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CHEST IMAGING

PICTORIAL ESSAY

Thoracic manifestations of paradoxical immune reconstitution inflammatory syndrome during or after antituberculous therapy in HIV-negative patients

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) is a consequence of exaggerated and dysregulated host's inflammatory response to invading microorganism, leading to uncontrolled inflammatory reactions. IRIS associated with tuberculosis (TB) is well recognized among human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy, but it is less common among HIV-negative patients. IRIS can manifest as a paradoxical worsening or recurring of preexisting tuberculous lesions or development of new lesions despite successful antituberculous treatment. Hence, the condition might be misdiagnosed as superimposed infections, treatment failure, or relapse of TB. This pictorial essay reviewed diagnostic criteria and various thoracic manifestations of the paradoxical form of TB-associated IRIS (TB-IRIS) that might aid in early recognition of this clinical entity among HIV-negative patients. The treatment and outcomes of TB-IRIS were also discussed.

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Immune reconstitution inflammatory syndrome (IRIS) is a consequence of exaggerated and dysregulated host's inflammatory response to invading microorganisms, typically *Mycobacterium tuberculosis*. It can also be found in other infections, e.g., cryptococcosis and cytomegalovirus infection, especially among human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy (1). Tuberculosis-associated IRIS (TB-IRIS) among HIV-negative patients has been increasingly observed, particularly in those with extrapulmonary TB (2). This clinical entity can be misdiagnosed as superimposed infections, treatment failure, or TB relapse (3).

There are two clinical scenarios related to IRIS, namely unmasking of an occult opportunistic infection and paradoxical worsening or recurring of a prior infection despite successful antimicrobial treatment (1). The pathogenesis of IRIS is not well understood in the latter. IRIS is postulated to be a consequence of immune recovery following appropriate antimicrobial therapy. The recovery results in an abrupt shift of the host's immune response from an immunosuppressive state towards a pathogenic hyperinflammatory state by increased production of proinflammatory cytokines from Th1 and Th17 cells and simultaneous suppression of anti-inflammatory cytokines from regulatory T cells and Th2 cells (4–6).

This pictorial essay reviewed diagnostic criteria and various thoracic manifestations that might aid in early recognition of TB-IRIS among HIV-negative patients. The treatment and outcomes of TB-IRIS were also discussed.

Diagnostic criteria

TB-IRIS is defined as a paradoxical worsening or recurring of preexisting tuberculous lesions or development of new lesions in patients receiving adequate anti-TB therapy and exhibiting initial improvement following the treatment. It can occur during or after completion of anti-TB therapy. Because of various clinical and radiologic manifestations, TB-IRIS might be misdiagnosed as superimposed infections, treatment failure secondary to inadequate anti-TB treatment, drug-resistant TB, or TB relapse (3, 4). Hence, the diagnosis of TB-IRIS requires the following criteria: 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 either at the primary or new locations during or after anti-TB treatment; 3) absence of conditions interfering with the efficacy of anti-TB drugs, e.g., poor compliance, drug malabsorption, or side effects from anti-TB drugs; and 4) lack of other explanations for clinical deterioration (2).

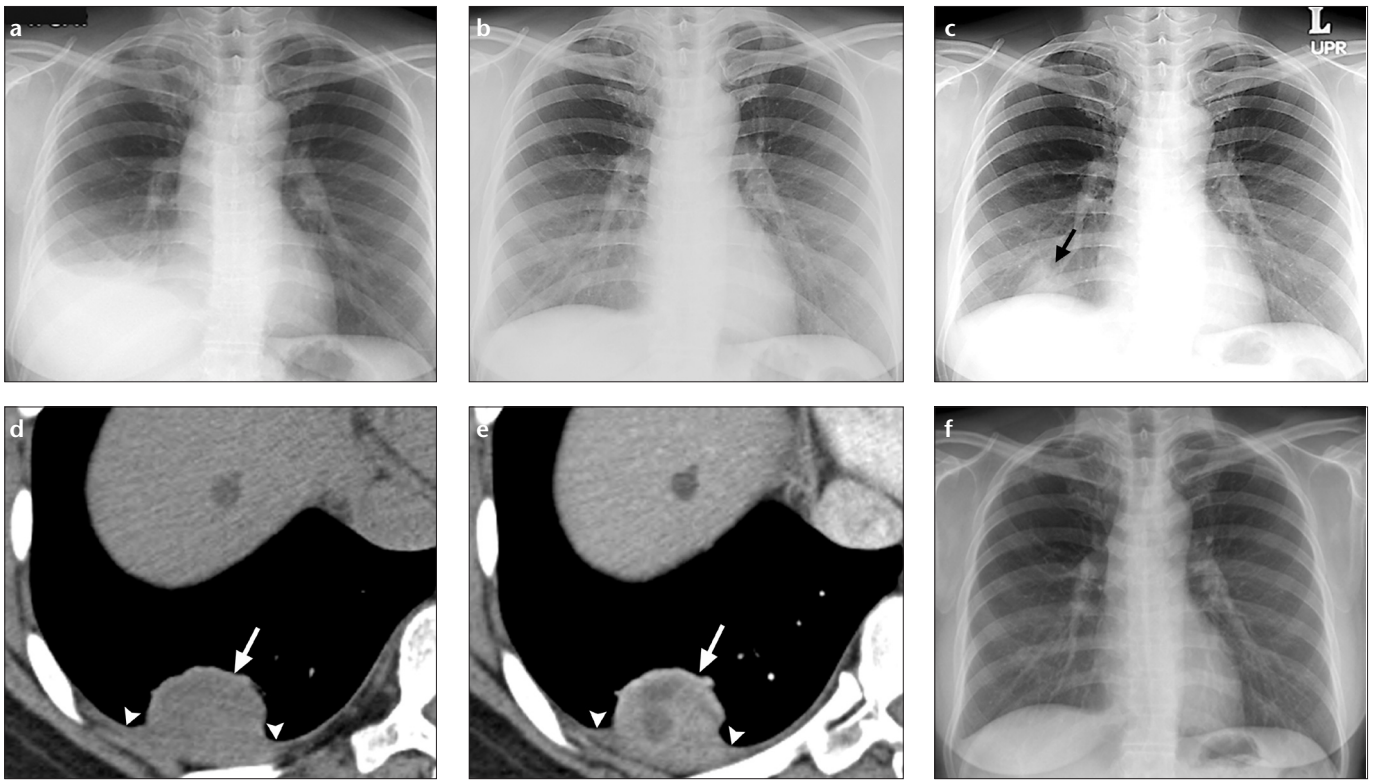

Figure 1. a–f. A 47-year-old woman with pleural TB. Initial chest radiograph **(a)** shows right pleural effusion with right apical fibrosis. Note complete resolution of the effusion after six months of anti-TB treatment **(b)**. Follow-up chest radiograph **(c)** and unenhanced **(d)** and contrast-enhanced **(e)** axial CT scans with mediastinal-window display obtained two months later reveal a newly developed pleural-based pulmonary mass *(arrows)* at the right lower lobe. It shows heterogeneous enhancement with a central low-attenuation area and abuts the thickened pleura *(arrow heads)*. Follow-up chest radiograph **(f)** obtained after six months of anti-TB treatment shows complete resolution of the mass.

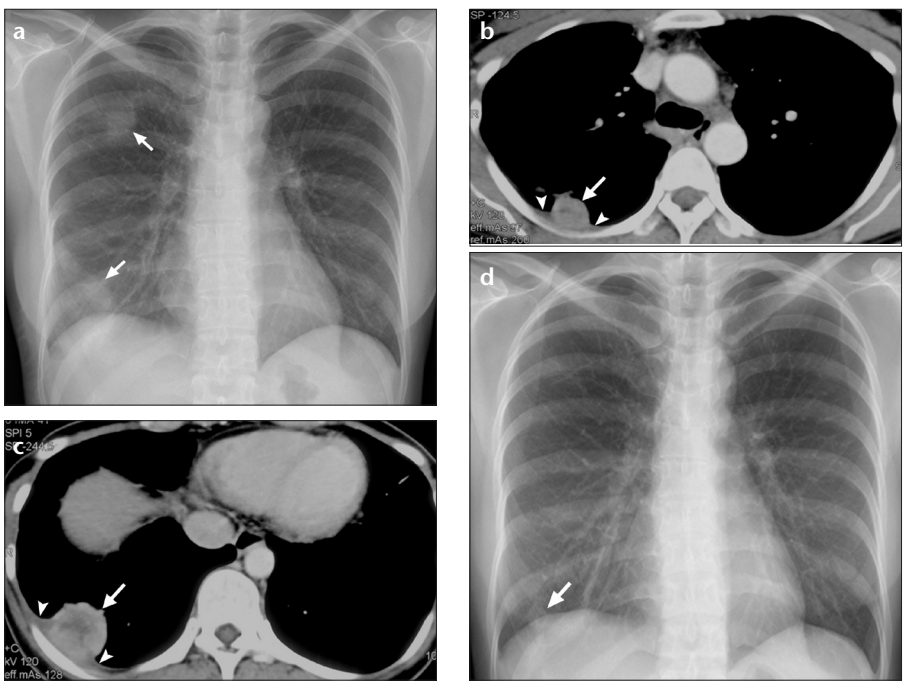

Figure 2. a–d. A 34-year-old woman with pleural TB. Chest radiograph **(a)** and contrast-enhanced axial CT scans with mediastinal-window display **(b, c)** obtained four months after anti-TB treatment reveal newly developed pleural-based pulmonary masses *(arrows)* in the right lung. The masses exhibit heterogeneous enhancement with a central low-attenuation area. Note adjacent pleural thickening (*arrowheads*, **b** and **c)**. Transthoracic needle biopsy of the mass revealed only epitheloid granuloma without acid fast bacilli or fungal organisms. Follow-up chest radiograph **(d)** obtained 12 months after complete treatment reveals marked improvement with a small residual cavitary nodule at the right lower lobe *(arrow)*.

In equivocal cases, biopsy may be required to exclude other diseases, particularly malignancy or other infections (7, 8). Although acid fast bacilli stain or polymerase chain reaction assay for *M. tuberculosis* can be positive (5), persistently active multidrug-resistant TB or other mycobacterial infections should not be discovered on culture of biopsied specimens obtained from the IRIS sites. However, due to high bacillary load in the IRIS abscesses, pus culture may grow *M. tuberculosis* (9, 10).

Granulomas with or without chronic inflammation and necrosis are common in histopathologic analysis of TB-IRIS (5, 7). However, these findings can be found in other diseases including various infections (e.g., nontuberculous mycobacteria, fungi, and toxoplasmosis), sarcoidosis, extrinsic allergic alveolitis, Wegener granulomatosis, foreign body granuloma, and Kikuchi's disease (11). Therefore, the histopathologic finding of granulomas should always be interpreted with other clinical indicators of TB-IRIS, e.g., robust microbiologic response and

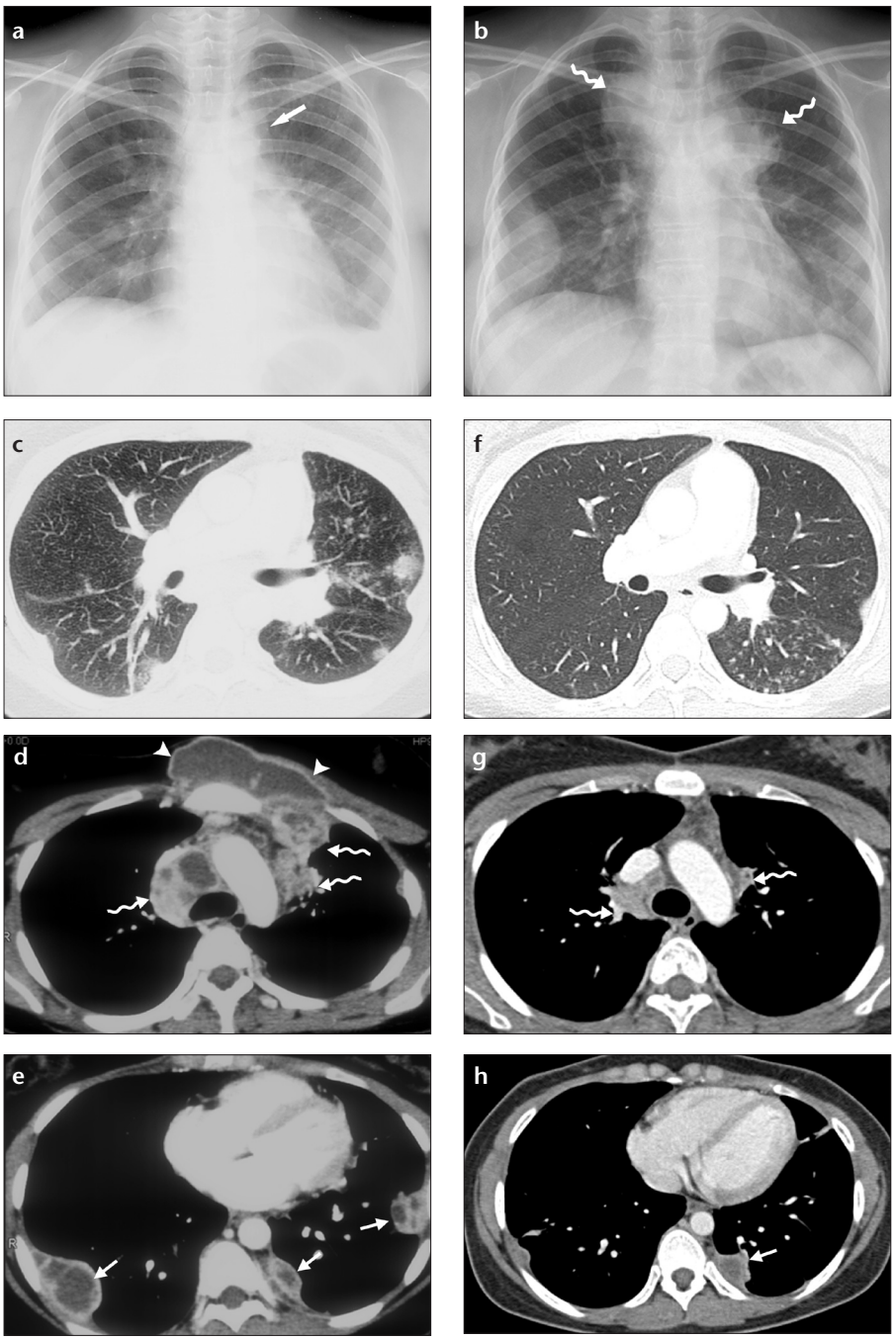

Figure 3. a–h. A 23-year-old woman with lymph node and pleural TB. Initial chest radiograph **(a)** shows a small loculated left pleural effusion, reticulonodular opacities at the bilateral upper lobes, and faint opacity *(arrow)* outlining the aortic knob. Follow-up chest radiograph **(b)** obtained five months after anti-TB treatment shows resolution of the effusion but reveals development of multiple pleural-based masses at bilateral lower lobes and progressive widening of the superior mediastinum *(arrows)*. Contrast-enhanced axial CT scans with lung-window **(c)** and mediastinal-window displays **(d, e)** reveal tree-in-bud opacities and nodular consolidation in the left upper lobe, a large abscess with rim enhancement (*arrowheads,* **d)** at the left anterior chest wall, multiple enlarged mediastinal and left internal mammary (*wavy arrows,* **d)**, and multiple pleural-based masses (*straight arrows,* **e)**. Follow-up CT scan with lung-window setting obtained after 12 months of continued anti-TB treatment **(f)** shows resolution of previous parenchymal lesions but reveals newly developed tree-in-bud opacities at the left lower lobe. Last follow-up CT scan obtained 10 months after completion of treatment **(g, h)** shows complete resolution of tree-in-bud opacities (not shown), chest wall abscess, and most lymphadenopathy and pleural-based masses, but reveals mild paradoxical enlargement of one of the pleural-based masses in the left lower lobe (*arrow,* **h**).

improvement without antimicrobial modification, and other granulomatous infections should be excluded. All patients in this pictorial essay fulfilled the diagnostic criteria for TB-IRIS.

Clinical and radiologic manifestations of TB-IRIS

TB-IRIS in HIV-negative patients is more frequent in extrapulmonary TB, notably in pleural and lymph node TB. The incidence varies from 2.4% to 25% (2, 3, 12). Predisposing factors for developing TB-IRIS include younger age, male gender, enlarging lymph nodes with local inflammation, anemia, and low lymphocyte count before treatment (2, 7). The median time to IRIS onset after initiating anti-TB drugs is typically within three months. Recurrent fever, enlarging lymph nodes and increasing dyspnea are the most common presenting symptoms (3).

Regardless of the sites of primary TB, TB-IRIS mainly involves the lymph nodes (68%) and lungs (16%) (2). Various thoracic manifestations in TB-IRIS include: new pulmonary parenchymal lesions (Figs. 1–3) (5, 7); enlarging preexisting lymphadenopathy or development of new lymphadenopathy (Figs. 3, 4) (3, 7, 8, 12); progression of preexisting pleural effusions or development of new pleural effusion (13, 14); development of new chest and abdominal wall lesions (Figs. 3, 5); and endobronchial lesions (Fig. 4). TB-IRIS usually develops ipsilateral to the side of primary TB, though contralateral or bilateral lesions can also occur (5).

Paradoxical enlargement of preexisting lymph nodes or development of new lymphadenopathy can occur in up to 25% of HIV-negative patients with peripheral TB lymphadenitis, but it is less common in those with TB meningitis and pulmonary TB (4). They usually develop within 4–14 weeks (mean, 8 weeks) after the initiation of anti-TB treatment. They can also develop within 1–13 months (mean, 3 months) after treatment completion (8, 12). Associated sinus discharge may be present.

New peripheral pulmonary nodules occur in 2.4%–11% of HIV-negative patients with pleural TB (5), and develop within three months (range, 1–9 months) after starting anti-TB therapy. Occasionally, they can develop

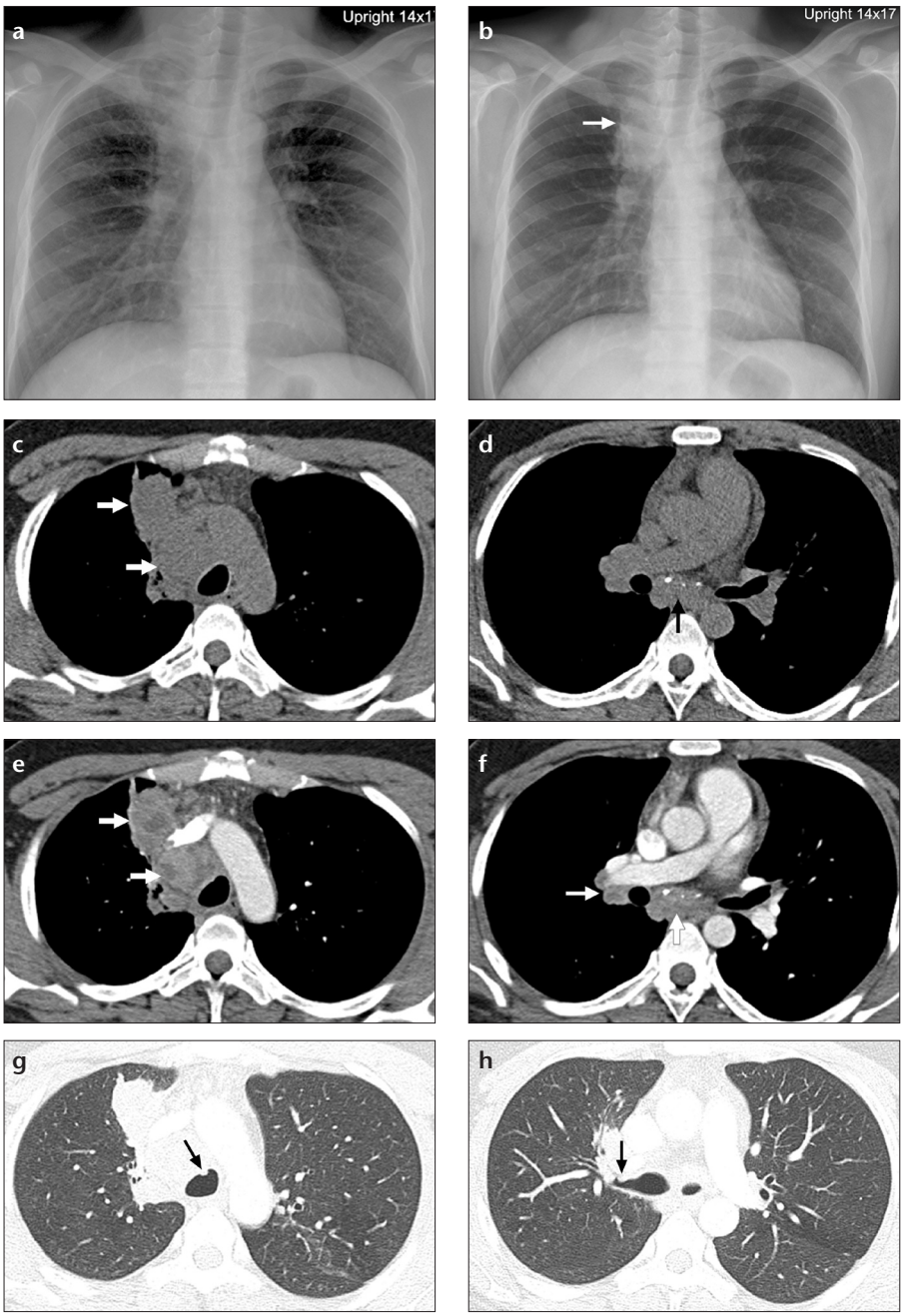

Figure 4. a–h. A 26-year-old man with pulmonary TB. Initial chest radiograph **(a)** shows right upper lobe opacities with thickening of the right paratracheal stripe. Follow-up chest radiograph **(b)** obtained three months after anti-TB treatment shows complete resolution of the right apical opacities, but with progressive thickening of the right paratracheal stripe *(arrow)*. Unenhanced **(c, d)** and contrast-enhanced **(e, f)** axial CT scans with mediastinal-window display reveal multiple enlarged mediastinal *(white arrows)* and right hilar *(thin arrow)* nodes. Note calcifications in the enlarged subcarinal nodes (*black arrow,* **d**). Axial CT scans with lung-window display **(g, h)** demonstrate new endobronchial nodules at the anterior wall of the tracheal carina and of the right upper lobe bronchus *(arrows)*. Biopsies of the endobronchial nodule and right paratracheal node revealed only granulomatous inflammation.

after complete anti-TB therapy (5). Computed tomography (CT) of the chest reveals single or multiple well- or ill-defined peripheral or pleural-based pulmonary nodules, which mostly occur ipsilateral to the pleural effusion (Figs. 1d, 1e, 2b, 2c, 3e). These nodules often abut normal or thickened pleura, contain a central low-attenuation (Figs. 1e, 2b, 2c, 3e), and usually vary 1–8 cm (mean, 3 cm) in diameter (5). These CT features may sometimes be indistinguishable from nontuberculous mycobacterial infection, rounded atelectasis, or malignancy. Unusual appearances such as new tree-in-bud opacities may also develop (Fig. 3c, 3f)

TB-IRIS presenting as a new or increased pleural effusion occurs in 16%–45% of HIV-negative patients with pleural (13, 14), lymph node (7), and pulmonary TB (4). In 80% of cases, effusions develop within 3–19 weeks of treatment initiation (14).

TB-IRIS presenting as new inflammatory or noninflammatory lesions within the skin, subcutaneous tissues, or muscles of the chest or abdominal wall is more frequently observed in HIV-negative patients with miliary or disseminated TB than in those with pleural and lymph node TB (Figs. 3d, 5c, 5d) (9, 10). After starting anti-TB treatment, lesions can occur within an average of three months (range, 17–202 days) (10), in isolation or coincident with enlarged lymph nodes or peripheral pulmonary masses (Fig. 3d, 3e).

TB-IRIS presenting as endobronchial lesions with or without associated obstruction (Fig. 4g, 4h) is rare. It can either be a newly developed paradoxical lymphadenitis with erosion or fistulation into the airways or a true *de novo* endobronchial paradoxical reaction (15).

Treatment and outcomes

Currently, there is no consensus regarding the standard treatment for TB-IRIS. Approximately half of the patients with TB-IRIS at lymph nodes experience spontaneous resolution (7). Because most of the *M. tuberculosis* strains in patients with TB-IRIS are susceptible to first-line anti-TB drugs, continuation of the standard treatment (isoniazid, rifampin, pyrazinamide, and ethambutol) for two months, followed by at least four months of isoniazid and rifampin is recommended (3). Alternative treatment is to prolong the course of anti-TB treatment to nine months, using the four drugs during the first 2–5 months, followed by isoniazid with one or two of the remaining drugs thereafter (5). Cho et al. (7) found no significant difference in relapse rates between 12 months and <9 months of treatment among patients with lymph node TB. Prolonged treatment may be required for patients with TB-IRIS involving the lymph nodes, main airways, and chest wall

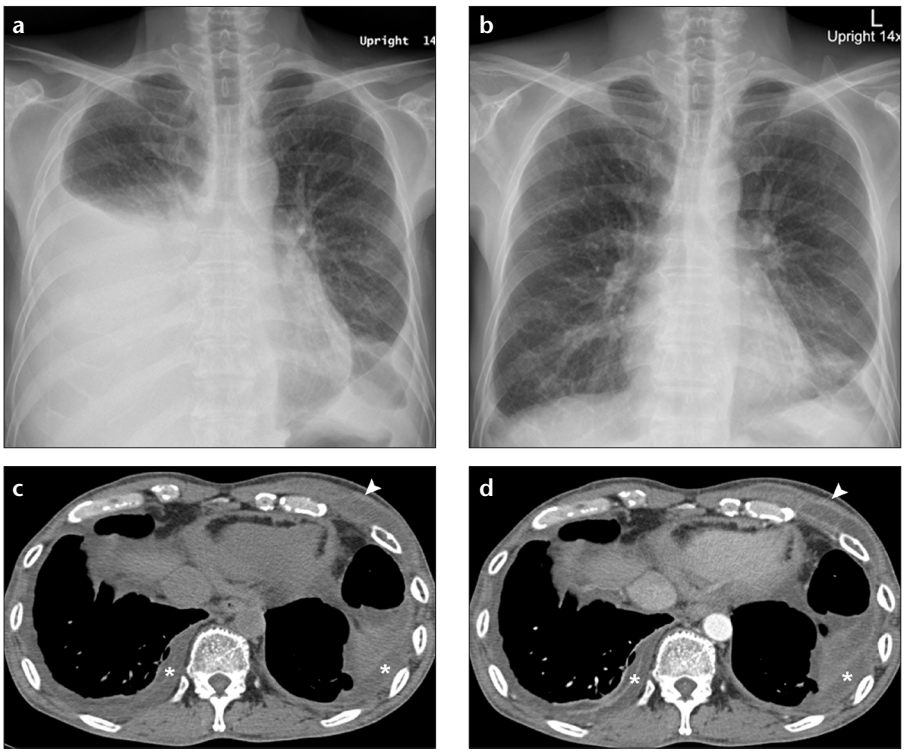

Figure 5. a–d. A 50-year-old man with pleural TB. Initial chest radiograph **(a)** shows bilateral pleural effusions. There is only residual left pleural effusion remaining at two months after anti-TB treatment **(b)**. Two weeks thereafter, he developed fever and swollen left anterior chest wall. Follow-up unenhanced **(c)** and contrast-enhanced **(d)** axial CT scans with mediastinal-window display reveal a subcutaneous abscess *(arrowheads)* at the left anterior chest wall with small loculated pleural effusions *(asterisk)* and thickened enhancing pleura, bilaterally. The aspirated pus was positive for acid fast bacilli stain and polymerase chain reaction assay for TB but negative for *M. tuberculosis* culture.

or having soft tissue abscesses. Treatments lasting 12–27 months have been reported (5). Nevertheless, the optimal treatment duration remains debatable.

There is no recommendation for treatment of TB-IRIS that develops after the completion of initial anti-TB therapy. We observed a good response with re-treatment using the standard regimen, i.e., the combined four drugs in the first two months and isoniazid and rifampin in the following seven months.

Most patients with TB-IRIS show clinical improvement in two months (range, 1–7 months) following the treatment (2). After 3–18 months of continued anti-TB treatment, lymphadenopathy and pulmonary lesions shrink or even disappear (Fig. 3g, 3h). However, the time needed for complete resolution is variable, and residual lesions may be observed (Fig. 2d). Delayed improvement with multiple recurrences can occur before complete resolution (2).

Depending on sites and severity of TB-IRIS, adjunctive therapy may be necessary. Patients with symptomatic pleural effusion generally require aspiration (14). Although soft-tissue abscesses heal within a few months, they can recur during or after treatment. In these circumstances, most patients require aspiration (10). Unlike pleural effusion and soft-tissue abscesses, only patients with severe paradoxical lymphadenopathy require aspiration (12).

Systemic corticosteroid administration for 4–6 weeks has been shown to be effective in HIV, symptomatic enlarging intracranial tuberculoma (16), and endobronchial obstruction (15), since it may reduce proinflammatory cytokines (16, 17). However, its role in other forms of TB-IRIS remains unclear.

The outcome of TB-IRIS in the thorax is favorable with a recovery rate of up to 95% (2, 12). Serious adverse sequelae or mortality is rare (4, 6).

Conclusion

Worsening or recurring preexisting tuberculous lesions or development of new lesions during or after anti-TB treatment should raise concern for TB-IRIS. Currently, the mainstay of treatment is continuation of anti-TB drugs. However, the optimal treatment duration remains debatable and should be individualized based on primary TB type and clinical response.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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