Very Early Onset of Amiodarone-Induced Pulmonary Toxicity

Wonho Lee, MD¹, Dong Rueol Ryu, MD¹, Seon-Sook Han, PhD¹, Sook-Won Ryu, MD², Byung Ryul Cho, MD¹, Hyucki Kwon, MD¹, and Bo Ra Kim, MD¹

¹Departments of Internal Medicine and ²Laboratory Medicine, Kangwon National University Hospital, Chuncheon, Korea

Amiodarone is a widely used antiarrhythmic agent. Among its various adverse effects, amiodarone-induced pulmonary toxicity (APT) is the most life-threatening complication, which has been described mostly in patients who have been in treatment with high accumulative doses for a long duration of time. However, amiodarone therapy in short-term duration induced APT was rarely reported. We describe a case of a 54-year-old man who is presented with symptoms of APT after a few days of therapy for post-myocardial infarction ventricular tachycardia. For early diagnosis and successful treatment, awareness and high suspicion of this rare type of early onset APT is crucial in patients with amiodarone therapy. (Korean Circ J 2013;43:699–701)

KEY WORDS: Amiodarone; Drug toxicity; Myocardial infarctions; Arrhythmias, cardiac.
Amiodarone-induced pulmonary toxicity occurred within a few days. Oxyribonucleic acid antibodies, rheumatoid factor, as well as C'3 and C'4 were all within normal limits. Pulmonary edema was also suspected and intravenous diuretics therapy (Lasix 100 mg/day for 3 days) was started; however, no interval change was noted on chest radiography after 3 kg of weight loss. A high resolution computed tomography scan of the chest showed bilateral diffuse consolidation, ground glass opacity and underlying emphysema (Fig. 1C). Owing to a high suspicion of amiodarone pulmonary toxicity (APT), amiodarone was discontinued after a total dose of 4035 mg over more than 8 days. Steroid therapy was not started due to mild respiratory symptoms. Pulmonary function tests showed mild obstructive impairment and carbon monoxide diffusing capacity (DLCO) was checked as 16.1 L (79%). As the clinical status was stabilized, bronchoscopy was performed. Bronchoalveolar lavage revealed a cell count of 200 cells/μL with prominent eosinophilia (8%) and foamy macrophages (Fig. 2). No bacteria or fungi were identified via microscopic examination or culture of the lavage fluid. Ten days after amiodarone was discontinued, the patient was discharged with mild dyspnea. Three months later, APT appeared to be reversible with the resolution of chest radiography findings (Fig. 1D) and recovery of symptoms.

**Discussion**

Amiodarone is a highly effective antiarrhythmic that is used to treat atrial fibrillation due to its high conversion rate, rapid onset of
action and minimal myocardial depression. However, amiodarone therapy has been associated with various side effects, including pulmonary toxicity, which may occur in up to 5-10% of treated patients. APT can present as several manifestations: chronic interstitial pneumonitis, organizing pneumonia, acute respiratory distress syndrome and solitary pulmonary mass. The mechanisms of amiodarone-induced pulmonary injury are incompletely understood. Two major hypotheses include direct cytotoxicity and a hypersensitivity reaction.

Risk factors for APT include a daily dose greater than 400 mg/day, a duration of therapy exceeding two months, increased patient age, preexisting lung disease, undergoing operation and pulmonary angiography. In the present case, the patient usually had no respiratory symptoms; however, a pulmonary function test and high resolution chest computed tomography showed a possibility of chronic lung disease. Additionally, cardiac catheterization was performed. Other cases of APT occurring within a week after cardiac catheterization exist. Thus, these could be the risk factors for APT. However, in our case, APT occurred only 2 days after 1635 mg of amiodarone. To our knowledge, this represents the most rapidly developed APT.

Amiodarone-induced pulmonary toxicity is a diagnosis of exclusion. Due to its non-specific nature and its ability to mimic other disease processes, such as congestive heart failure, acute pulmonary respiratory syndrome and pneumonia, the diagnosis of APT may be delayed or missed. The presence of foamy macrophages is suggestive of APT, but is not diagnostic. Increased lung attenuation on computed tomography, increased gallium uptake and abnormal pulmonary function tests are nonspecific. A reduction in DLCO of 15% is a strong indicator for the diagnosis of pulmonary toxicity due to amiodarone, with a sensitivity of 68-100% and a specificity of 69-95%. Lung biopsy may be helpful in excluding alternative etiologies and may be helpful in identifying the pathologic type of disease (e.g., chronic interstitial pneumonitis); yet, this procedure is also nonspecific for amiodarone-induced disease. In the present case, initial treatment included antibiotics and diuretics because pneumonia and pulmonary edema were suspected. Despite these treatments, symptoms and a chest X-ray were not improved until amiodarone was discontinued. Additionally, foamy macrophages were present in the bronchoalveolar lavage. Thus, our diagnosis was convincing.

Discontinuation of amiodarone is the primary therapy for amiodarone toxicity. Additionally, for patients with symptomatic pulmonary toxicity, systemic steroids may be valuable. Due to the long elimination half-life (approximately 45 days) of amiodarone, pulmonary toxicity may initially progress despite the drug discontinuation and may recur upon glucocorticoid withdrawal. In the present case, steroid therapy was not carried out due to mild respiratory symptoms.

Very early onset of APT appears to be unusual without surgery. The present case shows that APT can occur at anytime during therapy. As usage of amiodarone increases, one must be aware of a possible APT, even after a short course of amiodarone therapy.

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