

## CASE REPORTS

# Nitrofurantoin-Associated Lung and Liver Toxicity Leading to Liver Transplantation in a Middle-Aged Patient

Tony K L Kiang, Jo-Ann Ford, Eric M Yoshida, and Nilufar Partovi

## INTRODUCTION

Nitrofurantoin is indicated for the treatment or prophylaxis of uncomplicated urinary tract infections. Currently, it is considered as second-line treatment for this type of infection because of emerging bacterial resistance.<sup>1</sup> Nitrofurantoin is bioactivated to various reactive intermediates that interfere with bacterial ribosomal proteins and inhibit the synthesis of critical cellular macromolecules (e.g., DNA).<sup>2</sup> Nitrofurantoin is extensively absorbed by the gastrointestinal tract, is rapidly eliminated (with a half-life of about 0.3–1 h) by the kidneys, and is concentrated in the urine.<sup>3</sup> Typical dosages in adults with normal renal function (creatinine clearance > 60 mL/min) are 50–100 mg PO qid for 1 week (for treatment) or 50–100 mg PO at bedtime (for prophylaxis).<sup>4</sup> The clearance of nitrofurantoin depends on glomerular function, so its concentration in the urine, and hence its bactericidal effects, is reduced in patients with compromised creatinine clearance.<sup>5,6</sup>

Various adverse effects are associated with nitrofurantoin. Gastrointestinal complaints are common.<sup>7,8</sup> Very rarely, neurological, hematological, pulmonary, and hepatic reactions may occur.<sup>9</sup> Peripheral neuropathy of the sensorimotor type is a common neurological complaint.<sup>10</sup> Acute hemolytic anemia, typically associated with deficiency of glucose-6-phosphate dehydrogenase, is the predominant hematological adverse effect.<sup>11</sup> Most nitrofurantoin-induced pulmonary toxicity is acute and immunologic in nature, but cases of chronic pulmonary fibrosis have also been reported.<sup>9,11</sup> Likewise, hepatotoxicity caused by nitrofurantoin is generally of acute onset, but patients may also present with chronic, active hepatitis.<sup>12</sup>

Nitrofurantoin-associated pulmonary or hepatic toxicity is rare.<sup>9,12</sup> Even rarer are patients who present with concurrent pulmonary and hepatic complications.<sup>11</sup> We present a case of nitrofurantoin-associated lung and liver toxicity in a 57-year-old woman who required liver transplantation. We also provide an up-to-date summary of previously published cases.

## CASE REPORT

A 57-year-old woman presented to the emergency department after collapsing at home.\* A week before admission, the patient complained of darkened urine, low-grade fever, and pruritis. She had reported increasing fatigue and decreasing energy level for 6 months before admission. Jaundice had developed about 2 weeks before admission. Her medical history included Crohn disease, recurrent urinary tract infection, and multiple episodes of pyelonephritis (3 occurrences in the previous year). Her surgical history included appendectomy and 3 cesarean sections. On admission, the patient was not taking any medication for Crohn disease because the most recent flare-up had been more than 30 years ago. She had been taking oral nitrofurantoin 100 mg once or twice daily and ciprofloxacin (dose not reported) for 18 months for the management of urinary tract infections. The social history was not significant (she was not an active drinker and did not smoke), and the family history was negative for cancer and hepatitis. Interestingly, her son and daughter both had diagnosed immunodeficiency. The patient had no history of substance abuse and did not use herbal products. All other causes of liver disease were excluded through exhaustive pretransplant investigation and examination of the explanted liver by liver disease specialists.

At the time of admission, the patient appeared jaundiced and short of breath. On examination, the patient was alert and oriented. Asterixis was not evident, and no stigmata associated with liver disease were found. The results of an abdominal examination were normal, and no organomegaly or peripheral edema was evident. The liver echotexture did not have any coarseness or nodularity that would suggest cirrhosis or chronic liver disease. Computed tomography of the chest

\*The patient's consent for publication was not obtained; all identifying information has been removed from the article.

indicated interstitial lung disease with peripheral cavities. Chest radiography revealed bilateral infiltrates. Liver function tests showed elevation of aspartate aminotransferase (1444 units/L), alanine aminotransferase (1926 units/L), direct bilirubin (221  $\mu\text{mol/L}$ ), total bilirubin (309  $\mu\text{mol/L}$ ), alkaline phosphatase (169 units/L), and  $\gamma$ -glutamyltransferase (276 units/L). Laboratory findings included white blood cell count  $7.3 \times 10^9/\text{L}$ , hemoglobin 140 g/L, platelets  $292 \times 10^9/\text{L}$ , international normalized ratio 1.8, partial thromboplastin time 36 s, creatinine 61  $\mu\text{mol/L}$ , and albumin 26 g/L. Immunoglobulin A, immunoglobulin M, immunoglobulin G,  $\alpha_1$ -antitrypsin, ceruloplasmin, hepatitis B antigen, antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis C virus (anti-HCV), and anti-smooth muscle antibody were all negative or within normal limits. As well, serum levels of salicylate and acetaminophen were below the level of detection.

Nitrofurantoin was discontinued before admission, but the patient's liver dysfunction progressed despite oral administration of prednisone (20 mg/day) in hospital. Signs of hepatic encephalopathy developed, and the patient subsequently received a liver transplant, about 1 month after admission to hospital. Since the transplant, the patient's lung disease has been clinically silent, with no need for pulmonary medications, respirology consultations, or supplemental oxygen. Examination of a liver specimen showed large zones of necrotic liver, extensive bile duct proliferation, acute portal inflammation, and cholestasis. There was no evidence of malignancy or cirrhosis. At the time of writing, 2 years after the transplant, the patient was stable and had normal allograft function.

## DISCUSSION

In the case reported here, concurrent interstitial lung disease and hepatotoxicity developed in a 57-year-old woman secondary to long-term use of nitrofurantoin (over 18 months). The Naranjo probability score was 3, which indicated "possible" causality between nitrofurantoin and the development of concurrent lung and liver toxicity.<sup>13</sup> Clinical judgement on the part of various hepatic and pulmonary specialists ultimately led to the conclusion of causality. Autoimmune hepatitis was an unlikely differential diagnosis given the normal levels of immunoglobulin G and anti-smooth muscle antibody and the lack of autoimmune hepatitis features on histologic examination of the explanted liver. Ciprofloxacin, which was being taken concurrently by the patient, has also been associated with liver injury, but liver toxicity from ciprofloxacin is mainly of the cholestatic type,<sup>14,15</sup> and no case of combined lung and liver toxicity has been reported with ciprofloxacin. Accordingly, the pulmonary and hepatic manifestations observed in this patient were attributed to nitrofurantoin alone.

To summarize the published cases of nitrofurantoin-associated concurrent lung and liver toxicity, PubMed and

Embase were searched with various combinations of the following terms: nitrofurantoin, hepatotoxicity, pulmonary toxicity, liver, lung, hepatitis, liver necrosis, pulmonary fibrosis, and interstitial pneumonitis. Only articles published in English and searchable before October 2010 were included. The titles and abstracts were screened for relevance, and 9 published articles<sup>16-24</sup> describing 10 case reports were identified (Table 1).

To the best of our knowledge, this is the first summary incorporating all cases of nitrofurantoin-induced concurrent pulmonary and hepatic toxicity published in English. Most cases (9 of 10) occurred in women, most patients were generally older (in 8 of the 10 cases, the patients were older than 57 years; mean age 59 years), and most were receiving nitrofurantoin for the management of urinary tract infection. No clear dose-response relationship was evident, as the dose of nitrofurantoin ranged between 50 and 300 mg per day, which is within the recommended range.<sup>4</sup> The onset of symptoms could generally be described as "late" (i.e., 11 months to 11 years after initiation of therapy), and it was difficult to discern whether the pulmonary toxicity preceded the hepatotoxicity or vice versa. Common symptoms included jaundice, weight loss, malaise, dyspnea, and dry cough. Rales or crackles could be heard, usually from both lungs, and in the majority of cases, chest radiography indicated a pattern of interstitial lung disease. The results of pulmonary function tests, when available, suggested impairment of the restrictive type.

Most liver biopsies illustrated a pattern of chronic active hepatitis with piecemeal necrosis and/or infiltration by nonparenchyma cells, although normal biopsy results were also reported. Laboratory investigations often revealed increased erythrocyte sedimentation rate and markedly elevated transaminases, alkaline phosphatase,  $\gamma$ -glutamyltransferase, or bilirubin. Increased international normalized ratio, partial thromboplastin time, or activated partial thromboplastin time, suggesting compromised liver synthetic function, and positive antinuclear antibodies or anti-smooth muscle antibodies, suggesting immunologic involvement, were also commonly reported. Upon discontinuation of nitrofurantoin, most of the patients improved with respect to clinical status, pulmonary function, and liver function, in the absence of corticosteroid therapy. The time to recovery varied from 3 weeks to 6 months. Recovery of liver function was faster than or equal to that of pulmonary function in a few cases,<sup>16,19,20,24</sup> but not in others.<sup>17,22</sup> Two of the patients died of subsequent complications, despite corticosteroid therapy in one case.<sup>18,21</sup>

The incidence of pulmonary toxicity associated with nitrofurantoin has been estimated at 0.00002% to 0.0009%,<sup>9</sup> and that of hepatotoxicity at 0.0003%<sup>9</sup> to 0.035%.<sup>12</sup> The incidence of concurrent pulmonary and hepatic toxicity remains unknown, although it is probably less than the incidence of either form of toxicity alone. Reinhart and others<sup>17</sup> estimated

**Table 1. Summary of Cases Involving Nitrofurantoin-Associated Combined Pulmonary and Hepatic Toxicity**

Reference	Patient Characteristics*	Dose and Duration of NFT	Signs, Symptoms, Results of Laboratory Tests and Biopsy	Interventions and Clinical Outcome
Lundgren et al. <sup>16</sup>	<p>Case 1: 48-year-old woman (ethnicity not reported) with history of rheumatoid arthritis, recurrent cystitis</p> <p>Concurrent medications: none</p> <p>Allergies: sulfa drugs</p> <p>Hep B / Hep C status: not reported</p> <p>Family history and exposure: not reported</p> <p>Smoking and EtOH history: not reported</p> <p>Infectious pneumonia: not ruled out</p>	<p>100 mg once daily for 11 months</p>	<p>Signs and symptoms: dyspnea, joint pains, rales (right lung), enlarged thyroid gland, no jaundice</p> <p>Laboratory tests: ESR 54 mm/h, GOT 172 units (normal 5–17 units), GPT 165 units (normal 2–17 units), LDH 200 units (normal 50–150 units), bilirubin 0.6 mg/100 mL (normal 0.2–1.2 mg/100 mL), ALP 9.2 units (normal 2–8 units), positive for antinuclear factor, negative for anti-smooth muscle antibodies</p> <p>CXR: "disseminated opacities in irregular, interstitial pattern"</p> <p>Pulmonary function test: FEV<sub>1</sub> 57%, vital capacity 49%, total lung capacity 55%, residual volume 42%; "restrictive impairment"</p> <p>Liver biopsy: normal results</p>	<p>NFT stopped: dyspnea disappeared; pulmonary function, LFT, weight, and antinuclear factor normalized in 3 months; CXR results improved in 3 months; negative for antinuclear factor after 12 months</p> <p>No corticosteroid therapy</p>
	<p>Case 2: 63-year-old woman (ethnicity not reported) with history of erythema nodosum in 1933, bleeding myoma in 1959</p> <p>Concurrent medications: not reported</p> <p>Allergies: not reported</p> <p>Hep B / Hep C status: not reported</p> <p>Family history and exposure: not reported</p> <p>Smoking and EtOH history: not reported</p> <p>Infectious pneumonia: not ruled out</p>	<p>100 mg once daily for 11 months</p>	<p>Signs and symptoms: November 1972: fever, chills, dyspnea, cough (suspected pneumonia, not responsive to antibiotics); May 1973: fever, dyspnea, 9-kg weight loss, bedridden; September 1973: dyspnea at rest, enlarged thyroid gland, no jaundice</p> <p>Laboratory tests: ESR 50 mm/h, GOT 27 units (normal 5–17 units), GPT 22 units (normal 2–17 units), LDH 190 units (normal 50–150 units), bilirubin 0.9 mg/100 mL (normal 0.2–1.2 mg/100 mL), ALP 4.8 units (normal 2–8 units), positive for antinuclear factor, positive for anti-smooth muscle antibodies</p> <p>CXR: "disseminated, irregular and partly confluent opacities ... in both lungs"</p> <p>Pulmonary function test: FEV<sub>1</sub> 74%, vital capacity 62%, total lung capacity 55%, residual volume 42%; "restrictive impairment"</p> <p>Liver biopsy: not reported</p>	<p>NFT stopped: dyspnea disappeared; pulmonary function, LFT, ESR, weight, and antinuclear factor normalized in 3 months; antinuclear factor became negative 5 months after stopping NFT; CXR improved in 3 months</p> <p>No corticosteroid therapy</p>

continued on page 265

**Table 1. Summary of Cases Involving Nitrofurantoin-Associated Combined Pulmonary and Hepatic Toxicity (continued)**

Reference	Patient Characteristics*	Dose and Duration of NFT	Signs, Symptoms, Results of Laboratory Tests and Biopsy	Interventions and Clinical Outcome
Reinhart et al. <sup>17</sup>	67-year-old white woman with lumpectomy of left breast 3 years before admission, hypertension, hypercholesterolemia for 10 years, recurrent cystitis for 2 years Concurrent medications: methylodopa-hydrochlorothiazide, probucol, erythromycin (started 3 weeks before admission for rales), Robitussin Allergies: sulfa (brochospasm), penicillin (urticaria), cephalixin, tetracycline Hep B status: negative Hep C status: unknown Family history and exposure: none Smoking and ETOH history: half pack per day for 16 years, no ETOH usage Infectious pneumonia: ruled out	100 mg at bedtime for 2 years	Signs and symptoms: fatigue, malaise, anorexia, scleral icterus, 12-lb (26.4-kg) weight loss over 4 weeks, dry nonproductive cough and mild dyspnea for 3 weeks, "fine bibasilar inspiratory rales ... on the right side ... without egophony or dullness to percussion" Laboratory tests: total bilirubin 130 µmol/L, SGOT 1124 IU/L, SGPT 1184 IU/L, ALP 203 IU/L (normal 40–140 IU/L), GGT 305 IU/L (normal 8–78 IU/L), prothrombin time 13.5 s (normal 9.3–11.2 s), PTT 41.3 s (normal 22–36 s), Hgb 148 g/L, platelet count 215 × 10 <sup>3</sup> /mm <sup>3</sup> , positive for antinuclear antibody, positive for anti-smooth muscle antibody CXR: 2 weeks before admission, right lower lobe infiltrate suggesting atypical pneumonia, "patchy areas of increased densities at the right base and apex" Pulmonary function test: mild restrictive disease Abdominal CT: bibasilar pulmonary atelectases with interstitial changes Liver biopsy: "moderate infiltration of portal fields by lymphocytes and plasma cells, acute inflammatory cells, and eosinophils ... piecemeal necrosis in many areas and mild fibrosis ... extensive hydropic changes of hepatocytes ... indicative of severe chronic active hepatitis with significant acute component"	NFT and erythromycin stopped: respiratory function recovered "soon after stopping"; results of LFTs continued to be elevated, peaking at day 7 after admission (total bilirubin 1357 IU/L, SGPT 1345 IU/L); LFT results "normalized slowly" No corticosteroid therapy
Mulberg and Bell <sup>18</sup>	16-year-old female (ethnicity not reported), with history of thoracic laminectomy at 4.5 years of age, paraplegia, recurrent UTI, left lateral thigh cellulitis (5 weeks before admission) Concurrent medications: penicillin started (for cellulitis) and stopped (because of rash); cefotaxime and clindamycin after bursectomy during current admission; trimethoprim-sulfamethoxazole used intermittently for UTI Allergies: penicillin Hep B status: negative Hep C status: unknown Family history and exposure: not reported Smoking and ETOH history: not reported Infectious pneumonia: not ruled out	Dose not specified; used intermittently for 11 years	Signs and symptoms: 7 days into admission: respiratory distress, temperature 39.5°C, RR 30/min, pulse 120/min; dermatological symptoms: confluent erythroderma + desquamation, petechial eruption; lungs: rales of right base + right midaxillary area, splinting of left chest, left upper quadrant tenderness, leg edema Laboratory tests: ESR 140 mm/h, direct bilirubin 3.2 mg/dL (normal < 0.5 mg/dL), AST 144 U/L (normal 6–35 U/L), ALT 267 U/L (normal 10–30 U/L), ALP 610 U/L (normal 70–300 U/L), GGT 331 IU/L (normal 0–35 IU/L), prothrombin time 20 s (normal 8.9–10.6 s), PTT 68 s (normal 24.7–38.5 s), Hgb 148 g/L, albumin 2.2 g/dL (normal 3.5–5.0 g/dL), LDH 1040 U/L (normal 90–230 U/L), negative for antinuclear antibody, negative for anti-smooth muscle antibody CXR: poorly inflated lungs + left lower lobe pneumonia and effusion; repeat CXR indicated ARDS Pulmonary function test: not done Liver biopsy: not done	NFT therapy stopped 7 days after admission, because patient experienced seizures and ARDS requiring mechanical ventilation Corticosteroid therapy initiated: coagulopathy, LFTs, bleeding diatheses corrected "over several days" Patient died

continued on page 266



**Table 1. Summary of Cases Involving Nitrofurantoin-Associated Combined Pulmonary and Hepatic Toxicity (continued)**

Reference	Patient Characteristics*	Dose and Duration of NIT	Signs, Symptoms, Results of Laboratory Tests and Biopsy	Interventions and Clinical Outcome
Yalcin et al. <sup>19</sup>	62-year-old woman (ethnicity not reported) with history of chronic dysuria Concurrent medications: not reported Allergies: none Hep B / Hep C status: negative for both Family history and exposure: none Smoking and ETOH history: not reported Infectious pneumonia: not ruled out	50 mg qid for 5 years	Signs and symptoms: shortness of breath, dry cough, night sweat, weight loss, tachypnea, pulse 104/min, RR 24/min, bilateral inspiratory fine crackles (up to the midzone) Laboratory tests: ESR 76 mm/h, total bilirubin 0.9 mg/dL (normal 0.1–1.2 mg/dL), direct bilirubin 0.2 (normal 0.0–0.3 mg/dL), SGOT 130 IU/L (normal 7–39 IU/L), SGPT 178 IU/L (normal 2–54 IU/L), ALP 77 IU/L (normal 41–133 IU/L), GGT 41 IU/L (normal 5–40 IU/L), prothrombin time 12 s, Hgb 16.2 g/L, albumin 3.9 g/dL (normal 3.4–4.7 g/dL), positive for antinuclear antibody, positive for anti-smooth muscle antibody; arterial blood gases showed hypoxemia CXR: bilateral fibrotic thickening and patchy alveolar infiltrations Pulmonary function test: "restrictive pulmonary disease with impaired diffusion capacity" Transbronchial biopsy: "submucosal edema with fibrosis ... mononuclear cell infiltration with no tumoral or granulomatous lesion" Chest CT: "bilateral fibrotic thickening and patchy alveolar infiltrations" Liver biopsy: chronic active hepatitis	NFT therapy stopped: LFTs, CXR, clinical symptoms normalized in 2 weeks; serologic results normalized in 3 months No corticosteroid therapy
Kelly et al. <sup>20</sup>	75-year-old woman (ethnicity not reported) with hypertension, hypothyroidism, ischemic heart disease, type 2 diabetes mellitus, recurrent UTI Concurrent medications: furosemide, verapamil, flurazepam, glyclizide, thyroid hormone (no change to medications for past 5 years) Allergies: not reported Hep B / Hep C status: negative for both Family history and exposure: none Smoking and ETOH history: none Infectious pneumonia: ruled out	100 mg once daily for 1.5 years	Signs and symptoms: anorexia, malaise for 3 months, cough, dyspnea on exertion for 4 weeks; lungs: fine inspiratory crepitations, bilateral pitting, ankle edema Laboratory tests: 2 months before admission: ALP 126 U/L (normal 41–117 U/L), AST 132 U/L (normal < 40 U/L), ALT 238 U/L (normal < 45 U/L), GGT 84 U/L (normal 6–50 U/L), total bilirubin 13 µmol/L (normal < 17 µmol/L), PTT and aPTT normal, albumin normal. On admission: results of LFTs did not differ from above; positive for antinuclear antibody CXR: fibrotic lung disease bilaterally (mid and lower zones) Pulmonary function test: "restrictive pulmonary disease" Liver biopsy: "Marked acute and chronic inflammation on portal tracts ... proliferation of bile ducts ... prominent piecemeal necrosis ... some smaller bile ducts were inflamed ... fatty change and marked hydropic change in the hepatocytes were present"	NFT therapy stopped: LFT returned to normal in 6 months CXR and lung function "not recovered at same rate" No corticosteroid therapy

continued on page 267

**Table 1. Summary of Cases Involving Nitrofurantoin-Associated Combined Pulmonary and Hepatic Toxicity (continued)**

Reference	Patient Characteristics*	Dose and Duration of NIT	Signs, Symptoms, Results of Laboratory Tests and Biopsy	Interventions and Clinical Outcome
YSchattner et al. <sup>21</sup>	60-year-old woman (ethnicity not reported) with multiple sclerosis for 6 years, recurrent UTI secondary to self-catheterization for 3 years Concurrent medications: not reported Allergies: penicillin Hep B / Hep C status: negative for both Family history and exposure: not reported Smoking and ETOH history: not reported Infectious pneumonia: ruled out	100 mg once daily for 3 years	Signs and symptoms: dry cough for 6 weeks, dyspnea on exertion, fatigue, anorexia, jaundice, RR 24/min; lungs: "diminished breath sounds at the bases" Laboratory tests: ESR 10 mm/h, direct bilirubin 13.2 mg/dL, AST 1000 U/L, ALP 352 U/L, INR 1.45, PTT 65% of control, aPTT 37 s, Hgb 148 g/L, positive for antinuclear antibody, positive for anti-smooth muscle antibody CXR: "diffuse bibasilar reticular pattern", bilateral infiltrates, "unilateral effusion, interstitial lung disease" Liver biopsy: not done	Patient: experienced pneumococcal septicemia and died < 30 days after admission
Linnebur and Parne <sup>22</sup>	73-year-old white man with atonic bladder secondary to BPH (self-catheterization daily), transurethral prostatectomy, recurrent UTI, urosepsis, gentamicin-induced acute labyrinthitis, partial left kidney failure secondary to chronic hydronephrosis, right inguinal hernia repair, joint pain, seasonal rhinitis, eczema, onychomycosis Concurrent medications: terazosin 5 mg/day, cimetidine 400 mg bid, fluticasone nasal spray prn, diphenhydramine 50 mg/day twice weekly, ibuprofen 400–1200 mg/day, flucanazole ointment, Centrum Silver multivitamin daily, vitamin E 400 IU/day, calcium citrate 630 mg + 400 IU vitamin D daily, ASA 325 mg/day, calcium polycarbophil 500 mg/day, docusate sodium 400 mg/day; most recent new drug before admission: fluconazole 150 mg/week Allergies: not reported Hep B / Hep C status: not reported Family history and exposure: not reported Smoking and ETOH history: 13 pack-year for 40 years, 1–2 glasses of wine per day Infectious pneumonia: not ruled out	50 mg once daily for 5 years	Signs and symptoms: 2 months after starting fluconazole: fatigue, dyspnea with exercise, pleuritic pain, burning trachea pain, mildly productive cough Laboratory tests: 2 months after starting fluconazole: AST 223 U/L, ALT 108 U/L, ALP and bilirubin normal CXR: "bilateral pulmonary disease ... in the bases ... likely edema and fibrosis" Pulmonary function test: 16 days after stopping NIT: reduced forced vital capacity, FEV <sub>1</sub> , FEV <sub>1</sub> /FVC, total lung capacity; "mixed moderately restrictive and mildly obstructive pattern" Liver biopsy: not done	Fluconazole and NIT stopped 2 months after initiation of fluconazole, leading to slight improvement in symptoms in 3 weeks Fluticasone by inhalation (880 µg/day) was initiated, leading to improvement in pulmonary symptoms over next 8 days CXR 1 month after stopping therapy showed "improvement" in pulmonary disease Pulmonary function test 3 months after stopping therapy showed "improvement" LFT and pulmonary symptoms much improved 4 months after stopping therapy

continued on page 268

**Table 1. Summary of Cases Involving Nitrofurantoin-Associated Combined Pulmonary and Hepatic Toxicity (continued)**

Reference	Patient Characteristics*	Dose and Duration of NFT	Signs, Symptoms, Results of Laboratory Tests and Biopsy	Interventions and Clinical Outcome
Koulaouzidis et al. <sup>23</sup>	57-year-old woman (ethnicity not reported) with multiple sclerosis for 17 years, recurrent UTI secondary to self-catheterization Concurrent medications: salbutamol by inhaler, beclomethasone by inhaler, amitriptyline, lansoprazole Allergies: not reported Hep B / Hep C status: negative for both Family history and exposure: none Smoking and ETOH history: no smoking Infectious pneumonia: not ruled out	100 mg once daily for 16 months	Signs and symptoms: nonproductive cough for 8 months Laboratory tests: ESR 24 mm/h, ALT 424 IU/L (normal 0–40 IU/L), AST 301 IU/L (normal 0–40 IU/L), GGT 894 U/L (normal 0–55 U/L), ALP 282 U/L (normal 39–118 U/L), bilirubin 8 mmol/L (normal 0–17 mmol/L), no coagulopathy, negative for autoantibodies CXR: normal at 5 months before admission; “multiple opacities in both lungs” at time of admission Chest CT: airspace shadowing “pneumonitis” Abdominal CT: gallstones present and “liver ... abnormal with most of the parenchyma demonstrating abnormal low attenuation areas in patchy distribution ...” Pulmonary function test: “restrictive ventilatory pattern” Liver biopsy: not done	NFT stopped; oral prednisone started LFT normalized in 4 months “Gradual but steady improvement in respiratory function”
Peall and Hodges <sup>24</sup>	72-year-old woman (ethnicity not reported) with asthma, recurrent UTI, osteoporosis Concurrent medications: amoxicillin and prednisone for 5 days after presentation (for suspected lower respiratory tract infection), zopiclone 7.5 mg once daily, medroxyprogesterone acetate 5 mg once daily, conjugated estrogens 0.3 mg once daily, amitriptyline 10 mg once daily, fluticasone 250 µg once daily, naproxen 550 mg bid, hyoscine butylbromide 10 mg prn, paracetamol 1 mg prn, salbutamol 200 µg prn Allergies: none Hep B / Hep C status: not reported Family history and exposure: none Smoking and ETOH history: none Infectious pneumonia: not ruled out	100 mg once daily for 6 months, then 100 mg tid for 5 months	Signs and symptoms: gradually increasing breathlessness for 1 month (not improving with prednisone and amoxicillin), upper abdominal discomfort, nausea Laboratory tests: IgG 15 g/L (normal 7–14 g/L), positive for antinuclear antibody, positive for anti-smooth muscle antibody, ALP 178 U/L (normal 25–130 U/L), GGT 99 U/L (normal 5–50 U/L), AST 631 U/L (normal 1–40 U/L), ALT 825 U/L (normal 1–40 U/L), HgB 159 g/L (normal 115–155 g/L), albumin 37 g/L (normal 35–50 g/L) CXR: “bilateral interstitial and alveolar shadowing in middle and lower zones” Chest CT: “peripheral alveolar shadowing and fibrotic changes” Upper abdominal ultrasonography: “enlarged hypoechoic liver” Pulmonary function test: “impaired diffusional capacity (49% of predicted)”, FEV <sub>1</sub> 2.64, vital capacity 3.30, FEV <sub>1</sub> /FVC 79.9% Liver biopsy: “moderate lobular hepatitis ... zone 3 necrosis”	NFT stopped; oral prednisone 40 mg once daily started LFT normalized and pulmonary function improved by day 24

ALP = alkaline phosphatase, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, ARDS = acute respiratory distress syndrome, ASA = acetylsalicylic acid, AST = aspartate aminotransferase, BPH = benign prostatic hypertrophy, CT = computed tomography, CXR = chest radiography, ESR = erythrocyte sedimentation rate, ETOH = ethanol, FEV<sub>1</sub> = forced expiratory volume in the first second, FVC = forced vital capacity, GGT = γ-glutamyl transferase, GOT = glutamic oxaloacetic transaminase, GPT = glutamate pyruvate transaminase, Hep B = hepatitis B, Hep C = hepatitis C, HgB = hemoglobin, IgG = immunoglobulin G, INR = international normalized ratio, LDH = lactate dehydrogenase, LFT = liver function tests, NFT = nitrofurantoin, PTT = partial thromboplastin time, RR = respiratory rate, SGOT = serum glutamic oxaloacetic transaminase (equivalent to AST), SGPT = serum glutamate pyruvate transaminase (equivalent to ALT), UTI = urinary tract infection.  
\*Age, sex, ethnicity, indication for nitrofurantoin, concurrent medical problems, concurrent medications, allergies, history of hepatitis B or hepatitis C, family history, exposure, history of smoking or ETOH use.

the incidence of combined toxicity at  $3.9 \times 10^{-11}$  per course of therapy, which might explain the small number of cases that have reported in the literature.

According to Sovijarvi and others,<sup>25</sup> most cases of nitrofurantoin-associated pulmonary toxicity can be classified as having acute onset, although numerous reports of chronic pulmonary toxicity have also been published.<sup>25-28</sup> The mean delay before onset of chronic pulmonary toxicity has been reported as 30 months,<sup>29</sup> and this condition lacks a dose-response relationship, occurs predominantly in women, and is often slow to resolve.<sup>9</sup> Common manifestations have included interstitial pneumonitis and fibrosis, which may lead to shortness of breath and cough (often dry). Chest radiography often indicates bilateral pleural effusion, with or without pulmonary infiltrates.<sup>30</sup>

Similar to lung toxicity, acute liver toxicity from nitrofurantoin is more common than chronic liver injury.<sup>9,12</sup> Stricker and others<sup>12</sup> summarized cases published before 1988, noting that chronic hepatotoxicity occurred predominantly in women, had an onset later than 6 months, and lacked a clear dose-response relationship. Common signs or symptoms included jaundice, hepatomegaly, malaise, anorexia, weight loss, nausea, and vomiting. About 70% of patients had anti-smooth muscle antibodies, and about 80% had antinuclear factors. Liver biochemistry tests suggested hepatocellular with occasional mixed cholestatic-hepatocellular abnormalities, and liver biopsy often indicated a pattern of chronic active hepatitis.<sup>12</sup> Only a handful of case reports of nitrofurantoin-associated hepatotoxicity have been published since 1988,<sup>31-36</sup> and the clinical picture from these more recent cases was similar to that summarized by Stricker and others.<sup>12</sup>

The mechanism or mechanisms of pulmonary and hepatic toxicity remain unknown. In vitro and animal experiments have implicated a role for bioactivation and oxidative stress in both pulmonary toxicity<sup>37,38</sup> and hepatotoxicity,<sup>39,43</sup> although human studies are still lacking. Positive titres of antinuclear factor and anti-smooth muscle antibodies in cases of pulmonary toxicity<sup>44</sup> and hepatotoxicity<sup>12</sup> also suggest an immune-mediated reaction. Cases of rapid onset after drug rechallenge<sup>31,45</sup> and marked sensitization<sup>46</sup> support the immunological mechanism. From these observations, it might be hypothesized that there is more than one cause of nitrofurantoin-associated hepatotoxicity and that the immunologic injury could be the mechanism in some cases. Interestingly, signs and symptoms in cases of combined toxicity (Table 1 and the current case) corresponded to those described in cases of isolated lung or liver toxicity. This suggests that similar mechanisms are responsible for toxic effects in the individual organs, irrespective of the patient's presentation (i.e., singular organ toxicity or combined lung and liver toxicity). However, one can hypothesize that different mechanisms may be respon-

sible for pulmonary and hepatic toxicity, because a common mechanism would likely yield a much higher incidence of combined toxicity, which is not the case.

The patient described here resembled patients in previously published cases (summarized in Table 1) with respect to demographic characteristics (specifically age and sex) and onset of symptoms. The clinical symptoms and laboratory findings were also comparable, except for, in the current case, the lack of elevation of markers suggestive of an immunologic reaction (e.g., antinuclear factor and anti-smooth muscle antibodies). As discussed above, the mechanisms of concurrent lung and liver toxicity could be multifactorial, and there are certainly cases in the literature that also appeared to lack an immunological component (Table 1). Our comprehensive literature summary, in conjunction with the case reported here, suggests that a distinguishable pattern of toxicity is available to aid clinicians in recognizing or possibly preventing full-blown pulmonary and hepatic toxicity from nitrofurantoin. Conversely, a clear pattern of clinical resolution (e.g., rate of recovery or responsiveness to corticosteroids) is not discernible from the small number of cases available. However, in the majority of published cases, the patients appear to have recovered, with respect to hepatic and pulmonary function, after withdrawal of nitrofurantoin and provision of supportive treatment (Table 1). The case reported here certainly supports the "reversible toxicity hypothesis" with respect to the patient's lung disease and the successful and uneventful recovery after the liver transplant.

We recommend that clinicians use the findings in this case report and literature summary to identify patients at risk of nitrofurantoin-associated lung and liver toxicity. We also recommend that patients receiving long-term nitrofurantoin therapy who are in the demographic group identified here be considered at risk of toxicity and undergo monitoring of pulmonary and hepatic function.

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**Tony K L Kiang**, BSc(Pharm), PhD, ACPR, is a Clinical Pharmacist at Providence Health Care and a postdoctoral fellow (part-time) in the Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia.

**Jo-Ann Ford**, RN, MSc, is the Associate Director of the BC Hepatitis Program, Vancouver General Hospital, Vancouver, British Columbia.

**Eric M Yoshida**, MD, MHSc, FRCPC, FACP, FACG, is Professor of Medicine and Head of the Division of Gastroenterology, The University of British Columbia, Vancouver, British Columbia.

**Nilufar Partovi**, BSc(Pharm), PharmD, is Clinical Coordinator in the Pharmacy Department, Vancouver General Hospital, Vancouver, British Columbia.

**Address correspondence to:**

Dr Tony K L Kiang  
Department of Pharmacy  
St Paul's Hospital  
1081 Burrard Street  
Vancouver BC V6Z 1Y6

**e-mail:** [tkiang@gmail.com](mailto:tkiang@gmail.com)