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Case Report

Complication of *Mycobacterium tuberculosis* treatment: Isoniazid-induced pneumonitis

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ABSTRACT

Prolonged therapy with isoniazid is used for the treatment of pulmonary tuberculosis. Drug-induced lupus erythematosus is a rare, adverse event associated with isoniazid use and can complicate treatment, especially if it is associated with pneumonitis. The diagnosis is made by clinical suspicion, elevated serum titers of anti-nuclear antibody and anti-histone antibody, and new ground-glass opacities on chest tomography. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy of affected areas of the lung is useful to increase diagnostic accuracy and differentiate between drug-induced pneumonitis, concomitant infection, or other inflammatory processes. Treatment includes systemic corticosteroids and cessation of isoniazid therapy.

Case report

A 33-year-old Central American migrant worker developed productive cough, fevers, night sweats and weight loss over the course of one month. A chest X-ray showed a left upper lung zone opacity with cavitation. Computed tomography (CT) of the chest showed extensive, centrilobular tree-in-bud opacities primarily in the left upper lobe with small areas of cavitation (see Figure 1(a)). A sputum culture was positive for *Mycobacterium tuberculosis*, pan-susceptible to minimum inhibitory concentrations of first-line medications for pulmonary tuberculosis. He was started on a standard treatment regimen of isoniazid (INH), rifampin (RIF), pyrazinamide, and ethambutol.

After eleven weeks of treatment, he developed a worsening dry cough and fever during the continuation phase of treatment with INH and RIF. Chest auscultation was notable for rales in the right lung zones. CT chest was performed, showing improvement of nodular airspace opacities, but there was new ground-glass opacification of the right upper lobe and right lower lobe (see Figure 1(b)). The dry cough persisted, and the ground-glass opacities became progressively worse on chest imaging.

After 14 weeks of treatment, a flexible diagnostic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBBx) of the right upper lobe was performed to investigate the dry cough and CT chest findings. BAL fluid analysis was culture-negative but significant for lymphocyte predominance. Pathology of the TBBx showed organizing pneumonitis with septal fibrosis. A pulmonary function test revealed severe restriction and severe impairment of diffusion capacity. Serum studies were significant for anti-nuclear antibody (ANA) titer 1:160, anti-double-stranded DNA antibody 12 IU/mL, and positive anti-histone antibody of 2.3 units (compared to two months prior with ANA 1:40, DS DNA of 1). These findings raised suspicion for drug-induced lupus erythematosus (DILE), causing pneumonitis. INH was discontinued, and the patient was started on Prednisone 1 mg/kg daily. On this regimen, the dry cough and ground-glass opacities on CT chest gradually resolved (see Figure 1(c)). The patient was continued on ethambutol and RIF with a slow Prednisone taper until the successful completion of antitubercular therapy.

Discussion

Drug-induced lupus erythematosus is an autoimmune response triggered by medications which can result in a clinical syndrome with manifestations similar to systemic or cutaneous lupus erythematosus. Signs and symptoms vary greatly in DILE, with

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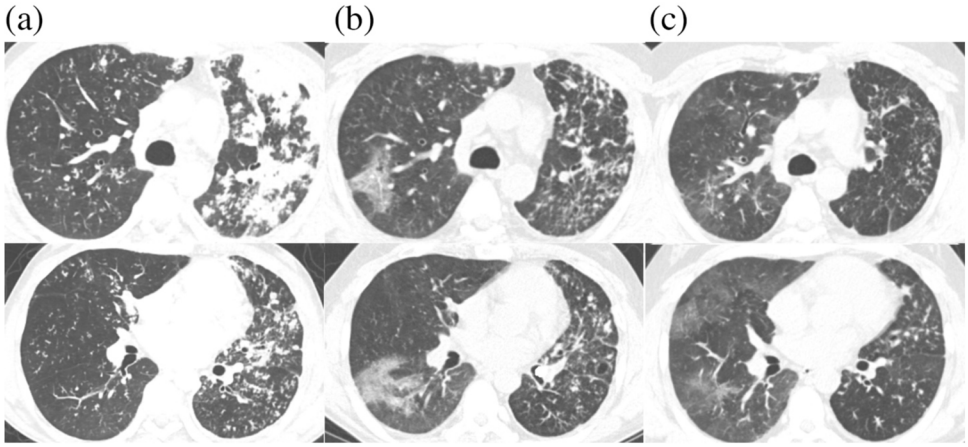

Figure 1. CT chest from left to right: upper lobes (top) and lower lobes (bottom) shown at (a) beginning of treatment for *Mycobacteria tuberculosis*, (b) onset of dry cough and fever, (c) eight weeks after cessation of INH and initiation of systemic glucocorticoid therapy.

the most common being fever, myalgias, rash, arthralgias, and serositis. Another less common associated manifestation is the development of pneumonitis. Various theories have been developed regarding the pathogenesis of drug-induced lupus; however, the exact mechanism remains unclear (Rubin, 2005). Involved factors include inherited differences in drug metabolism (e.g., acetylator status) and immunogenetic characteristics that may influence the risk of developing the disease. Autoantibodies associated with lupus induced by isoniazid are believed to target a complex of the histone dimer H2A–H2B and DNA (Rubin et al., 1992).

INH-induced pneumonitis is a rarely observed complication. We identified previous case reports utilizing a PubMed search with the keywords "pneumonia OR pneumonitis AND isoniazid OR INH." We found nine reported cases and subsequently reviewed them, focusing on presentation, diagnostic findings, and management. Eight patients developed some combination of cough, dyspnea, and fever nine days to eight months after initiating isoniazid. One denied respiratory symptoms but was evaluated for INH-induced pneumonitis after follow-up CT incidentally revealed ground-glass opacities (Migita et al., 2012). None of the patients reported specific SLE-like symptoms such as arthralgias, rash, or serositis. Our patient clinically developed a worsening cough and fever without these SLE-specific symptoms at around 2–3 months, consistent with previous reports.

Specific serum abnormalities in DILE were reflected in our patient: an elevated ANA antibody titer of 1:160, a normal DS DNA antibody titer of 12 IU/mL, and an elevated anti-histone antibody titer of 2.3 units. The rise in these serum markers coincided temporally with the ground-glass opacities found on chest CT and later diminished after discontinuation of INH and initiation of corticosteroid therapy. Similar lab findings were reported in only one other case, where a patient was found to be positive for RF, ANA, and LE-cells (Miyai et al., 1989).

In other reported INH-induced pneumonitis cases, CT scan findings varied, with most showing diffuse ground-glass opacities, abnormal lung density, and/or interstitial infiltrate or thickening. A diffuse, nodular pattern was less common and was only demonstrated in two cases (Chihara et al., 2016; Endo et al., 1998). Our patient's CT chest featured ground-glass opacities predominantly, but these were asymmetric with a predilection for the right lung fields. One possibility for our patient's asymmetry is that cavitation, and nodular opacities predominated previously in the left lung from tuberculosis resulting in scarring and fibrosis with less potential for pneumonitis.

Flexible fiberoptic bronchoscopy is often employed to evaluate the BAL's cellular patterns and examine tissue pathology with transbronchial biopsy. BAL in drug-induced pneumonitis may display either a lymphocytic cellular pattern, as in our case, or an eosinophilic pattern (Meyer et al., 2012). Transbronchial biopsies in the previous cases of INH-induced pneumonitis most commonly demonstrated lymphocytic or eosinophilic infiltration with interstitial thickening and/or alveolitis (Endo et al., 1998; Hatakeyama et al., 1998; Migita et al., 2012; Suzuki et al., 1992; Umeda et al., 2014). Our patient's transbronchial biopsy was consistent with organizing pneumonitis with septal fibrosis. This TBBx finding is nonspecific, reflecting a response of the lung to injury but has been reported with another case of INH-induced pneumonitis (Matsushima et al., 2003). Infection, collagen-vascular disease, hypersensitivity, and drug reaction are among the most common inciting factors for organizing pneumonitis (Kligerman et al., 2013). In this case, INH-induced DILE was implicated due to its idiosyncratic association with the condition combined with a lymphocyte-predominant BAL and coinciding changes in ANA and anti-histone antibody.

We managed our patient's INH-induced pneumonitis with corticosteroids and discontinuation of the medication, which was also done in four of the previous cases. However, in the other five patients, simply stopping isoniazid was sufficient to see the resolution of the episode. Additionally, two patients were placed on INH desensitization protocols and were successfully restarted on the medication without recurrence of pneumonitis (Nishizawa et al., 2004; Chihara et al., 2016). This complication of isoniazid can be challenging to diagnose due to its rarity. Still, if providers can recognize INH-induced pneumonitis, patients have previously responded well and made full recoveries after discontinuation of INH and corticosteroids, depending on severity.

Isoniazid rarely causes SLE-like interstitial pneumonia, but only one other case has described alterations in serum markers consistent with DILE (Miyai et al., 1989). Additionally, a relationship with anti-histone and DS DNA antibody has not been previously demonstrated. To our knowledge, this is the first case to demonstrate DILE as a probable pathophysiologic pathway resulting in isoniazid-induced pneumonitis. The World Health Organization (WHO) now recommends 36 months of prophylactic isoniazid therapy for those living with HIV in areas of high tuberculosis prevalence (WHO, 2015), more cases of isoniazid-induced pneumonitis should be expected. Clinicians should have a high index of suspicion if patients on isoniazid develop a new-onset dry cough, rales, and elevated serum ANA and anti-histone antibodies.

Declaration of interests

No competing interests to declare.

Ethical approval

The patient consented to publication of this case.

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