Tuberculosis-immune reconstitution inflammatory syndrome

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**ABSTRACT**

Tuberculosis-immune reconstitution inflammatory syndrome is an excessive immune response against Mycobacterium tuberculosis that may occur in either HIV-infected or uninfected patients, during or after completion of anti-TB therapy. In HIV-infected patients it occurs after initiation of antiretroviral therapy independently from an effective suppression of HIV viremia. There are two forms of IRIS: paradoxical or unmasking. Paradoxical IRIS is characterized by recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an antiretroviral-associated inflammatory manifestation of a subclinical infection with a hastened presentation. The pathogenesis is incompletely understood and the epidemiology partially described. No specific tests can establish or rule out the diagnosis. Treatment is based on the use of anti-tuberculosis drugs sometime with adjunctive corticosteroids. Mortality is generally low.

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**INTRODUCTION**

Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) is an abnormal, excessive immune response against alive or dead Mycobacteria tuberculosis that may occur in either HIV-infected or, more rarely, uninfected patients. In HIV-infected patients it occurs after initiation of antiretroviral therapy independently from an effective suppression of HIV viremia. Paradoxical worsening of tuberculosis in HIV-infected patients was indeed first described after introduction of antituberculous drugs in 1954 [1]. This review summarizes the available literature on epidemiology, pathogenic mechanisms, diagnosis, clinical manifestations, and treatment options of TB-IRIS.

**DEFINITION OF TB-IRIS**

TB-IRIS is a paradoxical worsening or recurring of preexisting tuberculous lesions, or a development of new lesions in patients on effective antituberculosis treatment. It may occur during or even after completion of anti-TB therapy. TB-IRIS might be misdiagnosed as superimposed infections, treatment failure following inadequate anti-TB treatment, drug-resistant TB, or TB relapse [2, 3]. Therefore, the following strict criteria must be applied to diagnose TB-IRIS [4]:

1. Initial improvement of TB-related symptoms and/or radiographic findings after adequate anti-TB treatment for a certain time;
2. Paradoxical deterioration of TB-related symptoms and/or radiologic findings at the primary or at new locations during or after anti-TB treatment;
3. Absence of conditions that reduce the efficacy of anti-TB drugs (e.g., poor compliance, drug malabsorption, drug side effects);
4. Exclusion of other possible causes of clinical deterioration.

In an attempt to develop diagnostic criteria, various definitions of IRIS were developed in HIV-infected patients, including those proposed by Shelburne et al. [5], French et al. [6], and Robertson et al. [7]. In 2008 a consensus definition for TB-associated IRIS was created for resource poor-settings [8] in order to have a standardized case definition which could assist in diagnosing TB-IRIS in countries with limited resources.

There are two forms of IRIS: paradoxical or unmasking. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of a treated case. Unmasking IRIS is an antiretroviral (ART)-associated inflammatory manifestation of a subclinical infection with a hastened presentation. In this latter form signs and symptoms not clinically apparent before, appear during ART.

**EPIDEMIOLOGY**

Different studies have estimated the frequency of TB-IRIS between 2% and 23% [3,9,10–13] in HIV-uninfected patients.
HIV-infected patients a retrospective meta-analysis of 54 cohorts showed that the incidence of TB-IRIS in patients on ART treatment was 15.7% with a mortality of 3.2% [14]. Neurological TB-IRIS occurred in 12% of TB-IRIS cases in a single center in a TB endemic area [15]. Nonetheless the frequency of tuberculosis-associated IRIS remains difficult to assess because of the heterogeneity of the definitions. Risk factors for a paradoxical response include disseminated tuberculosis [8], young age, male gender, anemia [4], lymphopenia or a CD4+ T lymphocyte count less than 50/μl³, use of biological agents (e.g., anti-TNFα), and a marked increase in lymphocyte count or suppression of HIV-RNA replication with antiretroviral therapy [8,13]. The median time to onset of the paradoxical response was 21–56 days after initiation of antituberculous treatment in HIV-uninfected patients [13], and two–four weeks in HIV-infected patients on antiretroviral therapy [8]. The overall mortality in patients with a paradoxical response has been estimated at 3% [14].

**Pathogenesis**

The immunopathogenesis of IRIS remains only partially understood. Qualitative and quantitative reconstitution of the immune system, host genetic susceptibility and mycobacterial load are supposedly involved in the pathogenesis of IRIS.

The role of the amount of mycobacteria in the pathogenesis is suggested by several observations. In patients with disseminated or extrapulmonary tuberculosis the increased risk of IRIS is attributed to a higher bacillary load [2,3]. In HIV-positive patients, the risk of IRIS is highest if the antiretroviral therapy is initiated early during antituberculous treatment, when the mycobacterial load is considerable [16], as shown in trials trying to establish the correct time of ART initiation [17–19].

The hasty killing of mycobacteria by anti-TB therapy may determine the release of large amounts of mycobacterial antigens, which can stimulate an excessive inflammatory response [20]. A prospective study recently showed a correlation between positive sputum culture (indicating high antigenic load) and inflammatory monocyte activation markers (strongly predictive of development of paradoxical TB-IRIS), suggesting that high antigen loads and inflammation may act together in the pathogenesis [21]. However host inflammatory responses (with the release of proinflammatory cytokines) may be stronger determinants of IRIS pathogenesis than mycobacterial factors [22]. Other studies also indicate that immune reconstitution is involved in the pathogenesis of IRIS, and in particular the reconstitution of T helper 1 CD4+ immune responses, as shown by the conversion of tuberculin skin tests to positive after treatment start [2,11]. ART initiation has been associated with a shift from T helper 2 to T helper 1 cytokine patterns, and with the restoration of T lymphocyte proliferative responses [23].

In conclusion, the immunopathogenesis of IRIS in both HIV-infected and uninfected patients appears to involve T helper 1-driven immune responses in the presence of multibacillary disease and immunodeficiency.

**Clinical manifestations**

TB-IRIS in HIV-uninfected patients is more frequent in extrapulmonary (especially in pleural and lymph node forms) than in pulmonary TB. The median time to IRIS onset after starting anti-TB drugs is generally up to three months. The most frequent presenting symptoms of TB-IRIS are recurrent fever, enlarged lymph nodes and worsening dyspnea [2]. The principal sites involved in TB-IRIS are lymph nodes (68%) and lungs (16%), independently of the sites of primary tuberculosis [4]. Thoracic TB-IRIS manifest as new pulmonary parenchymal lesions [24,25], development of new lymphadenopathy or increase in the size of a preexisting lymphadenopathy [2,9,25,26], development of new or progression of preexisting pleural effusions [27,28], new endobronchial lesions. TB-IRIS usually develops on the same side of primary TB, though contralateral or bilateral lesions can also occur [24].

Development of new lymphadenopathy or enlargement of preexisting lymph nodes can be observed in up to 25% of HIV-uninfected patients with peripheral TB lymphadenitis [3]. The median time to development is generally 4–14 weeks after the initiation of anti-TB treatment but can also be longer (1–13 months after treatment completion) [9,26]. In patients with pleural TB new peripheral pulmonary lesions occur in 2.4%–11%, developing 1–9 months after the beginning of anti-TB therapy [25].

Pleural TB-IRIS (manifesting as a new or increased pleural effusion) happens in 16%–45% of HIV-uninfected patients with pleural [27,28], lymph node [25], or pulmonary TB [3]. It generally develops within 3–19 weeks of treatment initiation [28].

In patients with milliary or disseminated TB the occurrence of soft tissue TB-IRIS (presenting as new inflammatory or non inflammatory lesions within the skin or subcutaneous tissues) is more frequent than in those with pleural or lymph node TB [29,30]. Endobronchial TB-IRIS, manifesting as partial or totally obstrusive lesions, is rare and can be due either to a fistulation or erosion of a lymph node into a bronchus or a de novo endobronchial reaction [31].

TB-IRIS in HIV-infected patients is one of the most common forms of IRIS and occurs in 15.7% of TB patients starting ART according to Müller's meta-analysis [14]. However some studies report higher rates; for instance, a 54.2% incidence was reported in patients with culture-confirmed pulmonary TB in India [32], and a 47% incidence of paradoxical TB-IRIS was found in South African patients with TB meningitis [15], determining a considerable disease burden [33].

Although both paradoxical and unmasking forms of TB-IRIS have been reported in HIV-infected individuals, paradoxical IRIS has been more extensively and better studied. In patients with pulmonary tuberculosis, paradoxical TB-IRIS presents as a worsening or recurrence of respiratory (shortness of breath, cough) and constitutional symptoms (fever, weight loss, night sweats), and often new or expanding infiltrates on chest X-ray images [34]. Lymph node paradoxical IRIS generally presents with rapid enlargement followed by suppuration [35].

Paradoxical neurologic TB-IRIS is a possibly life threatening condition and symptoms tend to manifest later than in forms not involving the central nervous system, generally 5-10 months after ART initiation. Neurologic TB-IRIS generally presents with new or worsening meningoitis and/or features of raised intracranial pressure, due to enlarging cerebral tuberculomas or intracranial abscesses; mortality is high and ranges from 12% to 25% [36–38]. It may also present with spondylitis, epidural abscesses, and radiculomylopathy [15,38].

Abdominal TB-IRIS can occur as granulomatous hepatitis, retroperitoneal lymphadenopathy, and peritonitis, whereas the musculoskeletal form manifests as mono- or polyarthritis [39].

“Unmasking TB-IRIS” is not as well defined as “paradoxical TB-IRIS” and refers to a form of TB that becomes clinically recognizable after the initiation of ART and presents with exaggerated inflammatory features. It usually develops within the first three months of ART. Unmasking TB-IRIS forms can vary widely in the degree of clinical presentation, often with features indistinguishable from those of paradoxical TB-IRIS. Two-thirds of unmasking forms present with lung involvement (often severe pulmonary tuberculosis leading to acute respiratory distress syndrome, or bronchiolitis obliterans organizing pneumonia) [40, 41].
Diagnosis

No specific tests can establish or rule out the diagnosis of TB-IRIS that must take into consideration a combination of clinical signs and symptoms, and laboratory findings. The following clinical features suggest a diagnosis of TB-IRIS: improvement of symptoms on TB treatment prior to initiating ART, deterioration of symptoms soon after starting ART, and exclusion of alternative causes for clinical deterioration.

The differential diagnosis of TB-IRIS must include poor adherence or malabsorption of antituberculous therapy, drug reactions, drug-resistant tuberculosis, malignancies, and other opportunistic or bacterial infections [42]. In a South African study, the most common alternative diagnosis was drug-resistant TB [42].

Treatment

There is no consensus yet on the standard treatment of TB-IRIS. Approximately half of the cases of lymph node TB-IRIS resolve spontaneously [25]. In some patients with lymph node, airways or soft tissue TB-IRIS, prolonged antituberculosis treatment may be required. However, the optimal treatment duration is unclear. Most patients with TB-IRIS show clinical improvement in the two months following antituberculosis treatment [3] but the range is wide (1–7 months) [3]. After 3–18 months of anti-TB treatment, pulmonary lesions and lymphadenopathy generally disappears. Again, the time needed for complete resolution is variable, and there may be residual lesions.

Depending on sites and severity of TB-IRIS, adjunctive therapy may be necessary. For instance, patients with soft-tissue abscesses or symptomatic pleural effusions often require aspiration [28]. Systemic corticosteroid administration for four–six weeks improves the outcome of certain forms of TB-IRIS (symptomatic enlarging intracranial tuberculosis, endobronchial obstruction) and reduces proinflammatory cytokines [31,43,44]. However, its role in other forms of TB-IRIS is unclear. Corticosteroids and nonsteroidal anti-inflammatory drugs have been used to treat IRIS, although only for corticosteroids a double blind, randomized, placebo-controlled clinical trial was performed in patients with paradoxical TB-IRIS [45]. Prednisone significantly reduced days of hospitalization and outpatient therapeutic procedures, more rapidly improving symptoms, quality-of-life score and chest radiography [45]. For most patients a four-week course of prednisone reduced morbidity from TB-IRIS. There was no difference in mortality between prednisone and placebo-treated participants, even though cases with neurologic involvement were excluded from the trial. Minor infections (oral candidiasis and uncomplicated herpes simplex) were more common in patients on prednisone. Most authors suggest treatment with corticosteroids for a maximum of four–six months.

In HIV-positive patients already on ART, antiretroviral therapy generally must be continued. In patients with active tuberculosis the timing to start ART has been established; early initiation of ART (within two–four weeks after the initiation of antituberculosis therapy) in patients with CD4 counts below 50/mm³ leads to decreased rates of AIDS-associated comorbidities and mortality even though there is an increased risk of IRIS events, when compared with patients who start therapy later [46]. Indeed the SAPIT trial showed that in patients with CD4 counts <50/mm³, the early therapy group (ART started around two weeks after TB treatment) had an IRIS incidence rate of 45.5, as compared with 9.7 among patients who started therapy three–four months after initiation of antituberculosis therapy [47]. Even though deaths were associated with IRIS in both the SAPIT trial and the CAMELIA trial [48], the benefit in terms of reduced mortality continued to favor early therapy.

In patients with pulmonary TB and a CD4 cell count higher than 50/mm³, ART can be initiated eight weeks after starting antituberculosis treatment without excess mortality. It remains to be seen whether patients with TB of the central nervous system would represent a subgroup at increased risk of IRIS death.

Tuberculous meningitis is the most severe form of TB with a poor prognosis in HIV-infected persons, independently of ART use [49]. Neurological TB-IRIS (manifesting as meningitis, intracranial tuberculoma, brain abscesses, radiculomyelitis, and spinal epidural abscesses) contributes to this poor outcome.

Oral or intravenous corticosteroids have shown benefit in some cases of neurologic TB-IRIS [49]. In HIV-infected patients with neurological TB-IRIS unresponsive to corticosteroids and with a depressed level of consciousness, temporary interruption of ART may be considered. If ART has not been started yet, a delayed initiation of antiretroviral therapy can be considered [50].

Conclusions

TB-IRIS (paradoxical and unmasking forms) constitutes a spectrum of clinical presentations that can occur during Mycobacterium tuberculosis infection. Mortality is generally low both in HIV-infected and uninfected patients. More studies are needed to elucidate the pathogenesis and establish better treatment modalities.

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