Case Report

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Nitrofurantoin-related interstitial lung disease: Case report and literature review

Emine Argüder, Osama Abuzaina, Ayşegül Karalezli

ORCID:
Emine Argüder: 0000-0002-4769-9328
Osama Abuzaina: 0000-0001-9485-3466
Ayşegül Karalezli: 0000-0003-3013-4061

Abstract:

Nitrofurantoin is an antimicrobial agent commonly used for urinary tract infections. This drug may cause pulmonary toxicities, the manifestations of which range from acute self-limiting reactions to chronic pathologies. Here, we report the case of a 72-year-old male who was admitted with progressive cough and dyspnea for 4 months. On physical examination, his respiratory rate was 26/min and oxygen saturation was 84% at rest while breathing room air. Chest examination revealed bilaterally fine crackles. His thorax computed tomography showed bilateral widespread ground-glass opacities and interlobular and intralobular septal thickening. His blood test revealed antinuclear antibody positivity. He had been using nitrofurantoin for a long time for urinary tract infection. He had a high score on Naranjo Adverse Drug Reaction Probability Scale. When he was a diagnosed, he had a respiratory failure due to lung damage. Patients using nitrofurantoin should be followed up closely for drug toxicity.

Keywords:

Interstitial, lung toxicity, nitrofurantoin

Introduction

Nitrofurantoin is an antimicrobial agent commonly used for urinary tract infections.[1] However, it may cause lot of adverse effects such as pulmonary or hepatic toxicities.[2] The spectrum of pulmonary toxicities may be acute, subacute, or chronic forms.[3] In this spectrum, hypersensitivity pneumonitis, eosinophilic pneumonia, organizing pneumonia, diffuse alveolar damage, organizing pneumonia, pulmonary hemorrhage, or granulomatous inflammation may be seen.[4,5] Here, we report one highly probable case, as determined by the Naranjo Adverse Drug Reaction Probability Scale score, who has been using nitrofurantoin for a long time for urinary tract infection.[6]

Case Report

A 72-year-old male was admitted with progressive cough and dyspnea for 4 months. He had a 45 pack-year history of tobacco use. His past medical history included diabetes mellitus, hypertension, and coronary artery disease. He also had recurrent urinary tract infections for which he had been receiving nitrofurantoin nearly for 2 years. He had no history of environmental or occupational exposure. On physical examination, his respiratory rate was 26/min and oxygen saturation was 84% at rest while breathing room

Department of Pulmonology, School of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Address for correspondence:
Prof. Emine Argüder, Department of Pulmonology, School of Medicine, Ankara Yıldırım Beyazıt University, İhsan Doğramacı Street 06800, No. 7 Bilkent, Ankara, Turkey.
E-mail: drgullu2000@gmail.com

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air. He had no fever. Chest examination revealed bilaterally fine crackles. Systemic physical examination was unremarkable otherwise. The analysis of blood biochemistry showed only mild hyperglycemia. Arterial blood gas analysis showed moderate hypoxemia (partial oxygen pressure [PaO_2]: 51.8 mmHg) while breathing room air. Antinuclear antibody (ANA) screen was found positive. However, all other auto-antibodies for collagen vascular disease were negative. Chest radiograph showed bilateral peripheral reticulonodular opacities in the mid and lower zones [Figure 1a]. A computed tomography (CT) revealed bilateral widespread ground-glass opacities, interlobular and intralobular septal thickening, traction bronchiectasis, and fibrosis, dominantly at the lower lobes [Figure 1b]. Pulmonary function test (PFT) revealed a restrictive pattern (forced vital capacity [FVC]: 56% of the predicted value). Diffusion capacity for carbon monoxide (DLCO) was also reduced (41% of the predicted value). Bronchoalveolar lavage (BAL) was done, which yielded the following: lymphocyte 25%, neutrophil 40%, eosinophil 6%, macrophage 29%, and CD4/CD8: 2:1. BAL culture and *Mycobacterium tuberculosis*-polymerase chain reaction were negative. Thus, pulmonary infection was excluded.

He did not have any risk factors for interstitial lung diseases except nitrofurantoin usage. His score according to the Naranjo Adverse Drug Reaction Probability Scale was 7. The score placed the patient under a "probable adverse drug reaction" category.[6] The drug was discontinued immediately and treatment with nasal oxygen, bronchodilators, and methylprednisolone 60 mg/day was commenced. Two weeks later, clinical improvement was observed. The patient was discharged while on methylprednisolone 40 mg/day. On follow-up visits, corticosteroid dose was tapered. By the end of 4 months, the drug was discontinued and pulmonary symptoms had completely improved. The control FVC and DLCO were 72% of predicted and 74% of predicted, respectively. Control Chest X-ray and thorax CT showed resolution of radiological abnormalities after 4 months [Figure 2a and b]. Written informed consent was obtained from the patient.

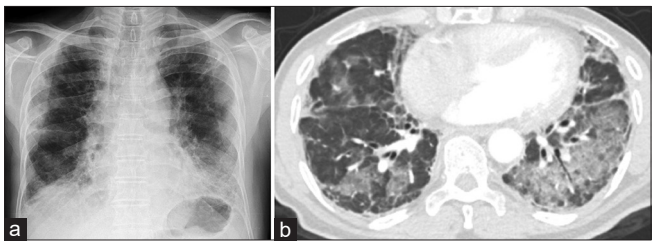

Figure 1: (a) Bilateral infiltration on chest X-ray. (b) Thorax computed tomography showing bilateral widespread ground-glass opacities and interlobular and intralobular septal thickening

Discussion

Nitrofurantoin has been widely used for the treatment of urinary tract infections for more than 50 years. It is highly effective against *Escherichia coli* which is the most common cause of urinary tract infections. Lately, this agent has been used as a first-line treatment option for uncomplicated lower urinary tract infection.[1,7] However, it has been associated with various pulmonary pathologies. The toxic effect increases in the cases of renal dysfunction, advanced age, and female gender.[4,8]

The acute reaction occurs in about 1/5000 women after the first exposure. Even though it is a rare situation, widespread use of the drug causes commonly encountered pulmonary drug toxicities.[4,8] Most of the nitrofurantoin-associated pulmonary reactions occur acutely and typically manifest as a hypersensitivity pneumonitis. Discontinuation of the drug is generally sufficient for recovery of the lungs. The symptoms may appear from a few hours to 4 weeks after the first dose. Dyspnea, cough, or fever may be seen. In addition, mild-to-moderate peripheral eosinophilia may be detected on blood tests. Eosinophilia was not detected in our patient.

Chest X-ray shows patchy infiltrates in acute cases. The histopathologic feature is acute cellular interstitial pneumonia. Furthermore, giant cells, vasculitis, or eosinophilic interstitial inflammation can be seen.[4] Clinical and radiologic findings generally disappear promptly after discontinuing nitrofurantoin treatment.[7]

The chronic form generally appears after months to even years following the first exposure with nitrofurantoin and presents as an interstitial pneumonitis and fibrosis.[4] Clinical findings of the chronic form are long-term cough and dyspnea. In addition, myalgia, weight loss, and fatigue can be seen.[2] Histopathologically, pulmonary interstitial inflammation, fibrosis, or vascular sclerosis can be seen.[9] Chest X-ray generally shows bilateral interstitial infiltrations on the lower zones. Thorax CT may reveal ground-glass attenuation, interlobular septal thickening, traction bronchiectasis, honeycombing, and organizing pneumonia.[2] An increased BAL fluid

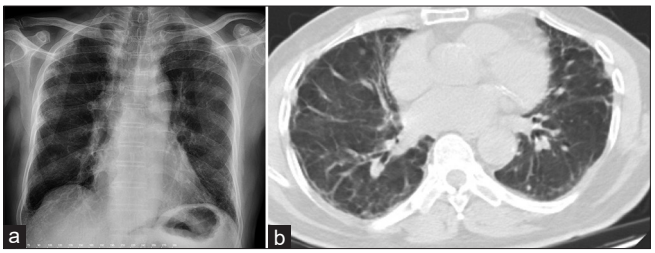

Figure 2: (a) Resolution of infiltration on control chest X-ray. (b) Thorax CT showed significant improvement in the parenchymal changes

eosinophil percentage may be shown. In our case, BAL results showed a mixed cellularity (lymphocyte 25%, neutrophil 40%, eosinophil 6%, and macrophage 29%). These results were similar to the BAL results seen in bronchiolitis obliterans organizing pneumonia (BOOP), but foamy macrophages were not seen.[10] The BAL results were also different from that of hypersensitivity pneumonitis. Because there was no significant lymphocytosis and the CD4/CD8 ratio was not low in the BAL fluid. ANA or anti-neutrophil cytoplasmic antibodies are sometimes positive in patients with chronic reaction to nitrofurantoin.[4] ANA was found to be positive during the first investigation. However, other serological markers for collagen vascular diseases were negative. Lung biopsy was not performed as the patient had a history of using a suspicious medication showing a high Naranjo score and compatible clinicoradiological features.

The prognosis of nitrofurantoin-associated pulmonary toxicities is generally good, with an overall mortality rate of 0.5%.[9] Chronic nitrofurantoin toxicity is more commonly seen in older patients and may spontaneously resolve after discontinuing nitrofurantoin. Glucocorticoids may prevent fibrosis in some patients. Treatment with corticosteroids is controversial; on the other hand, despite corticosteroid or immunosuppressive therapies, some patients could not survive due to severe alveolar damage, hemorrhage, fibrosis, and/or other organ toxicity.[2]

Conclusions

Therefore, nitrofurantoin is an important treatment for urinary tract infections. However, such patients on nitrofurantoin treatment may develop serious side effects at any time course. Thus, patients should be followed up closely for pulmonary findings such as oxygen saturation, PFT, and chest X-ray.

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Conflicts of interest

There are no conflicts of interest.

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