

Letter to the Editor

## Kounis syndrome secondary to amoxicillin/clavulanic acid use

Yusuf Tavil\*, Murat Turfan, Sedat Türkoğlu, Adnan Abacı

*Gazi University Medical School, Department of Cardiology, Ankara, Turkey*

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### Abstract

Myocardial injury and acute coronary syndrome have been rarely associated with amoxicillin/clavulanic acid intake. The responsible pathogenetic mechanism is described by an amplified mast cell degranulation inducing coronary artery spasm and/or acute myocardial infarction in susceptible individuals which is called Kounis syndrome. We report here a case of Kounis syndrome presented with acute coronary syndrome due to amoxicillin/clavulanic acid use. All other etiologies, including ischemic reinfarction were appropriately ruled out.

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### 1. Introduction

Amoxicillin/clavulanic acid (ACA) is a widely used broad-spectrum antimicrobial agent. ACA consists of the semisynthetic penicillin amoxicillin and the beta-lactamase inhibitor, clavulanate potassium [1]. Few adverse reactions to the molecule have been described so far. The most frequently reported adverse effects were diarrhea/loose stools (14.5%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). Although hypersensitivity reactions have been rarely reported, these reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens [2].

The concurrence of acute coronary syndromes (ACS) with mast cell activation induced by allergic or hypersensitivity and anaphylactic or anaphylactoid reactions have been reported infrequently. It was first described by Kounis as “allergic angina syndrome” progressing to “allergic myocardial infarction”. So, the condition has been called “Kounis syndrome” recently [3,4].

Herein, we present a patient who developed acute coronary syndrome following an allergic reaction after ACA administration and we describe the pathophysiology and clinical implications of this syndrome.

### 2. Case report

A 61-year-old man with a history of ischemic heart disease was admitted to our emergency department (ED) because of chest pain radiating to his left arm, dyspnea, and mild pruritic skin rashes. His complaints had started approximately 10 min after ingesting an oral dose of 1000 mg of ACA. He was admitted to the emergency room of 45 min after the onset of the symptoms. He had inferior wall myocardial infarction a month ago and had been treated with percutaneous coronary balloon angioplasty on his culprit coronary lesion. He was discharged from our cardiology department without any events. On admission, his electrocardiogram showed ST segment elevations in leads V<sub>1</sub>, V<sub>2</sub>, and V<sub>3</sub>, indicating acute antero-septal injury. (Fig. 1A) Troponin-T sent on arrival to the ED was 0.167 µg/L (reference value: 0.1 g/L). A repeat Troponin-T (4 h later) was 0.288 µg/L. Creatine kinase-MB fraction (CK-MB) measurements revealed values of 26, 55 and 86 mg/dL respectively on his follow-up period. Hence, acute coronary

\* Corresponding author. Erzurum m. Gul s. 5/23, Cebeci, Ankara Turkey.  
Tel.: +90 312 2025647; fax: +90 312 2129012.

E-mail address: yusuftavil@gmail.com (Y. Tavil).

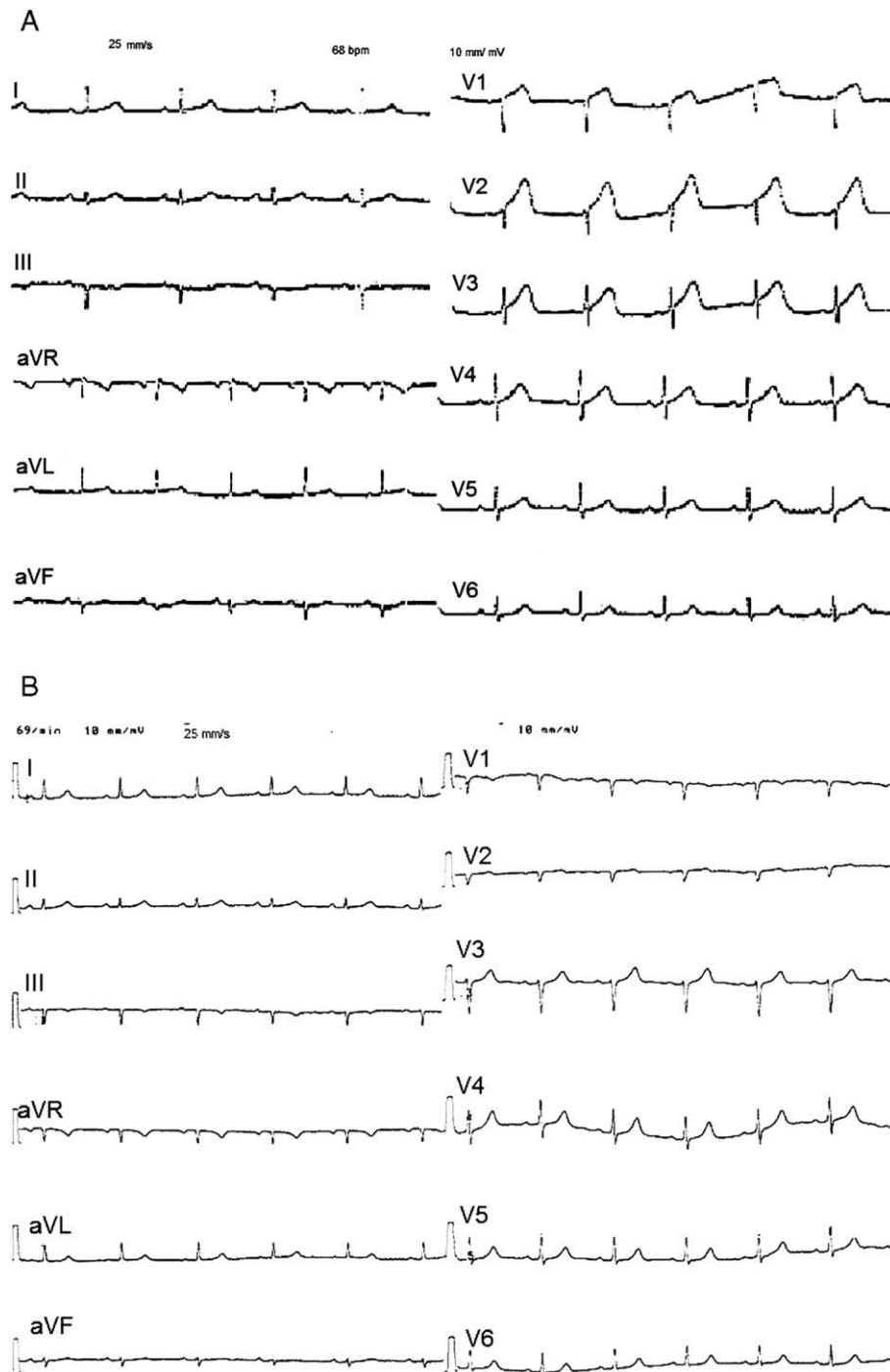


Fig. 1. A: Electrocardiogram showing ST elevation in V<sub>1</sub>–V<sub>4</sub> leads compatible with acute anterior myocardial infarction on admission. B: Electrocardiogram showing complete ST segment resolution in V<sub>1</sub>–V<sub>4</sub> leads before discharge from hospital.

syndrome was diagnosed and the patient was transferred to the coronary care unit. Therefore acute myocardial infarction was considered, coronary angiography was performed which did not demonstrate any additional significant obstructive coronary artery disease compared to previous one (Fig. 2). An allergic reaction was thought since his chest

pain stated instantly after ACA use. Detailed history revealed similar clinical picture including skin rashes and dyspnea after another dose of oral ACA 6 months ago. Unfortunately, the patient had received the same drug due to a sore throat without any consultation. After coronary angiography oral antihistamine therapy (pheniramine maleate

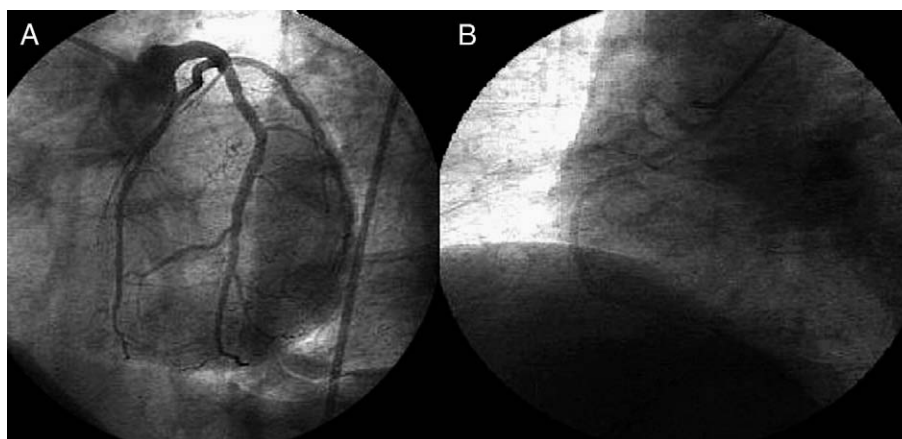


Fig. 2. Coronary angiogram revealing any obstructive lesion in coronary arteries, (A: left cranial view) (B: Right anterior oblique view).

25 mg, po) was started to the patient who has complete relief of chest pain and ST segment resolution (Fig. 1B). Troponin-T on the second day was 0.018 µg/L. The patient was discharged on the fourth day of admission.

### 3. Discussion

In this case, we describe a patient who developed acute coronary syndrome after receiving ACA. We believe that abnormalities in electrocardiogram and cardiac markers were ascribed to ACA use for several reasons. First, chest discomfort was started just after taking ACA and secondly clinical situation completely resolved after withdrawal of the drug. Furthermore, other etiologies of ACS (e.g., myocardial infarction due to restenosis of coronary vessel) were appropriately ruled out by angiography. Due to the presence of similar symptoms in his medical history, we possibly considered that Kounis syndrome (KS) was associated with this condition.

KS is characterized by the concurrence of ACS with mast cell activation induced by inflammatory mediators released during the allergic reaction. Two types of KS are recognized. The first exists in patients with normal coronary arteries in whom the allergic episode induces coronary spasm progressing to acute myocardial infarction; develops with or without raised cardiac enzymes and troponins. This type might be associated with endothelial dysfunction or microvascular angina. In the second type, coronary spasm occurs adjacent to a pre-existing atheromatous disease in which allergic stimulation can cause plaque erosion or rupture manifesting as an ACS. Accordingly, the present case was concordant with Type-II of KS [4–6].

In previous reports, only three ACA-induced KS cases were reported [7–9]. Two of them had developed after taking oral ACA in patients who had normal coronary arteries [8,9]. The third case had progressed after intravenous penicillin use in a cancer patient [7]. All of them were

concordant with type-I of KS. In this respect, our case is the first report of Type-II-KS due to ACA use. Of course ACS due to atherosclerotic coronary occlusion had to be ruled out by coronary angiography.

The main pathophysiologic mechanisms of KS were described as expressing an amplified mast cell degranulation which induces coronary artery spasm and/or acute myocardial infarction. This especially affects susceptible individuals who are more vulnerable to coronary artery spasm. During mast cell degranulation several vasoactive (e.g. Histamine, leukotrienes and serotonin), and collagen-degrading compounds (e.g. neutral proteases) are released locally and in the peripheral circulation. These mediators cause a powerful vasoconstriction in the coronary arteries. In addition, histamine activates the platelet which triggers thrombosis. Also, histamine mediated endothelial activation contributes to the progressing of ACS by provocation and initiation of coronary artery spasm and/or plaque erosion or rupture [5,6].

In closing, amoxicillin/clavulanic may cause acute coronary syndrome. Complete resolution of clinical symptoms, biochemical findings and exclusion of coronary stenosis may suggest that Kounis syndrome should be thought in the differential diagnosis of acute coronary syndromes. Clinicians should be aware of this adverse affect and consider it during diagnostic workup of myocardial injury.

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