

Poor medication history plus slow symptom onset delays a diagnosis

This elderly woman's condition was difficult to recognize because the slow, insidious onset of her symptoms mimicked the onset of other conditions.

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CASE

An 89-year-old white female presented to the emergency department (ED) with a 1-month history of fatigue, non-productive cough, and weakness, progressing over the previous 3 days to the point where she was unable to attend meals in her assisted living facility's cafeteria. Her cough was exacerbated with deep inspiratory effort. The patient denied fever, chills, night sweats, dyspnea, nausea, vomiting, weight loss, syncope, or chest pain.

The medical history included gastroesophageal reflux, grade 3 cystocele, hypertension, macular degeneration, mild to moderate dementia, osteoarthritis, osteopenia, recurrent urinary tract infection (UTI), and vertigo secondary to acoustic neuroma. The surgical history included an appendectomy and total abdominal hysterectomy with bilateral oophorectomy several years earlier. The patient could not remember all of her home medications, but she reported taking metoprolol, a sulfa agent for the UTIs, nitrofurantoin in the past, and an NSAID whose name she could not recall. She was allergic to penicillin. She denied tobacco and alcohol intake. She typically walked without assistance. Review of systems was significant for joint pain, back pain, anxiety, cough, constipation, reflux disease, and chronic UTI.

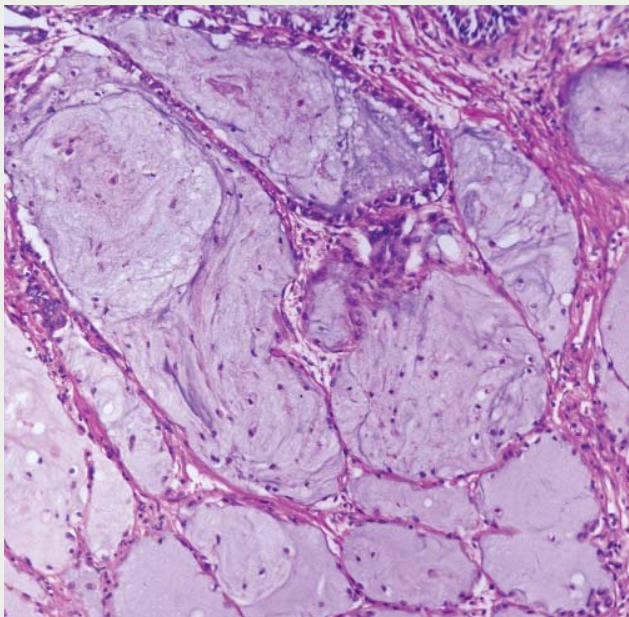
Physical examination On admission, the patient was alert and oriented. Pulse was 74 beats per minute; respiration, 20 breaths per minute; BP, 153/70 mm Hg; and oxygen saturation on room air (by pulse oximetry), 90%. Pupils were equal, round, and reactive to light. Extraocular movements were intact. The neck was supple and without lymphadenopathy. Cardiovascular examination demonstrated a regular rhythm with a rate in the 70s without murmur, rub, or heave. Chest auscultation revealed bilateral rales and cough with deep inspiratory effort. The abdomen was soft, nontender, and nondistended. The extremities were without clubbing or cyanosis, and 1-cm pedal edema with tenderness to palpation was present on the left.

Testing Abnormal laboratory test results included sodium, 130 mEq/L; and albumin, 2.0 g/dL; other laboratory

results were within normal limits. Arterial blood gas analysis results were a pH of 7.46, PCO₂ of 38 mm Hg, and PO₂ of 57 mm Hg. A chest radiograph demonstrated extensive interstitial changes with bilateral cyst formation or possible cavitation. These findings were not present on previous chest radiographs obtained 3 years earlier.

Hospital course The patient was placed in isolation for a workup for tuberculosis. She was initially treated empirically with furosemide and supplemental oxygen. A brain natriuretic peptide level and echocardiography findings were within normal limits. Collection of sputum culture was unsuccessful. A purified protein derivative test was negative.

Because of inconsistencies among the medication histories documented in the various patient records (ED, admission, nursing, and consultant records), nursing contacted the patient's assisted living facility to reconcile the home medication list. On day 2 of hospitalization, the patient was restarted on these home medications, including acetamino-



Photomicrograph showing diffuse interstitial pulmonary fibrosis

CASE REPORT | Nitrofurantoin toxicity

phen (500 mg every 6 hours prn for pain), galantamine (12 mg twice daily), metoprolol (125 mg once daily), nitrofurantoin (100 mg once daily), and an oyster shell calcium supplement (500 mg) plus vitamin D (3 times daily).

On day 3 of hospitalization, during unrelated medication monitoring, a clinical staff pharmacist recognized the possibility that nitrofurantoin could be the cause of the pulmonary symptoms and alerted the pulmonologist. The nitrofurantoin was discontinued, but corticosteroids were not administered. Diagnostic tests were continued to rule out other causes. High-resolution chest CT was ordered, which demonstrated extensive septal thickening and periseptal areas of infiltrate throughout all lung fields. Flexible bronchoscopy was performed. Visual inspections of the airways were normal. Bronchoalveolar lavage (BAL) was performed, and three transbronchial biopsies were obtained of the left lower lobe. Cultures were sent for cytology, acid-fast bacilli, fungi (*Pneumocystis*), viruses (cytomegalovirus), *Legionella*, and *Mycoplasma*. No malignant cells were identified, and all cultures were negative. BAL pathology showed a mild cellular

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specimen with macrophages and reactive bronchoepithelial cells. Transbronchial biopsy revealed chronic interstitial pneumonia, thickened alveolar septa, and increased alveolar macrophages. No acute inflammatory cells were identified. The injury pattern was nonspecific but, when combined with the clinical history, thought to be compatible with nitrofurantoin toxicity.

DISCUSSION

Nitrofurantoin-induced pulmonary toxicity Nitrofurantoin is an antimicrobial commonly prescribed for the treatment and prevention of uncomplicated UTI caused by susceptible gram-negative and some gram-positive organisms. Adverse reactions are generally mild but may include GI intolerance, cutaneous manifestations (exanthema, erythema, urticaria), hemolytic

anemia, neuropathy, hepatic toxicity and acute and chronic pulmonary toxicity.¹ Nitrofurantoin-induced pulmonary toxicity is typically categorized either as acute or chronic in presentation. The incidence of acute toxicity is estimated at 1 in 5,000 first administrations of nitrofurantoin,² with acute manifestations outnumbering chronic manifestations by 9 to 1.³

The first report of acute pulmonary toxicity from nitrofurantoin was published in 1957.⁴ Typical symptoms associated with acute pulmonary toxicity include fever, chills, cough (dry or productive), dyspnea, elevated ESR, eosinophilia, and chest pain.^{2,3} Diffuse pulmonary infiltrates are a common finding on chest radiograph.¹ The manifestations of acute pulmonary toxicity can be alarming and can imitate MI, pulmonary embolism, or pneumonia.¹ Development of acute toxicity most often occurs within 3 to 8 days of nitrofurantoin initiation but ranges from a few hours to 4 weeks. Acute toxicity is likely, in part, a hypersensitivity reaction.²

Sollaccio and colleagues were the first to publish a report of a delayed or chronic pulmonary reaction to nitrofurantoin.⁵ Unlike the acute form, chronic nitrofurantoin-induced pulmonary toxicity has a slow, insidious onset, often appearing months to years after treatment is initiated.^{1,6} Middle-aged and older women are most affected, a fact that may be explained by their susceptibility to recurrent UTI, which is frequently treated with nitrofurantoin.^{1,6} Patients typically present with gradually increasing dyspnea and nonproductive cough with bilateral, scattered crackles on physical examination.³ Diffuse, bilateral interstitial infiltrates are routinely seen on chest radiograph, and bilateral, patchy ground glass attenuation appears on chest CT.⁶ Pulmonary function tests demonstrate a restrictive pattern with diffusion capacity defect. Open lung biopsy results consist of a nonspecific pattern of diffuse interstitial pneumonitis and fibrosis.⁷ It does not appear that acute toxicity leads to chronic toxicity or that chronic lesions follow an acute reaction to nitrofurantoin.^{7,8}

The mechanism of chronic nitrofurantoin-induced pulmonary toxicity has not been fully elucidated, but it is thought to be related to direct oxidative damage to the lungs. Nitrofurantoin undergoes cyclic reduction and reoxidation that may produce superoxide radicals and/or deplete nicotinamide-adenine dinucleotide phosphate. Nitrofurantoin also inhibits glutathione reductase, an enzyme involved in the glutathione antioxidant system.⁹

Early diagnosis and discontinuation of nitrofurantoin after onset of symptoms is important in preventing irreversible

TEACHING POINTS

- Pulmonary toxicity is a rare but serious side effect of the commonly prescribed antibiotic nitrofurantoin.
- Nitrofurantoin-induced pulmonary toxicity can be acute or chronic.
- Symptoms of chronic toxicity can be slow and insidious in nature, making the diagnosis difficult.
- Primary treatment includes withdrawal of the nitrofurantoin. Benefits of corticosteroid treatment have not been proved, but this treatment may be considered.
- The first and key step toward identifying this type and other types of adverse drug reactions is obtaining and clearly documenting an accurate medication history.

“This case highlights the value of recording an accurate and complete medication history as part of the initial assessment.”

pulmonary fibrosis.^{6,7,10} In the majority of patients with chronic nitrofurantoin-induced pulmonary toxicity, symptoms will improve and radiologic abnormalities will resolve after cessation of nitrofurantoin or in combination with corticosteroid therapy; however, more than half of these patients may have some persistent pulmonary changes.^{6,7,10} Definitive evidence supporting the use of corticosteroids is lacking; thus, the role of corticosteroid therapy in the treatment of chronic nitrofurantoin pulmonary toxicity remains controversial.^{7,10} Many patients will have significant resolution of symptoms without corticosteroid treatment, while others with more significant disease may benefit from corticosteroid therapy.^{6,7,10} In patients with reversible disease, the duration of pulmonary symptoms appears to correlate with the amount of improvement. There does not appear to be any correlation between the length of time on nitrofurantoin therapy and either the severity of the toxicity reaction or its reversibility.⁷

Home medication documentation upon hospital admission

Although adverse drug reactions are a frequent cause of ED visits and hospital admission, they are commonly overlooked. Chronic nitrofurantoin-induced pulmonary toxicity is even more difficult to recognize because of the slow, insidious onset of general respiratory symptoms that may mimic pneumonia, pulmonary embolism, heart failure, and other conditions. The first and key step toward identifying this type and other types of adverse drug reactions is obtaining and clearly documenting an accurate medication history.

Discrepancies in home medication lists at hospital admission occur for a variety of reasons,¹¹ and this case also highlights the importance of recording an accurate and complete medication history as part of the initial patient assessment at hospital admission. The pulmonology consultants were unaware of this patient's history of nitrofurantoin use because home medications were poorly documented; therefore, the diagnosis was nearly overlooked. Had the medication not been clarified and restarted days later, it is not clear when the diagnosis would have been made. Because the patient's creatinine clearance was less than 60 mL/min, the pharmacy computer flagged the nitrofurantoin for review by pharmacy as a potential renal contraindication. It was only then, through a series of serendipitous events, that the pharmacist recognized the potential for the nitrofurantoin to be the cause of the respiratory symptoms and brought the drug to the attention of the pulmonologist.

PAs are often responsible for documentation of home medications as part of the initial history and physical examination. Thoroughly investigating any vagueness or incon-

sistency is important but can be difficult, especially when the patient is unknown to the clinician or is an unreliable historian. Resources to help clarify a patient's home medications include family members and caregivers, other medical records, the patient's retail pharmacy, and consultation with the hospital pharmacist. A hospital pharmacist is uniquely trained in recognizing inconsistencies or medications that “don't make sense” and can therefore be of valuable assistance.¹¹ Contacting the patient's community pharmacy can also be very helpful. The community pharmacy should have records of all the patient's current medications and dosages, regardless of the number of health care providers the patient sees.

CONCLUSION

This case created a diagnostic dilemma for clinicians. The combination of poor documentation of home medications and the slow, insidious onset of symptoms associated with chronic nitrofurantoin-induced pulmonary toxicity delayed the diagnosis and the discontinuation of nitrofurantoin. Clinicians must carefully document all home medications and think to consider this adverse reaction in patients taking nitrofurantoin, particularly in those who present with pulmonary symptoms. **JAAPA**

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DRUGS MENTIONED

Acetaminophen (Tylenol, generics)
Furosemide (Lasix, generics)
Galantamine (Razadyne, generics)
Metoprolol (Lopressor, Toprol, generics)
Nitrofurantoin (Furadantin, Macrobid, Macrodantin, generics)
Penicillin

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