

ADVERSE EFFECT OF LOW DOSE AMIODARONE MIMICKING PULMONARY MALIGNANCY

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ABSTRACT

A 74 year-old woman had history of persistent cough for approximately one week. The chest radiography and computed tomography images disclosed features mimicking lung cancer, which included a big solitary consolidation and hilar lymphadenopathy. She received low dose amiodarone (200 mg/day) for treatment of atrial fibrillation for more than 2.5 years. The tumor-like presentations did not disappear until discontinuation of amiodarone therapy. The association of low dose amiodarone causing tumor-like findings on radiography is unique. Once amiodarone induced tumor like changes have been diagnosed, the therapeutic options are limited but in most cases reversible, if diagnosed early. The history of an unusual case with amiodarone induced pulmonary abnormality is reported and relevant literature reviewed.

Key Words: Amiodarone; Anti-arrhythmic agent; Pneumonia; Respiratory failure; Pulmonary mimicry.

INTRODUCTION

Amiodarone is an effective anti-arrhythmic agent, which has been used since 1967¹. There has been a variety of side effects observed, including corneal microdeposits, pulmonary toxicity, hypothyroidism, hyperthyroidism, hepatitis, peripheral neuropathy and bone marrow suppression^{2,3}. Among these, pulmonary toxicity is one of the most life-threatening complications attributed to this drug. The use of lower dose amiodarone (200 mg per day) has been considered safe, but even lower doses have been associated with adverse effects⁴. We describe a case of low-dose, amiodarone-related pneumonitis with unusual tumor-like presentation on chest radiography which resulted in a dramatic hospital course.

Case Report

A 74-year-old female, non-smoker, suffered from fever and productive cough for 7 days prior to admission. An upright chest radiograph showed patchy infiltrates over the right upper lung field. The

history was significant for amiodarone use with a daily dose of 200 mg for the last 2.5 years for control of atrial fibrillation (a cumulative dose of 172 gm).

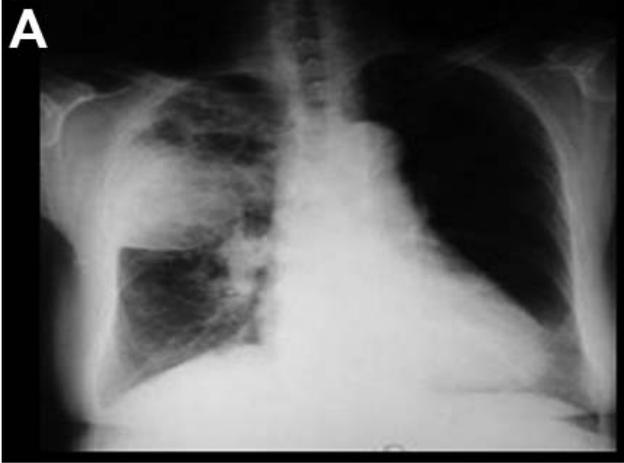
Physical examination revealed a temperature: 38°C; pulse rate: 102 beats/minute; respiratory rate: 26/minute; and the blood pressure: 140/80 mmHg. Auscultation of the heart disclosed crackles in the right upper lung and irregular heart beats with a grade 2/6 systolic ejection murmur over left lower sternal border. She was initially treated for community-acquired pneumonia at an outside hospital. Due to persistent cough and mild fever after 5 days of treatment, she was transferred to our tertiary care facility. The chest x-ray (Fig. 1A) upon admission revealed lobar consolidation of right upper lobe, lymphadenopathy over right hilum and reticulonodular infiltrates over right lower lung field. Three days after admission, she developed respiratory failure and was promptly started on mechanical ventilation. A chest computed tomographic scan (Fig. 1B) revealed a 5 × 6 cm heterogenous consolidation with inhomogenous enhancement at the right upper lung. She underwent a sonography-guided lung

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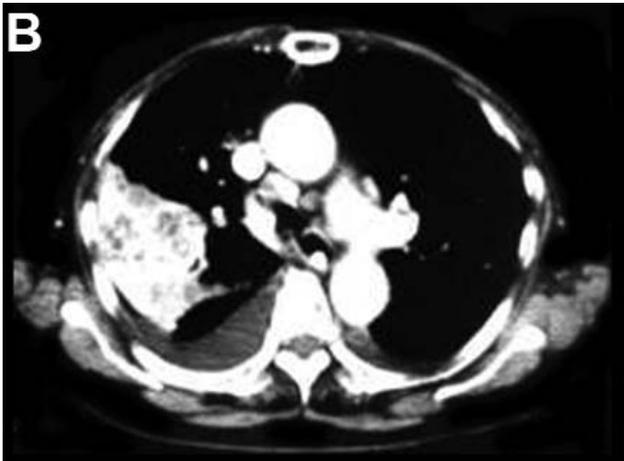
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Fig. 1A. Chest radiography on the 5th admission day showed lobar consolidation of right upper lobe, lymphadenopathy over right hilum (arrows) and reticulonodular infiltrates over right lower lung field.



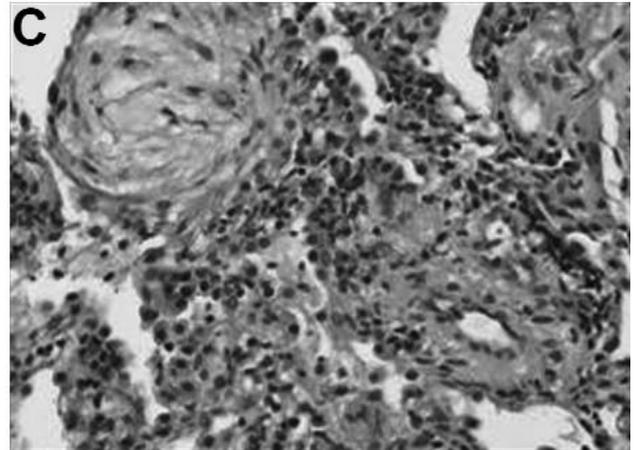
biopsy which revealed chronic inflammatory cells infiltrated within the interstitial area with multiple small loosely arranged fibrous nodules in the alveolar space (Figure 1C), consistent with organizing pneumonia.

Fig. 1B. Chest CT shows an area of heterogeneous consolidation with inhomogenous enhancement (arrow heads) over right upper lobe, right hilar lymphadenopathy (arrows) and bilateral pleural effusions (E).



A diagnosis of acute pneumonia secondary to amiodarone was made after excluding other possibilities for the observed illness. The findings of clinical, radiological, and bacteriological studies were compatible with adverse pulmonary effects of amiodarone. After discontinuation of amiodarone, her clinical condition improved. She was successfully weaned off the respirator and extubated four days after discontinuation of amiodarone and subsequently

Fig. 1C. Histology of the sonography-guided lung biopsy sample shows chronic inflammatory cells which infiltrate the interstitial area with multiple small loosely arranged fibrous nodules in the alveolar space.



discharged 2 weeks after hospitalization. The chest radiograph done on the 14th day after discontinuation of amiodarone revealed complete resolution of the pulmonary lesion (Fig. 1D).

Fig. 1D. Chest radiograph on the 14th hospital day shows completely resolution of consolidation of right upper lobe and only residual pleural-based infiltrates.



DISCUSSION

Amiodarone is an effective anti-arrhythmic agent commonly used in suppressing supraventricular and ventricular arrhythmias. Nevertheless, the drug has several potential side effects, the most life-threatening side effect being pulmonary toxicity^{1,2}. The incidence rate increases with increasing cumulative doses. Most previous studies have focused on patients taking a daily maintenance dose in excess of 400 mg. It was believed that the

pulmonary toxicity was positively correlated with a total cumulative dose of 140 to 230 g and associated with a high likelihood of clinically significant lung damage³. Our patient had taken a daily maintenance dose of 200 mg amiodarone with a total cumulative dose of 172 gm over the previous 2.5 years. The cumulative total dose was close to that of the pulmonary toxicity dose (>140 g) and was considered a probable cause of the pulmonary abnormalities. This finding indicates that daily maintenance low dose amiodarone should not be considered innocuous or free of adverse effects.⁴

The pulmonary side effects of amiodarone are listed in Table 1.^{5,6} Two mechanisms of acute interstitial pneumonitis secondary to amiodarone have been proposed. The first is a direct toxic effect in which cell injury occurs due to accumulation of cellular phospholipids secondary to inhibition of lysosomal phospholipases by the drug. The second mechanism may be due to the generation of free radicals that may induce the amiodarone toxicity⁷.

abnormalities on chest x-ray. Pulmonary function tests were within normal limits.

Pulmonary toxicity may resolve spontaneously after discontinuation of amiodarone; if warranted by clinical condition, a trial of corticosteroid therapy may be reasonable¹⁰.

In summary, we suggest that patients on amiodarone who develop pneumonia, the possibility of amiodarone-associated pneumonitis be kept in the differential diagnosis.

Table I
Pulmonary Abnormalities Associated with Amiodarone

Diffuse Alveolar Damage	Pulmonary Infiltrates
Bronchiolitis Obliterans Organizing Pneumonitis (BOOP)	Congestive Heart Failure
Hypersensitivity Pneumonitis	Bronchospasm
Interstitial Lung Disease	Pulmonary Fibrosis

The clinical manifestations of pulmonary abnormalities are protean, but the most common presentation is an indolent illness characterized by dyspnea, cough, fever, and non-responsive to antibiotic therapy. Reported amiodarone related pulmonary toxicities vary from insidious cough occurring after several months of therapy to rapidly fatal acute respiratory distress syndrome^{8,9}. The findings of rapidly progressive organizing pneumonitis mimicking a lung tumor in patients receiving amiodarone therapy is not well documented. It is possible that amiodarone toxicity is triggered by synergy of focal sepsis, which subsequently causes diffuse lung injury. It is conceivable that our patient suffered from organizing pneumonitis caused by amiodarone.

A follow-up chest x-ray after discontinuation of amiodarone showed complete clearing of pulmonary

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