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DRUG INDUCED LUNG DISEASE - AMIODARONE IN FOCUS

LEKOVIMA IZAZVANA PLUĆNA BOLEST SA POSEBNIM OSVRTOM NA AMIODARON

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Summary
More than 380 medications are known to cause pulmonary toxicity. Selected drugs that are important causes of pulmonary toxicity fall into the following classes: cytotoxic, cardiovascular, anti-inflammatory, antimicrobial, illicit drugs, miscellaneous. The adverse reactions can involve the pulmonary parenchyma, pleura, the airways, pulmonary vascular system, and mediastinum. Drug-induced lung diseases have no pathognomonic clinical, laboratory, physical, radiographic or histological findings. A drug-induced lung disease is usually considered a diagnosis of exclusion of other diseases. The diagnosis of drug-mediated pulmonary toxicity is usually made based on clinical findings. In general, laboratory analyses do not help in establishing the diagnosis. High-resolution computed tomography scanning is more sensitive than chest radiography for defining radiographic abnormalities. The treatment of drug-induced lung disease consists of immediate discontinuation of the offending drug and appropriate management of the pulmonary symptoms. Glucocorticoids have been associated with rapid improvement in gas exchange and reversal of radiographic abnormalities. Before starting any medication, patients should be educated about the potential adverse effects of the drug. Amiodarone is an antiarrhythmic agent used in the treatment of many types of tachyarrhythmia. Amiodarone-caused pulmonary toxicity is a well-known side effect (complication) of this medication. The incidence of amiodarone-induced lung disease is approximately 5–7%.
Key words: Lung Diseases + chemically induced; Amiodarone; Diagnosis; Drug-Related Side Effects and Adverse Reactions; Risk Factors; Tomography, X-Ray Computed

Sažetak
Poznato je da više od 380 lekova može da ispolji toksični efekat na pluća. Lekovi za koje je pokazano da su značajni u tom smislu svrstavaju se u sledeće kategorije: citotoksični, kardiovaskularni, antiinflamatorni, antibiotici, nedozvoljeni lekovi i ostali. Neželjena dejstva mogu da se ispolje na plućnom parenhimu, pleuri, disajnim putevima, plućnom vaskularnom sistemu i medijastinumu. Lekovima izazvane plućne bolesti nemaju patognomonični klinički, laboratorijski, fizički, radiografski ni histološki nalaz. Njihova dijagnoza se obično postavlja metodom eliminacije drugih bolesti i često je zasnovana na kliničkom nalazu. Laboratorijske analize ne pomažu u postavljanju dijagnoze. U dijagnostičkom smislu, kompjuterizovana tomografija visoke rezolucije je mnogo senzitivnija od standardnog radiograma. Lečenje zahteva isključivanje leka čiji toksični efekat je doveo do plućnog oboljenja i primenu simptomatske terapije. Primena glikokortikoida dovodi do brzog poboljšanja gasne razmene i povlačenja radiografskih promena. Pre početka terapije svakim lekom sa potencijalnim toksičnim efektom na pluća, bolesniku treba da se predoče mogući neželjeni efekti leka. Amiodaron je antiaritmik koji se koristi u lečenju mnogih oblika tahiaritmije. Njime izazvana plućna toksičnost je dobro poznata komplikacija koju daje ovaj lek sa učestalošću 5–7%.
Ključne reči: Bolest pluća + hemijski indukovana; Amiodaron; Dijagnoza; Nuspojave i neželjene reakcije izazvane lekovima; Faktori rizika; CT

Introduction

More than 380 medications are known to cause pulmonary toxicity. Selected drugs that are important causes of pulmonary toxicity fall into the following classes: cytotoxic, cardiovascular, anti-inflammatory, antimicrobial, illicit drugs, miscellaneous. The adverse reactions can involve the pulmonary parenchyma, pleura, airways, pulmonary vascular system, and the mediastinum. Drug-induced lung diseases (DILD) have no pathognomonic clinical, laboratory, physical, radiographic or histological findings. DILD is usually considered a diagnosis of exclusion of other diseases. Pulmonary physicians are well aware of drug-induced acute and chronic pulmonary toxicities; inhaled or systemically administered drugs can affect airway tone and cause cough, dyspnoea due to airspace disease, diffuse alveolar damage, pulmonary capillaritis or interstitial lung fibrosis, to name a few presentations and tissue manifestations. Well-studied drugs that cause pulmonary toxicity include methotrexate, bleomycin and amiodarone, all of which can cause interstitial lung disease [1].

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Abbreviations

DILD – drug-induced lung diseases
APT – amiodarone pulmonary toxicity
BOOP – bronchiolitis obliterans organizing pneumonia
ARDS – acute respiratory distress syndrome
BAL – bronchoalveolar lavage
BPT – bleomycin pulmonary toxicity
NILT – nitrofurantoin-induced lung toxicity
CT – computed tomography

Amiodarone Pulmonary Toxicity

Amiodarone is the antiarrhythmic drug that is commonly used for the treatment of lifethreatening ventricular, ventricular premature beats and some other supraventricular arrhythmia. It contains a compound of iodine, which has a tendency to accumulate in certain organs, including the lungs [2]. Acute and chronic interstitial lung diseases are the most common manifestations of amiodarone pulmonary toxicity (APT). Patients receiving amiodarone often have associated cardiopulmonary disease as well, which may mask the toxic effect of drugs and the diagnosis is made too late, when the disease has already developed. Acute respiratory distress syndrome (ARDS) can rarely develop, especially in the perioperative period, in the patients on amiodarone therapy [3]. APT is the most common form of pulmonary toxicity with prevalence of 0.1-0.5% in patients taking amiodarone 200 mg/day, 5-15% of patients taking 500 mg/day or more, up to 50% of patients taking 1,200 mg/day or more. Risk factors for the development of APT are: daily doses greater than 400 mg (toxic drug reactions are more common in patients with amiodarone serum concentration higher than 2.5 mg/L), disrupted existing pulmonary disease (chronic obstructive pulmonary disease), previous lung surgery, treatment longer than 2 months, age, ethnic (racial) differences. (DILD is more common in Japanese population), exposure to high concentrations of oxygen, with or without mechanical ventilation. The two most important risk factors for the APT are age and duration of therapy. There is no safe dose. Most cases develop changes in the lungs 12 to 18 months from the start of taking the medication [3].

Amiodarone pulmonary toxicity should be taken into consideration, especially in elderly patients with pulmonary symptoms and changes even if low dose of the drug is administred for years [4]. There are two main hypotheses of the pathogenesis of APT: direct cytotoxicity and indirect immunological drug, hypersensitivity reactions. Direct cytotoxicity is associated with long elimination half-life and high affinity of amiodarone. The lung tissue hypersensitivity reactions are presented in some patients with lymphocytic infiltration of CD8 T-lymphocytosis and positive IgG immunofluorescence in the lung. In addition, the development of toxicity may be associated with the existing lung disease. The connection between the existing lung disease and APT may be masked because of the earlier limited pulmonary reserve [5]. Four forms of pulmonary toxicity caused by amiodarone are described: 1. Chronic interstitial pneumonitis is the most common presentation. Subacute attacks begin with nonproductive cough, dyspnea and weight loss, after two or more months of therapy. There are focal or diffuse interstitial fogginess on chest x-ray with foamy macrophages in the alveolar spaces. 2. Organizing pneumonia with or without bronchiolitis obliterans (Bronchiolitis obliterans organizing pneumonia – BOOP) accounts for about 25% of cases. It presents as a more acute condition with non-productive cough at the beginning, often with symptoms of pleurisy. Auscultation reveals crackles, and standard chest x-ray shows speckled shadows. Sometimes the signs of pleural affection appear and the condition can mimic infectious pneumonitis. 3. Acute respiratory distress syndrome occurs rarely, and it is of particular interest to anesthesiologists because it is characterized by fulminant flow especially in patients after surgery or pulmonary angiography. The incidence of ARDS after lung surgery is 11% in patients treated with amiodarone as compared with the 1.8% of those not treated in that way. Acute lung injury in surgical patients also develops one to four days after extubation. It is characterized by diffuse alveolar damage, with acute interstitial pneumonitis with hyaline membranes. It is assumed that amiodarone sensitizes patients who are at high oxygen (O_2) concentrations and high inspired oxygen (FiO_2), or increased sensitivity to iodinated contrast materials. Due to possible development of ARDS after surgery in patients receiving amiodarone, thoracoscopy, open lung biopsy is performed only after all other diagnostic modalities have been exhausted. 4. Solitary pulmonary mass is also shown as a complication of amiodarone therapy [6]. Radiology plays a central role in the diagnosis of APT. On chest radiographies, it appears as localized or diffuse speckled shadows, usually bilateral (**Figure 1**). Some infiltrates look like "ground glass". It was found that the right lung, especially in the right upper lobe, is more often affected than the left lung (**Figure 2**). Computed tomography (CT) more frequently reveals the disease compared to standard chest x-ray: bilateral interstitial, alveolar, or mixed interstitial and alveolar infiltrates could be seen (**Figure 3**). Initial radiographic APT findings follow ground glass pattern. It is crucially important to recognize it at the initial stage since the changes are potentially reversible [7]. Pleural thickening is commonly seen in the densest areas of infiltration. Pleural effusions have been described, but are less common. The appearance of one or more pulmonary nodules or tumor-like shadows is an unusual APT finding. If present, they are most commonly seen in the peripheral parts of upper lobes, attached to pleura. It is assumed that these nodes are the consequence of localized drug accumulation in areas of previous inflammation. Findings on chest radiograph can take up to 18 months to complete

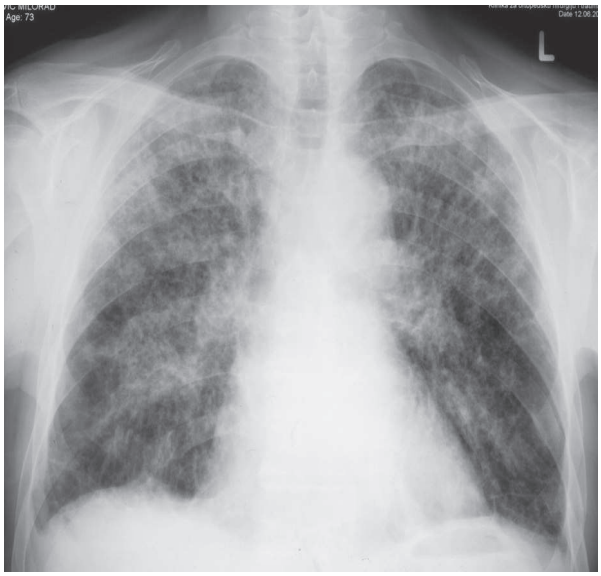

Figure 1. Chest x-ray shows thickened interstitium in both lungs
Slika 1. *Rendgentski snimak pluća pokazuje zadebljali intersticijum u oba plućna krila*

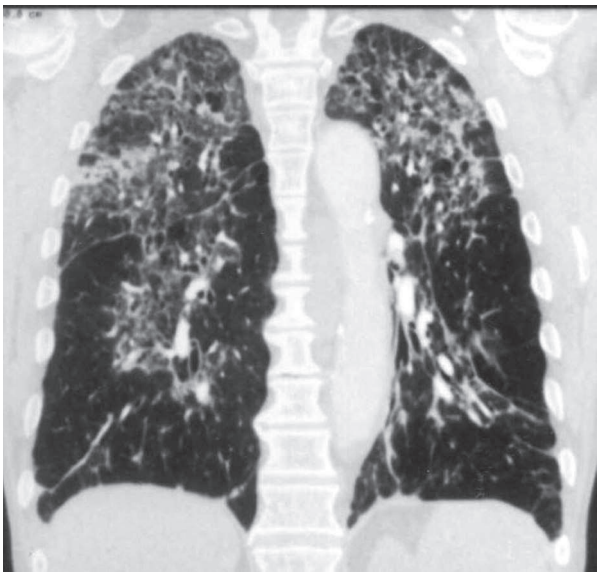

Figure 3. Chest CT in coronal view shows thickened intestitium more prominent in upper lobes
Slika 3. *CT snimak pluća, koronalni presek, pokazuje da je zadebljali intersticijum izraženiji u gornjim režnjevima*

withdrawal [2, 5]. Pulmonary function tests usually reveal a restrictive or mixed obstructive/restrictive model. Diffusing capacity of the lung for carbon monoxide (DLCO) is usually reduced. 20% decline in DLCO of the predicted value, or the value lower than 80% of the predicted one and reduces the total lung capacity (TLC) for more than 15% are the diagnostic criteria of APT. However, an isolated decrease in DLCO in the absence of clinical evidence of the disease is nonspecific and not diagnosed APT [8]. Fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) are useful in excluding other interstitial lung problems. Polymorphonuclear leukocytosis and CD8 + T suppressor cells are predominant in BAL. The presence of "foamy" macrophages is consistent with the diagnosis, but these cells can be seen in up to one-half of patients receiving amiodarone and without signs of APT. However, in the absence of foam cells, the diagnosis of APT is unlikely [6]. Amiodarone discontinuation is the primary step in APT treatment approach. Due to accumulation in fatty tissues and the drug long half-life, pulmonary toxicity may initially progress despite drug intake discontinuation, and can even be repeated after withdrawal of steroids. Okayasi, et al. [9] found that obese patients with a higher body mass index (BMI) have more frequent relapses due to intensive accumulation of lipophilic amiodarone in the fat tissue. Discontinuation of amiodarone intake as the only form of therapy may be sufficient in the early and limited course of the disease. Corticosteroids should be used in patients who demonstrate a significant affection of the pulmonary parenchyma registered by various imaging methods with or without concurrent hypoxemia. Systemic corticosteroids are recommended (prednisolone 40 to 60 mg/daily) with gradually decreased dose for at least 4-12 months to avoid disease relapse. The benefits of this treatment strategy are earlier recovery and less parenchymal fibrosis. Irreversible pulmonary fibrosis develops in about 30% of patients. When treatment is started early, most cases of this disease are reversible and have a good prognosis. Later discovered, advanced disease can lead to poorer outcome, including pulmonary fibrosis and/or death, especially in cases where the ARDS develops [10].

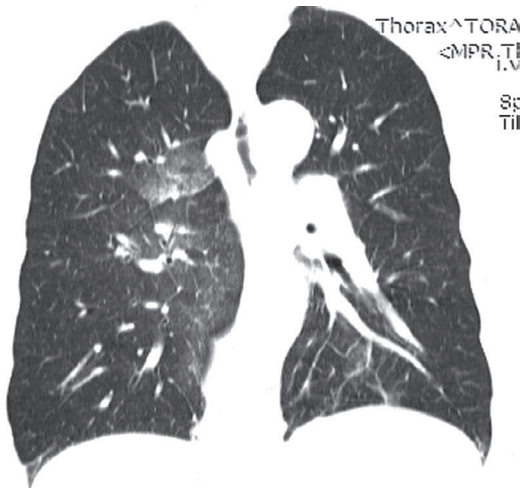

Figure 2. Chest CT in coronal view. Irregular ground glass opacities are present in posterior parts of the right lung
Slika 2. *CT snimak pluća – koronalni presek. Nepravilna zamućenja mlečnog stakla – prisutna su u zadnjim delovima desnog pluća*

Other Drug-Induced Lung Diseases-Cause Drugs

Methotrexate is a commonly prescribed antineoplastic and immune modulating compound that has gained wide acceptance in the management of rheumatoid arthritis, psoriasis, sarcoidosis and a number of neoplastic disorders. Although generally considered safe and easy to use, methotrexate has been associated with a number of adverse reactions. Pulmonary toxicity has been well-described and may take a variety of forms. Pulmonary infiltrates are the most commonly encountered form of methotrexate pulmonary toxicity and these infiltrates resemble hypersensitivity lung disease [11].

Bleomycin is a cytotoxic drug used in treatment of Germ Cell Tumours and is associated with pulmonary toxicity. Bleomycin pulmonary toxicity (BPT) manifests predominantly as pulmonary fibrosis, organizing pneumonia or nonspecific interstitial pneumonitis. The prevalence of BPT ranges from 0% to 46%, with mortality as high as 27%. Risk factors for the development of BPT include age, bleomycin regimen, bleomycin dose, renal insufficiency, radiation, underlying lung disease, smoking history, and granulocyte colony-stimulating factor (G-CSF) support [12].

Nitrofurantoin-induced lung toxicity (NILT) is relatively common. Patients usually use nitrofurantoin for urinary tract infections. Sometimes, histological patterns of lung damage are rare and may make the diagnosis difficult. The symptoms of NILT improve with cessation of nitrofurantoin, with steroids or without other therapy [13].

Leflunomide-induced pneumonitis (LEIP) usually occurs within the first 20 weeks of initiation of leflunomide, usually in patients with history of rheumatoid arthritis and either exposure to methotrexate or interstitial lung disease or both. Case mortality is about 20%. Poor prognostic indicators are diffuse alveolar damage on histological examination, pre-existing interstitial lung disease and ground glass shadowing on high resolution computerized tomography [14].

Conclusion

The drug-induced lung disease is an important and commonly neglected differential diagnosis in clinical practice. It may mimic a variety of pulmonary diseases. Amiodaron pulmonary toxity is found most frequently in pulmonology due to comorbidity treatment in these patients. The treatment of drug-induced lung disease consists of immediate discontinuation of the offending drug, and appropriate management of pulmonary symptoms. Drug-induced lung disease acute episodes usually disappear within 24-48 hours after the drug exclusion, but chronic syndromes may take longer to resolve. Complications, such as respiratory insufficiency, pulmonary thromboembolic disease, and pneumothorax, usually require hospital admission. Amiodaron pulmonary toxity should be taken into consideration in patients under long-term amiodarone use, especially in elderly patients with pulmonary symptoms, functional and radiographic changes even if low dose of the drug is administered for years.

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