

An Underestimated Cause of Dyspnea in an Emergency Setting: “Amiodarone Lung”. A Case Report and Review of the Literature

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Abstract: We are describing a case of acute onset of amiodarone-related pulmonary toxicity (amiodarone lung) presented with clinical findings of acute intractable dyspnea, and reversed after prompt drug discontinuation. A concise review of the characteristics of pulmonary toxicity is also provided. Lung adverse effects may occur approximately in 5-17% of treated patients, and are usually associated with older age, duration of the treatment, cumulative dosage, and probably previous co-existing lung disease may play a role. Such adverse pulmonary effects may occur either early (few days after starting treatment) or after several years, and onset of symptoms may be slowly insidious or acute, and dramatically progressive. Thus, a high level of alertness is necessary in comorbid and elderly patients receiving amiodarone, even in an emergency setting, to consider this kind of adverse reaction among all possible differential diagnoses.

Keywords: Amiodarone, Pulmonary toxicity, Dyspnea, Emergency Department.

INTRODUCTION

Amiodarone is a drug of choice for the management of atrial fibrillation in patients with impairment of ventricular function, and it is also indicated for treatment of life-threatening recurrent ventricular arrhythmias not responders to other antiarrhythmics [1]. Amiodarone is a lipophilic drug, characterized by large volume of distribution, long elimination time, predominant liver excretion, delayed onset of action, and long half-life (up to 142 days) [2]. Due to its high effectiveness, amiodarone is one of the most prescribed antiarrhythmic drugs in North America [2], despite the existence of several amiodarone-related adverse effects, i.e., thyroid, ophthalmic, hepatic, and pulmonary [3, 4].

As for the latter adverse effect, amiodarone assumption can be associated with a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, and pathological data consistent with pulmonary toxicity (amiodarone lung), also depending on the degree of exposure to the drug (dose and duration) [5]. The pulmonary toxicity ranges, in different reports, from 7% to 10-17% [1], and is the result from either indirect or direct toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively). The signs and symptoms are non-specific, and generally include dyspnea, cough, and fatigue, and occasional triggers may include heart surgery, oxygen therapy, or trivial lower respiratory tract infections [6]. We report here a case of acute onset of amiodarone-related pulmonary toxicity presented with clinical findings of acute intractable dysp-

nea, but reversed after prompt drug discontinuation. A brief review of the characteristics of pulmonary toxicity, i.e., incidence, pathology, clinical findings and therapy, is also provided.

CASE

A 68-year old patient was admitted to the Emergency Department (ED) of our hospital complaining of intractable dyspnea on exertion. Past medical history included chronic obstructive pulmonary disease (COPD), acute myocardial infarction (year 1987) with two relapses (after four months and six years, respectively) both rescued by percutaneous transluminal coronary angioplasty, paroxysmal atrial fibrillation, pulmonary thromboembolism. Medical therapy included warfarin, amiodarone, ACE-inhibitors, statins, nitrates, and bronchodilators.

CLINICAL FINDINGS

On admission in ED, her vitals were as follows: arterial blood pressure 110/60 mmHg, axillary temperature 36.7° Celsius, regular heart beat 65/min, right bundle branch block, no heart murmurs. Breath sounds were diminished in intensity; examination of abdomen was unremarkable. Laboratory data showed: white blood count 10,800/mm³ (67% neutrophils); hemoglobin 13.8 g/dL; platelets 331,000/mm³; creatinine 1.4 mg/dL; glucose 101 mg/dL; sodium 138 mEq/L, potassium 3.5 mEq/L; coagulation time (Index Normalized Ratio, I.N.R.) 2.30; erythrocyte sedimentation rate 55 mm; C-reactive protein 8.98 mg/dL; troponin 0.00 ng/mL; mioglobin 121 ng/mL. Pulse oxymetry: O₂ saturation 93% with O₂ therapy 2.5 lt/min. Arterial blood gas analysis showed pO₂ 69, pCO₂ 34, pH 7.40. Urinalysis was normal. Chest radiography showed bilateral alveolar opacities. The patient was hospitalized, and sent to our Department.

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INVESTIGATION AND RESULTS

The panel of clinical, and first-line laboratoristic (including D-dimer), and instrumental (including echocardiography) data excluded from differential diagnosis other diseases, ie, congestive heart failure and acute pulmonary cardiogenic edema, pulmonary thromboembolism, and acute exacerbation of COPD. In particular, acute COPD exacerbation was excluded since pulmonary function tests on spirometry resulted to be improved (although slightly) in comparison with those obtained in occasion of the last ambulatory visit some months before. In details: the volume of gas exhaled during the first second of expiration [forced expiratory volume (FEV) in 1 sec. or FEV₁]: 72.8 vs 58.2; the total volume exhaled [forced vital capacity or FVC]: 80.0 vs 75.2; the average expiratory flow rate during the middle 50% of the VC [forced expiratory flow or FEF]; 70.4 vs 53.2; FEV₁/FVC%: 94 vs 80.2.

Moreover, the thoracic high-resolution computed tomography (HRCT) showed focal patchy centriacinous emphysema areas mixed with aspects of panlobular pattern, and destruction of interlobular septi mainly at the upper lobes; diffuse bilateral micronodular opacities with focal area of consolidation at the right lung (Fig. 1A), scattered reticular densities and interstitium alterations, mainly localized to the lower lung zones (Fig. 1B). These findings were suggestive for amiodarone-associated pulmonary toxicity.

MANAGEMENT

Amiodarone (home daily maintenance dosage, 200 mg) was promptly discontinued, and steroid therapy (prednisone 0.5 mg/Kg in a once-daily morning oral dose) was started. The patient progressively improved, with complete resolution of cough within thirty days from admission. Four months after discharge, a second HRCT was performed: the focal apico-posterior opacification disappeared (Fig. 2A), and there was an evident clearing of the pulmonary interstitium reticular aspects (Fig. 2B).

The Naranjo adverse drug reaction probability classification [7] (although not appropriately validated for pulmonary toxicity), gave a final score of +4 = possible (Table 1).

DISCUSSION

Interstitial lung diseases (ILD) represent a large number of conditions involving the parenchyma of the lung, the alveolar epithelium, the capillary endothelium, and the spaces between these structures [8]. An increasing number of drugs can reproduce different patterns of ILD, including most forms of interstitial pneumonias and alveolar involvement. The diagnosis of drug-induced ILD essentially rests on the temporal association between exposure to the drug and the development of pulmonary infiltrates [9]. Amiodarone is a drug responsible of a peculiar type of lung disease: amiodarone-induced pulmonary toxicity.

Incidence

Although amiodarone toxicity increase with plasma concentrations, the total cumulative dose is more important than the amiodarone daily dose or plasma concentration [10]. Age is one of the most important risk factors for amiodarone-induced pulmonary side effects, that increases 3-fold every 10 years of age in patients aged >60 years compared with those aged <60 years [11]. Through its lipophilic distribution, amiodarone concentrates in organs with high lipid content such as adipose tissue, thyroid, liver and lung [12]. The extensive tissue binding of amiodarone results in pharmacologic profile with a high volume of drug distribution and an extremely long elimination half-life, so that both the therapeutic and toxic effects do not remit immediately after drug discontinuation and may occur day or months after initiation of treatment or at any time during treatment [4].

Pathology

Amiodarone pulmonary toxicity is primarily an interstitial pneumonia, sometimes characterized by prominent intra-alveolar macrophage accumulation partially resembling

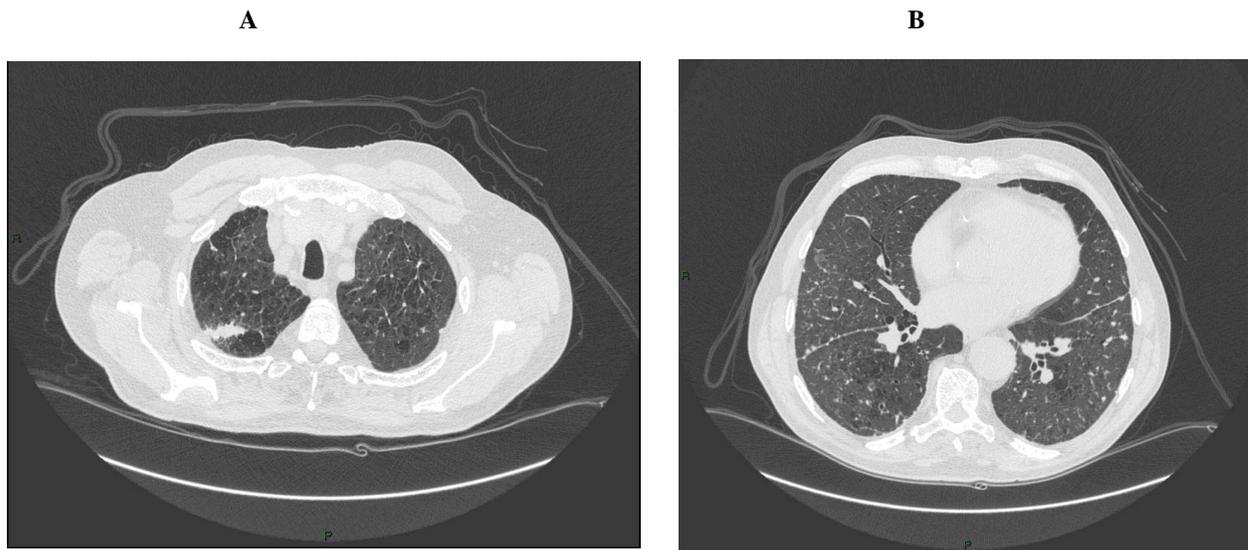


Fig. (1). Thoracic high-resolution computed tomography (HRCT) on admission.

Diffuse bilateral micronodular opacities with focal (apico-posterior) area of consolidation at the right lung (1A), scattered reticular densities and interstitium alterations at the lower lung zones (1B).

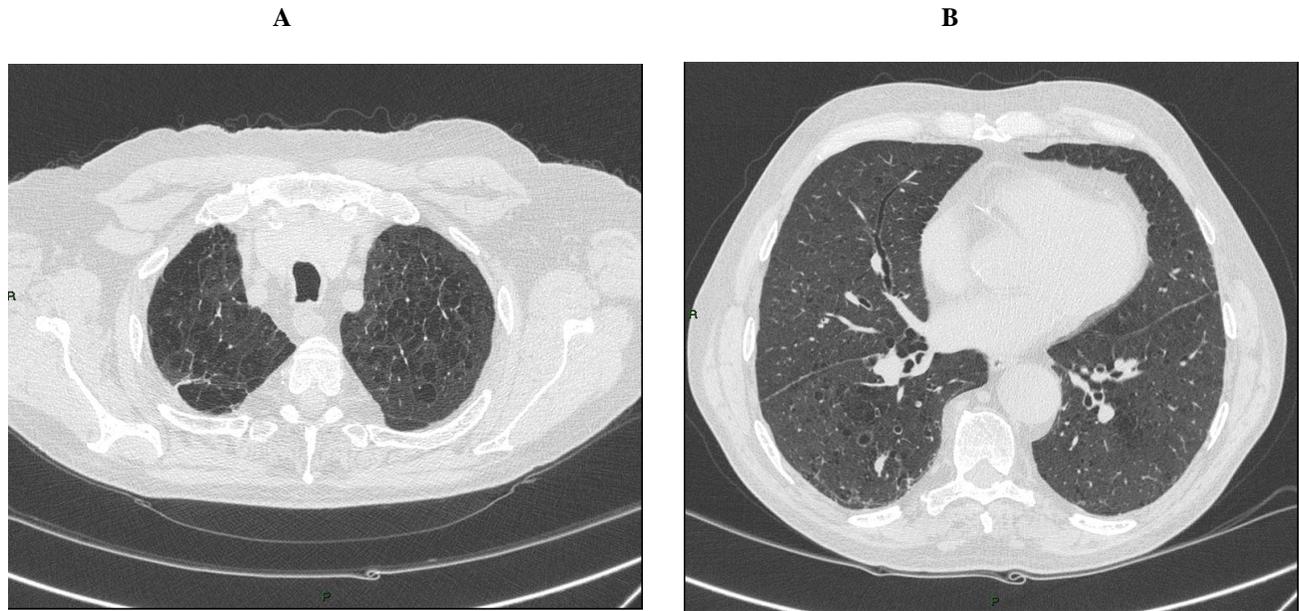


Fig. (2). Thoracic high-resolution computed tomography (HRCT) four months after discharge. Clearing of either the focal apico-posterior opacification (2A), and the pulmonary interstitium reticular aspects (2B).

Table 1. Evaluation of Possible Adverse Drug Reaction (ADR): the Naranjo ADR Probability Score⁴

	Yes	No	Do not know	Score
Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	+1
Did the adverse reactions appear when the drug was readministered?	+1	-2	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				+4

Total Score ADR Probability Classification
 9 Highly probable
 5-8 Probable
 1-4 Possible
 0 Doubtful

desquamative pneumonia pattern [13]. However, foamy alveolar macrophages and cytoplasmic lamellar inclusions are characteristic, but not specific [14], and their presence alone does not distinguish toxic from non-toxic patients. Mechanisms of amiodarone toxicity are probably related to a combination of mechanisms: (a) a cytotoxic effect to type II pneumocytes, inflammatory cells, endothelial cells and fibroblasts; (b) an immune-mediated mechanism in geneti-

cally-predisposed patients; and (c) the activation of the angiotensin enzyme system [4]. Observed anomalies include increase in phospholipids in macrophages, lymphocytes, and other cells types because of the inhibition of the lysosomal phospholipases A1, A2, and C with consequent decrease of phagocytic response and development of cell-mediated immunity [15]. In experimental animals, the differences in susceptibility to amiodarone-induced pulmonary toxicity might

be secondary to genetic differences in lung drug sequestration [16].

Clinical Findings

Several clinical presentation have been described. The most common presentation is an alveolar/interstitial pneumonitis with subacute onset, non-productive cough, progressive dyspnea on exertion, occasionally low-grade fever, malaise and weight loss in a patient with underlying cardiac morbidity and receiving amiodarone [4].

Pulmonary function testing usually shows low lung volumes and a restrictive pattern, with reduced CO transfer and hypoxemia, often severe and disproportionate with the extent of pulmonary opacities [17]. Chest X-rays may reveal patchy or diffuse infiltrates, which are commonly bilateral. However, HRCT is the gold standard radiological examination, and the main findings include: (a) ground-glass opacities, sometimes associated with consolidations, and (b) thin intralobular reticulations, or (c) both, with a subpleural or central location. High density areas, pleural thickening, and bronchial abnormalities, i.e., dilation or wall thickening, are also observed [18]. Amiodarone pneumonitis resolution is slow, owing to the prolonged retention of the drug in lung, and this explains why the disease can develop also after weeks or months after drug cessation. Moreover, an irreversible fibrosis is relatively common, developing in 5% to 7% of patients following typical amiodarone pneumonitis [19].

Otherwise, an acute pulmonary toxicity may occur as early as the second day of treatment, especially after intravenous cumulative doses of 1000-1500 mg. Risk factors associated with this acute clinical form may include pulmonary angiography, cardiothoracic surgery, or sudden corticosteroid withdrawal. Symptoms include fever, cough, dyspnea, pleuritic chest pain, and respiratory failure [4].

As for an emergency setting, an unfrequent presentation with bronchospasm, asthma exacerbation and angioedema has also been reported in a patient with history of previous reaction to an iodinated radiocontrast agent [20]. The mechanism is an anaphylactic-type reaction, and the clinical picture is fully reversible after appropriate treatment [20].

Therapy

When an amiodarone pulmonary toxicity is suspected, the drug should be immediately stopped. In the case of limited disease, most patients may show gradual improvement. In more advanced cases, systemic corticosteroid treatment is recommended, even in the lack of confirmatory controlled trials [4]. Empiric regimens of 0.5-1 mg/kg of prednisone daily are used, with gradual tapering for one year, since amiodarone may remain in lung tissue even one year after discontinuation [21]. Reduction of corticosteroids should be made with graduality and caution, since cases of aggressive diseases relapses have been reported [22].

CONCLUSIONS AND LESSON

It is generally believed that low-dose therapy is safe, but amiodarone-induced pulmonary toxicity has also been observed on 200 mg/die for 2 years, mainly in men [23], and a fatal downhill rapid course case within a few days had been recently reported in a 72-years man exposed to 200 mg/day

[24]. The symptoms are not specific, and diagnosis is mainly made by exclusion, based on a combination of clinical and radiographic data, keeping into the mind the need for detailed investigation of patient's medication history.

In the clinical case reported here, although the pulmonary and cardiac comorbidities played a confounding effect, the combination of contradictory respiratory tests and history of amiodarone assumption allowed the diagnostic suspect and suggested drug withdrawal, with complete resolution. The side effects of amiodarone has obtained large attention, but this kind of toxicity is often underestimated, especially, in comorbid elderly patients. Moreover, emergency doctors are usually more alert to acute and sometimes lethal effects of intravenous amiodarone, such as acute hepatitis [25], whereas amiodarone use is unpredictably linked to pulmonary toxicity. Because presentation and dose-related toxicity vary widely, cardiologists, emergency doctors and internists must be aware of amiodarone-induced pulmonary toxicity as well, and the first line therapy should include a prudent immediate discontinuation of amiodarone treatment at earliest suspicion.

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