Amiodarone Pneumonitis

Jeffrey I Stewart MD, Rashmi Chawla MD, Joshua M Lloyd MD, and Gregory C Kane MD

Introduction

Amiodarone is an iodinated benzofuran derivative that is widely used for the treatment of cardiac arrhythmia. The drug has an extensive adverse effect profile that involves the liver, thyroid, cornea, skin, lung, bone marrow, and neuromuscular system. Pulmonary toxicity is the most serious adverse reaction, and it often limits the drug's clinical use.[1,2]

We encountered a patient with suspected amiodarone pneumonitis who presented with several weeks of a nonproductive cough, shortness of breath, chest pain, weight loss, and fevers, along with radiographic findings of bilateral opacities. Though the patient's presentation was consistent with hospital-acquired or community-acquired pneumonia, the patient failed to respond to several courses of anti-infective therapy. Bronchoscopy with transbronchial biopsies and bronchoalveolar lavage (BAL) confirmed the diagnosis of a drug-induced interstitial pneumonitis, and ruled out an infectious etiology. The biopsy findings were consistent with amiodarone pneumonitis. Given the widespread use of amiodarone as an anti-arrhythmia agent, amiodarone pneumonitis must be considered by respiratory therapists, cardiologists, and general practitioners, in patients treated with amiodarone who have a persistent pneumonia-like illness.

Case Report

A 57-year-old white male, who had initially presented with signs of dehydration, had been treated for recurrent pneumonia during a prolonged hospital stay. The patient initially presented to an outside hospital with signs of dehydration. The patient's hospitalization was complicated by pneumonia, line sepsis with Gram-positive cocci, worsening renal failure that necessitated hemodialysis, and anemia that required multiple transfusions. The patient was transferred to our hospital for further management. At our hospital the patient also developed line sepsis, this time with *Escherichia coli*, and continued to be treated for recurrent pneumonia with 7-day courses of both piperacillin/tazobactam and moxifloxacin. The pulmonary service was consulted because of persistent fever and ongoing pulmonary infiltrates. The patient complained of several weeks of night sweats, intermittent shortness of breath, and a nonproductive cough. He also described a dull, intermittent chest pain and a 70-pound weight loss over the past year.

The patient was transplanted for end-stage liver disease secondary to hepatitis C 16 years prior. He also had a history of alpha-1 antitrypsin deficiency, type II diabetes, coronary artery disease, congestive heart failure, end-stage renal disease, gastroesophageal reflux disease, depression, atrial fibrillation, and chronic anemia. The patient's immunosuppressant regimen for his liver transplant had been 4 mg sirolimus daily for a number of years. The patient was also on aspirin, carvedilol, esomeprazole, ezetimibe, olanzapine, sertraline, tiotropium inhaled, levalbuterol inhaled, and warfarin. The patient had an automated implantable cardioverter-defibrillator. Two months prior the patient was placed on amiodarone 200 mg daily, after an initial load (150 mg intravenous over 10 min, 1 mg/min for 6 h, then 0.5 mg/min for 18 h, followed by 400 mg twice a day for 3 d) for atrial fibrillation. The patient had a history of a reactive purified protein derivative skin test a number of years ago, for which he was treated with 9 months of isoniazid. The patient denied any alcohol or drug abuse. Hepatitis C was contracted from an occupational exposure as a nurse. The patient had a 30 pack-year history of smoking, but quit 1 year prior to presentation. The patient was on disability, but previously worked as a steel worker, a car mechanic, and a nurse. As a car mechanic, the patient recalled working with asbestos brakes. The patient denied any recent travel.

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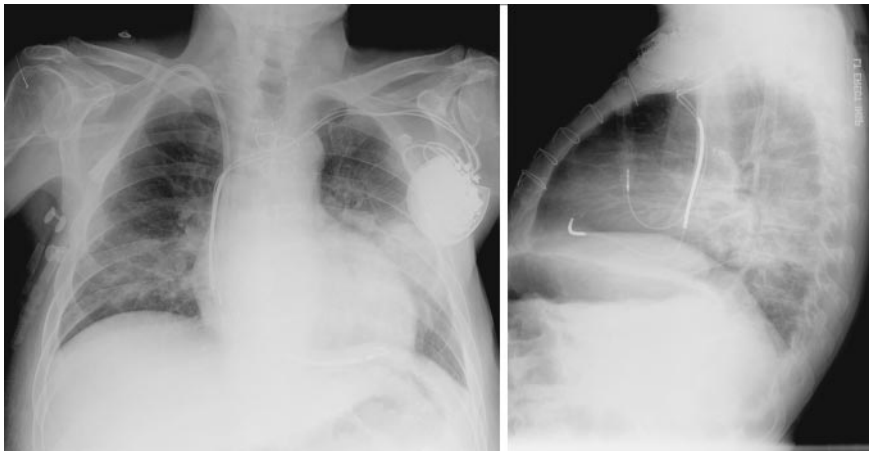

Fig. 1. Anterior-posterior (left) and lateral (right) chest radiographs showing bilateral parenchymal infiltrates.

On examination the patient was afebrile (maximum temperature in 24 h 37.4°C), blood pressure of 132/73 mm Hg, pulse of 69 beats/min, respiratory rate of 14 breaths/min, and blood oxygen saturation of 98% while on oxygen (2 L/min via nasal cannula). During the previous 4 days the patient spiked daily temperatures up to 39.1°C. The patient was in no apparent distress. On chest examination he had bilateral crackles, greater on the left, with no wheezes or rhonchi. The heart examination was notable for a II/VI systolic ejection murmur, loudest at the apex. There was no clubbing, cyanosis, or edema.

Laboratory findings included: leukocyte count 3,200 cells/mL, with a normal differential, hemoglobin 9.2 g/dL, hematocrit 30.4%, platelets 96,000/mL, blood urea nitrogen 25 mg/dL, creatinine 2.5 mg/dL, and alkaline phosphatase 240 IU/L. All other laboratory tests were within normal limits. We were unable to obtain adequate sputum samples for culture. The patient had 1 set of blood cultures positive for *E. coli*, which correlated with the patient's presumed line sepsis. All other blood cultures during the patient's admission were negative.

A chest radiograph taken one day prior to our consultation showed bilateral parenchymal infiltrates that were slightly increased, compared to previous radiographs from this admission (Fig. 1). Computed tomogram (CT) showed bibasilar dependent opacities, left greater than right, as well as some ground-glass opacities (Fig. 2). These findings were favored as being consistent with an infectious etiology. The patient had an echocardiogram that demonstrated an ejection fraction of 35%, moderate mitral regurgitation, and an estimated pulmonary artery pressure of 35 mm Hg, assuming a right atrial pressure of 10 mm Hg.

Our differential diagnosis was broad and included infectious and noninfectious etiologies. Infectious etiologies included hospital-acquired pneumonia with a resistant organism or fungal disease, given the patient's immunosuppressant regimen. Noninfectious etiologies on our differential included interstitial lung disease, post-transplant lymphoproliferative disease, drug-induced interstitial lung disease, cryptogenic organizing pneumonia, and vasculitis. Possible drugs that could have contributed to the patient's lung disease included amiodarone and sirolimus.

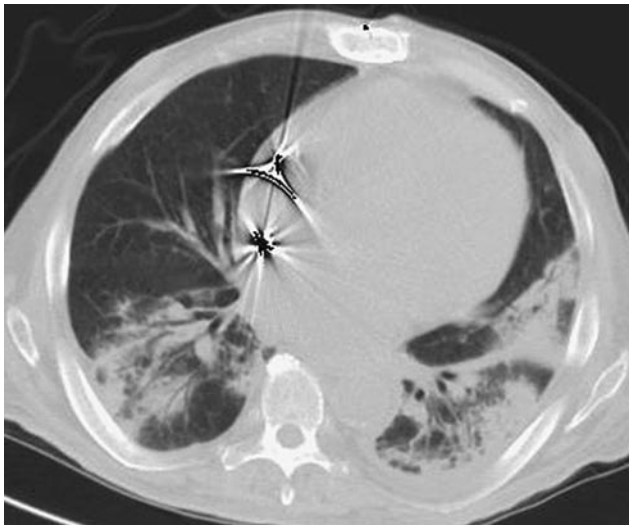

Fig. 2. Computed tomogram showing bibasilar dependent opacities, left greater than right, as well as some ground-glass opacities.

Further laboratory results included an erythrocyte sedimentation rate of 110 mm/h (normal range 0–20 mm/h). Rheumatoid factor, anti-Jo-1 antibody, immunoglobin A, antinuclear antibody, anti-single-stranded deoxyribonucleic acid (DNA), anti-double-stranded DNA, C anti-neutrophil cytoplasmic antibody (ANCA), P-ANCA, and X-ANCA were all negative. Human immunodeficiency virus antibodies were nonreactive.

The diagnostic procedure was a bronchoscopy with transbronchial biopsies and BAL in the superior segment of the lingula.

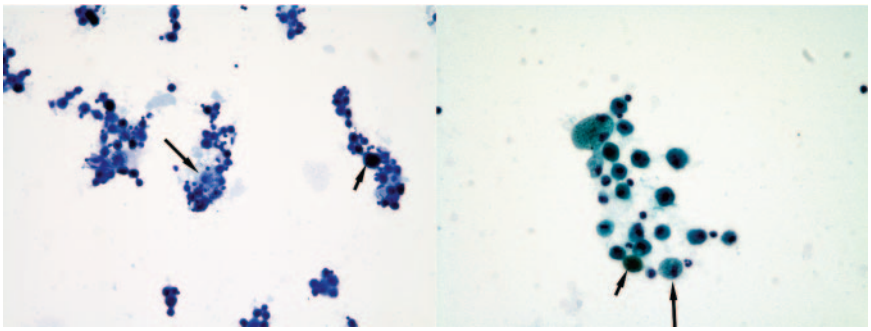

Fig. 3. Cytologic preparations from lung washings obtained via bronchoalveolar lavage show numerous foamy (long arrows) and hemosiderin-laden (short arrows) macrophages. Low and high power views: Diff-Quick stain (left) and Papanicolaou stain (right).

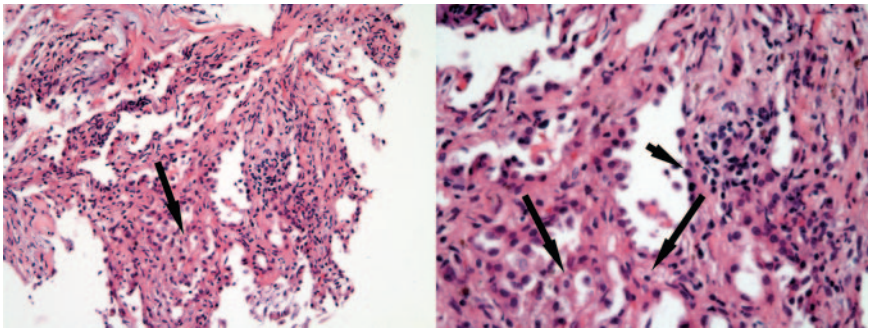

Fig. 4. Transbronchial, left-lung biopsy shows chronic interstitial pneumonitis. Lipid-laden macrophages fill air spaces and are also present within the interstitium (long arrows). Hyperplastic type II pneumocytes show cytoplasmic vacuolization (short arrow). These findings are consistent with amiodarone pneumonitis. Low and high magnification, hematoxylin and eosin.

Diagnosis

Bronchoscopy showed normal airways and no endobronchial lesions. Cytologic examination of the fluid was negative for malignant cells or pathogenic microorganisms, but did show numerous foamy and hemosiderin-laden macrophages (Fig. 3). Unfortunately, no cell counts were obtained from the BAL fluid. All cultures were negative. Biopsy revealed a chronic interstitial inflammatory infiltrate with intra-alveolar foamy macrophages and vacuolated type II pneumocytes (Fig. 4).

The findings were consistent with amiodarone toxicity. Amiodarone was discontinued, and the patient was started on oral prednisone 50 mg daily for 7 days, which was to be tapered as an outpatient. Piperacillin/tazobactam was discontinued. The patient's symptoms improved within 2 days of discontinuing amiodarone and beginning prednisone. Within 4–5 days the patient was symptom-free and was discharged from the hospital. On the day of discharge the patient's blood oxygen saturation was 96–98% on room air. Cough, fever, and dyspnea resolved on follow-up. A follow-up CT 4 weeks after discharge showed residual patchy parenchymal changes in the lingular division of the left lung and the anterior aspect of the superior segment of the left lower lobe (Fig. 5), consistent with resolving pulmonary disease.

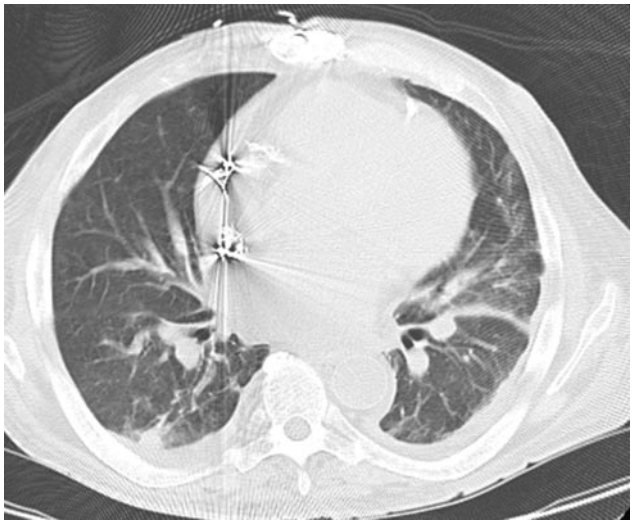

Fig. 5. Computed tomogram, taken 4 weeks after discharge, consistent with resolving pulmonary disease.

Discussion

We describe a patient with a history of atrial fibrillation who had developed cough, fever, and shortness of breath while being treated with amiodarone. Several factors al-

lowed us to narrow our differential diagnosis and suggested drug-induced pneumonitis. Our patient had persistent pulmonary symptoms and bilateral infiltrates that did not respond to antibiotics. The white-blood-cell count was normal. Serologies were negative.

On bronchoscopy with BAL we noted the presence of foamy and hemosiderin-laden macrophages. Transbronchial biopsy demonstrated the presence of foamy macrophages within air spaces and vacuolization of type II pneumocytes consistent with amiodarone pneumonitis. Once amiodarone was discontinued the patient's pulmonary symptoms resolved completely. A follow-up CT showed resolving pulmonary disease. This confirmed the diagnosis of amiodarone pneumonitis.

Amiodarone pneumonitis was first described in the early 1980s as the drug was becoming popular in the United States for the treatment of ventricular dysrhythmia. There are numerous adverse effects associated with the drug, including corneal deposits, hyperthyroidism, hypothyroidism, abnormal liver function tests, bluish discoloration of the skin, and peripheral neuropathies.[2] The most serious adverse effect of amiodarone is pulmonary toxicity, and this is one of the leading reasons for stopping the drug.[1] The reported incidence of amiodarone-induced pulmonary toxicity is 5–15% in those who take greater than 400 mg of amiodarone daily, and 1.6% in those who take up to 400 mg daily.[3]

Our patient developed amiodarone pneumonitis despite only receiving 200 mg amiodarone for 2 months, which puts him in the low-risk category. We speculate that this might be secondary to liver dysfunction, since amiodarone is extensively metabolized in the liver and excreted in the biliary system. Though the patient developed acute-on-chronic renal failure during this hospitalization, this was unlikely to contribute to the patient's amiodarone toxicity, since the renal excretion of amiodarone is negligible.

Amiodarone-induced lung toxicity is believed to be due to a combination of direct and indirect mechanisms. The indirect mechanism is immunologic and is characterized by entry of inflammatory or immune mediator cells into the lung. The direct mechanism is toxic and results in cell injury. Both amiodarone and its primary metabolite, desethylamiodarone, are classified pharmacologically as cationic amphiphilics.[4] These substances localize in cell lysosomes and block turnover of endogenous phospholipids, therefore causing an accumulation of phospholipids. This explains the findings of foamy lipid-laden macrophages that contain lamellar membranous inclusions ultrastructurally, on cytologic and histologic examination of specimens obtained from patients exposed to amiodarone. The accumulation of phospholipids occurs in the lungs as well as in the thyroid, eye, liver, and skin, which corresponds to the adverse-effect profile of the drug.[1,2]

Amiodarone pneumonitis can develop any time over the course of treatment with the drug, although most cases develop during the first 12 months of therapy. The risk of pulmonary toxicity increases with age, daily dosage, and low pretreatment diffusing capacity of the lung for carbon monoxide (D_{LCO}) on pulmonary function tests (PFTs).[5] There are 2 different patterns of presentation of amiodarone pneumonitis. An insidious onset occurs in roughly two thirds of cases, and an acute onset in the remaining cases. The insidious onset rarely begins before 2 months of therapy, and is uncommon in those treated with less than 400 mg of amiodarone daily. The acute presentation is more likely to mimic pneumonia, and in severe cases can result in acute respiratory distress syndrome.[6] There is a higher incidence of acute amiodarone pulmonary toxicity that presents as acute respiratory distress syndrome following cardiac or pulmonary surgery, and in the intensive care unit. This has been reported in patients who have been on long-term low-dose or short-term high-dose amiodarone therapy. Although the mechanism of injury is unclear, one prominent theory is that these patients are exposed to a high oxygen concentration during mechanical ventilation, which synergizes with amiodarone-induced free radicals to increase lung damage.[6-8]

Presenting symptoms of amiodarone-induced pulmonary toxicity are nonspecific. The most common symptoms include progressive dyspnea, cough, and fever. Less common symptoms include nausea, weakness and fatigue, weight loss, and pleuritic chest pain.[5] Laboratory findings are also nonspecific and include an increased erythrocyte sedimentation rate, leukocytosis, and increased leukocyte dehydrogenase. Radiographic findings include alveolar, interstitial, or mixed alveolar-interstitial shadows. Ground-glass opacities, areas of consolidation, and thin intralobular reticulations are seen on high-resolution CT. A subpleural distribution of the opacities is more common than a central distribution.[9] Though gallium[67] scintography has been shown to be a sensitive marker for the presence of amiodarone pneumonitis, it is rarely used because of its high cost, prolonged test interval, high radiation dose, and difficulty in interpretation.[2]

On bronchoscopy with BAL there may be an increase in CD8+ lymphocytes in individuals with amiodarone pneumonitis. In these patients the cell count, obtained via flow cytometric analysis, can be normal or can reveal an increase in lymphocytes, neutrophils, or both.[10] The microscopic findings of foam cells with lamellar inclusions ultrastructurally are present in almost all patients exposed to amiodarone and do not indicate drug toxicity. On the other hand, the diagnosis of amiodarone pulmonary toxicity is unlikely when foam cells are absent.[1,4,11] Hemosiderin-laden macrophages have been described in some patients with amiodarone pneumonitis, although they may be secondary to chronic pulmonary congestion from concomi-

tant heart failure, and not a feature of amiodarone pneumonitis.[12] The histopathologic appearance of amiodarone-induced lung toxicity, which was demonstrated in the present case, includes chronic interstitial pneumonitis with interstitial fibrosis, as well as the presence of lipid-laden macrophages within air spaces. Interstitial lipid-laden macrophages and vacuolated type II pneumocytes can also be identified. Other pathologic findings in patients can include acute interstitial pneumonia with diffuse alveolar damage and organizing pneumonia, with or without bronchiolitis. These findings have been reported in one third and one fourth of patients with amiodarone-induced pulmonary toxicity, respectively.[1,13]

The mainstay of treatment for amiodarone-induced lung toxicity is to discontinue the drug. Corticosteroids should be given to patients with hypoxia or substantial pulmonary involvement on imaging.[1] Though clinical symptoms usually resolve within 2–4 weeks, radiographic findings usually require 3 months. Slow resolution of up to 18 months has been reported.[9] Complete clearing on imaging is seen in 85% of patients. Clinical evidence has shown that corticosteroid therapy accelerates recovery and minimizes the chance of pulmonary fibrosis. Early mortality has been observed in patients with severe disease not treated with corticosteroids.[1]

The mortality in hospitalized patients with amiodarone pneumonitis is 21–33%.[1] As a result, patients who would benefit from amiodarone should be carefully selected, and the dose should be as low as possible. It is important to ensure frequent follow-up in patients on amiodarone therapy. Unfortunately, no consensus exists regarding the prevention and early detection of amiodarone-induced lung toxicity. Before beginning amiodarone, patients should undergo a radiograph and PFTs with D_{LCO} to serve as a baseline for comparison to future studies. Serial PFTs and radiographs are not recommended in patients with normal lung function on standard dosages of amiodarone ($<$ 400 mg/d) because of the low frequency of toxicity in those individuals. In patients on higher dosages or with poor baseline lung function, serial imaging and PFTs may be considered. In all patients on amiodarone, imaging and PFTs should be undertaken if the patient develops symptoms.[1,3] The earliest abnormality in amiodarone pneumonitis is a decrease in the D_{LCO} on PFTs. Magro et al determined that the best sensitivity and specificity corresponded to a decrease in the D_{LCO} of greater than 15% and 30%, respectively. A stable D_{LCO} can be used to exclude amiodarone pneumonitis.[14]

Given the relatively high frequency of pulmonary toxicity in patients on amiodarone therapy, clinicians should carefully select those who would benefit from the antiarrhythmia effects of the drug. Since the population of patients with dysrhythmia often have concomitant lung and heart disease, baseline radiograph and PFTs are necessary in order to compare future changes induced by amiodarone. Because of the high mortality of amiodarone pneumonitis, it should be considered in patients who develop respiratory symptoms even while on low-dose amiodarone therapy.

Table 1. Features of Amiodarone Pneumonitis

Exposure	5–15% in those who take $>$ 400 mg of amiodarone daily[3]
	1.6% in those who take $\leq$ 400 mg daily[3]
Clinical	Insidious, with gradual onset of cough and dyspnea[6]
	Acute, mimics pneumonia, with or without elevation in white-cell count or response to antibiotics[6]
	Acute form with ARDS-like presentation after surgery or long-term mechanical ventilation[6-8]
Pathology	Bronchoalveolar lavage fluid is not diagnostic, but the presence of lipid-laden macrophages does suggest treatment effect of amiodarone; also used to exclude other etiologies[1,4,11]
	Biopsy shows nonspecific interstitial inflammation and fibrosis, as well as the presence of lipid-laden macrophages within air spaces and vacuoles within hyperplasic type II pneumocytes[1,13]
Outcome	Favorable when recognized early, and amiodarone discontinued[1]
	Can have high mortality in acute presentation[1]
	Steroids can be helpful[1]
Prevention	Baseline imaging and pulmonary function studies recommended[1,3]
	In patients on higher dosages or with poor baseline lung function, serial imaging and pulmonary function testing may be considered[1,3]
	No requirement for routine monitoring[1,3]

ARDS = acute respiratory distress syndrome

Table 1 gives a summary of the key features of amiodarone pneumonitis. In the present case the patient had been treated with 200 mg of amiodarone for 2 months prior to becoming symptomatic. Because of the relatively nonspecific symptoms, laboratory tests, and diagnostic studies it was necessary to exclude other possible etiologies for the patient's symptoms. Intra-alveolar foamy macrophages, chronic interstitial pneumonitis, and prominent vacuolization of type II pneumocytes on transbronchial lung biopsy confirmed the clinical diagnosis of amiodarone-induced pneumonitis.

REFERENCES

1. Camus P, Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Clin Chest Med 2004;25(1):65–75.
2. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (part 1). Chest 1988;93(5):1067–1075.
3. Sunderji R, Kamji Z, Gin K. Pulmonary effects of low dose amiodarone: A review of the risks and recommendations for surveillance. Can J Cardiol 2000;16(11):1435–1440.

4. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (part 2). Chest 1988;93(6):1242–1248.
5. Dusman RE, Stanton MS, Miles WM, Klein LS, Zipes DP, FIneberg NS, Heger JJ. Clinical features of amiodarone-induced pulmonary toxicity. Circulation 1990;82(1):51–59.
6. Donaldson L, Grant IS, Naysmith MR, Thomas JS. Acute amiodarone-induced lung toxicity. Intensive Care Med 1998;24(6):626–630.
7. Van Mieghem W, Coolen L, Malysse I, Lacquet LM, Deneffe GJ, Demedts MG. Amiodarone and the development of ARDS after lung surgery. Chest 1994;105(6)1642–1645.
8. Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failire in the ICU? Chest 2001;120(1):275–282.
9. Vernhet H, Bousquet C, Durand G, Giron J, Senac JP. Reversible amiodarone-induced lung disease: HRCT findings. Eur Radiol 2001; 11(9):1697–1703.
10. Coudert B, Bailly F, Lombard JN, Andre F, Camus P. Amiodarone pneumonitis: bronchoalveolar lavage findings in 15 patients and a review of the literature. Chest 1992;102(4):1005–1012.
11. Bedrossian CW, Warren CJ, Ohar J, Bhan R. Amiodarone pulmonary toxicity: cytopathology, ultrastructure, and immunocytochemistry. Ann Diagn Pathol 1997;1(1):47–56.
12. Xaubet A, Roca J, Rodrigueez-Roisin R. Bronchoalveolar lavage cellular analysis and gallium lung scan in the assessment of patients with amiodarone-induced pneumonitis. Respiration 1987;52(4):272–280.
13. Myers JL, Kennedy JI, Plumb VJ. Amiodarone lung: pathologic findings in clinically toxic patients. Human Pathology 1987;18(4): 349–354.
14. Magro SA, Lawrence EC, Wheeler SH, Krafchek J, Lin HT, Wyndham CR. Amiodarone pulmonary toxicity: prospective evaluation of serial pulmonary function tests. J Am Coll Cardiol 1988;12(3):781–788.

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