



Kounis Syndrome: Report of Two Cases with Peculiar Presentation and Diagnostic Issues

Alessandro Maloberti^{1,2} · Francesco Pansera¹ · Oscar Sala¹ · Rossana Fusco¹ · Alessandra Pierri¹ · Irene Bossi¹ · Cristina Giannattasio^{1,2}

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1 Introduction

Kounis Syndrome (KS) is a coronary spasm caused by an allergic reaction that leads to myocardial ischemia or infarction [1]. The main pathological mechanism of KS is the epicardial coronary artery vasospasm due to the release of inflammatory mediators during the allergic reaction. These release is determined by the degranulation and activation of mast cells of the coronary artery wall, leading to vasospasm, erosion/rupture of atherosclerotic plaques or intrastent thrombosis, depending on the coronary anatomy [2].

The first case of association between acute coronary events and allergic reactions has been reported in 1950 [3]. From that paper, few case series and prospective studies [4] has been published.

Since it is an uncommon cause of acute cardiac events and, even more, it frequently goes unnoticed, many gaps in evidence are still presents [1]. Starting from its prevalence estimation and going to the therapeutic option through the diagnostic issues still many questions need to be answered. Here we present two cases of KS with peculiar clinical presentation and diagnostic issues.

2 Case Report 1

A 49 years-old caucasian man was referred to our Hospital with diffuse urticaria, malaise, difficulty in breathing and epigastric burning appeared a few minutes after a first dose of amoxicillin for a tooth abscess. Furthermore, the night before the events he had taken also a pill of ketoprofen.

The only cardio-vascular (CV) risk factor was smoking, while he doesn't present previous significant medical history. At admission blood pressure (BP) was 95/60 mmHg and heart rate (HR) was 55 bpm. Electrocardiogram (ECG) shows sinus rhythm with a right bundle branch (already present at previous ECG), without ST-segment or T-wave alterations. In the emergency room the patient was treated with methylprednisolone 40 mg endovenous and chlorphenamine 10 mg intramuscular. After an initial improvement a further deterioration was observed with an increase in cutaneous urticaria and itching. BP and HR fallen respectively to 60/40 mmHg and 40 bpm while O₂ saturation was 95% in ambient air. The patient was consequently treated with atropine, and after few minutes, he complained chest pain with a diffuse ST segment elevation in anterior-lateral leads when an ECG was repeated (Fig. 1). Hydrocortisone 500 mg was immediately administered and fluid load was started. Few minutes later chest pain regressed and no more ST alterations were seen on the ECG. An echocardiography did not show any pathological finding. Since hypotension persisted (BP 70/40 mmHg) and respiratory insufficiency with sign of poor peripheral perfusion were seen on blood gas analysis (pH 7.3; pO₂ 54 mmHg; pCO₂ 39 mmHg; satO₂ 87%; lactate 3.9 mmol/L) patients was transferred to cardiological intensive care unit and inotropes infusion (adrenalin) started while fluid load, corticosteroids and antihistamines were continued. Vital parameters rapidly normalized and persisted in normal range also after therapy weaning.

✉ Alessandro Maloberti
alessandro.maloberti@ospedaleniguarda.it

¹ Cardiology 4, De Gasperis Cardio Center, Niguarda Hospital, 20121 Milan, Italy

² School of Medicine and Surgery, Milano-Bicocca University, Milan, Italy

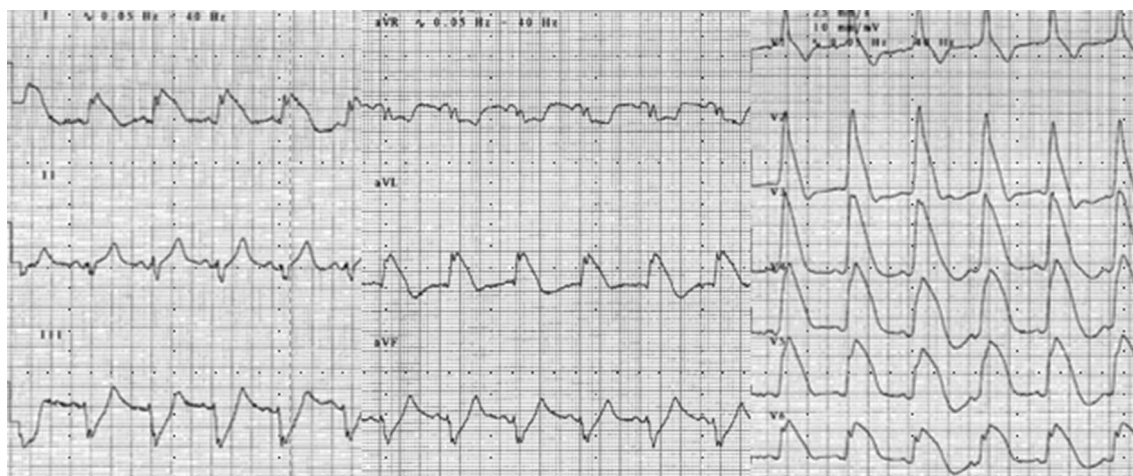


Fig. 1 ECG with diffuse ST segment elevation in anterior-lateral leads when the patients complained chest pain

Creatin-kinase isoenzyme MB and Troponin-T on blood sample were normal in three dosages repeated every 3 h, as well as an echocardiography repeated the day after admission. A maximal ECG stress test was then performed (Bruce 4th stadium; METs 13) that resulted negative for inducible ischemia.

Further laboratory tests revealed an increased total IgE (153 KU/L, normal range 0.35–3.5 KU/L) with a positive test for beta-lactamic antibiotics IgE. Autoantibodies (ANA, cANCA, pANCA,) were negative as well as tryptase, C3 and C4 complement fractions. Eosinophilic count was within the normal range (30 cell/mm³ corresponding to the 0.2% of the total leucocyte, normal range 0–45 cell/mm³ and 0–4.5%).

Patient was discharged on the 4th day after admission with the indication to continue corticosteroid for further 6 days (prednisone 25 mg od with progressive weaning) and antihistamine therapy for 15 days (cetirizine). He was discouraged from the use of beta-lactamic antibiotics and ketoprofen and no further allergic reaction or chest pain developed in the following years.

3 Case Report 2

A 50 years-old caucasian man was referred to our hospital for dyspnea and skin rash 30 min after a first dose of amoxicillin/clavulanic acid for a tooth abscess.

He presented many CV risk factors (arterial hypertension, type 2 diabetes, active smoking, and hypertriglyceridemia) and reported a personal history of chronic coronary artery disease. In 2007 he suffered of an inferior ST-elevated Myocardial Infarction (STEMI) treated with Percutaneous Coronary Intervention (PCI) with the placement of one Bare Metal Stent (BMS) in the circumflex coronary artery.

In 2012 he suffered another inferior-posterior-lateral STEMI treated with PCI with thromboaspiration and the placement of one BMS in the left marginal artery, during this exam a good result of the previously placed BMS in the circumflex was reported.

In 2013 a new myocardial ischemic episode occurred, and a coronary angiography was repeated. A subocclusive stenosis in the circumflex artery was noticed downstream to the previous stent and it was treated with PCI with the placement of a Drug-Eluting Stent (DES). In 2015 an exercise stress test was made for routine control and it was negative for both symptoms and ECG sings. His last echocardiography (2014) shows hypokinesia of the posterior wall and inferior septum of the left ventricle with an ejection fraction of 51%.

He presents also prostatic hyperplasia and a previous surgery for cholecystectomy. He took metoprolol 100 mg od, acetilsalicylic acid 100 mg od, prasugrel 10 mg od, enalapril 5 mg od, rosuvastatin 40 mg od and metformin 1000 mg bid.

At the Emergency Department (ED) admission BP was 75/40 mmHg and HR was 93 bpm. Evaluation revealed dif-fused erythrodermia and bronchospasm was founded on thoracic auscultation. Approximately after 45 min from the symptoms onset (15 min from the arrive into the ED) the patient was treated with methylprednisolone 40 mg and ranitidine endovenous, and chlorphenamine 10 mg intramuscular with clinical improvement and the normalization of the BP. After a further observation of 2 h the patient was discharged with the indication to continue corticosteroids and antihistamine therapy for 1 week (prednisone 25 mg od with progressive weaning and loratadine od).

Three days after he stopped that therapy, the patient complained chest pain and was conducted again to the ED of our institution. On the ECG an infero-lateral STEMI (Fig. 2) was diagnosed and he underwent a primary coronary angiography

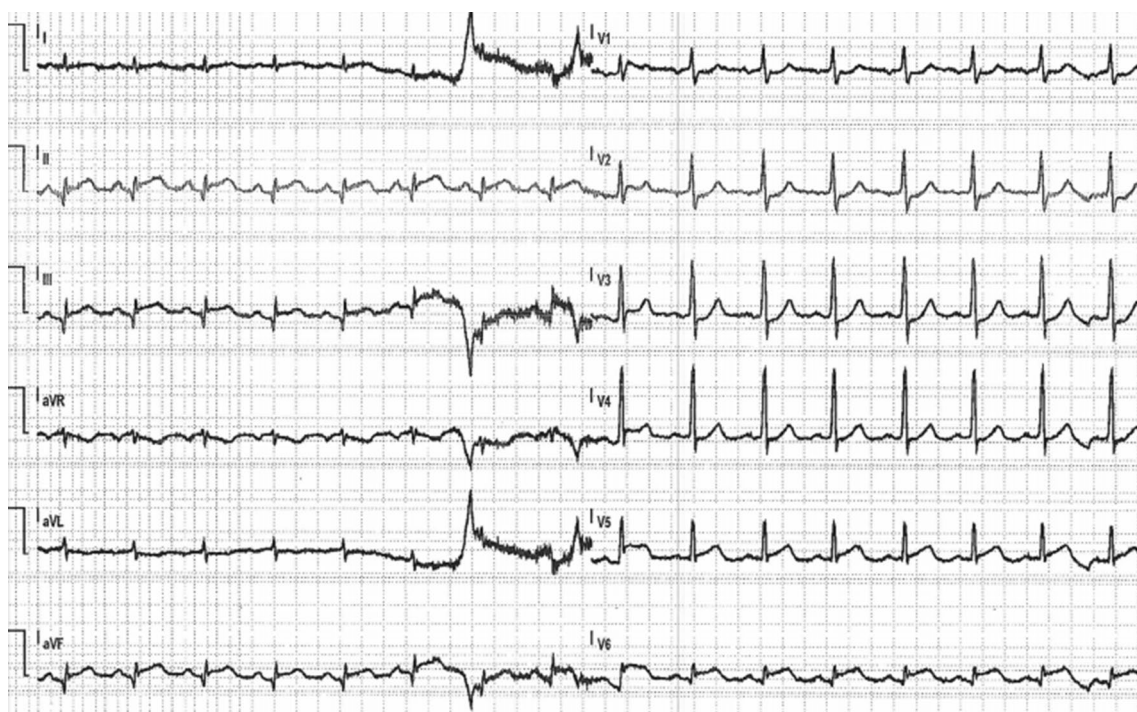


Fig. 2 Infero-lateral ST-elevated myocardial infarction 3 days after steroid and antihistamine therapy conclusion

with the finding of a stenosis 50–60% in the proximal circumflex artery while in the middle circumflex artery, an intrastent acute thrombosis of the distally placed stent (TIMI flow 0) was founded. After thrombus aspiration Intra-Vascular Ultra-Sound (IVUS) was performed revealing mild neointimal proliferation and lumen reduction (minimum lumen area 4.2 mm²) in the distal stent while no pathological changes were founded in the proximal one. An Everolimus DES was placed in the proximal circumflex artery, while a PCI with paclitaxel coated balloon was used to treat the intimal proliferation in the previously placed BMS.

The following echocardiography shows apical akinesia and infero-postero-lateral hypokinesia, with a decrease in the global systolic function (EF 43%). Acme creatin-kinase isoenzyme MB and Troponin-T were respectively 13.8 µg/L and 160 ng/dL. Eosinophilic count was within the normal range (40 cell/mm³ corresponding to the 4% of the total leucocyte, normal range 0–45 cell/mm³ and 0–4.5%).

The patient was discharged on dual antiplatelet therapy for 1 year (with prasugrel) and with the advice to avoid beta-lactamic antibiotics. No further allergic reaction or chest pain developed in the following years.

4 Discussion

The two cases reported allow us to speculate on some important and still unanswered issues in KS. Regarding the first case since we have not performed coronary angiography we cannot surely classify the kind of reaction. In fact, three variants have been described [1]: the type 1 is observed in patients without coronary arteries plaques and where the inflammatory cascade triggered by allergic insult can induce coronary artery spasm both with or without Myocardial Infarction (MI). The type 2 KS is observed in patients with atherosclerotic disease of the coronary arteries in which the vasospasm or the inflammatory mediators itself could determine the rupture of the atherosclerotic plaques with MI. Finally, the type 3 KS includes patients with intra-stent thrombosis, we will return on this variant when we discuss the case of the second patients.

Our first patients probably belong the first type of KS but we cannot classify it with certainty. So an important question is whether the coronary angiography has to be

always performed to make the diagnosis of KS. We choose not to do it for many reasons: firstly, the symptoms and the ECG alteration regressed few minutes after the appropriate anti-allergic therapy was administered and, furthermore, the ECG stress test performed was completely negative for inducible ischemia confirming the very low probability of atherosclerotic coronary disease.

Another point of this first case need to be discussed, i.e. the presence of bradycardia. It arise during ED visit and was treated with atropine. Just few minutes later, patient complained chest pain with the diffuse ST segment elevation determined by the coronary spasm. Most likely bradycardia is not related to the ischemic events (that doesn't affect the right ventricular vascularization) but to a vagal reflex (Bezold–Jarisch reflex) during the anaphylactic shock. In fact, the rapid decrease in vascular resistance determine a heart contraction in an underfilled ventricle that is able to increase the vagal tone, and so, to determine severe bradycardia.

The second case is the most complex one. The patient presents with intra-stent thrombosis allowing us to classify it as a third type variant. In this type of KS the aspirated thrombus typically shows the presence of eosinophils and mast cells confirming the allergic nature of its formation [5]. To classify our case as a type 3 KS we need to answer the question whether it could be a delayed intra-stent thrombosis after the allergic reaction. In fact, the allergic reaction was well treated in less than 1 h from its onset and it briefly improve. Patient was discharged with corticosteroid and antihistamine drug that help to control the allergic mediators and, only 3 days after the therapy conclusion, he develops chest pain with STEMI and intrastent thrombosis on angiography. Unfortunately, we did not perform histology after thrombus aspiration (because the possible connection between the event and KS was not immediately understood) so we are not able to confirm our hypothesis of a late onset intra-stent thrombosis due to allergic reaction. In favor of this hypothesis is the fact that on IVUS examination a neointimal proliferation with a reduction in the lumen area was found. In fact, Kounis et al described this pattern as a possible form of hypersensitivity reaction to the eluting stent [5]. Further discussion is needed on the possibility of an overlapping with takotsubo syndrome in the second case. Cases with possible overlapping of these two syndromes have been already reported [6], in fact, the allergic reaction that determine coronary spasm due to the inflammatory mediators, could also determine the stress induced cardiomyopathy. Differential diagnosis between the two syndromes could be very challenging due to the fact that both determine the same cardiac signs and symptoms as well as electrocardiographic, laboratory and coronary angiography results. Finally, also complete resolution of left ventricle contractile abnormalities within weeks is a characteristic of both syndromes. In

these cases, the evaluation of serum histamine, tryptase, specific IgE antibody, complement proteins and eosinophil levels can help differentiate takotsubo cardiomyopathy and KS.

As regards to diagnostic issues, one could speculate on the use of cardiac enzymes (particularly troponin) in all patients admitted to the ED with acute allergic reactions in order to timely diagnose and appropriately manage a potential cardiac injury manifesting as Kounis syndrome. In a recently published study [7] cardiac troponin was assessed in 300 patients admitted to ED for allergic reactions. Myocardial injury has been founded in 22 subjects (7.3%) while it determines ECG alterations only in 12 subjects and echocardiography alterations only in 7 patients. So, it's wide use surely help us in identifying subjects with myocardial damage due to the allergic reaction but if this will determine differences in management it is currently unknown.

Regarding treatment, as recently reviewed [8], it must be focused both on the therapy of the allergic reaction and of the acute coronary syndrome. Corticosteroid and antihistaminic drugs can help to control the allergic reaction while fluid load is crucial to treat the distributive shock. Regarding the latter in this specific case attention need to be putted on the fluid load that need to be titrated on the ejection fraction of the patient in order to avoid pulmonary edema.

The only life-saving drug in the course of anaphylaxis is epinephrine but it can aggravate myocardial ischemia, prolong the QTc interval and induce coronary vasospasm and arrhythmias that could further impair the heart function in this particular scenario. If necessary, intramuscular administration of a dose of 0.2–0.5 mg (1:1000) each 5–15 min, until either the resolution of symptoms or the appearance of epinephrine side effects, is warranted. In case of cardiac arrest, epinephrine shall be administered intravenously in a dilution of 1:10,000 to 1:100,000.

For the treatment of the acute coronary syndrome differences are present depending on the KS type. In fact, in the KS type 1 nitroglycerin abolish hypersensitivity-induced vasospasm due to the dilation of coronary vessels. Even if used more rarely also non dihydropyridine Calcium channel blockers (diltiazem, verapamil) may be used likewise.

In patients with type 2 KS above coronary artery spasm also the rupture of coronary plaque can be induced by the inflammatory mediators. In this case the patients should be treated rapidly and accordingly to the current acute coronary syndrome guidelines.

A further point need to be mentioned, i.e. the avoided drugs. Beta-blockers are contraindicated in the KS, due to the possibility of coronary spam caused by unopposed activity of α -adrenergic receptors. Finally, opioids drugs used for acute chest pain relief could induce mast-cell degranulation and need to be administered with caution in KS.

In conclusion, we have presented two cases of KS with peculiar presentation and diagnostic issues. In fact, many

gaps in evidence are still presents regarding this particular type of acute coronary syndrome. More case reports and prospective studies are needed in order to fully address all the unmet needs of this rare, but life threatening, diseases.

Compliance with Ethical Standards

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest All the authors declares that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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