Isoniazid (INH)-Induced Eosinophilic Exudative Pleural Effusion and Lupus Erythematosus
A Clinical Reminder of Drug Side Effects
Saakshi Khattri, M.D., Anurag Kushawaha, M.D., Kumud Dahal, M.D., Maryann Lee, M.D., and Neville Mobarakai, M.D.

Abstract
A 75-year-old Latin-American female was admitted for a 4-week history of dyspnea, nonproductive cough, and pleuritic chest pain. Her past medical history was significant for hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation. In addition to her routine medications and anti-coagulation for her atrial fibrillation, for the preceding 3 months, the patient also had been started on isoniazid (INH) 300 mg daily, along with pyridoxine supplements for latent tuberculosis (positive PPD skin test). She denied smoking, alcohol use, or illicit drug use. Her social history was unremarkable, except for exposure to one person with tuberculosis. As an outpatient, she had finished a one-week course of moxifloxacin for an upper respiratory tract infection prior to presentation.

In the emergency department, her vitals were the following: temperature, 98.6°F; blood pressure, 141/66 mmHg; heart rate, 101/min; and respiratory rate, 18/min. Her oxygen saturation was 98% on room air by pulse oximetry. Physical examination revealed fine crackles bilaterally, an irregularly irregular pulse, and mild pedal edema. A review of systems was notable for subjective chills and night sweats. Initial labs were notable for a β-natriuretic peptide (BNP) of 290 pg/mL. Her WBC count was 10.2 x 10^3 cells/µL. Her INR (international normalized ratio) was 1.5. The first set of cardiac enzymes was negative. Chest radiograph showed moderate bilateral pleural effusions and bibasilar opacities suggestive of a pneumonic process. The electrocardiogram showed rate-controlled atrial fibrillation. Blood cultures were drawn, and the patient was started on intravenous ceftriaxone and azithromycin for possible community-acquired pneumonia and admitted, with all of her outpatient medications, including INH and vitamin B6, continued in the hospital.

Over the next 4 days, she continued to complain of dyspnea, dry cough, and intermittent chest pain. Three sets of cardiac enzymes were negative. A two-dimensional echocardiogram revealed normal systolic function. Lower extremity duplex scanning was negative for deep venous thrombosis (DVT). Although the patient remained afebrile, her WBC counts increased to 13.6 x 10^3 cells/µL. Blood cultures were negative. A repeat chest radiograph revealed persistent bilateral pleural effusions. Antibiotics were continued.

On hospital day 7, chest computed tomography (CT) with contrast demonstrated right lower lobe consolidation with air bronchograms and a complex right pleural effusion; there was no evidence for pulmonary embolism. A diagnostic thoracentesis removed 40 cc of cloudy, orange-tinged fluid.
and had a persistent cough. She then began to develop gen-

eralized anasarca, metacarpalphalangeal joint pain, and right temporomandibular joint tenderness. The ESR was elevated at 66 mm/hr, and the CRP level also increased to 12.8 mg/dL. The patient’s ANA titer was positive (1:1280). Anti-MPO (myeloperoxidase) antibodies were also positive. RF testing was negative.

On hospital day 20, further testing revealed positive double-stranded DNA (dsDNA) antibodies and decreased C3 and C4 complement protein levels. She was started on oral prednisone for drug-induced lupus, likely secondary to INH therapy. INH was discontinued and rifampin was started for latent tuberculosis treatment. Over the next few days, her dyspnea improved, her cough resolved, and, subsequently, the chest tube was removed. Her anasarca and arthralgias markedly diminished. After 25 total days of hospitalization, the patient was discharged on oral prednisone (as well as her other medications) to a skilled nursing facility for physical therapy. Prior to her discharge, anti-histone antibodies were assessed. The anti-histone antibodies were reported markedly positive, 9U, (reference level, less than 1U). A repeat chest radiograph done 2 weeks later showed complete resolution of the pleural effusions.

**Discussion**

INH is one of the first-line anti-tuberculosis medications used for prevention and treatment. Patients with a recently positive PPD skin test and normal chest radiograph are routinely given 6 to 9 months of INH therapy. The mechanism of action of INH is to inhibit mycolic acid synthesis needed for integrity of the mycobacterial cell wall.

Several adverse effects from long-term ingestion of INH have been reported, including peripheral neuritis, CNS (central nervous system) effects, hepatitis, sideroblastic anemia, as well as others. The peripheral neuritis and CNS effects are related to pyridoxine (vitamin B6) depletion and are an important reason for pyridoxine supplementation in patients receiving INH.

A wide range of medications have the potential to induce side effects that mimic autoimmune syndromes. INH has been implicated as one of over 80 medications implicated in drug-induced lupus erythematosus (DILE), which has been defined as a lupus-like syndrome that is temporarily related to continuous drug exposure (from 1 month to over a decade) and resolves after cessation of the offending pharmacologic agent.1 INH is known to cause a positive ANA in 25% of patients and clinically apparent drug-induced lupus in approximately 1% of patients.2

There are currently no standardized diagnostic criteria for DILE, and the underlying pathophysiology has not yet been elucidated. However, the range of symptoms that are usually observed include four: arthritis, serositis, anti-nuclear, and anti-histone antibodies; in addition, the symptoms must have begun after initiation of the drug and resolve upon discontinuation of the medication.3,4 Our patient had evidence of systemic DILE. Her manifestations included typical lupus-
like symptoms, including joint pain, systemic involvement with pleuritis and pleural effusions, and positive antinuclear and antihistone antibodies. Her symptoms dramatically improved upon stopping INH therapy. This patient fulfilled all of the previously mentioned criteria, which provides strong supporting evidence that INH was the culprit causing the DILE. Furthermore, it was unlikely that this 75-year-old patient had underlying, long-standing systemic lupus that had gone undiagnosed.

While INH-induced lupus is a well-known medical entity, there have been few cases of INH-induced pleural effusion documented in the literature. INH-induced pleural effusion usually begins 3 to 12 weeks after starting the medication and regresses after a change of therapy or introduction of steroids, or both. In our patient, pleural effusion began after approximately 12 weeks, or about 3 months, following initiation of INH therapy. Similar to a recent case report describing INH-induced pleural effusion, an exudative effusion was revealed on each thoracentesis procedure. In contrast to transudative effusions, which are usually due to disequilibrium of local oncotic and hydrostatic forces, exudative effusions are often due to a variety of inflammatory conditions. While the exact pathogenic mechanism of INH-induced pleural effusion remains unclear, this indicates that the disease entity may have an underlying inflammatory component. The dramatic improvement of her autoimmune symptoms after starting prednisone, an anti-inflammatory agent and immunosuppressant, partially supports this notion. Postulates have been introduced to explain the phenomenon of INH-induced pleural effusion, including “immunological rebound” or an effect between mycobacterial products and improving host immunity. However, none of these theories have been substantiated.

Of note, the pleural fluid analysis done on hospital day 10 revealed 11% eosinophils. At least 10% eosinophils define the condition of “eosinophilic pleural effusion” (EPE) and account for about 5% to 8% of EPEs. Her peripheral eosinophil count was normal during her hospitalization, and, as such, the pleural fluid eosinophil count does not correlate with the number of blood eosinophils. While the majority of EPEs are caused by pneumonia, malignancy, or pulmonary embolism, infrequently they are caused by medications; case reports have described warfarin, propylthiouracil, and dantrolene as rare causes. Antimicrobial agents have also been associated as unusual causes of pleural fluid eosinophilia, including nitrofurantoin and piperacillin-tazobactam. In drug-induced EPE, chest pain and dyspnea are frequently seen.

The patient’s chief complaint included dyspnea and pleuritic chest pain. A CT of the chest revealed no evidence for pulmonary embolism and no pulmonary mass signifying a neoplasm; also, the patient had no smoking history. While the patient did have radiological findings consistent with pneumonia, in the course of time that the EPE was discovered, she had been on intravenous broad-spectrum antibiotics for 10 days and that should have successfully treated her suspected lung infection. In addition, she had completed a regimen of moxifloxacin as an outpatient prior to her admission. In view of this, since underlying pulmonary embolism, lung malignancy, and an untreated pneumonia were unlikely to be causing the EPE, INH emerged as the provoking factor.

Further implicating an inflammatory component, granules of eosinophils contain highly cationic proteins, such as major basic protein, eosinophil peroxidase, and eosinophil protein X have been noted in the effusions. Pettersson and colleagues have shown elevated levels of biologically-active eosinophil-derived proteins in pleural fluid, indicating an inflammatory component. This could also explain the rapid resolution of symptoms after corticosteroid therapy in our patient. In addition, the pleural fluid cytology yielded the presence of acute inflammatory cells on several occasions while the patient was receiving INH, further supporting a drug-induced immune phenomenon.

There were some aspects of the patient’s manifestations that made her an atypical subject. In most cases of described DILE, the presence of anti-dsDNA and reduced complement C3, C4 levels rarely have been reported. It is also uncommon to have symptomatic pleural effusions due to a medication. Up until this case report, INH has not been known to cause an EPE. In addition, we cannot disregard that our patient was diabetic. Diabetic patients are known to have numerous defects with their immune system, due to hyperglycemia and other factors, which not only puts them at higher risk of acquiring infections, but may also make them susceptible to drug-induced side effects that potentially have an immune origin.

DILE is an uncommon, reversible lupus-like condition caused by exposure to an increasing number of drugs. We have presented a rare case of INH-induced pleural effusion in conjunction with DILE that serves as a clinical reminder of the potential side effects of medications. Furthermore, in reviewing the literature, we believe this to be the first documented case of an INH-induced EPE.

Although the pathogenic mechanism of DILE remains to be ascertained, it may represent a defect of the immune response to a new substance (i.e., a hypersensitive immune reaction to a recently introduced medication). Today, systemic anti-inflammatory agents provide the cornerstone of treatment of DILE. In the future, more targeted modalities, such as anti-cytokine therapy, antihistamines, or even, anti-eosinophilic agents may provide management for patients with DILE that limits systemic side-effects. The possibility of DILE, and drug-induced side effects in general, should always be considered because of the potential reversibility of the patient’s symptoms and the importance of early recognition of the entity.

Conclusion

The patient we presented developed drug induced lupus following exposure to INH, which was complicated by de-
velopment of recurrent pleural effusions that were exudative in nature. These effusions had greater than 10% eosinophils, defining them as EPEs. In most cases of described DILE, the presence of anti-dsDNA and reduced complement C3, C4 levels have been rarely reported. It is also uncommon to have symptomatic pleural effusions due to a medication. Up until this case report, INH has not been known to cause an EPE. As well, to the best of our knowledge, there has been no reported case of drug-induced lupus with positive anti-dsDNA antibodies and, in addition, an exudative EPE.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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