Nitrofurantoin-induced acute pulmonary toxicity

Konstantinos Livianos, Eirini-Sofia Karampi, Adamantia Sotiriou, Kyriaki Tavernaraki, Panagiota Stylliara & Elias Kainis

10th Clinic of Pulmonary Medicine, Hospital of Chest Disease “Sotiria”, Athens, Greece.

Keywords
Bronchoalveolar lavage, drug-induced, interstitial lung disease, nitrofurantoin, pneumonitis.

Correspondence
Konstantinos Livianos, 10th Clinic of Pulmonary Medicine, Hospital of Chest Disease “Sotiria”, Mesogion 152, Athens, Attika, Greece. E-mail: klivanios@gmail.com

Received: 15 July 2015; Revised: 20 September 2015; Accepted: 25 September 2015.

Respirology Case Reports 2016; 4(1): 25–27
doi: 10.1002/rcr2.131

Abstract
We report a case of a female admitted to the emergency department with fever and severe type I acute respiratory failure. After detailed examination, all other potential causes were excluded and the patient was diagnosed with nitrofurantoin-induced acute pulmonary toxicity.

Introduction
Nitrofurantoin is an antimicrobial drug used for treatment of uncomplicated urinary tract infections (UTIs) and as prophylaxis against recurrent UTIs [1]. It is responsible for pulmonary adverse effects in a small percentage (1%) of patients [2–4]. Pulmonary toxicity may be acute/subacute or chronic [2–4]. Acute/subacute reactions are thought to be due to hypersensitivity reaction and they are independent of the dosage [3]. Chronic pulmonary reactions caused by nitrofurantoin include diffuse interstitial pneumonitis and pulmonary fibrosis and they are related to the total lifetime dosage. We report one case of nitrofurantoin-induced lung disease in a patient who was on short-term nitrofurantoin for UTI prophylaxis.

Case Report
A 57-year-old Caucasian female was admitted with a 3-day history of fever up to 39°C, non-productive cough, and progressive shortness of breath. Dyspnea worsened 12 h before admission. The patient had no relevant occupational exposure, known allergies, travel history, or previous lung disease. She was a smoker (10 pack-year) and her medical history included hypertension, hypothyroidism, depression, and recurrent UTIs which were treated with nitrofurantoin, 100 mg/day, for the previous 23 days.

On the day of admission, the patient was afebrile, blood pressure was 120/70 mmHg, pulse rate was 120/min and respiratory rate was 28/min. Auscultation of the chest revealed fine inspiratory crackles on the middle and lower lung zones bilaterally. The rest of physical examination did not reveal noteworthy findings. Arterial blood gas (ABG) on room air showed type I acute respiratory failure (pH = 7.46, partial pressure of carbon dioxide (PaCO₂) = 26 mmHg, partial pressure of oxygen (PaO₂) = 49 mmHg, bicarbonate (HCO₃⁻) = 21 mEq/L), while the clinical indicator of hypoxemia, the ratio of partial pressure arterial oxygen, and fraction of inspired oxygen (PaO₂/FiO₂) was 233 and the alveolar–arterial PO₂ difference ([A-a]PO₂) was 63. The electrocardiogram revealed sinus tachycardia without any other abnormalities. Laboratory results showed increased leucocytes (15.500 K/μL) and eosinophils (2.260 K/μL), with mildly increased inflammatory markers.
Chest X-ray showed reticular changes bilaterally on the mid and lower lung zones and bilateral pleural effusions (Fig. 1). High resolution computerized tomography (HRCT) scan of the chest showed bilateral inter- and intralobular septal thickening, centrilobular nodules and associated patchy ground glass opacities (Fig. 2). On the day of admission, computerized tomography-pulmonary angiogram ruled out pulmonary embolism and the echocardiogram showed no structural or functional abnormalities.

Differential diagnosis included diseases presenting with type I acute respiratory failure and reticulo-nodular opacities on HRCT, such as respiratory infections, pulmonary edema, acute respiratory distress syndrome (ARDS) and interstitial lung diseases with rapid onset and worsening (acute interstitial pneumonia, acute hypersensitivity pneumonitis, acute eosinophilic pneumonia, drug reaction, cryptogenic organizing pneumonia, connective tissue disease and diffuse alveolar hemorrhage).

The patient was supported with supplemental oxygen. Treatment with ceftriaxone and macrolide was administered pending the results of the laboratory tests. Nitrofurantoin was suspected to be the cause and it was discontinued immediately.

The patient’s condition rapidly improved within 24 h: she had no shortness of breath, auscultation of the chest revealed fine inspiratory crackles only on the lower lung zones, the chest X-ray improved with reticular shadowing on the lower lung zones and ABG’s on room air showed pH = 7.42, PaCO₂ = 36 mmHg, PaO₂ = 73 mmHg, and HCO₃⁻ = 24 mEq/L.

As part of the investigational process, bronchoscopy with bronchoalveolar lavage (BAL) was performed and the results showed 12% eosinophilia and CD₄⁺/CD₈⁺ ratio of 1.26 (normal). Microscopic examination and cultures of BAL for Mycobacterium tuberculosis, Pneumocystis jirovecii, bacteria and fungi were negative. Polymerase chain reaction of BAL for influenza and P. jirovecii was negative. Cytology test of BAL and sputum showed no malignant cells. Cultures of sputum, blood, and urine were sterile. Nasopharyngeal swab specimen testing for influenza was negative. Urine antigens for Legionella pneumophila and S Streptococcus pneumoniae were negative. Serology tests for Human Immunodeficiency Virus, Hepatitis C virus, Hepatitis B virus, chlamydia, mycoplasma, rickettsia, aspergillus, and common viruses were also negative. Complement factors, quantitative immunoglobulin levels, thyroid hormones, and serum angiotensin converting enzyme were within normal limits. Mantoux test was 0 mm. Rheumatoid factor and antinuclear antibodies were negative. Total Immunoglobulin (Ig)E of the blood was increased (203.54 UI/mL). Microscopic examination of peripheral blood smear showed eosinophilia.

Five days after admission, pulmonary function tests were performed and showed the ratio Forced expiratory volume in 1 sec to Forced vital capacity (FEV₁/FVC) = 81%, FEV₁ = 2.31(99%), FVC = 2.86(104%), Total lung capacity = 4.27(89%), Residual volume = 1.19(67%), Diffusing capacity of the lungs for carbon monoxide (DLCO) = 91%, DLCOadj = 99%.

The patient was diagnosed with pulmonary toxicity due to nitrofurantoin use.
Discussion

The patient was admitted with severe acute respiratory failure and her HRCT of the chest revealed a reticulonodular pattern. In patients with this presentation and rapid deterioration, it seems necessary to rule out any possible reversible condition, such as pulmonary infection, heart failure and pulmonary thromboembolism. Other less frequent etiologies should also be investigated: diffuse alveolar damage, acute injury related to drugs/fumes/toxins, rheumatic disease with pulmonary involvement, vasculitis, diffuse alveolar haemorrhage, acute exacerbation of chronic disease, acute interstitial pneumonia (idiopathic), ARDS, malignancy. In this case report, all other potential causes were excluded and nitrofurantoin was diagnosed to be the cause. The patient met the criteria for drug-induced pulmonary toxicity (exposure to drug, correlation of the drug with clinical/imaging/laboratory findings, exclusion of other potential causes and improvement after drug removal) [5]. Knowledge of the adverse effects of nitrofurantoin is very important, especially pulmonary toxicity which may be acute/subacute or chronic [2–4]. Early recognition and withdrawal of the drug is vital for the patients. Treatment with corticosteroids is not officially recommended [3, 4].

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Gupta K, Hooton T, Naber K, et al. 2011. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin. Infect. Dis. 52:e103–e120.
2. Holmberg L, and Boman G. 1981. Pulmonary reactions to nitrofurantoin. 447 cases reported to the Swedish Adverse Drug Reaction Committee 1966–1976. Eur. J. Respir. Dis. 62:180–189.
3. UpToDate 2014. Nitrofurantoin-induced pulmonary injury. http://www.uptodate.com/contents/nitrofurantoin-induced-pulmonary-injury (accessed 13 October 2014).
4. Mason R, and Broaddus C. 2015. Murray & Nadel’s textbook of respiratory medicine, 6th edn. Saunders, Philadelphia. Pp. 1285–1286.
5. Irey NS. 1976. Teaching monograph. Tissue reactions to drugs. Am. J. Pathol. 82:613–647.