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Case report

Kounis syndrome: from an unexpected case in the Emergency Room to a review of the literature.

Erika Poggiali[1], Irene Benedetti[1], Valeria Vertemati[1], Luca Rossi[2], Alberto Monello[2], Manuela Giovini[3], Andrea Magnacavallo[1], Andrea Vercelli[1]

[1] Emergency Department, "Guglielmo da Saliceto" Hospital, Piacenza, Italy; [2] Division of Cardiology, Department of Cardiovascular and Emergency, "Guglielmo da Saliceto" Hospital, Piacenza, Italy; [3] Intermediate Care Unit, Emergency Department, "Guglielmo da Saliceto" Hospital, Piacenza, Italy. * the authors equally contributed to this work.

Abstract. Kounis syndrome (KS) is a coronary syndrome in the setting of allergic/anaphylactic reactions and can be classified in three variants: vasospastic allergic angina (type I), allergic myocardial infarction (type II) and stent thrombosis (type III). The early diagnosis is of paramount importance for the correct management and the prognosis, being KS a life-threatening emergency condition. KS is not uncommon, but it is frequently unrecognized or undiagnosed in virtue of its broad clinical manifestations. The diagnosis should be based on the combination of cardiovascular and allergic/anaphylactic clinical symptoms and signs, as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence. ECG monitoring, cardiac enzymes and troponin are mandatory to confirm or exclude KS in a patient with subclinical or clinical, acute, or chronic allergic reactions. Nevertheless, the treatment is a real challenge for the emergency clinicians because guidelines have not been established yet, and the therapy is based on the variant type. We herein report the case of type I KS in a woman with no prior history of allergy, admitted to our emergency department for abdominal pain, nausea and hematochezia. Starting from this case we conducted a systematic search of the following databases: PubMed, Google Scholar, Science Direct, Medline, using the keywords of "Kounis syndrome", "coronary spams", "cardiac arrest", "sudden death", "allergy", and "anaphylaxis". The main purpose of this review is to remind emergency clinicians to keep a high index of suspicion regarding KS when dealing with patients with allergic reactions or anaphylaxis to promptly identify and correctly manage KS. (www.actabiomedica.it)

Keywords: Kounis syndrome, cardiac arrest, allergy, anaphylaxis, coronary disease.

Case report

An 80-year-old woman presented to our Emergency Department (ED) complaining of hematochezia, nausea, and acute increasing diffuse abdominal pain. She had a history of hypertension, overweight and colon diverticulosis diagnosed by colonoscopy few years before. On admission she was apyretic with dry skin and mucous membranes, and a blood pressure, heart and respiratory rate of 170/100 mmHg, 90 bpm and 20 breaths/min, respectively. Heart auscultation findings were normal. Her abdomen was mild distended with marked rebound tenderness on palpation of the left quadrant and suprapubic region and absent peristalsis. On chest exam bibasilar fine crackles were found. The digital rectal exploration revealed bright red blood without hemorrhoids. Electrocardiogram (ECG) showed sinus rhythm, AV block I degree, and incomplete right bundle branch block (RBBB) (figure 1). Point-of-care ultrasonography documented bilateral B lines in the middle and basal fields, gastrectasis and dilated bowel loops with absent peristalsis. Shortly after physical examination, the patient presented a sudden episode of vomiting with nausea and severe abdominal

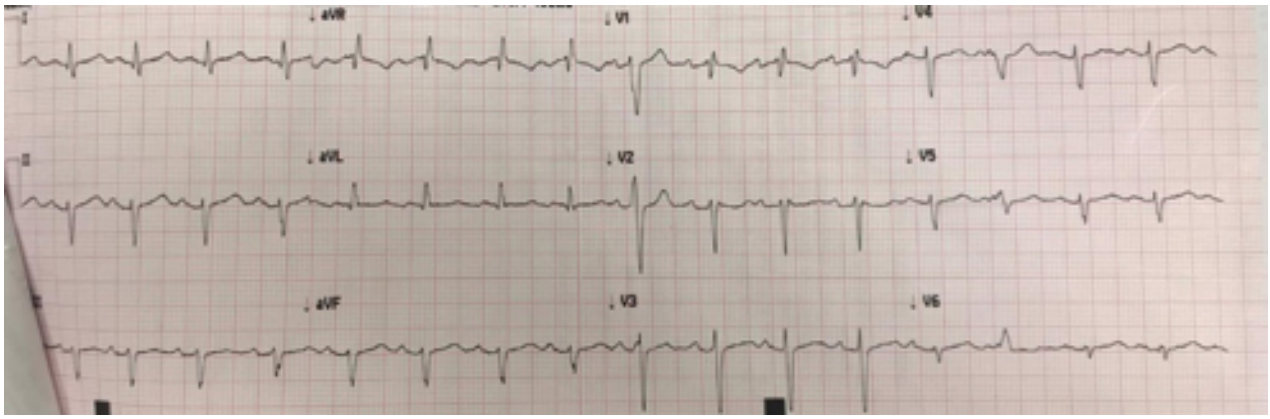

Figure 1. ECG at admission showed sinus rhythm, AV block 1 degree and incomplete RRBB.

pain, with partial relief after placement of the nasogastric tube and intravenous acetaminophen. Venous blood gas analysis showed increased hemoglobin and hematocrit levels (respectively, 14 g/dL and 43%), and mild hyperlactatemia (15 mg/dL, normal value 5-15). On laboratory tests, white blood cells (19.58 x 10^3/μL), neutrophils ratio (87.4 %), lactate dehydrogenase (423 U/L, normal value 0-248), C-reactive protein (19.84 mg/dL, normal value 0-0.05) and procalcitonin (1.6 ng/mL, normal value <0.5) were significantly increased. Platelet count, kidney and liver function, lipase and coagulation tests were all within normal limits. A RT-PCR nasopharyngeal swab for SARS-CoV-2 resulted negative. After hydration with crystalloids, hemoglobin and hematocrit levels decreased to 11 g/dL and 33.5%, respectively. Urgent abdominal CT scan with contrast confirmed the clinical suspicion of acute diverticulitis, documenting widespread signs of pancolic diverticulosis with edematous imbibition of the pericolic cell tissue in the hepatic and splenic flexure and fluid layers along the lateral bands. Since she has no history of allergy, an empiric broad-spectrum intravenous antibiotic therapy with piperacillin/tazobactam was initiated in the emergency room, but after a few minutes, the patient started coughing with an abrupt sense of smothering or gasping, followed by a subsequent pulseless electrical activity (PEA) cardiac arrest. She regained spontaneous circulation (ROSC) after 3 cycles of cardiopulmonary resuscitation (CPR) without the administration of adrenaline. Post-ROSC ECG showed ST segment elevation of more 2 mm in DII, DIII and aVF leads (figure 2), and subsequently complete AV block. Based on this findings, anti-ischemic therapy with lysine acetylsalicylate was started. During CPR, the patient developed a diffuse maculopapular erythema and rash on her neck. In the hypothesis of anaphylactic shock, treatment was started with parenteral corticosteroids and intravenous volume replacement, antihistamine, and ephedrine. In addition, intravenous amiodarone was administered for the onset of atrial fibrillation. The patient was intubated and immediately transferred to the coronary care unit (CCU). In the CCU, the ischemic ECG changes were absent and ECG monitoring confirmed the well-known AV block grade I and incomplete RBBB, suggesting an acute heart damage as vasospastic angina. The echocardiographic study showed an overall normal systolic function without segmental motility abnormalities or valvular disease. An urgent coronary angiography was performed showing the absence of thrombotic occlusions and the evidence of a unique critical (95%) stenosis of the mid-segment of the right coronary artery, and TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow. Based on the recent diverticular bleeding and the absence of thrombosis or unstable plate, angioplasty was not performed. A diagnosis of vasospastic angina during an anaphylactic reaction was done. Blood tests performed 12 hours after the cardiac arrest documented elevated troponin I (290 ng/mL, normal value < 31) and tryptase levels (13.8 μg/L, normal value < 11). Creatine phosphokinase and creatine kinase-MB were normal. IgE were not tested.

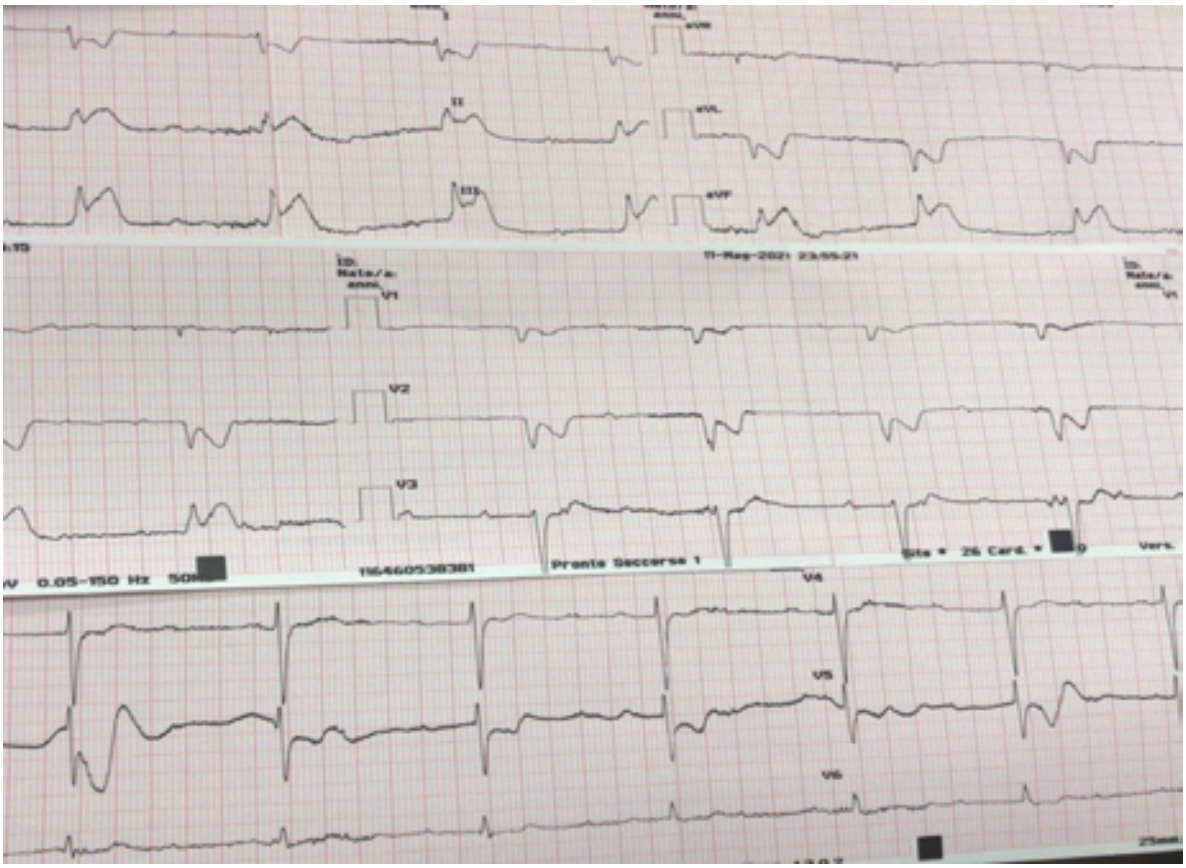

Figure 2. Post-ROSC ECG showed ST segment elevation of more 2 mm in DII, DIII and aVF leads (posterior STEMI).

The patient showed prompt response to the therapy, with a complete resolution of the allergic reaction in a few hours. The signs of ischemia and ECG changes disappeared along with the signs of allergic reaction, confirming the diagnosis of type I Kounis syndrome (KS). The patient was extubated after 24 hours, and she is still hospitalized in good clinical conditions in subintensive care unit.

Discussion

KS is a life-threatening emergency defined as acute coronary syndrome (ACS), including coronary spasm, acute myocardial infarction, and). KS can be induced stent thrombosis, in the setting of allergic, hypersensitivity, anaphylactic or anaphylactoid reactions (1,2) by several triggers, especially drugs used widely in daily clinical practice, such as non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics (3), antibiotics (4-6), anti-neoplastics (7), proton-pump inhibitors (8,9), contrast media (10-12), corticosteroids (13-15), anti-hypertensive medications (16), and others (17-19), but also environmental exposure (20), insect stings (21-27), foods (28-33), and stents (34-37). As reported in literature, drugs represent the most common cause of KS. In a meta-analysis by Raschi *et al.* (38) in 142 articles, drugs were considered responsible for KS; in 89 cases KS was triggered by non-pharmacological agents, and in 21 reports KS was stent related.

KS must be considered not a rare but a ubiquitous disease, that can affect any race, sex, and agen (39), even children (40-42) and adolescents (43-47). A retrospective study by Helbling *et al.* (48) estimated an incidence of 7.9–9.6 per 100,000 inhabitants per year, but the diagnosis is certainly underestimated due to missed, unrecognized and/or undiagnosed cases.

The International Pharmacovigilance Agency (VigiBase™) have reported 51 cases of KS in the period 2010–2014, most of them due to NSAIDs and occurred in the USA (49). In the last two decades, the cases of KS have been encountered worldwide, mainly for the increased awareness of physicians of the existence of KS (50).

The diagnosis of KS is not easy in the ED by reason of its broad spectrum of clinical manifestation, and it should be based on the combination of cardiovascular and allergic or anaphylactic clinical symptoms and signs, as well as on laboratory, electrocardiographic, echocardiographic, and angiographic evidence.

The background. The first case of KS has been reported in 1950 in a 49-year-old man, who developed an acute myocardial infarction associated with urticaria under treatment with penicillin in oil (51). Other cases have been afterward described as "allergic cardiac reactions" or "serum acute carditis" due to serum sickness and tetanus antitoxin (52-54). In 1991, Kounis and Zavras firstly described the pathophysiology of the disease as an "histamine-induced angina syndrome" due to endothelial dysfunction or microvascular angina (55). In some cases, the allergic reaction can promote plaque rupture by the action of some mediators released from the inflammatory cells, particularly mast-cells (56), or can induce vasospastic angina (57). As reported by Lippi *et al.* (58), the troponin I levels resulted higher in patients admitted to the ED with a diagnosis of anaphylaxis, angioedema, urticaria and urticaria-angioedema, compared to healthy controls, suggesting the coronary arteries as primary targets of severe allergic reactions. In another study by Cha *et al.* (59), between 300 anaphylaxis cases occurred in the ED, myocardial injury, including KS and Takotsubo cardiomyopathy, was present in 7.3% of patients.

The pathogenesis. KS can be classified as an ACS related to mast cell-associated disorders and inflammatory cell interactions. Inflammatory mediators released during the allergic insult, e.g., histamine, platelet-activating factor, arachidonic acid products, neutral proteases, cytokines, and chemokines (60), can activate inflammatory cells, including mast cells (61-62), macrophages, and T-lymphocytes (63-64). The activation–degranulation of mast cells via several mechanisms (63,65-66) is the primary mechanisms in the pathogenesis of KS, with the production and release of inflammatory mediators in the heart tissue and in the systemic circulation. The mediators released include histamine, platelet activating factor, cytokines, and neutral proteases as well as tryptase, chymase and cathepsin D, which can induce coronary vasoconstriction directly as histamine (67), or via angiotensin II as chymase and cathepsin D (68) or can promote platelet activation and plaque disruption or rupture (69), and the activation of the coagulation cascade (70). All these inflammatory mediators can cause coronary artery spasm, which can progress to acute myocardial damage, or immediate coronary or stent thrombosis (71), which are the three main clinical manifestations of KS (72). Furthermore, KS must be considered not a single-organ arterial disorder, but a complex multisystem disease, which can involve the skin, respiratory, and vascular systems (73). Mast cells can in fact penetrate all human tissues, as consequence KS can affect all the entire arterial system as well as the cerebral (74) and mesenteric arteries (75). The brain does not suffer from allergic reactions, because IgE antibodies cannot cross the blood–brain barrier, but during anaphylactic reactions, the mast cells resident within the cerebral vasculature can release their vasoactive mediators, inducing cerebral artery spasm and promoting blood–brain barrier damage, brain oedema, prolonged extravasation and even haemorrhage (76). Indeed, platelet-activating factor can reduce cerebral blood flow leading to post-ischemic hypoperfusion (77). As consequence, cerebral ischemic lesions are the result of low cerebral blood pressure or direct proinflammatory and/or vasoconstrictive mediator action in the cerebral arterial system (77), causing a severe and irreversible condition that leads to a fatal hypoxic-ischemic encephalopathy in KS (78,79).

The clinical symptoms. Patients with KS can be admitted to the ED suffering from cardiac symptoms, such as typical ischemic chest pain, chest discomfort, dyspnea, and syncope due to coronary vasospasm, angina pectoris, myocardial infarction, or acute cardiac failure, associated with subclinical or clinical, acute, or chronic allergic reactions, including skin itching and rash, or pruritus. Acute allergic skin manifestations, e.g., urticaria, rash, erythema, and angioedema, can be helpful in the diagnosis, even if some patients can

present delayed skin reactions due to vasoconstriction induced by reduced cardiac output and hypotension during rapidly progressive anaphylaxis. On the other hand, KS can be caused by chronic urticaria itself (80). Emergency clinicians should always remember that the lack of skin manifestations is not an exclusion criterion of KS, but on the contrary a sign of severe shock (81): the cardiac collapse dramatically may indeed reduce the venous return and delay the released anaphylactic mediators to reach and exert their action in skin areas (82). Some patients can also complain of headache, general malaise, nausea, vomiting, and faintness. Diaphoresis, cold extremities, pallor, palpitations, hypotension, tachycardia, or bradycardia are common clinical signs of KS. If untreated, KS can cause cardiorespiratory arrest or sudden death. Cardiac dysfunction is independent from the reaction severity and according to the current classification, KS can be divided in three variants: vasospastic angina (type I), acute coronary thrombosis (type II) and stent thrombosis (type III) (50,83). Patients with type I variant have normal coronary arteries, and the acute allergic reaction induces coronary artery spasm as manifestation of endothelial dysfunction or microvascular angina. In type II variant patients have a pre-existing atheromatous disease, and the acute allergic reactions can induce plaque erosion or rupture and an acute myocardial infarction. Type III variant has been introduced in 2010 for patients with hypersensitivity reaction following implantation of drug-eluting stents and stent thrombosis with thrombi infiltrated by mast cells and eosinophils (83,84).

As brain can be involved in anaphylaxis, patients with KS can suffer from headache, tiredness, somnolence or altered neurological status, that can be misinterpreted as "normal" after an allergic reaction when they are symptoms of anaphylaxis because of reduced brain perfusion (85). Magnetic resonance imaging (MRI) can show hyperintensity on T2-weighted imaging and hypointensity on T1-weighted imaging, corresponding to swelling of the brain due to anaphylactic shock (86).

The diagnosis. The suspicion of KS should be always postulated for patients with systemic allergic reactions associated with clinical, electrocardiographic, echocardiographic, or angiographic, and laboratory findings of acute myocardial ischemia. A careful history of previous atopy and allergic reactions is of paramount importance in the diagnostic process. Serum tryptase (87), IgE antibodies, cardiac enzymes, e.g., CK and CK—MB, and troponin should be tested in all cases to confirm or exclude the diagnosis of KS. As suggested by Kounis NG (88), tryptase should be measured half an hour after the initial symptoms and every 30 minutes thereafter during the following 2 hours. Emergency physicians should focus their attention on the possible cardiac damage resulting in troponin raising and anaphylactic cardiac shock (58,59). For this reason, troponin measurement should be always performed in all the patients admitted to the ED for acute allergic or anaphylactic reactions, to detect and treat immediately potential myocardial injury. ST-elevation or depression, or any degree of heart block and cardiac arrhythmias can be present on electrocardiogram (ECG) (89), even if in type I patients, cardiac enzymes and coronary angiography can be normal, and ECG changes transient (90). AS consequence, ECG-monitoring is crucial to early and promptly identify KS. ECG monitoring is diagnostic when a correlation between allergic/anaphylactic reaction and an electrocardiographic abnormality is detected. In type I variant coronary angiography shows normal coronary arteries, while cardiac SPECT (91) and cardiac MRI (92) are useful to reveal severe myocardial ischemia and subendothelial damage, or in cases of diagnostic uncertainty, such as KS and myocarditis (92).

The treatment. KS is a life-threatening medical emergency that requires a rapid treatment (93). The management of these patients is a real challenge for the emergency clinicians since no guidelines have been established yet (94). Type I patients should be treated with intravenous corticosteroids such as hydrocortisone at a dose of 5 mg/kg/day. Vasodilators such as calcium channel blockers and nitrates can abolish the vasospasm. Intravenous or sublingual nitroglycerin can be administered with caution if the blood pressure is satisfactory (1). Type II patients must be treated for the acute coronary events together with corticosteroids. Nitrates and calcium channel blockers can be given if necessary. On the contrary, epinephrine, the drug of choice for anaphylaxis, can worsen ischemia and coronary vasospasm, as also beta-blockers. Sulphite-free

epinephrine is preferable to be given intramuscularly at doses 0.2-0.5 mg (1:1000), but it can result ineffective in patients already on beta-blockers. In this case, glucagon can be infused with the following dosing schedule: 1-5 mg, intravenously over 5 min, followed by infusion 5-15 μg/min (95). Morphine should be avoided, since it can induce massive mast cell activation and degranulation and aggravate the allergic reaction (96). Fentanyl can be a good alternative, while paracetamol (acetaminophen) is not recommended, because it can cause severe hypotension due to reduction of cardiac output (97). Type III patients need an urgent aspiration of intrastent thrombus, and its histological examination with staining for eosinophils and mast cells. Liu *et al.* (98) reported a case of a 48-year-old man with KS type III who presented persistent elevated levels of immunoglobulin E and chronic urticaria after appropriate antithrombotic, antihistamine, and reperfusion strategies. Upon administration of omalizumab (Xolair®), the authors observed an improvement of chronic urticaria, a decrease in immunoglobulin E levels, and resolution of the ischemic attacks.

Conclusion

KS is not a rare disease, rather it is a rarely diagnosed disease with a high mortality for cardiac arrest or sudden death. The underdiagnosis is related to its broad spectrum of clinical manifestations, and its etiology with continuously increasing of new causes, including drugs, contrast media, foods, insect stings, and stents. Emergency physicians should always consider KS when dealing with any kind or degree of allergic reaction, in order to make a proper and timely diagnosis of KS, take immediate decisions, and administer an effective therapy, as misdiagnosis of this disease can be fatal. ECG monitoring and troponin are crucial to promptly diagnose and define KS, particularly in type I variant.

Contributions: EP, IB and AV collected details of the case. EP and IB drafted the manuscript. IB, VV, LR, AM and MG cared for the patient. LR, AM e AV critically revised the manuscript. All authors approved the final version and stated the integrity of the whole work.

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Availability of data and materials: All data underlying the findings are fully available.

Ethics approval and consent to participate: As this was a descriptive case report and data was collected without patient identifiers, ethics approval was not required under our hospital's Institutional Review Board guidelines.

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Correspondence:
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Erika Poggiali, Emergency Department,
"Guglielmo da Saliceto" Hospital,
Via Giuseppe Taverna 49, Piacenza, Italy.
Tel.: +39 0523 303044.
E-mail: poggiali.erika@gmail.com