CASE REPORT

Kounis Syndrome: Report of 5 Cases

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Abstract

Kounis syndrome has been defined as an acute coronary syndrome that manifests as unstable vasospastic or nonvasospastic angina, and even as acute myocardial infarction. It is triggered by the release of inflammatory mediators following an allergic insult. We report 5 patients attended at our hospital between January 2005 and May 2008 who were diagnosed with unstable angina or acute myocardial infarction—according to analytical parameters, electrocardiographic abnormalities, and/or coronary angiography—in the context of an anaphylactic episode. Age at the time of the episode, age ranged between 50 and 68 years. The results of an allergology study revealed the causal agents to be drugs in 4 cases (nonsteroidal anti-inflammatory drugs and omeprazole) and food in 1 case (kiwi). Coronary disease of a blood vessel was observed in 2 patients. Serious allergic reactions may be the cause of acute coronary syndrome in patients with healthy or altered coronary arteries and no cardiovascular risk factors.

Key words: Anaphylaxis. Allergic angina. Allergic myocardial infarction. Kounis syndrome.

Resumen

El Síndrome de Kounis se ha definido como la asociación de un síndrome coronario agudo en forma de angina inestable, vasoespástica o no, e incluso infarto agudo de miocardio, desencadenado por la liberación de mediadores inflamatorios secundaria a un proceso alérgico. Presentamos 5 pacientes estudiados entre enero de 2005 y mayo de 2008, diagnosticados de angor inestable o infarto agudo de miocardio en el contexto de un episodio de anafilaxia según parámetros analíticos, cambios electrocardiográficos y/o cateterismo cardíaco. La edad de los pacientes estaba comprendida entre 50 y 68 años. El estudio alergológico identificó como agentes causales fármacos en cuatro casos (antiinflamatorios no esteroidales y omeprazol) y un alimento (kiwi) en el quinto caso. Se objetivó enfermedad coronaria en 2 de los casos. Concluimos que las reacciones alérgicas graves pueden ser la causa de síndrome coronario agudo en pacientes con coronarias sanas o alteradas y sin factores de riesgo cardiovascular.

Palabras clave: Anaphylaxis. Allergic angina. Allergic myocardial infarction. Kounis syndrome.

Introduction

Kounis syndrome, also known as allergic angina syndrome, was described in 1991 by Kounis and Zafras [1] as "the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classic angina pectoris caused by inflammatory mediators released during the allergic insult." They called the progression from chest pain to acute myocardial infarction "allergic myocardial infarction" [2,3]. The heart condition occurs in a considerable number of patients during episodes of anaphylaxis [4], and frequently in patients with prior coronary disease, although it has also been observed in patients with healthy coronary vessels. Vasospasm of the coronary arteries has been suggested to be the main pathophysiologic mechanism [5].

Case Descriptions

We report 5 patients with Kounis syndrome. The main characteristics of each are summarized in the Table.

Case 1

A 66-year-old man with a history of oral allergy syndrome caused by kiwi and no cardiovascular risk factors attended our institution in January 2005 with acute urticaria, vomiting, and chest pain following ingestion of a piece of kiwi. Hypotension

and electrocardiographic abnormalities (ST depression in leads V3-V6 and inferior lead) were observed on arrival at the emergency room. Blood tests revealed elevated serum tryptase values (54 μg/L) and elevated levels of troponine I (6.52 ng/mL), an enzyme indicative of myocardial damage. A prick test gave highly positive results for kiwi, thus confirming the causal agent. The patient recovered completely and electrocardiogram values returned to normal.

Case 2

A 50-year-old woman with no cardiovascular risk factors and a history of sensitivity to acetylsalicylic acid (ASA) and bronchial asthma received treatment for acute sinusitis with ibuprofen and amoxicillin-clavulanic acid in June 2005. Fifteen minutes after taking the drugs, she began to present sudden shortness of breath, feeling of instability, palpitations, chest tightness, and excessive sweating. She was immediately taken to the nearest health center, where severe hypotension (64/39 mm Hg) and arterial oxygen saturation of 65% were observed. She was given 1 mg of subcutaneous adrenaline, after which she reported episodes of self-limiting ventricular tachycardia. The electrocardiogram revealed ST elevation of 2 mm in leads III and aVF, with a specular reflection on leads I and aVL, and asymmetrical negative T waves for leads V1-V4. Blood tests revealed troponine I and tryptase values of 1.2 ng/mL and 14.1 μg/L, respectively. Following administration of serum therapy, parenteral bronchodilators, antihistamines, and corticosteroids, the patient became hemodynamically stable. After several hours' administration of adrenaline, she experienced a further episode of chest tightness and electrocardiographic abnormalities indicative of inferior myocardial infarction that required fibrinolytic treatment with tenecteplase. The electrocardiogram did not reveal any contractility abnormalities or valvular disease, and the ejection fraction was normal. Heart catheterization revealed the presence of angiographically normal lesion-free coronary arteries. Computed tomography of the paranasal sinuses revealed massive occupation of the frontal and maxillary paranasal cavities that was indicative of polyps. Forty-eight hours later, serum tryptase values had returned to normal (3.23 μg/L). Determination of immunoglobulin E specific for penicillin V, penicillin G, and amoxicillin was negative.

Case 3

A 57-year-old man with no history of atopy or cardiovascular risk factors presented precordial pain, epigastric pain, and general malaise after taking an ibuprofen tablet in December 2006. Upon arrival at the emergency room, electrocardiographic abnormalities indicative of acute myocardial infarction were observed (ST elevation in the inferior lead), in addition to acute arterial ischemia of the left lower leg. Blood tests revealed elevated levels of troponin I (6.12 ng/mL) and moderate eosinophilia. During admission, the patient experienced various episodes of precordial pain with repolarization abnormalities after taking metamizole and ASA. During 1 episode, serum tryptase values increased (13 μg/L), although they later returned to normal (4.5 μg/L). Heart catheterization revealed lesions in small-caliber vessels that were reversible with nitroglycerine and were suggestive of coronary vasospasm (in the absence of other lesions). The electrocardiogram values were normal and the ejection fraction was maintained. During a subsequent admission, the patient underwent a rapid ASA desensitization protocol [6] by implantation of an intracoronary stent. Daily doses of 100 mg were tolerated for a period of 6 months.

Case 4

A 68-year-old man (ex-smoker, 20 years) with no history of atopy and no other known cardiovascular risk factors had been

Table. Patient Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	66	50	57	68	67
Sex	Man	Woman	Man	Man	Woman
Atopy	Yes	Yes	No	No	Yes
Cardiovascular risk factors	No	No	No	Yes	Yes
Allergic cause	Kiwi	Ibuprofen	Ibuprofen, ASA, metamizole (3 episodes)	Omeprazole (2 episodes)	Metamizole
Cutaneous tests	Positive	Not performed	Not performed	Positive	Positive
Electrocardiogram	↓ST	↑ST and negative T waves	↑ST	↑ST and ventricular fibrillation	↑ST
Troponine I, g/mL[a]	6.52	1.2	6.12	5.98	4.2
Tryptase, μg/L[b]	54	14.1	13 (baseline 4.5)	Not performed	Not performed
Coronary angiography	Not performed	Normal	Normal	Abnormal	Abnormal

[a]Normal values: <0.04 ng/mL
[b]Normal values: 5.5 μg/L to 13.0 μg/L

diagnosed with a hiatus hernia at the age of 40. His habitual treatment was daily oral lansoprazole. In January 2008, after taking an omeprazole tablet, the patient attended the emergency room because of dizziness, excessive sweating, generalized pruritis, erythema, and subsequent loss of consciousness with cardiorespiratory arrest requiring orotracheal intubation and mechanical ventilation. The electrocardiogram revealed ST elevation on the anterolateral lead and the patient presented ventricular fibrillation, which was treated with electrical defibrillation. Later, during admission, an identical episode occurred after ingestion of another omeprazole tablet. Blood tests showed a peak in troponine I of 5.98 ng/mL. A subsequent allergy workup revealed positive skin test results (intradermal injection) for omeprazole and pantoprazole at a concentration of 1 mg/mL. The results were negative for lansoprazole. Coronary angiography revealed coronary disease of the anterior descending artery.

Case 5

A 67-year-old woman with hypertension as the only cardiovascular risk factor and an unstudied history of adverse reaction to pyrazalones accidentally received intravenous metamizole in May 2008. Five minutes after the perfusion started, the patient presented generalized skin rash, palmoplantar pruritis, chest tightness, profuse sweating, and presyncope. The patient was transferred immediately to our emergency department, where an anteroapical acute myocardial infarct with ST elevation on leads V2-V6 was observed. Following oxygen therapy, serum therapy, and administration of intravenous corticosteroids and antihistamines, the patient progressed favorably. The electrocardiogram revealed apical akinesia with maintained systolic function. Heart catheterization revealed a lesion in the anterior descending artery that required balloon dilatation. Blood tests revealed a peak in troponine I of 4.2 ng/mL. An allergy workup revealed hypersensitivity to metamizole with a clearly positive prick test result (400 mg/mL).

Discussion

Kounis syndrome has been defined as an acute coronary syndrome that manifests as unstable vasospastic or nonvasospastic angina, and even as acute myocardial infarction triggered by the release of inflammatory mediators following an allergic insult. There are currently 2 variants of Kounis syndrome. The first is observed in patients with no cardiovascular risk factors and healthy coronary arteries in which the inflammatory cascade triggered by the allergic insult causes a coronary vasospasm accompanied by elevated levels of markers of myocardial damage. The second is observed in patients with pre-existing atheromatous disease (whether known or not) in whom the release of these mediators would also produce a coronary vasospasm, which occurs with normal cardiac enzymes or rupture of the atheromatous plaque, manifesting in this case as an acute myocardial infarction [7]. In the case of the patients described above, 2 (patients 2 and 3) had normal coronary vessels and 2 (patients 4 and 5) presented coronary disease in 1 vessel (anterior descending artery) in addition to cardiovascular risk factors. In patient 1, who had no known coronary risk factors, it was not possible to perform cardiac catheterization; nonetheless, this patient has not presented any subsequent cardiologic event, remains asymptomatic, and is not taking any medication.

The term “cardiac anaphylaxis” refers to the functional and metabolic changes in the heart caused by the release of histamine and metabolites arising from the arachidonic acid cascade following a serious allergic insult [1,8].

Several pathophysiologic mechanisms have been described to explain the involvement of the heart in anaphylactic reactions. The existence of mastocytes in heart tissue and their participation in the anaphylactic reaction that triggers tachycardia, coronary vasoconstriction, dysfunctional ventricular contractility, and blockade of atrioventricular conduction is well known. These abnormalities are attributed to the release of mediators such as histamine, thromboxane, prostaglandins, leukotrienes, and platelet activation factor. The release of renin during episodes of anaphylaxis and its involvement in consequent heart dysfunction has recently been described [9]. Cases of angina or infarction following administration of adrenaline (a drug capable of causing ventricular fibrillation and severe vasoconstriction) to treat anaphylactic shock have also been described [10]. Only 1 of our patients received treatment with adrenaline (patient 2), after which she presented episodes of self-limiting ventricular tachycardia as a possible immediate side effect, although they may also have been due to the coronary syndrome. The episode of chest pain and electrocardiographic changes that occurred hours after administration of this drug suggest a biphasic anaphylactic reaction; we can therefore deduce that the allergic reaction would have played a major role in ischemic heart disease. In this case, the effect of the adrenaline was probably secondary to the initial reaction as a joint vasoconstriction factor in the vasospasm triggered by the hypersensitivity reaction.

Several allergens have been reported to trigger Kounis syndrome (drugs, Hymenoptera venom, latex, food, and contrast media) [5,7,11-13]. In our series, the main cause was drugs, principally nonsteroidal anti-inflammatory drugs [NSAIDs] (3 out of 4 patients) and omeprazole (1 case); etiology was food-related in only 1 patient (kiwi). The diagnosis of hypersensitivity was confirmed in all patients using skin tests, exposure tests, or both for the allergens involved in each of the reactions. The cross-reactivity between omeprazole and pantoprazole but not with lansoprazole—demonstrated by skin tests and tolerance to lansoprazole—was notable; this was presented by patient 4. Patients 2 and 3 were diagnosed with intolerance to NSAIDs (hypersensitivity to 2 or more drugs). Furthermore, patient 2 presented an ASA triad (intolerance to NSAIDs, asthma, and nasal polyps). Management of patient 3 in particular was complicated, because, despite a clear diagnosis of NSAID-induced Kounis syndrome, a rapid ASA desensitization protocol was necessary and the patient required antiaggregation with both ASA and clopidogrel. Although we were accustomed to this desensitization protocol in routine clinical practice, this was the first time we had performed it on a patient whose coronary process was induced by an NSAID. Our review of the literature revealed no similar cases.

Age at the time of the episode ranged between 50 and 68 years. Although Kounis syndrome has mainly been described in adults,

cases have recently been published in pediatric patients [14,15].

Elevated serum tryptase levels are useful in the diagnosis of an anaphylactic reaction, since this is one of the main markers of this condition. The blood sample should be taken between the first and second hour after onset of symptoms. Recent studies have suggested serum tryptase as a new marker of the instability of atheromatous plaque in relation to the existence of mastocytes in heart tissue [16].

Conclusions

Involvement of the heart during an anaphylactic episode has been reported. Although many questions about the exact pathophysiologic mechanism of Kounis syndrome remain unanswered, the increasing number of cases published in the last few years shows that this condition should be taken into consideration in the differential diagnosis of ischemic heart disease. Kounis syndrome should be borne in mind when diagnosing patients with no cardiovascular risk factors who experience acute coronary syndrome and who report accidental ingestion of a drug (either one to which they are allergic or a new drug) or a food accompanied by symptoms of anaphylaxis.

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Manuscript received May 21, 2009; accepted for publication July 16, 2009.

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