Title

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CLINICAL VIGNETTE

Nitrofurantoin Induced Pulmonary Hypersensitivity

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Case Report

A 43-year-old woman with a past medical history of recurrent urinary tract infections (UTIs) presented to an urgent care clinic with complaints of pleuritic left sided chest pain, fevers, chills, shortness of breath, and fatigue. Her symptoms started the prior night. She was recently diagnosed with a UTI by her primary care physician who prescribed nitrofurantoin two days prior. On physical exam, the patient's pulse was 138 and her temperature was 102 degrees Fahrenheit. There were no other pertinent exam findings. An electrocardiogram (EKG) showed sinus tachycardia with no significant ST segment or T wave abnormalities. The patient was given 1 liter of intravenous normal saline (NS), acetaminophen, and ibuprofen. With these interventions the patient improved symptomatically but became hypotensive with a blood pressure of 88/42 mmHg and pulse of 117. Another liter of NS was delivered and urine and blood cultures were drawn. Because the patient did not respond to initial resuscitation, she was subsequently transferred to the emergency department. The patient was stabilized with further aggressive fluid resuscitation totaling 4 liters of NS. Initial laboratory studies demonstrated a neutrophil predominant leukocytosis of $11x10^3$/uL and urinalysis consistent with ongoing UTI. Based upon this information, she received a dose of ciprofloxacin. Her chemistries, cardiac enzymes, and erythrocyte sedimentation rate (ESR) were within normal limits. A radiograph of the chest was obtained showing no acute cardiopulmonary process. Because of a concern for pulmonary embolism (PE), a computed tomography angiogram (CTA) of the chest was performed showing no acute PE but new trace bilateral pleural effusions, bilateral lower lobe subsegmental atelectasis with retained airway secretions within the subtending bronchi, and a small to moderate pericardial effusion with pericardial thickening (see figure 1). The patient was then admitted to the inpatient medicine service for continued care. Antibiotics were resumed while further investigation continued in order to diagnose her pulmonary and cardiac findings, which could not be explained by UTI alone. A lactase dehydrogenase level, thyroid stimulating factor level, rheumatoid factor assay, and a mycobacterial quantiferon ELISA were normal. Her antinuclear antibody screen (ANA) showed a 1:80 homogeneous titer. In addition, a subsequent CBC showed development of relative peripheral eosinophilia of 9.5%. The patient's blood and urine cultures remained negative. Further questioning revealed similar, though less severe, symptoms 1-year prior after completing a 5 day course of nitrofurantoin for a UTI. At that time, the patient also went to the ED and a CTA of her chest showed no PE but bronchial wall thickening, bronchiectasis, scattered pulmonary parenchymal micronodules, scattered subcentimeter axillary, supraclavicular, and intrathoracic lymph nodes, and small bilateral pleural effusions. Her symptoms resolved in the ED and she was discharged home. Based upon this information, the diagnosis of nitrofurantoin induced lung disease was made. Within 24 hours of admission, her symptoms resolved with supportive care, withdrawal of nitrofurantion, and antibiotics. An echocardiogram prior to discharge showed resolution of the pericardial effusion. She continues to be followed by her primary care physician.

Background

Nitrofurantoin is a synthetic nitrofuran antibiotic that has been used in the treatment of UTIs for over 50 years. Although it is generally safe and efficacious, pulmonary toxicity is a rare but well reported side effect[1]. Nitrofurantoin induced pulmonary disease occurs in two forms: acute and chronic. The acute form generally occurs hours to days after initiation of therapy and is by far the more common of the two. The chronic form is exceedingly rare and follows a prolonged course of therapy. Clinical symptoms may not manifest until months after initiation of therapy[1, 2]. Although the absolute number of reports of this condition from several countries are available, the relative incidence compared to number of total administrations of the drug has not been measured[4, 5]. It is estimated however that the acute form may occur in up to 1 out of every 5000 initial administrations and that the chronic form may occur in up to 1 out of every 750 chronic users[5].

Pathophysiology

The pathophysiology of nitrofurantoin induced lung injury is not well defined. It is suggested that acute

injury may be related to an immune complex type III hypersensitivity syndrome given the drug's ability to cross the alveolar capillary membrane[3]. Other possible causes include a T-cell mediated auto-immune reaction which may be responsible for both the acute and chronic forms of the disease[1, 6].

Signs and Symptoms

Nitrofurantoin induced lung disease occurs 3 to 4 times more often in women than in men[2]. It primarily affects elderly individuals but may occur at any age[2]. The distribution of disease likely is related to the population which is most exposed to the drug for the treatment of UTIs. The acute and chronic forms of this disease present in different ways. Patients with the acute form most commonly have sudden onset dyspnea, cough, fever, chills, malaise, chest pain, and bronchospasm[1-3, 5]. The case presented also suggests that repeated exposure to the medication may cause a sensitization resulting in more severe and rapid onset of symptoms with each subsequent exposure. To the authors' knowledge, this sensitization effect has not yet been described in the literature.

Symptoms seen in the chronic form are more gradual in onset and are similar to symptoms of pulmonary fibrosis. Dyspnea on exertion and cough as well as chest pain are the most common features. Myalgias, fatigue, and weight loss are less common. Fever is much less prominent in this form of the disease[1].

Diagnosis

There are no criteria for the diagnosis of this condition. Thus diagnosis is based on a combination of high clinical suspicion, history compatible with the disease, and laboratory and imaging findings. In either form, blood tests may reveal a leukocytosis with eosinophilia, an elevated ESR, elevated immunoglobulins, and elevations in liver enzymes[1,2]. Positive ANA titers may be seen as well but are much less common[1,2]. In the acute form, chest radiography characteristically reveal a diffuse interstitial pattern with basal predominance similar to that of interstitial pulmonary edema. Pleural effusions can also be seen. In the chronic form radiographs show only bibasilar interstitial markings which resemble patterns seen with chronic interstitial pulmonary fibrosis[2]. This is corroborated on CT scan which may demonstrate varying combinations of ground glass opacities, consolidation, centrilobular nodules, septal thickening, and reticular densities with a subpleural and bronchovascular predominance[1, 7]. Although not necessary for diagnosis, pulmonary function tests show a primarily restrictive pattern[8].

Treatment

The treatment of nitrofurantoin induced lung injury is prompt withdrawal of nitrofurantoin and supportive care. Steroids have been used in some reported cases but do not appear to hold extra benefit[1-2, 9]. The vast majority of patients with the acute form will have spontaneous resolution of their symptoms and imaging abnormalities but a very small number may progress to the chronic form[1, 2]. Even so, the prognosis for the chronic form is very good as well with most individuals recovering within a few months. Only a very limited number of people sustain permanent fibrosis. Death is rare with only a handful of cases reported in the literature[2].

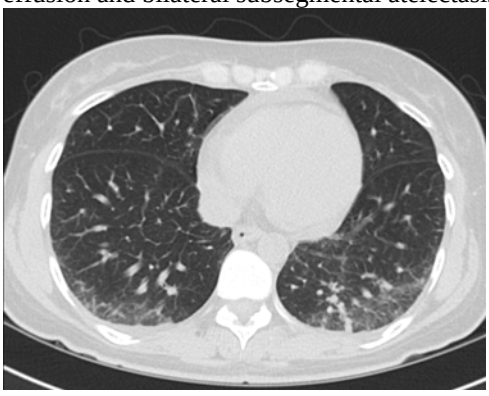
Complications

Complications from this disease have been rarely reported. These include chronic eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, non-fatal pulmonary hemorrhage, and desquamative interstitial pneumonia [7, 10-12]. We have found no reports of pericardial effusion as seen in our patient. This may represent a novel presentation of the disease. However, complete evaluation of the pericardial effusion had not been completed and it is possible that the effusion was due to an unrelated infiltrative or inflammatory process.

Conclusion

We have presented a case of a 43-year-old woman who developed nitrofurantoin induced lung injury after treatment for a UTI. Although this is a relatively rare entity, given the frequent use of this medication, physicians should be aware of its presentation and clinical course.

Figure 1. CT of the chest showing pericardial effusion and bilateral subsegmental atelectasis



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