Acute coronary syndrome secondary to clarithromycin: the first case and review of the literature

Klaritromisin kullanımı sonrası akut koroner sendrom görülmesi: Literatürdeki ilk olgu

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Summary– Kounis syndrome (KS) is characterized by concurrent acute coronary syndrome and allergic reaction, in which acute inflammatory mediators cause spasm and/or erosion and rupture of coronary atheromatous plaque. In this report, we remind clinicians to consider KS in patients who are subjected to allergenic substances and demonstrate acute chest pain. A 36-year-old woman had chest pain, severe dyspnea, hypotension, and symmetrical negative T waves on the anterior leads during electrocardiography approximately two hours after the use of clarithromycin. KS was considered as a possible diagnosis based on the presentation. Laboratory tests revealed an elevated level of troponin I, suggesting myocardial infarction, and an elevated level of serum tryptase level, suggesting an allergic reaction. The patient promptly underwent coronary angiography, which revealed only plaques in all main coronary arteries without any obstructive lesion. To the best of our knowledge, we report herein the first case in the literature describing an association between clarithromycin and KS.

Özet– Kounis sendromu, alerjik reaksiyonla eş zamanlı olarak ortaya çıkan, enflamatuvar mediyatörlerin yol açtığı koroner spazmı veya aterom plağı çatlamasının neden olduğu akut koroner olayları tanımlamaktadır. Bu olgu sunumunda klinikçilere alerjik maddelere maruz kalıp akut göğüs ağrısı tanımlayan kişilerde bu sendromu hatırlatmak istedik. Akut sinüzit nedeniyle oral antibiyotik (klaritromisin) aldıktan iki saat sonra şiddetli retrosternal göğüs ağrısı ve ciddi nefes darlığı yakınmalarıyla başvuran 36 yaşında kadın hastada hipotansiyon ve elektrokardiyografide ön duvarı gören derivasyonlarda simetrik dalgası negatifliği saptandı. Serum troponin ve triptaz seviyeleri yüksek bulunan hastada olası tanı olarak Kounis sendromu düşünüldü. Koroner anjiyografide tıkayıcı olmayan koroner arter hastalığı tespit edildi. Bildiğimiz kadarıyla olgumuz, klaritromisin sonrası Kounis sendromu gelişen literatürdeki ilk vakadır. Bu yazıda, üst solunum yolu enfeksiyonu için oral klaritromisin kullanımı sonrası akut koroner sendrom gelişen bir olgu sunuldu.

The association of an acute coronary syndrome (ACS) and allergic reaction following the administration of penicillin was first described in 1950. In 1991, Kounis and Zavras coined the term Kounis syndrome (KS) as "the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult".[1] Cases of KS seem to be encountered more in everyday clinical practice than anticipated. It is believed that the lack of awareness of this association may lead to underreporting. In this report, we describe a case of ACS induced by clarithromycin (CLM) intake, which was administered as treatment for acute sinusitis.

Abbreviations:

ACS	*Acute coronary syndrome*
CLM	*Clarithromycin*
KS	*Kounis syndrome*
LAD	*Left anterior descending*

CASE REPORT

A 36-year-old woman with a history of bronchial asthma and hypersensitivity to penicillin received CLM treatment for acute sinusitis. She had no cardiovascular risk factor. She began to complain of chest pain, severe dyspnea, sweating, nausea, vomiting, and

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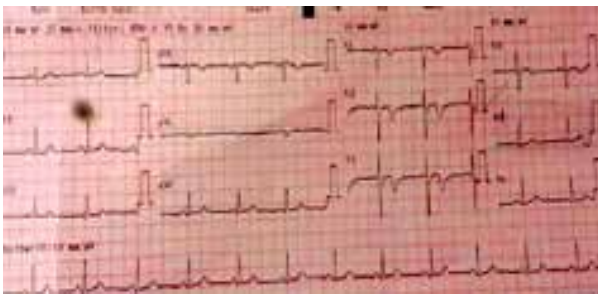

Figure 1. Electrocardiography at presentation shows symmetrical negative T waves in the anterior leads.

urticarial and edematous lesions approximately two hours after the use of CLM. She was brought immediately to our emergency department. On the physical examination, swelling of the lips and mouth mucosa was noted as well as urticarial lesions on the abdomen and legs. Her blood pressure was 86/58 mmHg, and the electrocardiogram (ECG) revealed sinus rhythm, with a heart rate of 96 bpm with symmetrical negative T waves on the anterior leads, compatible with ACS (Figure 1). Laboratory tests revealed an elevated level of troponin I (1.086 ng/mL), suggesting myocardial infarction, and an elevated level of serum tryptase (14.9 µg/L), suggesting an allergic reaction. In the emergency department, acetylsalicylic acid (300 mg), clopidogrel (loading dose of 300 mg) and intravenous heparin were administered for ACS. Accordingly, parenteral bronchodilators, antihistaminics, and corticosteroid therapy were given for her allergic symptoms. Within a couple of minutes, her urticarial lesions had regressed and her chest pain resolved. The transthoracic echocardiography was within normal limits.

The coronary angiogram showed a normal right coronary artery, a normal left circumflex artery and 40% stenosis in the mid-segment left anterior descending artery (LAD) (Video 1*). The possible contribution of coronary artery spasm to the etiology of stenosis in the mid LAD was considered, and nitroglycerine was given via the intracoronary route. Approximately one minute after the intracoronary injection of nitroglycerine, the left coronary angiogram was repeated, which showed no resolution of the coronary lesion. Fifteen minutes after the infusion was given, the fractional flow reserve (with adenosine) was measured as 0.89, suggesting a hemodynamically non-significant stenosis (Video 2*). The anginal symptoms of the patient recovered markedly. It was considered that the anti-allergic drugs that were given in the emergency department might have resolved a significant coronary artery spasm, since her symptoms regressed after appropriate therapy in the emergency room. The patient was discharged three days later without complication.

DISCUSSION

Clarithromycin is a semi-synthetic macrolide antibiotic with a broad antibacterial spectrum. CLM interferes with ribonucleic acid (RNA)-dependent bacterial protein synthesis, resulting in a bacteriostatic effect on pathogens. It is indicated for the treatment of bacterial infections, such as sinusitis, tonsillitis and pneumonia. It is a relatively safe drug, since it has been reported that CLM rarely causes allergic reactions such as bronchospasm, fixed drug eruption, serum sickness-like reaction, leukocytoclastic vasculitis, toxic epidermal necrolysis, or Henoch-Schönlein purpura.[1] Although very unusual, it is also reported that CLM may cause anaphylaxis in children.[2]

The development of ACS after exposure to an allergic insult is an unexpected and rarely reported phenomenon. In 1991, "Kounis syndrome" (KS) was described as "coincidental occurrence of chest pain and an allergic reaction accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult".[3,4] The underlying pathophysiology in KS is coronary artery vasospasm due to the release of vasoactive mediators secondary to mast cell degranulation.[5,6] Mast cells generally exist within atherosclerotic lesions. The mediators released from mast cells, such as histamine, tryptase, platelet activating factors, cytokines, and chemokines, have been cited as inducing coronary artery vasospasm. They activate platelet aggregation and transform a pre-existing stable atheromatous coronary artery plaque to an unstable plaque, which eventually leads to plaque rupture.[7]

Histamine has also been implicated in activating platelets and triggering thrombosis.[8] The mast cells in the heart tissue participate in the anaphylactic reaction, which eventually triggers tachycardia, coronary vasoconstriction, ventricular contractility abnormalities, and atrioventricular conduction block.[9] Many triggering insults have been proposed, such as poisons, venoms, drugs, and contrast agents. Among these, antibiotic-related ACS is rare.[10] Recently, Biteker et al.[11] proposed a new classification for KS,

according to which our case was classified as type 1 KS, which refers to ACS secondary to coronary artery vasospasm without underlying significant coronary artery disease.

In conclusion, KS is not a rare clinical entity but it is seldom diagnosed because of limited awareness. Because the treatment is simple and very effective, awareness of KS should be increased. It should also be noted that CLM can cause KS.

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****Supplementary video file associated with this article can be found in the online version of the journal.***

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Key words: Acute coronary syndrome; clarithromycin; Kounis syndrome.

Anahtar sözcükler: Akut koroner sendrom; klaritromisin; Kounis sendromu.