SP-D as a Marker of Amiodarone-induced Pulmonary Toxicity

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Abstract

Two patients with amiodarone-induced pulmonary toxicity (APT) showed abnormally increased serum SP-D concentrations, although their KL-6 level was within the normal range. In a 59-year-old man with ischemic heart disease, APT progressed rapidly and required steroid pulse therapy. During the clinical course, SP-D was as high as 375 ng/ml, although the KL-6 level was only 289 U/ml. In a 58-year-old man treated for dilated cardiomyopathy, SP-D increased to 289 ng/ml, while KL-6 remained at less than 500 U/ml. These cases indicate that SP-D is a useful and early diagnostic marker for APT even when KL-6 is not elevated.

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Introduction

Amiodarone is used increasingly to treat life-threatening arrhythmias (1, 2). However, use of this drug is restricted due to concerns of adverse effects, especially pulmonary toxicity (1-4). Although the pulmonary carbon monoxide diffusion capacity (DLco) has been measured to detect amiodarone-induced pulmonary toxicity (APT) (5), the sensitivity, specificity and applicability to acutely ill patients remain unclarified. Recently the serum KL-6 concentration had been advocated as a useful marker for APT (3, 4). Here, we describe two patients with APT, who did not demonstrate an abnormally increased serum KL-6 concentration. However in these cases, SP-D, a marker for interstitial lung disease (6, 7) was significantly increased.

Case Report

Case 1

A 59-year-old man (case 1) had a history of anteroseptal and lateral myocardial infarction in 1988, followed by five hospitalizations for congestive heart failure (CHF) and two coronary artery bypass procedures to treat three-vessel disease in 1990 and 1995. Even after surgical procedures, he was hospitalized four times for CHF. When he was referred to our hospital in September 2000, he complained of dyspnea and general fatigue. An electrocardiogram (ECG) demonstrated complete atrioventricular block with ventricular escape beats at a rate of 40 bpm. He was admitted and underwent implantation of a permanent pacemaker (VDD pacemaker). On echocardiography, the left ventricular ejection fraction (LVEF) was 39%, LV diastolic and systolic dimensions were 67 and 54 mm, respectively, and the left atrial dimension (LAD) was 46 mm. On ambulatory ECG, multiple forms of premature ventricular complex (PVC; 17,966 beats/day) and 10 polymorphic non-sustained ventricular tachycardias were observed in association with complaints of palpitations; the longest episode was four PVC beats. Amiodarone (200 mg/day) was prescribed to treat the ventricular arrhythmia. Six months later, the patient presented to the out-patient clinic with a dry cough and chest discomfort. A chest radiograph showed increased density in both lungs, especially the right lower lobe (Fig. 1A), and he was hospitalized. The chest computed tomography (CT) disclosed bilateral ground-glass opacification (Fig. 1B), indicative of interstitial pneumonia. Slight hypoxia, increased inflammation markers and radiographic findings together with a history of treatment with amiodarone indicated a diagnosis of APT. Discontinuation of amiodarone was accompanied by treatment with antibiotics, diuretics, and inotropic agents. However, his clinical state deteriorated. Controlled mechanical ventilation was initiated, as was steroid pulse therapy with methylprednisolone 1 g × 3 days; (Fig. 2). The patient's condition gradually improved and artificial ventilation was discontinued after one week. KL-6, which was <100 U/ml before administration of amiodarone, had increased to 224 U/ml at the time of admission and subsequently increased to 289 U/ml. However, it never reached the abnormal range (>500 U/ml). In contrast, SP-D rose to 375 ng/ml, more than three times the upper limit of normal (110 ng/ml). As the patient recovered, SP-D gradually declined to 118 ng/ml over 4 months.
Figure 1. Case 1. A: A chest radiograph obtained on admission reveals increased density in the lung, especially in the right lower lobe, as well as cardiac dilation. B: A Computed tomography shows ground-glass opacities in bilateral lungs.

Figure 2. Clinical course of case 1. Peak SP-D concentration in serum is 375 ng/ml, more than three times the upper limit of the normal range (110 ng/ml, indicated by dashed line). KL-6 remains normal during the entire clinical course.

Case 2
A 58-year-old man (case 2) had undergone medical therapy for dilated cardiomyopathy since 1998, including one hospitalization for CHF before he was re-admitted to assess cardiac function. Echocardiography showed diffuse hypokinesis, LVEF was 25%, LV diastolic dimension and systolic dimensions were 68 and 60 mm and LAD was 48 mm. In hemodynamic measurements by catheterization, LVEF was 18%, cardiac index
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was 2.0 l/min/m², and LV end-diastolic pressure was 38 mmHg. Ambulatory ECG recorded 250 PVCs including one couplet, and 9,054 premature atrial complexes per day. Two days after catheterization, atrial fibrillation (Afib) with rapid ventricular response 110 to 120 bpm developed, accompanied by severe dyspnea and palpitation. Intravenous administration of digoxin (0.25 mg) and disopyramide (50 mg) and a 360-J direct-current shock were unsuccessful attempts to restore sinus rhythm. Amiodarone was initiated orally at 300 mg/day to control the heart rate and to restore sinus rhythm (Fig. 3). Two days after

![Graph showing AMD mg/day vs. time with markers for KL-6 and SP-D levels]

Mar 26  Apr 12  May 9
WBC 6,550  6,740  6,480
CRP 10.7  1.4  <0.3 mg/dl
LDH 347   260  185 IU/l

Figure 3. Clinical course of case 2. SP-D increases from 160 to 289 ng/ml, while KL-6 remains in normal during the entire course.

![Image of chest radiograph and computed tomography]

Figure 4. Case 2. A: A chest radiograph reveals only cardiomegaly without lung abnormality. B: Computed tomography shows slight ground-glass opacities peripherally and inferiorly (arrow)
the initiation of amiodarone, sinus rhythm was restored. After a week, amiodarone was continued at 200 mg/day to prevent recurrence of Afib. On the first day of amiodarone administration, KL-6 was 296 U/ml and SP-D was 160 ng/ml. Two weeks later, both KL-6 and SP-D had increased to 455 U/ml and 227 ng/ml, respectively. While KL-6 remained in the normal range, SP-D was more than two times higher than the upper limit of normal. Although a chest radiograph did not show abnormal density (Fig. 4A) and the patient was asymptomatic, chest CT showed a ground-glass appearance posteriorly in both lower lobes (Fig. 4B), indicating interstitial pneumonia. We made a diagnosis of APT, and discontinued the drug. The patient was discharged one month later, and KL-6 and SP-D gradually decreased.

Discussion

Clinical use of amiodarone is associated with concerns about adverse effects, particularly APT which reportedly occurs in 0.8 to 17% of the treated patients, and has a high mortality rate (1, 2). In managing patients treated with amiodarone, clinicians closely monitor symptoms, laboratory data, and DLco (5). However, these indicators are neither sensitive nor specific. Additionally, DLco cannot be measured in the seriously ill patients such as in the present cases.

KL-6 has been reported to be a useful marker for the detection and evaluation of APT (3, 4), and measurement of the KL-6 level is valuable for discriminating APT from other types of pneumonia and from CHF. However, in the present cases, the KL-6 level did not reach an abnormal range, while another marker, the SP-D level exceeded twice the upper limit of normal subjects. SP-D is reported to be specific for lung disease, particularly interstitial lung disease; it reflects disease activity and is useful to predict the prognosis (6, 7). As a serum marker, it can be measured even in critically ill patients. However the clinical usefulness of SP-D in patients with APT has not been reported.

The disparity between KL-6 and SP-D in the present two cases remains unexplained. SP-D is a hydrophilic surfactant protein synthesized by type II alveolar cells and Clara cells. While KL-6 is believed to be synthesized mainly by regenerating alveolar type II cells (4). Therefore KL-6 may increase more during intense alveolar regeneration. Sakamaki et al differentiated two types of APT (8). One shows characteristics of respiratory distress syndrome (ARDS) resembling pulmonary edema. The other one is a fibrosis type characterized by interstitial inflammation. The first type shows more rapid deterioration and more extensive abnormality in the chest radiograph reflecting parenchymal infiltration (8). In this type, SP-D may leak from alveolar spaces into vessels because of increased permeability associated with damaged alveolar epithelium, resulting in a particularly prominent increase in SP-D as in our first case. In the second type, possibly representing an early phase such as in our asymptomatic second case, a ground-glass appearance was demonstrated only in the lower lobes, presumably indicating an early phase of toxicity. In this case SP-D increased abnormally while KL-6 remained within the normal range. This suggests that SP-D can detect the early phase of APT, before the epithelial cells regenerate, decreasing only gradually during clinical improvement. SP-D is now measured for early detection and repeated assessment of pulmonary fibrosis of unknown etiology, and it may be similarly useful in either phase of pulmonary toxicity from amiodarone.

References