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CLINICAL INFORMATION

Drugs that may provoke Kounis Syndrome

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Abstract

Kounis Syndrome (KS) is the contemporary occurrence of Acute Coronary Syndromes (ACS) with an allergic or hypersensitivity reaction. This syndrome has been reported in association with a variety of drugs, food, insect stings, environmental exposures and medical conditions. Cases of KS seem to be more often encountered in everyday clinical practice than anticipated. It is believed that the lack of awareness of this association may lead to underreporting. We report a case of KS secondary to diclofenac intake.

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Introduction

In 1991, Kounis and Zavras described the “syndrome of allergic angina” and “allergic myocardial infarction”, currently known as Kounis syndrome (KS).¹ KS is the concurrence of Acute Coronary Syndrome (ACS) with conditions associated with mast cell activation including allergic, hypersensitivity, anaphylactic and anaphylactoid reactions. The possible mechanism involves the release of inflammatory mediators through mast cell activation which induce coronary artery spasm and/or atheromatous plaque erosion or rupture.²

KS has been increasingly reported in the literature and has been linked with several conditions, environmental exposures and a variety of drugs^{2,3}, leading many experts to believe that KS is not rare, only “rarely diagnosed”.⁴

We report a case of KS secondary to Nonsteroidal Anti-Inflammatory drug (NSAID) allergy.

Case report

A 62 year-old obese man with a history of bronchial asthma and hypertension was brought to our institute’s emergency room after syncope. Upon admission, he was confused, complaining of precordial pain. He presented diaphoresis, with a cutaneous rash that affected his whole body, a pulse rate of 100 bpm, SpO₂ 96% (FiO₂ 60%) and hypotension (78/34 mmHg). He had a prolonged expiratory time and diffuse wheezing at the base of both lungs.

We recorded a 12-lead ECG, which showed ST segment elevation in the inferior leads. He was medicated with metoclopramide 10 mg intravenously (IV), morphine and aspirin 500 mg IV. Because of refractory hypotension, we started dopamine infusion. Blood tests revealed elevated levels of Troponine I (0.8 ng.mL⁻¹) and CKMB (7.7 ng.mL⁻¹).

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He was submitted to cardiac catheterization, failing to show lesions on coronary vessels or contractility abnormalities.

Due to his confusion upon admission, we could only take a detailed history one hour after the initial symptoms, revealing NSAID ingestion (75 mg of diclofenac) for shoulder pain ten minutes before the syncope accompanied by palmoplantar pruritus, vomiting, sweating, palpitations and chest pain.

His family and past medical history revealed atopy, with frequent allergic conjunctivitis and rhinitis, food allergies (nut) and bronchial asthma. After the suspicion of an allergic event, he was medicated with hydrocortisone 200 mg and ranitidine 50 mg IV and was admitted in the Intensive Care Unit (ICU).

Within the first hours of admission, the patient became asymptomatic with normalization of ECG and improvement of laboratory findings (Troponine I - 0,05 ng.mL⁻¹; CKMB - 1,2 ng.mL⁻¹). Echocardiography revealed no motility disorders of the heart wall muscle or other abnormalities. He was discharged of ICU 24 hours after admission.

We obtained a tryptase (7,9 µg.L⁻¹), immunoglobulin E (IgE) antibody level and complement proteins which were normal. We discussed intradermal provocative tests which were not performed for safety reasons.

Discussion

KS has two variants described.⁵ Type I variant includes patients with normal coronary arteries in whom the acute allergic reaction induces coronary artery spasm. Type II variant defines the patient with culprit but quiescent preexisting atheromatous disease in whom acute allergic reactions can induce plaque erosion or rupture to cause an acute myocardial infarction (MI). Our patient belongs in the KS type I variant.

The primary mechanism appears to be the presence of mast cells in heart tissue^{6,7} and subsequent degranulation in anaphylactic or anaphylactoid reaction setting with release of inflammatory mediators. This activation-degranulation can take place by several mechanisms, including via IgE, by histamine-releasing factors from macrophages or T-lymphocytes or by anaphylatoxins from complement system activation.⁸⁻¹¹ The mediators released include tryptase, chymase, histamine, platelet activating factor, cytokines and others, as well as prostaglandin and leukotriene synthesis.² In many clinical and experimental studies, these mediators have been said to induce coronary artery spasm and/or acute myocardial infarction.^{12,13}

KS has been linked with several diseases (bronchial asthma, urticaria, food allergy), environmental exposures (viper, wasp or bee venoms) and a variety of drugs used widely in daily clinical practice, such as antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, nonsteroidal anti-inflammatory drugs and others.⁵ There are recent reports of KS associated to rocuronium¹⁴ and cisatracurium¹⁵ immediately following induction of general anesthesia. Although cisatracurium is reportedly less allergenic than atracurium, it does not induce the release of histamine and has no clinically significant cardiovascular effects at doses eight times its ED₉₅ (0.4 mg.kg⁻¹), there are reports of severe anaphylactic reactions. The reported case

by Ya-Ling Yang et al.¹⁵ not only confirms that cisatracurium can induce severe anaphylaxis, but also reveals that it can cause KS and highlights the possibility for cross-reaction between muscle relaxants.

It is difficult to identify the drugs that could result in anaphylactic reaction during anesthesia, since many drugs are administered in a relatively short time, especially during the induction phase. Skin tests may be useful in identifying the culprit agent.

In our case report, several factors support the diagnosis of KS, including a past medical history of atopy, bronchial asthma and food allergies, all known risk factors for anaphylactic reactions; short time interval between the ingestion of the drug (NSAIDs are a common cause of drug-induced anaphylaxis) and the development of signs and symptoms of anaphylaxis (involvement of the skin, gastrointestinal and respiratory system, reduced BP culminating in syncope)¹⁶ with cardiac involvement. Although the patient complained of precordial pain, had ST elevation segments on ECG and elevation of troponines, the absence of lesions on coronary vessels or contractility abnormalities in cardiac catheterization favors the hypothesis of coronary vasospasm.

The NSAID intolerance is believed to be non-IgE mediated and occurs due to shunting of the arachidonic acid pathway by cyclooxygenase-1 inhibition with overproduction of cysteinyl leukotrienes and release of inflammatory mediators, including histamine and tryptase, from mast cells and eosinophils.¹⁷ Reactions appear to be medication specific as there is no clinical cross reactivity with structurally unrelated NSAIDs.

The diagnosis of anaphylaxis is clinical, and the search for laboratory confirmation should not be allowed to delay the immediate management. Elevated serum histamine and tryptase levels strongly support the possibility of an ongoing allergic reaction, but they are impractical for routine use as they have very short half lives, remaining elevated for 10 minutes maximum for histamine and 90 minutes for tryptase.¹⁸ We found a normal tryptase level, but the clinical presentation did not allow us to take a detailed anamnesis upon admission and the sample was obtained several hours after the presentation. Nonetheless, a negative tryptase test does not exclude anaphylaxis.

Treatment may be challenging because it needs to consider both cardiac and allergic symptoms simultaneously, and the drugs administered for these manifestations can aggravate an allergic reaction and heart function.

Cevik et al.¹⁹ have summarized recommendations concerning the treatment of KS from available data, since most information about KS comes from case reports. The authors argue that:

- 1) Aspirin has the potential risk of aggravating an ongoing anaphylactic reaction since it might shunt arachidonic acid into the leukotriene pathway with overproduction of leukotrienes. Therefore, the utility of aspirin in patients with KS is unknown.
- 2) Nitroglycerin causes hypotension and tachycardia, which may further complicate anaphylactic reaction, but seems safe in KS if blood pressure is satisfactory.

- 3) Beta-blockers may induce more vasospasm due to unopposed α -adrenergic effect and may offset some of the beneficial effects of epinephrine.
- 4) Coronary spasm is very responsive to calcium channel blockers, so they may be considered the initial anti-ischemic drug of choice in patients with KS.
- 5) Morphine and meperidine should be used cautiously since these opiates can induce mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives show only a slight activation of mast cells and may be the drugs of choice when narcotic analgesia is necessary.
- 6) Corticosteroids have a major role in the treatment of allergic reactions, and may prevent recurrent or protracted anaphylaxis. A meta-analysis of the studies of corticosteroid treatment in acute MI reported no harm and possible mortality benefit with these drugs in this setting. Therefore, their use is probably safe and appropriate.
- 7) Epinephrine is the drug of choice in anaphylaxis, but in KS the risks may outweigh the benefits. Epinephrine can aggravate the ischemia as well as induce coronary vasospasm and arrhythmias. The majority of epinephrine preparations contain sulfite which itself may trigger anaphylaxis in sensitive individuals. It may also promote more vasospasm secondary to unopposed alpha-adrenergic effect in patients who have received beta-blocking agents. More case studies are needed to establish the appropriate use of epinephrine in patients with KS.
- 8) Mast cell membrane stabilizers may be considered in KS.

Larger prospective studies are needed to establish definitive treatment guidelines.

Involvement of the heart during an anaphylactic episode has been reported and an increasing number of cases in literature has been emerging. Although the exact pathophysiologic mechanism remains unclear, KS should be born in mind when treating patients with no cardiovascular risk factors who experience ACS, especially when accompanied by symptoms resembling anaphylaxis and a testimony of recent allergen exposure.

The management of these patients may be challenging and, unfortunately, guidelines have not been established yet.¹⁹

Conflicts of interest

The authors declare no conflicts of interest.

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