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# Kounis syndrome: an underestimated emergency

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**Key words**

*Anaphylaxis; coronary vasospasm; hypersensitivity; drugs; Hymenoptera.*

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**Impact statement**

*This report has a relatively large number of patients diagnosed with Kounis syndrome from one center with potential messages about triggers and an allergy work-up.*

***Summary***

***Background.*** *Kounis syndrome (KS) is defined as a rare cause of an acute coronary syndrome associated with systemic allergic reactions. To establish the prevalence of KS among the patients with diagnosis of anaphylaxis, we described clinical features, cardiological and allergological outcomes of patients evaluated in our allergy outpatient clinic.* ***Methods.*** *A retrospective study was carried out in the Allergy Unit of Novara hospital, from January 2008 to March 2020. Skin tests and in vitro tests were performed with suspected etiological agents.* ***Results.*** *We found 9 adults with KS (2%) out of 444 subjects who had experienced anaphylactic reactions (4/9 to Hymenoptera stings, 5/9 to drugs).* ***Conclusions.*** *The present study highlights the importance of suspicion of KS that appears not so uncommon in patients with anaphylaxis. KS seems to be a rare disease because unrecognized in diagnosis of anaphylaxis.*

## Introduction

Kounis syndrome (KS) is a hypersensitivity coronary disorder of which three types have been characterized (1, 2). The type I variant refers to the syndrome in patients with no history of coronary artery disease experiencing coronary vasospasm with or without progression to myocardial infarction in response to an allergic reaction. The type II KS includes patients with preexisting atheromatous disease in whom an allergic reaction can induce either coronary artery spasm with normal cardiac biomarkers and troponin levels or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction. The type III KS includes patients in whom stent thrombosis (subtype a) or stent restenosis (subtype b) occurs in response to an allergic reaction.

KS is caused by inflammatory mediators, such as histamine, platelet-activating factor, and eicosanoids, which are released during the allergic reaction. Most of these mediators have important

cardiovascular actions and during anaphylaxis they contribute to vasoconstriction and coronary artery spasm. Mast cells are present in cardiac tissue, including coronary arteries, and their density is increased in patients with coronary heart disease (1, 3-5). This implies that heart and especially coronary arteries can constitute primary targets in anaphylaxis (6) so that acute ischemic events, including angina and myocardial infarction, are considered currently as part of the clinical picture of anaphylaxis (3). Kounis-like syndromes can also affect mesenteric (7) and cerebral arteries (8-10).
Patients with systemic allergic reactions associated with clinical, electrocardiographic, angiographic, echocardiographic, and laboratory (*i.e.*, increase in cardiac enzyme and troponin levels) findings of acute myocardial ischemia should be diagnosed as having KS (2). Allergic symptoms, compatible history, increase in serum tryptase levels, positive skin tests (STs), and/or positive serum specific IgE (sIgE) assays constitute the basis for diagnosing an allergic reaction. The KS triggers reported most frequently are drugs, foods, environmental exposures (*e.g.*, Hymenoptera stings, insect bites, and latex contact), and clinical conditions (*e.g.*, anisakiasis, idiopathic anaphylaxis, mastocytosis, and intracoronary stenting) (1, 2). Almost all of the works in the literature are the report either of single cases or of a very small number of patients, mainly in adults (11, 12). In this study, we describe a series of nine KS patients, six of whom underwent complete allergy work-up which included STs and *in vitro* tests.

## Materials and methods

### *Patients*

A retrospective study was carried out in the Allergy Unit of Novara hospital (northwest Italy), from January 01, 2008, to March 05, 2020.
During this period, out of 24,535 patients seen for allergic diseases, 444 were diagnosed with anaphylaxis and 9 of these were diagnosed with KS. Anaphylactic reactions were diagnosed according to the clinical criteria proposed by Sampson *et al.* (13). The severity of reactions was graded according to Ring and Messmer (14).
All patients signed an informed consent for the diagnostic procedure.
Since the study was strictly retrospective, based on routine clinical practice, no approval by ethical review board was required.

### *In vivo tests*

*Skin testing*
Patients who had experienced hypersensitivity reactions to Hymenoptera stings underwent STs with Hymenoptera venoms according to international guidelines (15-17).
Patients who reported hypersensitivity reactions to drugs (beta-lactams and iodinated contrast media) underwent a standardized allergy work-up according to the EAACI drug allergy interest group guidelines (18-21).

### *In vitro tests*

*Serum tryptase assay*
Serum basal tryptase (sBT) was measured with an immunofluorimetric assay (ImmunoCAP Thermofisher Scientific, Uppsala, Sweden) during an asymptomatic period. The cutoff value of tryptase was considered to be ≥ 11.4 μg/L in accordance with the manufacturer's instructions. In subjects in whom tryptase assay was performed within 2-4 hours of reaction, values above 120% of the baseline value + 2 (baseline value × 1.2+2) were considered significant for an anaphylactic event (22).

*Serum specific IgE assay*
We performed assays for serum specific IgE (sIgE) to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, and cefaclor with ImmunoCAP (Phadia, Uppsala, Sweden, now Thermo Fisher Scientific) in all subjects with reactions to β-lactams. Subjects who had reacted to Hymenoptera stings underwent assays for sIgE to their venoms. A value of 0.35 kUA/L or greater was considered positive.

*Basophil activation test*
A basophil activation test (BAT) was performed for drugs for which no alternative *in vitro* tests were available and if the symptoms in the patient history suggested that skin testing could provoke systemic reactions (23). The BAT was carried out at the immunology laboratory of IRCCS of Pavia with the responsible drug and alternative ones for evaluating patterns of cross-reactivity, using CD63 as activation marker. A result with CD63 > 5% and Stimulation Index > 2 was considered significative (24).

## Results

**Tables I** and **II** show the demographics, clinical features, cardiological and allergological outcomes of the 4 subjects who had reacted to Hymenoptera stings (2 patients had type I KS and 2 patients had type II KS) and of the 5 individuals with anaphylactic reactions to drugs (4 patients had type I KS and 1 patient had type II KS), respectively.
In the first four subjects (**table I**), an IgE-mediated hypersensitivity to the responsible Hymenoptera venom was diagnosed.
The first subject had experienced severe anaphylaxis in July 2016 after being stung in his garden by three *Polistes dominula* (PoD), despite having immunotherapy with 100 μg of PoD venom every 8 weeks and being given a dose of intramuscular self-injectable epinephrine. In the previous reaction of 2010, he had had desaturation and loss of consciousness after a PoD sting. In that occasion, a slight increase in troponin value was found and doubtful alterations in repolarization were noted on the electrocardiogram (ECG); a coronarography was excluded for negativity of ergometric test.

***Table I*** *- Demographics, clinical features, cardiological and allergological outcomes of the 4 subjects who had reacted to Hymenoptera stings.*

| | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** |
|---|---|---|---|---|
| Gender/Age | M/67 | M/60 | M/40 | M/71 |
| Atopy | No | Yes (HDM AR) | No | No |
| Cardiovascular risk factors | Yes (dyslipidemia, smoke, blood hypertension) | Yes (dyslipidemia, blood hypertension) | Yes (dyslipidemia, smoke) | Yes (type-2 diabetes, blood hypertension) |
| Allergic triggers | *Polistes dominula* venom | Vespula species venom | Vespula species venom | Vespula species venom |
| Symptoms | Eyelid angioedema, throat tightness, dyspnea, desaturation, hypotension, loss of consciousness | Urticaria, dyspnea, severe epigastralgia | Generalized itching, throat tightness, chest pain | Itching of palms, erythema, face edema, throat tightness, dyspnea, loss of consciousness, cardiac arrest |
| Severity grading | Grade III | Grade II | Grade II | Grade IV |
| ECG | ↓ ST | Anterior STEMI | Transient ↓ ST | PEA |
| Troponin-I[a] | 2.4 ng/mL | 4.38 ng/mL | np | 4.55 ng/mL |
| Tryptase, AS[b] | np | 13 mcg/L | np | np |
| Basal tryptase[c] | 11.2 mcg/L | 4 mcg/L | 4 mcg/L | 4.5 mcg/L |
| Coronary angiography | Three-vessel disease | Mono-vessel disease | Normal | np |
| Echocardiography | np | np | np | Negative |
| Kounis type | II | II | I | I |
| Venom specific IgE assay | PoD: 0.51 kUA/L; HB and YJ: < 0.1 kUA/L | YJ: 2 kUA/L; PoD: 0.4 kUA/L; HB: < 0.1 kUA/L | YJ: 23 kUA/L; PoD: 3.9 kUA/L; HB: < 0.1 kUA/L | YJ: 4 kUA/L; PoD: 1.4 kUA/L; HB: < 0.1 kUA/L |
| Skin testing | IDT positive to PoD at 1 µg/mL; STs negative to HB and YJ | IDT positive to YJ at 0.1 µg/mL; STs negative to HB and PoD | IDT positive to YJ at 0.1 µg/mL; STs negative to HB and PoD | IDT positive to YJ at 0.01 µg/mL; PoD at 0.01 µg/mL; HB at 1 µg/mL |
| VIT | Yes (for PoD) | Yes (for YJ) | Yes (for YJ) | Yes (for YJ) |

AS: acute setting; ECG: electrocardiogram; HB: honey bee; HDM AR: house dust mite allergic rhinitis; IDT: intradermal test; M: male; np: not performed; PEA: pulseless electrical activity; PoD: *Polistes dominula*; STs: skin tests; STEMI: ST-elevated myocardial infarction; VIT: venom immunotherapy; YJ: yellow jacket; [a]normal values: < 0.04 ng/mL; [b]normal values: < 2 + (1.2 × basal tryptase level) mcg/L; [c]normal values: < 11.4 mcg/L.

On the occasion of the second reaction, a coronarography evidenced a multivessel artery disease for which the patient underwent coronary artery bypass graft surgery. Therefore, a diagnosis of type-I KS is likely for the first reaction and type II for the second reaction.

After three months an allergy workup confirmed a mono-sensitization to PoD venom; therefore, PoD venom immunotherapy (VIT) was continued at the dose of 200 µg.

Patient 2 had suffered an anaphylactic reaction after a vespid sting in June 2018. He was admitted to the emergency department (ED) where he was immediately treated with intravenous glucocorticoid and intramuscular epinephrine. The ECG showed a diffuse anterior ST-elevated myocardial infarction (ST-elevated myocardial infarction (STEMI), (**figure 1**)). He underwent percutaneous transluminal coronary angioplasty for critical single-vessel coronaropathy (stenosis in the interventricular anterior coronary artery).

Four months later, an IgE-mediated hypersensitivity to yellow jacket (YJ) venom was diagnosed and the related VIT was prescribed.

Patient 3 had experienced moderate anaphylaxis after a vespid sting in September 2008. Two months later we diagnosed IgE-mediated hypersensitivity to YJ venom and prescribed the VIT concerned.

Patient 4 had had severe anaphylaxis after vespid sting in March 2014. Multiple sensitizations to Hymenoptera venoms were found two months later at the allergy evaluation. Since the patient and his wife reliably identified YJ as stinging insect, we prescribed immunotherapy for its venom.

***Table II*** *- Demographics, clinical features, cardiological and allergological outcomes of the 5 subjects who had reacted to drugs.*

| | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 |
|---|---|---|---|---|---|
| Gender/Age | F/49 | F/60 | F/78 | F/54 | F/65 |
| Atopy | No | Yes (drug allergy) | No | No | No |
| Cardiovascular risk factors | Yes (hypertension) | Yes (smoke) | No | Yes (smoke) | Yes (smoke) |
| Allergic triggers | Unknow ICM | Oral AX/clav | Intravenous CT | Oral AX/clav | IOV |
| Symptoms | Throat tightness, dyspnea, loss of consciousness, cardiac arrest | Vomiting, dyspnea, bronchospasm, hypotension, loss of consciousness | Erythema, dyspnea, urinary incontinence, cardiac arrest | Erythema, dyspnea, cyanosis, loss of consciousness, cardiac arrest | Throat tightness, hypotension, coronary spasm, peri-cardiac arrest |
| Severity grading | Grade IV | Grade III | Grade IV | Grade IV | Grade IV |
| ECG | PEA | Transient ↑ ST | PEA | PEA | STEMI* |
| Troponin-I[a] | 1.13 ng/mL | 1.55 ng/mL | 3.75 ng/mL | 0.04 ng/mL | 180 ng/L* |
| Tryptase[b], AS | np | np | 92.4 mcg/l | np | np |
| Basal tryptase[c] | np | 7.8 mcg/L | 5.7 mcg/L | 4.6 mcg/L | 8.1 mcg/L |
| Coronary angiography | np | np | np | np | Mono-vessel disease |
| Echocardiography | Negative | Negative (also ergometric testing) | Inferobasal hypokinesia | Negative | np |
| Kounis type | Type I | Type I | Type I | Type I | Type II |
| *In vitro* testing | np | Specific IgE assay: AX: 0.31 kUA/L; PG, PV, AM, and CE: < 0.10 kUA/L | Specific IgE assay: PG, PV, AM, AX, and CE: < 0.10 kUA/L | Specific IgE assay: PG: 0.25 kUA/L PV: 0.47 kUA/L AX: 0.14 kUA/L CE: 0.15 kUA/L | BAT: Positive to IOV, IOM, IOB, IOP; negative to IOH, IOPR. |
| Skin testing | np | SPT positive to AX and AM at 20 mg/mL; IDT positive to CFT, CFR, CFZ and CFX at 2 mg/mL; STs negative to CTZ at 2 mg/ml and meropenem at 1 mg/ml | np | np | STs negative to IOPR |

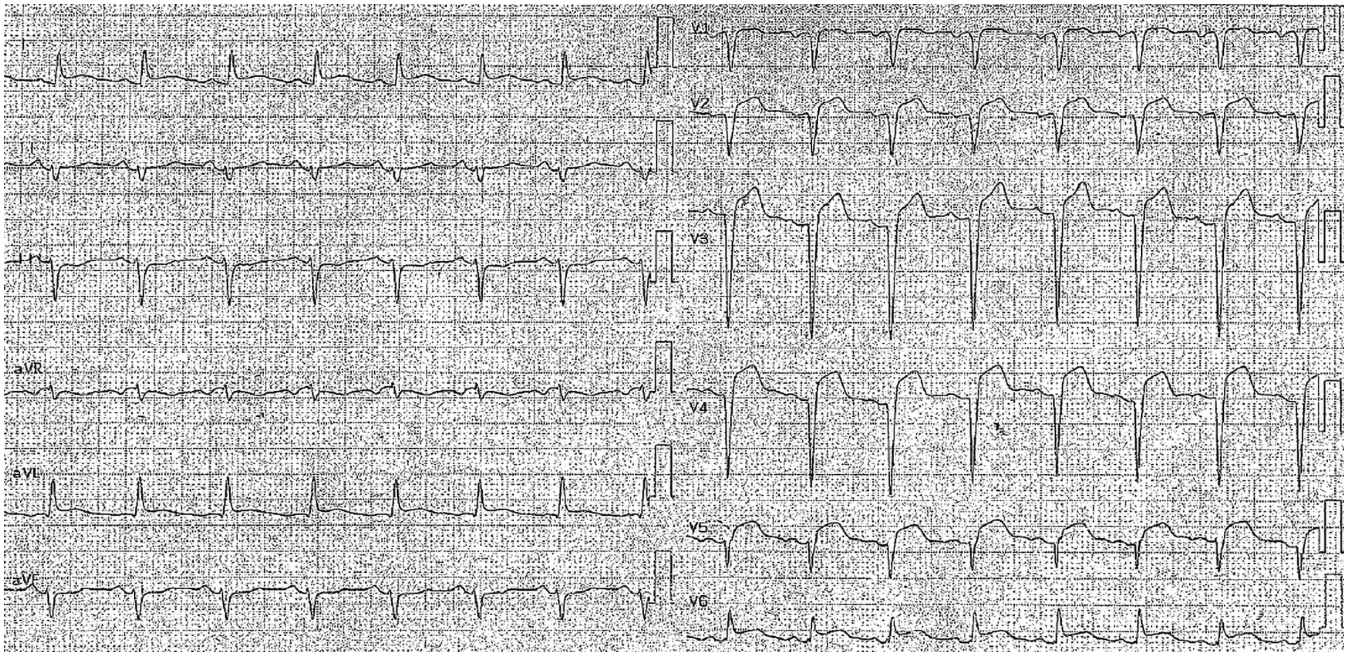
ACLS: advanced cardiac life support; AM: ampicillin; AX: amoxicillin; AS: acute setting; clav: clavulanic acid; CE: cefaclor; CFT: ceftriaxone; CFR: cefuroxime; CFZ: cefazolina; CFX: cefotaxime; CTZ: ceftazidime; ECG: electrocardiogram; F: female; ICM: iodinated contrast media; IDT: intradermal test; IOB: iobitridol; IOH: iohexol; IOM: iomeprol; IOP: iopamidol; IOPR: iopromide; IOV: ioversol; np: not performed; PEA: pulseless electrical activity; PG: penicilloyl G; PV: penicilloyl V; SPT: skin prick test; STs: skin tests; STEMI: ST-elevated myocardial infarction. *STEMI: ST-elevated myocardial infarction was just present at admission; [a]normal values: < 0.04 ng/mL and < 37 ng/L; [b]normal values: < 2 + (1.2 × basal tryptase level) μg/L; [c]normal values: < 11.4 μg/L.

Regarding individuals reporting reactions to drugs (**table II**), patient 5, who had experienced a severe anaphylaxis after administration of an unknown iodinated contrast media (ICM) in July 2014, was evaluated in our center 5 years later for suspected food allergy.

Patient 6 had suffered severe anaphylaxis few minutes after the assumption of the first tablet of amoxicillin + clavulanic acid (AX/clav) for treatment of pharyngitis in February 2016. One month later she was referred to our center and she reported conjunctival hyperemia and eyelid angioedema a few months earlier while she was giving a syrup of amoxicillin to her grandson. An IgE-mediated hypersensitivity to aminopenicillins and other β-lactams was diagnosed on the basis of positive responses to STs.

Patient 7 was hospitalized in June 2018 for a community-acquired pneumonia, which was treated with intravenous ceftri-

***Figure 1*** *- ECG of patient number 2 at the Emergency Department.*




Sinus rhythm, 95 bpm, antero-lateral ST segment elevation and Q waves on V1-V4 leads.

axone that she had tolerated six months earlier. Ten minutes after the first dose (2 g), she had experienced severe anaphylaxis.

One month later she was referred to our allergological center. In relation to the severity of the reaction, in a history clearly suggestive for IgE mediated allergy, STs were not performed, nevertheless negativity of measurement of sIgE for beta-lactams antibiotics.

Patient 8 had had severe anaphylaxis few minutes after the first dose of AX/clav orally in January 2019. One month later she underwent allergy work-up, displaying positive results to penicillins sIgE.

Patient 9 was hospitalized in a cardiology unit for a STEMI in January 2020.

During percutaneous transluminal coronary angioplasty, that showed a critical single-vessel disease, she developed a severe allergic reaction to ioversol with coronary spasm (**figure 2**) and a peri-arrest condition. She was immediately treated with intravenous glucocorticoid and intracoronary epinephrine at dose of 0.1 mg which induced an initial resumption of the circle, followed by a ventricular tachycardia and hypotension which required treatment with cardiac electroshock, amiodarone, and noradrenaline.

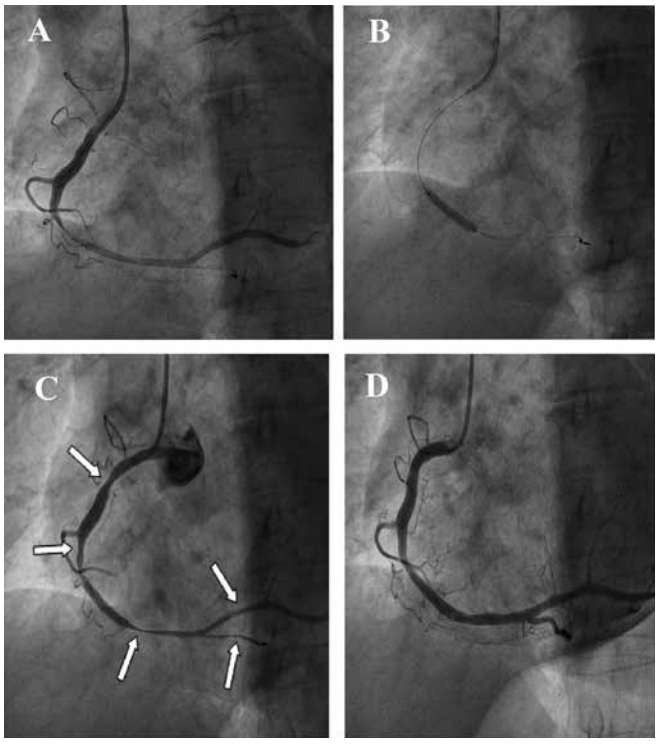
Six months later, she underwent BAT with iomeprol, iobitridol, iopamidol, iohexol, iopromide, and ioversol, presenting positive responses to four ICM, including the responsible one. STs with iopromide were performed (Skin Prick Test (SPT) at 370 mg/ml; intradermal test (IDT) at 37 mg/ml) with negative results.

**Discussion**

In our study the overall prevalence of KS among the patients with diagnosis of anaphylaxis was 2% (9 of 444 subjects). KS diagnosis was made in only 2 cases at the discharge from ED (by a cardiologist) and from Internal Medicine Unit (by an allergist, with subsequent reporting of adverse reaction to the pharmacovigilance system), respectively. In the other cases, the diagnosis was made retrospectively in the allergy unit based mainly on the clinical manifestations, ECG, and laboratory examinations. Cardiovascular involvement (chest pain, hypotension, loss of consciousness, cardiac arrest) was described in 8 patients, respiratory symptoms (dyspnea, bronchospasm, desaturation, cyanosis) in 7, muco-cutaneous manifestations (itching, erythema, urticaria, angioedema) in 6; throat tightness in 5, gastrointestinal symptoms (vomiting, abdominal pain) in 2, and urinary incontinence in one. Two patients had reactions of grade III and 5 patients had reactions of grade IV. The grades III and IV of the Ring and Messmer system may correlate with KS symptomatology (2).

In all four patients with pulseless electrical activity (PEA) the recovery was complete without cerebral or neurological sequelae.

***Figure 2*** *- Coronaric spasm after ioversol administration in patient number 9.*




**(A)** Baseline angiography of right coronary artery (RCA) shows culprit lesion on middle segment; **(B)** Direct coronary stent implantation on mid RCA; **(C)** Angiographic evidence of diffuse coronary spasm involving the proximal RCA, distal RCA, posterior descending artery and postero-lateral artery (white narrows); **(D)** Angiographic control of RCA after intracoronary epinephrine injection.

In three patients cardiological alterations were found (Kounis type II), while the other six patients had normal coronary arteries (Kounis type I).

A variety of electrocardiographic changes ranging from ST segment elevation or depression to any degree of heart block and cardiac arrhythmias can be observed in KS (1).

Vasospasm of the coronary arteries has been suggested to be the main pathophysiologic mechanism. Images from coronarography of patient 9 may confirm this hypothesis (**figure 2**).

Anaphylactic reaction presenting as acute angina or myocardial infarction are being reported increasingly (3).

There are several observations of myocardial infarction and severe arrhythmia following intravenous epinephrine injections, but in our study only two patients had received epinephrine intramuscularly in the outside of the thigh (patient 1 used an epinephrine autoinjector and patient 2 was treated at the admission to the ED) and in this way the risk of cardiac side effects is minimized (3). However, myocardial infarction after therapeutic doses of intramuscular epinephrine has been rarely reported (25, 26).

In 8 out of 9 patients, basal serum tryptase levels were determined with normal result (< 11.4 μg/L), while tryptase measurement in acute phase was performed only for patients 2 and 7, with positive results.

Regarding etiologic agents, in our series, drugs (*i.e.*, β-lactams and ICM) and Hymenoptera stings were responsible for KS. In two patients, KS was caused by the same agent responsible for a previous reaction (PoD in patient 1 and amoxicillin in patient 6).

Our findings are consistent with observation that drugs, especially antibiotics, represent the most common cause of KS (27, 28). Two reviews (29, 30) analyzed 17 case reports of patients with KS due to β-lactams (aminopenicillins in 10 out of 17 patients) and 15 of patients with KS related to amoxicillin or AX/clav, respectively. The review by Ridella (29) identified middle-aged man as the typical patient with KS, while in our case series patients presenting with KS secondary to drugs were all of female gender and patients with Hymenoptera allergy were all males.

Literature also provides description of case reports of KS associated with ICM (1, 2, 31-45) and with Hymenoptera stings (46-54).

Note that only few subjects with KS related to drugs and Hymenoptera stings underwent allergy tests, particularly STs, and presented positive results to the culprit drugs, specifically, amoxicillin (55-58), ceftriaxone (59), cefazolin (60-64), cefuroxime (65), ICM (37, 44) or to Hymenoptera venoms (49, 54).

In patients with drug allergy and PEA we didn't perform STs thinking that in this type of patients at higher risk skin testing may result in systemic response (18).

In fact, a case of KS after IDT with amoxicillin was reported, even if the concentrations used for STs were not specified (66).

Other systemic reactions after STs in patients with KS related to amoxicillin administration were described after SPT with a high-diluted concentration of amoxicillin (0.1 mg/ml) (55) and after ID with 20 mg/ml amoxicillin (56). Only for patient 9, on the base of risk-benefit analysis for a future risk for other ischemic heart diseases, we performed STs with iopromide, after a negative result at BAT.

Regarding our patients with KS related to Hymenoptera stings, a complete diagnostic work-up (*i.e.*, sIgE assays and STs) was performed in all four patients, nevertheless reactions severity, with positive results. REMA score was negative (< 2) for all the patients. VIT was therefore initiated which was well tolerated.

An incomplete allergy diagnostic work-up can be considered as a limit of this study, mainly for hypersensitivity reactions to drugs, justified by severity and rarity of this syndrome. Because of KS reactions' severity, performing *in vitro* tests before STs

may reduce the need for the latter, lessening the risk of systemic reactions (18, 23, 67).

In conclusion, the present case series highlights the importance of suspicion and early recognition of this syndrome that appears rare in general population but not so uncommon in patients with diagnosis of anaphylaxis, which in our study was 2%. It is advisable to refer subjects who experienced KS to allergy centers in order to undergo diagnostic work-up, even if at present time data regarding a complete allergy diagnostic work-up are lacking.

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None.

**Contributions**

GZ: conceptualization, data curation, writing - original draft, writing - review & editing. AP: writing - original draft support. MGM: clinical data, imaging review. All authors: final version agreement.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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