CASE REPORT

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Nitrofurantoin-induced immune-mediated lung and liver disease

Bolest pluća i jetre indukovana nitrofurantoinom i imunološki posredovana

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Abstract

Introduction. Nitrofurantoin, a furan derivative, introduced in the fifties has widely been used as an effective agent for the treatment and prevention of urinary tract infections (UTI). Spectrum of adverse reactions to nitrofurantoin is wide, ranging from eosinophilic interstitial lung disease, acute hepatitis and granulomatous reaction, to the chronic active hepatitis, a very rare adverse effect, that can lead to cirrhosis and death. **Case report.** We presented a 55-year- old female patient with eosinophilic interstitial lung disease, severe chronic active hepatitis and several other immune- mediated multisystemic manifestations of prolonged exposure to nitrofurantoin because of the recurrent UTI caused by *Escherichia coli*. We estimated typical radiographic and laboratory disturbances, also restrictive ventilatory changes, severe reduction of carbon monoxide diffusion capacity and abnormal liver function tests. Lymphocytic-eosinophylic alveolitis was consistent with drug-induced reaction. Hepatitis was confirmed by liver biopsy. After withdrawal of nitrofurantoin and application of high dose of glicocorticosteroids, prompt clinical and laboratory recovery was achieved. **Conclusion.** Adverse drug reactions should be considered in patients with concomitant lung and liver disease. The mainstay of treatment is drug withdrawal and the use of immunosuppressive drugs in severe cases. Consideration should be given to monitor lung and liver function tests during long term nitrofurantoin therapy.

Key words:
nitrofurantoin; urinary tract infections; drug toxicity; immunologic factors; hepatitis; pneumonia.

Apstrakt

Uvod. Nitrofurantoin, derivat furana, ušao je u upotrebu pedesetih godina i široko je upotrebljavan kao efikasan agens za terapiju i prevenciju infekcija urinarnog trakta. Spektar neželjenih reakcija na nitrofurantoin je veliki, od eozinofilne intersticijske bolesti pluća, akutnog hepatitisa, granulomatoznih reakcija, do veoma retkih efekata u vidu hroničnog aktivnog hepatitisa koji može dovesti do ciroze jetre i smrti. **Prikaz bolesnika**. Predstavili smo bolesnicu, staru 55 godina, sa eozinofilnim intersticijskim oboljenjem pluća, teškim hroničnim aktivnim hepatitisom i drugim imunološki posredovanim multisistemskim manifestacijama nakon produžene ekspozicije nitrofurantoinu zbog rekurentnih infekcija urinarnog trakta uzrokovanih *Escherichia coli*. Nađeni su tipični radiografski i laboratorijski poremećaji, takođe restrikcijski poremećaj ventilacije, teško oštećenje difuzijskog kapaciteta za ugljen monoksid i poremećeni testovi funkcije jetre. Limfocitno- eozinofilni alveolitis bio je konzistentan sa neželjenom reakcijom na lek. Hepatitis je potvrđen biopsijom jetre. Nakon ukidanja nitrofurantoina primenjene su visoke doze glikokortikosteroida, što je dovelo do brzog kliničkog i laboratorijskog oporavka. **Zaključak.** Neželjene reakcije na lekove trebalo bi razmatrati kod bolesnika sa istovremenim oboljenjem pluća i jetre. Osnova lečenja je ukidanje leka koji je doveo do reakcije i davanje imunosupresivnih lekova u težim slučajevima. Može se preporučiti praćenje funkcije pluća i jetre tokom dugotrajne primene nitrofurantoina.

Ključne reči:
nitrofurani; urinarni trakt, infekcije; lekovi, toksičnost; imunski faktori; hepatitis; pneumonija.

Introduction

Nitrofurantoin, a furan derivative, was introduced in the fifties and has widely been used as an effective agent for the treatment and prevention of urinary tract infections (UTI). Nitrofurantoin-induced hepatic injury was first reported in 1961 [1]. Since then a spectrum of adverse reactions to nitrofurantoin has been reported, ranging from eosinophilic interstitial lung disease, acute hepatitis, granulomatous reaction, to the very rare adverse effect of chronic active hepatitis that can lead to cirrhosis or death [2]. Autoimmune liver disease is not uncommon cause of chronic

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hepatitis in women. Although autoimmune destruction usually occurs without an identifiable trigger, some drugs such as methyldopa, minocycline and nitrofurantoin are associated with autoimmune liver disease [3]. Today, nitrofurantoin is well recognized as a cause of adverse drug reactions. Although the combination of lung and liver toxicity is rare, concomitant pulmonary and liver disease can occur together and it may well be that these share a common autoimmune mechanism [4–8]. Eighty five percent of patients having nitrofurantoin-associated pulmonary reactions are women. This observation may be related to the fact that women are more susceptible to recurrent UTI [9, 10].

We presented a middle age female patient with eosinophilic interstitial lung disease, severe chronic active hepatitis and several other immune–mediated multisystemic manifestations after prolonged exposure to nitrofurantoin.

Case report

A 55-year-old female was admited to hospital because of breathless, nonproductive cough and fever during six weeks. Few months prior admission the patient began to suffer from general weakness, nausea, weight lost and polyarthralgia without morning rigidity. Her past medical history included mesangioproliferative glomerulonephritis (diagnosed in 1985 and treated with systemic glicocorticosteroids), hypothyreosis (because of that she used levotiroxin substitution). The patient had been treated with nitrofurantoin 100 mg twice daily for the last six months because of the recurrent UTI caused by *Escherichia coli*. There was no history of liver disease; she denied consumption of any other medications, alcohol or tobacco. Physical examination on admission revealed profound jaundice, obesity, dark colour of skin with excoriated papulomatous rash on the face and arms (Figure 1). Auscultation of the lungs revealed normal breath sound with diffuse, bilateral, fine end-inspiratory crackles. Initial laboratory tests revealed an erythrocyte sedimentation rate (ESR) of 24 mm/h (normal range 0–12 mm/h), elevated C-reactive protein – 9 mg/L (normal 0–4 mg/L), a normal blood count with eosinophilia (880/mL, normal 100–250/mL), deranged liver function with total serum bilirubin of 139 μmol/L (normal range 2–21 μmol/L) with a direct fraction of 37 μmol/L (normal range 0–5 μmol/L), aspartate aminotransferase (AST) – 466 IU/L (normal range 0–34 IU/L), alanine aminotransferase (ALT) – 430 IU/L (normal range 7–49 IU/L), lactate dehydrogenase (LDH) – 535 IU/L (normal range 200–378 IU/L), alkaline phosphatase–1,111 IU/L (normal range 7–290 IU/L), gama-glutamyl-transpeptidase 1,590 IU/L (normal range 0–38 IU/L), normal total protein – 69 g/L, low albumin – 29 g/L (normal range 32–48 g/L). Other biochemical parameters and coagulation screen were normal. Antinuclear antibodies (ANA) were positive (++++ speckled pattern of fluorescence), also anti-smooth muscle antibodies – ASMA (++). Antibodies for extractable nuclear antigens, anticardiolipin, anti-mitochondrial, anti-CCP (cyclic citrullinated peptide), anti-neutrophil cytoplasmic (against myeloperoxidase and proteinase 3) were normal. Relative values of subpopulations of T lymphocytes in peripheral blood (CD4+ and CD8+) were normal, with normal CD4+/CD8+ ratio, so values of natural killer cells (CD16+, CD56+) were mildly elevated. There was an accompanying hyper-gammaglobulinemia with elevated IgG – 22 g/L (normal range 7–16 g/L), IgA 4.41 g/L (normal range 0.7–4 g/L), IgE 902 IU/mL (normal range 0–100 IU/mL) and normal IgM level. Serological tests for intestinal parasites, hepatitis A, B, C, human immunodeficiency, Epstein Barr and cytomegaloviruses were negative. No eggs of parasites were found in feces. Chest radiography (X-Ray) showed bilateral ground-glass and micronodular opacities, predominantly in lower lung fields (Figure 2). Computed

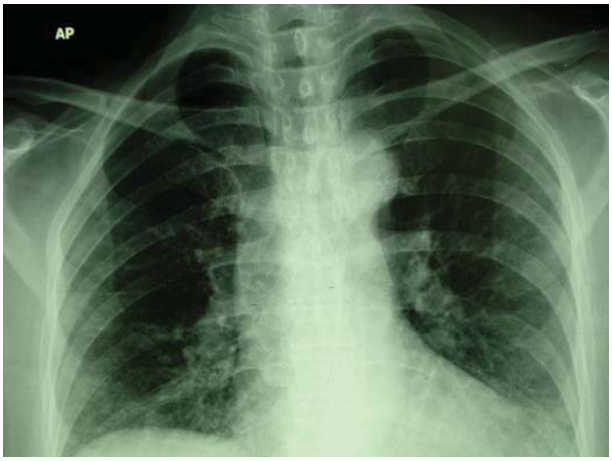
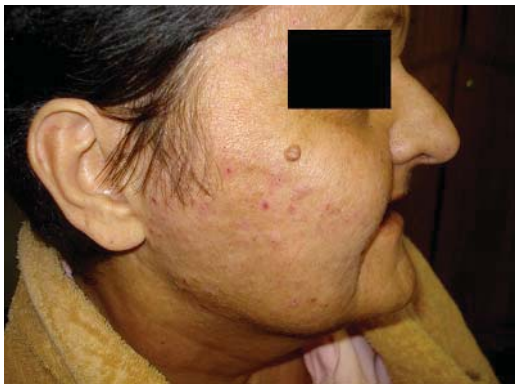
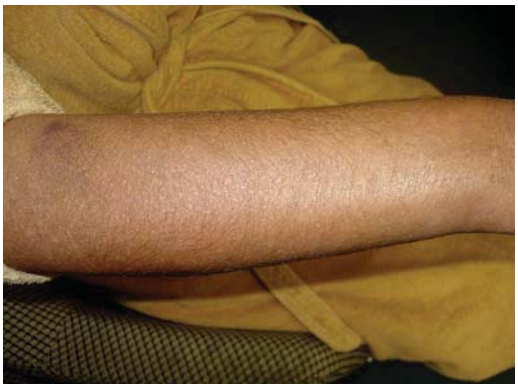


Fig. 2 – Chest radiography: ground glass and micronodular opacities, predominantly in lower lung fields



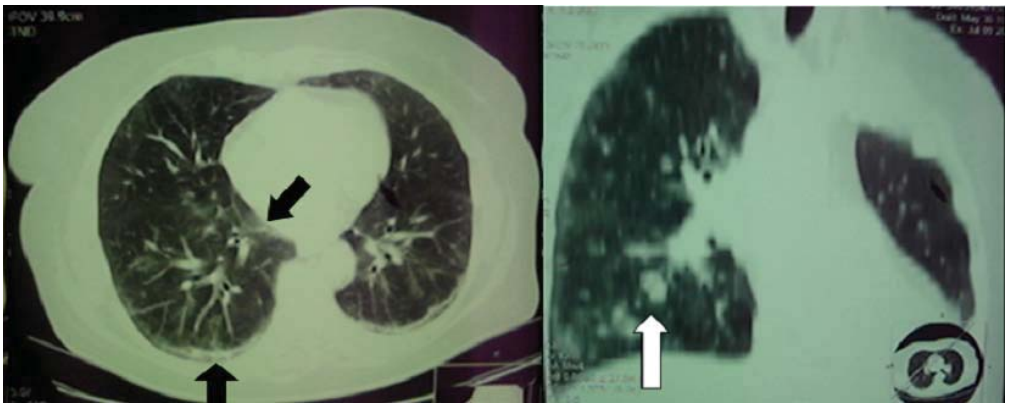
a



b

Fig. 1 – A female patient, 55-year-old, with lichen simplex chronicus on the face (a) and the arm (b)

tomography (CT) revealed ground-glass opacities and consolidations without significant fibrotic changes (Figures 3). Pulmonary function tests showed moderate restrictive ventilatory changes (forced vital capacity was 55% predicted) and severe reduction carbon monoxide diffusion capacity (DLCO 47%, DLCO/VA 49% predicted). The respiratory arterial blood gases analysis at rest revealed mild hypoxemia with pO2 8 KPa (9.6 KPa normal for her age), oxygen saturation at 90% and severe hypocapnia with pCO2 2.8 KPa (normal range 4.6–6 KPa). Echocardiography and electrocardiography were normal. Abdominal ultrasonography found mild enlargement of spleen and liver with hyperechogenic structure with no evidence of gallstones or biliary dilatation. Doppler ultrasound showed no evidence of portal or hepatic vein occlusion. Bronchoscopic findings were normal. Histological finding of transbronchial biopsy was nonspecific. Bronchoalveolare lavage (BAL) fluid analysis did not show bacterial, fungal agents or acid fast bacilli. BAL cytology cell profile showed macrophages 14%, lymphocytes 75% and eosinophils 11% with decreased CD4/CD8 ratio. A liver biopsy was performed showing severe chronic active hepatitis, which was considered to be consistent with a drug induced hepatitis (Figure 4). Apperance of eyes and mouth dryness Shirmer`s test was performed which showed reduced secretion of tears (3 mm/5 min). Dermatological examination established Lichen simplex chronicus (Figure 1). After withdrawal of nitrofurantoin, high dose of glicocorticosteroids was applied – metylprednisolon in daily dose of 80 mg (60 mg in the morning and 20 mg in the evening). The result was a prompt clinical and laboratory recovery (symptoms and signs wanished, normalisation of acute phase reactants, liver and lung function parameters). The patient was discharged two weeks later and swiched to oral prednisone with taper to maintenance dose of 10 mg daily. Control examinations after three, six and twelve months showed normal physical findings, laboratory tests, chest X-ray and CT (Figure 5), abdominal ultrasonography, spirometry and carbon monoxide diffusion capacity. Follow-up was recommended.



a b

Fig. 3 – Chest computerized tomography: a – ground-glass opacities (black arrows); b – consolidation (white arrow) without significant fibrotic changes

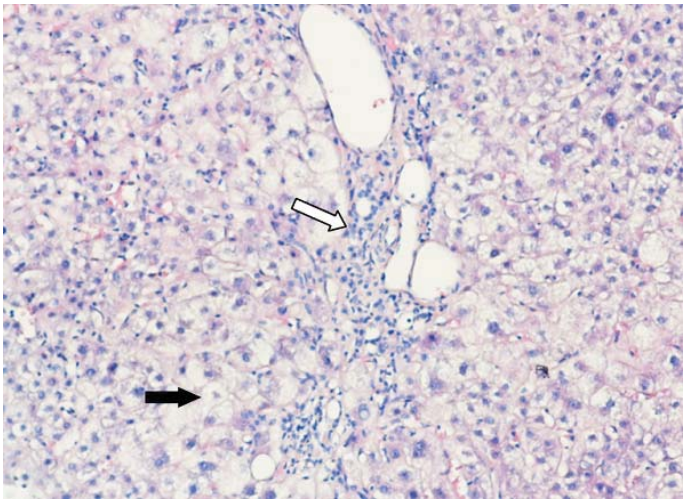
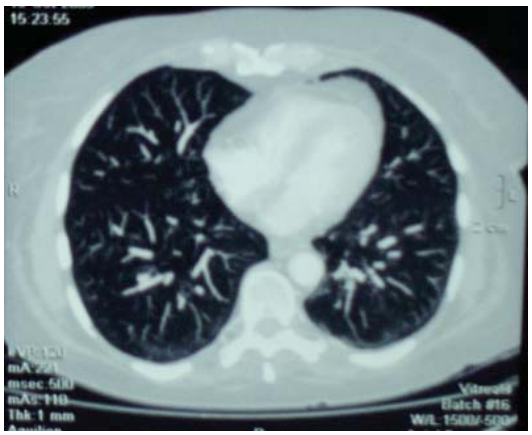


Fig. 4 – Histopathological finding of liver biopsy demonstrates chronic active hepatitis (H&E, 40×): a portal tract is expanded by a lymphoplasmacytic inflammatory infiltrate (white arrow). The interface between a portal tract and the parenchyma is disrupted by inflammation. The parenchymal sinusoids are suffused with lymphocytes and there is disruption of normal lobular hepatocyte architecture with ballooning of damaged hepatocytes (black arrow)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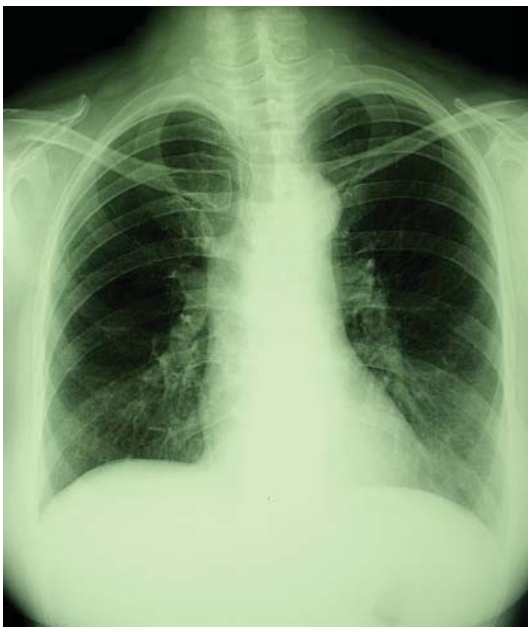
b)

Fig. 5 – Disappearance of pathological pulmonary changes six months after the treatment shown by multi-slice computerized tomography (a) and chest radiography (b)

Discussion

Nitrofurantoin is widely used for both acute and chronic management of UTI. It is cheap and effective, with a low incidence of resistance in common urinary pathogens; it is also safe in pregnancy [11]. Adverse drug reactions to nitrofurantoin include pulmonary reactions, hepatic toxicity, blood dyscrasias, peripheral neuropathy, etc [9]. Concomitant pulmonary and hepatic toxicity secondary to nitrofurantoin is rare with few reported cases [4–8]. The vast majority of pulmonary reactions to nitrofurantoin (90%) are acute and characterised by fever, cough, dyspnoea, and peripheral eosinophilia [9–10]. Nitrofurantoin also causes a range of subacute or chronic pulmonary disease, often presenting with insidious onset of increasing dyspnoea, dry cough and radiological evidence of fibrosis [10]. Because of that optimal duration of nitrofurantoin treatmen should not be over 14 days. Also, profilactic treatment of recurrent UTI should be discontinued, with switch by other effective antibacteriale medications. In patients who have some pulmonary, hepatic, alergic, neurologic disorder, anemia, diabetes or vitamin B deficiency special caution is necessery. Although severe adverse reactions caused by nitrofurantoin are rare, consideration should be given to monitoring lung and liver function tests during a long-term nitrofurantoin therapy. Pulmonary function tests (PFTs) may show a restrictive pattern with a reduced carbon monoxide diffusion capacity. Nitrofurantoin has been linked to autoimmune hepatitis, but in view of the rarity of the association, almost all reports of the association have been single case reports or small series [1–3]. Further information has been obtained from national adverse drug reaction monitoring agencies in the Netherlands [12] and Denmark [13] and it has been estimated that the incidence of nitrofurantoin-induced hepatic injury is low at about three cases in 1,000,000 [14].

The underlying mechanism behind nitrofurantoin toxicity remains uncertain; an immunological response is suggested by the presence of autoantibodies (ANA, ASMA). Direct cytotoxic mechanisms, for example by increased oxidative stress, have also been suggested [15]. Cytotoxic T-cells play a pivotal role in the pathogenesis of nitrofurantoin-induced liver injury. It has been hypothesized that a breakdown product of the drug or the drug itself, bound to an endogenous peptide, is presented by the class 1 HLA antigen on the hepatocyte cell membrane; this induces cytotoxic T-cell activation and subsequent hepatocyte death [16]. Ethnicity or genetic background may be a risk factor because of the variability in detoxification mechanisms (acetylator phenotype, human leukocyte antigen group) [17]. Our patient had a clear autoimmune disposition (mesangioproliferative glomerulonephritis and hypothireosis), and according to anamnestic, clinical, laboratory, imaging and other findings we estimated the existence of nitrofurantoin-induced, immune-mediated eosinophilic interstitial lung diseases, autoimmune hepatitis and several other multisystemic manifestations as lichen simplex chronicus and sicca syndrome, as well. There were no criterias for any diffuse connective tissue diseases, however it was possible that nitrofurantoin induced lupus-like syndrome associated with hepatitis [18]. Lung disease had subacute presentation with characteristic symptoms, clinical, X-ray, CT and PFTs findings. Lymphocytic-eosinophylic alveolitis was consistent with drug-induced reaction (DIR). Liver disease had chronic course. The positive ANA and ASMA results, hyper-gammaglobulinemia, histological features of liver biopsy and clinical response to immunosuppressive drugs were strongly suggestive of autoimmune hepatitis-type 1, triggered by nitrofurantoin. Definitive confirmation of DIR was positive rechallenge test according to WHO method [19]. Rechallenge, however, is not ethical due to severity of our patient`s clinical presentation. We applied the Naranjo algorithm for determination the likelihood of whether a DIR is actually due to the nitrofurantoin rather than the result of other factors and score was 6 – probable DIR. Initial treatment consists of drug withdrawal. In addition, we elected to use parenteral glucocorticosteroids because of the severe damage of lung and liver function. If glucocorticosteroid treatment fails, azathioprin may be introduced.

Conclusion

Adverse drug reactions should be considered in patients with concomitant lung and liver disease. The mainstay of treatment is drug withdrawal and the use of immunosuppressive drugs in severe cases. Consideration should be given to monitoring lung and liver function tests during a long term nitrofurantoin therapy.

REFERENCES

1. *Ernaelsteen D, Williams R.* Jaundice due to nitrofurantoin. Gastroenterology 1961; 41: 590−3.
2. *Stricker BH, Blok AP, Claas FH, Van Parys GE, Desmet VJ.* Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology 1988; 8(3): 599−606.
3. *Appleyard S, Saraswati R, Gorard DA.* Autoimmune hepatitis triggered by nitrofurantoin: a case series. J Med Case Reports 2010; 4: 311.
4. *Reinhart HH, Reinhart E, Korlipara P, Peleman R.* Combined nitrofurantoin toxicity to liver and lung. Gastroenterology 1992; 102(4 Pt 1): 1396−9.
5. *Koulaouzidis A, Bhat S, Moschos J, Tan C, De Ramon A.* Nitrofurantoin-induced lung- and hepatotoxicity. Ann Hepatol 2007; 6(2): 119−21.
6. *Peall AF, Hodges A.* Concomitant pulmonary and hepatic toxicity secondary to nitrofurantoin: a case report. J Med Case Reports 2007; 1: 59.
7. *Yalçin S, Sahin A, Yalçin B, Altinok G.* Nitrofurantoin toxicity to both liver and lungs. Liver 1997; 17(3): 166−7.
8. *Schattner A, Von der Walde J, Kozak N, Sokolovskaya N, Knobler H.* Nitrofurantoin-induced immune-mediated lung and liver disease. Am J Med Sci 1999; 317(5): 336−40.
9. *Holmberg L, Boman G, Böttiger LE, Eriksson B, Spross R, Wessling A.* Adverse reactions to nitrofurantoin. Analysis of 921 reports. Am J Med 1980; 69(5): 733−8.
10. *Holmberg L, Boman G.* Pulmonary reactions to nitrofurantoin. 447 cases reported to the Swedish Adverse Drug Reaction Committee 1966-1976. Eur J Respir Dis 1981; 62(3): 180−9.
11. *Brumfitt W, Hamilton-Miller JM.* Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. J Antimicrob Chemother 1998; 42(3): 363−71.
12. *Stricker BH, Blok AP, Claas FH, Van Parys GE, Desmet VJ.* Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology 1988; 8(3): 599−606.
13. *Dam-Larsen S, Kromann-Andersen H.* Hepatic toxicity of nitrofurantoin. Cases reported to the Center for Monitoring Adverse Drug Reactions 1968-1998. Ugeskr Laeger 1999; 161(48): 6650−2. (Danish)
14. *D'Arcy PF.* Nitrofurantoin. Drug Intell Clin Pharm 1985; 19(7−8): 540−7.
15. *Suntres ZE, Shek PN.* Nitrofurantoin-induced pulmonary toxicity. In vivo evidence for oxidative stress-mediated mechanisms. Biochem Pharmacol 1992; 43(5): 1127−35.
16. *Kelly BD, Heneghan MA, Bennani F, Connolly CE, O'Gorman TA.* Nitrofurantoin-induced hepatotoxicity mediated by CD8+ T cells. Am J Gastroenterol 1998; 93(5): 819−21.
17. *Wijnen PA, Drent M, Nelemans PJ, Kuijpers PM, Koek GH, Neef C,* et al. Role of cytochrome P450 polymorphisms in the development of pulmonary drug toxicity: a case-control study in the Netherlands. Drug Saf 2008; 31(12): 1125−34.
18. *Salle V, Lafon B, Smail A, Cévallos R, Chatelain D, Andréjak M*, et al. Nitrofurantoin-induced lupus-like syndrome associated with hepatitis. Rev Med Interne 2006; 27(4): 344−6. (French)
19. *World Health Organization.* Safety Monitoring of Medicinal Products. Guidelines for setting up and running a Pharmacovigilance Centre. Uppsala: WHO; 2000. (French)

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