

Nitrofurantoin-induced lung disease: a case report

GNN Fernando¹, KHPUD de Silva²

¹Registrar in Medicine, ²Consultant Physician, Teaching Hospital Karapitiya, Galle.

e-mail address of the corresponding author, Dr. G.N.N. Fernando: nilukshignn@yahoo.com

A 75 year-old house wife presented with one month history of progressive shortness of breath worsening on exertion, dry cough producing scanty whitish sputum, on and off low grade fever, fatigability and loss of appetite. There were no symptoms of arthralgia or wheezing. She was a non-smoker, had no exposure to animals and no relevant occupational or family history. She was generally in good health apart from recurrent urinary tract infection following dilatation of urethral stricture for which she was on prophylactic nitrofurantoin.

On examination she was febrile but not pale or cyanosed. There was no ankle oedema or finger clubbing. She was dyspnoeic with respiratory rate of 24 per minute and O₂ saturation of 85 - 90% on room air. Chest expansion was decreased bilaterally with inspiratory crackles on auscultation. Breath sounds were vesicular in type. Examination of cardiovascular system, abdomen, and musculo-skeletal system was unremarkable.

White cell count was 14.6 10⁹/L (with 70% neutrophils), erythrocyte sedimentation rate was 84 mm/in first hour, blood picture showed excessive rouleaux formation and increased number of polymorphs implying chronic inflammatory disorder or bacterial infection. Her echocardiography was unremarkable and arterial blood gas measurements showed a picture of Type-I respiratory failure (PO₂ - 48.9 mmHg, PCO₂ - 39.6 mmHg, O₂ saturation - 87%, pH - 7.47, HCO₃ - 28 mmol/L). Lung function test showed forced expiratory volume in first second of 0.47 L (31% of predicted), vital capacity of 0.57 L (30% of predicted) indicating restrictive type lung disease. In Flow Volume Loops both inspiratory and expiratory limbs showed low lung volumes (Figure 1) indicating restrictive lung disease. Chest radiograph (Figure 2) showed evidence of interstitial infiltrate prominent on lower zones of both lung fields with loss of lung volumes. High Resolution CT scan of

thorax (Figure 3) revealed coarse fibrotic shadowing with compromised lung volumes and some traction bronchiectasis, supporting the diagnosis of pulmonary fibrosis. Her renal functions were normal while Rheumatoid Factor and Anti Nuclear Antibody were negative.

The patient had been on nitrofurantoin 100 mg daily for the preceding 6 months for recurrent urinary tract infections. With the suspicion of nitrofurantoin-induced lung disease nitrofurantoin was stopped. Prednisolone was started with other supportive care. She clinically improved within one month allowing gradual reduction of steroid dose. The follow-up radiograph (Figure 4) showed resolution of the lower zone infiltrate. Instead of nitrofurantoin; amoxicillin 250 mg once daily was started for prophylaxis of urinary tract infection.

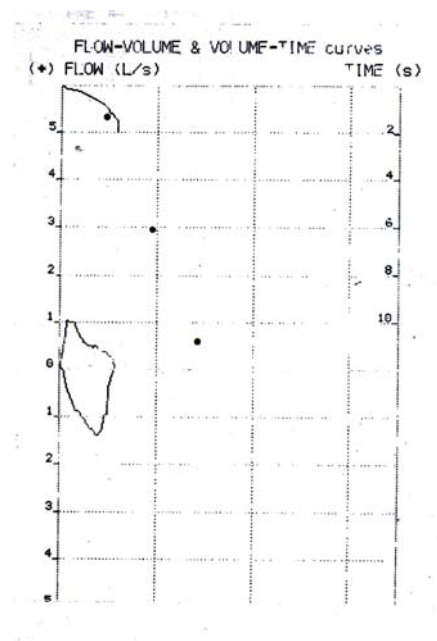


Figure 1 - Flow volume loop

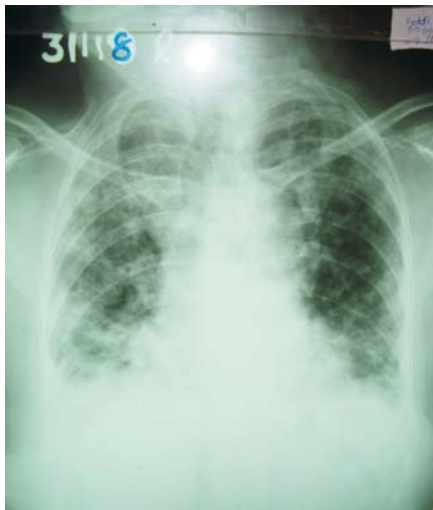


Figure 2 - Chest radiograph showing interstitial infiltrate of the lower zones

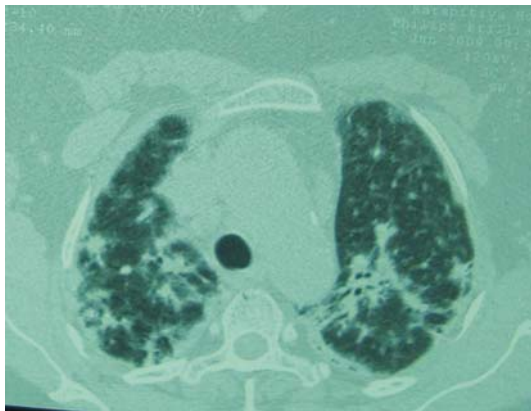


Figure 3 - High resolution CT scan of thorax showing coarse fibrotic shadows



Figure 4 - The follow-up chest x-ray

Discussion

The combination of progressive dyspnoea and cough, audible crackles on auscultation of the lungs and the radiographic appearance of interstitial infiltrate in the lungs suggest the diagnosis of fibrosing alveolitis. Whereas the epithet “cryptogenic” can reasonably be applied to the majority of such cases where a specific causal factor cannot be identified, it is important to consider potential aetiological agents. Though uncommon, the recognition and removal of such agents can result in significant clinical improvement. Nitrofurantoin is one of many drugs that can be implicated (Table 1)¹. Extrinsic allergic alveolitis can also present with a similar picture.

Table 1 - Drugs commonly associated with interstitial pulmonary disease

Antibiotics <ul style="list-style-type: none"> • Sulfasalazine • Nitrofurantoin Antiarrhythmics <ul style="list-style-type: none"> • Amiodarone • Flecainide Anti-inflammatory drugs <ul style="list-style-type: none"> • Gold • Penicillamine • Methotrexate 	Chemotherapeutic agents <ul style="list-style-type: none"> • Mitomycin C • Bleomycin • Busulfan • Cyclophosphamide • Azathioprine Toxins <ul style="list-style-type: none"> • Paraquat
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Nitrofurantoin is widely used in treating acute urinary tract infections and in suppression of chronic asymptomatic bacteruria^{2, 3}. It was one of the first drugs to be implicated as a cause of pulmonary disease and is associated with various toxic pulmonary manifestations (Table 2)^{1,4}. Nitrofurantoin-induced pulmonary disease is postulated to result from the generation of free radicals as a result of redox cycling of the drug in the lung causing direct tissue damage to the endothelium and the alveoli. Antioxidant depleted tissues are the most vulnerable⁴.

Table 2 - Toxic pulmonary manifestations of nitrofurantoin

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- Hypersensitivity pneumonitis.
 - Interstitial fibrosis.
 - Pulmonary eosinophilia.
 - Bronchiolitis obliterans organizing pneumonia.
 - Pulmonary vasculitis.
 - Pleural disease.
 - Airway disease.
 - Desquamative interstitial pneumonia.
 - Adult respiratory distress syndrome.
 - Pulmonary haemorrhage.
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Classically, the pulmonary reaction to nitrofurantoin is divided into acute and chronic forms^{2,4,5}. The acute form begins hours to several days after the initiation of therapy. Symptoms include fever, dyspnoea, bronchospasm, rash, arthralgia, and cough. An eosinophilic leucocytosis, high ESR, pleural effusions, and an interstitial infiltrate on chest radiography are common findings. Management entails discontinuation of the medication and supportive measures. While the role of steroids is unclear, they are often prescribed and are effective (except in established pulmonary fibrosis) as these drug-induced reactions are immunologically mediated².

The chronic form of reaction is less common in which fever and eosinophilia occur less frequently. It usually affects older females and occurs many months or years after initiation of treatment.

The onset of cough and dyspnoea is usually insidious and is commonly accompanied by constitutional symptoms of fatigue and weight loss. The outcome tends to be less favorable in the chronic disease. A positive rheumatoid factor, antinuclear antibodies and raised immunoglobulin levels may be associated features⁴.

Chest radiograph show a diffuse interstitial process. HRCT is particularly helpful in outlining the extent of pulmonary injury and evaluating disease activity. Some apparently irreversible radiological abnormalities will resolve with effective management⁶. Pulmonary function tests demonstrate a restrictive pattern with a reduced diffusion capacity. Bronchoalveolar lavage shows a lymphocytic reaction while histology shows inflammation and interstitial fibrosis.

The relevance and importance of this patient's medication history was not fully realized at the time of presentation. A detailed drug history should always be sought and the possibility of a drug induced illness should be considered in the differential diagnosis.

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