CASE REPORT

Tuberculosis-immune reconstitution inflammatory syndrome in HIV-negative children

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Abstract
Even though tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) is usually found in HIV-positive patients receiving antiviral treatment, it can also occur in HIV-negative patients especially if they have risk factors. We report a unique case of TB-IRIS in an immunocompetent child presenting with new onset of pleuritic chest pain after receiving anti-TB drugs. TB-IRIS should be considered as a differential diagnosis in case of clinical deterioration or appearance of new typical lesions despite appropriate anti-TB treatment for more than 2 weeks in the absence of persistently active TB or any other alternative causes. This will prevent physicians from misdiagnosis as superimposed infections, treatment failure or TB relapse.

Keywords
children, HIV-negative, TB-IRIS, tuberculosis

INTRODUCTION

Children with tuberculosis (TB) can have an unexpected deterioration despite good drug compliance. This paradoxical reaction has been described largely in HIV-positive children as TB-immune reconstitution inflammatory syndrome (TB-IRIS). Likewise, the emergence of TB-IRIS has also been found in immunocompetent children especially in patients with risk factors. This case report described a unique case of TB-IRIS in an HIV-negative child presenting with new onset of pleuritic chest pain after anti-TB treatment. Even though he had no risk factor except for pleural involvement, we emphasized that TB-IRIS should be considered as one of the differential diagnoses.

CASE REPORT

A 15-year-old HIV-negative boy with pulmonary TB presented with chronic cough for a month. He denied fever, chest pain, dyspnoea, night sweats, malaise or weight loss. He had no known index case of pulmonary TB in his family or close contact. He also received Bacillus Calmette–Guérin (BCG) vaccine after birth and had no history of allergy.

At diagnosis, his body weight was 51.4 kg (50th percentile). Physical examination showed no retraction, good air entry and normal breath sounds. His initial chest x-ray (CXR) showed reticulonodular infiltration at both upper lung zones with plate-like atelectasis at the right upper lung zone and left perihilar region, and minimal right pleural effusion (Figure 1). Sputum specimens were positive for acid-fast bacilli and culture yielded Mycobacterium tuberculosis susceptible to all first-line anti-TB drugs. All family members including his mother, grandmother and sister had normal CXR. His complete blood count showed haemoglobin of 12.2 g/dl; haematocrit of 40.0%; white blood cells of 15,330 (neutrophils 74.5%, leukocytes 16.0%, macrophages 5.7%, eosinophils 3.7%, basophils 0.1%); and platelets of 255,000. Blood chemistry including electrolyte and renal function were normal.

He started a standard regimen consisting of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide with...
good compliance; he initially showed improvement but then developed right pleuritic chest pain 3 weeks thereafter. On examination, he had no fever and stable vital signs. Follow-up CXR revealed newly detected two mass-like pleural-based opacity at the right lower lung zone, reticulonodular infiltration at both upper lung zones, plate-like atelectasis at the right upper lung zone and left perihilar region and minimal right pleural effusion. Chest computed tomography showed multiple centrilobular nodules with tree-in-bud pattern at both upper lobes, two heterogenous enhancing pleural-based masses with central necrosis at basal segment of the right lower lobe and multiple enlarged mediastinal lymph nodes.

Figures 1 and 2: Initial chest x-ray at diagnosis of pulmonary tuberculosis showed reticulonodular infiltration at both upper lung zones with plate-like atelectasis at the right upper lung zone and left perihilar region and minimal right pleural effusion. Chest imaging at diagnosis of tuberculosis-immune reconstitution inflammatory syndrome. (A) chest x-ray revealed newly detected two mass-like pleural-based opacity at the right lower lung zone, reticulonodular infiltration at both upper lung zones, plate-like atelectasis at the right upper lung zone and left perihilar region and minimal right pleural effusion. (B) Chest computed tomography showed multiple centrilobular nodules with tree-in-bud pattern at both upper lobes, two heterogenous enhancing pleural-based masses with central necrosis at basal segment of the right lower lobe and multiple enlarged mediastinal lymph nodes.
symptoms and radiographic findings after adequate anti-TB treatment for a certain time; (2) paradoxical deterioration of TB-related symptoms and radiological findings after anti-TB treatment; (3) absence of conditions interfering with the efficacy of anti-TB drugs, for example, poor compliance, drug malabsorption or side effects from anti-TB drugs; and (4) lack of other explanations for clinical deterioration.

Prednisolone was administered at a dose of 1 mg/kg/day for a month and then tapered off in 6 weeks. Improvement of his clinical and radiological findings was found at the follow-up visit 1 month thereafter without change in anti-TB regimen.

**DISCUSSION**

TB-IRIS is an immune reaction that occurs with the recovery of the patient’s immunity. It was defined as the deterioration of the existing lesion or appearance of a new lesion in the chest radiological examination despite appropriate anti-TB treatment for more than 2 weeks in the absence of persistently active TB or any other causes of clinical deterioration such as non-sensitivity to initial treatment or poor drug compliance.

TB-IRIS commonly manifests with new or worsening fever, lymphadenitis, dyspnoea, pulmonary infiltration/nodules, pleural or pericardial effusion. Enlarging lymph node may cause airway compression. The median time to deterioration from previous study was 80 days (range, 10–181 days). It can occur during or after the completion of anti-TB treatment.

The pathogenesis of TB-IRIS in HIV-negative children remains unclear. At first, TB is phagocytosed by alveolar macrophages. The triggering of a bactericidal reaction is therefore avoided, favouring a state of immunosuppression. The production of interleukin 10 and transforming growth factor-beta is increased, which induces T-lymphocyte apoptosis, reduces interferon-gamma (IFN-γ) production, decreases the recruitment of new macrophages and promotes this state of immunosuppression. After the initiation of treatment, the immune system improves, either as consequence of the treatment or spontaneously. This is the main cause of clinical worsening.

Elimination of *M. tuberculosis* by anti-TB drugs results in restoration of host cellular immune response and subsequent inflammatory response, while the microorganism itself co-opts host immune responses towards Treg and Th2 cells that facilitate survival of the mycobacteria. The restoration of immune response results in the increased production of pro-inflammatory cytokines from Th1 and Th17 cells and the suppression of anti-inflammatory cytokines from regulatory T cells and Th2 cells. CD8 T lymphocyte, a key effector cell of cellular immunity, secretes excess pro-inflammatory cytokines, synergists with activated macrophages to elicit a cytokine storm. Moreover, 1, 25-dihydroxyvitamin D3 secreted from activated macrophage together with Th1 cytokines such as IFN-γ and granuloma formation may also cause hypercalcaemia.

In HIV-positive patients, high d-dimer, low CD4-positive T cells, high HIV viral load, low body mass index and sputum smear-positive pulmonary TB have been known as risk factors of TB-IRIS.

In HIV-negative patients, the involvement of more than one site at initial presentation, weight below the 25th percentile, young age at diagnosis, absence of BCG vaccination, anaemia, low serum lymphocytes, hypoalbuminaemia, elevated eosinophil counts, low total protein in the pleural effusion at the time of tuberculous pleuritis diagnosis, usage of tumour necrosis factor-alpha inhibitors, history of allergy and serum hypercalcaemia have also been reported as risk factors of TB-IRIS but were all not found in this case except for pleural involvement.

Regardless of the sites of primary TB, TB-IRIS mainly involves the lymph nodes (68%) and lungs (16%). Various thoracic manifestations in TB-IRIS include new pulmonary parenchymal lesions, enlarging pre-existing lymphadenopathy or new lymphadenopathy, progression of pre-existing pleural effusion or new pleural effusion, new chest or abdominal wall lesions and endobronchial lesions. TB-IRIS usually develops in the ipsilateral side of primary TB, hence contralateral or bilateral lesions can also occur.

Currently, there is no consensus guideline in the standard treatment for TB-IRIS. Half of the patients with TB-IRIS at lymph nodes have spontaneous resolution. Most of the *M. tuberculosis* strains in patients with TB-IRIS are susceptible to the standard regimen (isoniazid, rifampicin, pyrazinamide and ethambutol). Therefore, continuation of the standard regimen for 2 months, followed by at least 4 months of isoniazid and rifampicin is recommended.

Prolonged treatment may be required for patients with TB-IRIS involving the lymph nodes, main airways, and chest wall or having soft tissue abscesses. Treatments lasting 12–27 months have been reported, using the four drugs during the first 2–5 months, followed by isoniazid with one or two of the remaining drugs thereafter.

Systemic corticosteroid may reduce pro-inflammatory cytokines and is effective in HIV, symptomatic enlarging intracranial tuberculoma and endobronchial obstruction. Although its role in other forms of TB-IRIS remains unclear, corticosteroids have been proposed as adjunctive treatment. Although there is no clear indication, most authors suggested that steroids could be beneficial for severe cases. Regarding the dose of steroids, most studies have recommended an initial dose of 1 mg/kg/day, with a progressive tapering off over 4 or 6 weeks. Improvement after corticosteroid treatment supports immunopathological mechanism of this condition.

Most patients with TB-IRIS have clinical improvement in 2 months (range, 1–7 months) after the treatment. After 3–18 months of anti-TB drugs, lymphadenopathy and pulmonary lesions shrink or even resolve. However, the time to complete resolution is variable, and residual lesions may be observed.

In conclusion, TB-IRIS should be suspected in pulmonary TB children with new or worsening symptoms with typical radiographic findings after the exclusion of alternative causes such as drug-resistant TB, poor adherence, other co-infections, neoplasm or drug reaction even if no risk factor was found.
This concern will prevent physicians from misdiagnosis as superimposed infections, treatment failure or TB relapse. Only few studies in children have been reported; therefore, further studies are still needed to identify risk factors of TB-IRIS especially in HIV-negative children with pulmonary TB.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTION
Apinya Palamit, Prakarn Tovichien and Ramida Amornsitthiwat drafted the manuscript and contributed to patient care. Prakarn Tovichien and Ramida Amornsitthiwat revised the manuscript as corresponding authors. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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