

Missed Diagnosis

Pulmonary infiltrates and fever induced by isoniazid

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Summary: An 88 year old woman with bacteriologically confirmed pulmonary tuberculosis was first treated with isoniazid, rifampicin and pyrazinamide. Two weeks later she developed pulmonary infiltrates with fever. A drug-induced reaction was suspected but the reaction recurred three times until isoniazid was identified as the cause. The reaction became worse each time, finally being nearly fatal.

Introduction

Isoniazid is the key drug in the treatment of tuberculosis and is of definite value in chemoprophylaxis. It is a well tolerated drug and side effects are encountered only in about 2–3% cases.^{1,2} Fever and rash are the most frequent.³ Pulmonary infiltrates are rare, only few case reports of hypersensitivity pneumonitis having been previously described.

We report a patient with a very severe isoniazid-associated reaction which included pulmonary infiltrates, fever and hypoxia.

Case report

An 88 year old woman was admitted because of cough, purulent sputum and occasional fever for about 3 months. Chest X-ray showed left upper and right middle lobe inflammatory infiltrates (Figure 1). Sputum smears for acid-fast bacilli were positive and cultures grew fully sensitive strains of *M. tuberculosis*.

Chemotherapy was started with single daily doses of isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1.5 g and pyridoxine 20 mg per day. After 2 weeks' chemotherapy the patient became febrile (38.5°C). She also had pain in the abdomen, nausea, vomiting and diarrhoea. No rash was seen, liver function tests remained normal and urine cultures were negative. Chemotherapy was discontinued and the temperature fell within 4 days. After an afebrile day isoniazid and rifampicin were introduced and pyrazinamide was stopped since it was less significant and suspected of causing the reaction. Within 6 hours the temperature rose

again (39.3°C) and the patient became dyspnoeic. Intravenous theophylline and corticosteroids were given and the reaction subsided within a few hours. The erythrocyte sedimentation rate was 56 mm/h (previously 26 mm/h), C-reactive protein 116 mg/l (previously < 5 mg/l), white cell count $15.8 \times 10^9/l$ with no eosinophils. Liver function tests remained normal. A chest radiograph showed new widespread infiltrates in the lower lobes of both lungs, the right pleural sinus was rounded and the interlobar fissures were thickened.

The blood culture was taken because of spiking fever and it was positive for *Bacillus subtilis*. The chemotherapy was again discontinued, and, on the assumption of septicaemia, antibiotic therapy was administered intravenously for 11 days. However, the positive blood culture was probably a contamination. Deep venous thrombosis was confirmed by venography and anticoagulant therapy was commenced. Four days after the previous chest X-ray the new lung infiltrates were diminished and there was no sign of pulmonary embolism.

After becoming afebrile she was given isoniazid 300 mg alone, 4 weeks after the start of chemotherapy. Within 2 hours her temperature was 38.2°C, she was very ill and experienced severe dyspnoea. The respiratory rate was high at 25/minute, and there were inspiratory rales on auscultation. The arterial blood oxygen was 6.2 kPa in spite of continuous oxygen administration, carbon dioxide 6.0 kPa. With corticosteroids, theophylline and adrenaline she recovered in a few hours and was afebrile the next day. A chest X-ray showed pleural fluid and new diffuse alveolar and interstitial infiltrates (Figure 2). The blood gas abnormalities and chest X-ray changes had resolved within 6 days.

The patient thus received isoniazid on three occasions and each time the reaction became worse. Treatment was established on rifampicin and ethambutol without further side effects.

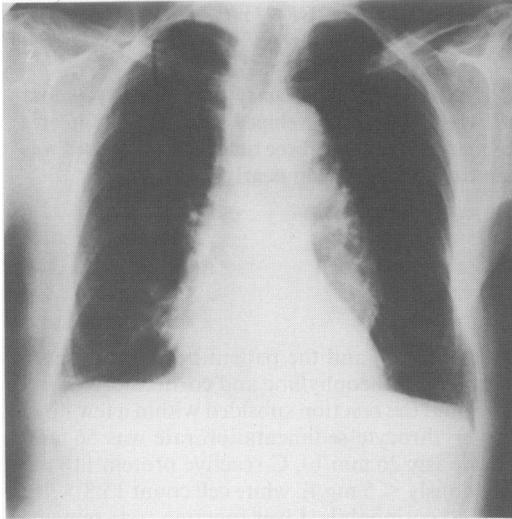


Figure 1 Chest X-ray on admission. Left upper lobe and right middle lobe infiltrates.

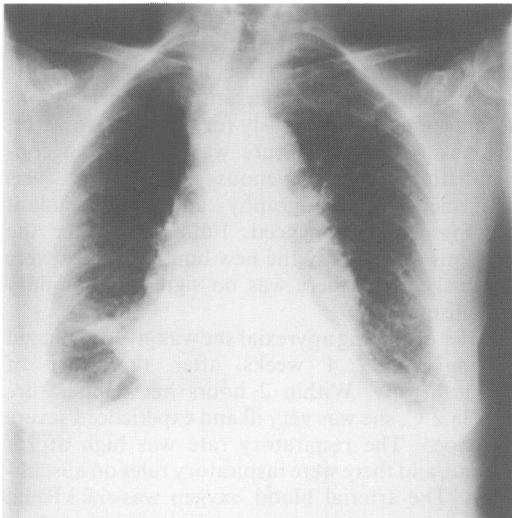


Figure 2 Chest X-ray a day after the third febrile reaction. Diffuse alveolar and interstitial infiltrates in lower lobes and pleural fluid.

Discussion

Krasnitz was among the first to describe isoniazid-induced fever in 1953.⁴ Fever is encountered in about 1% of patients receiving isoniazid,^{1,2} either alone or with rash, joint symptoms or hepatitis. Lung infiltrates have been acute,⁵ as in our patient, or of slow onset interstitial pneumonia as reported recently in one patient.⁶ Peripheral eosinophilia has been demonstrated occasionally^{7,8} but was not seen in our patient. Isoniazid-induced infiltrates and fever may lead to diagnostic confusion: they may be attributed to the tuberculous infection itself, to a concomitant bacterial infection or to other drugs.

Fever due to isoniazid occurs within 9–47 days after starting chemotherapy, a delay compatible with an immunological process.^{9,10} On rechallenge, fever usually occurs in 2–5 hours. This was also the case in our patient. The diagnosis of drug fever depends primarily on clinical observation. No laboratory test is diagnostically useful as far as hypersensitivity-type drug fever is concerned. The demonstration of antibodies to a drug by serological or skin tests is not helpful.¹¹ Febrile reactions to isoniazid should lead to the discontinuation of chemotherapy, because the clinical symptoms may become even life-threatening. There are reports that chemotherapy might be continued without complications by desensitization which is easily achieved in most patients with gradually increasing doses.^{2,4,10} Pulmonary or cutaneous reactions, providing they are not severe, might be suppressed by corticosteroids. In our patient the severity of reaction left no choice but to discontinue the drug.

The diagnosis of isoniazid reaction was delayed in our patient because of misleading findings, a bacterial infection suspected on the basis of laboratory tests, a previous urinary tract infection, the positive blood culture due to contamination, and pulmonary infiltrates mimicking pneumonia. A deep venous thrombosis further added to the confusion. We also delayed the correct conclusion by reintroducing simultaneously two drugs after the first reaction.

Although pulmonary infiltrates with a febrile reaction to isoniazid are uncommon, a high index of suspicion could prevent an expensive diagnostic work-up and needless drug therapy.

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