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CASE REPORT

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Kounis syndrome in a patient with multivessel coronary artery disease and DRESS

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Abstract

A 68-year-old man was admitted with ST-elevation myocardial infarction and intense rash. He was diagnosed with type 2 Kounis syndrome elicited by drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and received complete revascularization with percutaneous coronary intervention. This case highlights the complex pathophysiology of acute coronary syndrome, and the elusive link between coronary occlusion and ST-segment deviations at ECG.

KEYWORDS

acute coronary syndrome, acute myocardial infarction, DRESS syndrome, drug-eluting stent, Kounis syndrome, Lyell's syndrome, toxic epidermic necrolysis

1 | INTRODUCTION

Kounis syndrome was described in 1991 as an acute coronary syndrome (ACS) secondary to an allergic reaction or a strong reaction of the immune system,[1] with massive release of vasoactive mediators and cytokines from eosinophils and mast cells,[2] that in turn determines a major acute endothelial dysfunction, resulting in either vasospasm or complication of an atherosclerotic plaque.[3,4] It can be elicited by foods, allergens, drugs, insect bites, chemicals or foreign bodies, blood component transfusion and vaccines as well.[2–5]

A recent US inpatient sample-based study, conducted from 2007 to 2014, demonstrated an ACS likely due to Kounis syndrome in 1.1% of 235,420 patients primarily hospitalized with allergy, hypersensitivity, or anaphylactic reactions: 0.2% were diagnosed with unstable angina, 0.2% with ST-elevation myocardial infarction (STEMI), and 0.7% with non-STEMI. In general, they were White and older (65.9 ± 14.1 years) men compared to non Kounis syndrome patients.[6]

Three forms have been described[3]:

1. Type I (with no established coronary artery disease): patients without risk factors or coronary artery lesions reporting chest pain during an acute allergic reaction in whom the allergic event induces coronary spasm and secondary electrocardiographic and ischemic changes. Cardiac biomarkers and troponins may be normal or can reflect progression to acute myocardial infarction.
2. Type II (with established coronary artery disease): includes patients with preexisting, previously quiescent, or symptomatic, atherosclerotic coronary disease, in whom hypersensitivity reactions cause erosion or rupture of a plaque, culminating in acute myocardial infarction.
3. Type III: patients having received coronary stent implantation because of preexisting coronary artery disease who develop definite in-stent thrombosis.[7]

We hereby present the case of a 68-year-old male patient, admitted to our department for typical chest pain and typical electrocardiographic ST/T changes consistent with inferior-wall STEMI together with intense urticarial skin manifestations of the trunk and the four limbs.

2 | CASE REPORT

A 68-year-old man alerted the emergency system for intense oppressive retrosternal chest pain that did not resolve with rest and deep breathing acts and was not associated with dyspnea. The patient was admitted to the emergency room where triage of vital signs was unremarkable (blood pressure 130/80 mmHg, heart rate 80 beats per minute, oxygen saturation 97%); an electrocardiogram (ECG) was recorded (Figure 1) and evident ST-segment elevation in leads aVR, III, and V1, and ST-segment depression in leads I, II, aVL, and V2 were observed. The QTc interval was prolonged at 490 ms. At bedside, a transthoracic echocardiogram confirmed infero-septal hypokinesia and apical akinesia; left ventricular ejection fraction was depressed at 40%. The patient was directly brought to the catheterization laboratory to undergo coronary angiography and possible primary percutaneous coronary intervention.

Coronary angiography revealed critical three-vessel coronary artery disease: moderate disease of the distal left main artery (LM), critical stenosis of the proximal left anterior descending artery (LAD) with an additional stenosis in the mid segment, significant stenosis in the proximal circumflex artery (LCx) and in the dominant proximal right coronary artery (RCA), subtotal occlusion in the mid segment of the RCA with TIMI 1 distal flow (culprit lesion). Primary intervention of the RCA up to the crux cordis was performed (Figure 2) and the coronary anatomy of the RCA and the distal branches was ultimately restored by implanting four drug-eluting stents (DES) and obtaining successful reperfusion.

At the time of careful medical history collection, the patient reported arterial hypertension, stage 4 chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of 17 mL/min/1.73 m^2, dyslipidemia, type 2 diabetes mellitus with stage II obesity and retinopathy. Relevantly, according to the clinical presentation, it emerged that 10 days before the patient had developed an urticarial rash in the trunk and limbs and had been prescribed prednisone and an antihistaminic. Because of the worsening of such dermatological manifestations, 5 days later he had sought for a visit at the emergency room where he was discharged with prescription of increased doses of oral glucocorticoid and antihistaminic therapy. At home he was also receiving clopidogrel, furosemide, nebivolol, olmesartan/hydrochlorothiazide, glargine insulin and repaglinide, oral supplementation of iron, calcium carbonate, and vitamin D and, importantly, the attending

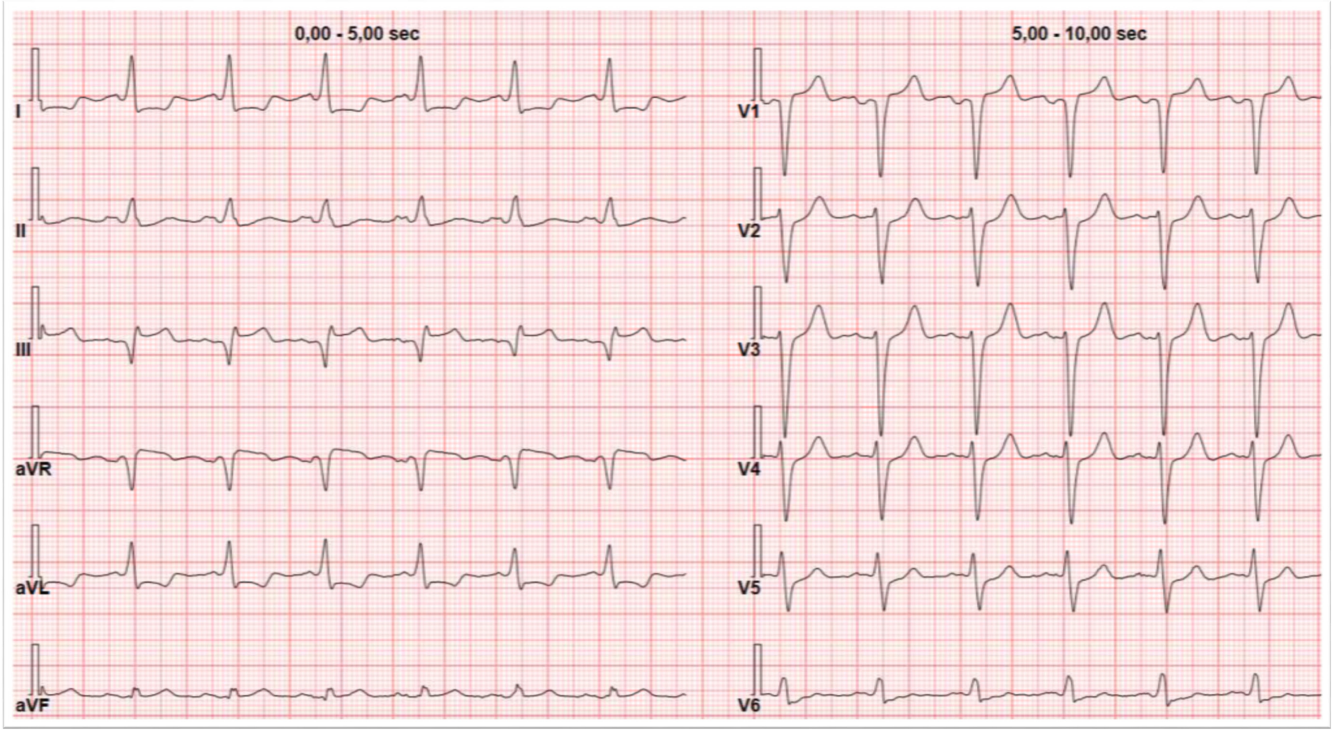

FIGURE 1 ECG at admission. Normal sinus rhythm at 82 beats per minute is observed. ST segment elevation in leads III, aVR, and V1 is evident, as well as ST-segment depression in leads I, II, aVL, and V2. QTc interval is prolonged at 490 ms.

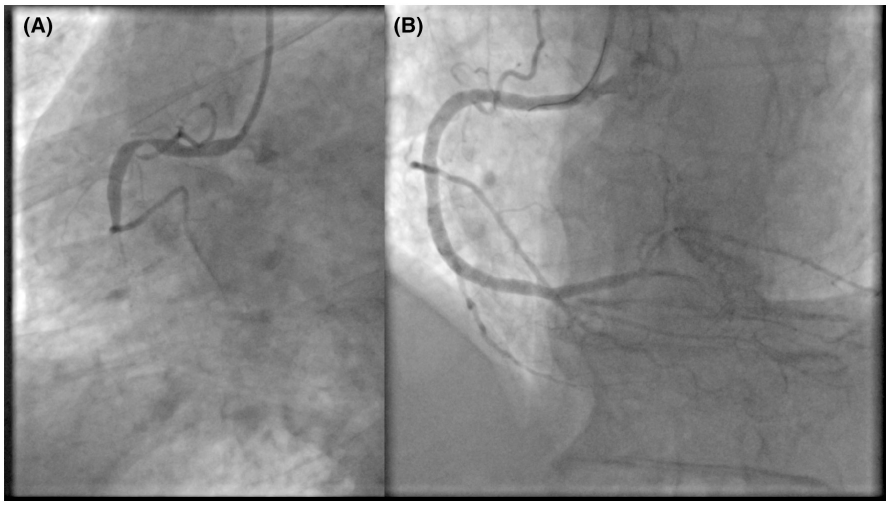

FIGURE 2 Right coronary angiogram in the left oblique view (A) at admission and (B) after percutaneous coronary intervention.

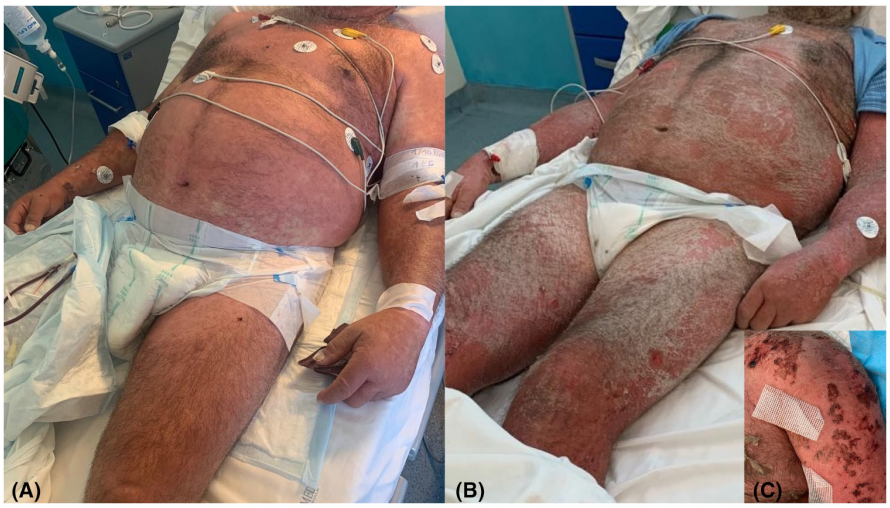

FIGURE 3 (A) Itchy skin erythema observed at admission consistent with drug rash with eosinophilia and systemic symptoms syndrome. (B) Bubbles and desquamative lesions on the skin with erosions and areas of dermo-epidermal detachment at the time of the diagnosis of toxic epidermic necrolysis or Lyell's syndrome. (C) Magnification of (B).

nephrologist had recently prescribed allopurinol because of elevated serum uric acid levels.

Dual antiplatelet therapy (DAPT) with aspirin 100 mg and ticagrelor 90 mg twice daily was started, and an indication was given to complete myocardial revascularization with elective coronary artery bypass grafting (CABG) in view of the high residual Syntax score (29 points), of diabetes mellitus, and of moderate left ventricular dysfunction.[8] We observed an episode of atrial fibrillation (AF) that converted to normal sinus rhythm after a short course of amiodarone. During the in-hospital course, the itchy skin erythema persisted (Figure 3A) and was associated with increasing leukocytosis and eosinophilia (white blood cells 20,000/mmc, eosinophils 35%, CRP 10.1 mg/dL). The consultant allergologist suggested the clinical picture was consistent with DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, indicating allopurinol as the only drug related to the onset of such skin manifestations. Allopurinol was discontinued immediately, and intravenous methylprednisolone therapy was started.

Twelve days after percutaneous coronary intervention (PCI), the patient was transferred to the cardiac surgery department to undergo CABG operation; unfortunately, fever (39°C) and pneumonia developed, positive blood cultures for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were obtained, surgery was postponed until resolution of the infection and the patient was transferred back to our department. Importantly, worsening of the dermatological manifestations was dramatically apparent, so we asked for consultation to a multidisciplinary team consisting of dermatologists, allergologists, plastic surgeons, infective diseases experts. The physical examination (Figure 3B,C) showed bubbles and desquamative lesions on the skin with erosions and areas of dermo-epidermal detachment, extended to a total body surface area of 95%, and lesions were observed also at the visible mucous membranes. The clinical picture was at this stage compatible with toxic epidermic necrolysis (TEN) or Lyell's syndrome. The patient was transferred to the closest burns center intensive care unit (ICU), aiming for a conservative management of skin lesions. Ten days later,

after intense secondary desquamation of the skin lesions, the patient was again transferred back to our cardiological unit for the continuation of the therapeutic workup.

Given the stability of the clinical conditions and the inherent high risk of the CABG operation (STS risk of short-term mortality was 8.2%), after Heart Team consultation[8] the patient received a new indication to complete myocardial revascularization percutaneously. Therefore, we electively performed (Figures 4 and 5) PCI and DES implantation of the proximal LCx, the mid LAD and the LM bifurcation with crossover single-stent provisional strategy toward the LAD.[9] We observed a further progressive improvement in the dermatological and clinical conditions and left ventricular ejection fraction was improved at 50%. The patient was ultimately discharged home on prednisone therapy with the indication to close nephrological surveillance, because of advanced CKD, and regular cardiological follow-up. DAPT was mandated for at least 12 months, with the indication to continue $P2Y_{12}$ inhibitor indefinitely.[10]

3 | DISCUSSION

The clinical case described above is an example of type II Kounis syndrome, the form where ACS manifests itself in the context of severe systemic allergic reaction with hyper-eosinophilia,[11] in this case with a likely iatrogenic etiology, thus triggered by the use of allopurinol. Noteworthy, the allopurinol-induced dermatologic condition, namely DRESS, progressively evolved toward TEN and required prolonged ICU admission.

Allergic mediators released by mast cells during an enhanced immune response can, in patients with preexisting coronary artery disease,[12] result in plaque rupture or ulceration[13] with activation of the coagulation cascade and acute vessel thrombosis.[14] There are no specific diagnostic tests for Kounis syndrome[15]; however the diffuse skin rash with the laboratory finding of hyper-eosinophilia, in a patient with multiple atherosclerotic risk factors and complex coronary artery disease, suggest that this was the case of a type II Kounis syndrome.[4] A possible increase

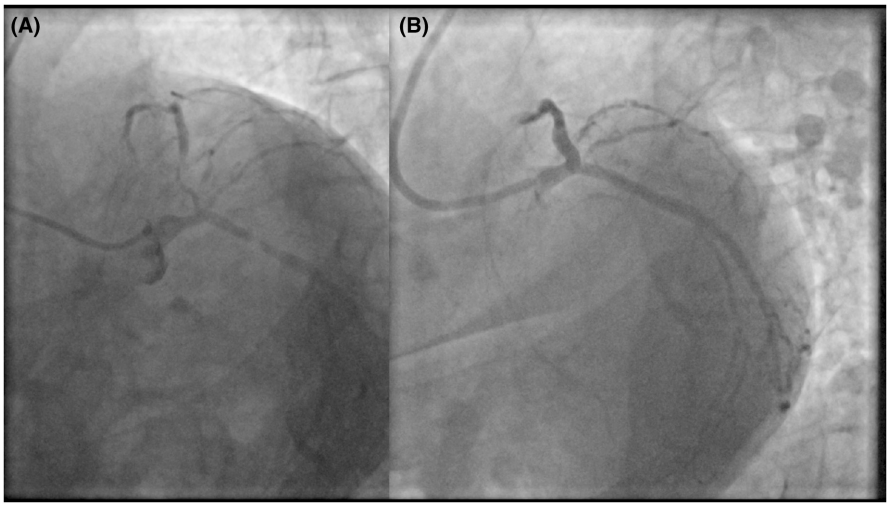

FIGURE 4 Left coronary angiogram in the caudal left oblique view (A) at admission and (B) after percutaneous coronary intervention of the left main coronary artery, the left anterior descending artery, and the left circumflex artery.

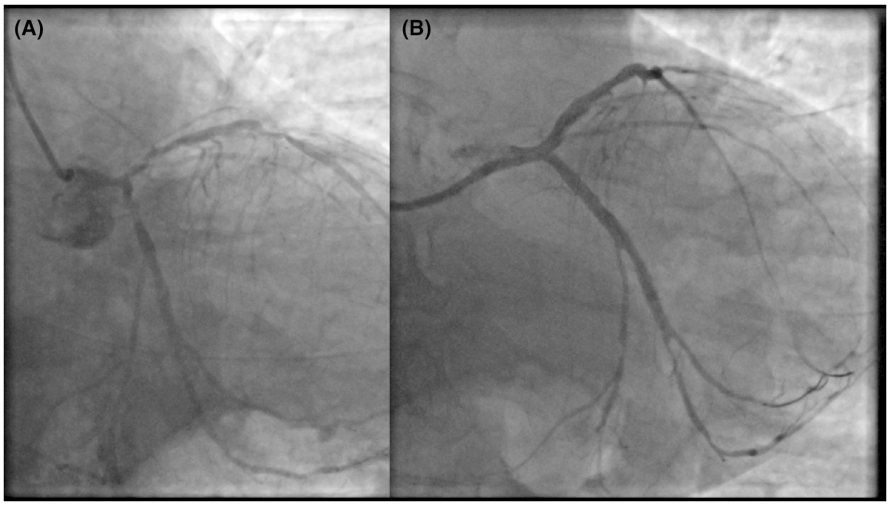

FIGURE 5 Left coronary angiogram in the caudal right oblique view (A) at admission and (B) after percutaneous coronary intervention of the left main coronary artery, the left anterior descending artery, and the left circumflex artery.

in the arrhythmic burden, ranging from AF to ventricular tachycardia, has also been reported in patients with leukocytosis because of the role in causal role of leukocytes in arrhythmogenesis,[16] and therefore the episode of AF occurring in our patient is likely be related to the cytokine cascade triggered by the systemic reaction of the immune system,[17] while we can also speculate on a protective role on AF recurrences exerted by glucocorticoid therapy.[18]

Another interesting feature of our clinical case concerns the ECG alterations in relation to the extent and distribution of atherosclerotic coronary arteries lesions. While this patient had an acutely occluded dominant RCA and, therefore, we would have expected ST-segment elevation in the inferior leads II, III, and aVF, the ECG showed a clear ST-segment elevation in the only lead III without further alterations in the inferior leads beyond a trivial ST-segment depression in lead II. This pattern of ST-segment elevation can be explained by the coronary patho-anatomy. Indeed, while the culprit lesion was in the mid RCA, there was a critical disease of the proximal LAD, consistent with the ischemic apical wall motion abnormalities, that is expected to somehow counterbalance the ECG alterations of the inferior STEMI, while the ST-elevation in leads aVR and V1 and the QT-interval prolongation should not be overlooked as they were clearly consistent with a large area of ischemia, going beyond the extent of a single coronary artery. Of note, we cannot rule out that apical akinesia was also, at least partially, related to a takotsubo-like[19] phenomenon triggered by the combination of two stressful conditions such as systemic allergic reaction and STEMI. Briefly, because of this extent of ischemia, the ST-segment vector was mainly directed rightward and only slightly downward (around +150°) as to be evident in leads aVR and III.

4 | CONCLUSIONS

This case report highlights the complexity of ACS in its pathophysiology,[20] especially when non-atherosclerotic causes[21] overlap with established atherosclerosis,[22] and in the interpretation of the ECG tracings. No doubt exists that while this patient had an important burden of risk factors for atherosclerotic multivessel coronary artery disease, the acute event that triggered culprit plaque rupture can be traced back to the systemic endothelial dysfunction secondary to the cytokine storm during DRESS, consistently with a type II Kounis syndrome.[4] Also, the episode of atrial fibrillation could be an expression of the impressive immunological reaction, consistent with previous reports of increased arrhythmic burden in the setting of a massive release of inflammatory mediators. The ECG tracing at clinical presentation makes this case even more intriguing, as it highlights the elusive correlation between the site of STEMI-inducing coronary occlusion and the corresponding ST-segment changes in the context of multivessel disease.

AUTHOR CONTRIBUTIONS

Olga La Cognata: Conceptualization; investigation; writing – original draft. **Giancarlo Trimarchi:** Conceptualization; investigation; writing – original draft. **Armando Lo Savio:** Investigation. **Vittorio Virga:** Investigation. **Giuseppe Andò:** Investigation; methodology; supervision; validation; writing – review and editing. **Cesare de Gregorio:** Conceptualization; investigation; methodology; supervision; validation; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to report pertinent to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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