

Kounis syndrome during an oxaliplatin desensitization protocol

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Anaphylaxis is a clinical emergency and represents the most dangerous manifestation of hypersensitivity reaction due to its systemic involvement [1]. Kounis syndrome (KS) describes the simultaneous occurrence of an acute coronary syndrome during the development of a hypersensitivity reaction [2,3]. Inflammatory mediators released during anaphylaxis extend to heart-resident mast cells, directly involved in the pathophysiology of KS. This leads to coronary artery spasm and atheromatous plaque erosion or rupture, resulting in a myocardial infarction [3,4]. Three variants of KS have been described based on coronary artery conditions (online supplementary table) [2,3, 4]. We report a case of KS (type I) developed during oxaliplatin desensitization. To our knowledge, this is the first reported case of KS during an oncology desensitization procedure.

A 59-year-old woman with no history of atopy, affected by stage IV rectal carcinoma, experienced dyspnoea, epigastric pain and hives in chest and face within a few minutes of the seventh cycle of oxaliplatin treatment. She was treated with antihistamines and corticosteroids. Oxaliplatin was discontinued, receiving successive lines of chemotherapy that didn't include platinum administration. Two years later, for the progression of oncological disease, the reintroduction of oxaliplatin was necessary. The patient was referred to our Allergy Unit. Prick tests at a concentration of 5 mg/ml and intradermal tests at 0.5 and 5 mg/ml with oxaliplatin were performed, yielding negative results [5]. After risk-assessment and multidisciplinary team discussion, we considered the patient for rapid drug desensitization (RDD), as a drug challenge was deemed too risky in her case. We follow the protocol of three bags and ten steps established by the group of Ramon y Cajal University Hospital (RCUH) [6]. RDD was carried out in an allergy-led recovery ward that was risk-assessed for these procedures, under constant monitoring and supervision by allergy nurse and clinician at the bedside, as per World Allergy Organization's guidelines [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 mm Hg, and her oxygen saturation was 97% on room air. The 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), with quick improvement. 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 ultra-sensitive cardiac troponin were initially 19 ng/L, increasing to 335 ng/L at 2 h after the onset of symptoms.

Serum tryptase and IL-6 levels were measured half an hour after the initial symptoms being 4.74 mcg/L and 6.8 pg/mL, respectively (basal serum tryptase 2.9 mcg/L). Due to the unexpected clinical situation and the cardiac involvement, a second tryptase determination was not achieved and patient was immediately transferred to Intensive Care Unit. Coronary angiography was performed, revealing normal coronary arteries. Six weeks after this event, allergologic study with oxaliplatin was repeated. Intradermal test at a concentration of 0.05 mg/ml yielded a positive result, presumably showing a IgE mechanism of sensitization to oxaliplatin. Based on the clinical history, electrocardiographic, laboratory, and angiographic results, the patient was diagnosed with KS type 1.

Anaphylactic reactions with concomitant cardiac involvement have been rarely reported 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 [2,3,4].

Laboratory evidence has demonstrated that mast cells residing in the heart, 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 [2,3,4].

Oncology patients are particularly susceptible to cardiac complications, likely due 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 refers to a dose-dependent cardiovascular adverse reaction that persists despite the discontinuation of the causative treatment, the term cardiohypersensitivity represents an immunologic effect (IgE or no-IgE mediated), not-dose dependent that may occur at any time during the treatment, even with minimal drug dose, being the main mechanism associated to the different coronary syndromes or cardiac insults developed immediately after chemotherapy.[8] Cases of KS associated with antineoplastic agents have been reported in the literature. Chang et al. documented a case of KS induced by oxaliplatin, diagnosed on concurrence of anaphylaxis and cardiology symptoms together with ECG abnormalities. However neither cardiological (troponin and angiographic tests) nor allergological study (tryptase and skin testing) were done to confirm the diagnosis of KS [9].

RDD for antineoplastic and biological agents represents a therapeutic approach that allow a temporarily tolerance to the drug. RDD is a cost-effective procedure that grants the administration of the most efficacious line drug therapy for patient's condition with the same life expectancy as non-hypersensitive patients. RDDs are personalized procedures adapted to the high complexity of patients, requiring of a multidisciplinary collaboration lead by an expert allergist whose role is fundamental to grant the maximum safety of patient [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 anti-neoplastic agents [6,10].

KS diagnosis requires high suspicion, which should be supported by clinical symptoms and evidence from laboratory, electrocardiographic, and angiographic evaluations [2]. The treatment and management of KS present challenges due to the convergence of two potentially life-threatening conditions: anaphylaxis and myocardial involvement [2,3]. The concurrence of two potentially life-threatening conditions, anaphylaxis and myocardial involvement, makes the management of KS a challenging endeavour [1-3]. Clinicians need to 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 it otherwise could lead to persistent hypotension and end-organ failure, which could in turn cause ischaemia and worsen coronary vasospasm [1].

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

Patient's written consent to publication has been signed.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Figure 1. ST-segment depression in V3-V6, D2-D3-AVF, and ST elevation in V1-AVL.

