

Amiodarone induced lung toxicity: a radiological overview that simulating COVID19 infection disease

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Abstract: Amiodarone-induced pulmonary toxicity (AIPT) is among the most serious adverse effects and is one of the leading causes of death associated with its use. It is a clinical pathology that is conditioned by dose, patient's age, and pre-existent pulmonary pathologies. Those effects reach a plateau at a cumulative dose bigger than 150g. Patient's comorbidities; oxygen therapy, invasive procedures or surgical interventions can trigger the pulmonary symptoms induced by amiodarone toxicity. The increased risk of developing amiodarone-induced pulmonary fibrosis is directly related to the dose and the duration of the intake. Despite significant advances in the understanding of AIPT, its aetiology and pathogenesis remain incompletely understood. The role of steroids in the management of pulmonary toxicity from amiodarone is debatable, however, most reports of improvement after amiodarone withdrawal differ little from those in which concomitant steroid therapy was employed. Therefore, the addition of therapeutic doses of corticosteroids in amiodarone-induced pneumopathy may be indicated. Typically, prednisone is started in doses of 40 to 60 mg/day orally and slowly reduced. Again, the pharmacodynamics of amiodarone dictate a treatment period of four to 12 months. The case report describes a patient with AIPT who after therapy with Prednisone at a dosage of 50mg/day by gradually scaling down the doses as reported in the above clinical studies, had a clinical, functional and CT radiological

picture that was markedly improved with disappearance of most of the scattered ground glass areas and the previously reported thickening with associated bi-apical fibrotic outcomes.

Keywords: AIPT, Amiodarone-induced Pulmonary Toxicity, Amiodarone, Hyper-reactivity, OCS, Ground Glass Opacity

Introduction

Amiodarone is an effective antiarrhythmic that is often used in the perioperative period after cardiac surgery. The drug can create significant adverse reactions. After the first dose, amiodarone reaches its plasmatic peak levels in 3 to 7 h. The onset of action can take from a few days to a few weeks. Biodisponibility can be influenced by age, liver pathology and interactions with other drugs or substances that can inhibit or stimulate cytochrome P450. Because of the lipophilic structure, both amiodarone and its metabolites accumulate in high quantities in tissues and interact with the phospholipid's metabolism. These tissues are represented by adipose tissue and well-perfused organs: liver, lung or skin tissue. The most frequent affected organs by the accumulation of amiodarone and, respectively, the high risk of developing injuries induced by amiodarone are the eyes (cornea deposits, photophobia), the thyroid gland (hypo/hyperthyroidism), the liver (drug-induced hepatitis, dyspeptic syndromes), the skin (photosensitivity) and the nervous system (peripheral neuropathy). Although the lungs are rarely affected (approximately 4–6% of all complications), pulmonary injury has the most clinically significant impact, which can lead to the patient's demise¹. Evidence from the scientific literature has highlighted the fact that cells of the innate immune system as well as the adaptive one and the mediators that these cells release cause the appearance of interstitial changes. Macrophages are phagocytic cells belonging to the innate immune system. Present in all tissues of the body, most commonly in the lung and liver, macrophages function as immune sentinels, with the aim of defending the body against pathogens and injuries². Resident macrophages are distinct from bone marrow-derived inflammatory macrophages that accumulate in tissues in response to injury or infection. Inflammatory macrophages are mainly involved in the development of pulmonary fibrosis. Macrophages have been classified into M1-pro-inflammatory/cytotoxic and M2-anti-inflammatory/reparative, which develop in response to signals present in the

tissue microenvironment³. Amiodarone-induced pulmonary toxicity (AIPT) is the most serious adverse effect and a major cause of death. AIPT is classified as acute, subacute, and chronic⁴. It can frequently develop within the first 1 to 1.5 years after the start of therapy and occurs quickly in patients using high doses of amiodarone. Signs and symptoms of AIPT are non-specific and are general malaise, dry cough, pleuritic chest pain and progressive dyspnoea, accentuated if drug-induced hyperthyroidism is present. The pattern for drug-induced lung injury may vary in many forms, but amiodarone can cause polymorphous injuries such as diffuse alveolar damage (DAD), chronic interstitial pneumonia (CIP), organizing pneumonia, pulmonary hemorrhage, lung nodules or pleural disease⁵. Amiodarone therapy also interferes with other drug classes, such as warfarin, simvastatin, atorvastatin as well as antiretroviral medication used in patients with HIV. Considering these facts, and the frequent use of amiodarone in medical practice, physicians must know the indications, contraindications, dosage, adverse effects, and drug interactions of amiodarone treatment. Usual doses between 200–600 mg/day have minimal hemodynamic adverse effects. They cause a negative inotropic effect related to the administered dose by reducing systemic vascular resistance⁶. It has no effect on the ejection fraction of the left ventricle, and arterial hypotension rarely occurs during oral treatment with amiodarone. Diagnosis is possible if there are clinical manifestations in the lungs, thyroid, liver, and eye. Laboratory tests show increased erythrocyte sedimentation rate (ESR), leucocytosis, increased lactate dehydrogenase (LDH) and circulating eosinophils. On chest CT the following are present: areas of alveolar, interstitial, or mixed alveolar-interstitial ground glass opacity⁷. Lung involvement in asymmetric or bilateral form, reticular and peribulbar interstitial opacities, basal traction bronchiectasis one or more sub-pleural nodules (6–12%), pleural thickening with pleuritic chest pain or chafing on physical examination, sometimes dense, bibasilar, and reticular opacities, with gross crackles on chest auscultation, significant

hypoxaemia, and weight loss. The response to corticosteroids is widely debated in terms of efficacy, as the disease is irreversible and has a negative prognostic impact on the patient. Lung function tests in most cases reveal a restrictive type of abnormality, with reduced DLCO values, the latter being greater in patients with pre-existing lung disease such as COPD⁸.

Clinical case presentation

The patient is a 67 years old Caucasian female, former 30-year smoker of 10packs/years, with recent admission on December 2022, to the emergency department for dyspnoea, febrile serotinous episodes. On Anamnesis: oesophageal jatal hernia, in July 2022 episode of SARSCoVID19 infection with pauci-symptomatic evolution and no recovery, chronic atrial fibrillation and previous surgery for aneurysm on therapy for about two years with amiodarone at a dosage of 200mg/day, allergy to amoxicillin/clavulanic acid denies environmental exposure to moulds and does not keep farm animals. On echocardiography: cardiac ejection fraction: 62%, mild mitral valve insufficiency. At thyroid ultrasound: diffuse nodular formations, some cystic and thyroid enlarged in volume. On blood examination: ESR: 120 CRP: 13.9, LDH: 683 Positive faecal occult blood, TSH: 12 Anti-thyroglobulin antibodies: 107, Vitamin D: 17.9, WBC: 11,850 with neutrophilia: 7,610 cells and eosinophilia: 1230 cells Swab for SARSCoV2 negative. On thoracic examination: vital parameters normal except for peripheral oxygen saturation: 93% in room air, reduced vesicular murmur with bilateral "Velcro-like" crepitations, hypo transmitted tactile vocal tremor bilaterally, clear pulmonary sound. The Global spirometry at time zero, showed moderate restrictive pattern (Table 1).

I decide to start with ICS/LABA 2 x 2 /die and therapy with OCS Prednisone 25mg BID for 20 days⁹ then reduced to ½ cp BID for 20 days then reduced to ¼ cp BID for 30 days then reduced to ¼ cp/day until next clinical and spirometry check at 3 months, antibiotic therapy with quinolone and macrolide for 8 and 6 days. Blood gas analysis performed subsequently showed no hypoxaemia. At the clinical spirometry at 3 months, the spirometric functional values had improved, persisting mild restrictive pattern (Table 1), with the presence of +45% PEF (indicative of bronchial hyper-reactivity); and +18% of TLC. The CT scan at time zero and at three months post-therapy showed (Figure 1 from A to I): “Extensive areas of Ground Glass thickening are noted in both parenchyma, predominantly centre-lobular, more extensive on the right side, a picture compatible with non-specific interstitial pneumopathy. The finding is in significant regression compared with the previous examination performed 3 months ago with some small lymph nodes in the mediastinum (14mm maximum diameter)”. On blood examination at 3 months: ESR: 115 CRP: 2, LDH: 468, WBC: 8,000 with neutrophilia: 5,160 cells eosinophils: 230 cells. The patients have no previous spirometry and CT scan after infection of SARS COVID19.

Discussion: Amiodarone-induced pulmonary toxicity is conditioned by dose, patient’s age, and pre-existent pulmonary pathologies. The pattern for drug-induced lung injury may vary in many forms, but the amiodarone can cause polymorphous injuries such as diffuse alveolar damage, chronic interstitial pneumonia, organizing pneumonia, pulmonary hemorrhage, lung nodules or pleural disease¹⁰. The pathological mechanism of pulmonary injury induced by amiodarone consists of the accumulation of

Global Spirometry time zero	Global Spirometry at three months
FEV1/FVC: 125% of predicted value	FEV1/FVC: 120% of predicted value
FVC: 79% of predicted value	FVC: 88% of predicted value
FEV1: 100% of predicted value	FEV1: 73% of predicted value
PEF: 78% of predicted value	PEF: 123% of predicted value (+45% of predicted value)
FEF25-75: 242% of predicted value	FEF25-75: 201% of predicted value
TLC: 56% of predicted value	TLC: 74% of predicted value (+18% of predicted value)

Table 1. Time zero global spirometry where you can see a moderate restrictive pattern, and new global spirometry at three months of therapy where you can see mild restrictive pattern with improves of PEF and TLC.

Legend:

FEV1%: Percentage of predicted value of FEV1

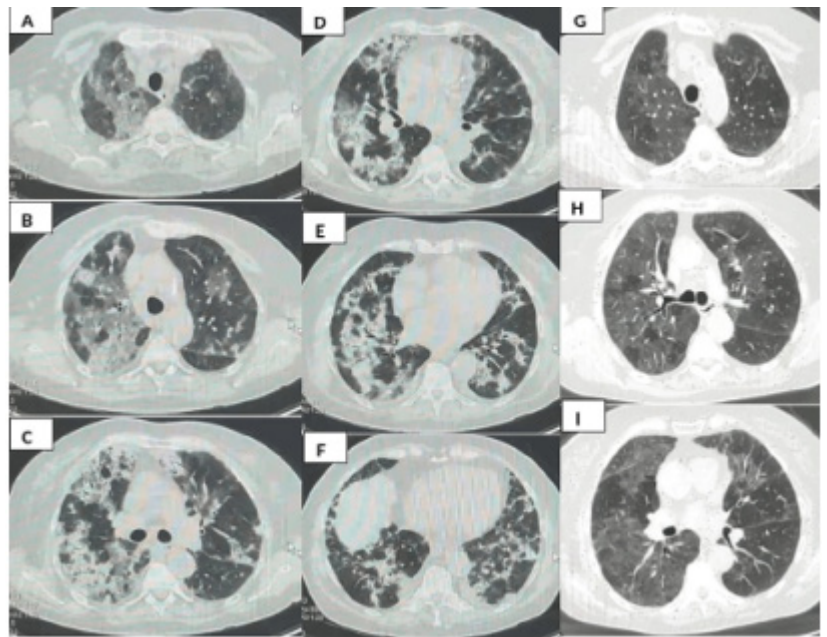
FVC%: Percentage of predicted value of FVC

FEV1: Maximum Expiratory Volume at first second

FVC: Forced vital capacity

TLC: total lung capacity

FIGURE 1: A: Time zero chest CT scan showing areas of bilateral apical centrilobular consolidation with thickening of the pulmonary reticular interstitium of the intra- and interlobular septa, with predominance in the right apical areas. B: Time zero chest CT scan showing areas of bilateral apical centrilobular consolidation with thickening of the pulmonary reticular interstitium of the intra- and interlobular septa, with predominance at the right apical zones with presence in both lungs at the submantellar zones of solid centrilobular consolidations. C: Chest CT scan at time zero showing areas of right perilobular consolidation with thickening of the reticular pulmonary interstitium of the intra- and interlobular septa and prevalence in the right middle field of areas of solid centrilobular consolidation. D-E-F: Time-zero chest CT scan showing areas of peri- and mid-basal centrilobular consolidation prevailing on the right, thickening of the reticular pulmonary interstitium intra- and interlobular septa, and predominance in the mid-right field of areas of solid centrilobular consolidation. G-H-I: Chest CT scan carried out at three months of therapy with an oral corticosteroid, inhaled corticosteroid, and a long-acting bronchodilator, showing apical, middle, and basal areas almost complete regression of the areas of



phospholipid complexes in histocytes and type II pneumocytes. Differential diagnosis of pulmonary fibrosis induced by amiodarone is made mainly with idiopathic pulmonary fibrosis, left ventricular failure or infectious disease¹¹. From a functional point of view, a moderately restrictive type of pattern is frequently highlighted, with a decrease in forced vital capacity (FVC) and a moderate decrease in the diffusing capacity for carbon monoxide (DLCO) in approximately 45% of patients¹². A nonspecific inflammatory syndrome can also be highlighted, characterized by a mild leucocytosis, increased erythrocyte sedimentation rate and increased C-reactive protein (CRP) value, but these are nonspecific and are associated with interstitial inflammation¹³. Amiodarone-induced interstitial lung damage includes varying forms of presentation, from mild to moderate/severe¹⁴. These include organizing pneumonia, interstitial pneumonitis, or respiratory failure. Evidence from the scientific literature has highlighted the fact that cells of the innate immune system as well as the adaptive one and the mediators that these cells release cause the appearance of interstitial changes¹⁵. Macrophages are phagocytic cells belonging to the innate immune system¹⁶. The typical presentation of amiodarone-induced lung damage is subacute, with dry cough, progressive dyspnea, low-grade fever and weight loss¹⁷. The incidence of these complications has decreased

considerably with the use of reduced doses, but nevertheless, in some cases, the clinical presentation is acute and may be life-threatening¹⁸. Although the adverse effects produced using amiodarone are known, the adherence of medical staff and patients to the guidelines for monitoring therapy is poor. Worldwide, there are medical centers where it is possible to determine the serum level of amiodarone. Values higher than 2.5 mg/L are indicators of a high level of toxicity¹⁹. Pulmonary functional exploration highlights a restrictive syndrome. DLCO decreased by 15% advocates pulmonary toxicity in a patient under amiodarone treatment¹⁹. Although amiodarone is a potent antiarrhythmic, studies in the specialized literature have demonstrated the occurrence of pulmonary toxicity associated with this treatment²⁰. The increased risk of developing amiodarone-induced pulmonary fibrosis is directly related to the dose and the duration of the intake. The prevention of adverse effects is the responsibility of the entire team that interacts with the patient: the attending physician, the one who prescribes the treatment, primary care physician, specialist physician and pharmacist²¹. The multidisciplinary approach remains essential to improving the quality of life and the patient's outcome²². Effective follow-up of the patient after initiation of amiodarone therapy involves responsibility on the part of the entire medical team as well as the patient. Current

information and effective communication between patient and doctor are essential for further development²³. The effects of amiodarone are multiples and pleiotropes, interested many organs like thyroid, eyes, kidneys, liver and lungs, so for that it is important to evaluate all kind of districts that are interested from toxicity of this drug.

Conclusions

The patient improved functionally, instrumentally, and clinically on continuous steroid therapy. Bronchoalveolar lavage was not performed in that case presented. The diagnosis of pulmonary toxicity induced by amiodarone is difficult, it is a diagnosis of exclusion, based on clinical phenomena of respiratory insufficiency, imaging interstitial type affection, sometimes even usual interstitial pneumonia, which makes the differential diagnosis with idiopathic pulmonary fibrosis and/or biological. Early recognition of respiratory complications induced by amiodarone treatment and intensive treatment can cause a favourable evolution of the patient. Any delay in discontinuing amiodarone treatment when there is clinical suspicion may lead to an unfavourable prognosis for the patient. Further imaging and functional monitoring (volumes and respiratory flows) is mandatory. The role of steroids in the management of amiodarone pulmonary toxicity is debatable, but the clinical resolutions of the clinical case are no different from discontinuation of the drug and monitoring over time. Patients who have developed drug toxicity have been reported to have maintained it at the same or lower doses, improving with the addition of steroids. An exact dose or duration of treatment has not been established. Regimens of 0.5–1 mg/kg of prednisolone with gradual tapering are usually prescribed for months, often for a period of 1 year. Tapering of corticosteroids depends on the response time of each patient, since there is evidence that amiodarone remains in lung tissue even 1 year after discontinuation of the drug. Caution is needed in the gradual reduction of corticosteroids. Cases of aggressive disease relapse have been described after reducing the dose of prednisolone by over 5 mg daily or even 8 months after complete cessation of treatment. In cases where amiodarone is considered absolutely essential for its antiarrhythmic properties, regimens with the lowest possible dose of amiodarone in combination with corticosteroids have been successfully used. Despite treatment, disease may progress to irreversible pulmonary fibrosis and/or death in certain refractory or

fulminant cases. In respiratory failure, oxygen therapy or even mechanical ventilation are applied as necessary. Furthermore, the administration of a wide spectrum antimicrobial therapy initially is required until respiratory infection is reliably excluded. Therefore, the addition of corticosteroids in AIPT may be indicated. Prednisone is started at doses of 40 to 60 mg/day orally with progressive de-escalation. The pharmacodynamics of amiodarone dictate prolonged treatment for four to 12 months.

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