

Drug-induced acute pneumonitis following initiation of flecainide therapy after pulmonary vein isolation ablation in a patient with mitral stenosis and previous chronic amiodarone use



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Introduction

Atrial fibrillation (AF) is the most commonly encountered sustained tachyarrhythmia. Flecainide is a class IC antiarrhythmic drug used frequently for treatment of supraventricular tachyarrhythmias.¹ Common cardiac and noncardiac side effects of flecainide are well described and recognized in clinical practice. Subacute flecainide lung toxicity has been described in a small number of case reports^{2–4} but is not commonly recognized or well understood. Here we report a case of acute drug-induced pneumonitis after flecainide administration and discuss key points in the recognition and management of this rare but potentially serious clinical scenario.

Case report

A 70-year-old woman with a past medical history of rheumatic mitral stenosis, status post percutaneous transseptal mitral valvotomy in 2012, hypertension, persistent AF, and amiodarone-induced hepatotoxicity was referred to the electrophysiology clinic for evaluation and management of symptomatic AF. She was subsequently scheduled for pulmonary vein isolation (PVI) ablation.

The patient's presenting rhythm on the day of her procedure was AF. She had stopped taking amiodarone 6 weeks before ablation. Amiodarone was the only antiarrhythmic medication the patient had taken in the past. She underwent radiofrequency PVI with successful acute isolation of all 4 of her pulmonary veins with evidence of exit and entrance block. She was discharged the next morning on warfarin for anticoagulation and off any antiarrhythmic medications.

KEYWORDS Amiodarone; Atrial fibrillation; Drug-induced interstitial pneumonitis; Drug-induced lung injury; Flecainide; Pneumonitis (Heart Rhythm Case Reports 2019;5:53–55)

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KEY TEACHING POINTS

- Because of tissue-specific drug accumulation properties, recognizing the association between flecainide and drug-induced acute lung injury is important. Early withdrawal of the offending agent is critical to clinical recovery.
- Flecainide-associated lung injury remains a diagnosis of exclusion. Infectious processes and cardiogenic pulmonary edema must be ruled out. A radiographic pattern of bilateral or unilateral opacities with a ground-glass pattern has been described in previous cases of pneumonitis as well as in our patient. The diagnosis must be made rapidly given the potentially severe consequences of misdiagnosis.
- The proposed mechanism of injury in flecainide drug toxicity is a cell-mediated immunologic reaction. Corticosteroids are the treatment of choice, and response to them plays a key role in the diagnostic process.

The patient presented 2 days after her ablation procedure with symptomatic AF. She was admitted to the hospital and successfully cardioverted to sinus rhythm with a single 360-J shock. After cardioversion, she was started on flecainide 100 mg every 12 hours. Approximately 5 hours later the patient developed fever of 38.7°C, chills, and dry cough. In addition, her oxygen requirements increased from 2 L of oxygen via nasal cannula to high-flow nasal cannula. Laboratory findings showed leukocytosis of 12,000. Blood cultures were collected, and a respiratory pathogen panel was performed. Portable chest radiograph performed at that time

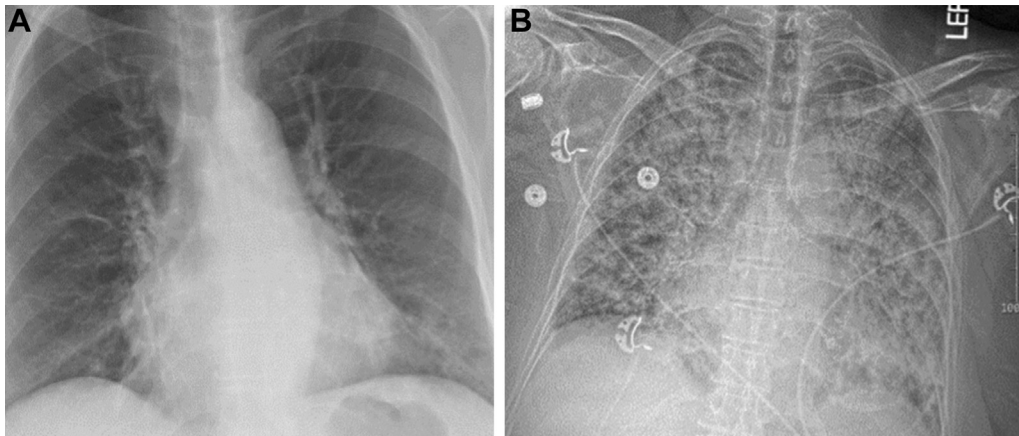


Figure 1 A: Baseline portable chest radiograph on the day of pulmonary vein isolation ablation. B: Portable chest radiograph a few hours after the onset of symptoms on hospital day 1.

showed increased interstitial markings (Figure 1) compared to baseline chest radiograph (Figure 1A). The patient was given a 20-mg intravenous dose of furosemide. Her symptoms of fever, chills, and cough slowly improved during the rest of the day.

Three hours after receiving her second 100-mg dose of flecainide, fever recurred with shortness of breath. The patient's oxygen requirements increased from high-flow nasal cannula to bilevel positive airway pressure support within a few hours. Laboratory findings showed increased leukocytosis to 16,000. With worsening clinical picture, computed tomographic scan of the chest was performed and showed diffuse ground-glass opacities bilaterally, predominantly in the upper lobes (Figure 2). In addition, the lower lobes showed multifocal areas of consolidation in a peribronchovascular distribution. The airways within these changes seemed to demonstrate at least mild traction bronchiectasis and bronchiolectasis. The findings of computed tomographic scan were interpreted as compatible with changes of acute lung injury, that is, a combination of changes of likely scattered noncardiogenic edema and organizing pneumonia

pattern. The patient remained on bilevel positive airway pressure support. Bedside echocardiography showed left ventricular ejection fraction of 65%–70% and no evidence of mitral valve stenosis. The inferior vena cava was noted to be small and looked collapsed, suggestive of low central venous pressures. Serum brain natriuretic peptide levels were only mildly elevated at 186 pg/mL (normal 0–100 pg/mL). Flecainide was immediately discontinued. Consultation with the pulmonology service indicated a diagnosis of acute hypoxemic respiratory failure due to evolving diffuse airspace filling process. At the time, the differential diagnosis of the patient's presentation was believed to be hospital-acquired pneumonia, postcardioversion pulmonary edema, cardiogenic pulmonary edema, flecainide pneumonitis, or delayed amiodarone toxicity.

Given the patient's rapid clinical deterioration and suspicion of drug-induced pneumonitis, the decision was made to start the patient on empiric intravenous methylprednisolone therapy (1 mg/kg/day). Infectious workup (influenza A, legionella, sputum culture, gram stain) was negative, and

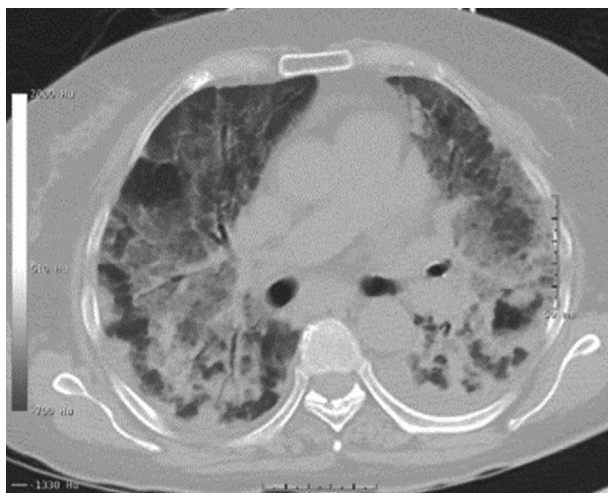


Figure 2 Computed tomographic scan of the chest on hospital day 2.

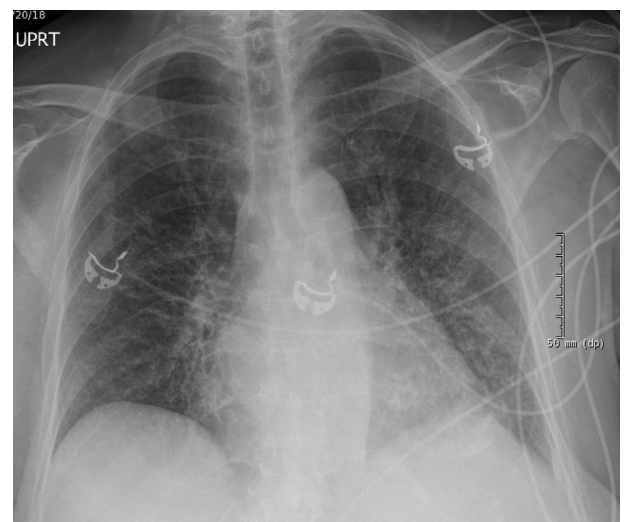


Figure 3 Portable chest radiograph 3 months after index hospitalization.

empiric intravenous antibiotics were stopped within 24 hours. The patient remained afebrile after cessation of flecainide, and her respiratory status and oxygen requirement improved over the next 4 days. She was transitioned from IV methylprednisolone to oral prednisone 72 hours after initiation of steroids. While in the hospital, she underwent another direct current cardioversion for symptomatic AF without complication.

The patient was discharged on hospital day 6 with home oxygen (with the intention to wean off as an outpatient), metoprolol 25 mg orally every 12 hours for rate control, warfarin for chronic anticoagulation, and tapering course of oral prednisone. She was seen at follow-up 2 months later and no longer requires supplemental oxygen. Follow-up chest radiograph at 3 months showed significant visualized improvement (Figure 3).

Discussion

Only five cases of flecainide-induced lung injury have been reported in the literature. In each case, symptom onset seemed to be subacute in nature, and the disease courses were such that radiographic lung injury patterns developed over weeks to months after increasing cumulative dose exposure. Histologic findings in those reports were consistent with diffuse infiltrative lung disease with lymphocytic alveolitis.^{2–4} In our case, the patient's symptoms and radiographic findings developed acutely (within 24 hours of initial drug administration), and clinical deterioration was rapid. Radiographic findings in this case were consistent with those described previously. As in the previous case reports, the diagnosis was made after exclusion of other causes of sudden hypoxic respiratory failure. Cardiogenic pulmonary edema was eliminated based on the absence of elevated filling pressures and failure to improve clinically with effective diuresis. Clinical improvement and resolution of fever (despite early cessation of antibiotic therapy)

occurred after withdrawal of flecainide and initiation of corticosteroid therapy, a scenario consistent with acute drug-induced lung injury rather than an infectious etiology.

Drug-induced lung injury is believed to be a cell-mediated immunologic reaction. This mechanism involves phagocytosis of antigen by an antigen-presenting cell macrophage, monocyte, or dendritic cell and presenting it to T cells.⁴ Flecainide in particular has high affinity for concentrating in lung tissue.⁵ It is interesting to speculate whether chronic accumulation of amiodarone (well known to cause different types of pulmonary toxicity) could have influenced the severity of or accelerated this immune process after flecainide exposure in our patient.

Conclusion

Our report describes the first acute presentation of flecainide-induced lung injury. Although drug-induced lung injury from flecainide is rare, clinical recognition of this phenomenon is important because prolonged flecainide exposure may lead to severe or potentially fatal pulmonary compromise. Cessation of the offending agent and rapid exclusion of other etiologies such as cardiogenic edema and infection are pivotal in choosing optimal treatment.

References

1. Henthorn RW, Waldo AL, Anderson JL, Gilbert EM, Alpert BL, Bhandari AK, Hawkinson RW, Pritchett EL. Flecainide acetate prevents recurrence of symptomatic paroxysmal supraventricular tachycardia. The Flecainide Supraventricular Tachycardia Study Group. *Circulation* 1991;83:119–125.
2. Hanston P, Evrard P, Mahieu P, Wallemacq P, Friob M, Hassoun A. Flecainide-associated interstitial pneumonitis. *Lancet* 1991;337:371–372.
3. Haas M, Perault MC, Bonnefoy P, Rodeau F, Caron F. [Interstitial pneumopathy due to flecainide]. *Presse Med* 2001;30:1062.
4. Pesenti S, Lauque D, Daste G, Boulay V, Pujazon MC, Carles P. Diffuse infiltrative lung disease associated with flecainide. Report of two cases. *Respiration* 2002; 69:182–185.
5. Latini R, Cavalli A, Maggioni AP, Volpi A. Flecainide distribution in human tissues. *Br J Clin Pharmacol* 1987;24:820–822.