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Association of Alveolar Hemorrhage with Amiodarone: Role of Bronchoscopy

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ABSTRACT

*A common pulmonary complication due to the toxicity of amiodarone is chronic interstitial pneumonitis. Alveolar hemorrhage, with or without hemoptysis, is an exceedingly infrequent presentation of amiodarone toxicity. We report a 69-year old patient with dyspnea, hypoxemia and bilateral diffuse interstitial and alveolar infiltrates occurring four months after treatment with amiodarone. An initial and comprehensive work-up did not reveal the cause of infiltrates. Bronchoalveolar lavage (BAL) fluid demonstrated foamy macrophages and alveolar hemorrhage, not caused by either vasculitis or autoimmune diseases. We speculate that amiodarone may have been associated with BAL findings since cessation of the drug resulted in resolution of the infiltrates. In amiodarone-induced lung injury, diffuse interstitial and alveolar infiltrates can be suggestive of alveolar hemorrhage and should be further investigated by bronchoscopy and BAL.**(Tanaffos 2008; 7(2): 75-78)*

Key words: *Amiodarone, Alveolar hemorrhage, Capillaritis, Vasculitis, Bronchoscopy*

INTRODUCTION

Pulmonary manifestations of amiodarone range from diffuse interstitial pneumonitis to acute respiratory distress syndrome (1-3). With the exception of a few cases (seen in the setting of diffuse alveolar damage) (3), alveolar hemorrhage, and/ or hemoptysis, are extremely uncommon presentations of amiodarone-induced lung disease. Bronchoscopy with BAL is not commonly used in such patients.

We report a patient with alveolar hemorrhage and a cumulative intake of 4.5 grams of amiodarone over a four-month period. The interstitial and alveolar presentation of his disease were suggestive of interstitial pneumonitis. However, bronchoscopy and BAL showed diffuse alveolar hemorrhage in the absence of an auto-immune process or vasculitis. We suggest that bronchoscopy and BAL, although not routinely performed for patients on amiodarone therapy with radiographic abnormalities should be considered as part of the work-up for interstitial and alveolar infiltrates in such patients in order to rule-out alveolar hemorrhage.

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CASE REPORT

A 69- year- old male presented to the emergency room with gradual progression of shortness of breath over a period of several weeks. He was unable to walk beyond 10 meters. Review of systems was negative for fever, chills, weight loss, hemoptysis, orthopnea, proxysmal nocturnal dyspnea, or chest

pain.

A few weeks prior to his visit, he was admitted to hospital with similar symptoms. At the time, his dyspnea was attributed to heart failure, requiring a two- day support on mechanical ventilation.

The patient's past medical history included a four-vessel coronary artery bypass graft conducted 4 months earlier. The postoperative course was complicated by respiratory insufficiency and failure to wean, as well as renal failure, requiring tracheostomy and chronic hemodialysis. He was ventilator- dependent for 2 months. Subsequently, the patient was re-hospitalized on another occasion with the diagnosis of congestive heart failure.

Other medical problems included hypertension, hypercholesterolemia, and previous myocardial infarctions. He was on chronic oxygen supplementation and had a 60 pack/year history of smoking.

Medications included amiodarone 400 mg every day (started after the bypass surgery- cumulative dose of 4.5 grams), aspirin, beclomethasone and ipratropium inhalers, diltiazem, and isosorbide.

Hospital course: In the emergency room, the patient had a respiratory rate of 40/min. Arterial blood gas showed pH: 7.1, PCO_2 :82 mm Hg, and PO_2: 68 mm Hg. He was intubated and supported by mechanical ventilation for respiratory failure for 4 days during which he was dialyzed several times below his dry weight.

On physical examination after extubation, the patient was afebrile with a respiratory rate of 25/min, pulse rate of 100 beats/min, and blood pressure of 100/70. The skin had a tanned appearance. Heart had a regular rate and rhythm and a 2 over 6 systolic ejection murmur. Crackles were audible diffusely throughout the lungs; there was no dullness to percussion. Hepatosplenomegaly was not present. Lower extremities had trace edema.

Laboratory data revealed a white blood cell count of 18,900/mm3, hemoglobin: 11.8 g/dl, blood urea nitrogen: 79 mg/dl, and creatinine: 2.4 mg/dl. Liver function tests (including transaminases), prothrombin time (PT), and partial thromboplastin time (PTT) were within normal limits. Erythrocyte sedimentation rate was 48 mm/hr. Urinalysis did not show any red blood cell cast or proteinuria. Electrocardiogram displayed a left bundle branch block and a first degree atrioventricular block. Chest radiograph and computed tomography (CT) displayed diffuse bilateral interstitial and alveolar infiltrates and slight pleural effusion (Figure 1).

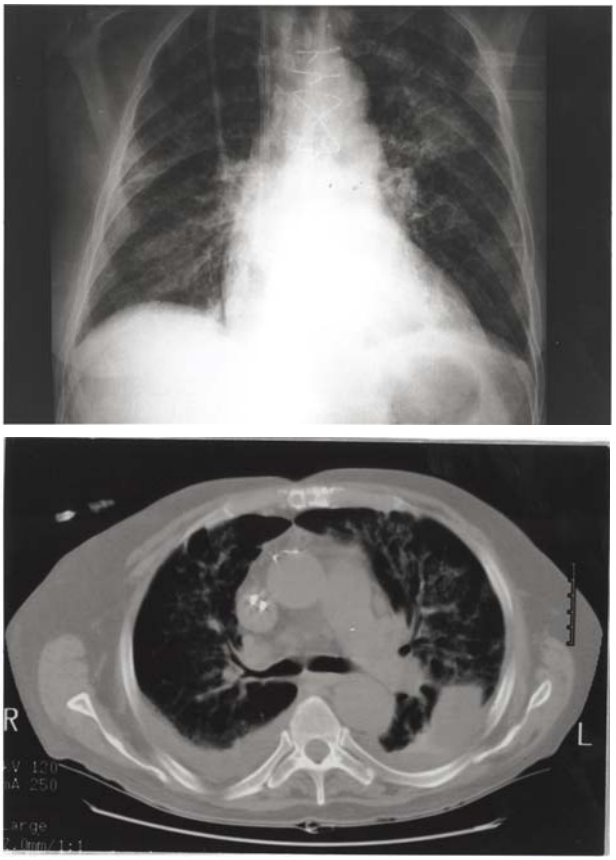

Figure 1. Radiograph (A) and CT (B) of the chest; significant findings are bilateral interstitial alveolar infiltrates and minimal pleural effusion. The tip of the hemodialysis access catheter is visible in the superior vena cave.

A bronchoscopy with BAL was performed which revealed a sanguinolent specimen. Sequential instillation and aspiration of normal saline did not

diminish the intensity of blood in the recovered aliquots, a finding highly indicative of alveolar hemorrhage. Due to renal impairment and high risk of fatal bleeding, transbronchial biopsies were not performed. The fluid white cell count had a normal differential; but an abundance of hemosiderin- laden and foamy macrophages (Figure 2). The fluid cytology was negative for malignancy. Bacterial, fungal, and viral cultures as well as special stains were non-contributory.

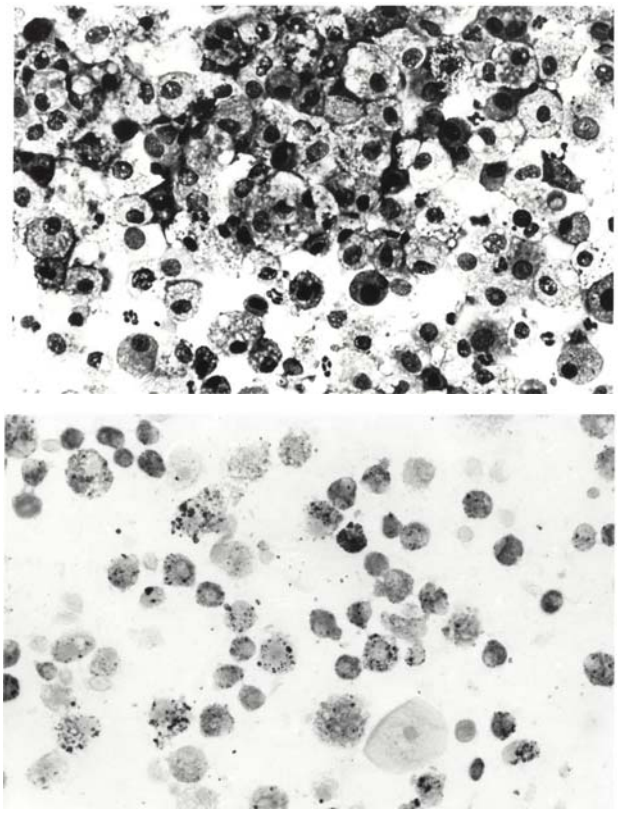

Figure 2. *Plate A)* The bronchoalveolar lavage specimen demonstrating abundance of foamy marrophages (H&E stain). *Plate B)* Hemosiderin appears as dark spots within the macrophages (iron stain).

Work-up for alveolar hemorrhage included measurement of serum levels for complements (C3 and C4), anti-nuclear and anti-DNA antibodies, rheumatoid factor, proteinase-3 and myeloperoxidase, anti-neutrophilic cytoplamic antibodies, and anti- glomerular basement membrane antibody. Their respective values were all within the normal limits.

Amiodarone, as the possible offending agent, was stopped. The patient's dyspnea gradually resolved. A 3-week follow-up radiograph showed near total resolution of the interstitial and alveolar infiltrates.

DISCUSSION

An iodinated benzofuran derivative, amiodarone is a frequently used antiarrhytmic drug that can cause considerable pulmonary toxicity in 5 to 15% of patients (2). The most common toxicity is chronic interstitial pneumonitis (2), followed by organizing pneumonia with or without bronchiolitis obliterans (3), and rarely respiratory distress syndrome (4). Risk factors for amiodarone-induced lung disease comprise drug dosage of greater than 400 mg per day, and intake of the drug for more than two months (2). Reports suggest that the total cumulative dose of the drug may be a more substantial risk factor than the daily dose (5). Toxicity can also become evident in patients taking 200 mg of the drug per day over a span of years. Foamy alveolar macrophages, increase in both polymorphonuclear leukocytes, and T-suppressor/ T-cytotxic lymphocytes in the bronchoalveolar lavage fluid; all may indicate exposure to the drug (2).

Alveolar hemorrhage is a very rare complication of amiodarone. Dean has reported the largest series of amiodorane-induced alveolar hemorrhage (3). In his study of 171 patients, minimal alveolar hemorrhage was noted in only a few patients on transbronchial, open lung, and post-mortem specimens (3). Only one patient had evidence of significant alveolar hemorrhage on post-mortem study (an elderly male with chronic lung disease and cumulative amiodarone dose of 101 grams, fever, sedimentation rte of 150 mm/hr, and white blood cell count of 22,000/mm3). Of importance, diffuse alveolar damage in different stages of evolution was the common denominator in all the cases of alveolar

hemorrhage in the series. It was therefore, difficult to determine if the alveolar hemorrhage could also be seen in the absence of diffuse alveolar damage.

Other reports have also suggested amiodarone as the cause of hemoptysis and alveolar hemorrhage. Vizoli reported a case of a patient on 200 mg of amiodarone twice daily for two months, who presented with severe hypoxemia and hemoptysis (6). On transbronchial biopsies, hemosiderin- laden macrophages and focal bronchiolitis obliterans organizing pneumonia (BOOP) were observed. In another report, a patient presented with hemoptysis and fever two weeks after treatment with amiodarone (7). Bronchoscopy demonstrated diffuse inflammatory changes but the source of bleeding could not be identified. Work-up for vasculitis and autoimmune diseases was inconclusive.

In another report, acute alveolar hemorrhage and orthodeoxia were seen in a patient with severe ischemic cardiomyopathy receiving intravenous amiodarone for ventricular tachycardia (8). The patient was discharged after his first hospital stay during which he received 4 days of maintenance infusion of amiodarone. During his second admission one week later, he developed hemoptysis and had a 3 g loss of hemoglobin.

Due to platypnea and orthodeoxia, he required 100 percent oxygen supplement. A BAL displayed abundant hemosiderin-laden macrophages. Heart failure and fluid overload were not the precipitating factors because of a normal pulmonary artery wedge pressure. Serologies for vasculitis and autoimmune diseases were negative. The patient subsequently required mechanical ventilation for hypoxemia. His condition improved upon cessation of amiodarone and administration of methylprednisolone (8). In the majority of the aforementioned cases, hemoptysis and/ or alveolar hemorrhage ceased upon termination of amiodarone, implicating it as the offending cause.

In conclusion, the present report demonstrated that amiodarone may be associated with alveolar hemorrhage in the absence of acute respiratory distress syndrome, renal-pulmonary syndrome, or auto-immune diseases. In our patient, infectious etiologies, i.e. fungal, bacterial, and viral, were not the precipitating cause of alveolar hemorrhage, either.

Congestive heart failure and fluid overload were not present because the patient was dialyzed below his dry weight several times. Amiodarone can, therefore, be a cause of diffuse interstitial infliltrates and alveolar hemorrhage in patients who do not present with hemoptysis. Bronchoscopy with BAL, although not routinely performed, and possibly transbronchial biopsies, should be considered in establishing the above-mentioned diagnosis and for excluding vasculitides.

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