CASE REPORT

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The Heart Does Not Itch, But it Feels Pain: Three Cases of Kounis Syndrome

Kalp Kaşınmaz Ama Ağrıyı Hisseder: Üç Kounis Sendromu Vakası

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ABSTRACT

Background: Kounis syndrome is defined as the occurrence of acute coronary artery syndrome as a result of activation of inflammatory cells after conditions such as allergy, hypersensitivity, anaphylaxis or anaphylactic reactions. This case reports were presented to provide the latest knowledge on Kounis syndrome, increase awareness of this disease among healthcare providers and researchers, and promote early and appropriate diagnosis and management of this syndrome.

Summary of Cases: In the first case, a 45-year-old female patient with no history of coronary artery disease developed anaphylaxis due to a locally applied anesthetic drug. This led to transient coronary artery vasospasm and acute coronary syndrome. In the second case, a 70-year-old male patient with a history of coronary artery disease developed anaphylaxis due to a bee sting. This caused rupture of the coronary artery plaque, resulting in inferior myocardial infarction. In the third case, a 73-year-old male patient with a stent in his coronary artery developed an allergic reaction/anaphylaxis to midazolam, which was administered for sedation before the biopsy procedure. This reaction resulted in restenosis of the old stent and caused an anterior myocardial infarction.

Conclusion: Kounis syndrome is a life-threatening condition that requires attention. Ensuring coronary artery patency in the treatment of ischaemia is important to protect cardiomyocyte health and prevent arrhythmias. Ischaemia caused by allergens can be resolved with a combination of antiallergenic treatments. Therefore, for effective management of suspected cases of Kounis syndrome, collaboration between cardiology and allergy-immunology clinics is essential.

Keywords: Kounis syndrome, allergic myocardial infarction, stent restenosis, ventricular tachycardia, chest pain

ÖZ

Giriş: Kounis sendromu, alerji, aşırı duyarlılık, anafilaksi veya anafilaktik reaksiyonlar gibi durumlar sonrasında inflamatuar hücrelerin aktivasyonu sonucu akut koroner arter sendromunun ortaya çıkması olarak tanımlanmaktadır. Bu olgu sunumları, Kounis sendromu hakkında en son bilgileri sağlamak, sağlık hizmeti sağlayıcıları ve araştırmacılar arasında bu hastalık hakkındaki farkındalığı artırmak ve bu sendromun erken ve uygun tanısını ve tedavisini teşvik etmek amacıyla sunulmuştur.

Vakaların Özeti: Birinci vakada geçmişinde koroner arter hastalığı öyküsü olmayan 45 yaşında kadın hastada lokal olarak uygulanan anestezik ilaç, geçici koroner arter vasospazmı ile akut koroner sendroma sebep olan anafilaksi gelişmesine neden oldu. İkinci vakada geçmişinde koroner arter hastalığı öyküsü olan 70 yaşında erkek hastada arı sokmasına bağlı anafilaksi gelişti. Anafilaksi, koroner arter plağının rüptürüne neden olup inferiyor miyokart enfarktüsüne neden oldu . Üçüncü vakada ise koroner arterinde stenti olan 73 yaşındaki erkek hastaya biyopsi işlemi öncesi sedasyon amacıyla yapılan midazaloma sekonder alerji/anafilaksi gelişti ve bu durum eski stent restenozuna sebep olup anteriyor miyokart enfarktüsü gelişmesine neden oldu.

Sonuç: Kounis sendromu dikkat gerektiren hayatı tehdit eden bir durumdur. İskemi tedavisinde koroner arter açıklığının sağlanması, kardiyomiyosit sağlığının korunması ve aritmilerin önlenmesi açısından önemlidir. Alerjenlerin neden olduğu iskemi, antialerjenik tedavilerin de bulunduğu kombinasyon ile çözülebilir. Bu nedenle Kounis sendromundan şüphelenilen vakaların etkin tedavisinde kardiyoloji ve alerji-immünoloji klinikleri arasında işbirliğinin yapılması önemlidir.

Anahtar Sözcükler: Kounis sendromu, alerjik miyokart enfarktüsü, stent restenozu, ventriküler taşikardi, göğüs ağrısı

INTRODUCTION

Kounis Syndrome (KS) is an allergy-induced acute coronary syndrome (ACS). Although allergy-related cardiovascular events started to be reported in the early twentieth century, they were first described in the article published by Kounis and Zavras in 1991 (1). Basically, there are inflammatory mediators released by activation of mast cells secondary to triggers. In its presentation, chest pain, shortness of breath, palpitation, hypotension, weakness, fainting, itching, rash and similar conditions are encountered. There are three defined types of KS. In type 1, the patient without a history of coronary disease has normal coronary arteries accompanying a wide range of conditions, from ischemia to myocardial infarction after an allergic event. In type 2, a patient with coronary artery disease has plaque rupture or erosion secondary to allergy. In type 3, stent thrombosis or restenosis occurs secondary to an allergic event. Anamnesis (especially questioning of symptoms and allergic history), physical examination findings, electrocardiography (ECG), echocardiography (ECHO), laboratory tests and coronary angiography (CAG) play an important role in diagnosing the disease. Supportive diagnostic tools are intracoronary ultrasonography, computed tomography (CT), and dynamic cardiac magnetic resonance imaging. In the treatment of the disease, allergy-specific treatment is applied if there is no coronary artery disease accompanying the allergic condition, while ACS treatment is also applied if there is a critical lesion in the coronary arteries (2,3).

Current data reveal that KS is not as rare as thought. It is of great importance to be more conscious about this syndrome, as allergens and their triggers increase with the innovations caused by the changing lifestyle and pose a threat to human health (2,3). Therefore, the aim of the three case reports presented here is to raise awareness of KS in the light of current literature data and to consider it in the differential diagnosis.

CASE REPORT

Case 1

Type 1 Kounis Syndrome, Acute Coronary Syndrome Induced by Lidocaine Anaphylaxis

A 45-year-old woman with known diagnoses of hypothyroidism, insulin resistance, fibromyalgia and chronic suppurative otitis media applied to the rheumatology outpatient clinic due to complaints of low back pain and knee pain. Since HLA B27, Antinuclear Antibody, Anti-SSA, Anti-SSB and Anti Ro-52 results were negative in the laboratory tests, but Anti Centromere B was positive, a minor salivary gland biopsy was planned and she was hospitalized for preparation.

Her ECG, seen for routine control before the procedure, was normal and her vitals were stable (blood pressure 110/70 mmHg, oxygen saturation 98% (without oxygen support), pulse 78 beats / minute and respiratory rate 24 / minute). The patient was taken to the operating room for the biopsy procedure and the drug lidocaine was administered subcutaneously for local anesthesia. 5 minutes after lidocaine administration, she began to describe palpitations and pressure-like pain in her chest. At the same time, the patient's blood oxygen saturation dropped to 92% (measured with a fingertip meter), her respiratory rate increased to 32 / min, and her blood pressure dropped to 70/30 mmHg. Intravenous fluid was started immediately and an ECG was taken. In her ECG, ST segment elevation in the aVR lead and ST segment depression and T wave inversion in leads D1, D2 and V1-6 were observed (Figure 1, 2). This situation was different from the pre-procedure ECG. The patient's heart was evaluated with ECHO, and no motility or regional wall motion abnormalities were detected in heart wall movements. During this period, the patient's complaints began to decrease, with her blood pressure rising to 90/40 mmHg, her blood oxygen saturation rising to 98%, her respiratory rate dropping to 25 beats / minute, and her pulse dropping to 90 beats/minute , and a recovery was observed in her ECG. In the first blood test taken, CK-MB mass was 3.28 μg/L (reference range (R): 1.39 - 4.88 μg/L) and hs-Troponin T was 0.110 ng/ml (R: 0 - 0.014 ng/ml). In control assays, CK-MB mass increased to 17.74 μg/L and hs-Troponin T increased to 0.596 ng/mL (Table 1). The patient with suspected ACS was taken to the CAG laboratory. No critical stenosis was detected in the coronary arteries in the CAG (Figure 3A,B).

The patient, who developed anaphylaxis symptoms after drug administration, was diagnosed with Type 1 KS because no significant stenosis was observed in her coronary arteries, although her ECG showed signs of ischemia and a significant progression in her cardiac markers. Since no coronary artery disease was detected in the patient, no additional treatment was required other than antihistamines and hydration.

(Written and verbal informed consent was obtained from the patient for case presentation)

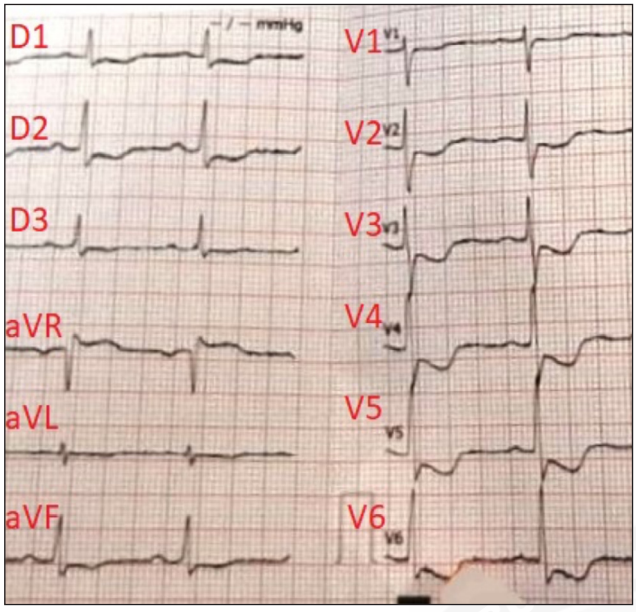

Figure 1: Post-syncope ECG shows ST segment depression and T negativity in leads D1, D2 and V1-6, and ST segment elevation in lead AVR.

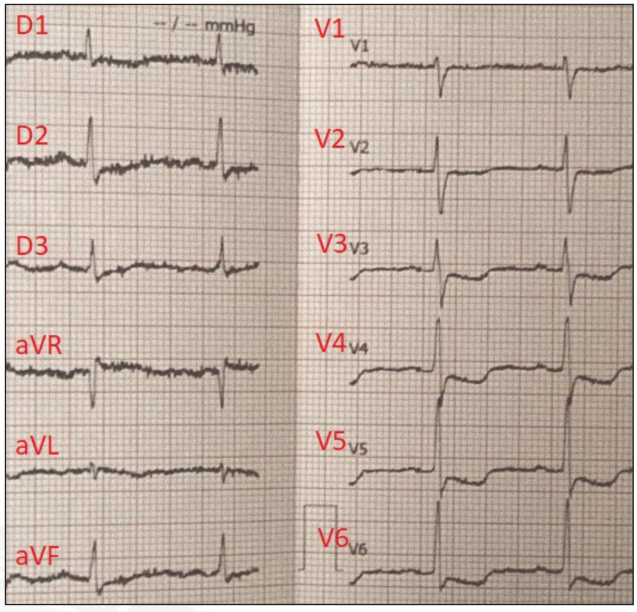

Figure 2: There is a regression in ST segment deviations in the ECG after supportive treatment.

Table 1. Laboratory parameters at time of incident.

Parameters	Case 1	Case 2	Case 3	Ranges
BUN (mg/dL)	11.26	22	15.65	7 - 22
Urea (mg/dL)	24.1	46	33.5	16.6 - 48.5
Creatinin (mg/dL)	0.7	0.99	1.15	0.7 - 1.2
Sodium (Na^+) (mmol/L)	140	138	136	135 - 145
Potassium (K^+) (mmol/L)	5.07	4.08	4.85	3.5 - 5.1
Calcium (Ca^{++}) (mg/dl)	9.7	8.55	8.80	8.6 - 10.2
AST (SGOT) (U/L)	33	46	43	5 - 40
LDH (U/L)	-	332	658	135 - 225
CK (IU/L)	81	1028	144	0 - 190
CK-MB mass (μg/L)	17.74	-	7.36	1.39 - 4.88
CK-MB (U/L)	-	86	-	4 - 24
hs-Troponin T (ng/ml)	0.110	-	0.044	0 - 0.014
Troponin I (ng/ml)	-	>25	-	<0.16
Total IgE (U/ml)	-	-	118.5	0 - 100

Case 2

Type-2 Kounis syndrome, Inferior Myocardial Infarction Associated with Ventricular Tachycardia After Bee Sting

A 70-years-old male patient with known hypertension and atherosclerotic heart disease was admitted to the emergency department with typical complaints of chest pain, dizziness, palpitations and shortness of breath, which started five minutes after the bee sting. When he arrived at the emergency room, his vitals showed a pulse of 102 bpm, blood pressure of 97/64 mmHg, oxygen saturation of 93%, and respiratory rate of 27/minute. Anaphylaxis was considered due to the clinical complaints and deterioration in vitals following the bee sting. In the treatment of allergy, 40 mg prednisolone and 45.5 mg pheniramine were administered intravenously and 1000 cc isotonic fluid was started. In the second hour of the patient's follow-up, ventricular tachycardia (VT) developed and sinus rhythm was restored by defibrillation with 200 j DC. In the ECG taken after defibrillation,

there was ST segment elevation in the inferior leads. Due to reciprocal ST segment depression in the lateral leads, a preliminary diagnosis of inferior myocardial infarction was made and he was immediately taken to the CAG laboratory. In the angiography of the patient, whose coronary artery plaque was detected in the CAG just a month ago, total stenosis with thrombus was detected in the distal left circumflex (CX) coronary artery. From the other vessels, the left main coronary artery was normal, the left anterior descending coronary artery (LAD) has a plaque and slow flow was observed in the right coronary artery. A balloon predilatation was applied to the total stenosis with thrombus in the CX, and then a 2.75*19 mm drug-eluting stent was implanted at 14 atmospheres to the area with the lesion. The final angiographic results were satisfactory as demonstrated by thrombolysis in myocardial infarction grade 3 flow in the patient and his vitals were followed in the coronary intensive care unit with stable vitals (Figure 4A-C).

The patient was diagnosed with type 2 KS because myocardial infarction is the rupture of a stable plaque in the coronary artery that develops secondary to anaphylaxis. He was discharged after the intraluminal patency of the occluded coronary artery was achieved and no new pathologies developed during follow-up. He was told what to do and what to pay attention to in case of allergic events after discharge. Additionally, peroral (PO) acetylsalicylic acid + clopidogrel (75/75 mg, 1*1), PO bisoprolol (5 mg, 1*1) and PO pitavastatin (4 mg, 1*1) treatment was prescribed due to comorbid coronary artery disease.

(Written and verbal informed consent was obtained from the patient for case presentation)

Case 3

Type 3 Kounis Syndrome, Anterior Myocardial Infarction Due to Stent Restenosis

A 73-year-old male patient with known atherosclerotic heart disease (a stent was placed in the proximal left anterior descending coronary artery four years ago) and a history of laryngeal squamous cell carcinoma was admitted to the hospital with a complaint of hoarseness that had been ongoing for 2 months. On examination, left vocal cord edema

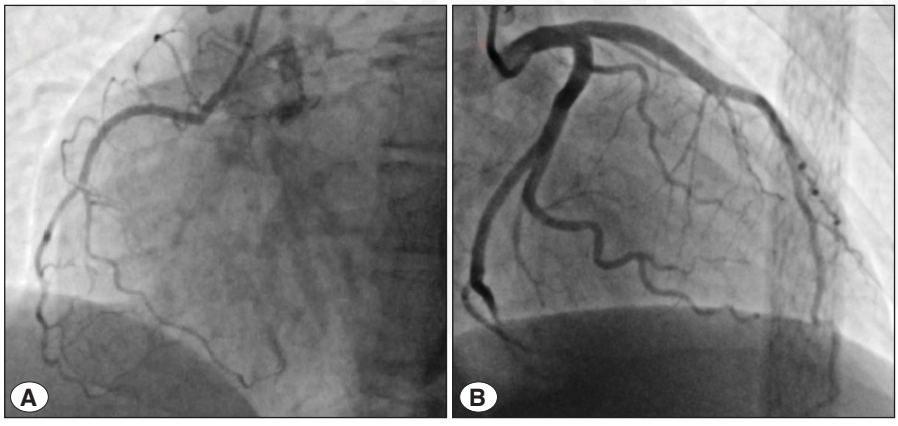

Figure 3: Image of Coronary Angiography: **A)** Right coronary artery **B)** Left main coronary artery, left anterior descending coronary artery and circumflex coronary artery.

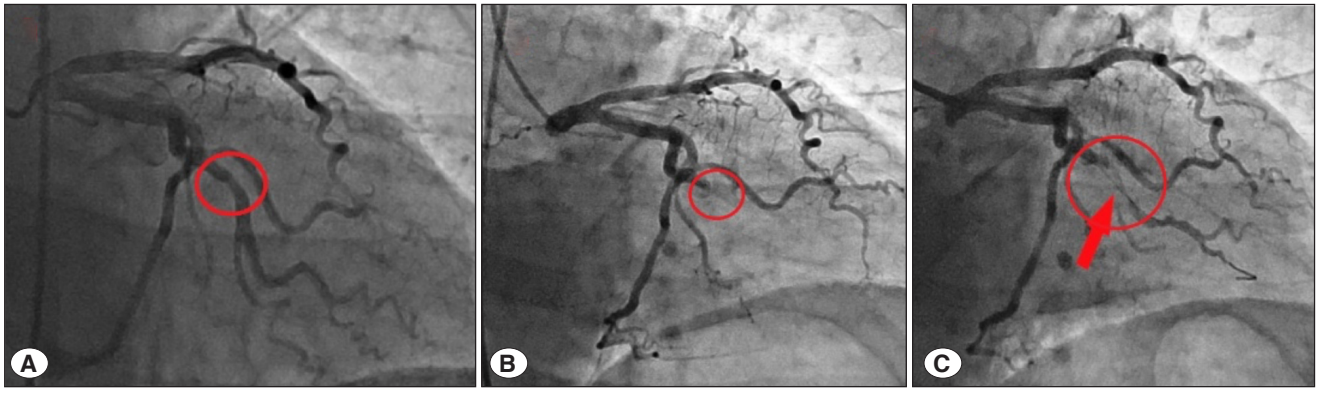

Figure 4: A) Plaque image in the circumflex coronary artery. **B)** Total stenosis with thrombus distal to the circumflex coronary artery. **C)** After passing through the lesion in the circumflex coronary artery with a floppy wire.

and polyp in its anterior aspect, nodular locophagic lesion on the left epiglottis endolaryngeal face and palpable nodule in bilateral thyroid were observed. Direct laryngoscopy biopsy was planned. The patient was sedated with midazolam and a laryngeal biopsy was performed. Shortly after the procedure, the patient developed tachycardia and hypotension and began experiencing severe chest pain. His ECG showed ST segment elevation in leads V3-V4 and a diagnosis of anterior myocardial infarction was made. The old stent in the LAD of the patient, who was taken to the angiography laboratory, was observed to be completely occluded with thrombosis. An attempt was made to predilate the lesion with non-compliant balloons, but despite repeated predilatations, there were stenoses that developed again. Finally, appropriate patency was achieved in the lumen and a 2.75*33 mm drug-eluting stent was applied into the lumen, ensuring TIMI 3 blood flow (Figure 5A-C).

In this case, type 3 KS was considered because the myocardial infarction occurred after allergy symptoms, the stent thrombosis was in the very late stent thrombosis class, and the IgE level was high, which could be an indicator of allergy. In fact, performing thrombus aspiration and demonstrating mast and basophil cells in the thrombus material is important to confirm the diagnosis of type 3 KS. We could not examine the thrombus material because the case was urgent during the procedure and we did not have a catheter to aspirate the thrombus material at that time. For the patient whose total IgE value was determined to be 118.5 U/ml (reference value: 0 - 100 u/ml) in laboratory blood tests, the combination of stent restenosis accompanied by high IgE value is important for the diagnosis of KS type 3. Since the patient had coronary artery disease accompanying allergic coronary syndrome, his prescription was adjusted in accordance with the ACS guide and he was discharged with recommendations for testing for his allergy.

(Written and verbal informed consent was obtained from the patient for case presentation)

DISCUSSION

Kounis syndrome is an important acute coronary syndrome that needs to be known. In this article, 3 different types of KS are presented with 3 different cases. In the first case, an allergy that developed after lidocaine administration caused ACS, but Type 1 KS was diagnosed because the coronary arteries were found to be normal by CAG. The second case had inferior myocardial infarction accompanied by VT after bee sting and was diagnosed with Type 2 KS. In the third case, a patient who had anterior myocardial infarction due to stent thrombosis, which is in the category of very late stent thrombosis accompanied by allergic symptoms after biopsy, was presented. Type 3 KS was considered because there were allergy symptoms before the myocardial infarction, the IgE value was high in the blood test, and the stent was occluded with thrombus. Stent thrombosis that develops 12 months after stent implantation is called very late stent thrombosis, and if this condition is accompanied by allergy symptoms, there are articles in the literature stating that the diagnosis with high accuracy is type 3 KS (4,5).

Events caused by allergy, hypersensitivity, anaphylaxis or anaphylactoid reactions over arterial structures are called KS. Although cardiovascular syndromes seen after allergy have been reported since the beginning of the twentieth century, they were first described in detail by Nicholas Kounis and George Zavras in their article published in 1991 (1). The incidence of KS was found to be 2 per hundred thousand in a prospective study conducted by Akoz et al. in 2012 (6). In the study, it was reported that 793 of 138911 patients who applied to the emergency department had allergic symptoms and 27 of these patients were diagnosed with KS. In another study, it is stated that KS is independent of age, gender, race and geography (2). Therefore, it shows that the rate of KS among patients with allergic symptoms is approximately 3.4% (6).

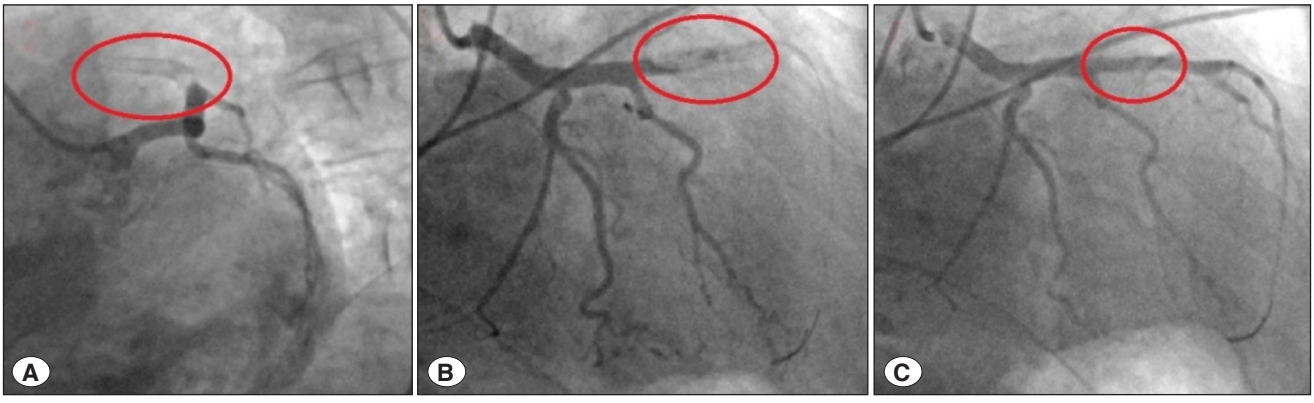

Figure 5: A) Total stenosis in stent in the left anterior descending artery. **B)** Recurrence of intra-stent total stenosis despite repeated ballooning. **C)** Predilations with balloon applied to left anterior descending coronary artery stent and full patency after stent.

The main inflammatory cells that cause the development of KS are macrophages and mast cells that interact with T-lymphocytes. Trigger antigens interact with IgE antibodies and cause the release of histamine, tryptase, chymase, platelet activating factor, cytokines, chemokines, arachidonic acid products and proteases from mast cells. These released mediators have effects on the cardiovascular structure, increasing the heart rate, vasospasm in the coronary artery, plaque erosion and rupture, thrombotic and fibrinolytic, platelet aggregation and similar effects on the coagulation cascade. Drugs (anesthetics, analgesics, antibiotics, antihypertensives and proton pump inhibitors), contrast agents, bee stings, fish poisoning (scombroid syndrome), spices, systemic mastocytosis are examples that may trigger allergies (2,3). Anesthetic drugs are divided into two groups: ester and amide. The incidence of allergy side effects of anesthetics with ester structure is higher than those with amide structure (7). However, there are case reports of KS from both groups. As an example of KS caused by the amide group, Ignacio Garcia-Nunez and colleagues (8) presented a 52-year-old male patient with type 1 KS who developed compressive chest pain and subsequent cardiac arrest after lidocaine used for local anesthesia. As an example of KS caused by the ester group, the article published by Ateş and Kul (9) presents a case of type 1 KS that developed due to midazolam administration in a 70-year-old male patient.

Chest pain, dyspnea, dizziness, nausea, vomiting, sweating, hypotension, syncope, itching, skin rash, cardiac arrest and respiratory arrest can be seen in the KS clinic (2,3). In the diagnosis of KS, cardiovascular symptoms in the foreground accompanied by allergy symptoms and ECG, ECHO, laboratory tests and CAG have an important place. In laboratory tests, especially CK, CK-MB, troponin, IgE, histamine, tryptase levels are important. However, histamine that have 8 minutes of half-life and being also 90 minutes of tryptase are not helpful assays in late period diagnosis. Other diagnostic tools are intracoronary ultrasonography, CT, and dynamic cardiac magnetic resonance imaging. Hypersensitivity myocarditis, takotsubo syndrome and stress-related cardiomyopathy should be excluded in the differential diagnosis (2).

There is no general guideline recommendation for the treatment of the syndrome. However, the application of treatment procedures for allergic symptoms for the type 1 variant of the common opinion in academic publications is the application of additional ACS treatment for type 2 and type 3 variants (2,3). In the treatment of type 1, fluid support for hypotension, administration of steroids and antihistamines to suppress the mediators themselves and their interactions have been shown to relieve symptoms alone. In addition, nitrate (in those who tolerate blood pressure) and calcium channel blockers can be used to prevent vasospasm due to hypersensitivity (2,3). Intramuscular administration of sulfide-free epinephrine at a dose of 0.2 - 0.5 mg in aqueous solution at a rate of 0.001 is recommended in patients presenting with severe anaphylaxis attact (2,3). Patients with a history of beta-blocker use may be seen to resistant to epinephrine. In this case, 1-5 mg of glucagon is implementatied intravenously in 5 minutes, and after that it is suggested by an infusion of 5-15 μg/min (2). The administration of morphine and codeine medical treatment in patients with severe chest pain is not recommended as it may cause mast cell degranulation, instead fentanyl and its derivatives are recommended, which do not affect cardiac output (2,3).

This case series presents three cases of KS and describes the process from diagnosis to treatment based on a literature review. When patients present with myocardial infarction, doctors typically perform an interventional procedure to open the vessel and follow standard coronary artery disease treatment. However, in some cases, allergies may also contribute to the etiology of myocardial infarction. If exposure is not removed, ischemic events may persist. The treatment of patients with suspected allergic exposure should be coordinated and monitored in cooperation between cardiology and allergy-immunology clinics to avoid serious consequences such as congestive heart failure or ventricular arrhythmias.

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Author Contributions

Conception, design, supervision, resource, data collection and/or processing, analysis and/or interpretation, literature review, writing, critical review: **Ömer Faruk Yılmaz,** Conception, supervision, materials, analysis and/or interpretation, literature review, critical review: **İbrahim Etem Dural.**

Conflicts of Interest

The authors declared no conflict of interest.

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Ethical Approval

Written informed consent was obtained from patients participating in these cases to share their relevant medical history and laboratory results.

Review Process

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