Case Report

Reversible interstitial lung disease with prolonged use of nitrofurantoin: Do the benefits outweigh the risks?

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ABSTRACT

We describe the case summary of a 70-year-old man diagnosed with interstitial lung disease due to prolonged nitrofurantoin therapy. Despite honeycombing confirmed by computed tomography of the thorax, symptoms and radiographic findings disappeared within 1 month after withdrawal of nitrofurantoin. The case highlights the fact that nitrofurantoin-induced lung disease may run a benign course and respond favorably despite radiographic evidence of established lung fibrosis (honey combing).

KEY WORDS: Interstitial pneumonia, nitrofurantoin, pleural effusion, pulmonary fibrosis

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INTRODUCTION

Nitrofurantoin is a broad-spectrum antibiotic used for the treatment of uncomplicated urinary tract infections and prophylaxis of chronic one. Although relatively rare, nitrofurantoin is one of the most common causes of drug-induced pulmonary disease.[1-3] Nitrofurantoin induced pulmonary toxicity may manifest as acute or chronic interstitial pneumonia, pulmonary hemorrhage, bronchoconstriction, anaphylaxis, and pleural effusion. Knowledge of such adverse effects is essential for the early recognition and withdrawal of the drug. Patients on nitrofurantoin should be regularly followed for any such complications. Here, we describe the case summary of a 70-year-old man with nitrofurantoin induced interstitial lung disease and the spectrum of nitrofurantoin induced lung toxicity.

CASE REPORT

A 70-year-old man was admitted for the evaluation of dry cough and progressive shortness of breath of 8 weeks duration. His past medical history was remarkable for diabetes mellitus, hypertension and benign hyperplasia of prostate (BHP). He underwent trans-urethral resection of the prostate 1 year back for BHP. He had recurrent urinary tract infections and was on nitrofurantoin, 100 mg at night, for 6 months preceding the onset of symptoms. There was no significant work place exposure, previous lung disease or significant smoking history. Physical examination revealed a respiratory rate of 20 breaths/min, blood pressure of 140/90 mmHg, pulse of 100/min and a saturation of 93% while room air. Respiratory system revealed bibasilar fine end-inspiratory, velcro crackles. Rest of the physical examination was unremarkable. His routine biochemistry and hemogram were normal. Arterial blood gas analysis while breathing room air showed a pH of 7.43, PaO_2 of 64 mm Hg, $PaCO_2$ of 37 mm Hg, and bicarbonate of 25 mEq. Chest radiograph carried out revealed bilateral lower zone reticulo-nodular opacities [Figure 1a]. He was euthyroid and enzyme-linked immuno sorbent assay for human immunodeficiency virus was negative. Antinuclear antibody, antineutrophil cytoplasmic antibody and rheumatoid factor were normal. Computed tomography of the chest demonstrated symmetric bilateral reticulation, architectural distortion, and honeycombing involving mainly the subpleural lung regions and lower lobes [Figure 1b]. Pulmonary function tests showed moderate restrictive defect (forced vital capacity was 58% predicted) with severe reduction carbon monoxide diffusion capacity (DLCO 48%, diffusing capacity corrected for alveolar volume (DLCO/VA), 49% predicted). Electrocardiograph and echocardiography were

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normal. Open lung biopsy was offered to the patient, but he didn't agree to it. Nitrofurantoin-induced lung disease was suspected and the drug was discontinued and prednisone 40 mg daily was initiated. Follow chest radiograph [Figure 2a] and computed tomography [Figure 2b] at 1 month showed significant improvement.

DISCUSSION

Nitrofurantoin is used to treat uncomplicated acute urinary-tract infections and to prevent chronic ones in patients with predisposing factors. The daily dosage of nitrofurantoin for adults is 5-7 mg/kg in four divided doses (not to exceed 400 mg). A single 50-100 mg dose at bedtime may be sufficient to prevent recurrences. A course of therapy should not exceed 5 days and repeated courses should be separated by rest periods.[2]

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses. Nitrofurantoin use to treat or prevent infections should be restricted to the bacterial isolates susceptible to it. Further, due to lack of broader tissue distribution of the drug, many patients who are treated with nitrofurantoin are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with nitrofurantoin, other therapeutic agents with broader tissue distribution should be selected. In considering the use of nitrofurantoin, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance.

Before advising continuous antibiotic prophylaxis for recurrent urinary tract infection, detailed urological evaluation to diagnose and detect structural abnormalities, urinalysis, and midstream urine culture and sensitivity should be undertaken. The patients in whom continuous

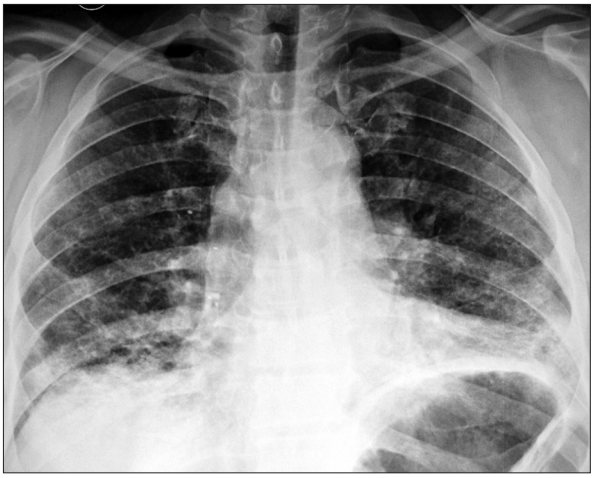

Figure 1a: Chest radiograph showing bilateral lower zone reticulonodular opacities

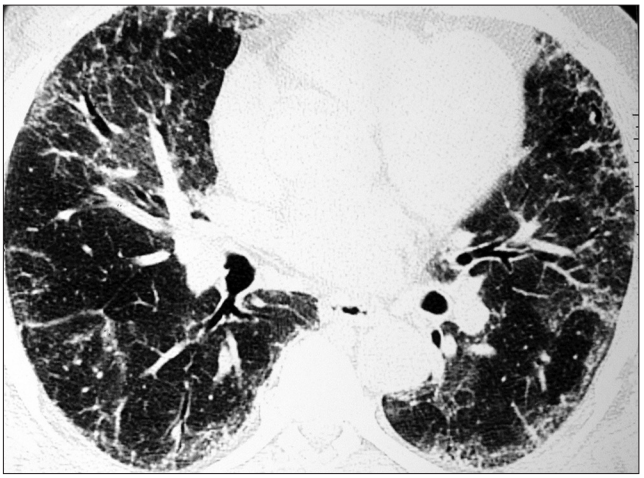

Figure 1b: High resolution computed tomography of chest showing symmetric bilateral reticulation, architectural distortion, and honeycombing involving subpleural lung regions of both the lower lobes

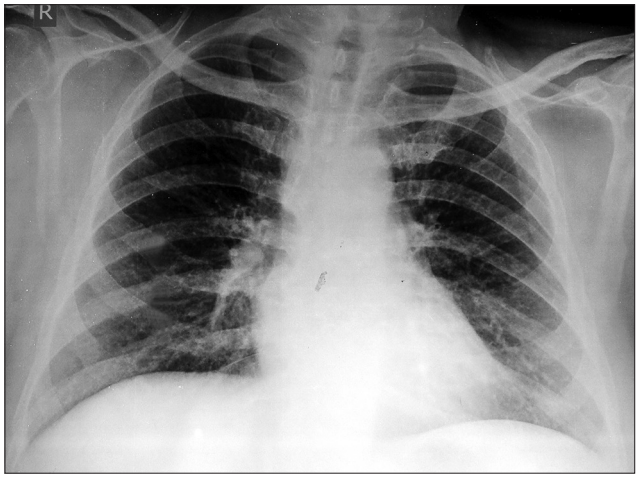

Figure 2a: Chest radiograph carried out at 1 month interval shows clearing of the opacities

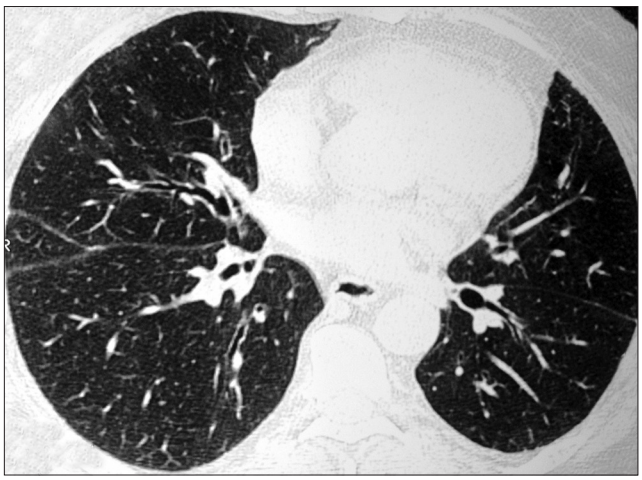

Figure 2b: High resolution computed tomography chest carried out at 1 month interval shows clearing of the reticulation and restoration of normal architecture

antibiotic prophylaxis with nitrofuraintoin is being considered for recurrent UTI should be carefully screened for various adverse events and side-effects. Its most frequent side-effects are usually minor, ranging from nausea, flatulence, and headache. Various hypersensitivity reactions occur occasionally. These include chills, fever, leukopenia, granulocytopenia, hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency, cholestatic jaundice.

Uncommon but serious adverse events include aplastic anemia, polyneuritis, and liver and pulmonary toxicity. Nitrofurantoin induced lung toxicity appears to occur in less than 1 in 1000 exposures. The spectrum of nitrofurantoin induced pulmonary toxicity includes acute or chronic interstitial pneumonia, pulmonary hemorrhage, bronchoconstriction, anaphylaxis, and pleural effusion.

Acute pulmonary reactions are probably underestimated. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals.[3] Acute toxicity is nearly 10 times more common than chronic.[4] Toxicity can occur at relatively small doses, and does not appear to be dose-related.[4] Acute pulmonary reaction generally present with fever, chills, cough, chest pain, dyspnea within days to weeks after the first dose of nitrofurantoin. The chest roentgenogram may reveal alveolar or an interstitial process or both. There may be peripheral and bronchoalveolar lavage eosinophilia. If unrecognized and the drug is continued, acute nitrofurantoin pulmonary toxicity has 10-15% mortality.[5] Acute reactions are usually reversible with cessation of therapy and symptoms usually resolve within 72 h of discontinuing the drug.

Chronic pulmonary reaction to nitrofurantoin occurs far less common than acute pulmonary reactions and acute reactions do not predispose to a chronic one. Lung involvement is common in elderly women as long-term nitrofurantoin prophylaxis is used for recurrent urinary tract infections.[6,7] Further, elderly population may have underlying cardiopulmonary disease and early recognition of its potential contribution to a patient's respiratory decline is important. It generally presents with insidious onset of dyspnea and cough usually, beginning 6 months to years after nitrofurantoin use. Fever, eosinophilia, and obstructive airway disease are usually absent. The chest roentgenogram shows a diffuse interstitial infiltrates and spirometery demonstrates a restrictive pattern. High resolution computed tomography of chest may reveal ground-glass attenuation, honeycombing, inter- and intralobular septal thickening, traction bronchiectasis, and organizing pneumonia.[8-10] Bronchoalveolar lavage usually shows a lymphocytic reaction. Clinico-radiologically, this condition masquerades other forms of interstitial lung disease with the exception that there is history of nitrofurantoin use. The treatment consists of discontinuing the medication and providing supportive care. It is not known whether corticosteroids accelerate the resolution. There is no role for re-challenge to confirm the diagnosis.

Our patient presented with radiographic evidence of irreversible pulmonary fibrosis (honeycombing pattern) and the patient's clinical symptoms and radiographic findings resolved rapidly within a month of stopping nitrofurantoin and use of prednisolone.

CONCLUSION

Nitrofurantoin can cause potentially serious and even fatal pulmonary reactions. Patients on long-term nitrofurantoin should be reviewed and monitored regularly, and the drug should be discontinued at the first sign of any abnormalities. Clinical improvement tends to be rapid following withdrawal of nitrofurantoin and initiation of corticosteroid treatment.

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