CASE REPORT

Nitrofurantoin related pulmonary disease:
a clinical reminderTimothy David Reynolds,¹ Jose Thomas²¹University Hospital of Wales,
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Abergavenny, UK**Correspondence to**Dr Timothy David Reynolds,
reynoldstd@doctors.org.uk**SUMMARY**

A 57-year-old woman presented to the admissions unit with a 2-month history of malaise, chest tightness and non-productive cough. An outpatient chest radiograph arranged by her general practitioner was reported as showing 'changes in keeping with a severe chest infection' and she had been started on oral antibiotics but her clinical condition subsequently deteriorated. On admission she was febrile (39.2°C) and her oxygen saturation was 99% on 60% oxygen via facemask (rapidly desaturating when supplementary oxygen was removed). Auscultation revealed fine mid-late inspiratory crackles over both lung bases. It transpired that 4 months prior to the onset of symptoms she had been started on nitrofurantoin for prophylaxis against urinary tract infections. The nitrofurantoin was stopped and she was started on prednisolone. Her fever and oxygen saturation gradually improved and she was discharged home after 11 days in the hospital. Her improvement was sustained on outpatient review 8 months later.

BACKGROUND

This case demonstrates the importance of taking a thorough history and chronological account of events.

The case also shows the importance of interpreting signs and the results of investigations in the correct clinical context. It would have been very easy to rely upon radiology reports that describe possible severe infective changes and seeing high fevers and raised inflammatory markers and prescribing antibiotics, which would have been the wrong treatment and she would have deteriorated further.

CASE PRESENTATION

A 57-year-old woman presented with a 2-month history of malaise, chest tightness and non-productive cough with onset several weeks after returning from a holiday in Australia.

She had a background of chronic back pain related to a prolapsed disc, sinusitis and interstitial cystitis for which she was taking prophylactic antibiotics.

She was a non-smoker and had no significant occupational exposure.

After 1 month she had seen her general practitioner who had started her on a 1-week course of oral clarithromycin with no significant improvement. Her chest radiograph at this stage was reported as showing 'linear and peri-bronchial shadowing with patchy airspace shadowing in keeping

with a severe chest infection on a background of chronic obstructive airways disease'.

She was referred to a chest physician as an outpatient; however, while awaiting her appointment her symptoms worsened and she was restarted on oral antibiotics and referred urgently to the medical admissions unit.

On admission her temperature was 39.2°C, pulse 80/min and regular and blood pressure was 122/58 mm Hg. She had a soft ejection systolic murmur over the aortic area and fine mid-late inspiratory crackles over both lung bases.

Her oxygen saturation was 99% on 60% oxygen via non-rebreathe facemask (she rapidly desaturated when supplementary oxygen was removed).

INVESTIGATIONS

Her blood tests revealed a raised white cell count ($14.1 \times 10^9/l$) and C reactive protein (200.1 mg/l) but normal haemoglobin (12.5 g/dl) and eosinophil count ($0.1 \times 10^9/l$).

Her antinuclear antibody was subsequently found to be positive at 1:2560 and perinuclear antineutrophil cytoplasmic antibody was positive at 1:80 titre. Extractable nuclear antigens, double-stranded DNA and myeloperoxidase/serine proteinase 3 antibodies were all negative. Her serum ACE was also normal.

Her chest radiograph was repeated on admission (figure 1) and again the film was reported as showing right-sided infection or pulmonary oedema.

She went on to have a high resolution CT scan (figure 2) that was reported as showing extensive

Figure 1 Chest radiograph at initial presentation.

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Figure 2 CT imaging at presentation.

ground-glass opacification in keeping with acute alveolitis or interstitial pneumonitis.

DIFFERENTIAL DIAGNOSIS

Although this woman was markedly hypoxic, provided she was supplied with adequate supplementary oxygen therapy, she could communicate reasonably comfortably with family and medical staff.

Despite the fevers, radiology reports and raised inflammatory markers we never convinced that there was an infective process underlying her symptoms.

Her symptoms and signs were more in keeping with a diagnosis of interstitial lung disease for which there were obviously a wide variety of possible causes.

On taking a thorough history we found out that she had been started on nitrofurantoin for prophylaxis of urinary tract infections 4 months prior to the onset of symptoms. At present this seems the most likely cause of her symptoms (however, if her symptoms do flare-up again despite discontinuation of the nitrofurantoin then this may need to be reconsidered).

TREATMENT

We stopped the oral antibiotics (that had been restarted prior to admission to cover for a pneumonia). Her nitrofurantoin was also stopped and she was started on prednisolone 40 mg daily. She was placed on controlled oxygen support using a venturi

Figure 3 Repeat chest radiograph after 2 months.

facemask that was gradually reduced, as possible, until she was able to maintain her oxygen saturations independently.

OUTCOME AND FOLLOW-UP

Her fevers, inflammatory markers and oxygen requirements progressively settled on oral steroids and she was discharged home without the need for supplementary oxygen after 11 days in hospital following a good clinical response. Her steroid doses were slowly tapered and subsequently stopped. Her chest radiograph was much improved at 2 months of follow-up (figure 3) and she was discharged from follow-up 8 months after presentation.

DISCUSSION

Nitrofurantoin is a common chemotherapeutic agent used in the acute treatment of, and prophylaxis against, urinary tract infections.

The drug is activated by bacterial enzymatic activity to produce the active reduced form. This active form inhibits bacterial ribosomal protein synthesis with consequent effects on DNA, RNA and cell wall synthesis.¹

The most common side effects encountered include nausea and mild gastrointestinal disturbance, but on rare occasions it is associated with pulmonary side effects.

It has been recognised that nitrofurantoin can induce both an acute hypersensitivity reaction (occurring around 1 week after a short course) and a chronic pulmonary reaction (occurring after months to years of exposure).^{2 3}

The mechanism underlying pulmonary toxicity appears to relate predominantly to the direct effects of nitrofurantoin metabolites on lung tissue.⁴

On review of recent literature, similar cases have been reported worldwide. For example, Lin *et al* documented a 67-year-old woman in Auckland, New Zealand who had been taking nitrofurantoin for 5 years for prophylaxis against urinary tract infections who developed persistent breathlessness, malaise and cough. She had a good response to oral prednisone but was still discharged with a need for home oxygen.²

Mendez *et al* described a series of 18 patients presenting to the Mayo clinic in Rochester, Minnesota with chronic nitrofurantoin-induced lung disease. They found that the median age at the onset of symptoms was 72 years and that 17 of the 18 (94%) were women. They reported that the median duration of treatment with nitrofurantoin at the time of symptom onset was around 23 months.⁵

Furthermore, Goemaere *et al* reported a case from the Netherlands of a 51-year-old woman who was assessed for lung transplantation and was found to have been on long-term nitrofurantoin and subsequently died. Her autopsy findings of end stage interstitial fibrosis with honeycombing were consistent with pulmonary fibrosis secondary to nitrofurantoin.³

These cases illustrate the importance of recognising this entity as early as possible to prevent a potentially fatal and eminently treatable condition.

The most common presenting symptoms of nitrofurantoin-induced lung disease appear to be a gradual onset of breathlessness, lethargy and non-productive cough, usually of at least 1 month duration (although this can be earlier in acute hypersensitivity). Typically there are fine inspiratory crackles and evidence of hypoxia on examination. The blood may or may not show signs of an inflammatory response and radiographic evidence of interstitial infiltrates/ground-glass opacities.¹⁻⁵

Learning points

- ▶ Take a thorough history—it really is the key to most diagnoses!
- ▶ Investigations are only there to guide the requesting doctor.
- ▶ Rely on your own clinical judgement—if the clinical picture is not representative of an infective process then stop the antibiotics and look for the true cause.
- ▶ Although nitrofurantoin is generally tolerated very well, all patients on long-term treatment should be closely monitored for side effects and advised to seek medical advice if they find that they have persistent unexplained chest symptoms.

Contributors TDR reviewed and treated this patient in the admissions unit before she was admitted under the care of JT. TDR performed a literature search and

followed the progress of the patient as an inpatient and outpatient. TDR wrote the draft paper that was revised by JT. TDR made the amendments recommended by the editor.

Competing interests None.

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