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【 CASE REPORT 】

An Acute Adverse Reaction with ST Elevation Induced by Magnetic Resonance Contrast Media: Kounis Syndrome

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Abstract:
A 78-year-old man with mild coronary arteriosclerosis on coronary CT angiography underwent MRI of the prostate with the administration of Gadolinium-based contrast agent (GBCA) (gadopentetate dimeglumine). He developed acute coronary syndrome immediately after the intravenous injection of GBCA, and recovered after the administration of nitroglycerine, atropine sulfate, and hydrocortisone. He was discharged on the ninth day of hospitalization without recurrent chest symptoms. This is the second reported case of Kounis syndrome caused by GBCA. Kounis syndrome caused by MR contrast media is rare, but we should recognize that all contrast agents have the potential to cause Kounis syndrome.

Key words: Kounis syndrome, MR contrast media

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Introduction

Kounis syndrome is defined as the concurrence of acute coronary syndrome with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid attacks (1). The causes of Kounis syndrome include several conditions, environmental exposure to various substances, and various drugs (2). We herein report the second case of type 2 Kounis syndrome induced by Gadolinium-based contrast agent (GBCA).

Case Report

A 78-year-old male patient was referred to our hospital with an elevated serum prostate specific antigen level. He was a non-smoker and his medical history was unremarkable, with the exception of essential hypertension, which was treated with amlodipine (2.5 mg). He had no previous history of chest pain and no significant family history of vasospastic angina. Electrocardiography (ECG) showed a flat or inverted T wave (Fig. 1A). A treadmill exercise test demonstrated upsloping ST-segment depression in leads II, III, and aVF. Coronary CT angiography exhibited mild sclerotic change without hemodynamically significant stenosis (Fig. 2). He had no history of allergy and had not experienced any side effects from the contrast medium. After one week, contrast-enhanced magnetic resonance imaging (MRI) of the prostate was performed with the administration of GBCA (5,199.6 mg of gadopentetate dimeglumine). Immediately after the intravenous injection of GBCA, he complained of a tingling sensation throughout his body and throat discomfort, followed by chest discomfort, dry cough, and shortness of breath. Image acquisition was immediately interrupted, but he exhibited a decreased level of consciousness. ECG monitoring demonstrated ST segment elevation and bradycardia. He accepted assisted ventilation with a bag valve mask and fluid replacement. The 12-lead ECG revealed ST segment elevation in the inferior leads with complete atrioventricular block (Fig. 1B). A physical examination revealed a blood pressure and heart rate of 122/99 mmHg and 42 bpm, respectively. Following the immediate treatment with sublingual nitroglycerine (0.3 mg), isosorbide dinitrate (2.5 mg), atropine sulfate (0.25 mg), and hydrocortisone (200 mg, intravenous), his blood pressure became de-

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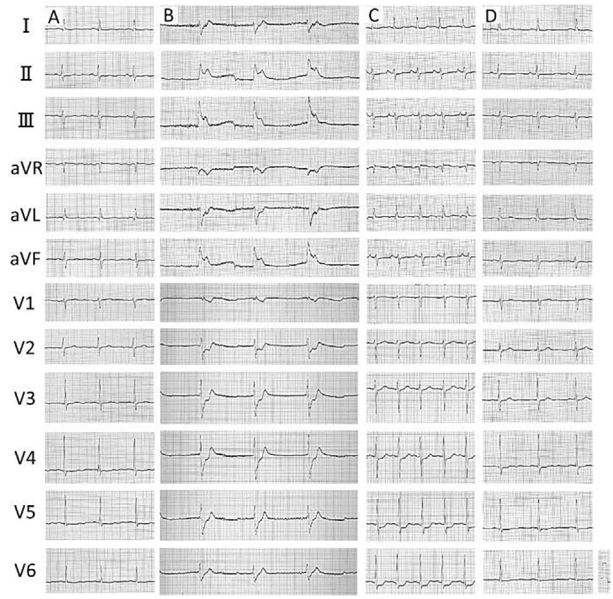

Figure 1. **Time course of ECG changes. The 12-lead ECG on first visit (A) and at the time of chest symptoms (B). When illness appeared, ECG demonstrated ST segment elevation in the inferior leads with complete atrioventricular block. Repeat ECG demonstrates improvement of ST segment elevation and depression after treatment (C) and completely resolved ST segments changes on the seventh day of hospitalization (D).**

pressed and measured 72/48 mmHg. Afterwards, his cardiac rhythm reverted to a sinus rhythm, and his blood pressure recovered to 110/74 mmHg. His consciousness level and symptoms gradually improved. ECG revealed resolving ST-segment elevation and depression (Fig. 1C). After his circulation stabilized, echocardiography revealed no regional wall motion abnormalities or intracardiac shunt. On admission for observation, his blood pressure was 91/67 mmHg and his pulse rate was 60 bpm. Intravenous heparin was continued for one day. The patient's remaining stay at the hospital was uneventful, with the exception of nasal discharge, which persisted for a few days. Repeat ECG revealed the further resolution of ST segment depression and showed the complete resolution of the ST segment changes on the seventh day of hospitalization (Fig. 1D). The results of a blood examination at the time of admission revealed normal levels of cardiac enzymes, troponin T, and blood eosinophils. However, creatine kinase-MB was elevated to 32.9 (normal value: 15 U/L), and a qualitative test for heart-type fatty acid-binding protein was positive. A repeated workup revealed that the creatine phosphokinase, aspartate aminotransferase, and alanine aminotransferase levels were within the normal limits, while lactate dehydrogenase was mild elevated to 224 U/L (normal range: 106-211 U/L) on the third day and mild eosinophilia (7.1%) was observed on the sixth day. The non-specific total immunoglobulin E levels were within normal limits and a drug-induced lymphocyte stimulation test was negative for gadopentetate dimeglumine. The patient refused to undergo coronary artery angiography, and was discharged on the ninth day of hospitalization.

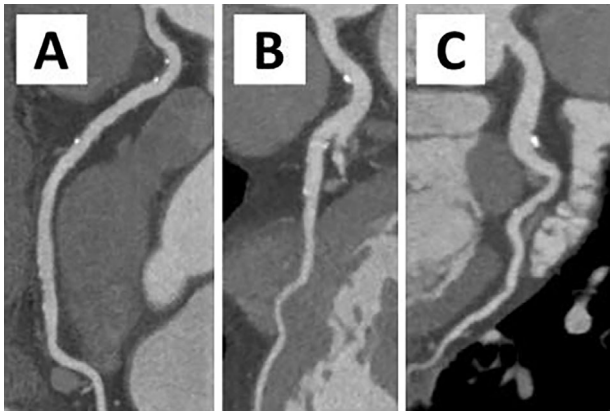

Figure 2. **Coronary CT angiography of the right coronary artery (A), left anterior descending artery (B), and left circumflex coronary artery (C). Coronary arteries exhibit mild sclerotic change without significant stenosis.**

Discussion

The diagnosis of Kounis syndrome is based on clinical symptoms and signs, as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence. In this case, the diagnosis mainly relied on the patient's typical symptoms and ischemic ECG change. The right coronary artery spasms, which were not confirmed by angiography in this case, were suggested by coronary CT angiography performed one week previously and serial ECGs.

The actual incidence of Kounis syndrome is yet to be determined. In a retrospective study, the annual incidence of severe life-threating anaphylaxis with circulatory symptoms per 100,000 inhabitants per year ranged between 7.9 and 9.6 cases (3). On an analysis of adverse drug-related events through VigiBase™, 51 cases of Kounis Syndrome were reported during the period of 2010-2014 (4). An increase in the number of cases of Kounis syndrome is expected in the future as more physicians become aware of the condition. On the other hand, the incidence of adverse reactions to GBCA is much lower than that observed with iodinated contrast media. In cases of immediate hypersensitivity reactions to GBCA, most reactions are classified as mild. The incidence of acute severe adverse reaction and anaphylactic shock to GBCA is 0.002-0.01% (5-9), and 0.0005-0.01% (6, 9), respectively. Thus, GBCA is still considered to be very safe, with severe adverse reactions being extremely rare. Although the drug-induced lymphocyte stimulation test was negative for GBCA in our case, we hypothesize that GBCA may have been the causative agent because Kounis syndrome occurred immediately after its administration. To the best of our knowledge, there is only one previous report of Kounis syndrome attributed to GBCA (10). The patient in the first report had multiple drug allergies.

Mast cells play a central role in the mechanism underlying Kounis syndrome. The degranulation of mast cells leads to the release of mediators of allergic inflammation, includ-

ing histamine, proteases, leukotrienes, tromboxanes, and platelet activation factor (11). In the case of immediate hypersensitivity reactions to MR contrast media, the pathophysiological mechanism is largely unknown. However, an experimental report suggests that MR contrast media can induce mast cell degranulation *in vitro* (12).

Three variants of Kounis syndrome have been described (11). Type 1 refers to patients with normal coronary arteries without any cardiovascular risk factors. Type 2 occurs in patients with existing coronary artery disease, and type 3 occurs in patients with stent thrombosis. The present case is consistent with type 2 Kounis syndrome, as sclerotic change in the coronary vasculature was observed on CT angiography.

The therapeutic management of Kounis syndrome is challenging because it requires addressing both the allergic reaction and acute coronary syndrome. In patients with the type II variant, treatment should be initiated with an acute coronary event protocol together with corticosteroid and antihistamine treatment. Vasodilators, such as nitroglycerin or Ca Channel blockers, can reverse the coronary spasms, but may induce hypotension and tachycardia, as was observed in the present case (2, 4).

We presented a rare case of Kounis syndrome due to the usage of GBCA. This syndrome should be kept in mind during MRI with GBCA.

The authors state that they have no Conflict of Interest (COI).

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