Severe Nitrofurantoin-Induced Lung Toxicity
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Introduction
Nitrofurantoin is a frequently used antibiotic for treatment and prophylaxis against urinary tract infections. It is a relatively safe medication with rare side effects, however, cases of severe pulmonary injury secondary to its use have been reported.\textsuperscript{1} We report a patient with pulmonary infiltrates with eosinophilia, pleural effusion, and interstitial lung disease induced by the chronic use of nitrofurantoin. The association of severe eosinophilic bronchopneumopathy with interstitial fibrosis makes this case rare and shows the possible deleterious effect of chronic nitrofurantoin use.

Case Report
An 83-year-old male with a two-year history of chronic cough and shortness of breath presented with progressive worsening of symptoms over the two months prior to presentation. He denied hemoptysis, fever, chills, or sick contacts. He was a non-smoker and denied any occupational exposures.

The patient was taking nitrofurantoin 100 mg daily for recurrent urinary tract infections. It was started two years ago before his symptoms began. His past medical history was significant for coronary artery disease and diabetes mellitus II treated with insulin.

On physical examination, he had no fever. Oxygen saturation by pulse oximetry was 61% on room air and increased to 90% on four liters of oxygen. Bilateral coarse crackles were noted on both lung fields, more prominent on the right side with decreased air entry at the bases. Laboratory workup revealed a normal blood count, chemistry, and liver panel. Arterial blood gas analysis revealed hypoxemia with a PaO2 of 66 mmHg on 6 liters oxygen, PCO2 was normal.

A chest radiograph showed diffuse, bilateral infiltrates most concentrated in the right upper lobe, and a small right pleural effusion. A review of previous chest x-rays over the prior two years revealed the same findings with temporal progression (see Figure 1). High resolution CT scan of the chest showed diffuse fibrosis, right upper lobe and lingular consolidation, and small right pleural effusion (see Figure 2).

The patient underwent a bronchoscopy with bronchoalveolar lavage and transbronchial biopsies. The bronchoalveolar lavage was obtained from the right upper lobe and revealed numerous white blood cells with significant eosinophilia (25%). Fungal and bacterial cultures were negative as well as viral PCR, pneumocystis carinii pneumonia (PCP) stain, and acid fast bacilli
Figure 1. A chest x-ray revealed bilateral interstitial infiltrates more prominent in the right upper and lower lung and at the periphery. Also, a small right pleural effusion is noted.

Figure 2. A high resolution CT scan of the lung showed mild right pleural effusion (arrow) and right upper lobe, right lower lobe, and lingular infiltrate (stars).

Figure 3. A transbronchial biopsy showing: (a) a normal alveoli (star) compared to thickened alveoli with fibrosis (arrows) and (b) of normal bronchial epithelium (star) with numerous eosinophils (arrows) involving the adjacent connective tissue.
(AFB) stain. Transbronchial biopsies from the right upper lobe showed fibrosis and eosinophilic infiltrates without evidence of malignancy (see Figure 3).

Drug-induced lung toxicity was suspected and nitrofurantoin was stopped. The patient was treated with prednisone 20 mg daily. There was marked clinical and radiologic improvement in a follow-up examination one month later.

Discussion

Based on World Health Organization criteria, nitrofurantoin was the “probable” cause of the lung toxicity. There was a reasonable time sequence of the lung toxicity to administration of the drug. It was unlikely to be attributed to concurrent disease or other drugs or chemicals, and followed a clinically reasonable response on withdrawal of nitrofurantoin.

Nitrofurantoin has been associated with several lung diseases. The first pulmonary reaction to nitrofurantoin was described in 1957. Subsequently, cases of bronchiolitis obliterans with organizing pneumonia (BOOP), pulmonary infiltrates with eosinophilia (PIE) syndrome, diffuse alveolar hemorrhage, diffuse alveolar damage (DAD), and acute, subacute, and chronic interstitial lung disease have been reported.

Two forms of nitrofurantoin-induced lung injury have been described: acute and chronic. The acute form is a hypersensitivity reaction (type I or III), clinically characterized by fever (82%), dyspnea (60%), cough (43%), rash (20%), chest pain, and cyanosis. On the other hand, the chronic form may be either an allergic or a toxic response, and usually presents with nonspecific symptoms including dyspnea (73%), dry cough (63%), and fatigue (37%). Fever might also occur in chronic forms but it is unusual. Oxidative stress also has been implicated in lung injury as reported by in vivo studies conducted on rats. Symptoms usually start within a few days in acute forms, while chronic forms manifest after 1 to 6 months of treatment.

Among the pulmonary toxicity of nitrofurantoin, PIE syndrome rarely has been reported. It was first described after the use of sulfonamide, however, currently more than 100 drugs can cause this disease. The most common medications causing PIE syndromes include antibiotics (e.g., minocycline, sulfasalazine, sulfamethoxypyridazine, sulfamethoxazole), angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, imipramine, and carbamazepine.

The diagnosis of PIE syndrome is established by the presence of pulmonary infiltrates and eosinophilia, detected in blood, bone marrow, bronchoalveolar lavage, or lung tissue. Marked peripheral eosinophilia may not be present primarily because of the sequestration of eosinophils in the lung tissue or secondary to previous use of steroids.

The cause of PIE syndrome is not only limited to drugs. It includes infectious causes (e.g., fungi or parasites), and idiopathic and autoimmune diseases. It also was reported in patients with AIDS, lymphoma, a variety of inflammatory lung diseases, and collagen vascular diseases.

Treatment of PIE syndrome varies depending on the etiology. In case of drug-induced syndrome, the treatment consists of withdrawal of the offending agents. The same applies for the other drug-induced infiltrative lung diseases. Patients with mild-to-moderate inflammatory interstitial lung diseases (ILD) will respond quickly, whereas drugs that cause acute interstitial reactions or pulmonary fibrosis may not. In this situation, corticosteroids often are used in conjunction with drug discontinuation. Discontinuation is more complex in patients on multiple drugs.
this case, sequential discontinuation sometimes is performed beginning with the drug most likely to have caused the syndrome, then withdrawing the others until improvement occurs.\textsuperscript{16}

In our case, the presence of eosinophils in the lung tissue as well as the significant eosinophilia (25\%) in the bronchoalveolar lavage confirmed the diagnosis of pulmonary eosinophilia with infiltrates. Prednisone was initiated because of the severity of symptoms and the presence of fibrosis on the pathology. This case showed the possible deleterious effect of a commonly used medication. It also emphasized the importance of monitoring patients taking nitrofurantoin for prolonged periods, at least by history, and possibly regular chest x-rays and pulmonary function tests.\textsuperscript{17}

References
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