A 56-year-old female was referred to the respiratory clinic by her general practitioner with a 3-month history of dyspnoea and cough. She was a non-smoker. Her cough persisted despite several trials of medication, including antibiotics and inhaled bronchodilator and steroid therapy. Her past medical history included cervical cancer in 1997 with vault relapse in 1999, treated by hysterectomy, chemotherapy and radiotherapy; breast cancer in 2001 treated with wide local excision, chemotherapy and radiotherapy subsequently troubled with leg and arm lymph oedema. Following her gynaecological illnesses, she had been troubled with recurrent urinary tract infections and for the last 12 months she had been treated with prophylactic Nitrofurantoin.

On examination, she was tachypnoeic at rest. Room air saturations were 88%, falling to 76% on minimal exertion. Chest auscultation revealed bilateral inspiratory crackles. Spirometry showed an FEV1 1.38 (59%), FVC 1.54 (57%) with a ratio of 89%. Transfer factor was significantly reduced at 49% predicted. Chest radiograph showed diffuse air space shadowing most prominent at the right base. The working diagnosis was of Nitrofurantoin-induced lung injury with a differential diagnosis to include interstitial lung disease, atypical infection or lymphangitis. Nitrofurantoin was discontinued and she was commenced on Trimethoprim as an alternative. A high resolution CT (HRCT) showed widespread patchy areas of ground glass shadowing in both lung fields with minor peripheral sub-pleural interlobular septal thickening. The differential diagnosis included hypersensitivity or chemical pneumonitis, atypical pneumonia and acute interstitial pneumonia.

At review, 4 months later, the patient’s symptoms had resolved, there was normalization of her lung function (transfer factor 94%) and there had been a marked improvement in the interstitial changes on her HRCT. Her recurrent urinary tract infections were controlled on Cefradine.

Discussion
Nitrofurantoin is an antibiotic commonly prescribed for urinary tract infections. It has a very valued place in the treatment of urinary infections, not least in light of its efficacy against ESBL coliforms.

Since the early 1960’s, significant side effects from its use have been reported. These include a spectrum of lung disease presenting as acute, sub-acute and chronic interstitial lung disease. The acute and sub-acute reactions are thought to represent a hypersensitive pneumonitis and often resolve after withdrawal of the drug. In the chronic form, Nitrofurantoin has been reported to cause diffuse interstitial pneumonitis and bronchiolitis obliterans organizing pneumonia, thought to reflect an allergenic or toxic response. Those patients most likely to develop Nitrofurantoin-induced pneumonitis also reflect those most likely to have urinary tract infections, i.e. middle aged or elderly women or those with a structural abnormality of the genitourinary tract. The acute hypersensitivity reaction often presents with fever, dyspnoea and cough. There is a short (mean 9-days) lag between drug exposure and evolution of respiratory symptoms. In the sub-acute and chronic reactions, the most common symptoms are dyspnoea and cough which develop after! at least 1 month of treatment.
Radiological findings include diffuse parenchymal changes or mixed interstitial alveolar shadowing in the lower zones on chest radiograph. CT findings in chronic Nitrofurantoin-induced lung disease are reported as bilateral ground glass opacities in the more acute phase and a mixed picture of ground glass, consolidation and fibrosis in chronic presentations though with no clearly defined distribution.

From 1963 through 2010, the Medicines and Healthcare products Regulatory Authority (MHRA) has been notified of 2595 adverse drug reactions and 26 fatalities related to Nitrofurantoin; 392 of these were respiratory-related and 11 of these fatal. We have seen 4 patients in the last year in which we feel Nitrofurantoin has been responsible for their lung injury. Prescription data for the UK and Northern Ireland show that Nitrofurantoin prescriptions have more than doubled from 656,480 to 1,452,108 between 2007 and 2011 and this increased use may predispose increasing numbers to respiratory side effects.

This case report highlights the recognized adverse respiratory impact of Nitrofurantoin use. As prescription numbers are on the increase, clinicians must be aware of, and alert to, the spectrum of side effects from use of the drug. As symptoms may not be evident until several months after treatment commencement, the correlation between drug use and morbidity may remain stubbornly elusive.

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References