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Manifestations of Lung Toxicity: Amiodarone-induced Bronchiolitis Obliterans Organizing Pneumonia

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Pulmonary toxicity is one of the most serious adverse effects associated with the antiarrhythmic drug amiodarone. Presentation varies from mild illness to rapidly progressing and even fatal acute respiratory distress syndrome. Bronchiolitis obliterans organizing pneumonia has rarely been reported with this drug. We describe a case of amiodarone-induced bronchiolitis obliterans organizing pneumonia and review the central features of the diagnosis of amiodarone-induced lung toxicity. Other types of amiodarone-related pulmonary toxicity are also discussed.

Pulmonary toxicity is one of the most serious adverse effects of the antiarrhythmic medication amiodarone HCl (Cordarone, Pacerone). A rare event secondary to therapy with this drug is bronchiolitis obliterans organizing pneumonia (BOOP), which has only rarely been reported in the literature.

Illustrative Case

An 81-year-old woman was admitted with a 3-week history of dyspnea, dry cough, pleuritic chest pain, and generalized weakness. Her history included

atrial fibrillation, ischemic heart disease, hypertension, and type 2 diabetes. She had no history of lung disease and had never smoked. Physical examination showed the patient was febrile, tachypneic, and hypoxic. Lung evaluation was remarkable for bilateral basilar crackles. Chest x-ray revealed extensive bilateral alveolar and interstitial infiltrates (Figure 1). The patient required mechanical ventilation for respiratory failure.

Computed tomography (CT) demonstrated extensive ground-glass opacities and airspace consolidation of both lungs, with bilateral pleural effusions (Figure 2). No significant adenopathy was found. Workups for an infectious etiology and vasculitis were negative. Echocardiography revealed moderate pulmonary hypertension with normal left ventricular systolic function. Diffuse airway inflammation was detected on bronchoscopy. Bronchoalveolar lavage was nondiagnostic. The patient did not respond to empiric broad-spectrum antibiotic and diuretic therapy. She was, therefore, treated empirically with intravenous (IV) methylprednisolone sodium succinate (A-Methapred, Solu-Medrol).

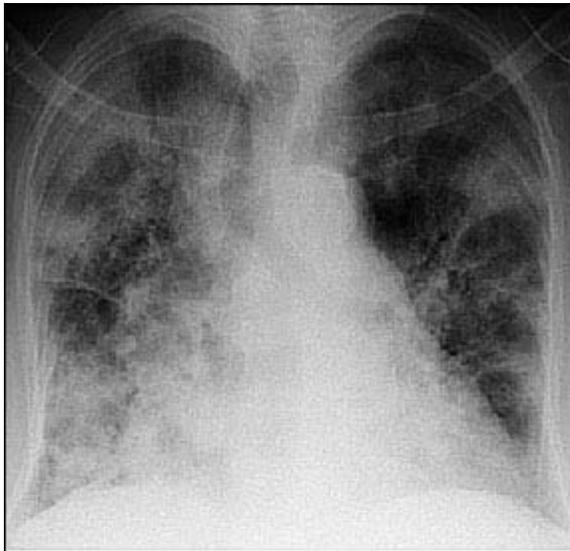


Figure 1—The admission chest radiograph is showing extensive bilateral alveolar and interstitial infiltrates.

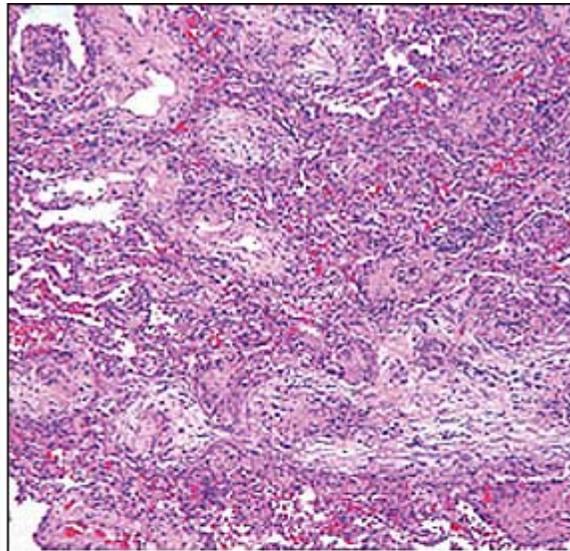


Figure 3—Polypoid proliferations of edematous stroma, with mixed inflammation branching in the airways and filling the surrounding airspaces (hematoxylin and eosin staining; magnification, 1002).



Figure 2—Chest CT scan demonstrates extensive ground-glass opacities and airspace consolidation of both lungs.

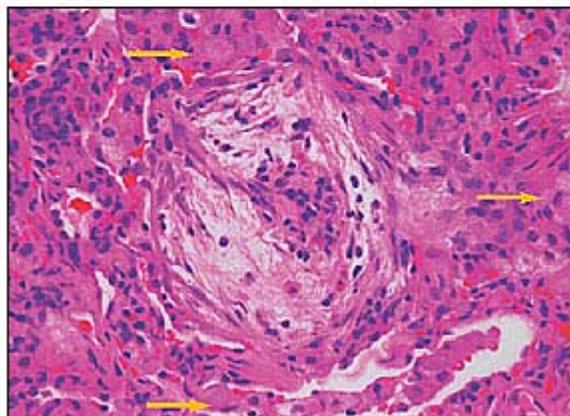


Figure 4—Edematous granulation tissue fills the airspace seen in the center. Foamy intraalveolar macrophages (arrows) can also be seen in numerous surrounding airspaces (hematoxylin and eosin staining; magnification, 4002).

The diagnosis of BOOP was finally made by open lung biopsy. Histologic examination revealed a patchy chronic interstitial infiltrate with numerous temporally synchronous, edematous, polypoid plugs of granulation tissue that filled the bronchioles, alveolar ducts, and airspaces (Figure 3). Intraalveolar foamy macrophages were present but were not a prominent feature of the biopsy (Figure 4). Granuloma, vasculitis, neoplasia, viral cytopathic effect, and neutrophilic pneumonia were not evident.

In this patient, BOOP was thought to be a side effect of amiodarone. She had been taking the drug for 2 years, using dosages of 100 mg and 200 mg on alternate days for the past several months. The amiodarone was stopped, and the corticosteroid therapy was continued. The patient's pulmonary status improved during the following week, and she was extubated. She was discharged with a prescription for prednisone (eg, Deltasone), 60 mg/day. She also required oxygen therapy at night. Pulmonary function tests 1 month later demonstrated a mild restrictive process with a moderately reduced diffusing capacity. Her symptoms and pulmonary function improved gradually over the next few months, and her need for oxygen therapy decreased. Follow-up chest x-rays showed remarkable clearing of the lung fields (Figure 5). The prednisone was tapered gradually over 6 months.

Lung Toxicity Secondary to Amiodarone

Drug-induced pulmonary toxicity occurs in 5% to 10% of patients who take amiodarone.¹ Presentation may vary from a mild, subacute illness to rapidly progressive and fatal acute respiratory distress syndrome (ARDS). No clinical predictors of amiodarone-induced pulmonary toxicity have been reported. Lung injury has been reported with amiodarone treatment for periods as short as 3

weeks and with dosages as low as 200 mg/day.²⁻⁴

Chronic interstitial pneumonitis is the most common presentation of amiodarone-induced lung toxicity. It is characterized by an insidious onset of cough, dyspnea, and weight loss, and presents as focal or diffuse lung opacities on chest radiographs. Toxicity is usually recognized after 2 to 3 months of therapy, especially in patients taking dosages higher than 400 mg/day.⁵ Histopathologic examination reveals an intraalveolar accumulation of foamy macrophages, with distinctive cytoplasmic lamellar inclusions.⁶

ARDS is a rare but potentially fatal form of amiodarone-induced pulmonary toxicity. It has a fulminant course and is usually seen in patients who undergo surgery or pulmonary angiography.^{7,8} It is hypothesized that amiodarone may sensitize susceptible individuals to either high concentrations of inspired oxygen or to iodinated contrast media.

A solitary pulmonary mass simulating pulmonary malignancy is another reported complication of amiodarone use.⁹ BOOP, alveolar hemorrhage, and diffuse alveolar damage occur in a minority of patients.¹⁰

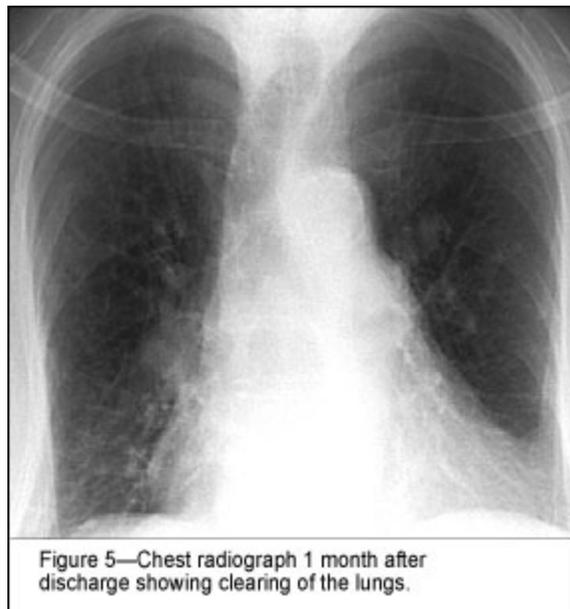


Figure 5—Chest radiograph 1 month after discharge showing clearing of the lungs.

What Is BOOP?

BOOP represents injury to the small conducting airways that is repaired by the proliferation of granulation tissue, in which polypoid projections of edematous fibroblastic stroma protrude into and fill airway lumens. This common histopathologic pattern of repair could be either idiopathic or associated with allergies, organizing infections, aspiration of gastric contents, toxic fume inhalation, drug reactions, or collagen vascular disease.¹¹ BOOP can be distinguished from many other forms of interstitial lung disease by its acute onset, response to steroids that occurs in many patients, and relatively good prognosis.

Amiodarone-induced BOOP

Few cases of amiodarone-induced BOOP have been reported.^{2,12-18} In this context, BOOP is often associated with a chronic interstitial pneumonia.¹¹ Patients usually present with cough, dyspnea, pleuritic chest pain, fever, and generalized weakness.¹⁰ CT findings include diffuse interstitial infiltrates and ground-glass opacities.^{10,19} The characteristic high-attenuation opacities in the periphery of the lung parenchyma result from incorporation of amiodarone breakdown products in hyperplastic type II pneumocytes.^{19,20} The mechanisms of lung injury are complex and may involve the direct toxic effects of free radicals or indirect inflammatory injury to cells.¹²

Diagnostic bronchoalveolar lavage is nonspecific and may show mixed cellularity²¹ and CD8 lymphocytosis.^{1,22} The presence of foamy macrophages suggests amiodarone exposure, whereas their absence indicates that another cause is probably responsible for the interstitial lung disease.²¹ Open lung biopsy is usually required for diagnosis. Electron microscopy reveals vacuolation within alveolar macrophages corresponding to membrane-bound cytoplasmic lamellar inclusions.⁶ Essentially, amiodarone-induced BOOP remains a diagnosis of exclusion, although histopathology and electron microscopy can be helpful for confirmation in the appropriate clinical context.²²

Amiodarone-induced BOOP is reversible with amiodarone withdrawal and steroid treatment. Methylprednisolone, 125 mg to 250 mg IV for 3 to 5 days, has been recommended as initial treatment for patients with rapidly progressive, severe disease. Therapy can also begin with prednisone, 1.0 to 1.5 mg/kg daily, which is gradually tapered over 3 to 6 months. Overall prognosis is good. Patients who die generally have ARDS⁶ or an associated fibrosing process.²³

Conclusion

Amiodarone lung toxicity may manifest as chronic interstitial pneumonitis, organizing pneumonia, ARDS, or a solitary pulmonary mass. It is a clinicopathologic diagnosis of exclusion. The mechanisms involved in amiodarone-induced pulmonary injury are incompletely understood. Presence of intraalveolar foamy macrophages suggests amiodarone exposure and may be found in asymptomatic patients. Their presence in the appropriate clinical setting is helpful in making the diagnosis, but their absence cannot rule out amiodarone lung toxicity with certainty. In most cases the lung toxicity is reversible with amiodarone withdrawal and treatment with corticosteroids. Prognosis is variable, with a high mortality rate in patients with ARDS.

Self-assessment test

1. What is the most common type of amiodarone-induced lung toxicity?

- A. BOOP
- B. ARDS
- C. Chronic interstitial pneumonitis
- D. Pulmonary mass

2. Which of these statements about pulmonary toxicity with amiodarone is NOT true?

- A. Women are at higher risk than men
- B. Toxicity can occur with dosages of 200 mg/day
- C. Toxicity may appear after 3 weeks of therapy
- D. Presentation includes a mild subacute illness

3. All the following characteristics distinguish BOOP from other forms of interstitial lung disease, except:

- A. Acute onset
- B. Most patients respond to steroids
- C. Relatively good prognosis
- D. Ground-glass opacities on chest x-ray

4. Which of these tests provides confirmation of amiodarone-induced lung injury?

- A. Bronchoalveolar lavage
- B. Chest x-ray
- C. Chest CT
- D. Open lung biopsy

5. Which of these options is NOT appropriate treatment for amiodarone-induced BOOP?

- A. Immediate discontinuation of amiodarone therapy
- B. Inhaled albuterol
- C. IV methylprednisolone
- D. Oral prednisone

(Answers at end of reference list)

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Answers: 1. C; 2. A; 3. D; 4. D; 5. B.

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