



Two sides of the coin: Amiodarone-induced lung toxicity – Case Report

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Abstract

Introduction. Amiodarone is often used in the treatment of arrhythmias. Despite its undoubtedly excellent antiarrhythmic effect, its use can also cause serious adverse effects. This case report presents a patient who, after several months of treatment with amiodarone, developed severe pulmonary complications and transient liver injury. Despite discontinuation of the drug and implementation of optimal treatment aimed at harm reduction, a full resolution of the pulmonary lesions was not achieved.

Objective. The aim of the report is to draw attention to the risks to the respiratory system associated with the use of amiodarone. It is worth noting that some symptoms of post-amiodarone lung damage may resemble the exacerbation of heart failure, which contributes to the delay of a correct diagnosis and prolongs the time to the start treatment.

Key words

pneumonia, amiodarone, lung toxicity

INTRODUCTION

Amiodarone is one of the most commonly used drugs in the treatment of arrhythmias. It is an ionized derivative of benzofuran, with a structure similar to thyroid hormones. The biological activity of amiodarone is determined by the content of kelin (C₁₄H₁₂O₅), obtained from khella (Ammi visnaga), a herbaceous plant belonging to the celery family, found in natural conditions in western Asia (e.g. Cyprus, Iran, Iraq, Israel, Lebanon, Syria, Turkey), northern Africa (e.g. Algeria, Libya, Morocco, Tunisia), Canary Islands and southern Europe (e.g. Albania, Greece, Italy) [1]. In its composition, it contains about 37% organic iodine, and a daily dose between 100 – 600 mg provides from 3.5 – 21 mg of iodine, which is up to 100 times the daily dose of this element [2]. For this reason, there is a possibility of endocrine complications, but the most important is the possibility of harmful effects of amiodarone on the lungs.

OBJECTIVE

The aim of the study is to present the case of the patient with post-amiodarone pulmonary injury in which, despite the discontinuation of amiodarone exposure, after about 2 years of observation, clinical and radiological symptoms of interstitial lung disease and respiratory failure were still observed.

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MATERIALS AND METHOD

The material for this case report was collected from the real-life clinical process and medical records of the Chair and Department of Pneumology, Oncology and Allergology at the Medical University in Lublin, Poland. The patients' personal data was anonymized, therefore according to local law, the report did not require the consent of the Bioethics Committee.

CASE STUDY

A 68-year-old patient, an ex-smoker with dilated cardiomyopathy diagnosed in 2017, with an implanted resynchronizing stimulator, was referred to the Department of Pneumology, Oncology and Allergology in Lublin due to respiratory failure in the course of interstitial pneumonia.

It was known from the anamnesis that the patient had been treated with amiodarone in a dose of 200mg/daily for 4 months. On the contrast computed tomography (CT), apart from mediastinal lymphadenopathy (enlarged paratracheal, prevascular and subspiratorial lymph nodes), parenchymal densities were found on both sides, mainly of subpleural distribution, as well as thickening of the interlobular septa, thickening of the bronchial walls, areas of milky glass character and moderately intensified honeycomb lesions were noted (Fig. 1 a-c). In the arterial blood gasometry, features of hypoxemic respiratory failure were found. In addition, laboratory tests showed an increase in transaminase activity with a predominance of alanine aminotransferase, without other tangible causes (viral background and other drugs

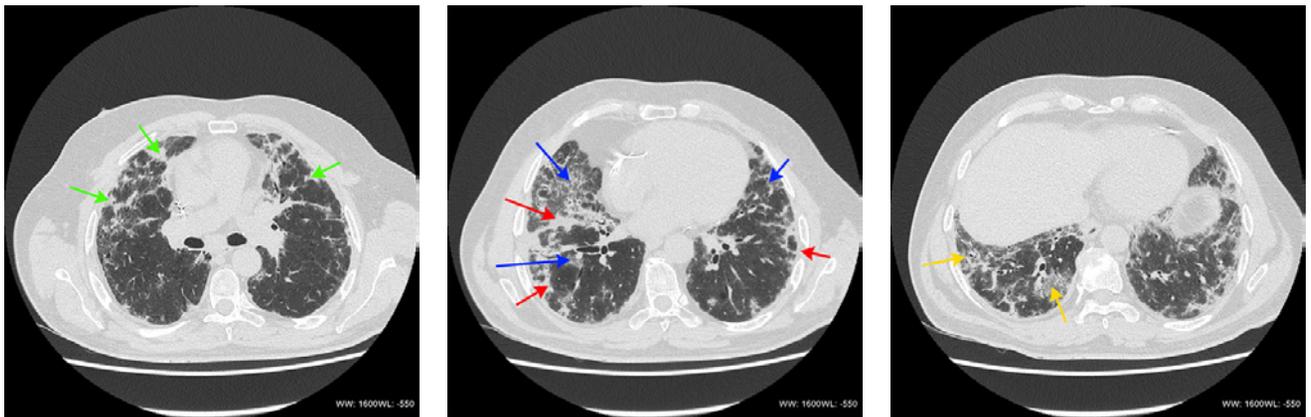


Figure 1 a-c. CT examination on admission to hospital. Axial pulmonary images show multiple diffuse parenchymal opacities (a, green arrows) on both sides, of subpleural distribution, reticulation with thickening of the interlobular fissures and septa (b, red arrows). Multiple ground glass opacities (b, blue arrows), bronchectasis and moderate honeycomb lesions can be noted (c, arrows) with mild mediastinal lymphadenopathy.

toxicity were excluded). Bilirubin concentration remained normal. Thyroid function was not affected.

Because of the anamnesis suggesting drug damage, treatment with systemic glucocorticosteroid (methylprednisolone at a dose of 80 mg/day) was implemented, with a spectacular improvement in the patient's exercise capacity. Although the patient did not present any other symptoms, antibodies for systemic connective tissue diseases were determined. Due to increased anti-nuclear antibodies (ANA) antibody titer (1:640) and increased rheumatoid factor (RF) concentrations, the patient was consulted by a rheumatologist, who stated that the presence of antibodies was rather accompanying the basal disease.

After a significant clinical improvement, a bronchoscopic examination with transbronchial ultrasound and bronchoalveolar lavage was performed to obtain material for histopathological examination. The presence of cancer cells was not confirmed. The representation of the cell types was not typical for any particular disease. The patient received hepatoprotective therapy which, after two weeks of treatment, allowed normalization of the activity of liver enzymes.

The patient was discharged home, continuing with treatment by prednisone at a dose of 0.75mg/kg body weight (60mg/daily). After a month of treatment, a high-resolution control computed tomography was performed in which a significant reduction in the areas of milk glass was observed. However, many fibrous changes remained, which had not been reduced (Fig 2. a-c).

Due to the features of hypoxemic respiratory failure, the patient was qualified for home oxygen treatment, using oxygen therapy about 12–15 hours/day, maintaining saturation at the level of 95–97%. Arterialized blood gas performed at each outpatient visit does not reveal carbon dioxide retention.

Within a few months, the dose of prednisone was reduced to 15mg/day. An attempt to further reduce the dose resulted in a significant deterioration in the patient's well-being in the form of increased shortness of breath. Finally, the method of very slow dose reduction (2.5mg per month) was able to safely establish the maintenance dose at the level of 10mg/day. A recent CT study described the stabilization of fibrous lesions (Fig. 3 a-c).

Given the significant increase of dyspnoea in attempts to limit steroid doses, it seems unlikely that it will be possible to completely withdraw from steroid treatment, although it is known that the resolution of already established fibrous lesions seems impossible.

The patient receives prevention treatment of osteoporosis. Blood pressure and glycaemia are well controlled. Body weight remains at similar values. The patient maintains good physical activity, is able to go for walks, performs household chores that do not require significant effort. He has been under the care of a pulmonary out-patient clinic for nearly 2 years.



Figure 2 a-c. High resolution computed tomography image after 1 month: Note significant reduction of parenchymal consolidations and partial reduction of ground glass opacities with better visualisation of diffuse fibrotic changes (arrows)



Figure 3 a-c. HRCT axial images after two years of follow-up show further stabilization of multiple fibrous changes, visualized on Figure 2 two years before, with significant further reduction of ground glass opacities. Note also some progression of fibrous lesions forming moderate honeycomb areas in basal areas of lower lobes (c, arrows).

DISCUSSION

Although amiodarone is considered one of the most effective drugs in suppressing tachyarrhythmia of supraventricular and ventricular origin, it can also cause adverse reactions from many organs.

The incidence of amiodarone pulmonary toxicity was estimated by Kwok et al. on the level of 1.9% [3]. Other reports, however, indicate a higher incidence of pulmonary complications through use of this drug [4].

The risk of amiodarone pulmonary toxicity (APT) depends on the cumulative dose. Some studies show a post-amiodarone interstitial pneumonia risk reduction thanks to lowering of the drug dose; however, symptoms may be provoked even with low doses of amiodarone [5]. Cases of APT have previously been reported within days to weeks of amiodarone therapy [6], but most cases develop within 12 – 18 months of initiation of the therapy [7]. Other risk factors predisposing to APT include: male gender, nicotine use, previous lung diseases, and thoracic surgery [8]. A case of acute lung injury in the course of treatment with amiodarone triggered by heart transplantation has also been described [9].

Unfortunately, not all cases end with the regression of changes in the lungs after discontinuation of amiodarone and the use of optimal treatment. Cases with a fatal course have also been described [10,11].

The pathogenesis of APT is not yet well understood. Amiodarone accumulates in type II pneumocytes and is lipophilic in nature, therefore it accumulates in the phospholipid bilayer, which negatively affects cellular functions. Additionally, this drug promotes the production of oxygen radicals, which are toxic and also damage cells.

APT can occur in many clinical forms, among which interstitial pneumonias, organizing pneumonias, acute respiratory distress syndrome, diffuse alveolar haemorrhage, pleural effusions, pulmonary nodule, and even solitary masses are worth mentioning [5].

The most common histopathological effects of the toxic effect of amiodarone on interstitial lung tissue are: presence of intra-alveolar foamy macrophages, intra-alveolar giant cells, diffuse lymphoid hyperplasia, follicular bronchiolitis, and poorly formed granulomas and lymphocytes.

Classically, amiodarone lung disease (ALD) presents as an organizing pneumonia with intrafollicular foamy macrophages, although other patterns are also possible,

such as lymphoid hypertrophy (LH) and eosinophilic pneumonia (EP) [12,13].

The main hypotheses raised in relation to the body's reaction to amiodarone are: hypersensitivity reactions, and activation of the angiotensin enzyme system, as well as direct cytotoxicity. Unfortunately, the exact toxicity mechanisms of this preparation and its predictive factors are not fully known; therefore, patients should take the lowest effective doses during treatment and remain under constant medical observation during treatment – chest X-ray, computed tomography, lung functional tests every 3 – 6 months and monitoring the diffusion capacity of carbon monoxide [14].

Examples of symptoms of APT in a patient include the onset of previously unprecedented breathlessness, cough and exercise intolerance. As clinical experience shows, the rate of increase of symptoms and their intensity can vary greatly. However, in a patient treated with amiodarone who presents new respiratory symptoms that cannot be otherwise explained, APT should be taken into account.

In the case of suspicion of ALD, diagnostics should be implemented immediately. The anamnesis regarding drug use and radiological examinations of the lungs, especially computed tomography of the chest, are of the highest value in APT diagnosing.

If post-amiodarone lung damage is suspected, immediate drug cessation plays a key role, which was done in the patient in this case report. However, it should be noted that due to the long half-life of amiodarone (up to 45 days), its toxic effects may persist for a long time. For this reason, early diagnosis of potential APT in the patient is very important, as it can increase the chances of recovery and prevent development of irreversible changes. In the case of severe pulmonary symptoms, a 12-month glucocorticoid therapy should be used, with a gradual reduction in the dose of steroids to avoid relapse [8]. Adherence to the above-mentioned recommendations may result in a significant improvement in the pulmonary function and regression in radiological changes. In the presented case, however, complete resolution of the changes was not achieved. On the other hand, the patient had never previously had a lung tomography, therefore it is not absolutely sure that before the exacerbation of the disease, his lung CT picture was completely unchanged.

Amiodarone is also highly toxic to other organs. Liver function should be checked in people treated with this drug

due to possible side-effects, as we observed in the presented patient.

As previously mentioned, amiodarone is a lipophilic drug which can accumulate in the liver causing amiodarone-induced liver disease, histologically similar to alcoholic and no-alcoholic steatohepatitis [15]. Amiodarone causes liver damage, ranging from asymptomatic increases in serum transaminases to liver failure requiring liver transplant [16]. Patients infected with the hepatitis B and C viruses are at high risk of developing cirrhosis. However, the relationship between treatment and the risk of cirrhosis in high-risk patients with chronic hepatitis B and C is unknown. Long-term monitoring of liver toxicity in high-risk patients treated with amiodarone is recommended [17]. Long-term use of amiodarone may also cause toxic iodine accumulation in the liver, which can be found in a non-invasive dual-energy computed tomography [18].

CONCLUSION

This case report presents a patient with acute lung and liver damage during the treatment with amiodarone. In the era of widespread use of this drug by cardiac patients, it is worth paying attention to the possibility of these adverse events. Sometimes, patients present symptoms on physical examination such as crackles over the pulmonary areas on auscultation, which are interpreted as symptoms of heart failure exacerbation. In such cases, diuretic treatment may be escalated which prolongs the time to correct diagnosis.

Due to the very common use of amiodarone in the treatment of tachyarrhythmias, attention should be paid to the possibility of post-amiodarone lung toxicity, as early cessation of the drug and implementation of adequate treatment may result in a reduction of health for the patient.

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