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Case Report

Nitrofurantoin Induced Lung Disease

Authors
Harikrishnan Puliassery, Krishnaprasad Maniyan, Gayathri Karedath, Ravindran Chetambath

Abstract
Nitrofurantoin is a synthetic nitrofuran antimicrobial commonly used for the treatment and prevention of recurrent urinary tract infections (UTIs). Although rare nitrofurantoin can cause acute and chronic lung diseases. We report the case of an 81-year-old woman diagnosed with interstitial lung disease (ILD) due to long-term use of Nitrofurantoin for UTI prophylaxis. Despite widespread lung parenchymal changes in the form of fibrosis and ground glass opacities, she responded very well to corticosteroids. This case report highlights the importance of early recognition and favorable response to corticosteroids in nitrofurantoin-induced ILD.

Keywords: *Nitrofurantoin, Lung Diseases, Interstitial Fibrosis, Corticosteroid.*

Introduction

Nitrofurantoin is a synthetic nitrofuran antimicrobial commonly used for the treatment and prevention of lower urinary tract infections (UTIs). Even though it has a better side effect profile, nitrofurantoin is known to produce acute and chronic lung reactions. An acute nitrofurantoin-induced lung disease (NILD) was first described by Fisk in 1957 [1] and chronic NILD was reported by Rosenow et al in 1958 [2]. Chronic NILD is 10-20 times much less than acute reactions.

Acute reactions usually manifest as fever dyspnea, cough, and rash and manifest usually nine days after starting therapy [3]. Chronic toxicity usually presents as insidious onset dyspnea, dry cough, and fatigue. Chronic toxicity occurs after several months or years of nitrofurantoin therapy[4]. The majority of NILD patients are women, it is attributable to greater susceptibility of women to recurrent UTI[4].

We report the case of a woman who was on long-term Nitrofurantoin therapy who developed ILD with radiographical findings of fibrosis which responded very well to corticosteroid therapy. Early recognition of pulmonary symptoms and prompt initiation of therapy can aid rapid recovery.

Case Report

An 81-year-old female known to have type 2 diabetes and systemic hypertension and a history

of recurrent urinary tract infection was admitted with complaints of progressive exertional dyspnea of 6 weeks, chest pain, and dry cough of 2 weeks durations. Dyspnea was insidious in onset and gradually progressed over 6 weeks, no history of orthopnea or paroxysmal nocturnal dyspnea.

4 weeks later she developed a cough, non-productive. No postural or diurnal variation, no history of cough syncope. It was associated with chest pain more on the lateral aspect of both chest and worsens over coughing. No history of palpitations, syncope, pedal edema, abdominal distension, jaundice decreased urine output, frothing of urine, or seizures. No history of joint pains, rashes, photosensitivity, oral ulcers, hair loss, dry mouth, dry eye, or dysphagia.

She had a history of recurrent urinary tract infections and was on Nitrofurantoin (100mg once daily) Prophylaxis for the past 5 months. No history of passive smoking or exposure to chemicals, pets, or birds.

On examination, she was pale, tachypneic and tachycardiac but there was no cyanosis, clubbing, or generalized lymphadenopathy. She was Afebrile, and SPO_2 was 94% room air. Respiratory system examination showed reduced chest expansion (Chest expansion 1.5 cm, hemithorax expansion 0.75cm on both sides), with signs of volume loss and abundant fine end-inspiratory crackles over the lower two-thirds of both lung fields. Cardiovascular, gastrointestinal, and nervous system examinations were within normal limits.

Arterial blood gas analysis showed arterial oxygen tension (PaO2) of 76 mmHg on room air. Hematology investigation showed anemia of chronic disease (increased serum ferritin and decreased iron). Liver function tests, renal function tests, and other biochemical parameters were normal. Anti-nuclear antibodies, RA factor, and CCP were negative.

Her chest X-ray showed bilateral reticulonodular shadows. HRCT thorax showed Areas of subpleural reticulations with inter and intralobular septal thickening noted in bilateral lung fields, predominantly in bilateral lower lobes, and patchy ground glass opacities noted in bilateral lung fields, predominantly in bilateral lower lobes. There was no evidence of mediastinal lymphadenopathy or pleural effusion. Echocardiography showed good LV systolic function and grade 2 LV diastolic dysfunction.

Based on clinical and imaging findings in the background of chronic nitrofurantoin exposure Nitrofurantoin induced ILD was considered. Nitrofurantoin was withdrawn and she was initiated on oral prednisolone (1mg/kg). Glycemic control and blood pressure control were achieved with appropriate medication. Patients' respiratory symptoms improved throughout therapy and discharged with tapering doses of steroids. In the second month of post-admission repeat chest X-ray showed resolution of shadows and repeat HRCT, 2 months later showed a significant reduction in fibrosis and ground glass opacities. Within 4 months, she was asymptomatic and was able to do her premorbid activities.

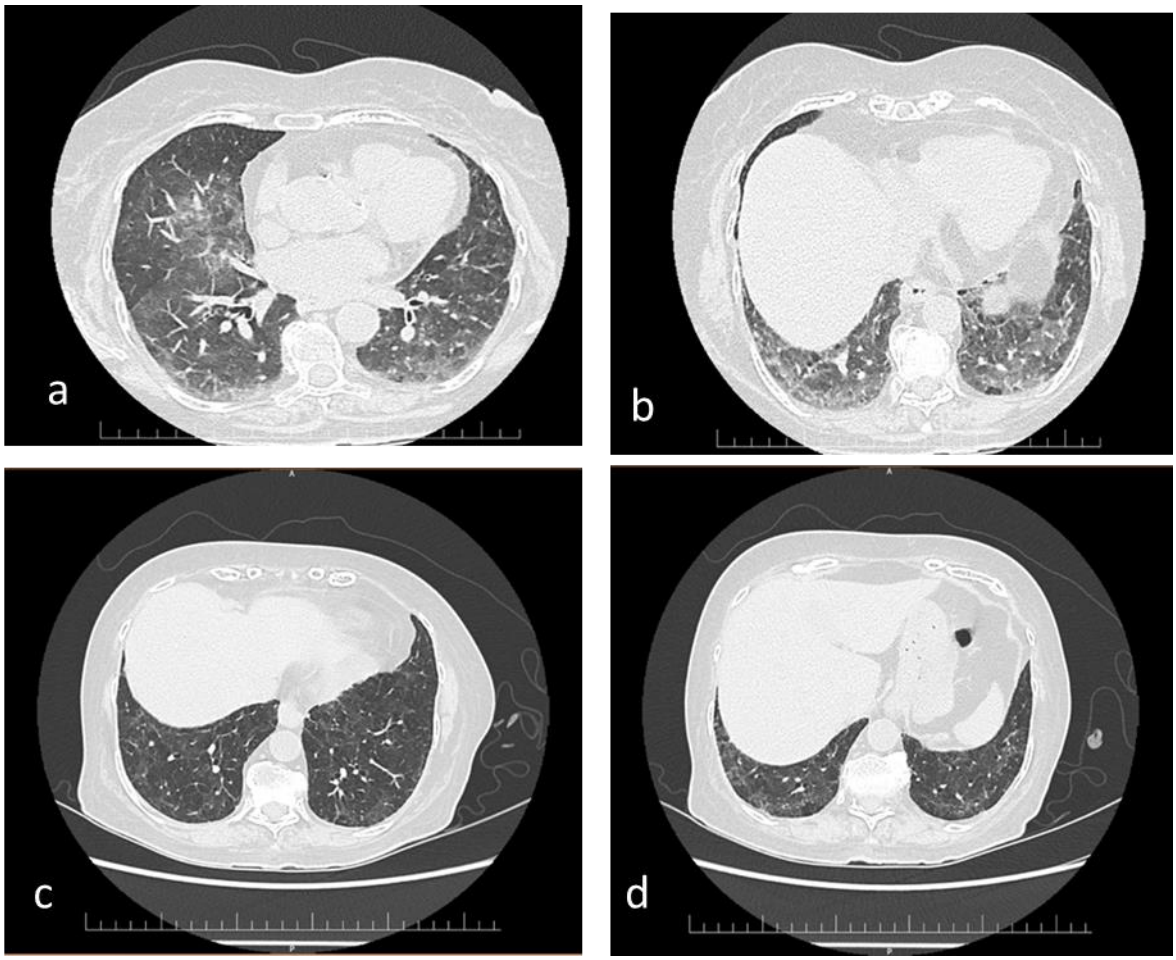

Figure 1: HRCT thorax lung window showed areas of ground glass opacities (a), and subpleural reticulations with inter and intralobular septal thickening (b) in bilateral lung fields, predominantly in the lower lobes. HRCT repeated after 4 months of treatment showed a significant reduction in ground-glass attenuation (c) and fibrosis (d).

Discussion

Nitrofurantoin is a synthetic nitrofuran antimicrobial used for the treatment and prevention of recurrent UTIs. Long-term use can result in pulmonary, hepatic, and renal injury. Previous studies show that the incidence of pulmonary injury due to nitrofurantoin used to be between 0.0001% and 0.001% [5]. The majority of patients who present with pulmonary reactions are women, which is attributable to more prevalence of chronic UTI among them. The median age of presentation for acute lung injury is 60 and that of chronic lung injury is 70 [6].

There are mainly two forms of lung injury, acute and chronic. Acute hypersensitivity reaction to nitrofurantoin occurs after 8.7 days after initiation and presents with fever, dyspnea, cough, and rash[3]. Inspiratory crackles can be heard in most of the patients in basal lung fields [7]. Pathologically acute form represents type 1 or 3 hypersensitivity reaction. Blood investigation may show eosinophilia, leukocytosis, and elevated ESR.

Chronic pulmonary reactions develop overexposure of several months to years of low-dose treatment. Patients usually present with progressive dyspnea, dry cough, and fatigue[2]. Scattered crackles may be present on bilateral lung fields, and diffuse bilateral interstitial infiltrates on chest radiographs and bilateral patchy ground glass attenuation and fibrosis on HRCT[4]. Blood investigation may show eosinophilia, elevated transaminases, elevated serum globulins, ANA, and ANCA positivity[8]. Pathologically chronic form may be either a cell-

mediated or toxic response. Pulmonary function tests (spirometry, lung volumes, diffusing capacity of carbon monoxide, and six-minute walk test) are done to assess the severity of the disease. A lung biopsy may be considered when there is no substantial improvement with drug withdrawal. When performed it may show chronic interstitial pneumonia in chronic disease and eosinophilic interstitial inflammation in acute disease[4].

Discontinuation of nitrofurantoin therapy is the cornerstone of therapy in acute and chronic forms of lung injury[9]. Oral glucocorticoids may be given to patients with severe respiratory symptoms. Oral prednisolone 1mg/kg per day is given with tapering doses over several weeks [10]. Prognosis is good when the disease is identified at the earliest. Recovery took from 2 weeks to 3 months and resolution of advanced interstitial disease on CT is also reported[3].

In a case series published by Yasser Madani et al, 3 similar cases were discussed[11]. Two out of three patients discussed had a similar case scenario as our case and showed good clinical response and radiological resolution to prednisolone therapy. One lady had additional connective tissue disorder and was eventually oxygen dependent.

Elias Mir et al described a similar case of an old lady who was on chronic nitrofurantoin therapy for 3 years and presented with chronic dyspnea[12]. Clinical, radiological, and pulmonary function tests were suggestive of nitrofurantoin-induced lung injury. Unlike our case she was not initiated on prednisolone, instead offending nitrofurantoin was discontinued for her and was managed conservatively. She showed spontaneous improvement both clinically and radiologically.

Our patient with classical symptoms in the background of chronic drug exposure, had radiologic evidence suggestive of advanced pulmonary fibrosis. With prompt recognition and early therapy, she showed clinical improvement from 1st week of treatment and radiological resolution after 2 months.

Conclusion

Pulmonary toxicity of nitrofurantoin should be considered in patients with chronic exposure in an appropriate clinical background and the drug should be discontinued immediately. Radiological investigations such as HRCT are useful in detecting and assessing fibrosis. Corticosteroid treatment should be initiated at the earliest to revert the pulmonary changes. Clinical improvement tends to be rapid, but radiological resolution may take more time.

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