Case Report

Isoniazid-induced flu-like syndrome: A rare side effect

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ABSTRACT

Drug-induced flu-like syndrome is very rare. It is mainly produced by rifampicin. We report a case of pulmonary tuberculosis (PTB) that developed isoniazid-induced flu-like syndrome, but could be cured with a modified regimen replacing isoniazid with levofloxacin. A 10-year-old girl with PTB was treated with isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). She developed features of flu from the sixth day. Symptoms occurred everyday within 1 h of drug ingestion and subsided automatically by next 12 h. After admission, HREZ were continued. She developed symptoms of flu after 1 h of drug ingestion. Antitubercular therapy (ATT) was stopped and symptoms subsided automatically. Individual drug was started one by one after three days. Severe symptoms of flu developed after taking isoniazid, while other drugs were tolerated well. Levofloxacin was used as an alternative to isoniazid. She was cured after 6 months of chemotherapy. Isoniazid can possibly cause flu-like syndrome and the treating physician should be aware of this possible side effect when using ATT.

KEY WORDS: Flu-like syndrome, isoniazid, pulmonary tuberculosis

INTRODUCTION

Flu-like syndrome is variably defined in different countries.\(^1\) Sudden onset fever (more than 38°C or 100.4°F), chills, malaise, dry cough, loss of appetite, body aches, and nausea are the common manifestations of flu-like syndrome. It mostly occurs in influenza virus infection but may also occur in infections with rhinovirus, adenovirus, respiratory syncytial virus, malaria, acute human immunodeficiency virus infection, herpes, dengue fever, etc., and use of pharmaceutical agents like interferon, monoclonal antibodies, bisphosphonates, levamisole, and antitubercular drugs (ATD). Among the antitubercular drugs rifampicin is the most commonly responsible for this syndrome. Though the precise mechanism of rifampicin-induced flu-like syndrome is not known, it is possibly related to production of rifampicin-dependent antibody. Ethambutol also can cause flu-like illness. Many cases of isoniazid-induced drug fever have been recorded so far, but none of those patients had any symptoms of flu. Only three cases of isoniazid-induced flu-like syndrome have been recorded from China till date.\(^2\) We have reported a case of isoniazid-induced flu-like syndrome.

CASE REPORT

A 10-year-old girl presented to a local physician with fever, productive cough, and weight loss for 3 months. Sputum smear for acid fast bacilli (AFB) was positive and chest radiograph had cavitary lesion right upper zone. She was put on daily therapy with HREZ. From the sixth day, she developed high fever with chill and rigor, rhinorrhea, dry cough, mild breathlessness, and generalized body ache. She was referred to our hospital after 40 days of chemotherapy. On admission she had body weight of 22 kg, axillary temperature of 38°C, and pallor. Examination of respiratory system revealed coarse crepitation in the right infraclavicular region. Other systems were normal.

Blood examination revealed hemoglobin 12 g/dL, normal total and differential leucocyte count with normal blood biochemistry. Sputum smear was positive for AFB. Chest radiography revealed right upper zone thin-walled empty cavity.
HIV serology I and II were nonreactive. No organism grew on aerobic and anaerobic culture of blood and urine after 72 h. Viral culture facility was not done due to lack of facility. Real-time PCR for influenza virus was negative.

She was put on WHO category I ATD regimen (2H₃RₑZₑ/4HₑRₑ). After 1 h of taking the drugs, she developed fever (39°C) with chill, cough with blocked nose, mild breathlessness, body ache, and nausea. 100 mg intravenous hydrocortisone, 25 mg intramuscular promethazine, and 250 mg oral paracetamol were given immediately, but no improvement was noted in next 1 h. Except chill, all other symptoms persisted for next 14 h, after which they subsided spontaneously.

ATD was stopped for next 3 days and she remained asymptomatic. There was no change in the total leucocyte count, hepatic enzymes, or any increase in the serum immunoglobulin E (Ig E) level.

On the fifth day, 400 mg ethambutol was reintroduced orally which she tolerated well.

On the sixth day, 100 mg isoniazid was reintroduced orally. After 1 h she developed high fever (38.8°C) with chill, blocked nose, cough, body ache, and nausea. Symptomatic management was given. Fever with chill subsided after 4 h, other symptoms subsided gradually in next 12 h. Isoniazid was withheld.

Subsequently, oral rifampicin (250 mg) and pyrazinamide (500 mg) were reintroduced successfully without any adverse reaction in next 2 days.

Suspecting the drug isoniazid as culprit, it was reintroduced orally on the ninth day. Similar symptoms developed within an hour and recovered as before.

On the tenth day, isoniazid was given in a very small dose (10 mg) orally and the same symptoms developed after 1 hour but with less severity. There was fever, nasal blockage, and body ache, but no chill or breathlessness.

On the eleventh day, a similarly looking placebo tablet was given in empty stomach. There was no adverse reaction noted. Considering isoniazid as the culprit drug, it was withdrawn from the regimen and oral levofloxacin (LFx) (200 mg) was introduced, which she tolerated well. Anti-isoniazid antibody in serum was not done due to lack of facility.

Finally, she was put on a modified regimen comprising REZLFx daily. Patient tolerated the regimen very well without any evidence of chondropathy. Her sputum smear for AFB was negative on 2nd, 4th, and 6th month of therapy. There was significant improvement in the chest X-ray also. She was declared cured at the end of chemotherapy.

**DISCUSSION**

Among the ATDs, rifampicin is the commonest drug to produce flu-like syndrome.[3] Rifampicin-induced flu-like syndrome typically begins 2-3 h after drug ingestion and lasts up to 8 h.[4] It often occurs with intermittent high dose of rifampicin, when patient has been irregular in taking daily rifampicin or when the drug has been resumed after a gap of few days to months. The precise steps in the evolution of rifampicin-induced antibody are uncertain. It is possible that rifampicin acts as a hapten, being bound to macromolecules in plasma. This become antigenic and stimulates antibody formation. These hapten–antibody complexes bind complements and result in different hypersensitivity reactions of rifampicin.[5] Ethambutol also can cause flu-like illness.[6] Though isoniazid has been responsible for drug fever on several occasions,[7,8] flu-like syndrome due to isoniazid is very rarely reported.[2] Ethambutol-induced hypersensitivity reaction has been reported from Taipei.[9] In our case, the flu syndrome followed similar time course, but was not associated with any hypersensitivity reaction like skin rash, eosinophilia, raised serum IgE level, or abnormal liver enzymes. Anti-isoniazid antibody could not be assessed due to nonavailability of this antibody detection facility. Although the confirmatory viral culture could not be done in our patient, but intermittent signs and symptoms of flu are unlikely in true influenza or any other viral infection. The Naranjo adverse drug reaction probability scale is now accepted worldwide to establish the cause and effect relationship between a drug and its adverse effect.[10] In our patient total score is 11 (Table 1). So, it definitely

**Table 1: The Naranjo adverse drug reaction probability scale: (It is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4, and doubtful if the score is 0)**

| Questionnaire                                                                 | Yes | No | Don’t know |
|------------------------------------------------------------------------------|-----|----|------------|
| 1. Are there previous conclusive reports on this reaction? 1/0/0               | 1   | 0  | 0          |
| 2. Did the adverse event occur after the suspected drug was administered? 2/-1/0 | 2   | 0  | 0          |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? 1/0/0 | 1   | 0  | 0          |
| 4. Did the adverse reaction reappear when the drug was re-administered? 2/-1/0 | 2   | 0  | 0          |
| 5. Are there alternative causes (other than the drug) that could have caused the reaction? 1/2/0 | 0   | 2  | 0          |
| 6. Did the reaction reappear when a placebo was given? -1/1/0                | 0   | 1  | 0          |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? 1/0/0 | 0   | 0  | 0          |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? 1/0/0 | 1   | 0  | 0          |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? 1/0/0 | 1   | 0  | 0          |
| 10. Was the adverse event confirmed by any objective evidence?                | 0   | 0  | 0          |

Total score = 11
establishes the fact that the flu-like syndrome in our patient is due to the drug isoniazid.

CONCLUSION

Isoniazid-induced flu-like syndrome, though very rare, should be considered in a patient getting isoniazid and presenting with flu-like syndrome. Simple stoppage of isoniazid and its replacement with a suitable alternative drug is the best possible management in these cases.

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Announcement

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