Kounis Syndrome During an Oxaliplatin Desensitization Protocol

Giangrande N[1], Carral Maseda A[2], Lopez Arias JA[3], Perez Casares L[4], Martin Lazaro J[5], Nuñez Orjales R[5], Gonzalez Guzman LA[5], Carballada Gonzalez F[5]

[1]*Allergy Department, Hospital Publico Da Mariña, Burela, Spain*
[2]*Oncology Department, Hospital Publico Da Mariña, Burela, Spain*
[3]*Anesthesiology and Reanimation Department, Hospital Publico Da Mariña, Burela, Spain*
[4]*Cardiology Department, Hospital Publico Da Mariña, Burela, Spain*
[5]*Allergy Department, Lucus Augusti University Hospital, Lugo, Spain*

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Anaphylaxis is a clinical emergency and the most dangerous manifestation of hypersensitivity reaction owing to systemic involvement [1]. Kounis syndrome (KS) is the simultaneous occurrence of acute coronary syndrome during a hypersensitivity reaction [2,3]. Inflammatory mediators released during anaphylaxis extend to cardiac mast cells, which are directly involved in the pathophysiology of KS. This leads to coronary artery spasm and erosion or rupture of atheromatous plaque, followed by myocardial infarction [3,4]. Three variants of KS have been described based on coronary artery conditions (online supplementary table) [2-4]. We report a case of KS (type I) that developed during an oxaliplatin desensitization protocol. To our knowledge, this is the first reported case of KS during an oncology desensitization protocol. The patient gave her written informed consent for the publication of her medical data.

A 59-year-old woman with no history of atopy who had stage IV rectal carcinoma experienced dyspnea, epigastric pain, and hives on the chest and face within a few minutes of her seventh cycle of oxaliplatin. She was treated with antihistamines and corticosteroids. Oxaliplatin was discontinued, and successive lines of platin-free chemotherapy were administered. Two years later, owing to progression of her cancer, oxaliplatin was reintroduced. The patient was referred to our allergy unit. Prick tests performed with oxaliplatin at 5 mg/mL and intradermal tests at 0.5 and 5 mg/mL yielded negative results [5]. After a risk assessment and multidisciplinary team discussion, we considered rapid drug desensitization (RDD), as a drug challenge was deemed too risky. We follow the protocol of 3 bags and 10 steps established by the Ramon y Cajal University Hospital (RCUH) group [6]. RDD was carried out in an allergy-led recovery ward that was risk-assessed for these procedures under constant monitoring and supervision by an allergy nurse and clinician at the bedside, as per the guidelines of the World Allergy Organization [7]. The first RDD with oxaliplatin was uneventful. During the second desensitization cycle, at step 8 of the protocol, the patient developed hives on her head and neck, profuse sweating, dyspnea, and severe epigastric/chest pain. Her blood pressure was 70/40 mmHg, and her oxygen saturation was 97% in room air. Administration of oxaliplatin was stopped. The patient was immediately treated with intramuscular adrenaline (0.3 mg), intravenous methylprednisolone (80 mg), dexchlorpheniramine (5 mg), and fluid therapy (500 mL). Her condition improved rapidly. A 12-lead electrocardiogram showed a sinus rhythm with ST-segment depression in V3-V6 and D2-D3-AVF and ST elevation in V1-AVL (Figure). Serial measurements of ultrasensitive cardiac troponin were initially 19 ng/L, increasing to 335 ng/L at 2 hours after the onset of symptoms. Serum tryptase and IL-6 levels were measured half an hour after the initial symptoms (4.74 µg/L and 6.8 pg/mL, respectively [basal serum tryptase, 2.9 µg/L]). Given the unexpected clinical situation and the cardiac involvement, a second tryptase determination was not performed, and the patient was transferred immediately to the intensive care unit. Coronary angiography revealed normal coronary arteries. Six weeks after this event, an allergology study with oxaliplatin was repeated. Intradermal testing at a concentration of 0.05 mg/mL yielded a positive result, presumably showing an IgE-mediated mechanism of sensitization to oxaliplatin. Based on the clinical history and electrocardiographic, laboratory, and angiography results, the patient was diagnosed with KS type 1.

Anaphylactic reactions with concomitant cardiac involvement have received little attention in the scientific literature. In 1991, Kounis and Zavras described *allergic angina syndrome* as the occurrence of endothelial dysfunction or microvascular angina resulting in an allergic acute myocardial infarction [2-4].

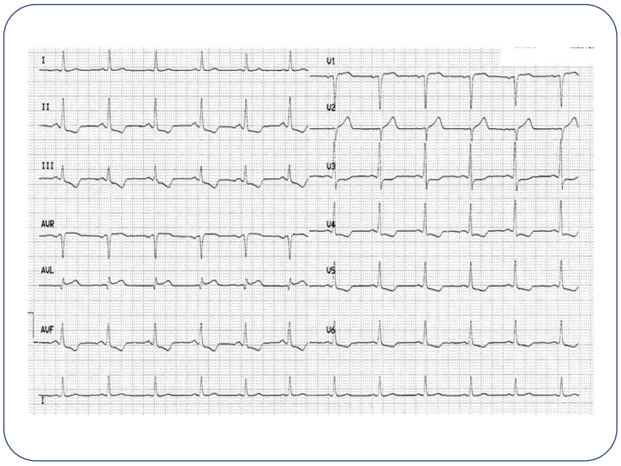

Figure. ST segment depression in V3-V6 and D2-D3-AVF and ST elevation in V1-AVL.

Laboratory evidence has demonstrated that cardiac mast cells, particularly in the vicinity of coronary plaques, play a key role in the pathophysiology of KS. Inflammatory mediators released by mast cells contribute to endothelial dysfunction, plaque erosion or rupture, and subsequent microvascular angina associated with cardiac insult and allergic reactions [2-4].

Oncology patients are particularly susceptible to cardiac complications, likely owing to the cardiotoxic effects of various chemotherapeutic agents. The risk of hypertension, dyslipidemia, early atherosclerosis, and coronary artery disease can vary depending on the specific antineoplastic agent used, potentially predisposing patients to coronary artery insults. Unlike cardiotoxicity, which refers to a dose-dependent cardiovascular adverse reaction that persists despite the discontinuation of the causative treatment, the term *cardiohypersensitivity* refers to a non–dose-dependent immunologic effect (IgE-mediated or non–IgE-mediated) that may occur at any time during treatment, even with a minimal drug dose, the main mechanism being associated with the coronary syndromes or cardiac insults that develop immediately after chemotherapy [8]. Cases of KS associated with antineoplastic agents have been reported in the literature. Chang et al [9] documented a case of KS induced by oxaliplatin that was diagnosed based on co-occurrence of anaphylaxis and cardiology symptoms, together with ECG abnormalities. However, neither cardiological assessments (troponin and angiographic tests) nor an allergology study (tryptase and skin testing) were performed to confirm the diagnosis of KS.

RDD for antineoplastic and biological agents enables temporary tolerance. It is a cost-effective procedure that makes it possible to ensure the most efficacious drug therapy for the affected patient, with the same life expectancy as for nonhypersensitive patients. RDDs are personalized procedures that are adapted to the high complexity of affected patients, requiring multidisciplinary collaboration led by an expert allergist whose role is fundamental in maximizing safety [5,7].

In a series of RDDs reported by the RCUH group, no breakthrough reactions were observed in 88% of the desensitizations, and in cases where reactions did occur, they were typically mild [6]. To our knowledge, no cases of KS have been reported in the major published series of RDD to antineoplastic agents [6,10].

Diagnosis of KS requires a high degree of suspicion, which should be supported by clinical symptoms and evidence from laboratory, electrocardiographic, and angiographic evaluations [2]. The treatment and management of KS is challenging owing to the convergence of 2 potentially life-threatening conditions, anaphylaxis and myocardial involvement [2,3], which make management of KS a challenging endeavour [1-3]. Clinicians must navigate the complex balance between treating anaphylaxis and the potential adverse effects of adrenaline [1,2]. However, prompt treatment of anaphylaxis must take precedence, as, otherwise, it could lead to persistent hypotension and end-organ failure, which could in turn cause ischemia and worsen coronary vasospasm [1].

In conclusion, we report the first case of KS resulting from a breakthrough reaction during the administration of an antineoplastic agent (oxaliplatin) via RDD. In this case, the diagnosis of KS type 1 is based on the clinical history and supported by laboratory, electrocardiographic, and angiographic findings. Positive intradermal test results suggest an IgE-mediated immunological mechanism.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Nicola Giangrande
E-mail: giangrande.nicola@gmail.com

