



## Case report

# Successful desensitization therapy for a patient with isoniazid-induced hypersensitivity pneumonia



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## ABSTRACT

A 57-year-old male was diagnosed with mycobacterium tuberculosis and was treated with isoniazid, rifampicin, ethambutol, and pyrazinamide. Three weeks after initiation of treatment, he presented with fever and appetite loss. Chest radiograph showed diffuse micronodular shadows on both lung fields. High-resolution chest computed tomography findings were diffuse parenchymal micronodules in both lungs, which was consistent with hypersensitivity pneumonia. Because drug-induced pneumonia was suspected, the antituberculous regimen was discontinued. The symptoms and diffuse micronodular shadows improved. A drug lymphocyte stimulation test was only positive for isoniazid, so we suspected that the pneumonia was induced by isoniazid. Rifampicin and ethambutol were reintroduced without any recurrence of the abnormal shadows. Next, we tried desensitization to isoniazid over a period of two weeks, which was successful without any adverse events. Although isoniazid-induced pneumonia is extremely rare, it is important to recognize that isoniazid can cause such an adverse reaction. In addition, drug desensitization may be useful in drug-induced pneumonia.

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## 1. Introduction

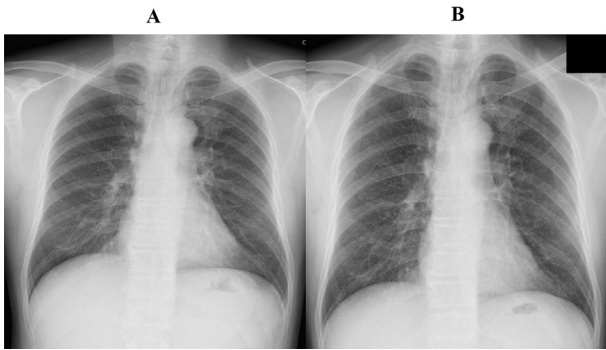
Isoniazid (INH) plays an important role in treating mycobacterium tuberculosis. Several drugs can cause drug-induced pneumonia, but INH-induced pneumonia is extremely rare. In addition, desensitization to INH in a patient with INH-induced pneumonia has not been reported. Here we report the successful desensitization to INH in a patient with hypersensitivity pneumonia that was induced by INH.

## 2. Case report

The case was a 57-year-old man who presented with abnormal shadows in the left upper lung field on a chest radiograph that was taken during a routine health examination (Fig. 1-A). He had a history of dyslipidemia, which was not treated with medications. Computed tomography (CT) of the chest showed a lung nodule measuring 28 × 20 mm in the left upper lobe. A transbronchial lung biopsy was performed, and the nodule specimen consisted of a

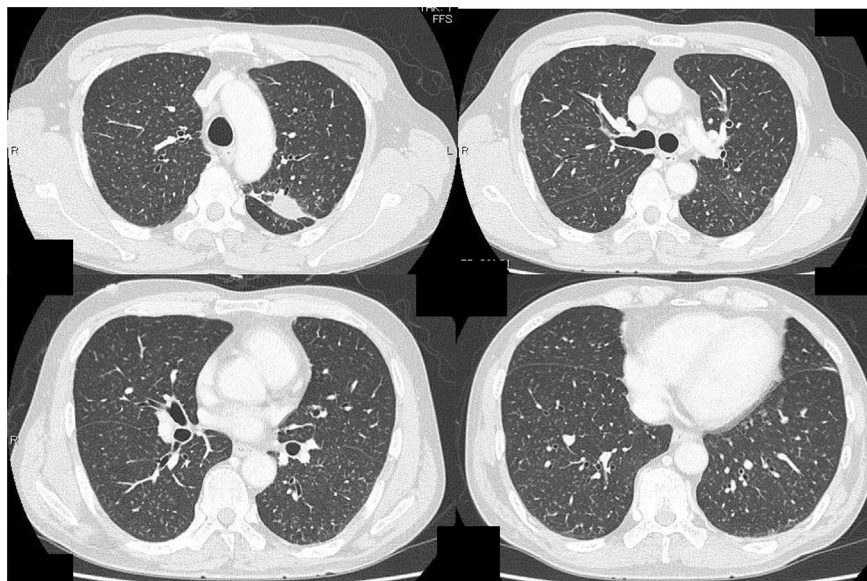
granuloma with necrosis. On Ziehl–Neelsen stain, the sputum, bronchial lavage, and nodule specimen were negative. After 6 weeks, the bronchial lavage culture yielded *Mycobacterium tuberculosis*. Therefore, we made the diagnosis of mycobacterium tuberculosis, and treated the patient with INH (0.3 g/day), rifampicin (RFP) (0.45 g/day), ethambutol (EB) (0.75 g/day), and pyrazinamide (PZA) (1.2 g/day). Three weeks later, he developed fever, headache, and appetite loss. On physical examination, body temperature was 39.1 °C, blood pressure was 96/64 mmHg, pulse rate was 112 beats/min, and percutaneous oxygen saturation (SpO<sub>2</sub>) on room air was 96%. Chest examination was normal, and no lymph nodes were palpable. At this time, a chest radiograph showed diffuse micronodular shadows in both lung fields (Fig. 1-B) and on high-resolution CT (HRCT) of the chest there were diffuse numerous parenchymal micronodules in both lungs such as in hypersensitivity pneumonia (Fig. 2). He was admitted for further evaluation. The white blood cell (WBC) count was elevated to 8700/μl with 67.9% neutrophils, 12.6% lymphocytes, 12.1% monocytes, 6.5% eosinophils, and 0.9% basophils. C-reactive protein and lactate dehydrogenase (LDH) were also elevated to 10.4 mg/dl and 243 IU/l. Other laboratory data including those for liver function, renal function, electrolytes, KL-6 (179 U/ml), and surfactant protein-D (104 ng/ml) were within normal range. Cultures of sputum, urine,

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**Fig. 1.** Chest radiographs. Before treatment with antituberculous drugs, chest radiograph showed an abnormal shadow in the left upper lung field (A). On admission, diffuse micronodular shadows in both lung fields appeared on the chest radiograph (B).

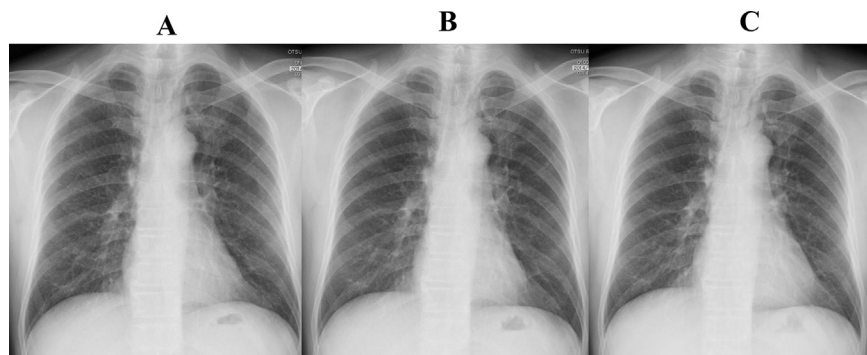
and HRCT (Figs. 3-B, 4-B) rapidly improved without any medication, including corticosteroid. A drug lymphocyte stimulation test (DLST) on a serum sample was performed. As a result, only INH was positive with an increase in the [3H]-thymidine uptake by 219% (normal < 180%), while RFP (112%), EB (90%), and PZA (98%) were negative. Based on this result, we concluded that the pneumonia was induced by INH. Ten days after the cessation of the antituberculous drugs, the patient was discharged. Two weeks after discontinuing the antituberculous drugs, PZA (1.2 g/day) was reintroduced. Although the abnormal shadows and symptoms did not return, liver dysfunction developed, and PZA was discontinued again. Since liver function recovered to normal by only stopping PZA, RFP (0.45 g/day) was reintroduced one week after discontinuing PZA, and EB (0.75 g/day) was reintroduced two weeks after discontinuing PZA. Next, we attempted desensitization to INH over a period of two weeks. The regimen for desensitization was as



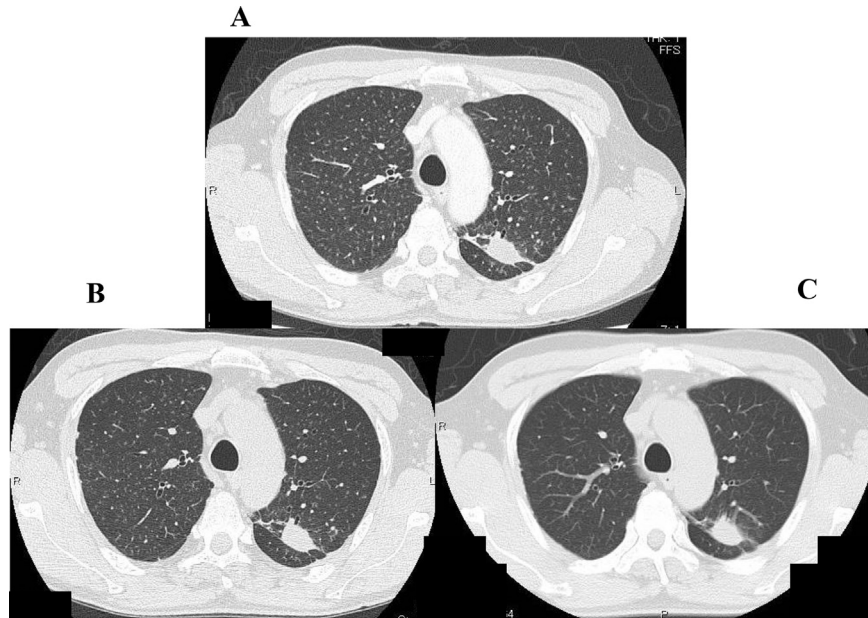
**Fig. 2.** On admission, HRCT of the chest showed diffuse numerous parenchymal micronodules in both lungs such as in hypersensitivity pneumonia. Abbreviations: HRCT, high-resolution computed tomography.

and blood showed no growth. We suspected drug-induced pneumonia and stopped the antituberculous drugs, after which his symptoms and diffuse micronodular shadows on chest radiograph

follows: days 1–3 25 mg/day, days 4–6 50 mg/day, days 7–9 100 mg/day, days 10–12 200 mg/day, and days 13 and 14 300 mg/day. Desensitization to INH was successful, and RFP, EB, and INH



**Fig. 3.** Chest radiographs on admission (A), one week after discontinuing the antituberculous drugs (B), and after reintroducing rifampicin, ethambutol, and isoniazid to which the patient was desensitized (C). One week after discontinuing the antituberculous drugs, diffuse micronodular shadows on chest radiograph rapidly improved without any medication (B). After reintroducing rifampicin, ethambutol, and isoniazid, there was no recurrence of abnormal shadows on the chest radiograph. (C).



**Fig. 4.** HRCT of the chest on admission (A), one week after discontinuing the antituberculous drugs (B), and after reintroducing rifampicin, ethambutol, and isoniazid to which the patient was desensitized (C). One week after discontinuing the antituberculous drugs, the numerous diffuse parenchymal micronodules on HRCT rapidly improved without any medication (B). After reintroducing rifampicin, ethambutol, and isoniazid, there was no recurrence of the abnormal shadows on HRCT (C). Abbreviations: HRCT, high-resolution computed tomography.

were given for 9 months without any adverse events, including recurrence of the abnormal shadows on the chest radiographs and HRCT (Figs. 3-C, 4-C).

### 3. Discussion

INH is well known to cause various adverse effects such as fever, rash, liver dysfunction, and peripheral neuropathy. On the other hand, INH-induced pneumonia is rare and case reports have been few [1,2]. It was reported that HRCT findings for INH-induced pneumonia were similar to those of eosinophilic pneumonia and were observed as diffuse patchy ground-glass opacity, interlobular septal line thickness, centrilobular opacity, and intralobular interstitial thickening [2]. In the present case, the HRCT findings mainly consisted of the appearance of diffuse parenchymal micronodules such as in hypersensitivity pneumonia. Since drug-induced pneumonia by the same drug can cause various HRCT patterns, it should be recognized that a diagnosis of drug-induced pneumonia can be complicated.

In the present case, we made the diagnosis of INH-induced pneumonia based on the negative results of the culture, rapid improvement in symptoms, findings by chest radiograph and HRCT after the antituberculous drugs were discontinued, and results of DLST. The usefulness of the DLST for antituberculous drugs was controversial [3,4]. However, in this case the DLST was only positive for INH, and RFP, EB, and PZA could be reintroduced without any recurrence of the abnormal shadows. Therefore, we concluded that the pneumonia was induced by INH.

The efficacy of desensitization to INH was described previously [5]. Although the guidelines for providing desensitization therapy may vary by country or region, desensitization to INH succeeded in 19 of 24 patients (79.2%) according to the regimen recommended by the Japanese Society for Tuberculosis. However, there has been

no previous report on the desensitization to INH in a patient with INH-induced pneumonia. Using the regimen recommended by the Japanese Society for Tuberculosis, we succeeded in desensitization to INH in a patient with INH-induced pneumonia. Therefore, we consider that desensitization to INH is useful in the treatment of INH-induced pneumonia. On the other hand, desensitization therapy is recommended only for isoniazid or rifampicin induced fever or eruption by Japanese Society for tuberculosis. We must be watchful for the reappearance of hypersensitivity pneumonia during the desensitization therapy.

In conclusion, we experienced a case of INH-induced pneumonia. Although this adverse event is very rare, clinicians should be aware of INH-induced pneumonia when a new pulmonary infiltrate develops in patients being treated by INH. In addition, our results raise the possibility that desensitization to INH may be a useful tool for reintroducing INH in patients with INH-induced pneumonia.

### Disclosure of conflict of interest

The authors state that they have no conflict of interest.

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