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Case Report

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Amoxicillin-clavulanic Acid-induced Kounis Syndrome

Amoksisilin-klavulanik Asitin İndüklediği Kounis Sendromu

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ABSTRACT

Kounis syndrome (KS) is a condition in which an acute coronary syndrome occurs simultaneously with allergy, hypersensitivity, anaphylaxis, or anaphylactoid reactions caused by the activation of mast cells. The release of various mediators primarily histamine due to degranulation of mast cells plays a role in the pathophysiology of certain diseases. We report a case of KS with acute inferior ST-segment elevation myocardial infarction following oral use of an antibiotic containing amoxicillin-clavulanic acid.

Keywords: Amoxicillin, allergic myocardial infarction, acute coronary syndrome, Kounis syndrome

ÖZ

Kounis sendromu (KS) (alerjik miyokard infarktüsü), mast hücrelerinin aktifleşmesiyle oluşan alerji, hipersensitivite, anafilaksi veya anaflaktoid reaksiyonlar ile ilişkili akut koroner sendromun eş zamanlı meydana gelmesi durumudur. Patofizyolojide mast hücrelerinin degranülasyonuna bağlı olarak başta histamin olmak üzere çeşitli mediyatörlerin salınımı rol almaktadır. Amoksisilin-klavulanik asit içeren antibiyotiğin oral yoldan kullanımını takiben gelişen akut inferior ST-segment elevasyonlu miyokard infarktüsü tablosu ile başvuran KS olgusunu sunduk.

Anahtar Kelimeler: Amoksisilin, alerjik miyokard infarktüs, akut koroner sendromu, Kounis sendromu

INTRODUCTION

Kounis syndrome (KS) is a rare but clinically critical syndrome characterized by the development of coronary artery vasospasm, plaque rupture or stent thrombosis due to systemic inflammatory mediators during allergic or anaphylactic reactions. First described by Kounis (1) in 1991, it is also called "allergic myocardial infarction (MI)" and is usually associated with a pathophysiological process in which myocardial ischemia is triggered by histamine, tryptase, and other mediators released from mast cells. KS may present with symptoms of acute coronary syndrome in atopic individuals following exposure to various triggers such as drugs, food, and insect stings. In this case report, a clinically instructive case of the diagnosis and management of KS will be shared.

CASE REPORT

A 42-year-old male smoker with no known diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, or history of alcohol consumption was admitted to the emergency unit of our hospital with complaints of pruritus, rash, urticaria, dyspnea, and burning chest pain that started approximately 1 hour after taking 1000 mg amoxicillin-clavulanic acid orally. Vital signs were stable (temperature 36.6 °C, pulse rate 85 beats/minute, blood pressure 125/72 mmHg, SpO^2 98%, respiratory rate 12/minute) and he was rapidly administered diphenhydramine 45.5 mg intravenously, methylprednisolone sodium succinate 80 mg, and 500 mL saline. After the electrocardiogram showed ST segment elevation in leads DII, DIII, aVF, V5, and V6 and ST segment depression in leads D1, aVL, V1, and V2 (Figure 1), the patient was quickly taken to the catheterization laboratory for emergency selective coronary angiography with a preliminary diagnosis of acute inferior ST-elevation myocardial infarction (STEMI).

Right-left selective coronary angiography was performed (Figure 2). Normal epicardial coronary anatomy was found in the left circumflex artery and left anterior descending artery territory. In the right coronary artery (RCA) territory, 80% stenosis was observed in the distal lumen before crux. After the intracoronary administration of 400 micrograms glyceryl trinitrate, a complete patency was observed in the lumenogram. There was no evidence of coronary dissection, coronary plaque, or intracoronary thrombus in this region. This lesion in the RCA was evaluated as coronary

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vasospasm (Figure 2). The coronary angiography procedure was terminated. Ventriculography did not show any finding consistent with apical ballooning syndrome. In the anamnesis, it was learned that the patient had not experienced intense emotional stress recently. Myocarditis and tako-tsubo syndrome were ruled out in the differential diagnosis because of electrocardiography (ECG), transthoracic echocardiography, and auscultation findings (no friction rub). The patient was evaluated for antibiotic-associated coronary vasospasm and diagnosed with KS type 1 variant. ECG performed after coronary angiography showed a left ventricular ejection fraction of 55%. The left ventricular inferior wall was mildly hypokinetic, and no segmental motion defects were observed in the other walls. Valve structures and functions were reported as normal. In laboratory tests, the troponin was 388 ng/L (0-16), low-density lipoprotein was 105 mg/dL (20-100), thyroid-stimulating hormone was 0.396 mUI/L (0.34-5.6), alanine aminotransferase was 23 U/L (5-50), aspartate aminotransferase was 25 U/L (5-50), urea was 28 mg/dL (17-43), creatinine was 0.67 mg/dL (0.67-1.17), sodium was 134 mmol/L (136-146), potassium was 4.7 mmol/L (3.5-5.5), glucose was 98 mg/dl (74-106), c-reactive protein was 13.4 mg/L (0-5), erythrocyte sedimentation rate was 4 mm/h (0-15), hemoglobin was 15.2 g/dL (12.5-16.3).

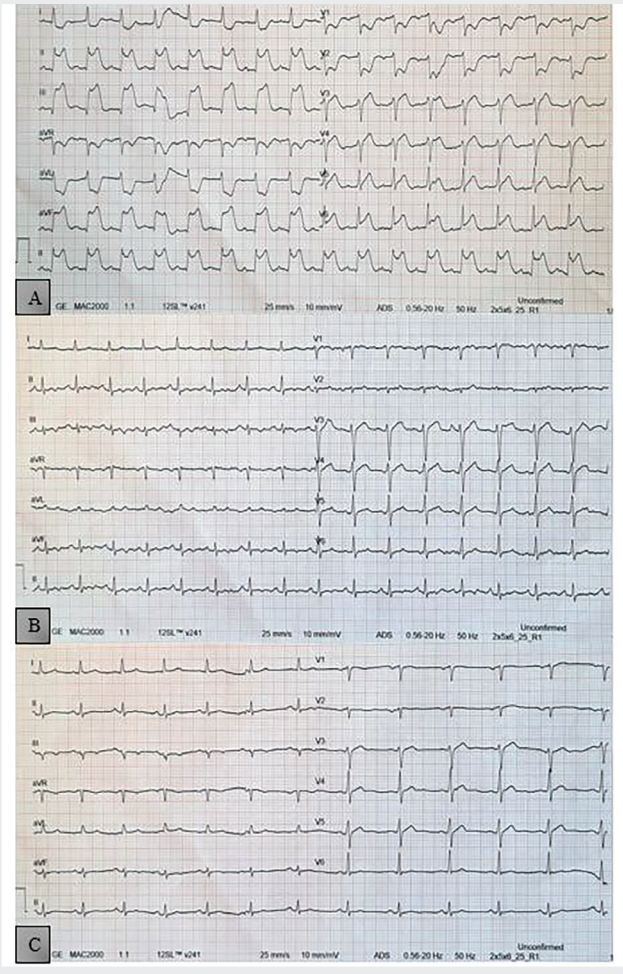

Figure 1. Electrocardiograms obtained at the time of presentation to the emergency department (A), 1 hour (B) and 24 hours (C) after the selective coronary angiography procedure

Our patient did not have chronic drug use, a history of previous allergic reactions, or any atopic diseases such as atopic dermatitis, asthma, and rhinitis. However, since KS develops as a result of an allergic reaction, the risk of recurrence may be high upon re-exposure to the triggering agent. The patient should be educated about exposure to the triggering agent. Treatment options such as antihistamines, corticosteroids, and epinephrine autoinjectors can be offered to the patient in case of recurrence.

After 48 hours of clinical follow-up, oral anti-histamine (fexofenadine 180 mg/day), calcium channel blocker (dilazem 120 mg/day), and antibiotic (clarithromycin 1000 mg/day) treatments were prescribed, education was given about exposure to the causative agent, and the patient was discharged with healing. Informed consent was obtained from our patient.

DISCUSSION

KS is characterized by the simultaneous occurrence of acute coronary syndromes such as coronary spasm (type I variant), acute MI (type II variant), and stent thrombosis (type III variant) in the context of allergic or hypersensitivity reactions, including anaphylactic or anaphylactoid events (1-4). KS can be triggered by various drugs (aspirin, antihypertensives, corticosteroids, antibiotics and non-steroidal anti-inflammatory drugs), foods, environmental factors (insect stings, snake bites), and clinical conditions (1-4). KS is triggered by the release of inflammatory mediators including histamine, platelet-activating factor, arachidonic acid derivatives, neutral proteases, various cytokines and chemokines during the allergic activation process. The KS type I variant includes patients without atherosclerotic coronary artery disease who develop coronary artery spasm secondary to acute release of inflammatory mediators (1-4). The KS type II variant includes patients with atherosclerotic heart disease who develop MI in the background of coronary plaque rupture or erosion secondary to acute release of inflammatory mediators (1-4). The KS type III variant includes patients with prior percutaneous coronary intervention who present with stent thrombosis or stent restenosis following a severe allergic reaction (5).

The diagnosis of KS is based on clinical symptoms and signs as well as laboratory, ECG, echocardiographic, and angiographic evidence. The main clinical signs of KS are cardiac symptoms accompanied by allergic reactions (1-3). Acute chest pain, chest tightness, dysphagia, dyspnea, syncope, headache, weakness, nausea, vomiting, and skin itching are observed as clinical symptoms, whereas cold extremities, hypotension, pallor, tachycardia, skin flushing, bradycardia, cardiorespiratory

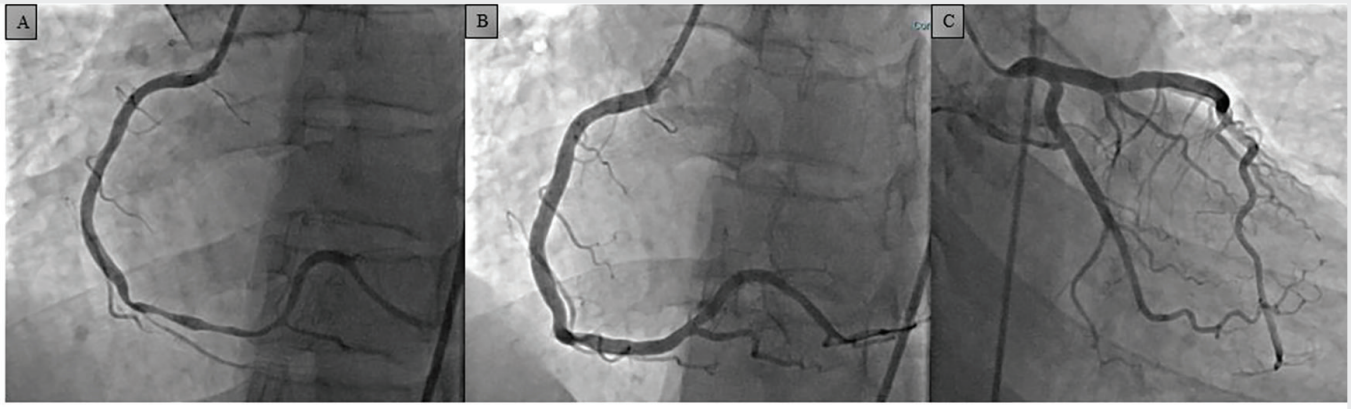

Figure 2. Selective coronary angiography recordings (A) Left oblique fluoroscopic image of severe vasospasm in the distal portion of the right coronary artery (RCA) (B) Left oblique fluoroscopic image showing complete resolution of this vasospasm after intracoronary nitrate administration (C) Right caudal fluoroscopic image showing normal left coronary system (LAD and LCx) LAD: Left anterior descending artery, LCx: Left circumflex artery

arrest, and sudden death may be observed as clinical findings (1-3). Various ECG changes including ST-segment elevation or depression, heart blocks, and cardiac arrhythmias are almost always associated with cardiac symptoms and signs. These symptoms/findings and ECG changes, which are often accompanied by allergic symptoms, aid in making the correct diagnosis (1-3).

Chatterjee et al. (4) recently presented a case of KS in a 44-year-old female patient who presented with sweating, dizziness, rash, chest tightness, and epigastric discomfort 1 hour after 625 mg of oral amoxicillin clavulanate, whose electrocardiogram revealed ST segment changes and troponin I elevation, and who had no comorbidities.

Chest pain in 63.6% and allergic reaction in 75.8% were the most common clinical findings in a review of 33 cases (median age 58 years, 81.8% male) by Wang et al. (5) who developed KS following amoxicillin use (6 cases (48.5%) amoxicillin, 7 patients (51.5%) amoxicillin-clavulanic acid) (4). In the diagnostic evaluation, troponin elevation was detected in 72.7%, ST-segment elevation, on electrocardiogram in 81.2%, and coronary artery thrombosis in 53.6% (4,5).

Ridella et al. (6) found skin reactions in 13 cases, respiratory symptoms in 7 cases, gastrointestinal system symptoms in 2 cases, chest pain in 11 cases, hypotension in 12 cases, ST segmen elevation on electrocardiogram in 16 cases, and troponin elevation in 10 cases (mean age 60 years, 76% male) who developed KS related to beta-lactam antibiotics (oral, intravenous or intramuscular route) (4). They found that all reactions occurred within 30 minutes and ST segment elevation was found in all patients, except one. In 10 cases, they found normal coronary arteries (4,6). In this series, as in our case, acute inferior STEMI was the most common type, and the RCA was found to be the coronary artery responsible for vasospasm.

Corticosteroids, antihistamines, and supportive treatment are usually sufficient in the KS type I variant. Calcium channel blockers may be used to eliminate coronary spasm. In the KS type II and III variant, appropriate acute coronary syndrome protocols need to be followed, in addition to the administration of antihistamines and steroids. In the KS type III variant, urgent aspiration of the thrombus and desensitization methods are required (4).

Our case describes type I KS following the use of oral amoxicillin clavulanic acid. This case highlights coronary vasospasm during an ongoing allergic reaction and its management with antihistamines, steroids, calcium channel blockers, and antiplatelet drugs.

The long-term follow-up of patients with KS should include careful monitoring for cardiovascular health and allergic reactions. Regular cardiac monitoring (echocardiography, biomarkers), education on avoiding triggering allergens, and allergic prophylaxis when necessary are important. With a multidisciplinary approach, it is important to ensure the cooperation of cardiology and allergy specialists.

In conclusion, in addition to clinical, ECG, and laboratory indicators of acute myocardial ischemia, patients presenting with systemic allergic reactions should be evaluated for the possibility of MI.

CONCLUSION

During allergic or anaphylactic shock reactions following the use of amoxicillin-clavulanic acid, it should be considered that KS may develop in the presence of symptoms suggestive of acute coronary syndrome, such as (chest pain, shortness of breath) electrocardiogram changes/or elevated levels of markers of myocardial damage (troponin). Therapeutic management of KS

requires simultaneous treatment of cardiac and allergic symptoms.

Although KS is a rare entity, its development in our case after an oral antibiotic, commonly used in community-acquired infections, suggests that this syndrome is a diagnosis that should be considered in clinical practice.

Ethics

Informed Consent: Informed consent was obtained from our patient.

Footnotes

Author Contributions

Surgical and Medical Practices: İ.K., H.C., B.C.K., M.E., Concept: İ.K., H.C., B.C.K., M.E., Design: İ.K., H.C., B.C.K., M.E., Data Collection or Processing: İ.K., H.C., B.C.K., M.E., Analysis or Interpretation: İ.K., H.C., B.C.K., M.E., Literature Search: İ.K., H.C., M.E., Writing: İ.K., M.E.

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