IBJ Clinical Pharmacology
IberoAmerican Journals

Kounis syndrome secondary to heparin in a new-born with hypoplastic left heart

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Abstract:
Kounis syndrome (KS) is an acute coronary syndrome (ACS) described in relationship with drugs or stents. KS was suspected in a full-term newborn who underwent a Rashkind-atrioseptostomy and stenting that periodically developed episodes of ACS. Skin test with nickel and titanium were performed being negatives. Basophil activation (BAT) and lymphocyte transformation (LTT) tests were performed for the suspected drugs. Non-responder basophils in BAT and a positive LTT for heparin were found. A new dose of heparin was administered by error, after which a new ACS was developed. We described the first report of KS by drug in a newborn.

Keywords: Kounis syndrome, newborn, adverse drug reaction, coronary artery spasm
Recibido November 10, 2019 **Acepted** January 10, 2020 **Published** July 13, 2020.

Editor: Alberto Borobia
Cite as: López Ortego P , Queiruga Parada J, Bravo Gallego L . Y , Gómez Traseira C , Arreo V , Rey J , Rodríguez Mariblanca A , Seco Meseguer E , González-Muñoz M , Ramírez E . Utility of a computer tool for detection of potentially inappropriate medications in older patients in a tertiary hospital. IBJ Clin Pharmacol 2020 1(1):e0015. DOI: 10.24217/2530-4984.20v1s1.00015
Funding: There is no funding related to this article.
Competing Interests: The authors declare no conflicts of interest.

CASE REPORT

A full-term new-born male of 39 weeks and 4 days of gestational age was diagnosed of hypoplastic left heart syndrome at week 27 of gestation. Prenatal genetic study was performed revealing a de novo deletion of the long arm of chromosome 9 (9q34.3) including the NOTCH1 gene. Further complementary explorations discarded the presence of associated malformations. Patient subsequently underwent a Rashkind atrioseptostomy surgery. At 5 days of age, patient developed low cardiac output in the context of pulmonary hyperflux requiering support with extracorporeal membrane oxygenation (ECMO) was required. After 24 hours of ECMO, a hybrid procedure with ductal stenting and pulmonary bibanding was perfomed, allowing for the removal of ECMO support at 72 hours and a scheduled extubation after a week.

At 14 days of age the patient began to present intermittent episodes of agitation, peripheral vasoconstriction, hepatomegaly, arterial hypertension, severe increase in central venous pressure, decrease in regional cerebral oxygen saturation, metabolic acidosis, hyperlactatemia, moderate thrombocytopenia, elevation of transaminases and troponin I (Fig.1 A and B). No skin symptoms suggestive of anaphylaxis were observed nor were trigger episodes identified. Through serial echocardiography and Computed Tomography angiography, it was ruled out that the origin of these episodes was related with thrombosis of the ductal stent. At 26 days of age, a new stenting was performed in the aortic isthmus to try to guarantee coronary perfusion. At 2 months of age, echocardiography showed obstruction to the left ventricular outflow tract with the presence of a subaortic membrane and an intrastent gradient of 75 mmHg. A third stenting was performed in the pulmonary trunk, and consequently the gradient disappeared. During this period of time, the patient continued to have episodes similar to those described above. A Kounis Syndrome was suspected based on ECG signs, myocardial enzymes and angiography and the Clinical Pharmacology, Immunoallergy and Allergy departments were contacted in order to create a multidisciplinary approach.

All the medications received by the patient were exhaustively collected. The algorithm of the Spanish Pharmacovigilance System (SPVS) [1] was applied to study possible pharmacological causality. This algorithm evaluates the following parameters: the chronology, referred to as the interval between drug administration and effect; the literature defining the degree of knowledge of the relationship between the drug and the effect; the evaluation of drug withdrawal, the re-exposure effect, and the alternative causes. The final case evaluation is listed as improbable (not related), conditional (not related), possible (related), probable (related), or definitive (related). Alternative causes were evaluated as a practical approach. Initially it was established as possible (+4 score) for the stents, cefotaxime, esmolol, heparin and vancomycin. The suspected drugs were interrupted and extended diagnostic tests were performed (Fig. 2).

Serum tryptase determinations were performed at the time of an CAS episode and no changes were observed (Fig. 1.C). In order to explore if a type I hypersensitivity was involved in the CAS, a basophil activation test was performed with suspected drugs but no valuable result was obtained because the patient has non-responder basophils. The absence of skin symptoms and elevated tryptase suggested that mechanisms other than anaphylaxis could be involved. Therefore, heparin-PF4-IgG immune complex formation and skin testing with the components of stents, nickel and titanium, were assessed with negative results. On the other hand, T cell-mediated reactions were analysed with a lymphocyte transformation test (LTT). The LTT was positive for heparin and negative for esmolol, vancomycin and cefotaxime.

With the established clinical judgment of allergic angina due to sodium heparin, it was replaced by fondaparinux. In the clinical course of the patient, clinical instability persisted after the withdrawal of heparin, but without electrocardiographic changes or elevated cardiac enzymes. Twenty-five hours after an accidental intravenous administration of a minimum dose of heparin, the patient developed an episode of fever, low cardiac output, hypertransaminasemia, elevation of troponin and severe thrombocytopenia (Fig.1. D), being negative all the microbiological studies. As a result, heparin was scored as +8, and KS in relation to sodium heparin was established.

Finally, at 4 months of age it was decided to limit therapeutic efforts because of the different comorbidities that the patient presented and the presence of severe cerebral atrophy in the imaging tests together with a severely altered neurological examination, eventually leading to death. According to Spanish data protection law, we obtained the informed consent signed by patient's relatives. The case has been reported to the National Pharmacovigilance Agency of Spain (Pharmacovigilance Center in Madrid), number NR4002.

DISCUSSION

Kounis syndrome (KS) has been established as an coronary artery spasm (CAS) concurrent with an allergic event [2]. During an allergic event, the activation of mast cells leads to histamine, leukotrienes and serotonin release [3]. Depending on the severity of the condition, these mediators produce a generalized vasodilatation that leads to anaphylaxis or shock [4]. The same inflammatory mediators can cause a spastic reaction of smooth muscle cells coronary.[5] A classification of KS has been described in three categories: Type I (with normal coronary arteries), type II (underlying atheromatous coronary disease) and type III (stent thrombosis) [6]. Eosinophils and T lymphocytes are also found in histological reports [7]. It has been described in relationship with multiple drugs, stents, environmental agents and atopic condition.[8] It can affect patients of any age group, although the first cases described in children date from 2009 [9].

The mechanism and precipitating factors of CAS are not well understood. The absence of skin symptoms and no

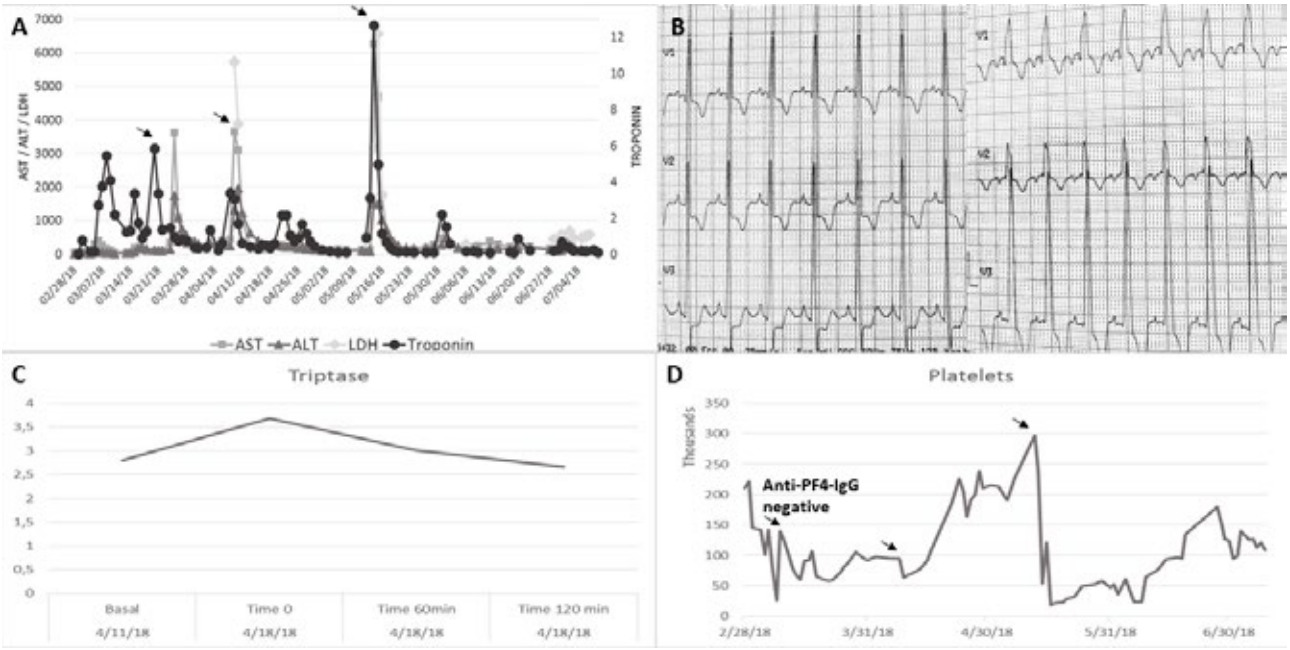

Fig. 1. **A**. Cardiac and hepatic enzymes evolution (ALT, AST and LDH units = UI/L, troponin unit = ng/mL), B. Electrocardiogram (ECG) changes during CAS episodes: ST depression and widening of the QRS. C. Evolution of serum tryptase (µg/L) during an CAS event. D. Evolution of platelets (x10e3/µL) after the accidental administration of heparin. The arrows indicate the CAS episodes.

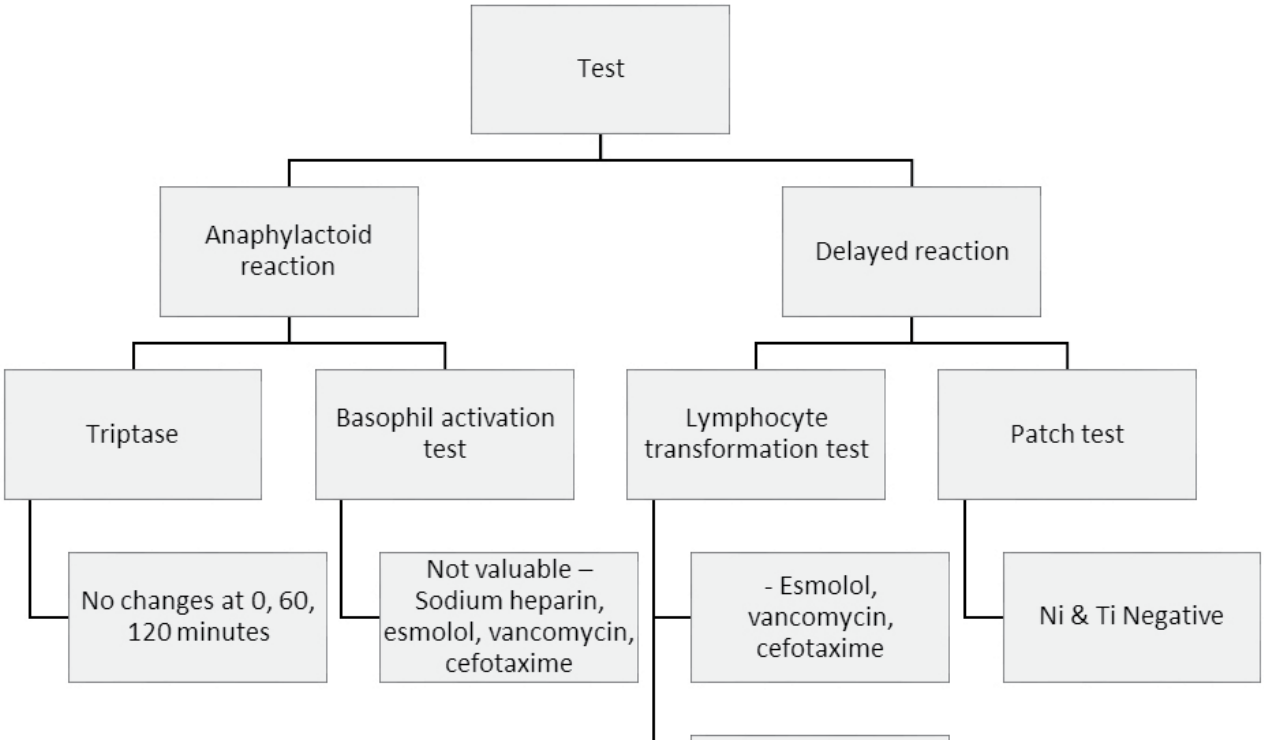

Fig. 2. Diagnostic tests performed.

increase in tryptase levels did not allowed us to determine that anaphylaxis was associated to the CAS. However, skin manifestations and tryptase are not always present in anaphylaxis [10,11,12]. Other types of pro-inflammatory cells can participate in the pathogenesis of KS such as eosinophils, neutrophils and T lymphocytes [13,14]. In this sense, a latency greater than 24 hours from heparin re-exposure to the reappearance of CAS together with a positive LTT result support a cell-mediated delayed hypersensitivity reaction or type IV as the probable mechanism of KS in the case.

In conclusion, KS can occur in neonates although it is an unusual diagnosis. Possibly KS is an underdiagnosed condition, in which the clinical suspicion plays a fundamental role, since there are not pathognomonic signs. The causality algorithms and in vitro tests to evaluate the culprit drug and different mechanisms of the reaction should be considered.

ACKNOWLEGEMENTS

The authors are grateful to other colleagues of the Neonatology, Clinical Pharmacology, Allergy and Immunology departments for their contribution to this report.

STATEMENT OF ETHICS

According to Spanish data protection law, we obtained the informed consent signed by the parents of the patient to publish their case.

Conflict of interest: No conflicts of interest have been declared

Source of funding: No funding has been received

AUTHOR CONTRIBUTIONS

Conceptualization: PLO, ER, MGM.

Data curation: JQP, CGT, VA, JR, ARM, ESM.

Formal analysis: LYBG.

Writing original draft: PLO.

Writing – review & editing: ERG, MGM.

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