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Amiodarone-induced loculated pleural effusion without pulmonary parenchymal involvement: A case report and literature review

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Amiodarone is an extremely effective antiarrhythmic drug that is known to cause many adverse effects such as pulmonary, thyroid, and liver toxicities. Of these, pulmonary toxicity is most serious. Pulmonary toxicity can present as interstitial pneumonitis, organizing pneumonia, pulmonary nodules and masses, and very rarely pleural effusions. We present a case of a 73-year-old male who presented with progressive exertional dyspnea, nonproductive cough, generalized fatigue, and weakness. He was found to have multiorgan toxicity secondary to long-term treatment with high doses of amiodarone. This case illustrates that amiodarone may cause toxicity involving multiple organs simultaneously in patients receiving long-term therapy and represents the first reported case of amiodarone-induced loculated pleural effusion without associated lung parenchymal involvement.

Introduction

Amiodarone is a widely used Class III antiarrhythmic drug that can be utilized for the management, treatment, and prevention of ventricular and atrial arrhythmias. However, long-term use of amiodarone is limited secondary to its adverse effects. Pulmonary toxicity is the most adverse side effect, with an incidence that ranges from 1% to 10%, depending on the cumulative dose of amiodarone.[sup][1]

Case Report

A 73-year-old male presented to our service with complaints of worsening exertional dyspnea for 1 month duration. He had a medical history of coronary artery disease, with a previous coronary artery bypass grafting, hypertension, refractory ventricular tachycardia (VT) with a prior cardiac arrest, catheter ablation of VT, and an automated implantable cardioverter-defibrillator (AICD) insertion. He also reported chronic nonproductive cough, generalized weakness, fatigue, anorexia, malaise, and

unintentional eight pounds weight loss over the last 3 months. He was maintained on amiodarone 400 mg/daily for the past 3 years due to recurrent episodes of VT and frequent AICD shocks. His vital signs were significant for a blood pressure 110/70 mmHg, heart rate 76 beats/min, respiratory rate 23 breaths/min, and oxygen saturation 95% on room air. Physical examination was significant for decreased air entry over the left lung base. Laboratory workup showed white blood cell (WBC) count of 7500/uL, hemoglobin level 14.4 g/dL, thyroid stimulating hormone <0.01 uIU/ml, free thyroxine 5.58 ng/dl, total T4 19.2 [micro]g/dl, triiodothyronine 1.7 ng/ml, aspartate aminotransferase 112 U/l, alanine aminotransferase 163 U/l, alkaline phosphatase 152 U/l, total bilirubin 0.6 mg/dl, creatinine 1.16 mg/dl, thyroid stimulating immunoglobulin 41%, and total ferritin 717 ng/mL. Chest X-ray showed the left side pleural effusion [Figure 1]. Chest computed tomography (CT) scan showed a loculated left pleural effusion with associated pleural thickening and adjacent atelectatic changes and no evidence of lymphadenopathy or parenchymal lung involvement [Figure 2]. In addition, diffuse increased hepatic attenuation, with an average of 110 Hounsfield units (HU) (normal attenuation in the liver: 30–70 HU), was noted on the lower chest CT scan images, consistent with amiodarone hepatotoxicity [Figure 3]. A diffusely heterogeneous, enlarged thyroid gland was noticed on thyroid ultrasound. Thyroid uptake scan showed a 24 h uptake of 1.1%, consistent with thyroiditis.{Figure 1}{Figure 2}{Figure 3}

Subsequently, an ultrasound-guided diagnostic thoracentesis and a bronchoscopy with bronchoalveolar lavage were performed. Pleural fluid analysis showed exudative effusion, with WBC 10,800/mm³ (82% polymorphs, 18% lymphocytes), red blood cell 300 cells/mm³, protein 2.9 g/dL, glucose 95 mg/dL, pH - 7.51, and lactate dehydrogenase 250 U/L. The pleural fluid's Gram and acid-fast stains; aerobic, anaerobic, fungal, and tubercular cultures; adenosine deaminase, and tumor cytology were negative.

After excluding other causes of the loculated effusion and given the patient's presentation, with thyroid and hepatic toxicities secondary to long-term amiodarone use, the effusion was attributed to amiodarone toxicity.

Given the patient's refractory arrhythmias, amiodarone was continued at a lower dose of 200 mg daily. The patient has also started on prednisone 30 mg daily for the management of both, amiodarone-induced thyrotoxicosis and lung toxicity. Three months after amiodarone dose reduction and prednisone tapering, the patient was asymptomatic and a follow-up chest CT scan showed significant improvement of the effusion [Figure 4].{Figure 4}

Discussion

Amiodarone is a highly effective antiarrhythmic drug. It was initially used to treat angina pectoris and was later approved for the treatment of ventricular and atrial arrhythmias. It is currently one of the most commonly prescribed drugs in the USA, especially for the management of ventricular and atrial arrhythmias. Although it is considered a Class III antiarrhythmic drug, it also has Classes I, II, and IV actions, making it a unique and effective antiarrhythmic drug. Amiodarone is well-known to have many serious toxic adverse effects, thus limiting its long-term use. They include acute and chronic pulmonary toxicity, thyroid dysfunction, hepatotoxicity, dermatologic discoloration, corneal deposits, and peripheral neuropathy.^[2]

Pulmonary toxicity is the most serious side effect of amiodarone. It can present as interstitial pneumonitis, organizing pneumonia, acute respiratory distress syndrome (ARDS), pulmonary nodules and masses, and very rarely pleural effusions.^{[3],[4],[5]} The patients usually present with cough and dyspnea and have infiltrates on chest X-ray or high-resolution CT. The incidence of pulmonary toxicity ranges from 1% to 10% and appears to depend on the accumulative amiodarone dose.^{[1],[5]} The complex mechanisms by which amiodarone causes pulmonary toxicity are not entirely understood. It is thought to be secondary to direct cytotoxic effects on type II pneumocytes and lung parenchyma or an immune-mediated hypersensitivity-based mechanism.^[6] Amiodarone pulmonary toxicity appears to correlate more with the total cumulative dose, rather than the daily dose or plasma concentration.^{[2],[3]}

Pleural diseases due to amiodarone long-term therapy are rare, and they tend to manifest in the form of pleural thickening or effusion.^[7] Back in 1987, Stein et al . were the first to report pleural effusion secondary to amiodarone treatment.^[8] Since then, nine further cases have been reported.^{[9],[10],[11],[12],[13],[14],[15]} Most of the patients developed pleural effusions after approximately 6 months of therapy. However, it was reported to occur as early as 2.5 months and as late as 6 years after amiodarone initiation. The pleural effusion can be unilateral, with a predilection to the right side, or bilateral. Fluid analysis usually shows a lymphocytic exudate, rich in proteins, and infrequent foamy macrophages. The pleural effusion is usually accompanied by parenchymal involvement; however, isolated pleural effusion has been reported.^[9] One case of loculated pleural effusion secondary to amiodarone toxicity has been reported in literature. However, the effusion was the first seen bilaterally and then progressed to a loculated effusion and was accompanied by parenchymal lung involvement.^[14] Our case was the first isolated loculated pleural effusion secondary to amiodarone toxicity without parenchymal involvement.

Once the diagnosis of amiodarone pulmonary toxicity is suspected, an effort should be made to discontinue the drug. Worsening and progression of the disease can still be noted despite stopping amiodarone. This has been attributed to the long half-life of the drug and the tendency to concentrate in tissues such as lung.^{[15],[16]}

Corticosteroids are the mainstay treatment of amiodarone pulmonary toxicity. Prednisone is usually started in doses of 40–60 mg daily and tapered over a 4–12 months period. Cases of relapse with early steroid withdrawal have been reported.^[17] Amiodarone-induced lung diseases usually have a good prognosis when diagnosed and treated early. Patients who develop ARDS or pulmonary fibrosis have worse prognosis. In our case, the pleural effusion improved, with oral corticosteroids, despite amiodarone therapy continuation as reported in previous cases.^[18] The North American Society of Pacing and Electrophysiology suggests yearly chest X-ray, biennial thyroid and liver function tests, and ophthalmologic evaluation at baseline and on any visual impairment. Pulmonary function test can be obtained if symptoms of pulmonary toxicity occur or if there is any change on the chest X-ray.^{[19],[20]}

Conclusion

Our case represents a very unusual presentation of amiodarone-induced lung toxicity and emphasizes that amiodarone should be considered in the differential diagnosis of patients with exudative pleural effusions after excluding other causes. If clinically feasible, amiodarone should be replaced with alternative antiarrhythmic therapy when pulmonary toxicity is suspected, and corticosteroids therapy may be beneficial.

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Conflicts of interest

There are no conflicts of interest.

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