Kounis syndrome due to iodinated contrast

Síndrome de Kounis por contraste yodado

Kounis Syndrome (KS) was first described in 1991 by Kounis and Zavras[1] and is defined as the simultaneous occurrence of acute coronary events in the context of an anaphylactic or anaphylactoid reaction.[2] Among the allergens capable of triggering this syndrome are drugs, foods, environmental agents, and insect stings. The most important inflammatory mediator involved in vasospasm is histamine, which exerts its effect on the H_1 receptors of the coronary smooth muscle.[3] The following is a case of KS due to the IV administration of iodinated contrast.

A 73-year-old man with no cardiovascular risk factors or known allergies, with a past medical history of femoropopliteal bypass (under treatment with aspirin 100 mg/24 h) and localized prostate adenocarcinoma, underwent an oncologic staging study by computed tomography (CT) with iodinated contrast (100 mL of iopromide). Five minutes after IV contrast administration, he developed pruritus of the head and tongue, followed by sudden loss of consciousness and generalized rigidity, with partial recovery and no cutaneous, respiratory, or hemodynamic abnormalities. Cranial CT ruled out acute disease. The patient then reported non-radiating precordial pain. Electrocardiography (ECG) showed sinus rhythm at 100 beats per minute, ST-segment elevation in leads II, III, and aVF, and ST depression with T-wave inversion in aVR, aVL, V_1, and V_2 (Figure 1). Emergency echocardiography showed no segmental wall motion abnormalities. After 15 minutes, the patient developed generalized erythema and sudden hypotension (50/30 mmHg). Treatment was initiated with crystalloids (2,000 mL of normal saline), hydrocortisone (200 mg), and dexchlorpheniramine (5 mg). Because of refractory shock, norepinephrine was administered up to 0.40 µg/kg/min (preferred over epinephrine due to the suspicion of vasospasm). The condition gradually improved until complete resolution, except for the persistence of anterior T-wave inversion (Figure 2). Tryptase levels (reference range 0.00–11 µg/L) at baseline, 2 hours, and 24 hours were 87.90, 106.00, and 7.79 µg/L, respectively, confirming the anaphylactic nature of the clinical episode. Immunoglobulin E and complement levels were normal. High-sensitivity troponin I (normal range 0–16 ng/L) was 2 ng/L at baseline, 178 ng/L at 6 hours, and 379 ng/L at 24 hours. After 72 hours of hospitalization, the patient was discharged. The temporal overlap of anaphylactic shock and transient

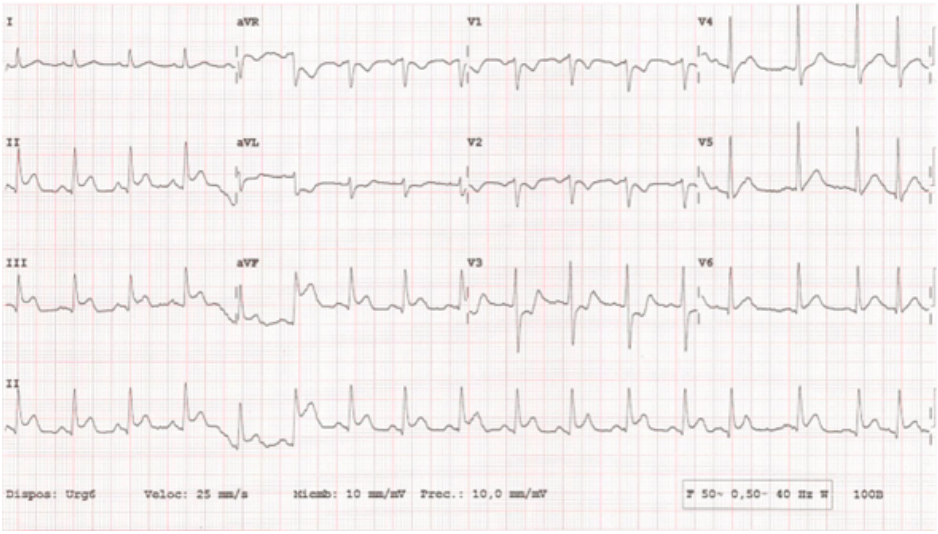

Figure 1. Initial electrocardiogram: ST-segment elevation in leads II, III, and aVF. ST-segment depression and T-wave inversion in aVR, aVL, and V_1–V_3.

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Ethical Responsibilities:
All authors have confirmed their authorship, the nonexistence of external funding, and the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement, and assignment of rights to Revista Española de Urgencias Emergencias.

Editor in Charge:
Guillermo Burillo-Putze.

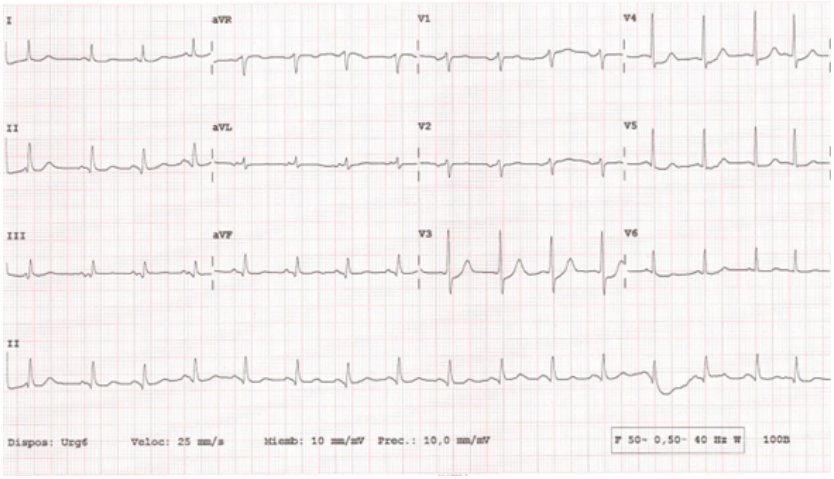

Figure 2. Electrocardiogram after ST-segment normalization. Flattened T wave in V_1–V_2.

acute ischemic event suggested a diagnosis of type I KS.

KS is a medical emergency whose diagnosis is based on the combination of signs, symptoms, and complementary tests compatible with myocardial ischemia occurring in the context of a systemic anaphylactic reaction.[4] Although the exact incidence rate of KS is difficult to determine due to its underrecognition in clinical practice and the scarcity of studies investigating its prevalence, a prospective study conducted in an emergency department by Akoz *et al*. reported an incidence rate of 19.4 per 100,000 hospitalized patients.[5]

The key pathophysiological event that triggers KS is mast cell activation, resulting in the release of inflammatory mediators such as histamine, leukotrienes, tryptase, chymase, and cathepsin D, all of which exert potent vasoconstrictor effects on the coronary circulation.[6]

The clinical signs in KS result from both the acute ischemic event and the symptoms derived from the allergic reaction. Three variants of KS have been described. Type I occurs in patients without risk factors or coronary lesions, in whom the allergen triggers coronary vasospasm. Type II occurs in patients with atherosclerotic coronary disease in whom the release of inflammatory mediators induces plaque rupture. Type III results from an allergic reaction to the metallic component of a stent, leading to thrombosis.[7]

Four mechanisms have been proposed for mast cell degranulation induced by iodinated contrast: direct action on the mast cell membrane, hypertonicity of the contrast medium relative to plasma, complement activation, and an IgE-mediated immunologic mechanism.[8]

During the hypersensitivity reaction, the release of inflammatory mediators stored in mast cells produces the characteristic features of KS. Regarding histamine, *in vitro* studies have shown that its vasoconstrictive effect on coronary circulation is mediated by H_1 receptors.[9] However, in vivo studies demonstrate that the effect of histamine on H_1 receptors is predominantly vasodilatory,[10] except in patients with variant angina or endothelial dysfunction, where vasoconstriction predominates[11] due to increased calcium permeability through the cGMP pathway.[12] Moreover, the effect of histamine on H_1 receptors is dose-dependent, producing vasoconstriction at high concentrations and vasodilation at low concentrations.[13] Chymase and cathepsin D act as enzymes that convert angiotensin I to angiotensin II, which exerts its vasoconstrictor action on smooth muscle via AT receptors.[14]

There is no definitive treatment for KS, and available information comes from isolated case reports and small case series. The therapeutic approach consists of two components: management of the acute coronary syndrome (ACS) and treatment of anaphylaxis. Regarding ACS, aspirin may worsen anaphylaxis. Calcium channel blockers are useful for treating vasospasm but should be avoided in hypotension or shock because of their negative inotropic effect. In patients with persistent angina despite nitrate therapy, opioids may be added—fentanyl is preferred, since morphine can induce mast cell degranulation and worsen the allergic reaction. For anaphylaxis, there is controversy regarding the use of intramuscular epinephrine, as it may exacerbate coronary vasospasm. H_1-receptor antagonists may precipitate hypotension and should be administered only after hemodynamic stabilization. Corticosteroids, though their anti-inflammatory effects are delayed, are indicated to prevent biphasic reactions.[15] In the present case, signs and symptoms of myocardial ischemia resolved after IV administration of hydrocortisone and dexchlorpheniramine. The recent diagnosis of iodinated contrast allergy contraindicated immediate coronary angiography, and although a multislice CT coronary angiography was considered, it was ruled out due to rapid symptom resolution with medical treatment. Hypotension and shock also contraindicated the use of calcium channel blockers.

Although the pathophysiology of KS remains poorly understood, from the above we can conclude that both immunologic and non-immunologic mechanisms are involved in mast cell degranulation induced by iodinated contrast. Coronary vasoconstriction appears to occur only in predisposed individuals and depends on histamine concentration, which may explain the low incidence of KS compared with anaphylactic or anaphylactoid reactions.

Regarding treatment, both the ischemic and anaphylactic components of KS must be considered, with individualized management in each case. KS generally has a favorable prognosis if recognized and treated promptly. Considering KS in any allergic reaction, regardless of severity, could allow early treatment and reduce the morbidity and mortality associated with delayed diagnosis and therapy.

Note of the editors: This is a BOWMAN-generated English translation of the officially indexed Spanish-language article, which should be cited as Rev Esp Urg Emerg. 2024;3:64-66. In this translated version, the editors have supervised the process; however, it cannot be ruled out that some errors resulting from the artificial intelligence translation process may have gone unnoticed.

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