Kounis syndrome, a disease to know: Case report and review of the literature

Edoardo Sciatti, Enrico Vizzardi, Dario S. Cani, Assunta Castiello, Ivano Bonadei, Daria Savoldi, Marco Metra, Antonio D'Aloia

Cardiology Unit, University and Spedali Civili of Brescia, Italy

Abstract

The case deals with an anaphylactoid reaction to intravenous ampicillin/sulbactam resulting in cardiogenic syncope and myocardial damage. Symptoms and ECG modifications promptly disappeared after corticosteroids administration.

The Kounis syndrome is an acute coronary syndrome, including coronary spasm, acute myocardial infarction and stent thrombosis, resulting from an anaphylactic or anaphylactoid or allergic or hypersensitivity insult. First described in 1991, it can be caused by a lot of substances, particularly antibiotics. The management should be directed to both the allergic reaction and the myocardial damage.

The Kounis syndrome is a not rare disease that every physician should know because of the wideness of triggers and the possible fatal evolution if not promptly recognized.

Case Report

A 70-year old man came to the Emergency Department (ED) suffering of acute left-sided lumbar pain. He was affected by ischemic heart disease with mid-range left ventricular ejection fraction (LVEF). Few months before he had had an infero-lateral myocardial infarction complicated by apical endoventricular thrombosis and paroxysmal atrial fibrillation, treated with oral anticoagulant (Figure 1A). No documented history of anaphylactic/hypersensitivity reactions was known. He reported a history of recidivant hepatocarcinoma waiting for surgical resection of the III liver segment. He urgently underwent an abdominal CT scan revealing a bleeding retroperitoneal hematoma, treated with urgent left ileo-lumbar artery percutaneous embolization. Anticoagulation was stopped and he was hospitalized in the Surgery Department for monitoring and subsequent liver lesion surgical treatment. The hemodynamic parameters were stable (blood pressure 105/70 mmHg, hemoglobin 9.9 g/dL). As per protocol, he was administered ampicillin/sulbactam for infective prophylaxis. Suddenly during the infusion, the patient felt severe chest pain and presented a syncopal episode (blood pressure dropped to 60/40 mmHg, heart rate increased to 90 bpm). An electrocardiogram (ECG) was performed, showing sinus rhythm, inferior ST segment elevation, infero-lateral necrosis (Figure 1B). The patient was treated with infusion of corticosteroids (betametasone 4 mg iv bolus), lisine acetylsalycilate (500 mg iv), saline solution and ephedrine (25 mg twice) and admitted to the Coronary Care Unit. Blood pressure and ECG rapidly normalized (F Figure 1C) and angor improved. A transthoracic echocardiogram revealed postero-lateral mid-distal hypokynesia, while inferior akynesia with fibrosis and basal posterior septal akynesia were confirmed (LVEF 47%). Other causes of cardiogenic syncope were excluded, as well as endoventricular thrombosis. Troponin I values raised to 0.291 ng/mL. Ticagrelor and heparin were not administered considering the high hemorragic risk. The patient underwent coronary angiography, revealing diffuse moderate coronarosclerosis and a noncalcific plaque in the mid tract of the right coronary artery determining a 50% stenosis (Figure 2 A,B). Medical therapy was continued, except for anticoagulant since the patient was re-transferred to the Surgery Department and underwent a successful liver resection without complications.

Discussion

The case described deals with a typical presentation of Kounis syndrome (KS), type II variant. The patient had an anaphylactoid reaction to betalactamics with syncope, hypotension and coronary vasospasm superimposed to coronarosclerosis. Symptoms and ECG modifications promptly disappeared after corticosteroids administration. No immunological tests to definitely prove the diagnosis were performed considering the patient's critical conditions after the cardiac event. However, the severe comorbidities of the patient, namely the liver cancer and the retroperitoneal hemorrhage, probably facilitated the onset of an immune-mediated reaction.

The KS is an acute coronary syndrome, including coronary spasm, acute myocardial infarction and stent thrombosis, resulting from an anaphylactic or anaphylactoid or allergic or hypersensitivity insult (clinical conditions characterized by mast cells activation with massive release of histamine). It is classified in three types according to the atheromatous state of the coronary arteries (Table 1).

Even in hypersensivity myocarditis myocardial damage is mediated by inflammation. The difference between the myocarditis and the KS is histological: in myocarditis there is presence of eosinophils, atypical

Corresponding author: Edoardo Sciatti, Piazzale Spedali Civili, 1 25123 Brescia, Italy. Tel. +39.030.3995536 - Fax: +39.030.3995013. E-mail: edoardo.sc@tin.it

Key words: Kounis syndrome; anaphylactoid reaction; ampicillin/sulbactam; coronary artery; acute coronary syndrome.

Contributions: ES, DSCi, AC, wrote the paper; IB, MM, EV, ADA, DS, revised the paper.

Received for publication: 13 November 2017
Accepted for publication: 2 March 2018

Tipografia PI-ME Editrice, Italy
Monaldi Archives for Chest Disease 2018; 88:898
doi: 10.4081/monaldi.2018.898

pime EDITRICE

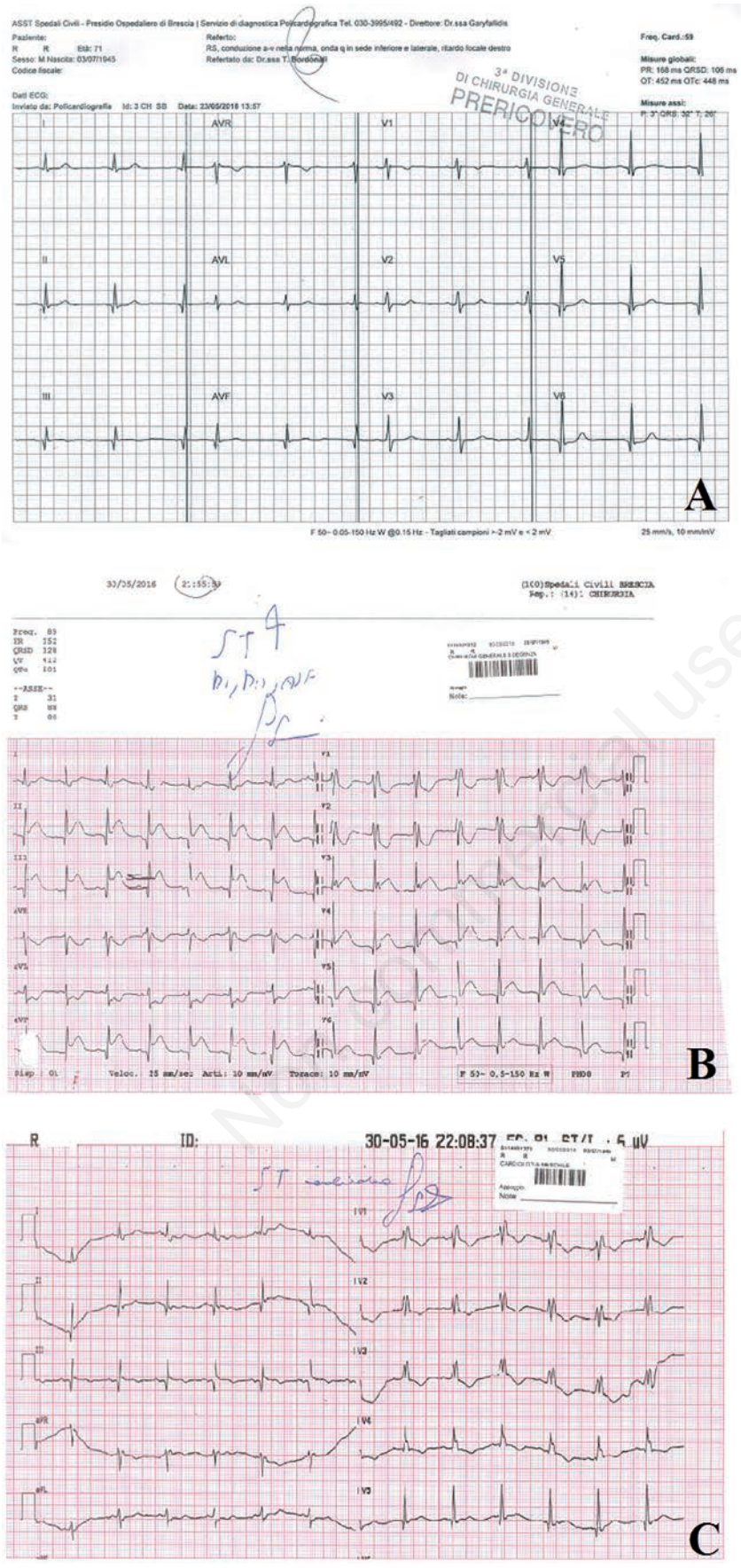

Figure 1. ECG evolution before (A), during (B) and after (C) Kounis syndrome.

lymphocytes and giant cells in myocardial biopsy, whereas in KS these inflammatory cells are present in coronary intima, media and adventitia [1].

The first to talk about an allergic angina syndrome was Nicholas G. Kounis in 1991, but the association between an allergic reaction and an acute coronary syndrome had been described for the first time in 1950. The incidence is estimate at 7.9-9.6/100,000 per year and the case-fatality rate seems to be 0.0001% [2].

KS has been observed in every age group, every race and geographical location. Although the syndrome is not rare, it is often not recognized and therefore not diagnosed nor well treated.

In this field, Lippi *et al.* analyzed TnI levels in all patients who were admitted to the ED with the diagnosis of anaphylaxis, angioedema or urticaria and they found them significantly increased in patients with anaphylactic or anaphylactoid syndrome compared with healthy controls [3]. This denotes that the heart and especially the coronary arteries constitute primary targets in anaphylaxis. Moreover, Cha *et al.* measuring both TnI levels and LVEF (assessed by echocardiopraphy) in 300 cases of anaphylaxis demonstrated that myocardial injury was present in 7.3% of patients [4].

The allergic activation process causes the release of inflammatory mediators such as histamine, platelet-activating factor, arachidonic acid products (leukotriene, thromboxane), neutral proteases and a variety of cytokines and chemokines. During an allergic or anaphylactic reaction, a lot of mediators can cause myocardial damage. In particular, the major role is played by the activation of mast cells secondary to the exposure to an antigen who is responsible for their degranulation, with release of inflammatory mediators and induced expression of lots of others factors (Table 2).

Various causes can induce KS: foods, drugs, environmental exposures. Since the syndrome was discovered, and in particular in recent years, several cases of KS have been described, secondary to allergic reaction to different substances. In Table 3 the most important cases in literature are reported. Clinically, KS manifests both with by signs and symptoms of an allergic reaction (headache, malaise, nausea, pruritus, vomiting, wheezing, skin rash, hypotension, diaphoresis, sweating) and those of an acute coronary syndrome (acute chest pain, dyspnoea, chest discomfort, palpitation, tachycardia

or bradycardia, cardiorespiratory arrest). ECG signs are: ST segment elevation or depression, T-wave flattening and/or inversion, tachyarrhythmias or bradyarrhythmias. Laboratory tests often show leukocytosis with eosinofilia and increase in myocardial enzymes. Alterations in coronary angiography are different as different according to the KS type: spasm (type I), thrombosis (type II) or thrombosis on pre-existing drug eluting stent (type III).

Management of KS is tricky because the treatment of the allergic reaction may worsen the myocardial damage (*e.g.*, anti-H1 drugs can cause hypotension and coronary hypoperfusion epinephrine can increase myocardial oxygen consumption); vice versa the treatment of myocardial infarction cannot ameliorate the anaphylactic reaction. In this case, both conditions should be managed tailored on patient's clinical presentation. A recent review revealed intravenous steroids (76%), nitroglycerin (47%), H1-blockers (70%), and H2-blockers (35%) to be the most commonly used treatment options. A guide to approach the treatment options of this intricate syndrome is proposed in Figure 3.

To conclude, KS is a not rare disease that every physician should know because of the wideness of triggers and the possible fatal evolution if not promptly recognized. Our case report aims at underlying these two aspects, since the patient was receiving an antibiotic prophylaxis at the Surgery Department like thousands of people and necessitated of immediate resuscitation and coronary care unit stay in order to survive.

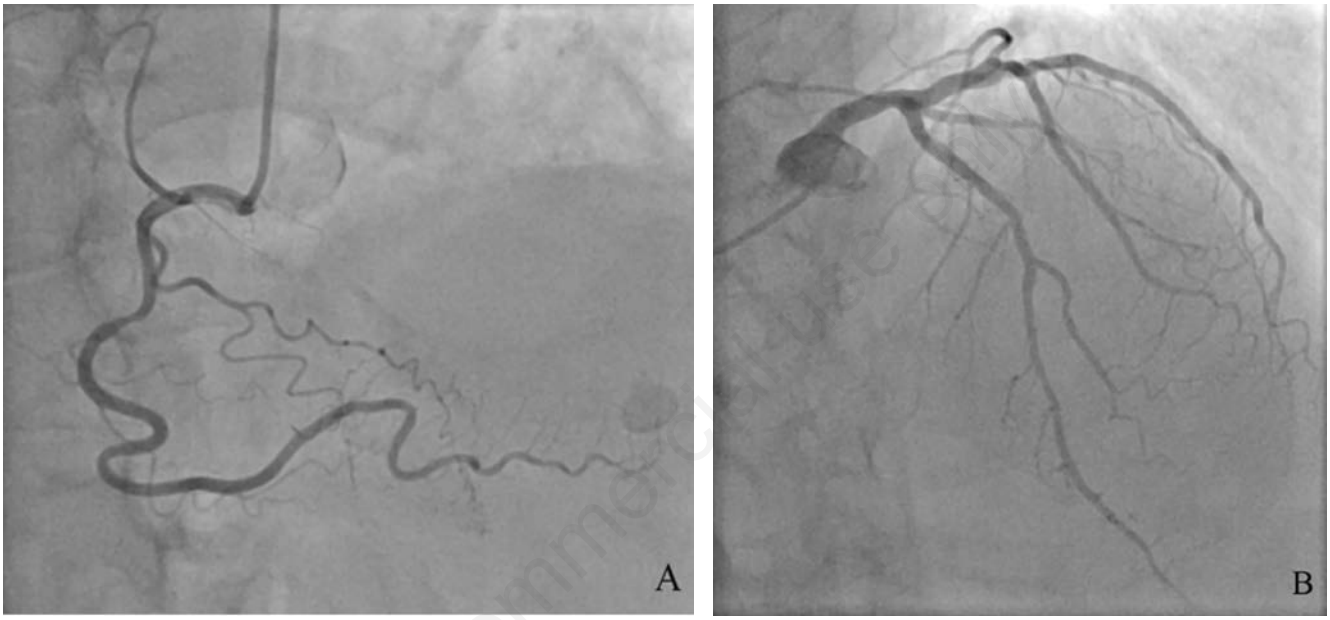

Figure 2. Angiography of right (A) and left (B) coronary arteries.

Table 1. Types of Kounis syndrome.

Types of Kounis syndrome	Description
Type I	Coronary artery spasms at the epicardial and/or microvascular levels in patients without coronary disease
Type II	Plaque erosion or rupture in patients with pre-existing coronary atheromatous disease previously silent
Type III	Stent thrombosis in patients with previous implantation of coronary drug eluting stent, with demonstrated presence of mast cell by Giemsa stain and eosynophils by ematoxylin-eosin stains

Table 2. Role of various inflammatory agents on coronary arteries.

Inflammatory agent	Activity
Histamine	Coronary vasoconstriction by H1 endothelial receptors, induction of tissue factor expression, and platelets activation
Tryptase	Activation of metalloproteinases with subsequent erosion of plaque collagen cap
Chymase and Cathepsin D	Increased vasoconstriction by converting angiotensin I to angiotensin II
Leukotrienes	Increased vasoconstriction
Thromboxane	Platelets aggregation
Platelets (FcγRI, FCγRII, FCεRI and FCεRII)	Enhanced adhesion, activation and aggregation

pime EDITRICE

Table 3. Case reports of Kounis syndrome in literature.

Cause	Type	Temporal relation	LVEF	ECG	Acute treatment	Regression of ECG alterations	Prick test or RAST +
Anisakis simplex [5]	I	Yes	Moderate dysfunction	Anterior ST elevation	-	Yes	Yes
Scombroid syndrome [6]	II	Yes	-	Infero-lateral ST changes	PTCA + stent	Yes	Histamine intoxication
Losartan [7]	I	Yes	-	Lateral ST elevation	Anti-allergic treatment, inotropic support, IABP	Yes	Yes
Gelofusine substance [8]	I	Yes	-	-	Metaramirol, epinephrine, steroids, antihistamine	-	Yes
Ultrasound contrast [9]	II	Yes	-	Inferior ST changes	-	Yes	-
Actinidia chinensis [10]	I	Yes	-	-	-	-	Yes
Warble fly bite [11]	II	Yes	-	Anterio ST elevation	PTCA	-	-
Corticosteroids [12]	I	Yes	-	-	-	Yes	-
NSAIDS [13]	I	Yes	-	Bradycardia, biphasic T waves	Calcium channel blockers	-	-
Autoimmune urticaria [14]	I	Yes	-	Anterio ST elevation	Cetirizine, methylprednisolone	Yes	Yes
Metamizole [15]	I	Yes	Normal	ST elevation	Inotropic support, hydrocortisone	Yes	-
Clarythromycin [16]	-	Yes	-	-	Sudden death	Sudden death	-
Cefotaxime ev [17]	I	Yes	Normal	ST depressionV3-V5, ST elevation V1-aVR	Standard protocol for ACS, anti-H2	-	-
Ibuprofen [18]	I	Yes	-	Inferior ST elevation	Trinitrine, intracoronary epinephrine, IABP	-	-
Unknown [19]	I	Yes	20%	Infero-lateral ST elevation	Steroids, histamine blockers	Yes	-
Iopromide (contrast agent) [20]	I	Yes	Normal	Inferior ST elevation	Steroids, epinephrine, vasodilators, anti-H2	Yes	-
Multiple bee stings [21]	II	Yes	25%	Infero-lateral ST elevation	Steroids, epinephrine, PTCA	-	-
Pea salad [22]	I	Yes	-	Inferior ST elevation	Intracoronary nitroglycerine, hydrocortisone	Yes	-
Bee sting [22]	I	Yes	-	Inferior ST elevation	-	Yes	-
Amoxicillin/clavulanic acid [23]	Angiography refused	Yes	Normal	ST elevation	Epinephrine, hydrocortisone, ACS therapy	-	-
Bonsai [24]	-	Yes	Inferior hypokinesis	ST elevation	Thrombolytilc	Yes	-
Sulphur hexafluoride [25]	III	Yes	-	Inferior ST elevation	Hydrocortisone, thrombus aspiration, PTCA	-	-
Spider bite [26]	No angiography	Yes	22%	ST segment depression	Treatment for HF	-	-
During TAVR [27]	I	Yes	-	Inferior ST elevation	Steroids, antihistamine, epinephrine, nitrates	-	-
Mushroom[28]	I	Yes	-	ST elevation DI aVL, V1-V4	Intracoronary nitrates	Yes	Yes
Anaesthesia [29]	I	Yes	-	Inferior ST elevation	-	-	-
Capecitabine [30]	I	Yes	40-50%	FV → Lateral ST elevation	-	Yes	-
Midazolam [31]	I	Yes	-	Anterio ST depression	Flumazenil, ACS therapy, anti-H2, corticosteroids	-	-
Wasp sting [32]	I	Yes	40%	T inversion	Epinephrine, hydrocorotisone	Yes	-
Ciprofloxacine [33]	I	Yes	-	ST elevation on inferior	Thrombolysis, ACS therapy → prednisone, ranitidine, amlodipine	Only after second treatment	-
After fish consumption [34]	I	Yes	Normal	ST elevation DI-aVL, infero-lateral depression	Antihistamine, ACS therapy	-	-
Bee sting [34]	I	Yes	-	Inferior ST elevation	Epinephrine, hydrocorotisone, dual antiplatelet therapy, heparin	Yes	-
Wasp sting [35]	I	Yes	Normal	Biphasic T wave	Methilprednisolone, chlorpheniramine	-	-
Spider bite [36]	II	Yes	Normal	Inferior ST elevation	Thromboaspiration	-	-
Ceftriaxone [37]	I	Yes	Normal	-	Intracoronary nytroglicerin	-	Negative
Metimazole [38]	II	Yes	Mild dysfunction	Inferior and anteriori ST elevation	Nitroglycerine thromboaspiration, PTCA + BMS	-	-
Amiodarone [39]	I	Yes	Infero-lateral hypokinesis	-	Epinephrine, dobutamine	-	-
Tramadol [40]	I	Yes	-	Cardiac arrest → inferior ST elevation	Epinephrine, nitroglycerine	-	-
Celecoxib [41]	I	Yes	Normal, apical akynesis	Inferior ST elevation	Diphenhydramine, albuterol, methilprednisolone, heparin, clopidogrel	Yes	-
After rupture of echinoccocal cyst [42]	I	Yes	-	ST elevation	Chlorphenamine, hydrocortisone	Yes	-
Tramadol ev [43]	I	Yes	55%	ST elevation DI-aVL, depression DIII-V3-V5	ACS therapy	Yes	-
Clopidogrel [44]	I	Yes	-	Inferior ST elevation	Dexamethasone	-	-

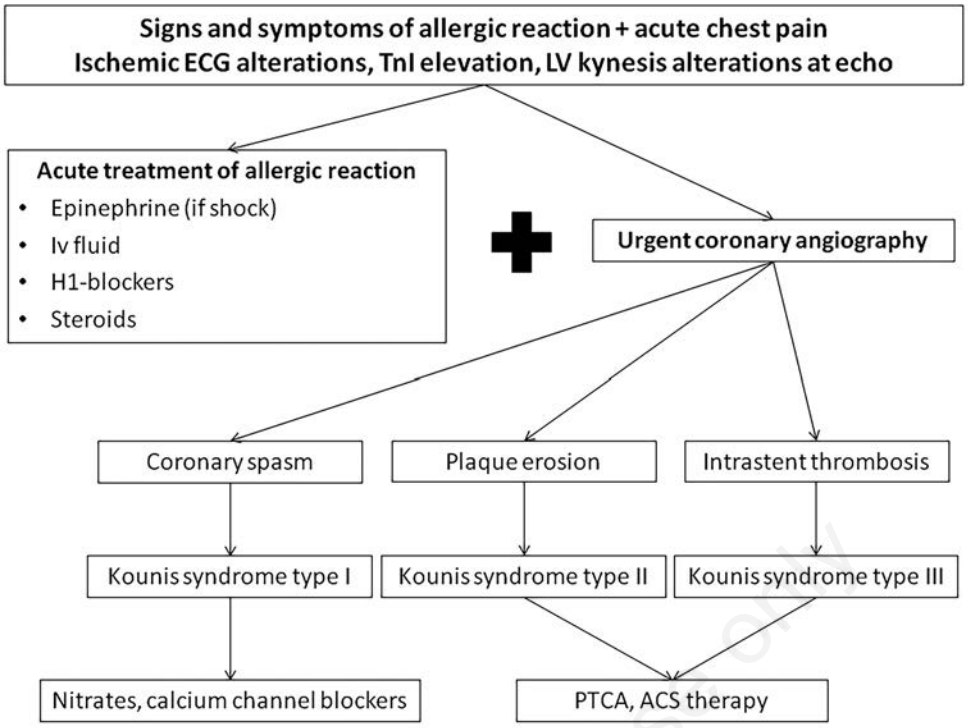

Figure 3. Proposed urgent treatment options of Kounis syndrome.

References

1. Kounis NG, Mazarakis A, Tsigkas G, et al. Kounis syndrome: a new twist on an old disease. Future Cardiol 2011;7:805-24.
2. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: A study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. Clin Exp Allergy 2004;34:285-90.
3. Lippi G, Buonocore R, Schirosa F, Cervellin G. Cardiac troponin I is increased in patients admitted to the emergency department with severe allergic reactions. A case-control study. Int J Cardiol 2015;194:68-9.
4. Cha YS, Kim H, Bang MH, et al. Evaluation of myocardial injury through serum troponin I and echocardiography in anaphylaxis. Am J Emerg Med 2016;34:140-4.
5. Barbarroja-Escudero J, Rodriguez-Rodriguez M, Sanchez-Gonzalez MJ, et al. Anisakis simplex: a new etiological agent of Kounis syndrome. Int J Cardiol 2013;1676:e187-9.
6. Coppola G, Caccamo G, Bacarella D, et al. Vasospastic angina and scombroid syndrome: a case report. Acta Clin Belg 2012;67:222-5.
7. Josefsson J, Fröbert O. Losartan-induced coronary artery spasm. BMJ Case Rep 2012;2012. pii: bcr2012006252.
8. Shah G, Scadding G, Nguyen-Lu N, et al. Peri-operative cardiac arrest with ST elevation secondary to gelofusin anaphylaxis - Kounis syndrome in the anaesthetic room. Int J Cardiol 2013;164:e22-6.
9. Van Ginkel AG, Sorgdrager BJ, de Graaf MA, et al. ST-segment elevation associated with allergic reaction to echocardiographic contrast agent administration. Neth Heart J 2013;15:725-6.
10. Guler Y, Kalkan S, Esen AM. An extremely rare trigger of Kounis syndrome: Actinidia chinensis. Int J Cardiol 2014;172:24-5.
11. Karadeniz M, Akyel A, Celik IE, et al. An unusual etiology of Kounis syndrome; warble fly. Indian Heart J 2013;65:358-359.
12. Arslan Z, Iyisoy A, Tavlasoglu M. Acute myocardial infarction after prednisolone administration for the treatment of anaphylaxis caused by a wasp sting. Cardiovasc J Africa 2013;24:e4-e6.
13. Rayner-Hartley E, Chou A, Saw J, Sedlak T. A case of Kounis type I in a young woman with Samter's triad. Can J Cardiol 2016;32:1261.e1-1261.e3.
14. Erxun K, Wei L, Shuying Q. Kounis syndrome caused by chronic autoimmune urticaria: A case report. J Emerg Med 2016;50:37-40.
15. Juste JF, Garces TR, Enguita RG, et al. Cardiac complications in a metamizole-induced type I Kounis syndrome. Braz J Anesthesiol 2016;66:194-6.
16. Kounis NG, Kounis GN, Soufras GD, et al. Postmortem diagnosis of drug-induced anaphylactic death: Kounis syndrome and hypersensitivity myocarditis are the likely culprit in death of severe anaphylactic reactions. J Forensic Leg Med 2016;40:40-1.
17. Venkateswararao S, Rajendiran G, Sundaram RS, Mounika G. Kounis syndrome secondary to intravenous cephalosporin administration. J Pharmacol Pharmacother 2015;6:225-7.
18. Ihdayhid AR, Rankin J. Kounis syndrome with Samter-Beer triad treated with intracoronary adrenaline. Catheter Cardiovasc Interv 2015;86:E263-7.
19. Arora S, Patel R, Fadila M, Wool K. The atopic heart: a curious case of coronary hypersensitivity. Neth J Med 2016;74:130-2.
20. Oh KY, In YN, Kwack CH, et al. Successful treatment of Kounis syndrome type I presenting as cardiac arrest with ST elevation. Chin Med J (Engl) 2016;129:626-7.
21. Pelli JR Jr, Wieters JS, Firozgary B, Montalvo T. Multiple bee stings resulting in ST elevation myocardial infarction (the Kounis syndrome). Proc (Bayl Univ Med Cent) 2016;29:298-300.

22. Memon S, Chhabra L, Masrur S, Parker MW. Allergic acute coronary syndrome (Kounis syndrome). Proc (Bayl Univ Med Cent) 2015;28:358-62.
23. Ralapanawa DM, Kularatne SA. Kounis syndrome secondary to amoxicillin/clavulanic acid administration: a case report and review of literature. BMC Res Notes 2015;8:97.
24. İnci S, Aksan G, Doğan A. Bonsai-induced Kounis Syndrome in a young male patient. Anatol J Cardiol 2015;15:952-954.
25. Portero-Portaz JJ, Córdoba-Soriano JG, Gallego-Page JC. Type III Kounis syndrome after administration of an echocardiography contrast agent. Eur Heart J Acute Cardiovasc Care 2016. pii: 2048872616655943. [Epub ahead of print].
26. Yaman M, Mete T, Ozer I, Yaman E, Beton O. Reversible myocarditis and pericarditis after black widow spider bite or Kounis syndrome? Case Rep Cardiol 2015;2015:768089.
27. Benedetto D, Agostoni P, de Waal E, Stella PR. Kounis syndrome with cardiogenic shock during transfemoral transcatheter aortic valve replacement. Coron Artery Dis 2015;26:726-7.
28. Tepetam FM, Dağdeviren B, Bulut İ, et al. A patient with mushroom allergy; a new etiological agent of Kounis syndrome. Tuberk Toraks 2016;64:171-4.
29. Goto K, Kasama S, Sato M, Kurabayashi M. Myocardial scintigraphic evidence of Kounis syndrome: what is the aetiology of acute coronary syndrome? Eur Heart J 2016;37:1157.
30. Kido K, Adams VR, Morehead RS, Flannery AH. Capecitabine-induced ventricular fibrillation arrest: Possible Kounis syndrome. J Oncol Pharm Pract 2016;22:335-40.
31. Ateş AH, Kul S. Acute coronary syndrome due to midazolam use: Kounis syndrome during a transurethral prostatectomy. Turk Kardiyol Dern Ars 2015;43:558-61.
32. Anandan PK, Hanumanthappa NB, Bhatt P, Cholenahally MN. Allergic angina following wasp sting: Kounis syndrome. Oxf Med Case Reports 2015;2015:306-8.
33. Ntuli PM, Makambwa E. Kounis syndrome. S Afr Med J 2015;105:878.
34. Katsanou K, Karagiannidis I, Oikonomou G, Kounis NG. Kounis syndrome: Report of 3 cases. Int J Cardiol 2015;197:222-3.
35. Venturini E, Marabotti C, Magni L, et al. Myocardial bridge as a trigger of Kounis syndrome. Int J Cardiol 2016;202:87-9.
36. Cervellin G, Neri G, Lippi G, et al. Kounis syndrome triggered by a spider bite. A case report. Int J Cardiol 2016;207:23-4.
37. Barbarroja-Escudero J, Sánchez-González MJ, Antolín-Amérigo D, et al. Kounis syndrome induced by cefditoren pivoxil. Int J Cardiol 2016;207:112-4.
38. Lorca R, Velasco E, Madera J, et al. Kounis syndrome: Identifying the trigger. Int J Cardiol 2016;209:179-80.
39. Cheung M, Seres T, Cleveland J, Kounis NG. Kounis syndrome, a coronary hypersensitivity disorder: A rare case of amiodarone-induced coronary vasospasm and simultaneous peripheral vasodilation intraoperatively. Int J Cardiol 2016;218:267-8.
40. Kim HI, Cha KC, Cha YS, et al. A subset of type I variant Kounis syndrome: Allergic angina syndrome and persistent presence of coronary spasm. Int J Cardiol 2016;223:959-61.
41. Regis AC, Germann CA, Crowell JG. Myocardial infarction in the setting of anaphylaxis to celecoxib: A case of Kounis syndrome. J Emerg Med 2015;49:e39-43.
42. Mirijello A, Pepe G, Zampiello P, et al. A male patient with syncope, anaphylaxis, and ST-elevation: Hepatic and cardiac echinococcosis presenting with Kounis syndrome. J Emerg Med 2016;51:e73-7.
43. Gormel S, Ege T, Koklu M, Celik M, Yuksel UC. Acute lateral myocardial infarction secondary to tramadol-induced Kounis syndrome. J Cardiothorac Vasc Anesth 2015;29:1599-602.
44. Liping Z, Bin H, Qiming F. An extraordinary case associated with an allergic reaction to clopidogrel: Coronary artery spasm or Kounis syndrome. Heart Lung Circ 2015;24:e180-3.