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Systemic Inflammatory Response Syndrome from Nitrofurantoin: A Case Report

Ryan A O'Connor

Vaidahi Patel

Valerie Lang

Wunnie Brima

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AEF 1 Ryan A. O'Connor
EF 2 Vaidahi Patel
E 1 Valerie Lang
FG 1 Wunnie Brima

1 Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
2 Department of Cardiology, Henry Ford Hospital, Detroit, MI, USA

Corresponding Author: Wunnie Brima, e-mail: Wunnie_Brima@URMC.Rochester.edu
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Patient: Female, 66-year-old
Final Diagnosis: Adverse drug reaction
Symptoms: Chills • fever • shortness of breath
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual clinical course

Background: Nitrofurantoin is an antibiotic that is commonly used and preferred to treat lower urinary tract infections due to its relatively safe adverse effects profile. However, with the increased emphasis on antibiotic stewardship, it is important to recognize the rare, yet serious adverse effects profile of this medication. One of the rare adverse reactions is the development of systemic inflammatory response syndrome from nitrofurantoin.

Case Report: We present a case of a 66-year-old woman who developed a classic systemic inflammatory response syndrome, including leukocytosis and fevers, after 2 repeated exposures to nitrofurantoin after a urological procedure. The patient had an initial infectious workup which was negative. A suspected adverse reaction to nitrofurantoin was suspected and the patient was found to have complete resolution of symptoms with discontinuation of the drug and with supportive treatment.

Conclusions: This case demonstrates that although nitrofurantoin is known to be relatively well tolerated, clinicians should still be aware of the adverse reactions, including a potential systemic inflammatory response, from nitrofurantoin use. This information should be used to educate patients going forward on potential adverse effects to be aware of.

Keywords: Drug-Related Side Effects and Adverse Reactions • Nitrofurantoin • Systemic Inflammatory Response Syndrome

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Background

Systemic inflammatory response syndrome (SIRS) is an exaggerated defense response of the body to a noxious stressor, which localizes and then eliminate the endogenous or exogenous source of the insult. However, although the response is defensive, it can cause a widespread inflammatory cascade leading to end-organ dysfunction [1]. At the molecular level, SIRS can occur from either a damage-associated molecular pattern (DAMP) or from a pathogen-associated molecular pattern (PAMP). Medication adverse reactions are known to be a common cause of DAMP leading to SIRS [1].

Nitrofurantoin is an antibiotic that is commonly used and preferred to treat lower urinary tract infections (UTI) due to its relatively safe adverse effects profile [2]. The most commonly reported adverse effects include nausea, vomiting, and diarrhea, with more severe adverse reactions being drug-induced liver injury and pulmonary toxicity [2]. SIRS is not described as a possible adverse effect in the summary of product characteristics of nitrofurantoin; however, a few cases worldwide have been reported [3-7]. This case report describes the diagnosis and subsequent management of a 66-year-old woman with SIRS associated with nitrofurantoin use.

Case Report

A 66-year-old woman with a past medical history of type 2 diabetes mellitus complicated by diabetic neuropathy, hypertension, hyperlipidemia, recurrent UTIs, and overactive bladder presented to the Emergency Department (ED) with acute-onset shortness of breath. The morning prior to admission, her urologist performed multiple botulinum toxin type A injections into the posterior wall, floor, and lateral walls of the bladder to treat her overactive bladder. This procedure was done via a transurethral approach with intraurethral lidocaine anesthesia. She had a temperature of 37.6°C prior to the procedure. A urinalysis (UA) obtained after her botulinum toxin injections showed pyuria of greater than 50 WBC/high-powered field (hpf) (reference range 0-5/hpf). She had no dysuria, urgency, or frequency at the time. She was discharged home on nitrofurantoin 100 mg twice a day by mouth (PO) for 5 days for a presumed UTI. Several hours later, she developed acute-onset shortness of breath and a pulsatile headache associated with photophobia, chills, and myalgias. She reported no contributory family history, including no family history of adverse reactions to nitrofurantoin. Her medications were notable for atorvastatin 10 mg daily PO, metformin 1 g twice a day PO, losartan 50 mg PO, diltiazem 360 mg daily PO, hydrochlorothiazide 25 mg daily PO, and duloxetine 120 mg daily PO, all of which she was compliant with and had not experienced any adverse reactions to. She had multiple drug allergies, manifesting as urticaria, to levofloxacin, penicillin, cephalosporin, sulfamethoxazole-trimethoprim, and pregabalin.

Upon arrival to the ED, her vital signs were notable for a temperature of 37.9°C, tachycardia (118 beats/min), tachypnea (28 breaths/min), and oxygen saturation of 92% on 2 L of oxygen. A physical examination was notable for decreased lung sounds at the posterior lung bases bilaterally and mild bilateral pedal edema. A chest X-ray (CXR) showed cephalization of pulmonary vasculature and left lower-lobe peribronchial opacities. CT angiography of her chest was negative for a pulmonary embolism. Laboratory evaluation was notable for a creatinine clearance (CrCl) of 60 mL/min, leukocytosis of 23.7 THOU/uL (reference range 4.2-9.2 THOU/uL), an absolute eosinophil count of 0.1 THOU/uL (reference range 0.0-0.5 THOU/uL), and a venous lactate of 2.2 mmol/L (reference range 0.5-2.2 mmol/L).

The repeat UA was notable for positive leukocyte esterase, nitrites, and pyuria with WBC >50/hpf (reference range 0-5/hpf), concerning for UTI. The urine culture subsequently grew >100 000 colony-forming units (CFU) of *Escherichia coli* with susceptibility to nitrofurantoin and resistance to trimethoprim-sulfamethoxazole. Blood cultures were ordered at the same time and they had no growth of any bacteria. The differential diagnosis at this time was an acute viral upper respiratory infection, an atypical pneumonia, anaphylaxis, acute pneumonitis due to nitrofurantoin, and heart failure. We treated her symptomatically with nebulized albuterol, but given her CXR and only a mildly elevated temperature, her symptoms were attributed to a viral upper respiratory infection with a stress response causing her significant leukocytosis; therefore, we held antibiotics initially, with a low threshold to start them if her symptoms worsened. She improved clinically over the next day with supportive care. However, her absolute eosinophil count increased to 0.7 THOU/uL (reference range 0.0-0.5 THOU/uL) the next day. We then restarted her nitrofurantoin (100 mg twice a day PO for 5 total days) that had been prescribed by her urologist prior to admission and continued the nitrofurantoin on discharge 2 days after presentation. At the time of discharge her SaO2 was 96% on room air, the leukocytosis had improved to 13.9 THOU/uL (reference range 4.2-9.2 THOU/uL), and the absolute eosinophil count dropped from 0.7 THOU/uL to 0.2 THOU/uL (reference range 0.0-0.5 THOU/uL). She took the next dose of nitrofurantoin immediately after returning home from the hospital.

Six hours after discharge, she returned to the ED with dyspnea, tachycardia, tachypnea, fever (38.6°C), and SaO2 93% on 2 L of oxygen. Laboratory evaluation was notable for CrCl 61 mL/min, leukocytosis of 29.8 THOU/uL (reference range 4.2-9.2 THOU/uL), an absolute eosinophil count of 0.0 THOU/uL (reference range 0.0-0.5 THOU/uL), and a venous lactate of 2.8 mmol/L (reference range 0.5-2.2 mmol/L). At the time of readmission,

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we started her on our sepsis protocol with fluid resuscitation of 30 cc/kg/h, as well as meropenem i.v. 1 g every 8 h due to several allergies to medications. However, the antibiotics were discontinued after 24 h given our suspicion of a nitrofurantoin-related reaction. Her white blood cell count then decreased to 13.8 THOU/uL (reference range 4.2-9.2 THOU/uL), but once again, she had a rise in her absolute eosinophil count to 1.1 THOU/uL (reference range 0.0-0.5 THOU/uL). Nitrofurantoin was then discontinued, and the absolute eosinophil count decreased from 1.1 THOU/uL to 0.2 THOU/uL (reference range 0.0-0.5 THOU/uL). Her symptoms again improved after discontinuation of the antibiotics and with supportive care.

Discussion

Urinary tract infections (UTI) are common, with a lifetime incidence of 50-60% in adult women [8]. With the increased incidence in UTIs, there has been an increase in antibiotic use to treat this disease. Nitrofurantoin is an antibiotic that covers common Gram-positive and Gram-negative species, with natural resistance from *Pseudomonas* [9]. Nitrofurantoin is well absorbed from the gut and has a half-life of less than 1 h, thus not achieving therapeutic plasma concentrations, but instead achieving high urinary concentrations [9]. Due to this, nitrofurantoin is a first-line choice only for patients with acute uncomplicated cystitis, per IDSA guidelines [10].

A Cochrane review on antimicrobial agents for uncomplicated cystitis in women suggests that nitrofurantoin is a good choice for uncomplicated UTIs as it does not have cross-reactivity with other common antibiotics and has a lower risk of causing adverse effects due to its localized effect [11]. Severe adverse reactions include pulmonary hypersensitivity and hepatotoxicity, which are exceedingly rare [11]. In a recent retrospective review article, Geerts et al [12] noted that in women with lower estimated glomerular filtration rates (eGFR <60) taking nitrofurantoin, there is no evidence that nitrofurantoin is less effective; however, the number of adverse events leading to hospitalization was significantly increased. The most common adverse reactions in this article were pulmonary reactions [12]. Reactions were thought to be more prevalent in the patients with renal insufficiency due to accumulation of a toxic nitrofurantoin-derived metabolite (5-nitrofuran moiety) [12].

We found 5 previous descriptions of nitrofurantoin-induced SIRS reactions [3-7]. Forster et al [3] described a patient with stage IV bladder cancer who was treated with a radical prostatectomy, ileostomy, and chemotherapy. The urine grew pan-resistant bacteria and he was treated with nitrofurantoin with subsequent development of a SIRS response. Smith et al [4] reported a case of a 79-year-old woman who was being treated with nitrofurantoin for recurrent UTIs, developed SIRS after initiation, then had rapid improvement of symptoms with discontinuation. Gandotra et al [5] also described a similar phenomenon in a patient with a history significant for urinary bladder prolapse who presented with fever and chills 7 h after taking nitrofurantoin for a suspected UTI. She was hospitalized and evaluated for worsening UTI and sepsis. The patient was found to meet SIRS criteria, with a new left bundle branch block (LBBB), thrombocytopenia, and elevated transaminases, which resolved with cessation of the nitrofurantoin. Gohar and colleagues [6,7] reported a case of SIRS due to nitrofurantoin use in an 83-year-old woman with a history of recurrent UTIs. She developed fevers, chills, and lethargy and was treated for presumed sepsis from a UTI. Her symptoms resolved after discontinuing the nitrofurantoin and treating the sepsis; however, the patient was restarted on nitrofurantoin for UTI prophylaxis and symptoms re-occurred. Lastly, McGarry et al [7] described a case of a 58-year-old woman who developed SIRS with abrupt onset of fever, leukocytosis, and hypotension within 24 h after nitrofurantoin administration, which was prescribed for an uncomplicated cystitis. The symptoms resolved with discontinuation of the medication; however, the patient was re-challenged with nitrofurantoin 2 months later due to recurrent UTI symptom, which led to a similar episode of SIRS.

Our case brings up the challenging question of differentiating a nitrofurantoin-related SIRS response from a SIRS response secondary to a UTI. According to the Agency for Healthcare Research and Quality (AHRQ), an adverse event from a drug reaction must display the following: occurrence after challenge with or without a re-challenge with the drug, resolution with removal of the drug, and a plausible connection [13]. In our case, the patient's signs of systemic inflammation occurred both times after initiation of nitrofurantoin and subsequent re-challenge, and resolved each time with removal of the medication.

In such cases it can be challenging to determine whether the SIRS response is due to nitrofurantoin vs an infection, and it is especially difficult to differentiating between a nitrofurantoin-induced SIRS-like reaction vs nitrofurantoin-induced pulmonary toxicity [14,15]. Patients who present with nitrofurantoin-induced acute pulmonary toxicity typically develop symptoms at around 8 days after exposure to nitrofurantoin [15]. These patients present with dyspnea, tachypnea, hypoxia, non-productive cough, peripheral blood eosinophilia, and imaging showing reticulo-alveolar infiltrates in the bilateral lung bases [16]. Our patient had some findings similar to those reported with nitrofurantoin-induced pulmonary toxicity; however, the onset of symptoms was more acute and started within 12 h after nitrofurantoin exposure, compared to roughly the 8 days after nitrofurantoin exposure described in nitrofurantoin-induced pulmonary toxicities [16,17]. Also, radiographically, there are subtleties that can the help differentiate the 2

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processes. In our patient, the CXR on presentation was notable for pulmonary vascular cephalization and left lower-lobe peribronchial opacities, which is not consistent with the imaging typically seen with acute nitrofurantoin-associated pulmonary reactions, which is usually described as reticulo-alveolar infiltrates. These findings support the diagnosis of a SIRS response due to nitrofurantoin- rather than nitrofurantoin-induced pulmonary toxicity.

While there is no consensus about the mechanism involved in nitrofurantoin-induced SIRS adverse effects, the increase in T lymphocytes in bronchoalveolar lavage (BAL) is suggestive of an immunological mechanism [18]. Other proposed mechanisms for nitrofurantoin-induced pulmonary toxicity include nitrofurantoin production of superoxide free radicals and subsequent oxidative destruction, either through direct cytotoxicity or indirect recruitment of activated neutrophils [18].

Using the lymphocyte transformation test (LTT) and enzyme-linked immunosorbent assay (ELISA), Bäck et al performed specific antibody determination and lymphocyte stimulation tests in 18 verified nitrofurantoin-sensitive patients with symptoms including fever, malaise, cough, pleuritis, and leukocytosis [19]. Results demonstrated promotion of lymphocyte stimulation, transformation of sensitized lymphocytes, and formation of nitrofurantoin-specific IgG antibodies [19]. Results also demonstrated an association between high IgG titers and nitrofurantoin sensitivity; the degree of association is dependent on the amount of specific IgG antibodies, antibody avidity, and propensity toward immune-complex formation [19]. The aforementioned factors, coupled with the presence of IgG in most patients on nitrofurantoin without adverse effects, makes the predictive value of specific IgG antibody levels useless.

Conclusions

Our case illustrates a classic SIRS response including leukocytosis and fevers in our patient after 2 repeated exposures to nitrofurantoin, with complete resolution of symptoms with discontinuation of the drug and supportive treatment only. This highlights that although nitrofurantoin is known to have a limited adverse effects profile, clinicians should still be aware of a potential systemic inflammatory response from nitrofurantoin use and should be wary of it when prescribing this medication in the future.

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