CASE REPORT

Rare adverse effect of a common drug:
nitrofurantoin-induced ANCA-associated vasculitisAbhishek Agarwal,¹ Abhinav Agrawal,² Karim Nathan,³ Satyajeet Roy³¹Cooper University Hospital, Philadelphia, Pennsylvania, USA²Department of Internal Medicine, Monmouth Medical Center, Long Branch, New Jersey, USA³Department of Internal Medicine, Cooper University Hospital, Camden, New Jersey, USA**Correspondence to**
Dr Abhishek Agarwal,
agarwal-abhishek@
cooperhealth.edu

Accepted 3 April 2015

SUMMARY

Nitrofurantoin is commonly prescribed to treat urinary tract infections (UTI). Reported adverse effects include gastrointestinal, pulmonary, hepatic and neurological disorders. We report a case of a 67-year-old woman treated for UTI with nitrofurantoin who presented with antineutrophilic cytoplasmic antibody (ANCA)-associated renal and skin vasculitis 3 days after starting treatment. The symptoms resolved following withdrawal of the drug and treatment with steroids. This is the first reported case of nitrofurantoin causing ANCA-associated vasculitis.

BACKGROUND

Nitrofurantoin is a nitrofuran derivative commonly prescribed to treat urinary tract infections (UTI). The most common adverse effects of nitrofurantoin are gastrointestinal (GI) disturbances. Other reported adverse effects include acute eosinophilic interstitial lung disease, lung vasculitis and subacute interstitial pulmonary fibrosis. While cases of acute granulomatous interstitial nephritis have been reported as a complication of nitrofurantoin therapy, we report the first case of nitrofurantoin-induced antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.

CASE PRESENTATION

A 67-year-old Caucasian woman with hypertension and hyperlipidaemia, on hydrochlorothiazide (HCTZ) and pravastatin, presented with non-itchy leg rashes and fever of 1-day duration. Three days prior she had received nitrofurantoin for a UTI. She denied insect bite, sinus or other pain, epistaxis, cough, haemoptysis or wheezing. She had a temperature of 101°F and diffuse palpable purpura on her legs ([figure 1](#)). The rest of her physical examination was normal.

INVESTIGATIONS

Her comprehensive metabolic panel and complete blood count were only abnormal for elevated creatinine 1.13 mg/dL, blood urea nitrogen (BUN) 32 mg/dL and eosinophils 0.56 K/ μ L. Erythrocyte sedimentation rate was 58 mm/h and C reactive protein was 0.86 mg/dL. Urinalysis showed red (RBC) and white cell count casts. Chest X-ray and renal ultrasonography were normal. Her peripheral ANCA with antimyeloperoxidase specificity (P-ANCA (MPO)) was positive and cytoplasmic ANCA with PR3 specificity was negative. Her ANA (antinuclear antibodies) was negative and her complement levels were normal. She was offered to undergo a renal biopsy, which she declined.

A diagnosis of vasculitis and microscopic polyangiitis was suspected. She was diagnosed as ANCA-associated drug-induced vasculitis. Eosinophilic granulomatosis with polyangiitis was considered less likely due to lack of asthma and atopy. Acute interstitial nephritis was also less likely given that the patient had RBC casts in urine, had palpable purpura and lacked eosinophiluria. Aetiology was suspected as secondary to nitrofurantoin because of the temporal relationship between starting the drug and the onset of symptoms.

DIFFERENTIAL DIAGNOSIS

- ▶ ANCA-associated drug-induced vasculitis
- ▶ Vasculitis and microscopic polyangiitis
- ▶ Eosinophilic granulomatosis with polyangiitis
- ▶ Acute interstitial nephritis

TREATMENT

Nitrofurantoin was discontinued and the patient was treated with prednisone for 10 days.

OUTCOME AND FOLLOW-UP

The patient's purpura and fever resolved in 2 days, and BUN, creatinine, eosinophils and urinalysis were normal at 1 week with a stable outpatient follow-up.

DISCUSSION

Nitrofurantoin is a very commonly prescribed urinary tract antiseptic for UTI. It is a synthetic nitrofuran derivative. It is reduced to highly active intermediates by bacterial enzymes, which damage the bacterial DNA.¹ Efficacy of nitrofurantoin has been found comparable to trimethoprim-sulfamethoxazole² with a clinical cure rate of 88–93% and a bacterial cure rate of 81–92%. Its

CrossMark

To cite: Agarwal A, Agrawal A, Nathan K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209253

Figure 1 Palpable purpura on lower extremities.

efficacy, along with minimal resistance and adverse effects, makes nitrofurantoin a good choice for treatment of uncomplicated cystitis. It has been recommended as a first-line antibiotic in empiric antibacterial treatment of uncomplicated cystitis in otherwise healthy women by Infectious Diseases Society of America (IDSA).³ It is also recommended for reinfection prophylaxis of recurrent uncomplicated UTI.

A wide spectrum of adverse effects has been reported with nitrofurantoin use, most common being GI disturbances. Many pulmonary adverse effects have been reported including acute eosinophilic interstitial lung disease, lung vasculitis and subacute interstitial pulmonary fibrosis.⁴ Other side effects such as cholestatic jaundice, acute and chronic hepatitis and severe polyneuropathies have also been seen. Acute renal failure (ARF) is a very rare complication of nitrofurantoin therapy and, to the best of our knowledge, there have only been two reported cases of acute granulomatous interstitial nephritis secondary to nitrofurantoin.^{5 6} Nitrofurantoin-induced ANCA-associated renal and skin vasculitis has never before been reported.

ANCA-associated drug-induced vasculitis is a type of small vessel vasculitis that is commonly associated with constitutional symptoms, arthralgias and skin involvement. However, in some cases it can be more severe, and also involve the kidneys and lungs. It usually occurs within 1–3 weeks after a drug is started. It has been reported in association with antithyroid drugs such as propylthiouracil, methimazole, carbimazole and other drugs including penicillamine,⁷ hydralazine, minocycline, rifampin, phenytoin, cefotaxime,⁸ indomethacin⁹ and clozapine. It is usually associated with high titres of ANCA antibodies with MPO specificity.¹⁰ Optimal management of these patients is uncertain because of limited reported cases. In mild cases, discontinuation of the drug can be sufficient but in severe cases involving the kidneys or lungs, treatment with corticosteroids or cyclophosphamide may be necessary.

We report the first case of nitrofurantoin-induced ANCA-associated skin and renal vasculitis. Our patient developed fever, palpable purpura, P-ANCA and ARF associated with RBC casts within a week of exposure to nitrofurantoin. Kidney involvement could not be confirmed by histology as our patient denied kidney biopsy. However, fortunately, her symptoms and ARF resolved within 10 days after nitrofurantoin was discontinued, and after she was given prednisone. She was also on HCTZ and pravastatin. Pravastatin has never been shown to be associated with ANCA-associated drug-induced vasculitis. There has been one case reported of thiazide-induced ARF in association with ANCA with MPO specificity. However, our patient had been on HCTZ for a long time and her symptoms resolved with discontinuation of nitrofurantoin. Naranjo Adverse Reactions Probability Scale (NADRPS) is used to determine the likelihood that the adverse drug reaction is due to the drug itself.¹¹ According to the Naranjo scale, in our patient's case, nitrofurantoin was a probable cause of drug-induced renal and skin vasculitis. Given the temporal relationship of our patient's symptoms and resolution of symptoms after discontinuation of nitrofurantoin, it was the most likely cause of our patient's symptoms.

It is very important to recognise ANCA-associated skin and renal vasculitis as a manifestation of nitrofurantoin toxicity, as it will aid in early identification of the adverse drug reaction and prompt treatment. It is necessary to withdraw the offending drug and treat patients with prednisone in severe cases to prevent long-term complications. A high degree of suspicion by the treating clinician is required to diagnose this rare side effect.

Learning points

- Importance of recognising antineutrophilic cytoplasmic antibody-associated skin and renal vasculitis as a manifestation of nitrofurantoin toxicity.
- Early identification of the adverse drug reaction, withdrawal of the drug and prompt treatment.
- Early treatment to prevent long-term adverse irreversible effects.

Twitter Follow Abhinav Agrawal at @re_innervated

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Petri WA, Jr. Chapter 52. Sulfonamides, Trimethoprim-Sulfamethoxazole, Quinolones, and Agents for Urinary Tract Infections. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edn: McGraw Hill, 2011. <http://accessmedicine.mhmedical.com.ezproxy.rowan.edu/content.aspx?bookid=374&Sectionid=41266263> (accessed 16 Apr 2015).
- 2 Iravani A, Klimberg I, Briefer C, et al. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with co-trimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *J Antimicrob Chemother* 1999;43(Suppl A):67–75.
- 3 Gupta K, Hooton TM, Naber KG, et al. 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* 2011;52:e103–20.
- 4 Sovijärvi AR, Lemola M, Stenius B, et al. Nitrofurantoin-induced acute, subacute and chronic pulmonary reactions. *Scand J Respir Dis* 1977;58:41–50.
- 5 Namagondlu G, Low SE, Seneviratne R, et al. Acute renal failure from nitrofurantoin-induced acute granulomatous interstitial nephritis. *QJM* 2010;103:49–52.
- 6 Korzets Z, Elis A, Beraheim J, et al. Acute granulomatous interstitial nephritis due to nitrofurantoin. *Nephrol Dial Transplant* 1994;9:713–15.
- 7 Bienaimé F, Clerbaux G, Plaisier E, et al. D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson disease. *Am J Kidney Dis* 2007;50:821–5.
- 8 Feriozzi S, Muda AO, Gomes V, et al. Cephotaxime-associated allergic interstitial nephritis and MPO-ANCA positive vasculitis. *Ren Fail* 2000;22:245–51.
- 9 Sakai N, Wada T, Shimizu M, et al. Tubulointerstitial nephritis with anti-neutrophil cytoplasmic antibody following indomethacin treatment. *Nephrol Dial Transplant* 1999;14:2774.
- 10 Choi HK, Merkel PA, Walker AM, et al. Drug-associated antineutrophil cytoplasmic antibody-positive vasculitis: prevalence among patients with high titers of antimyeloperoxidase antibodies. *Arthritis Rheum* 2000;43:405–13.
- 11 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow