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Pulmonary Fibrosis Due to Nitrofurantoin Therapy: A Case Report

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Abstract

We report the case of a patient with pulmonary fibrosis, developed as an adverse reaction to nitrofurantoin therapy received for totally 6 months for the prevention of recurrent urinary tract infections. Chest X-ray and CT scan revealed extensive elements of interstitial pulmonary fibrosis. After diagnosis, administration of nitrofurantoin was immediately stopped; and specific prolonged therapy with low-dose corticosteroids *per os* and inhaled steroids were administered. The patient responded successfully both clinically and biochemically and possible digestive system side effects were prevented through the administration of gastroprotection medication. For the prevention of urinary tract infection, the patient received well tolerated therapy with fosfomycin which was further continued as a prophylactic agent.

Keywords

Nitrofurantoin, Lung Toxicity, Fibrosis, Fosfomycin

1. Introduction

Prostatitis has always been considered as a difficult infection to treat due to limited penetration of many antimicrobial agents into the prostatic tissue. In order to bypass poor bioavailability, prolonged courses of antibacterial regimens are required that may extent to 12 weeks. Fluoroquinolones, once were the cornerstone of antimicrobial therapy for prostate infections, are nowadays frequently ineffective due to emergence of resistance. The high prevalence of multi-drug resistant organisms has negatively impacted the microbial epidemiology

of prostatitis and thus has limited oral treatment options. Frequently, nowadays the therapeutic approach mandates prolonged parenteral courses that unfortunately are frequently associated with high relapse rates [1] [2]. Nitrofurantoin is one of the drugs used to prevent urinary tract infections (UTIs) but it is also known to be associated with adverse pulmonary reactions [3] [4] [5] [6] [7]. Even though its incidence is not frequent, nitrofurantoin may be associated with lung injury [8]. Here we present the case of a 79-year-old male who developed pulmonary fibrosis which was finally attributed to the use of nitrofurantoin.

2. Case Presentation

A 79-year-old white male with unremarkable medical history, presented to the infectious diseases outpatient department with a history of recurrent UTIs. The patient began suffering from urine incontinence fifteen years ago following transurethral prostatectomy for benign prostate hyperplasia. He underwent cystoscopy three years ago and since then he presented with recurrent episodes of acute pyelonephritis due to Escherichia coli. The strain exhibited resistance to fluoroquinolones and trimethoprim/sulfamethoxazole during his first assessment in our Infectious Diseases Outpatient Unit (IDOU), precluding use of these two antibiotic classes as prophylaxis options.

Despite the patient's history of transurethral prostatectomy, we could not exclude the possibility of recurrences stemming from the remaining prostate tissue, although an MRI of the pelvis during a febrile episode did not reveal any inflammatory changes in the residual prostatic tissue. Given the available in vitro susceptible options, the patient was treated with prophylactic nitrofurantoin 100 mg once daily for a period of six months.

After six months, he presented to our IDOU with symptoms of dyspnea on exertion, crackles and fatigue that had intensified over the past two months. Physical exam revealed stable vital sings with mild hypoxemia (PaO_2 77 mmHg and SpO_2 90%). Presumptions that pulmonary intoxication may have occurred due to suppressive therapy with nitrofurantoin, led us to proceed to further pulmonary examination through chest radiography and computed tomography (CT).

The chest radiography (**Figure 1**) and CT scan (**Figure 2**) revealed elements of interstitial pulmonary fibrosis.

In particular, thickening of the interstitial tissue was observed, which was more pronounced in the middle and especially lower pulmonary area, locally accompanied by cystic bronchiectasis and honeycombing, without pleural effusion. As adverse reaction to nitrofurantoin was considered, its administration was immediately ceased. However, other conditions were also considered and a Gomori methenamine silver stain was performed which did not reveal the presence of any fungal organisms. When pulmonary function tests were performed, a restrictive pattern of lung function was revealed: forced vital capacity (FVC) within 57% of the reference value (3.53 L), forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio of 65% of the reference value

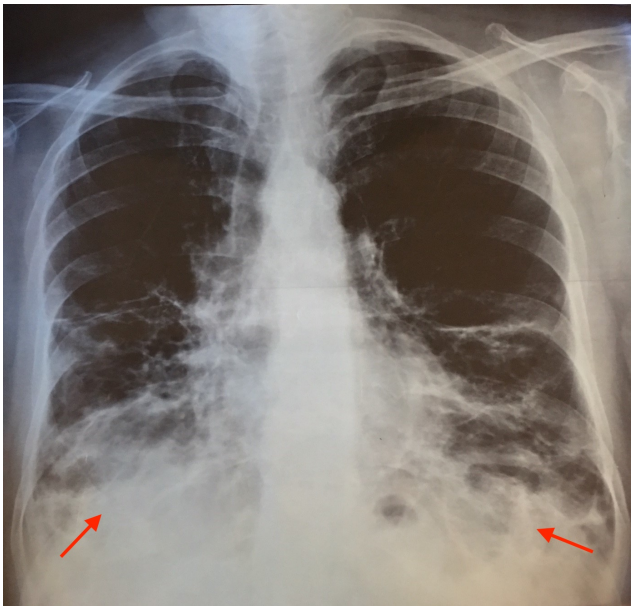

Figure 1. Chest radiography on admission showing extensive interstitial shadows in both lungs.

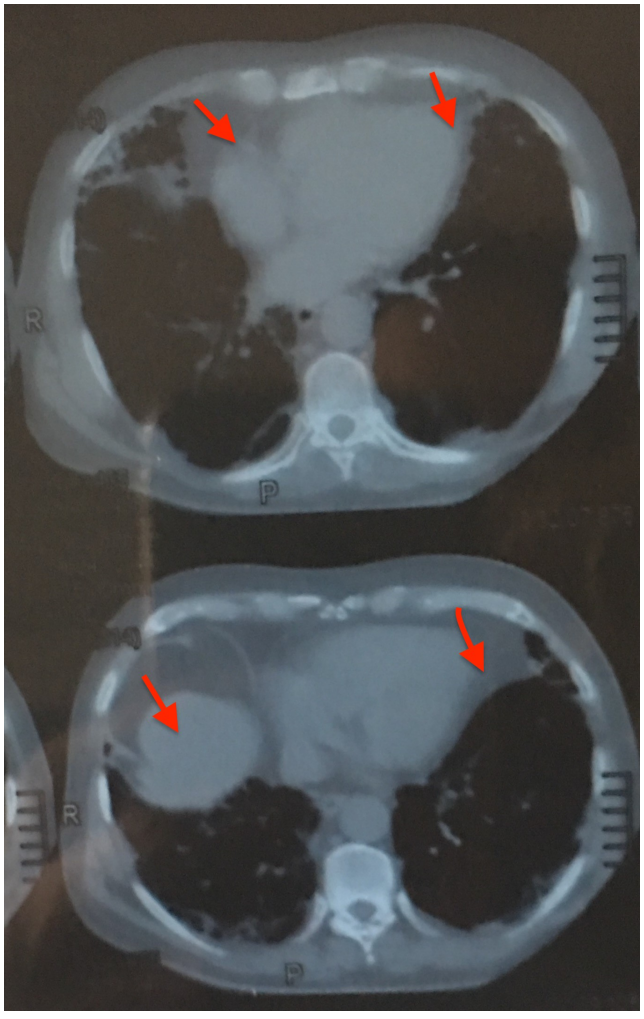

Figure 2. CT scan on admission showing extensive interstitial shadows in both lungs.

(86%), total lung capacity (TLC) was 70% of the one predicted (6.38 L) and the carbon monoxide diffusing capacity (DLCO) was 28% of the one predicted (21.2 ml/min/mmHg).

As both pathologic findings and clinical course of nitrofurantoin long-term administration complied with chronic adverse drug reaction to this specific drug, our patient was counseled to stop its use. We immediately initiated corticosteroid therapy with methylprednisolone (16 mg), which was administered *per os* (PO) for six months, initially at a loading dose of 48 mg/day for one month. The dose was then tapered every one month by 8 mg/day. After 6-month treatment, administration of methylprednisolone was ceased. Supplementary, daily inhalations with fluticasone (125 mcg/dose) three times per day were prescribed for twelve months. Corticosteroid therapy was well tolerated as we administered omeprozole (20 mg/day) every morning in order to prevent injuries to the upper gastrointestinal tract.

Following the discontinuation of prophylactic nitrofurantoin the patient was placed on a prophylactic regimen with once daily trimethoprim/sulfamethoxazole (800/160 mg). Follow-up urine culture one month later revealed more than 106 cfu/ml *E. coli*, resistant to trimethoprim/sulfamethoxazole, nitrofurantoin and quinolones. Resistance profile precluded other orally administered agents, except for tetracyclines, therefore he received therapy with fosfomycin which was further continued as prophylactic agent.

Within one month, our patient observed some improvement of his dyspnea while after three months, his symptoms significantly diminished and the elements of interstitial pulmonary fibrosis which were previously found on his CT scan (**Figure 3**) and chest X-ray were significantly recessed (**Figure 4**).

Pulmonary function tests performed regularly afterward revealed both normalization of his FVC (growing to over 90% of predicted) within twelve months and progressive improvement in his DLCO. Thus, he could restart his usual activities without dyspnea or fatigue. After two years, a new CT scan (**Figure 5**) and chest radiography (**Figure 6**) revealed significant improvement of the radiographic image with partial regression of the lesions through the pulmonary network (interstitial fibrosis alterations).

During this period he was asymptomatic, with repeatedly sterile urine cultures and no signs of toxicity from laboratory follow up. During re-challenge, fosfomycin was well tolerated, with minor episodes of diarrhea treated with loperamide as needed.

3. Discussion

Pulmonary reaction secondary to nitrofurantoin is a potentially serious, even fatal, adverse drug reaction [9]. Both acute and chronic forms of nitrofurantoin-induced pulmonary injury have been reported. The acute manifestation of this process is the most common and is thought to be due to a hypersensitivity reaction to the drug. Symptoms that develop after six months of therapy are generally considered to be chronic manifestation of the disease and have been thought

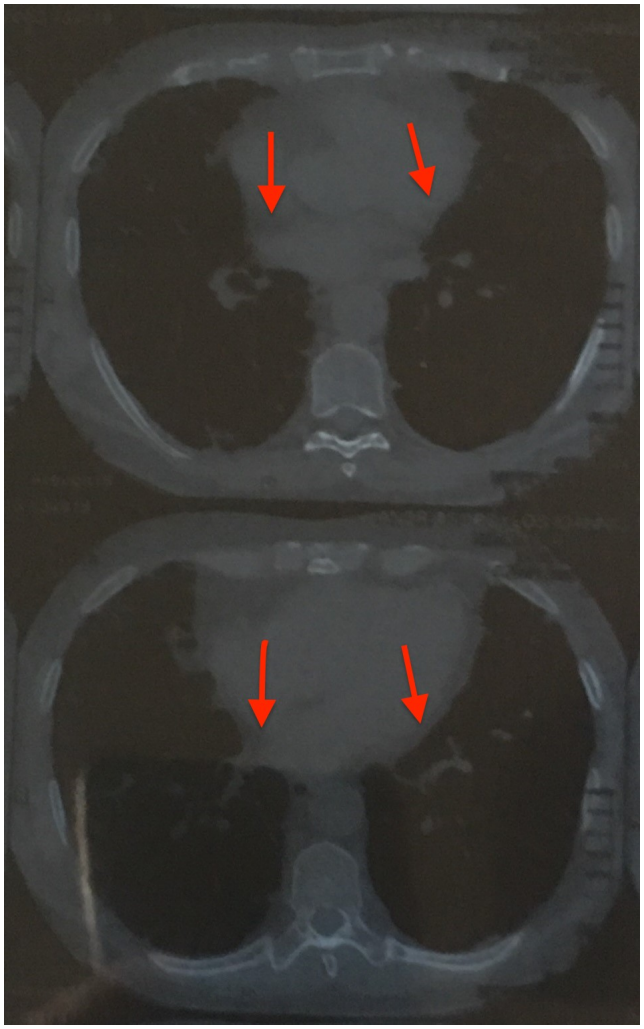

Figure 3. CT scan one month after treatment onset.

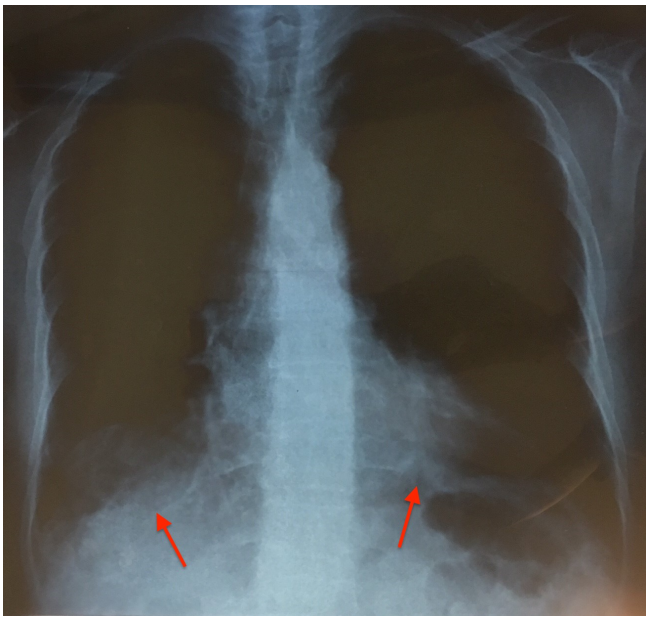

Figure 4. Chest radiography one month after treatment onset.

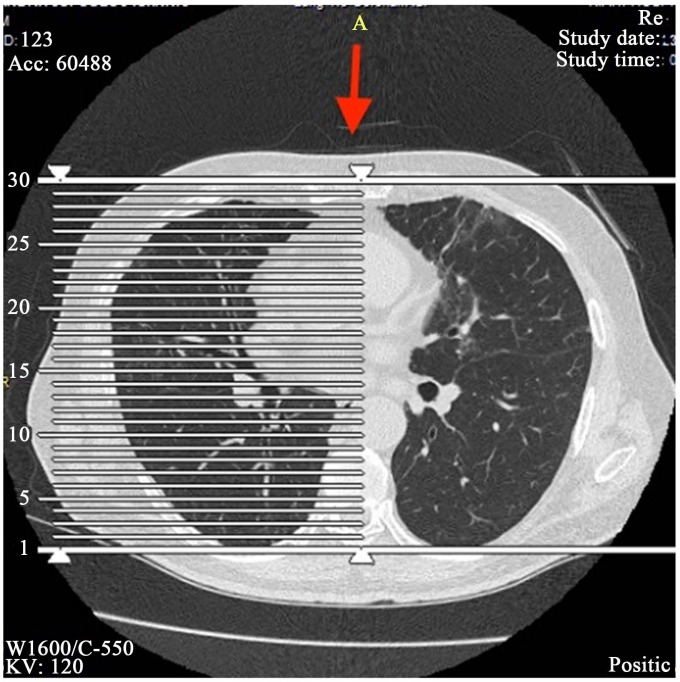

Figure 5. CT scan two years after the end of treatment.

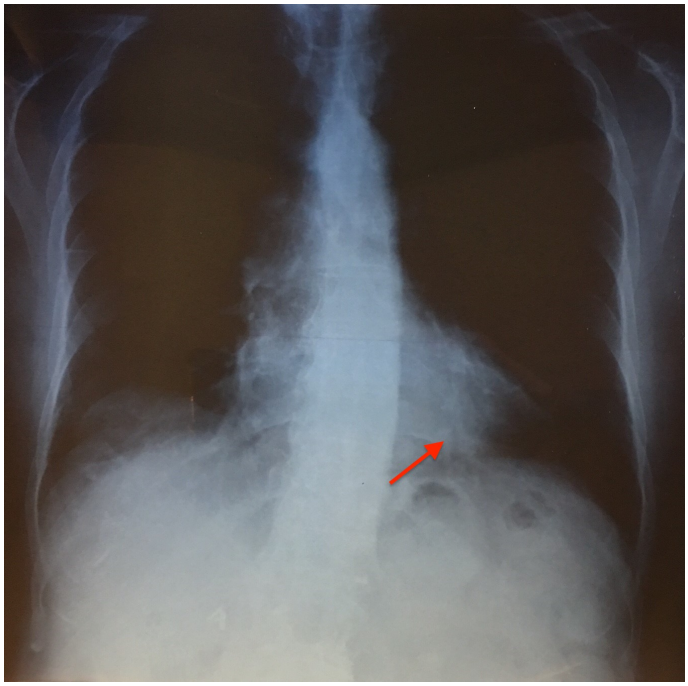

Figure 6. Chest radiography two years after the end of treatment.

to be the result of toxicity rather than hypersensitivity. Over the past decades, pulmonary reactions such as pulmonary fibrosis and bronchiolitis obliterans organizing pneumonia have been reported to be caused by exposure to nitrofurantoin [10]. Even though both timing and mechanisms of injury may be different, the treatment of chronic pulmonary injury from nitrofurantoin requires both drug interruption and therapy with corticosteroids [11] [12]. Recovery

from chronic reactions may take from months to a year [13] [14] [15]. However, in chronic reactions, not all patients respond to drug abdication.

In our case, patient's advanced age and history of UTIs led us to decide the immediate cease of nitrofurantoin administration and to start orally a low-dose corticosteroid therapy, while a close monitoring was applied. For the treatment of UTIs, nitrofurantoin administration was replaced with fosfomycin, which has been proposed to have a potential role in prophylaxis or treatment of prostatitis without any report of toxicity issues regarding its use [16] [17].

Within the first three months, the patient experienced relative improvement of his physical condition and serial pulmonary function tests documented reversal of the restrictive pattern. Our experience and other recent case descriptions [13] [14] suggest that the older classification of nitrofurantoin lung toxicity as either acute or chronic, with the latter frequently irreversible is incomplete. Nevertheless, it remains very important to suspect a drug reaction whenever a patient taking nitrofurantoin develops respiratory symptoms. On the contrary, fosfomycin long-term administration was proven to be efficacious and well tolerated in terms of toxicity and should be considered as an alternative agent, especially in patients with paucity of other prophylaxis options due to resistance profile or adverse events such as pulmonary fibrosis.

4. Conclusion

To conclude, we underline that in case of documented pulmonary fibrosis and concurrent nitrofurantoin administration; both nitrofurantoins should be immediately stopped, and specific prolonged therapy with low-dose corticosteroids and inhaled steroids should be started. In parallel, appropriate clinical and laboratory monitoring should be applied until the resolution of symptoms and improvement of lab tests results. Additionally, administration of gastroprotection medication effectively prevents the possible adverse effects on the digestive system due to corticosteroids' use.

5. Consent for Publication

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1975, as revised in 2000. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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