Antituberculous Therapy - Induced Toxicity

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Abstract
Antituberculous drugs are generally safe but can occasionally be associated with life-threatening complications. This is a case report of neurotoxicity, acute respiratory distress syndrome (ARDS) and drug fever, occurring in a patient after initiation of antituberculous therapy (ATT).

INTRODUCTION
Anti-tuberculous therapy is generally considered to be safe among the several long term treatment courses that are available for infectious diseases. However, these drugs can be associated with serious adverse drug reactions such as anaphylaxis,1 fulminant hepatotoxicity, and respiratory failure due to severe pneumonitis.2-4 We report a case of a patient who developed neurotoxicity, ARDS that required mechanical ventilation in the medical intensive care unit (MICU), and drug fever after the initiation of ATT.

CASE HISTORY
A 38-year-old diabetic male on glibenclamide 2.5 mg once daily (OD) presented with fever of ten days to a community hospital. He was started on a thrice weekly ATT regimen: 600 mg isoniazid (INH), 600 mg rifampicin (RIF), and 2000 mg pyrazinamide (PZA) for genitourinary tuberculosis (TB) diagnosed on detection of acid fast bacilli (AFB) in urine. The fever subsided but he developed persistent headache and one episode of generalized tonic-clonic seizure (GTCS) nine days after starting ATT. A computerized tomography (CT) of the head showed a calcified lesion in the right centrum semi-ovale. He was referred and hospitalized into our center on 25/10/1998, where physical examination and laboratory investigations including hemogram, electrolytes, urine, and cerebrospinal fluid (CSF) were found to be normal. However, a day later, he developed status epilepticus which was controlled by thiopentone in the MICU. As the seizures were associated with the recent introduction of ATT, it was discontinued. While in the MICU he acquired a ventilator-associated pneumonia caused by *Pseudomonas* spp. and was treated with ceftazidime. Following recovery the TB drugs were not rechallenged as there was no clinical evidence of TB and urine AFB were absent. He was advised to continue oral phenytoin (100 mg thrice daily).

After four symptom-free years while continuing phenytoin 300 mg daily, he developed a unilateral epididymal swelling which on histopathological examination showed caseating granulomas consistent with TB and ATT was restarted: INH + Vit. B₆ (450 mg + 10 mg), RIF (600), PZA (1200), and Ethambutol (EMB) (800) daily. After seven days of therapy he developed a low grade continuous fever associated with headache, vomiting, and delirium that required hospitalization. On examination the Glasgow Coma Scale was 9/15 (Eye 4; Verbal 1; Motor 4), temperature 101°F, pulse rate 92 per minute and blood pressure 110/70 mm Hg. The optic fundus was normal and there were no neurological deficits or signs of meningeal irritation.

The investigations included: hemoglobin 14.2 gm%; white blood cell count of 6,600/mm³, neutrophils 75%, lymphocytes 16%, monocytes 6%, eosinophils 3%. Three blood smears for malaria were negative and bleeding parameters were normal. Random blood sugar was 308 mg%. The serum electrolytes, creatinine and creatinine phosphokinase were normal. Total bilirubin was 2.1 mg%, direct bilirubin 1.5 mg%, total protein 6.6 g%, albumin 3.6 g%, AST 104 U/L, ALT 90 U/L, and LDH 661 U/L. Blood on aerobic culture was sterile. Urine culture showed >100,000/ml colonies of yeast. Three sputum AFB smears and culture for mycobacteria were negative. Weil-Felix, Widal, anti-nuclear antibodies, dsDNA and HIV ELISA were negative. Electroencephalogram was normal. Magnetic resonance imaging of the head revealed a small area of calcification in the right temporo-parietal region, corresponding to the lesion seen on the CT four years ago. CSF showed white cell count of 40/mm³ with a lymphocytic predominance (99%); red blood cells 5/mm³; glucose 89 mg%; protein 177 mg%. CSF aerobic and mycobacterial cultures were negative.

On the second hospitalization day he developed an episode of GTCS. A possible re-occurrence of INH neurotoxicity was considered and streptomycin (SM) (750 mg OD) substituted. However, a day later, he developed dyspnoea with rhonchi and extensive bilateral lung
crepitations. Chest radiograph revealed bilateral, non-segmental fluffy opacities (Fig. 1), and an arterial blood gas (ABG) analysis showed type I respiratory failure with a PaO$_2$: FiO$_2$ ratio <200 that was consistent with ARDS. The low central venous pressure was corrected with colloids, and he received ventilatory support for the worsening hypoxemia. The possibilities of an ATT-induced allergy or a septic shock were considered and therefore all anti-TB drugs were stopped. He received intravenous hydrocortisone (100 mg q6h), phenytoin (100 mg q8h), cefotaxime (2 gm q8h), and bronchodilators. Clearance of the pulmonary infiltrates on chest radiograph (Fig. 2) was seen after 36 hours alongwith a significant improvement in the ABG and he was extubated within four days.

This time as the epididymal histology and abnormal CSF suggested a disseminated form of TB, anti-TB drugs were restarted sequentially. He tolerated RIF (450 mg) and EMB (800 mg) once daily, but developed high grade fever with chills and rigors within six hours of starting PZA that settled in a day after its withdrawal and Ofloxacin (400 mg OD) was substituted for the latter. On follow up eight months later the epididymal swelling had disappeared and he was continuing the anti-TB drugs (RIF, EMB, OFX), glibenclamide, and phenytoin with no untoward reactions.

**DISCUSSION**

Isoniazid-induced neurotoxicity is a well described entity that includes seizures, memory loss, encephalopathy, ataxia, peripheral neuritis, and it is more commonly seen in slow INH acetylators. As our patient was seizure-free for four years while on regular doses of phenytoin, we attribute the seizure recurrence to one of the TB drugs, probably INH, or a lowered serum level of phenytoin due to induction of hepatic microsomal enzymes by RIF. However, he continued to receive both RIF and phenytoin with no further seizures suggesting that INH neurotoxicity was the most likely cause. In diabetes, the metabolism of INH is decreased and this may lead to drug accumulation, thereby increasing the likelihood of toxic side effects.5

The temporal relationship of ARDS with the initiation of ATT, and rapid recovery following its withdrawal, suggests a direct lung injury associated with it. There are case reports...
of INH-induced pneumonitis that has resolved after its withdrawal and treatment with steroids. EMB and RIF are rarely associated with hypersensitivity lung reactions, but our patient continued to receive them with no further adverse effects. Streptomycin can also induce anaphylaxis and bronchospasm, but is not known to cause such widespread pulmonary infiltrates. Sepsis-related ARDS, aspiration or other causes of infectious pneumonias would not have improved so soon after ATT withdrawal. It has been postulated that acute respiratory distress occurring in patients on ATT for advanced pulmonary TB may represent ‘local manifestations’ of heightened delayed hypersensitivity, mounted by increasing numbers of lymphocytes against antigens released from dying tubercle bacilli in patients whose cellular immunity is being enhanced as a result of chemotherapy. However, this is unlikely in our patient as he did not have pulmonary tuberculosis and the epididymal swelling which had shown evidence of TB on histology did not worsen after starting ATT. Hence the ARDS in this case was drug-induced and we felt that INH was the most likely cause in view of its reported association with pneumonitis.

Our patient had two other unusual side effects of ATT viz. INH neurotoxicity and PZA-induced drug fever. Hence clinicians should always consider, in situations of clinical deterioration when a firm diagnosis of TB is established, an adverse drug reaction after initiation of ATT.

REFERENCES


Announcement

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Date : 6th June - 8th June, 2003
Venue : Southern Railway Hospital Auditorium, Perambur, Chennai.
Registration Fee : Rs. 500/- (Rs. Five Hundred Only)
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SN Narasingan
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