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Amiodarone Pulmonary Toxicity: A Case of Clinical and Radiologic Improvement

Lis C, MD[1,2] | Pourzand L, MD[1]

Author Affiliation: [1] Department of Radiological Sciences, David Geffen School of Medicine at UCLA
[2] Now with Cedars-Sinai Medical Center, Los Angeles

Corresponding Author: L.P. (lpourzand@mednet.ucla.edu)

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Abstract: Amiodarone is an effective class III antiarrhythmic medication, the use of which is limited by its potentially severe side effects and toxicities. When amiodarone pulmonary toxicity (APT) is suspected in patients, amiodarone use should be discontinued. We report a case of APT, with a description of the clinical presentation and radiologic manifestations of the disease and a literature review of purported pathophysiology and treatment.

Keywords: *amiodarone pulmonary toxicity, computed tomography, pneumonia, steroid therapy*

Introduction

The use of the antiarrhythmic medication amiodarone is limited by potentially severe side effects and toxicities, such as amiodarone pulmonary toxicity (APT). In this report, we present the case of a 76-year-old man with APT, in which radiologic findings were crucial for diagnosis. Furthermore, this case clearly illustrates classic imaging features of APT at the time of diagnosis, after a period of disease progression, and after symptom resolution. This case report was prepared following the CARE Guidelines.[1]

Key Points

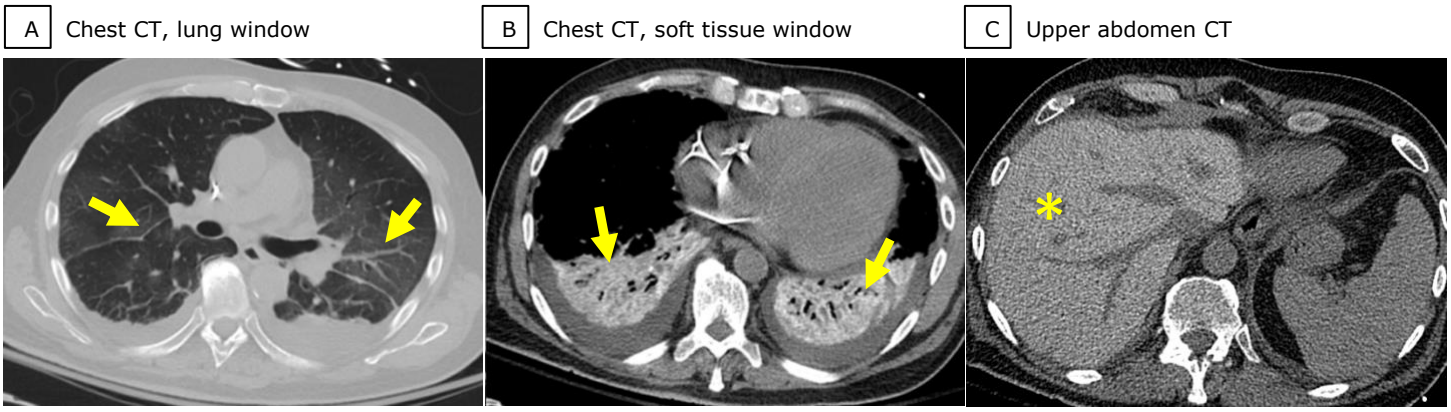
- Amiodarone is a widely used antiarrhythmic agent which has the potential to cause amiodarone pulmonary toxicity (APT), in both the acute and chronic setting.
- APT can potentially lead to acute respiratory distress syndrome (ARDS) in the acute setting, and irreversible interstitial lung disease (ILD) in the chronic setting.
- In subacute and chronic cases, early diagnosis and discontinuation of amiodarone therapy can result in the complete resolution of pulmonary symptoms and imaging findings.

Case Presentation

A 76-year-old man with a history of hypertension, coronary artery disease, ventricular tachyarrhythmia, and Parkinson's disease presented to the emergency department (ED) after sustaining a ground-level fall. Computed tomography (CT) of the patient's head showed a small subdural hematoma, and the patient was admitted to the neurologic intensive care unit (ICU) in guarded condition. At the time of admission, the patient had been receiving clopidogrel, aspirin, hydralazine, carbidopa and levodopa, and 200 mg of amiodarone twice daily, the latter of which was started approximately 2 years prior to the patient's admission.

Several days after admission, the patient developed shortness of breath and required increasing supplemental oxygen. Chest radiography showed bilateral parenchymal opacities, possibly indicating pneumonia, and the patient was started on empiric antibiotics. The patient's respiratory status continued to worsen,

Figure 1. Computed Tomography of the Chest and Upper Abdomen of a 76-Year-Old Man.



Computed tomorography images obtained during the patient's stay in the neurologic intensive care unit indicated possible amiodarone toxicity. (A) Bilateral diffuse ground-glass opacities are visible in the lung window (A, arrows). (B) Bilateral high-attenuation lung consolidation, atelectasis, and pleural effusions can be seen in the soft tissue window (B, arrows). (C) The upper abdomen shows high attenuation in the liver (C, arrows).

and he required high-flow oxygen. Subsequent chest CT showed bilateral pleural effusions with high-attenuation consolidation and atelectasis of lower lobes, areas of ground-glass density, evidence of pulmonary edema, and increased attenuation of the partially visualized liver (Figure 1). Given the patient's respiratory symptoms and his history of amiodarone use, the imaging findings were interpreted as possible amiodarone pulmonary toxicity. A cardiologic consultant recommended discontinuing amiodarone; however, the patient refused, as he wished to speak to his personal cardiologist before discontinuing therapy. With treatment of the pulmonary edema, the patient's respiratory status slightly improved, and eventually he was discharged to an acute rehab facility.

The patient, who had continued with the same regimen of amiodarone, presented again to the ED approximately 2 months later with worsening shortness of breath, weakness, and altered mental status. He had reportedly been treated for pneumonia twice since his prior discharge. Upon this presentation to the ED, he was hypoxic, with an oxygen saturation of 80%, and hypotensive with leukocytosis.

Chest radiographs showed persistent bilateral opacities. He was admitted to the ICU and was treated with empiric antibiotics for presumed sepsis secondary to pneumonia. Chest CT images were similar to those obtained during the patient's admission two months prior, and showed high-attenuation consolidation and atelectasis and increased ground-glass attenuation, with a component of hydrostatic pulmonary edema and effusion. These imaging findings were once again interpreted as possible APT.

Amiodarone was discontinued, and the patient was started on steroid therapy for amiodarone toxicity. The patient's pulmonary edema was nearly resolved by optimizing a diuretic regimen. Analysis of respiratory cultures was inconclusive. The patient was discharged 2 weeks later with a prescription for prednisone.

On an unrelated admission 2 months later, the patient's respiratory status had significantly improved. Chest CT at the time showed interval resolution of high-attenuation consolidation and atelectasis and nearly resolved ground-glass attenuation (Figure 2).

Discussion

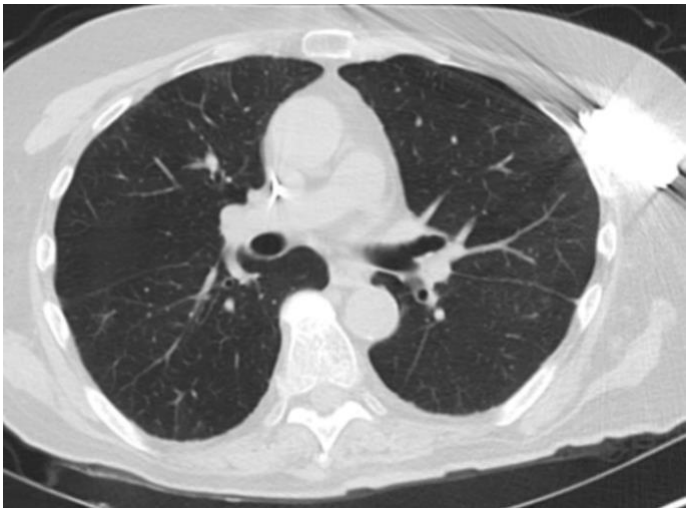
Amiodarone is a class III antiarrhythmic medication used in the treatment of atrial and ventricular tachyarrhythmia. Although it is generally considered to be an effective therapy, its use is limited by several side effects and toxicities, including APT. APT can potentially escalate to acute respiratory distress syndrome (ARDS) in the acute setting and to irreversible fibrosis in the chronic setting. One study found that acute APT-induced ARDS occurred in 15% of postoperative

cardiothoracic patients, with risk increasing significantly with age, particularly with each decade over 60 years.[2] APT has been reported to occur in approximately 5-15% of patients taking 400 mg/day or more.[3]

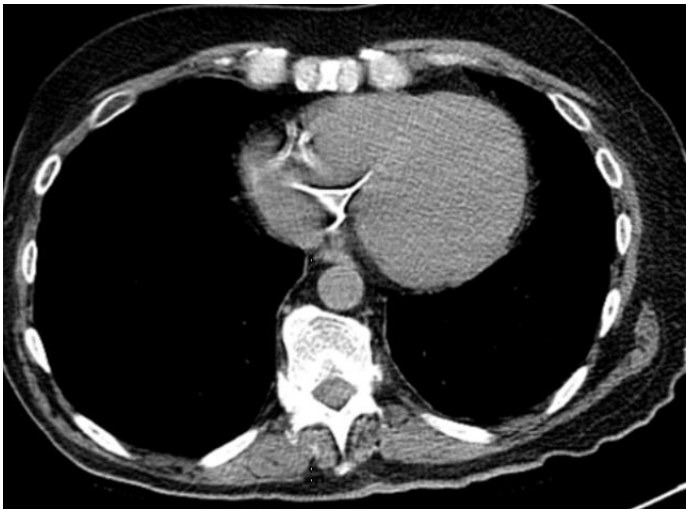
Susceptibility to amiodarone-induced lung damage may be particularly heightened in those undergoing major cardiothoracic surgery because of the frequent presence of chronic lung disease and the need for concomitant supplemental oxygen and mechanical ventilation in the perioperative period. Other risk factors for APT include age over 60 years, higher dosing, and angiography.[3-6] APT can be seen in patients with cumulative intravenous amiodarone doses as low as 1000–15 000 mg.[4]

Figure 2. Computed Tomography of the Chest of a 76-Year-Old Man 10 Weeks After the Discontinuation of Amiodarone.

A Lung window



B Soft tissue window



(A) Computed tomography image in the lung window shows interval resolution of the bilateral ground-glass opacities. (B) A Computed tomography image in the soft tissue window, shows interval resolution of high attenuation in the lung parenchyma, pleural effusions, and atelectasis.

Several clinical presentations have been described in patients with APT, most commonly subacute alveolar or interstitial pneumonitis. Typically, patients have been receiving amiodarone for months to years when symptoms develop, and they present with progressive shortness of breath and a nonproductive cough. Symptoms may also include fever, malaise, and weight loss.[3-8]

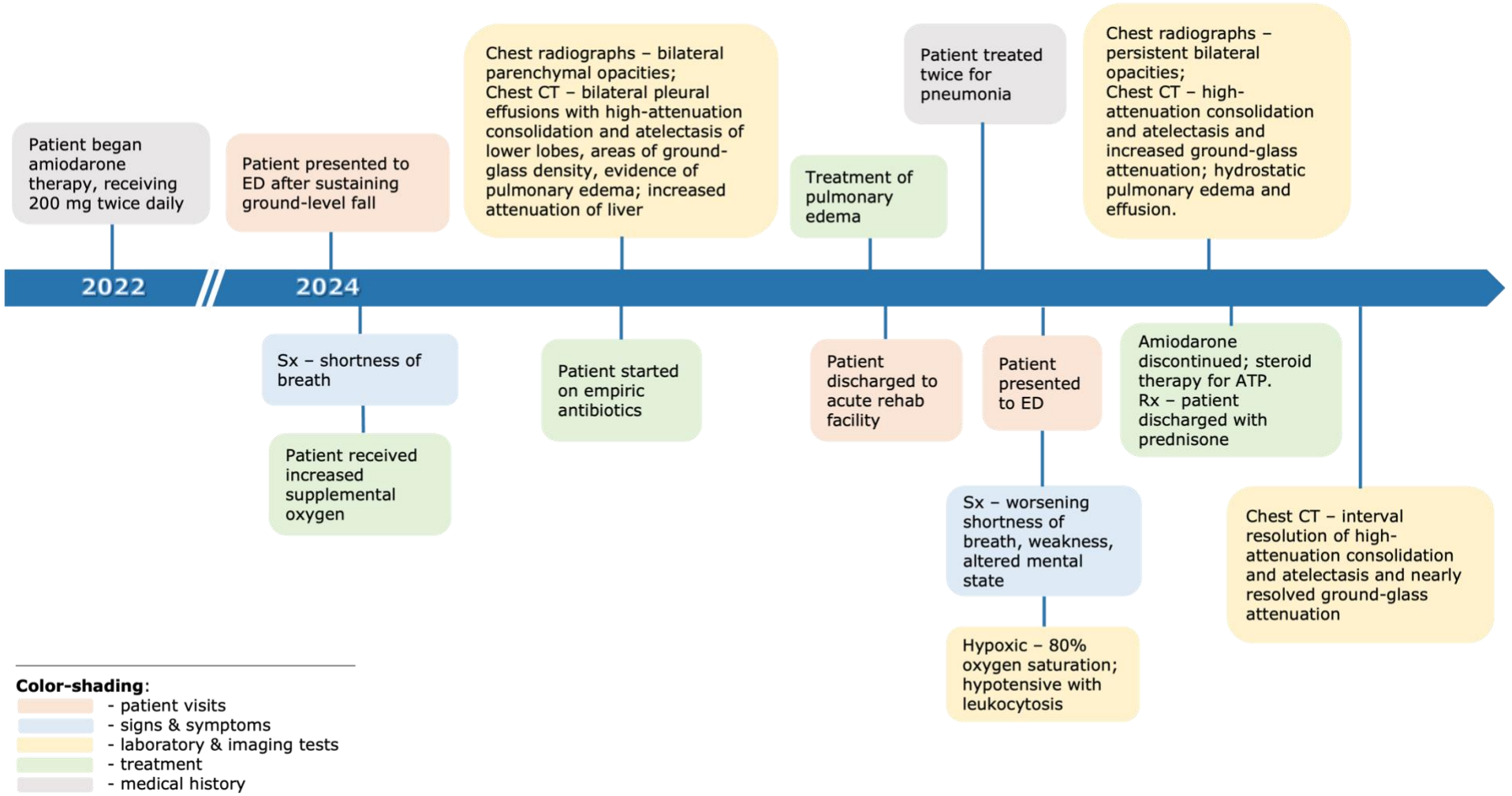
The most dramatic manifestation of APT is that of a rapidly progressing diffuse pneumonitis with acute respiratory failure and a picture typical of ARDS. It has been described in patients receiving contrast infusion for pulmonary angiography and particularly in patients undergoing cardiac or pulmonary surgery, especially pneumonectomy.[9]

Patients may present with features typical of individuals with advanced pulmonary fibrosis. This may evolve progressively after a documented episode of acute amiodarone-induced pneumonitis.[9] APT may, however, present without an obvious antecedent event. In these cases, it is possible that the pneumonitis phase was subclinical and not recognized.

Pulmonary function testing usually reveals a restrictive or mixed obstructive and restrictive pattern. The diffusing capacity of the lungs is usually reduced.[6]

Radiology plays a central role in diagnosis. Chest radiographs reveal patchy or diffuse infiltrates, commonly in both lungs. Chest CT images typically show ground-glass attenuation and peripheral high-attenuation consolidations. Pleural thickening and effusions are common and are seen particularly in association with dense consolidation.[3] High-attenuation consolidation is believed to be associated with the iodinated properties of the drug and its prolonged half-life in the lung. Ground-glass opacities are more easily identified and seen more frequently on CT than on chest radiography.[3-5] It has been speculated that the initial findings of APT are ground-glass

Case report timeline



Abbreviations: CT, computed tomography; ED, emergency department; Rx, prescription; Sx, symptoms

opacities and that these are a clue for detection of this complication at an early, potentially reversible stage.[10]

On high-resolution CT (HRCT), there are coarse interstitial reticular or reticulonodular densities and traction bronchiectasis. Honeycombing may be present but is less common.[3] Infrequently, high-attenuation pulmonary nodules or masses and pulmonary hemorrhage can manifest due to APT.[3] High attenuation may be noted incidentally on CT on views of the liver and spleen, and is related to the accumulation of amiodarone and its metabolites in tissue macrophages. This latter finding, although suggestive of amiodarone exposure, is not necessarily associated with APT.[3] Amiodarone and its metabolites can produce lung damage directly by a cytotoxic effect and indirectly by an immunological reaction.[8] The latter is supported by the finding of cytotoxic T cells in bronchoalveolar lavage (BAL) fluid from patients with diagnosed APT.[8,11] Amiodarone may induce the production of toxic oxygen radicals, which can directly damage cells.[8] Bronchoscopy with BAL and transbronchial biopsy can be useful in ruling out other causes of diffuse lung disease. BAL may reveal an inflammatory or immune response evidenced by an elevation in polymorphonuclear leukocytes and T suppressor CD8+ cells. The presence of "foamy" macrophages is consistent with a diagnosis of APT but it is not definitive, as these cells can be seen in up to one half of amiodarone patients who are not experiencing APT.[11] However, in the absence of foam cells, the diagnosis of APT is considered unlikely.[10,11]

When APT is suspected, amiodarone should be discontinued. Systemic corticosteroids are recommended for treatment, generally with oral prednisone 0.5–1 mg/kg/day and tapered over one year.[4] However, data supporting the efficacy of steroid therapy are generally lacking. When diagnosed early, the prognosis of amiodarone lung toxicity is typically favorable. Delay in diagnosis can result in irreversible and potentially fatal pulmonary fibrosis.[3-8] In the acute setting, prognosis is less favorable, particularly in those who develop ARDS.[2,4]

Author Contributions

Conceptualization, C.L. and L.P.; Acquisition, analysis, and interpretation of data, C.L. and L.P.; Writing – original draft preparation, C.L. and LP; Review and editing, C.L. and L.P.; Supervision, L.P. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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