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Case Report

Nitrofurantoin Induced Reversible Interstitial Lung Disease

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ABSTRACT

Drug-induced interstitial lung disease is an increasingly common cause of morbidity and mortality. Nitrofurantoin is a broad-spectrum antibiotic used for acute uncomplicated or simple cystitis as well as for prophylaxis of recurrent infection. We recently encountered a case of Nitrofurantoin-induced interstitial lung disease in an elderly patient who was on Nitrofurantoin for a year and a half for recurrent urinary tract infections. On further evaluation, she was diagnosed with drug-induced interstitial lung disease, which was confirmed by radiographic evidence. Nitrofurantoin was discontinued and managed with low-dose systemic glucocorticoids. This case report highlights the need for close vigilance of pulmonary toxicities in patients taking long-term Nitrofurantoin therapy.

Keywords: Pulmonary toxicity, Corticosteroids, Nitrofurantoin, Interstitial Lung disease, Urinary tract infection.

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INTRODUCTION

Nitrofurantoin is a bactericidal antibiotic commonly used in the treatment of acute or recurrent symptomatic UTIs and as prophylaxis for recurrent infections. It acts by inhibiting protein synthesis, RNA, DNA, and cell wall synthesis. Nitrofurantoin is derived from furan and added nitro group and a side change containing hydantoin.[1] It is effective against most urinary pathogens, including *E. coli*, *Klebsiella* species, *Enterobacter* species, *Citrobacter* species, and *Staphylococcus* species. However, all strains of *Pseudomonas* and many strains of Proteus and Serratia are resistant to Nitrofurantoin. Nitrofurantoin should be used with caution in patients with hepatic impairment, G6PD deficiency, or eGFR < 60 ml/min.[2] Nitrofurantoin is one of many acute, subacute, and chronic pulmonary toxicity-causing drugs. Women are especially prone to Nitrofurantoin-induced pulmonary toxicity because of their added exposure to this drug.[3] Cytotoxic and immune mechanisms are involved in acute and chronic forms of lung injury.[4] *In vitro* studies state that toxic products produced by metabolites of drugs may cause injury in the existing oxygen and lung microsomes.[5] Chronic pulmonary toxicity usually shows the features of ground-glass opacities with or without reticular changes and traction bronchiectasis. Nitrofurantoin can generate oxygen radicals and cause lung damage. Hence, patients on Nitrofurantoin should be closely monitored for adverse drug effects, and delivery of the drug should be discontinued at any sign of pulmonary injury.[6] Here, we describe a case of Nitrofurantoin-induced interstitial lung disease manifesting with worsening symptoms of fever, cough, and shortness of breath.

CASE PRESENTATION

An 81-year-old female patient presented to the critical care department with complaints of breathing difficulty, cough, and fever for three weeks. She was a known case of hypertension and type-II diabetes mellitus for which she was on cilnidipine and metformin. She had a history of recurrent urinary tract infections and was on Nitrofurantoin 100 mg for a year and a half. Detailed history revealed that she had a cough when taking Nitrofurantoin, which would ease if the drug was stopped, but, due to recurrent symptoms of UTI, it wasn't. She did not have any history of lung disease or exposure to allergens in the past. Physical examination revealed a pulse rate of 112/min, blood pressure of 188/110 mm/hg, and respiratory rate of 30 cycles/min. Chest auscultation revealed bilateral inspiratory crackles. Her saturation was 88% at room air. Laboratory findings showed Hb drop (10.9g/dL), decreased hematocrit value (32.5%), leukocytosis (15,380 cells/mm3), eosinophilia (00%), and lymphopenia (05%). ANA was found to be negative. Appropriate cultures were sent and the reports appeared sterile. On assessment, HRCT (High Resolution Computed Tomography) showed upper- and

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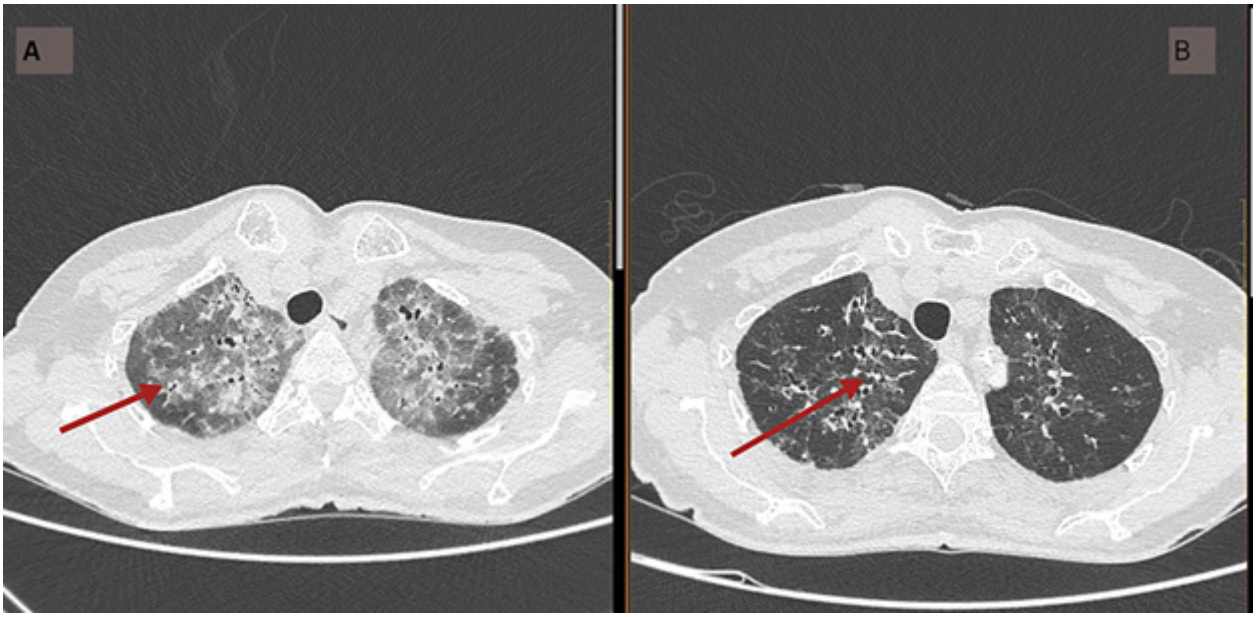

Figure 1: A) 81 year old female patient with Nitrofurantoin Induced Interstitial Disease. HRCT imaging shows bilateral ground glass opacities predominantly bilateral upper lobes and fibrosis with cylindrical and varicose bronchiectasis in bilateral upper lobe. B) Repeat HRCT imaging after 40 days shows significant reduction in bilateral reticular opacities and ground glass opacities after the discontinuation of Nitrofurantoin and initiation of low dose glucocorticoids

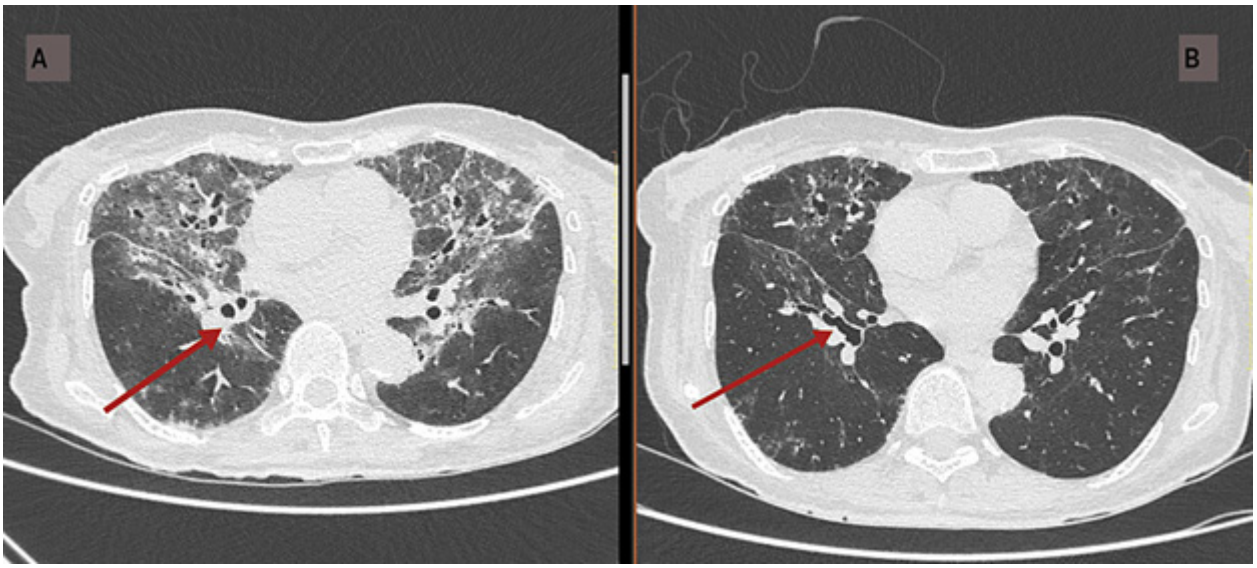

Figure 2: A) 81 year old female patient with Nitrofurantoin Induced Interstitial Disease. HRCT imaging on admission shows bilateral ground glass opacities in the right middle lobe with areas of smooth interlobular septal thickening. B) Repeat HRCT imaging after 40 days shows significant reduction in bilateral ground glass opacities and reticular opacities after the discontinuation of Nitrofurantoin and initiation of low dose steroids.

middle-lobe–predominant ILD features. Figures (1A and 2A) show bilateral reticular opacities with traction bronchiectasis along with peri Broncho vascular thickening and extensive ground glass opacities. Both findings were predominantly seen in the upper and middle lobes. She was subsequently diagnosed with Nitrofurantoin-induced interstitial lung disease. Nitrofurantoin was stopped immediately, and low dose methylprednisolone (glucocorticoids) was initiated. Her symptoms gradually ameliorated over the next few days. She was discharged with supplemental oxygen, methylprednisolone, and inhaled corticosteroids, and also instructed to avoid taking Nitrofurantoin to prevent further lung injury. She was asked to come for a follow-up after 40 days. Her vitals were stable, and her repeated HRCT (see Figures (1B and 2B)) showed significant reduction in bilateral reticular opacities and ground glass opacities. Follow-up CT imaging after 40 days demonstrated complete resolution of abnormalities.

DISCUSSION

DIILD (Drug-Induced Interstitial Lung Disease) presents as acute, subacute, or chronic pneumonitis. Acute hypersensitivity results within one to two weeks after initiation of Nitrofurantoin with symptoms of fever, dyspnea, irritating cough, rash, chest pain and cyanosis, whereas chronic pneumonitis develops after several months to several years of low-dose treatment with symptoms of dyspnea, dry cough, and fatigue.[7] Chronic Nitrofurantoin toxicity may spontaneously resolve after cessation of the drug. If there is a high index of suspicion, the investigation should include chest X-ray, HRCT imaging, pulmonary function tests, and spirometry. Abrupt withdrawal of Nitrofurantoin is the keystone for managing both acute and chronic lung disease. Studies state that there will be a rapid resolution of abnormalities in the withdrawal of Nitrofurantoin. Once the lung injury due to Nitrofurantoin is diagnosed, the patients shouldn't be re-exposed because drug re-challenge results in deterioration of lung functions.[8] Prophylactic use of Nitrofurantoin should not exceed more than 6 months unless the benefit clearly outweighs the risk.[9] Careful monitoring of pulmonary toxicity is needed in patients with Nitrofurantoin on long-term prophylaxis.[7]

CONCLUSION

This paper highlights a case of interstitial lung disease attributed to the use of Nitrofurantoin and the possible mechanisms of lung injury. It is important that clinicians be aware of the adverse drug effect of Nitrofurantoin when a patient is on long-term use. Many drugs and substances have been related to the possible onset of DIILDs. Medication reconciliation or drug history has a key role in confirming the etiology of interstitial lung disease. Identification and prompt discontinuation of the culprit drug is the first line management of DIILD. Thus, patients on Nitrofurantoin should routinely be monitored for lung injury.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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