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Case Report Open Access

Amiodarone-Induced Pulmonary Toxicity Mimicking Metastatic Lung Disease: Case Report

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Abstract

Amiodarone is an antiarrhythmic drug that is commonly used for the treatment of ventricular and supraventricular arrhythmias. It is an iodine-containing compound, and has a tendency to accumulate in certain organs, including in the lungs. We describe a case of amiodarone induced pulmonary toxicity with concurrent lung cancer which demonstrated good treatment response. A sixty nine-year old male smoker presented to our emergency department with a four-month history of progressive dyspnea, cough and 5 kilogram weight loss. Chest x-ray at admission showed enlarged heart shadow and prominent hilum bilaterally; CT revealed ground glass opacities in right lung and enlarged mediastinal lymph nodes. His past medical history was significant for dilated myocardiopathy and atrial fibrillation (for which he had been taking amiodarone for 5 years). Radiological findings, decrease in total lung capacity (TLC=84%), decrease in lung diffusing capacity (DLCOc=73%), and corneal epithelial opacities suggested amiodarone-induced pulmonary toxicity (APT) and/or advanced malignant disease. Amiodarone was eliminated from his medication profile due to suspicion of drug toxicity. The patient's clinical condition promptly improved, and chest x-ray performed after 7 days showed corresponding improvement. Subsequent bronchoscopy included a transbronchial biopsy which revealed lung adenocarcinoma. The patient's presumed APT was treated with methyl-prednisolone 40mg IV daily during the first two weeks, and subsequently with prednisone 20 mg/day orally for two months. One month after steroid therapy (and prior to chemotherapy) both lungs demonstrated radiographic improvement. Treatment response to chemotherapy was successful, with good performance status (ECOG1) after 10 months. This case with comorbid APT and lung cancer illustrates the importance of diligence in developing differential diagnoses for pulmonary infiltrates. Chest physicians should take care to remember that amiodarone induced pulmonary toxicity (APT) can sometimes mimic disseminated lung malignancy.

Keywords: Amiodarone; Pulmonary toxicity; Lung cancer

Introduction

Physicians should generally be mindful of drug-induced acute and chronic pulmonary toxicities. Inhaled or systemically administered drugs can cause a wide variety of difficulties, including: alteration in airway tone, cough, dyspnoea, diffuse alveolar damage, pulmonary capillaritis or interstitial lung fibrosis, and pneumonitis with unusual tumor-like findings.

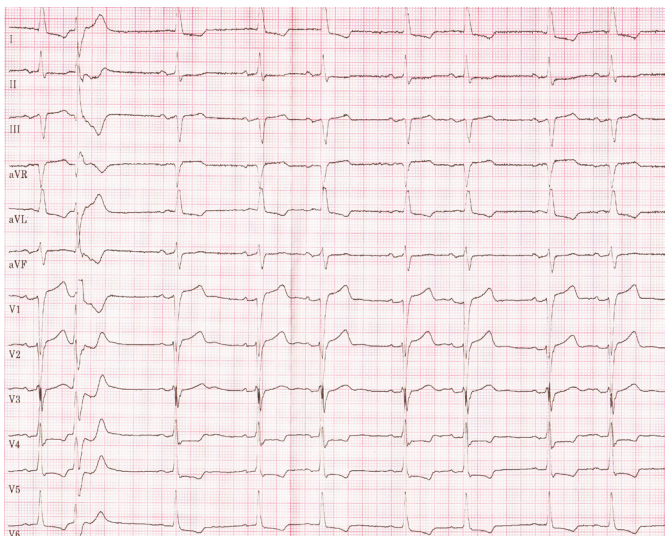

Figure 1: ECG At admission Left bundle branch block and monomorphic ventricular premature beats.

Case Report

A 69-year old male smoker presented to our emergency department with progressive dyspnea, cough and 5 kg-weight loss. His medical history was notable for ischemic dilated myocardiopathy. His medications included spironolactone (25 mg daily), ramipril (2,5 mg daily), warfarin (2,5 mg), and amiodarone (100 mg every other day for 5 years). At admission he was not in acute distress, and vital signs were as follows: respiratory rate 24 breaths/min, heart rate 120 beats/min, blood pressure 115/70 mmHg, oxygen saturation, 94% on room air. Pulmonary examination revealed abnormal breathing sound on right base and bilateral diffuse crackles (this is repetitive). Cardiac examination revealed an irregular rhythm, grade 2/6 systolic murmur heard at the apex of the heart, S3 gallop, with jugular venous distention and no peripheral edema.

ECG demonstrated left bundle branch block and monomorphic ventricular premature beats (Figure 1). Chest x-ray showed enlarged cardiac silhouette and prominent hilum bilaterally (Figure 2a). CT revealed ground glass opacities in the right lung (Figures 2b and 2c). Transthoracic echocardiography detected a dilated left ventricle

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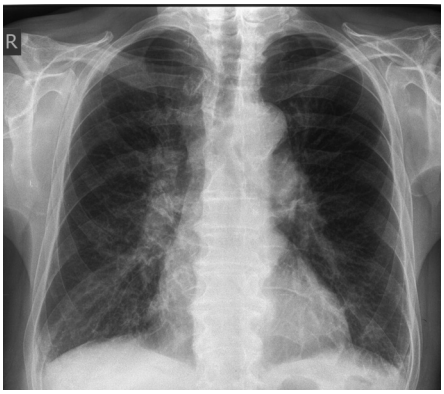

Figure 2a: Chest x-ray shows enlarged cardiac silhouette and prominent hilum bilateral.

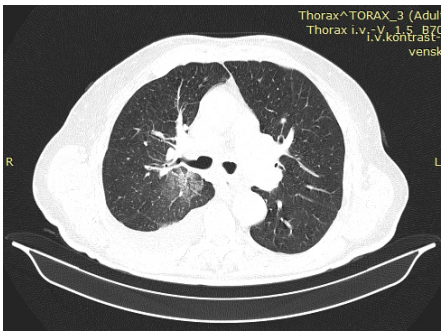

Figure 2b: Chest CT in lung window at the same time revealed ground glass opacities in posterior segment of right upper lobe and superior segment of right lower lobe.

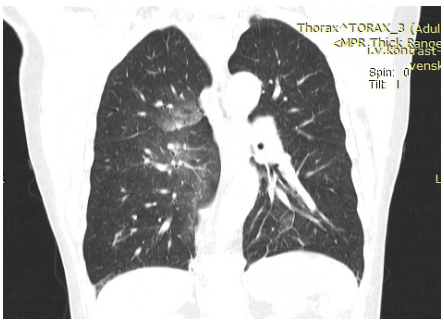

Figure 2c: Chest CT in lung window at the same time revealed ground glass opacities in posterior segment of right upper lobe and superior segment of right lower lobe.

and left atrium, and a globally-reduced ejection fraction of 30%. Laboratory studies yielded the following abnormal results: erythrocyte sedimentation rate 42 mm/h, CRP 49.5 mg/L, fibrinogen > 3 g/L. The pulmonary function tests showed normal ventilation ((FVC=95%pred, FEV1=97%pred, FEV1/FVC=78.6%) There was a decrease in total lung capacity (TLC=84%) and decrease in diffusing capacity of lung for carbon monoxide (DLCOc=73%). These findings suggested differential diagnoses including APT and advanced malignant disease.

Enhanced diuresis was ineffective. We later eliminated amiodarone from his medication regimen due to suspicion of APT. Accordingly, we also initiated methyl-prednisolone (40 mg/day) and an alternate antiarrythmic agent (sotalol 40mg bid). The APT was treated with methyl-prednisolone 21-(sodium succinate) 40mg daily i.v. during the first two weeks, followed by prednisone 20 mg orally for two months. The patient's condition promptly improved and chest x-ray performed after 7 days' treatment showed radiographic improvement (Figure 3). Ophthalmic exam revealed corneal epithelial opacities resembling a cat's whiskers. After the elimination of amiodarone, electrocardiogram registered transient atrial fibrillation and premature ventricular beats in a trigeminal pattern (Figure 4). Bronchoscopy was performed when the heart rate was regular, with histopathologic findings of transbronchial biopsy showing lung adenocarcinoma. One month after steroid therapy, and prior to chemotherapy, CT of the chest showed improvement in the interstitium with persistent mediastinal lymphadenopathy (Figure 5). The patient was subsequently treated with chemotherapy consisting of two courses of gemcitabine/carboplatin (CG) protocol and another 6 courses with vinorelbine. His treatment response was successful with chest CT performed ten months later showing improvement in the interstitium with persistent mediastinal lymphadenopathy (Figure 6), and good performance status (ECOG1).

Discussion

More than 600 medications are known to cause pulmonary toxicity.

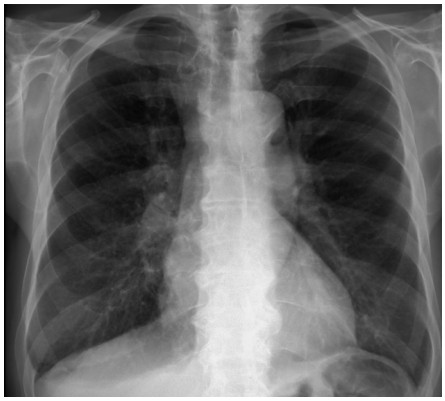

Figure 3: Chest x-ray after 7-days of methyl-prednisolone shows improvement.

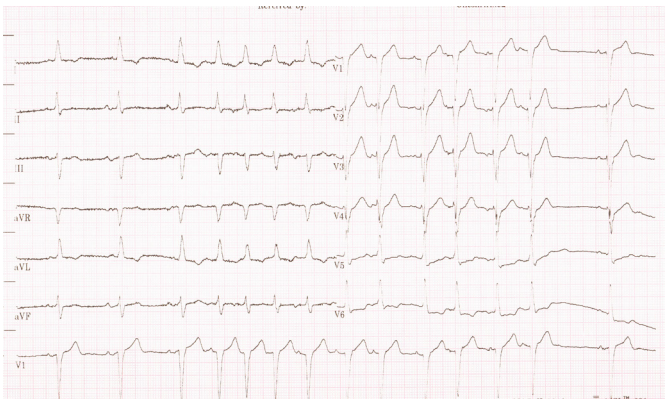

Figure 4: ECG transient atrial fibrillation and premature ventricular beats - trigemini.

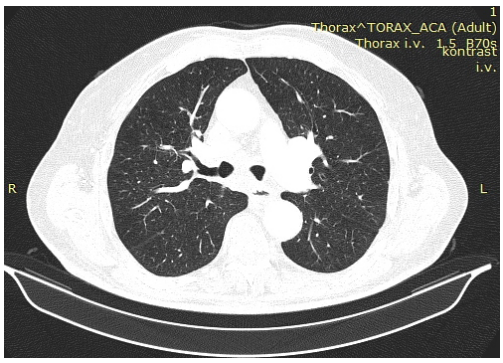

Figure 5: Chest CT in lung window one month after steroid therapy and prior to chemotherapy shows improvement in interstitium.

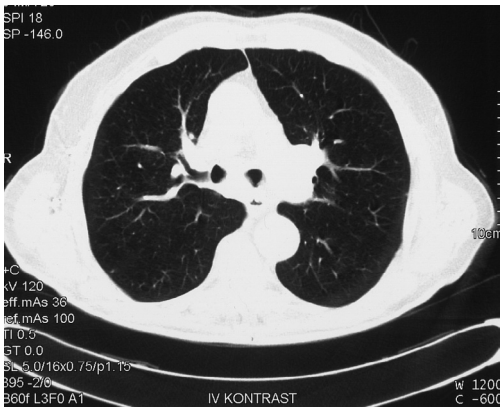

Figure 6: CT Chest scan performed 10 months after the introduction of chemotherapy shows good response.

Selected drugs that are important causes of pulmonary toxicity fall into the following classes: cytotoxic, cardiovascular, anti-inflammatory, antimicrobial, illicit, and miscellaneous. The adverse reactions can involve the pulmonary parenchyma, the pleura, the airways, the pulmonary vascular system, and the mediastinum. Amiodarone is an antiarrhythmic agent that has been used since 1967. It is commonly used for the treatment of ventricular and supraventricular arrhythmias. Amiodaron and its quantitatively-relevant metabolite, desethyl-amiodarone have tendency to accumulate in certain organs, including the lungs [1]. Acute and chronic interstitial lung diseases are the most serious manifestations. Patients receiving amiodarone often also have associated cardiopulmonary disease which may mask the toxic effect of drugs and the diagnosis is made too late, when the disease has already developed. Acute Respiratory Distress Syndrome (ARDS) can rarely develop, especially in the perioperative period, in patients on amiodarone therapy [2].

Amiodaronic pneumonitis is the most common form of lung toxicity; it occurs in 0.1-0.5% in patients taking amiodarone 200 mg/day, in 5-15% of patients taking 500 mg/day or more, and in up to 50% of patients taking 1200 mg/day or more. Risk factors for the development of APT include the following: daily doses greater than 400 mg (toxic drug reactions are more common in patients with amiodarone serum concentration higher than 2.5 mg/L), existing pulmonary disease (COPD), previous lung surgery, treatment duration longer than 2 months, age, ethnicity, exposure to high concentrations of oxygen(with or without mechanical ventilation). The two most important risk factors for the APT are age and duration of therapy. With respect to dosing, no dose is considered safe. Most cases develop changes in the lungs12 to18 months from the start of taking the medication [2].

There are two main hypotheses of the pathogenesis of APT: direct cytotoxicity and indirect immunological drug hypersensitivity reactions. Amiodarone may directly damage cells of the lung parenchyma inducing the production of toxic O_2 radicals and promoting the accumulation of phospholipids in lung tissues [3]. Typical histological finding of the lungs with APT is diffuse interstitial pneumonitis. Foamy macrophages are detected in the alveolar spaces.

Immune-mediated mechanism is based on disbalance between Th type 1 and Th type 2 lymphocyte subpopulations and production of cytokines. A hypersensitivity reaction is presented in some patients with lymphocytic infiltration of CD8T-lymphocytes and positive IgG immunofluorescence in the lung.

There are several APT clinical presentations but four clinical forms are the most common.

i. Chronical interstitial pneumonitis is the most common presentation. Sub-acute attacks begin with nonproductive cough, dyspnea, and weight loss; these generally occur after two or more months of therapy. Chest radiography demonstrates focal or diffuse interstitial thickening.

ii. Organizational pneumonia with or without bronchiolitis obliterans pneumonia (BOOP) accounts for about 25% of cases. It presents with more acute findings initially: non-productive cough, crackles and signs of pleurisy. There are irregular interstitial, alveolar or mixed infiltrates on chest X-ray. The clinical presentation mimics infectious pneumonitis.

iii. Acute respiratory distress syndrome (ARDS) is a potentially deadly form. It occurs rarely, and it is of particular interest to anesthesiologists because it is characterized by fulminant course, especially in patients who have undergone surgery or pulmonary angiography. The incidence of ARDS after lung surgery is 11% in patients treated with amiodarone as compared with the 1.8% of those not so treated. Acute lung damage develops one to four days after lung surgery. It is characterized by diffuse alveolar damage, showing signs of acute interstitial pneumonitis with hyaline membranes. Due to possible development of ARDS after surgery in patients receiving amiodarone, thoracoscopy and open lung biopsy are performed only after all other diagnostic modalities have been exhausted.

iv. A solitary or multiple pulmonary masses are typically located in upper lobes and may suggest lung neoplasm [4].

Radiology plays a central role in the diagnosis of APT. Some infiltrates bear a resemblance to a “glass of milk” and suggesting the early stage of disease, potentially reversible [5]. Chest radiographs appear speckled or diffusely infiltrated, usually bilaterally. It has been found that the right lung, especially in the right upper lobe, is more often affected than the left lung. CT often reveals disease better than chest radiography. Pleural thickening is commonly seen in the densest areas of infiltration. Pleural effusions have been described, but are less common. APT unusual radiographic finding is the appearance of one or more pulmonary nodules, or tumor shadows. They are most commonly seen in the upper lobes, often peripheral, and may about the pleura. It is assumed that these nodes for localized drug accumulation in areas of previous inflammation. Findings on chest radiograph can take up to 18 months to resolve [1,3].

Pulmonary function tests usually reveals restrictive or mixed obstructive/restrictive model. Diffusing capacity of the lung (DLCO) is usually reduced, with a 20% decline in DLCO from predicted value, or a value of less than 80% of predicted. There is also a reduction in the total lung capacity (TLC) of more than 15%. Isolated decrease in DLCO in the absence of clinical evidence of the disease is nonspecific and not diagnosed APT [6].

Fiberoptic bronchoscopy and BAL are useful in excluding other interstitial lung problems. Lavage results in findings of polymorphonuclear leukocytosis and CD8+ T suppressor cells. The presence of "foamy" macrophages is consistent with the diagnosis, but these cells can also be seen in up to one-half of patients receiving amiodarone and who have no signs of APT. In the absence of foam cells, the diagnosis of APT is unlikely [4].

Primary treatment of APT is the discontinuation of amiodarone. Due to accumulation in fatty tissues and a long half-life, pulmonary toxicity may initially progress despite not taking the drug, and can be repeated after withdrawal of steroids. Okayasi et al. [7] found that obese patients with a higher body mass index (BMI) have more frequent relapses APT with lowering doses of corticosteroids because of the accumulation of lipophilic amiodarone in fat tissue. Discontinuation of amiodarone as the only form of therapy may be sufficient in the early and limited course of the disease. Steroids should be used in patients who demonstrate significant effects on the pulmonary parenchyma registered by various imaging methods with or without concurrent hypoxemia. Systemic corticosteroids are recommended (prednisolone 40 to 60 mg daily) with gradually decreased dose for at least 4-12 months to avoid disease relapse. The evidence to show the benefit of this treatment strategy is earlier recovery and less parenchymal fibrosis [3]. Irreversible pulmonary fibrosis develops in about 30% of patients. When treatment is started early, most cases of this disease are reversible and have a good prognosis. With later detection, APT can lead to poorer outcomes, including pulmonary fibrosis and/or death, especially in cases where ARDS is developing [8].

We have illustrated a patient in whom diagnosis and evaluation of the malignancy was postponed due to prolonged use of amiodarone and the development of APT. With cessation of amiodarone and initiation of steroids, the clinical and radiological evidence of drug toxicity in the lung disappeared. This led to an improved assessment of performance status (ECOG 1), which facilitated decision making in oncological treatment. Cheng et al. [9] described a case of APT rapidly progressive organizing pneumonitis mimicking lung cancer. Mali et al. [10] focuses on the ever increasing evidence in the literature that suggests amiodarone therapy, especially with longterm use, may increase the potential risk of cancer development [10].

Conclusion

This case illustrates the importance of diligence in sifting through differential diagnoses of pulmonary infiltrates. Amiodarone induced pulmonary toxicity (APT) should be taken into consideration in patients treated with amiodarone, especially in the elderly with respiratory symptoms, poor lung function, and radiographic abnormalities. APT can mimic lung malignancy and lung cancer can mimic drug induced pulmonary infiltrates. We presented an unusual case in which both occurred simultaneously.

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