

Received: 2020.11.17

Accepted: 2021.02.12

Available online: 2021.02.24

Published: 2021.04.06

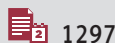
From the Heart to the Lung: A Case of Drug Toxicity

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection GABEFG 1 **Carina M. Rôlo Silvestre**
F 1 **André Nunes**
F 1 **Ricardo José Cordeiro**
E 1 **João Pereira Eusébio**
BD 2 **Maria Teresa Vilaça**
DF 1 **Teresa Falcão**
DE 1 **Antônio Carlos Domingos**

1 Department of Pulmonology, Centro Hospitalar do Oeste, Torres Vedras, Portugal

2 Department of Internal Medicine, Centro Hospitalar do Oeste, Torres Vedras, Portugal

Corresponding Author: Carina M. Rôlo Silvestre, e-mail: carinarolosilvestre@gmail.com**Conflict of interest:** None declared**Patient:** Female, 71-year-old
Final Diagnosis: Drug toxicity
Symptoms: Dry cough • dyspnea
Medication: —
Clinical Procedure: Drug withdrawal
Specialty: Pulmonology**Objective:** Unusual clinical course**Background:** Amiodarone is an anti-arrhythmic drug used to treat and prevent several types of dysrhythmias. This drug is known for multiple-organ toxicity. Lung toxicity occurs in about 1% to 5% of cases. A wide variety of lung manifestations have been described, from mild to severe forms. Pulmonary toxicity can be acute, sub-acute, or chronic. Amiodarone-induced lung toxicity is a diagnosis of exclusion. The main treatment is discontinuation of the drug. Lung disease may progress initially due to the prolonged half-life and the accumulation of amiodarone in adipose tissue. Regarding the prognosis, lung toxicity can be reversible, but in some cases, it is irreversible and is sometimes fatal. The risks associated with its use must always be considered. Amiodarone should only be used for short periods.**Case Report:** The authors present a case of a 71-year-old female patient, taking amiodarone 200 mg/day for 18 months. The patient presented with amiodarone-induced lung toxicity. After drug withdrawal, without corticosteroid therapy, we observed clinical, functional, and radiological improvement.**Conclusions:** This case shows that not all cases of amiodarone-induced lung toxicity require corticosteroid therapy, and highlights that is important to consider this diagnosis in patients on amiodarone therapy with respiratory symptoms.**Keywords:** Amiodarone • Drug-Related Side Effects and Adverse Reactions • Lung Diseases, Interstitial**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/929906>

1297



3

7



Background

Amiodarone, an iodinated benzofuran derivate, is a Vaughan-Williams class III antiarrhythmic drug used to treat ventricular and supraventricular dysrhythmias [1,2]. The daily maintenance dose, which is usually the lowest effective dose, varies from 100 to 600 mg [2]. Despite its excellent anti-arrhythmic effect, this drug is associated with a relatively high incidence of multiple organ toxicity, including thyroid, lungs, heart, eyes, skin, and liver. In about 1% to 5% of cases, lung toxicity occurs, and is the most serious adverse effect, depending on the dose of amiodarone [1,2]. Pulmonary toxicity can be acute, sub-acute, or chronic. Amiodarone has a long half-life and high lipid solubility; it can accumulate in the lung parenchyma, liver, thyroid and adipose tissue. This explains why, even after discontinuation of the drug, adverse effects occur. The most important risk factors for amiodarone-induced pulmonary toxicity are older age, duration of therapy exceeding 2 months, and cumulative dose. There is evidence that exposure to supplemental oxygen, especially in high concentrations, can potentiate amiodarone-induced lung toxicity. The prognosis of amiodarone-induced lung toxicity is favorable [1,3,4]. It usually responds to amiodarone discontinuation, with or without steroids. Pulmonary changes can completely resolve, or some fibrosis may persist. Mortality is not easy to assess and varies among studies. More advanced age, the need for hospitalization, and acute respiratory distress syndrome (ARDS) are associated with higher mortality, reaching 50% [1].

Case Report

We report the case of a 71-year-old woman with a medical history of multinodular goiter in euthyroidism, a former smoker with a 5-pack/year smoking history, with supraventricular and ventricular dysrhythmia, with several episodes of bigeminy and trigeminy, taking amiodarone 200 mg/day for 18 months. She had no other known diseases or environmental exposure to known risk factors.

The patient presented to our Emergency Department with a 2-month history of dry cough, dyspnea on exertion with progressive worsening, and weight loss of 5 kg in this period. She denied orthopnea, night sweats, and fever. The patient did not complain of any other symptoms suggestive of other organ involvement.

At presentation, she was afebrile (36.5°C), with normal blood pressure (130/75 mmHg) and a normal heart rate (78 bpm). She was eupneic, with peripheral oxygen saturation 97% on ambient air. Cardiopulmonary auscultation revealed an irregular pulse. Bilateral crepitations were worse at bases. The rest of the examination was unremarkable.

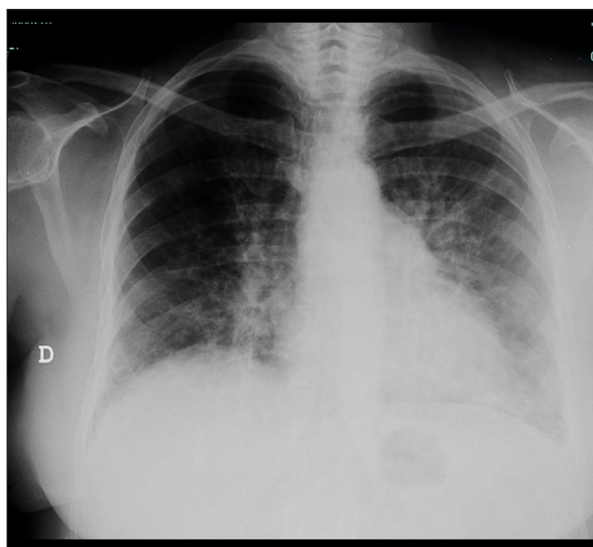


Figure 1. Chest X-ray – lung bases with bilateral interstitial infiltrates.

The laboratory tests revealed: hemoglobin 12.8 g/dL; white blood cell count 7280 cells/ μ L; 65.4% neutrophils, C-reactive protein 1.0 mg/dL, platelet count 350 000/ μ L, LDH 280U/L, brain natriuretic peptide 50 pg/mL, TSH 1.69 μ UI/L, free T4 1.36 ng/dL; free T3 1.81 pg/mL.

Autoimmune markers were negative (antinuclear antibodies; rheumatoid factor; anti-DNA; anti-Ro and La; anti-centromere; antineutrophil cytoplasmic antibody, and anti-ribonuclear protein).

The chest X-ray (**Figure 1**) showed bilateral interstitial infiltrates.

A high-resolution computed tomography (HRCT) lung scan (**Figure 2**) showed extensive areas of bilateral fibrosis and pleural thickening, predominantly basal, associated retractable bronchiectasis and ground-glass opacities, with a scattered and nodular pattern.

Flexible bronchoscopy had no relevant findings. The transbronchial lung biopsy performed revealed mild fibrosis and an inflammatory process of the parenchyma. These findings were suggestive of interstitial lung disease.

Bronchoalveolar lavage was negative for microbiological, mycological, and Mycobacterium smears, and cultures were negative. Malignant cell research was also negative. The cytomorphological study showed 526/uL nucleated cellular elements, with lymphocytosis of 80% and 16% eosinophils. Immunophenotyping showed 64.36% CD3+/CD4+/CD8+ T lymphocytes. Lung function tests showed a decreased diffusing capacity (DLCO) with moderate impairment of the alveolar-capillary transfer of CO, without other alterations. These changes were admitted as a pattern of fibrous interstitial pneumonia associated with

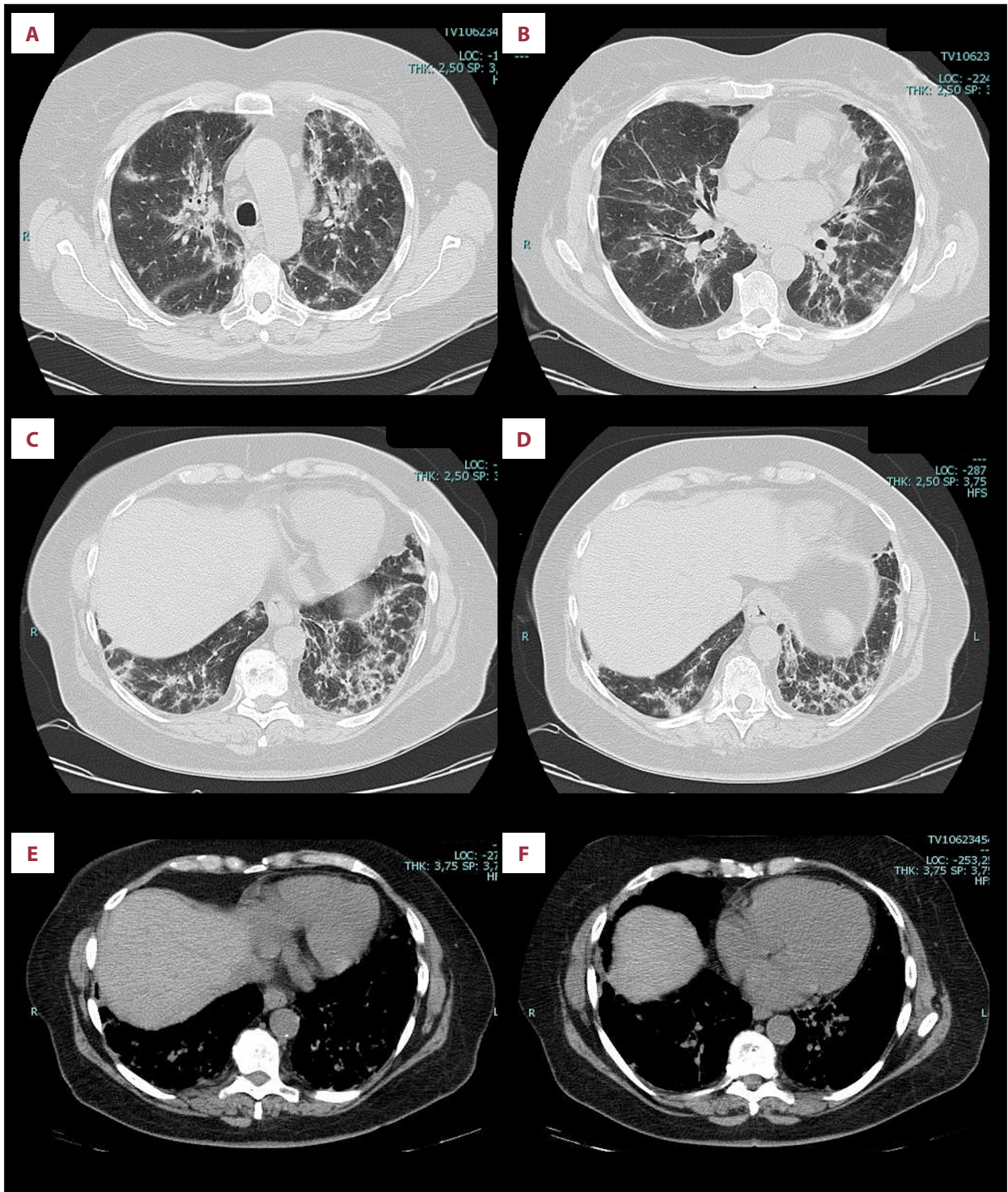


Figure 2. Axial reconstruction of chest HRCT, lung (A-D) and mediastinal (E, F) window: extensive fibrotic areas are observed in both pulmonary fields, predominantly at the base, and pleural thickening, associated retractable bronchiectasis, and with ground-glass opacities.

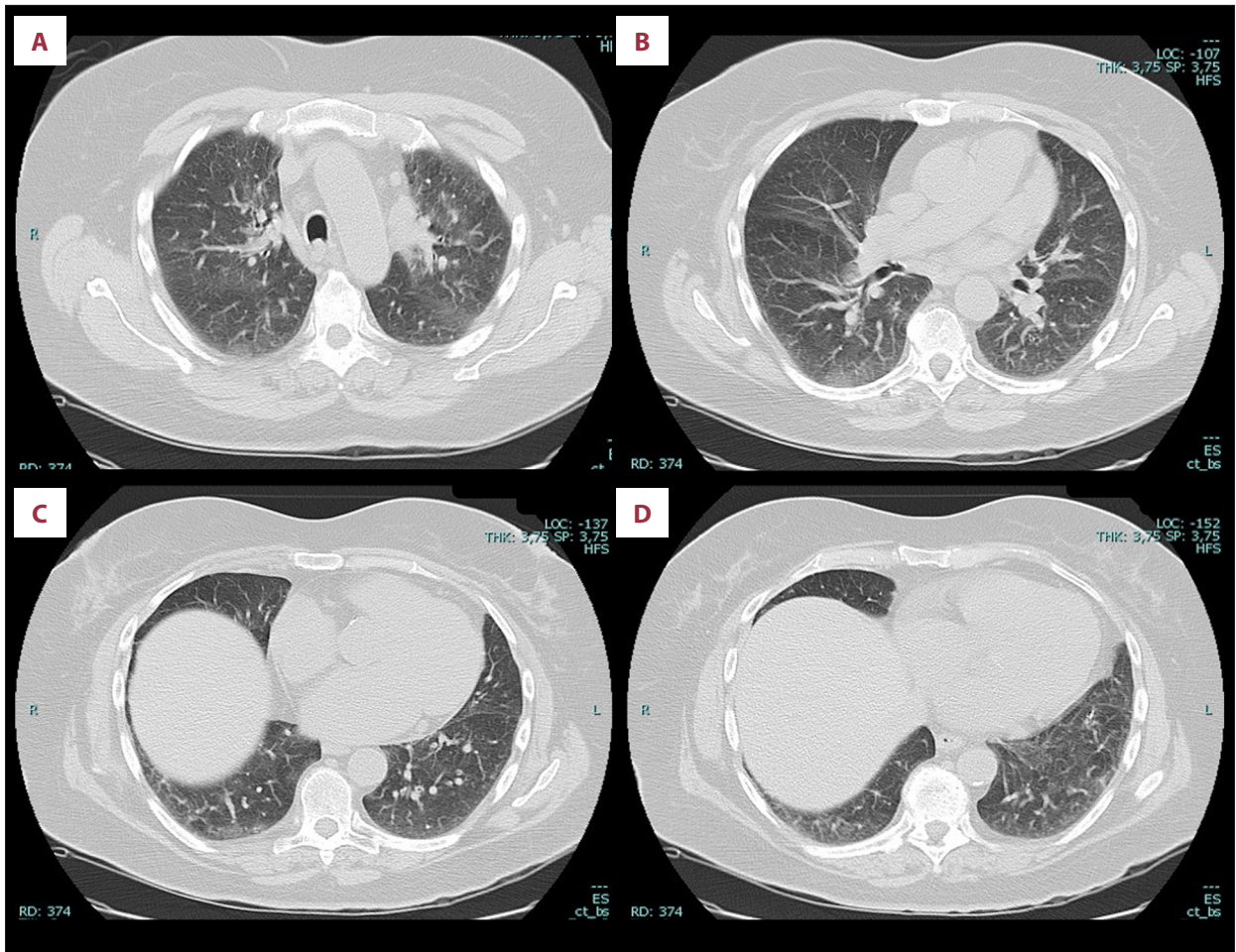


Figure 3. (A-D) Axial reconstruction of chest CT, lung window: evaluation 8 months after drug withdrawal with disappearance of the ground-glass opacities, and resolution of parenchymal and pleural fibrotic changes.

amiodarone toxicity. Given the high suspicion of drug-induced lung toxicity, amiodarone was suspended.

Given her good general condition and the absence of hypoxemia, it was decided not to start corticosteroid therapy and to do close surveillance of the patient. She was then discharged to outpatient follow-up.

At a 2-month follow-up visit, the patient had radiological improvement.

At a follow visit 8-month after amiodarone withdrawal the patient was asymptomatic. She presented with radiologic and lung function tests, including DLCO improvement (**Figure 3**).

At 18-month follow-up, the patient had experienced no relapse.

Discussion

Amiodarone-induced lung toxicity is one of the most serious effects in patients on this therapy. Pulmonary toxicity can be divided into manifestations associated with the parenchyma or pulmonary interstitium [1]. Factors such as age, doses higher than 400 mg/day, duration of treatment, the existence of earlier respiratory diseases, and thoracic or non-thoracic surgery seem to influence the appearance of lung injury [1,3]. Overall, low-dose amiodarone seems safer. However, lung toxicity can occur with doses lower than 200 mg/day, especially for periods longer than 2 years [5]. Our patient was taking amiodarone for less than 2 years and at a low daily dose of 200 mg. Even so, there is evidence that a 2-month period is enough for lung toxicity to develop. In this case, age and treatment duration were risk factors.

Symptoms may be absent or include a nonproductive cough, dyspnea, weight loss, fever, and pleuritic chest pain [2,3,6]. In this case, the patient had nonspecific symptoms compatible with the findings described in the literature.

Pulmonary involvement can present in various ways, including, interstitial pneumonitis with different degrees of fibrosis, eosinophilic pneumonia, organizing pneumonia, diffuse alveolar hemorrhage, ARDS, pulmonary masses or nodules, and, rarely, pleural disease, and exudative pleural effusions isolated or occur in association with interstitial pneumonitis [1-3,6,7]. Interstitial pneumonitis is the most common presentation of amiodarone-induced lung toxicity, and appears after 2 or more months of therapy [1,2]. Amiodarone-induced pulmonary toxicity can be found unilaterally [6].

The physiopathology behind amiodarone-induced lung toxicity is not well understood. Different hypotheses have been suggested, including direct toxicity to interstitial and alveolar cells by alteration of intracellular metabolic pathway and an immunologic reaction with lymphocytic infiltration, and stimulation of the renin-angiotensin-aldosterone system that may lead to lung cells apoptosis [1,3,4].

Pulmonary function testing in amiodarone-induced pulmonary toxicity often shows a restrictive pattern and a reduction in DLCO, but these findings are nonspecific [1-3].

This is a diagnosis of exclusion, and cardiac heart failure and infection need to be excluded in all cases. Idiopathic and secondary interstitial lung diseases are also in the differential diagnosis [1-3]. The clinical, laboratory, and radiologic evaluation are essential to achieve the diagnosis. The diagnosis of amiodarone-induced lung toxicity is difficult to establish because it lacks specific respiratory symptoms.

In most cases, the prognosis is favorable after drug withdrawal. The disease usually responds to amiodarone discontinuation

within 1 to 6 months [1]. In our case, in a short period of 2 months, the patient showed clinical, radiological, and functional improvement. The good clinical evolution remained at 8-month reassessment. During the follow-up of the patient, there were no recurrences.

Conclusions

Although amiodarone toxicity is widely known, this case stands out by its presentation of amiodarone-induced lung toxicity with parenchymal and pleural manifestations. This was a successful case, with an excellent outcome. The patient showed clinical and radiological improvement associated with normal DLCO values. Discontinuation of amiodarone is the primary treatment of all forms of lung toxicity. Not all cases need systemic corticosteroid therapy, as in this case, which was clinically mild, without hypoxia. Steroids are indicated in clinically severe cases. It also highlights that interstitial lung disease associated with amiodarone toxicity may be reversible on discontinuation of the drug. It is important to consider this diagnosis in patients with respiratory symptoms who are receiving amiodarone therapy, even in low drug doses, as in the present case. An early diagnosis and immediate withdrawal of the drug with or without corticosteroids are crucial to obtain a good outcome.

This clinical case highlights the importance of weighing the risks and benefits of using this drug, especially for long periods. Patients taking amiodarone and presenting with increased risk factors for drug toxicity may benefit from close surveillance monitoring.

References:

1. Papiris SA, Triantafyllidou C, Kolilekas L, et al. Amiodarone: Review of pulmonary effects and toxicity. *Drug Saf.* 2010;33(7):539-58
2. Colunga Biancatelli RM, Congedo V, Calvosa L, et al. Adverse reactions of Amiodarone. *J Geriatr Cardiol.* 2019;16(7):552-66
3. Terzo F, Ricci A, D'Ascanio M, et al. Amiodarone-induced pulmonary toxicity with an excellent response to treatment: A case report. *Respir Med Case Rep.* 2019;29:100974
4. Colby R, Geyer, H. Amiodarone-induced pulmonary toxicity, *JAAPA.* 2017;30(11):23-26
5. Ott MC, Khor A, Leventhal JP, et al. Pulmonary toxicity in patients receiving low-dose amiodarone. *Chest.* 2003;123(2):646-51
6. Mahmoud O, Ishikawa O, Gabra NI, et al. A crazy cause of crazy paving: An unusual case of amiodarone induced lung toxicity. *Chest.* 2019;156(4) A1219-20
7. LeVee A, Trieu M, Bhattacharyya S, et al. Eosinophilic pneumonia: A rare manifestation of amiodarone toxicity diagnosed using traditional bronchoscopy. *Respir Med Case Rep.* 2019;27:100856