Catheterization and Cardiovascular Interventions 47:61–63 (1999)

Acute Alveolar Hemorrhage and Orthodeoxia Induced by Intravenous Amiodarone

Sherif Iskander, MD, Donald G. Raible, MD, Susan C. Brozena, MD, Daniela M. Gaitanaru, MD, Gustavo Ayala, MD, and Ami E. Iskandrian,* MD

Key words: amiodarone; arrhythmia; side effects

INTRODUCTION

The manifestations of amiodarone pulmonary toxicity (APT) are nonspecific and the diagnosis requires exclusion of other diseases. APT occurs in up to 10% of patients receiving the drug; of these, death has been reported in 10% to 20%. The most common presentation of APT is insidious onset of dyspnea, cough, fever, weight loss, and diffuse radiographic abnormalities; it often resembles heart failure, pneumonia, acute respiratory distress syndrome, or pulmonary embolism [1–4]. We report here a case of early onset APT manifested by hemoptysis, severe hypoxia, platypnea (dyspnea in the upright position), orthodeoxia, and bilateral extensive pulmonary infiltrates after multiple boluses of IV amiodarone given to treat ventricular tacchycardia. Signs, symptoms, and radiological findings resolved after discontinuation of amiodarone and administration of glucocorticosteroid therapy.

CASE REPORT

A 59-year-old man was admitted to another hospital with an acute myocardial infarction complicated by ventricular tacchycardia and fibrillation. He was treated with intravenous amiodarone (150-mg bolus followed by maintenance infusion for 4 days). He underwent angioplasty of a totally occluded left circumflex coronary artery. A high-grade occlusion of the left anterior descending was also noted. Left ventricular (LV) ejection fraction was 20%. After 11 days, he was discharged on digoxin, furosemide, linsinopril, warfarin, and amiodarone 200 mg orally q 12 hours. He was readmitted 1 week later for severe heart failure and required intubation. An echocardiogram revealed LV dilation with severe systolic dysfunction. Hemodynamic monitoring revealed elevated LV filling pressure and depressed cardiac output.

He received intravenous furosemide, dopamine, and dobutamine. He had multiple episodes of sustained monomorphic ventricular tacchycardia requiring cardioversions, and received four boluses of intravenous amiodarone (150 mg each), temporary overdrive pacing, and a continuous amiodarone infusion at 0.5 mg/min. There was no evidence of myocardial infarction. After 5 days, he was transferred to our institution for further management and possible cardiac transplantation. On arrival, he was sedated and on mechanical ventilation. Arterial saturation was 98% on $FI0_2$ of 40%. Heart rate was 72 bpm and blood pressure 105/58 mm Hg. There was a soft murmur of mitral regurgitation and few basilar rales. After diuresis, his mean pulmonary capillary wedge pressure was 12 mm Hg, pulmonary artery pressure 34/18 mm Hg, and cardiac index 3.4L/min/m^2.

Over the next 2 days, dopamine was discontinued and dobutamine was used to maintain cardiac output. Intravenous diuretics were continued to maintain normal LV filling pressure. The patient improved and was extubated. The pulmonary artery catheter and pacing wire were removed and amiodarone was changed to oral administration. The following day, he began to develop hemoptysis, with 3-gm drop in hemoglobin and required blood transfusion. He became hypoxic and developed progressive pulmonary infiltrates (Fig. 1). He also developed platypnea and orthodeoxia, with a fall in oxygen saturation from 90% on 100% nonrebreather mask when recumbent, to 70% when upright. Broncho-alveolar lavage revealed numerous hemosiderin-laden macrophages compatible with alveolar hemorrhage. His clinical status worsened and he was reintubated. The mean pulmonary artery capillary wedge pressure was 8 mm Hg. He was afebrile, had no leukocytosis, and the blood cultures were

Department of Medicine, Division of Cardiology, Allegheny University of the Health Sciences, MCP Hahnemann School of Medicine.

*Correspondence to: Dr. Ami E. Iskandrian, Cardiovascular Research Center, Allegheny University of the Health Sciences, MCP Hahnemann School of Medicine, 230 North Broad Street, MS 471, Philadelphia, PA 19102. E-mail: iskandrian@auhs.edu

Received 24 July 1998; Revision accepted 18 November 1998

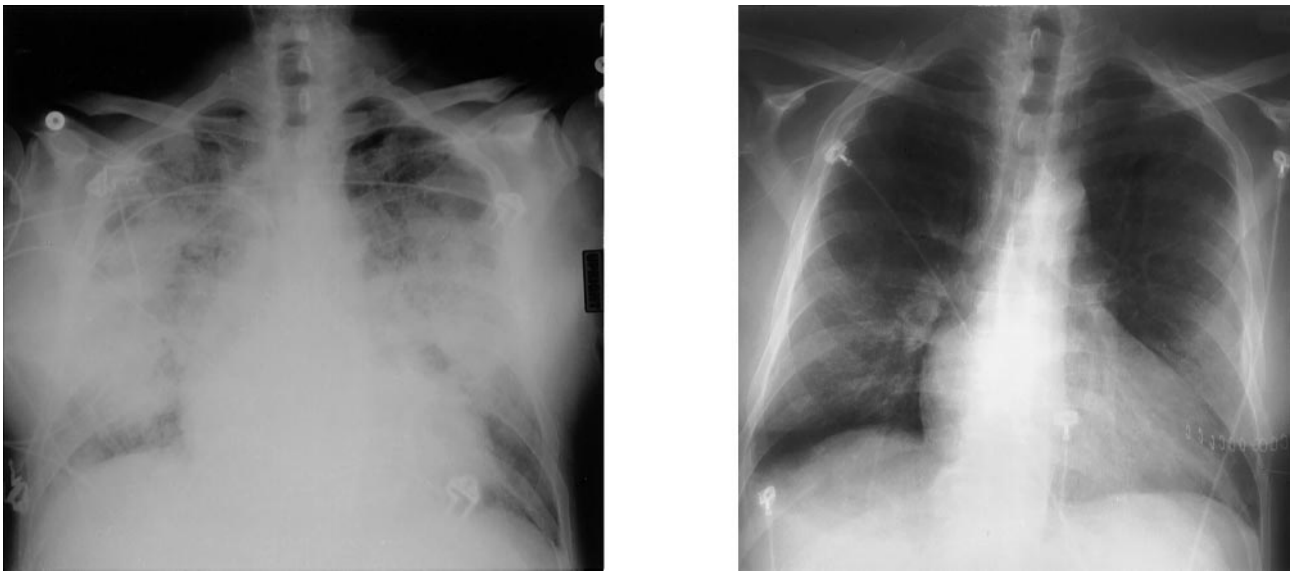

Fig. 1. Chest radiographs. Left: At onset of hemoptysis, within 2 weeks from receiving multiple boluses of IV amiodarone. Right: Eleven days after discontinuation of amiodarone and starting corticosteroids, showing clearing of pulmonary infiltrate.

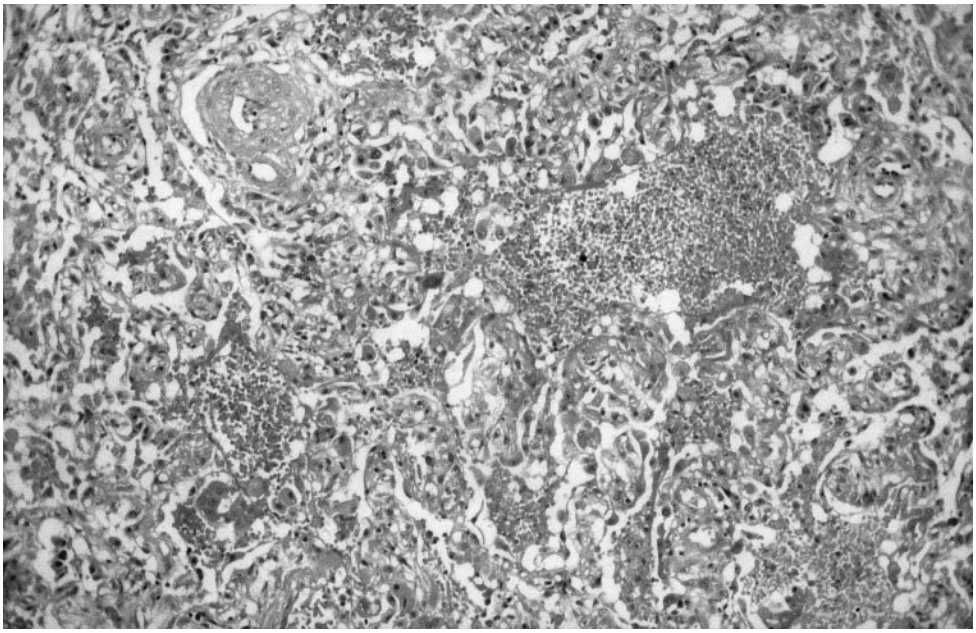

Fig. 2. Medium-power photomicrograph of the open lung biopsy, showing innumerable foamy alveolar macrophages and numerous alveolar red blood cells and focal areas of increased fibrosis in the intra-alveolar spaces. These changes are consistent with amiodarone toxicity.

negative. Serologic tests for other causes of alveolar hemorrhage were negative (C-ANCA, P-ANCA, anti-GMB). The urine analysis, electrolyte, and liver function tests were normal. The possibility of amiodarone pulmonary toxicity was considered and amiodarone was discontinued. Open lung biopsy revealed diffuse alveolar damage with a predominance of foamy intra-alveolar macrophages (Fig. 2). Intravenous methylprednisolone, 125-mg q 6 hours was started and over the next 2 days, hypoxia and pulmonary infiltrates improved, permitting extubation. By the 11th day on steroids, oxygen saturation was 98% on room air with no platypea or orthodexia. Because of the severe LV dysfunction, he underwent successful cardiac transplantation.

DISCUSSION

Amiodarone is a widely used antiarrhythmic drug and can be life-saving. Pulmonary toxicity is the most serious adverse effect and is associated with significant morbidity and mortality [1–9]. In our case, the patient developed severe pulmonary toxicity with hemoptysis, hypoxia, and orthodoxia, which occurred early after multiple boluses of IV amiodarone were given. The rapid clinical response to steroids and discontinuation of amiodarone, the pathological findings, and the exclusion of other diseases support the diagnosis of APT. The hemoptysis, hypoxia, and lung infiltrates were unlikely due to heart failure because of normal filling pressure and cardiac output. They are also unlikely due to pulmonary artery catheter-induced infarction because they were diffuse and bilateral. Hemoptysis associated with APT was reported in 2 cases [1,2], one of which had occurred early (15 days) after starting oral amiodarone. The mechanism of alveolar hemorrhage in APT remains unclear. Orthodeoxia (arterial desaturation that becomes evident in the upright position and improves in the recumbent position) as a manifestation of APT was reported in a single case after increasing the dose of oral amiodarone. The mechanism is not well understood [3]. A possible mechanism is obligatory gravitational perfusion of the basal alveolar units causing exaggeration of ventilation-perfusion mismatch.

The mechanisms of APT are either an indirect toxic mechanism, characterized by influx of inflammatory or immune effector cells to the lung by T-cell–mediated hypersensitivity pneumonitis, or a direct toxic mechanism, related to intracellular accumulation of phospholipids causing lung parenchymal ongoing and subsequent fibrotic response. The abrupt onset, the biopsy results, and the immediate response to treatment point to an immune-mediated mechanism. The multiple boluses of IV amiodarone may also had direct toxic effect by phospholipid accumulation within alveolar pneumocytes and macrophages.

A recent report described APT in a 7-month-old boy 8 days after two boluses of IV amiodarone followed by IV drip; pulmonary toxicity resolved few days after discontinuation of amiodarone, without steroid therapy. This infant had impaired hepatic function, which was thought to predispose to rapid accumulation of amiodarone [4]. Rapid accumulation of amiodarone, either by giving multiple or large doses of IV or oral amiodarone, or underexcretion secondary to hepatic dysfunction, might predispose to a higher risk for developing APT. Monitoring amiodarone levels would probably not have been helpful besides being not readily available. Our case is unusual as severe APT developed early after multiple IV boluses in addition to prior oral therapy with amiodarone. In addition to severe hypoxia, hemoptysis and orthodeoxia are both very rare manifestations of APT. The role of steroids in APT is controversial, as there are no controlled studies, but good responses have been well documented and recurrence of symptoms have been observed upon tapering of such therapy. A high degree of suspicion of APT early in the course of the disease and recognition of the atypical presentation may preclude the development of permanent loss of pulmonary function and potential fatal complication.

REFERENCES

1. Vizioli LD, Cho S. Amiodarone-associated Hemoptysis. Chest 1994;105:305–306.
2. Goldstein I, Topilsky M, Segev D, Isakov A, Heller I. Very early onset of acute amiodarone pulmonary toxicity presenting with hemoptysis. Chest 1997;111:1446–1447.
3. Papiris SA, Maniatti MA, Manoussakis MN, Constatopoulos SH. Orthodeoxia in amiodarone induced acute reversible pulmonary damage. Chest 1994;105:965–966.
4. Daniels CJ, Schutte DA, Hammond S, Franklin WH. Acute pulmonary toxicity in an infant from intravenous amiodarone. Am J Cardiol 1997;80:1113–1116.
5. Dusman RE, Stanton MS, Miles WM, Klein LS, Zipes DP, Finebuerg NS, Heger JJ. Clinical features of amiodarone induced pulmonary toxicity. Circulation 1990;82:51–59.
6. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Chest 1988;93:1067–1075.
7. Wilson BD, Clarson CE, Lippman ML. Amiodarone induced pulmonary inflammation: correlation with drug dose and lung levels of drug, metabolite and phospholipid. Am Rev Respir Dis 1991;143: 1110–1114.
8. Wilson JS, Podrid PJ. Side effects of amiodarone. Am Heart J 1991;121:158–171.
9. Tenholder MF, Russel MD, Knight E, Rajagopal KP. Orthodeoxia a new finding interstitial fibrosis. Am Rev Respir Dis 1987;136:170–173.