Adverse effect of low-dose amiodarone mimicking pulmonary malignancy

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A 74-year-old woman presented with a one-week history of persistent cough. A chest x-ray and computed tomography images revealed features mimicking lung cancer, which included a large solitary consolidation and hilar lymphadenopathy. She had received low-dose amiodarone (200 mg/day) for treatment of atrial fibrillation for more than 2.5 years. The tumour-like abnormalities did not disappear until

the discontinuation of amiodarone therapy. The finding of low-dose amiodarone causing tumour-like abnormalities on a chest x-ray is unique. Once amiodarone-induced tumour-like changes are diagnosed, therapeutic options are limited. In most cases, the tumour-like changes are reversible, if diagnosed early. An unusual case involving amiodarone-induced pulmonary abnormalities is reported, followed by a review of the relevant literature.

Key Words: Amiodarone; Antiarrhythmic agent; Pneumonia; Pulmonary malignancy; Respiratory failure

Amiodarone is an effective antiarrhythmic agent that has been used since 1967 (1). A variety of side effects have been observed, including corneal microdeposits, pulmonary toxicity, hypothyroidism, hyperthyroidism, hepatitis, peripheral neuropathy and bone marrow suppression (2,3). Among these side effects, pulmonary toxicity is one of the most life-threatening complications attributed to this drug. The use of low-dose amiodarone (200 mg/day) has been considered to be safe, but even lower doses have been associated with adverse effects (4). We describe a case of low-dose amiodarone-related pneumonitis with unusual tumour-like findings on chest x-ray, which resulted in a dramatic hospital course.

CASE PRESENTATION

A 74-year-old female nonsmoker experienced fever and productive cough for seven days before admission. An upright chest radiograph showed patchy infiltrates over the right upper lung field. Her medical history was significant for amiodarone use, with a daily dose of 200 mg over the previous 2.5 years for control of atrial fibrillation (a cumulative dose of 172 g).

A physical examination revealed a temperature of 38°C, a pulse rate of 102 beats/min, a respiratory rate of 26 breaths/min and a blood pressure of 140/80 mmHg. Auscultation of the heart revealed crackles in the right upper lung and an irregular heart beat with a grade 2/6 systolic ejection murmur over the left lower sternal border. She was initially treated for community-acquired pneumonia at another hospital. Due to persistent cough and mild fever after five days of treatment, she was transferred to

Jiannren Hospital, Kaohsiung City, Taiwan. A chest x-ray (Figure 1A) on admission revealed right upper lobe consolidation, lymphadenopathy over the right hilum and reticulonodular infiltrates over the right lower lung field. Three days after admission, she developed respiratory failure and was promptly started on mechanical ventilation. A chest computed tomography scan (Figure 1B) revealed a 5 cm × 6 cm heterogeneous consolidation with inhomogeneous enhancement in the right upper lung. She underwent a sonography-guided lung biopsy that revealed chronic inflammatory cell infiltration within the interstitial area, with multiple small, loosely arranged fibrous nodules in the alveolar space (Figure 1C), consistent with organizing pneumonia.

A diagnosis of acute pneumonia secondary to amiodarone was made after excluding other possible causes of 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, extubated four days after discontinuation of amiodarone and subsequently discharged two weeks after hospitalization. A chest radiograph performed 14 days after discontinuation of amiodarone revealed complete resolution of the pulmonary lesion (Figure 1D).

DISCUSSION

Amiodarone is an effective antiarrhythmic agent commonly used for suppressing supraventricular and ventricular arrhythmias.

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Figure 1 **A** Chest x-ray on the fifth admission day showing right upper lobe consolidation, lymphadenopathy over the right hilum (arrows) and reticulonodular infiltrates over the right lower lung field. **B** Chest computed tomography showing an area of heterogeneous consolidation with inhomogenous enhancement over the right upper lobe, right hilar lymphadenopathy (arrow) and bilateral pleural effusions (E). **C** Histology of the sonography-guided lung biopsy sample showing chronic inflammatory cell infiltration of the interstitial area with multiple small, loosely arranged fibrous nodules in the alveolar space. **D** Chest x-ray on the 14th hospital day showing complete resolution of right upper lobe consolidation and only residual pleural-based infiltrates

However, the drug has several potential side effects, the most life-threatening of which is pulmonary toxicity (1,2). The incidence rate increases with increasing cumulative doses. Most previous studies focused on patients taking a daily maintenance dose in excess of 400 mg. It was believed that pulmonary toxicity was positively correlated with a cumulative dose of 140 g to 230 g and associated with a high likelihood of clinically significant lung damage (3). Our patient had taken a daily maintenance dose of 200 mg amiodarone – a cumulative dose of 172 g over the previous 2.5 years. The cumulative dose was close to that associated with pulmonary toxicity (more than 140 g) and was considered to be 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 the generation of free radicals that induce amiodarone toxicity (7).

The clinical manifestations of pulmonary abnormalities are protean, but the most common presentation is an indolent illness characterized by dyspnea, cough, fever and no response 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 finding of rapidly progressive organizing pneumonitis mimicking a lung tumour in patients receiving amiodarone therapy is not well documented. It is possible that amiodarone toxicity is triggered by a 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 abnormalities. Pulmonary function tests were within normal limits.

Pulmonary toxicity may resolve spontaneously after discontinuation of amiodarone; if warranted by a clinical condition, a trial of corticosteroid therapy may be appropriate (10).

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TABLE 1
Pulmonary abnormalities associated with amiodarone

Diffuse alveolar damage
Pulmonary infiltrates
Bronchiolitis obliterans organizing pneumonitis
Congestive heart failure
Hypersensitivity pneumonitis
Bronchospasm
Interstitial lung disease
Pulmonary fibrosis

Data from references 5 and 6

SUMMARY

For patients taking amiodarone who develop pneumonia, we recommend that amiodarone-associated pneumonitis be considered in the differential diagnosis.