CASE REPORT

Amiodarone-related Pneumonitis

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Amiodarone-related pneumonitis is a potentially limiting factor for amiodarone usage. However, it is believed that amiodarone-related pneumonitis is unlikely to occur during low-dose and short courses of therapy. We report three patients who received low-dose amiodarone, 200 mg/day, for an average of 6.6 months and who developed amiodarone-related pneumonitis. All patients were male with age of 75, 93 and 85, respectively, and had the habit of cigarette smoking. The initial presentation was dyspnea without symptoms and signs of heart failure. Their chest radiographs showed diffuse interstitial pneumonitis pattern and chest computed tomography scan also confirmed interstitial pneumonitis. Treatment included cessation of amiodarone and corticosteroid usage. All patients improved symptomatically by early detection and early treatment. This case report implies that old age and possible pre-existing pulmonary abnormalities caused by smoking could be associated with amiodarone-related pulmonary toxicity. Clinicians must remain alert to detect amiodarone-related pneumonitis even under low dosage and short duration of amiodarone usage. Immediate withdrawal of amiodarone and prompt steroid therapy will ensure full recovery. [*J Formos Med Assoc* 2007;106(5):411–417]

Key Words: amiodarone, pneumonitis, antiarrhythmics, drug toxicity, amiodarone-induced pulmonary toxicity

Amiodarone is a benzofuran derivative with antiarrhythmic and vasodilatory properties which has been used since 1967 as an antiarrhythmic agent. However, a variety of cardiac and extracardiac side effects have been attributed to this drug such as corneal microdeposit, hypothyroidism, hyperthyroidism, pulmonary toxicity, symptomatic bradycardia, gastrointestinal disturbances, hepatic disease, bone marrow depression, peripheral neuropathy and dermatitis.[1] Among these, amiodarone-related pulmonary toxicity is the most serious of the extracardiac side effects. Amiodarone toxicity was first reported in 1980.[2] The reported outcome in patients who have amiodarone pneumonitis has ranged from total resolution to death. However, low-dose (200 mg/day) amiodarone is considered to be free of serious side effects.[3] We report a series of three patients with pulmonary pneumonitis during low-dose amiodarone therapy to emphasize that even low-dose amiodarone could lead to pulmonary effects. This result could remind us of detecting amiodarone pneumonitis in the early stage even under low dosage usage.

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The clinical records of three patients who received low-dose amiodarone with pulmonary pneumonitis are presented.

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Received: May 9, 2006
Revised: June 23, 2006
Accepted: September 5, 2006

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Case 1

A 75-year-old man was admitted to the hospital in June 2005 because of non-productive cough and increasing dyspnea for 1 week. He was an ex-smoker and was diagnosed with non-ST elevation myocardial infarction, inferior wall, Killip I status post percutaneous transluminal coronary angioplasty to left circumflex coronary artery in 1998. For the past 9 months, he had been diagnosed with paroxysmal atrial fibrillation and amiodarone had been prescribed for rhythm control, initially at a loading dose of 900 mg, which was then reduced to 200 mg daily. On physical examination, bilateral basal rales were auscultated. The results of routine laboratory tests and autoimmune profiles (antinuclear antibody, 1:40-; C3, 100.0 mg/dL; C4, 28.0 mg/dL) were within normal limits. The chest radiograph (Figure 1A) revealed fibrotic change

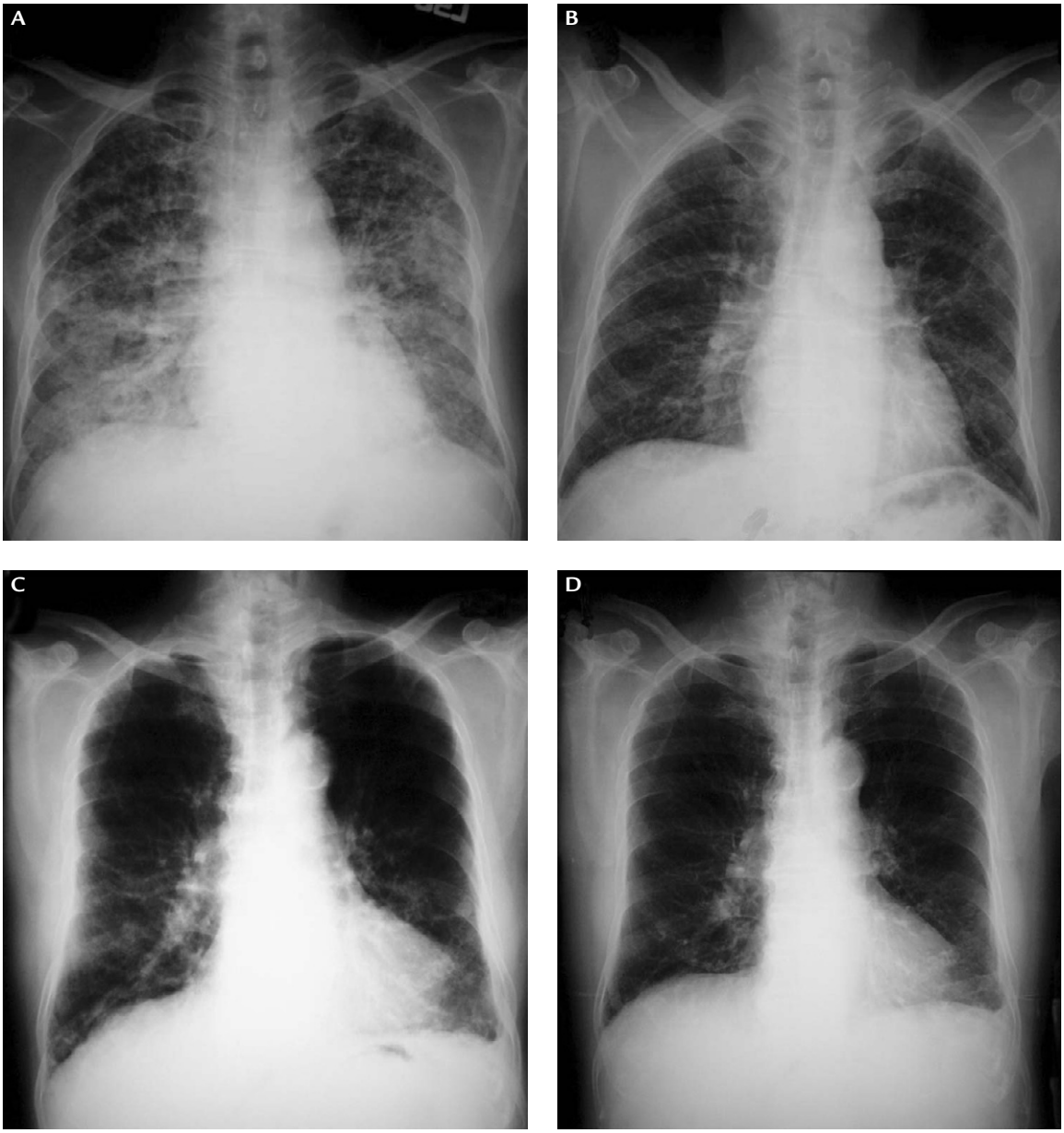

Figure 1. (A) Chest radiograph of patient 1 obtained on admission shows hyperinflation with chronic infiltration over bilateral lungs and increasing bilateral lung marking. (B) Chest radiograph of patient 1 obtained 10 days after admission shows improving infiltration in bilateral lower lung fields. (C) Chest radiograph of patient 3 obtained on admission shows diffuse and irregular increased lung markings in both lower lungs. (D) Chest radiograph of patient 3 obtained 9 months after admission shows linear interstitial infiltrations of left lower lung field improving.

of bilateral lung parenchyma superimposed increasing density, especially at bilateral peripheral regions. Chest computed tomography (CT) (Figure 2A) showed multiple ground-glass opacities in both lungs. Transthoracic echocardiogram showed good left ventricular (LV) contractility with a LV ejection fraction of 79%. Pulmonary function test showed restrictive ventilatory defect and impairment of diffusion capacity (Table 1). Infection workup was performed and neither bacterial nor atypical pathogens were isolated. After discontinuation of amiodarone and treatment with systemic steroid (intravenous methylprednisolone [Solu-medrol, 40 mg/vial] 160 mg/day initially for 3 days, then reduced to 40 mg daily for 1 week, steroid was gradually tapered to oral prednisolone 20 mg/day for 1 month), there was rapid improvement in breathlessness with return to normal exercise tolerance within 2 months. Serial chest radiographs (Figure 1B) showed clearing of pulmonary infiltration with complete resolution.

Case 2

A 93-year-old man was admitted to hospital in August 2001 because of dyspnea and nonproductive cough. The symptoms had progressed for 1 week. He was also an ex-smoker and had a history of ventricular tachycardia episodes. Amiodarone had been prescribed since April 2001 (200 mg/day). On examination, wheezing was heard over bilateral lower lung fields. Leukocytosis (white blood cell count, 15,280/μL; segments, 84%; eosinophils, 0%; lymphocytes, 4%) and elevation of C-reactive protein (24.6 mg/dL) were noted. The results of biochemical tests were normal. Chest radiography showed increased diffuse reticular infiltration in bilateral basal lungs. The high resolution CT of the chest without contrast enhancement showed pulmonary emphysema and

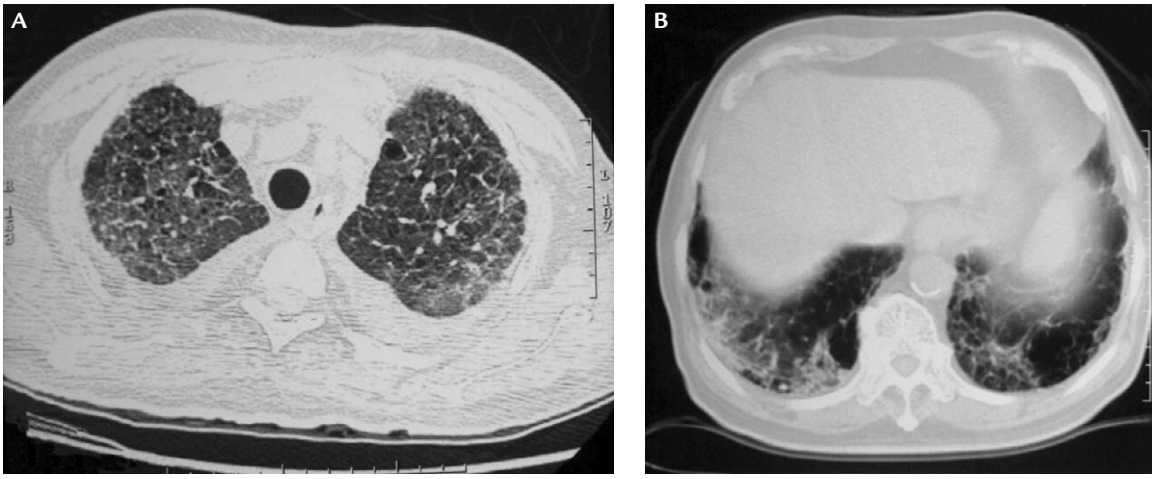

Figure 2. (A) Chest computed tomography (CT) of patient 1 (with contrast medium, lung window) obtained on admission shows multiple interstitial infiltrations. (B) Chest CT of patient 3 (without contrast medium, lung window) obtained on admission shows fibrotic patches with honeycomb appearance in both lungs.

Table 1. Patient 1 pulmonary function test

	Observed	Predicted	% Predicted
% FEV1.0	74.9	76.1	98.4
TLC (L)	3.42	4.42	77.4
RV (L)	1.20	1.70	70.6
DLCO (mL/min/mmHg)	11.02	16.78	65.7

% FEV1.0 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; DLCO = diffusing capacity of the lung for carbon monoxide.

prominent interstitial pattern of lung parenchyma with predominate reticulation and thickening of interlobular septa. The interstitial process was most evident at both lower lobes. The picture was consistent with interstitial pneumonitis. The density of the liver parenchyma (about 60–70 dihydrouridine [HU]) increased compared with normal soft tissue density (about 25–40 HU). Transthoracic echocardiography showed good LV ejection fraction. Initially, the patient accepted empirical antibiotic (ampicillin sodium/sulbactam) treatment for suspected pneumonia, but he showed no clinical improvement. Due to the history of amiodarone use, the possibility of amiodarone-related interstitial pneumonitis was highly suspected. The patient had both oxygenation and pulmonary compliance improvement after cessation of amiodarone and steroid usage (intravenous methylprednisolone [Solu-medrol, 40 mg/vial] 120 mg/day initially for 10 days, which was then reduced to 40 mg daily for 3 weeks).

Case 3

An 85-year-old man was an ex-smoker and diagnosed with paroxysmal atrial fibrillation in December 1999. Amiodarone 200 mg/day had been prescribed for 6 months. He suffered from exertional dyspnea and cough without sputum in May 2000. On examination, breath sounds were clear over bilateral lung fields. The results of routine laboratory examinations were within normal limits. The chest radiograph (Figure 1C) showed linear interstitial infiltrations of bilateral lower lung fields and chest CT (Figure 2B) showed fibrotic change in both lungs and confluent fibrosis was especially noted in both lower lungs. Transthoracic echocardiogram showed fair LV contractility (LV ejection fraction, 56%). Under the impression of amiodarone-related pneumonitis, amiodarone was stopped after admission and oral steroid was given (prednisolone, 30 mg/day for 1 week). Infection workup finally showed no positive results. The symptoms then improved and oral steroid (prednisolone 10 mg/day) was used for 2 months. Follow-up chest radiograph (Figure 1D) showed clearing of pulmonary infiltration.

Discussion

Amiodarone had been increasingly used in the treatment of supraventricular, ventricular arrhythmias and nonischemic cardiomyopathy. However, there have been many reports of side effects occurring during treatment. It has been difficult to predict which patients are at risk for the development of amiodarone-related toxicity. Amiodarone-related pulmonary toxicity affects 6% of patients at a daily dose of 400 mg or more over 2 or more months, with a mortality rate of 10–20%,[4] and therefore low-dose therapy has been deemed a safe alternative.[5] We performed a retrospective electronic chart search of our chart records by using the key words amiodarone pulmonary pneumonitis between 1996 and 2005. Approximately 73,530 medical records were searched by this method. We reviewed the charts of the patients who received amiodarone to evaluate the diagnosis of amiodarone pneumonitis. Only three patients associated with amiodarone pneumonitis were identified during these 10 years. Most different from the previous studies of amiodarone-related pneumonitis in Caucasians (Table 2)[6–12] is that our patients were all receiving low-dose amiodarone (200 mg/day), for an average of 6.6 months prior to developing pneumonitis (cumulative dose range, 30–54 g). That might indicate that Asian people have high possibility of amiodarone-related pulmonary toxicity compared to Caucasians, even under low-dose amiodarone treatment. The mechanisms underlying the myriad toxic effects of amiodarone on the lungs are complex and may involve both direct toxic effects of free radicals on cells and indirectly by inflammatory mechanisms. Besides, there were no other medications known to be associated with pulmonary toxicity in our patients and all had the habit of cigarette smoking and the average age of our patients was 84.3 years (range, 75–93). Other factors in addition to dose might also contribute to the pulmonary toxicity in these patients with amiodarone pneumonitis. Old age and possible pre-existing pulmonary disorders caused by cigarette smoking might be recognized as predisposing factors

Table 2. Amiodarone-related pneumonitis

Reference	Amiodarone dose (mg/d)	Total dose (g)	Time to recovery (mo)
5	600–1400	14.6–142.2	1.5–4
6	400–600	*	2
7	400–800	*	*
8	400–800	*	3.5
9	400–800	20.8–369	*
10	600–1400	144–225	3
11	300–900	*	*

Table 3. Patients' clinical data

	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Age (yr)	75	93	85
Arrhythmia	AF	VF	AF
Dose (mg/d)	200	200	200
Duration (mo)	9	5	6
Cumulative dose (g)	54	30	36
Symptoms	Dyspnea, non-productive cough	Dyspnea, non-productive cough	Dyspnea, non-productive cough
Smoking	1 ppd > 10 yr quit for 20 yr	1/2 ppd > 10 yr quit for 30 yr	< 1 ppd > 10 yr quit for 50 yr
Lung function	Restrictive pattern	Nil	Nil
UCG (LVEF)	79%	70%	56%
Steroid	Yes	Yes	Yes
Outcome	Improved	Improved	Improved

AF = atrial fibrillation; VF = ventricular fibrillation; ppd = pack per day; LVEF = left ventricular ejection fraction.

too. This observation suggested a possible relationship between low-dose amiodarone in Asian people, old patients and cigarette smoking. But further data should be collected to prove this point of view.

Amiodarone-related pneumonitis is diagnosed by the following criteria: (1) initial presentation as worsening dyspnea; (2) chest radiograph with diffuse interstitial or alveolar infiltrates; (3) pulmonary function with decline > 15% in the diffusing capacity of the lung for carbon monoxide or total lung capacity; (4) ruling out congestive heart failure; (5) bronchoalveolar lavage fluid with "foamy" cytoplasm in alveolar macrophages known as phospholipidosis and CD8+ lymphocytosis; (6) pathologic findings with pulmonary interstitium inflammation, fibrosis, pneumocyte hyperplasia, and hyaline membranes; and (7) drug withdrawal with or without steroid therapy reverses some or all of the abnormalities.[13] Our patients were diagnosed with amiodarone-related pneumonitis by clinical symptoms, examinations, radiographs, laboratory investigations, echocardiograms and treatment courses. The patients' data are summarized in Table 3. Dsypnea, particularly with exertion, has been the most commonly reported symptom of amiodarone pneumonitis and was the presenting complaint in our patients. All the patients' radiographic abnormalities disclosed the characteristic findings of nonspecific and diffuse interstitial infiltration.[14] In patient 2, the Hounsfield unit of the liver (60–70 HU) was higher than soft tissue density (25–40 HU) and that might be due to deposition of amiodarone

in the liver parenchyma. In the same way, amiodarone could deposit in the lung parenchyma as well at the same time. That might induce pulmonary toxicity of amiodarone and this radiographic finding could be used in the diagnosis of amiodarone-related pneumonitis. Pulmonary function test with decreasing diffusing capacity of the lung for carbon monoxide > 15% and decreasing total lung capacity were noted in patient 1. Congestive heart failure has a high prevalence rate among these patients with amiodarone-related pulmonary toxicity and the radiographic appearance of pulmonary edema may be mimicked by amiodarone toxicity. Therefore, if heart failure cannot be easily excluded, the pulmonary capillary wedge pressure should be measured. Serum assay of brain natriuretic peptide could also be used as a sensitive test to detect LV dysfunction. A diagnosis of amiodarone-induced pulmonary pneumonitis could be suspected if there is no elevation in the brain natriuretic peptide level in comparison with the patient's baseline values associated with clinical deterioration.[15] None of our patients were in congestive heart failure by clinical examinations (absence of jugular venous distension or S3). No patient underwent bronchoscopy and biopsy due to the family's decision. Amiodarone pulmonary toxicity may mimic infection or accompany infection and in such cases, a careful search must be undertaken for an offending organism. In patient 2, pneumonia might be accompanied by amiodarone pneumonitis, the clinical improvement of patient 2 could be attributed to the effects of steroid and discontinuation of amiodarone use during the course of treatment. Since the elimination rate of amiodarone and its metabolite diethyl amiodarone is extremely slow, which will efflux within 6–12 months,[16] thus, prompt reversal of pulmonary side-effects cannot be expected after withdrawal of the drug. Furthermore, steroid therapy must necessarily be continued for many weeks or months while the drug remains in the blood and tissues. Effective treatment of amiodarone associated pneumonitis must include prompt withdrawal of amiodarone and institution of steroid therapy.[17]

Amiodarone pulmonary abnormalities could develop in patients even under low-dose therapy. Drug-induced injury should be considered in all patients taking amiodarone who develop respiratory symptoms. Besides, amiodarone pneumonitis may be lethal if unrecognized and untreated. It is vital therefore to recognize it at an early stage and necessary to perform chest radiography every 1 to 2 months for the 1st year after the initiation of amiodarone therapy. This could help detect the earliest pulmonary changes and take appropriate steps such as steroid treatment to prevent further deterioration of pulmonary function. We have shown that amiodarone 200 mg/day for around half a year could lead to interstitial pneumonitis and this serves as a reminder of the clinical uncertainties of low-dose amiodarone usage. Besides, compared with the previous studies of amiodarone-related pneumonitis (Table 2),[6–12] improvements both clinically and in chest radiographs usually occurred several months after cessation of amiodarone and under steroid treatment. The rapid improvement in our patients might imply that low-dose amiodarone-related pneumonitis could be reversed by early detection and early treatment compared with high-dose amiodarone-related pneumonitis. Our report reminds clinicians to recognize that low-dose amiodarone (200 mg) is associated with some risk of developing pulmonary toxicity even under short-term use (6 months). Early diagnosis and treatment are mandatory to reverse this potentially fatal adverse reaction.

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