occurring in M. tuberculosis-infected patients with or without HIV coinfection. TB-IRIS is well known among HIV-positive patients receiving ART, but it is less common and understood among HIV-uninfected patients.1,2,5,6 TB-IRIS in HIV-negative patients receiving antituberculosis therapy is estimated to affect 2%–23%.7 Pooled by region, highest incidences were reported in studies conducted in Europe. Nevertheless, it has to be acknowledged that variation in incidence is influenced by variability in clinical setting and study design.8 In Switzerland, there is a low burden of TB disease with an incidence of 7.2 patients per 100,000 population.9–11 However, there is no report on incidence of TB-IRIS in this setting. Mortality is generally low, ranging from 2% to 3.2%.2,7,8 Regardless of a patient’s HIV status, it is considered that patients with a high degree of immunosuppression and/or a high bacterial load are at a greater risk of TB-IRIS development.1 Other risk factors for TB-IRIS are young age, male gender, anaemia, hypoalbuminaemia and the use of biological agents.2,12 The immunopathogenesis of IRIS remains not fully understood, but an underlying proinflammatory phenotype is suggested.2,12 Bell et al formulated the hypothesis that IRIS is the result of a drastic expansion of M. tuberculosis in the poorly inflamed or anergic environment of an immunocompromised patient, followed by an exuberant antigen-specific inflammatory reaction after resolution of immunosuppression.7 Accordingly, TB-IRIS presents as an exacerbated inflammation, commonly including B-symptoms and lymphadenopathy as leading symptoms.2,12 Predominant locations of TB-IRIS are lymph nodes and lungs, irrespective of the baseline form of TB.2 However, clinical presentations are very heterogeneous.1 In HIV-negative patients, TB-IRIS occurs more often in extrapulmonary TB,2 in particular in pleural and lymph node forms.2,12 Median time to onset after initiation of antituberculosis therapy varies in a wide range, but IRIS usually occurs within 3 months.2,13

There is no standard treatment for TB-IRIS. Treatment approaches differ according to the severity and site of TB-IRIS. In mild forms, continuation of an effective antituberculosis therapy and watchful waiting may be appropriate as spontaneous resolution is seen frequently.2 In some patients, an extended duration of the intensive or continuous phase of antituberculosis therapy is reported, but optimal duration in the case of patients with TB-IRIS remains unclear.5 In mild-to-moderate reactions, the use of non-steroidal anti-inflammatory drugs is reported,13,14 but evidence is limited.1 In severe cases, systemic corticosteroids are given.2,13,14 In a randomised controlled trial, the administration of prednisone for 4–6 weeks resulted in a reduction in morbidity from TB-IRIS and in a significant reduction in hospitalisation.1 Due to the side effects of long-term steroid application, the recommended maximal duration of treatment is 4–6 months.2 Nevertheless, in some cases, prolonged treatment and slower tapering of corticosteroids were required.7 Thus, the decision to administer corticosteroids is made on an individual basis and...
depends on the severity of clinical manifestation. In addition, there are cases reported where surgical interventions such as lymphadenectomy, abscess drainage or thoracic drainage were performed.

Our case presents this rare, but relevant complication of antituberculosis therapy. The patient showed various risk factors for TB-IRIS, such as young age, male gender and extrapulmonary TB. Diagnosis of TB-IRIS was made according to the definitions suggested by Lanzafame et al and INSHT, respectively. As we had access to a large set of diagnostic tools and the possibility of a strict MRI follow-up, a maximum of information regarding the course and outcome of the case can be presented. Prolonged antituberculosis therapy over 12 months and administration of 9 months of systemic corticosteroids were required and resulted in a positive outcome.

In conclusion, TB-IRIS manifests very heterogeneously, and there is no specific diagnostic tool. Therefore, strict adherence to a universal definition of TB-IRIS is fundamental. Although elaborated for HIV-positive patients in a low-income setting, we generally suggest to follow the definition of TB-IRIS developed by INSHT. Although TB, HIV and, in this context, TB-IRIS are in particular major problems of low-income countries, physicians in high-income settings should be familiar with this phenomenon. Regarding the management of TB-IRIS, individual therapeutic approaches are required.

**Learning points**

- Immune reconstitution inflammatory syndrome in patients with *Mycobacterium tuberculosis* infection (TB-IRIS) manifests very heterogeneously and may also occur in HIV-negative patients.
- Strict adherence to a universal definition of TB-IRIS is fundamental due to the lack of specific diagnostic tools and defined clinical, serological or radiological markers.
- Diagnosis of TB-IRIS is a diagnosis of exclusion.
- Close clinical follow-up of the patients and personalised therapeutic approaches are needed.

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