A Case of Coronary Spasm with Resultant Acute Myocardial Infarction: Likely the Result of an Allergic Reaction

Mustafa Yurtdaş¹ and Mehmet Kasım Aydın²

Abstract

Kounis syndrome has been known as allergenic angina and/or allergenic myocardial infarction following an allergic reaction. Probable allergic insults usually include drugs, latex, and food. Although ceftriaxone administration has been associated with various allergic reactions such as urticaria, angioedema, erythema, rash and anaphylactic shock, as far as we know, there is no published report that has shown an association between ceftriaxone use and Kounis syndrome. Here, we describe the first report of allergic vasospasm, culminating in acute inferior myocardial infarction, probably as the result of an acute allergenic reaction, after ceftriaxone use.

Key words: ceftriaxone, allergy, acute coronary syndrome

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Introduction

Angina and acute myocardial infarction (AMI) secondary to allergy-induced coronary vasospasm are referred to as Kounis syndrome (KS). Many allergenic factors including drugs, latex, food, contrast media and Hymenoptera venom have been implicated in causing KS. During allergic episodes, some chemical agents such as histamine, leukotrienes, and neutral proteases are increased in the peripheral circulation, and hence, these elevated agents may cause coronary artery spasm (CAS) and atheromatous plaque rupture (1). Ceftriaxone is a third-generation cephalosporin antibiotic that has broad spectrum activity against Gram-negative and Gram-positive bacteria (2). Although ceftriaxone administration has been associated with various allergic reactions such as urticaria, angioedema, edema, erythema, maculopapular rash and anaphylactic shock (2, 3), to the best of our knowledge, there is no report about whether ceftriaxone gives rise to allergenic acute coronary syndrome or not. Here, we define a case of severe CAS, culminating in acute inferior myocardial infarction (MI), as the result of an acute allergenic reaction, which was likely related to ceftriaxone use.

Case Report

A 42-year-old man with no history of known atopy or cardiovascular risk factors presented to our emergency department with the chest pain, severe dyspnea, sweatings, nausea, vomiting and, urticarial and edematous lesions approximately twenty minutes after the use of ceftriaxone. On clinical examination, swelling of the lip and mouth mucosa was noted as well as urticarial lesions with pruritis on the skin of the abdomen and leg; his blood pressure was 75/40 mmHg. Electrocardiogram (ECG) displayed sinus rhythm, heart rate of 60-65 bpm, and ST segment elevation on D_{II}, D_{III} and aV_F derivations, compatible with acute inferior MI (Fig. 1A). In the emergency department, for acute coronary syndrome, acetylsalicylic acid (300 mg), clopidogrel (a loading dose of 600 mg) and intravenous heparin (10,000 IU) were administered. Following intravenous fluid, parenteral corticosteroids and antihistaminics were given for his allergic symptoms; his blood pressure was elevated to 110/70 mmHg, his skin-mucosal membrane and urticarial lesions regressed, but AMI-related symptoms were not improved. Thereafter, the patient immediately underwent coronary an-

¹Department of Cardiology, Lokman Hekim Hospital, Turkey and ²Department of Internal Medicine, University of Mersin, Turkey

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Correspondence to Dr. Mustafa Yurtdaş, mustafayurtdas@yahoo.com

Figure 1. Electrocardiogram shows sinus rhythm and ST segment elevation during the first admission (A), and nearly complete resolution of ST segment elevation after intracoronary nitroglycerine injection (B) in inferior leads.

Figure 2. Left anterior oblique view of a severe spasm of the proximal part of the right coronary artery before (A), and left anterior oblique and slightly caudal view of TIMI III flow with no residual lesion of the right coronary artery after intracoronary nitroglycerine injection (B).

giography for primary percutaneous coronary intervention. Coronary angiogram demonstrated that the patient had minimal coronary plaques and irregularities, except for the 98% stenosis of the proximal part of the right coronary artery (RCA) associated with severe vasospasm (Fig. 2A). For this reason, nitroglycerine (300 µg) was given via intracoronary route. About one minute after intracoronary injection of nitroglycerine, right coronary angiogram was repeated, and showed complete resolution of the coronary vasospasm with no residual lesion (Fig. 2B). Anginal symptoms of the patient markedly recovered, and ECG displayed complete regression of ST segment elevation in inferior leads (Fig. 1B). At the first hour of admission, blood tests revealed tryptase and Troponin-T values of 29 µ/L (normal reference: 5-14) and 0.02 ng/mL (normal reference: <0.04), respectively.

Twelve hours later, plasma tryptase value returned to the normal range (4.7 µ/L) and Troponin-T value rose to 3.7 ng/mL. An allergic skin test was performed, and gave positive result for ceftriaxone. Factor V Leiden and prothrombin gene mutation tests were executed and identified to be normal variant. Other tests disclosed the following: total cholesterol 176 mg/dL (normal reference: 125-200), triglyceride 104 mg/dL (normal reference: 50-150), fibrinogen 2.6 g/L (normal reference: 2.0-4.5), homocysteine 5.2 µmol/L (normal reference: <12), antithrombin III activity 109% (normal range: 70-125%), prothrombin time 14 second (normal range: 10-14), and activated partial thromboplastin time 35 second (normal range: 25-36). The patient was discharged without any complication after five days.

Discussion

KS, defined as the co-incidental occurrence of acute coronary syndrome with hypersensitivity reactions following an allergenic event, was first described by Kounis and Zavras in 1991 as an allergic angina syndrome (4). Then, it was shown that KS is not only limited to anginal symptoms, but it also could progress to AMI. In addition, coronary vasospasm and/or plaque disruption can be provoked by allergic reactions on coronary vascular smooth muscle, resulting in a new cause of coronary vasospasm (1).

Several pathophysiologic mechanisms have been proposed to explain the cardiac involvement during anaphylactic reactions (1, 5). Mast cell activation takes place by antigen-antibody complex or the allergen itself following allergen exposure. Thereafter, several vasoconstricting and collagen degrading products, such as histamine, platelet activating factor, cytokines, chemokines, neutral proteases (tryptase, chymase), and renin are released into circulation (1, 5, 6). Moreover, the endothelial and platelet activation induced by histamine may further contribute to coronary plaque denudation and/or rupture, resulting in thrombus formation (1). Hence, during an anaphylactic reaction, all of these factors may act together on the emergence of coronary vasospasm, as in the present case, eventually progressing to an AMI.

There are two well-known variants of Kounis syndrome. The type-I variant is observed in patients with no cardiovascular risk factors and normal coronary arteries in whom the acute release of inflammatory mediators produces either CAS with normal cardiac enzymes and troponins or CAS leading to AMI accompanied by elevated levels of markers of cardiac damage. The type-II variant includes patients with culprit but reticent pre-existing atheromatous disease in whom acute hypersensitive reactions cause plaque erosion or rupture, culminating in AMI (1). More recently, a type-III variant of KS has been defined in patients with a drug-eluting coronary stent thrombosis (1, 7). In the present case, coronary arteriography displayed a severe CAS in the proximal portion of the RCA, with an elevated troponin level following an exposure to allergenic insult, ceftriaxone, and showed a normal coronary artery with luminal irregularities after intracoronary infusion of a vasodilator such as nitroglycerin. Based on these clinical data, our case corresponds to the type 1 variant of KS.

Some allergens have been implicated as the main trigger factors for KS. These allergens include drugs (antibiotics, analgesics, antineoplastics, thrombolytics, and others), contrast agent, latex, food and Hymenoptera venom (1, 5, 7-9). Although there are many antibiotics that have been previously reported to cause KS (8, 9), to the best of our knowledge, there is no case of KS related to the use of ceftriaxone, which is in a class of medication called cephalosporin antibiotic. Ceftriaxone injection is used to treat some infections caused by bacteria, including infection of the lungs, ears, skin, urinary tract, blood, bones and abdomen. It has

been reported that ceftriaxone may give rise to various allergic reactions such as urticaria, angioedema, edema, erythema, maculopapular rash and anaphylactic shock (2, 3). The present case is the first report of an AMI associated with severe CAS following ceftriaxone use.

CAS has been declared as a primary event or an important secondary factor in the pathophysiology of the variant angina, catheter-induced vasospasm and fixed obstructive coronary stenosis (10). Failure to identify and control for CAS may cause incompatible revascularization and medical therapy. The differential diagnosis between allergic CAS and variant angina, catheter-induced vasospasm should be considered owing to their similar clinical pictures. Variant angina is a form of angina pectoris that shows transient ST segment elevation during an attack of chest pain. Patients with variant angina have usually normal or near-normal angiographic findings and ischemic episodes that often occur at rest from midnight to early morning (10, 11). In addition, the diagnosis of a catheter-induced vasospasm should be punctiliously made. A catheter-induced spasm usually appears in a short segment of rough 1 mm with smooth concentric area of narrowing at the catheter tip (10), in contrast to the present case (angiogram delineated a vasospasm of eccentric, irregular features, and the location of spasm was more than 3-5 mm away from the ostium of the RCA).

Especially in younger patients, taking a careful history and performing hematologic and biochemical tests are very important to rule out some responsible etiological factors and diseases such as illicit drug abuse (cannabis and cocaine smoking), lupus anticoagulant, increased homocysteine level and deficiency of antithrombin III (12). The determination of plasma tryptase level is crucial for the diagnosis of an anaphylactic reaction, because this marker is elevated during cases of systemic anaphylaxis. A blood sample should be taken between 15 and 120 minutes after the onset of symptoms of acute allergenic event (1, 6).

The case presented was ascribed to acute coronary syndrome secondary to an allergic event for several reasons. First, the patient's cardiac and allergenic complaints started about twenty minutes after receiving ceftriaxone. Secondly, this case fulfills the diagnostic criteria for anaphylactic reaction, such as reduced blood pressure, involvement of the skin-mucosal membran and gastro-intestinal symptoms that rapidly improved with the therapies of fluid, parenteral corticosteroids and antihistaminics. Thirdly, coronary angiography clearly delineated the coronary vasospasm responding to intracoronary nitroglycerine, following a pre-treatment with antiplatelet and anticoagulant for AMI. Moreover, positive allergic skin test and increased tryptase levels observed in our case confirm cardiovascular hypersensitivity to ceftriaxone.

In conclusion, anaphylaxis by ceftriaxone is likely responsible for the severe CAS, culminating in acute inferior MI in the present case. Complete recovery of clinical symptoms, hemotological, biochemical and angiographic findings show that KS caused by ceftriaxone should be kept in mind for

the differential diagnosis of patients who presented with an AMI and allergenic findings.

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

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