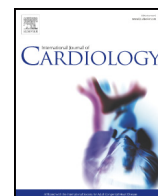




Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Kounis syndrome: A review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome☆☆☆

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ARTICLE INFO

Article history:

Received 12 July 2016

Received in revised form 30 December 2016

Accepted 26 January 2017

Available online xxxx

Keywords:

Kounis syndrome

Myocardial infarction

Stent thrombosis

Coronary vasospasm

Allergic acute coronary syndrome

ABSTRACT

Kounis syndrome (KS) is a hypersensitivity coronary disorder induced by exposure to drugs, food, environmental and other triggers. Vasospastic allergic angina, allergic myocardial infarction (MI) and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells constitute the three main variants of this syndrome. We reviewed 175 patients who fulfilled the definition of one of the three types of KS. The epidemiology, diagnostic findings, management and complications were reviewed in this article.

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1. Introduction

Cardiovascular allergic and anaphylactic reactions to various allergens have been well established for many years. In 1938, Eugene Clark reported reactive arteritis and carditis in a young patient after receiving large doses of *anti*-pneumococcus serum [1]. In 1950, Pfister and Plice reported the first acute MI associated with urticaria secondary to penicillin therapy [2]. However, it was not until 1991 when Kounis and Zavras described the “allergic angina syndrome” as coronary spasm progressed to allergic acute MI [3].

We searched MEDLINE through March 31, 2016 for reports of KS. A total of 175 patients fulfilled the definition of one of the three variants of KS. The age, sex, medical history, trigger to symptoms time, clinical presentation, ECG changes, laboratory abnormalities and echocardiography and angiographic findings were reported in each of these cases and summarized in Table 1.

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

☆☆ All authors had access to the data and a role in writing the manuscript; article type; key words; and running head.

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2. Review of literature and discussion

KS is defined as the concurrence of acute coronary syndromes associated with mast-cell and platelet activation in the setting of allergic or anaphylactic insults [4]. Although KS can happen at any age, the most common affected age group is 40–70 years old (68%). Risk factors of KS include history of previous allergy, hypertension, smoking, diabetes and hyperlipidemia. Various causes have been found to trigger KS and more triggers are being identified (Table 2). The most common triggers of KS were antibiotics (27.4%) followed by insects' bites (23.4%).

The pathophysiology of KS involves coronary artery spasm and/or atheromatous plaque erosion or rupture during an allergic reaction. The main inflammatory cells that are involved in the development of KS are mast cells that interact with macrophages and T-lymphocytes. In the cardiac tissues, mast cells are abundant [5] and preferentially locate at sites of coronary plaques [6]. Activated mast cells have the potential to infiltrate the areas of plaque erosion or rupture and act on the smooth muscle of the coronary arteries [7].

Mast cell degranulation and release of the inflammatory mediators is triggered by antigen antibody reaction on the surface of the mast and basophil cells, or activation of the complement system (C3a, C5a) [8–10]. This explains our finding that 80% of the cases occur within the first hour of exposure to the trigger. The inflammatory mediators include histamine, neutral proteases chymase, tryptase, heparin and cathepsin-D, with increased production of leukotrienes [11]. Histamine induces coronary vasoconstriction, decreases the diastolic blood pressure, increases intimal thickening, and activates platelets [10,12,13].

Table 1

The epidemiology, clinical presentations, diagnostic findings and complications of Kounis syndrome.

Sex	
Male	130 (74.3%)
Female	45 (25.7%)
Age	
0–10	3 (1.7%)
11–20	13 (7.4%)
21–30	8 (4.6%)
31–40	14 (8%)
41–50	26 (14.9%)
51–60	52 (29.7%)
61–70	41 (23.4%)
71–80	15 (8.6%)
81–90	3 (1.7%)
Past medical history	
Allergy	44 (25.1%)
Hypertension	32 (18.3%)
Smoking	23 (13.1%)
Diabetes	21 (12%)
Hyperlipidemia	20 (11.4%)
Triggers	
Antibiotics	48 (27.4%)
Penicillins	27
Cephalosporins	13
Insect bites	41 (23.4%)
Bee	18
Wasp	14
Others	86 (49.2%)
Trigger to onset time in hours	
0–1	105/131 (80%)
1–2	2/131 (1.5%)
2–3	6/131 (4.6%)
3–4	2/131 (1.5%)
4–5	2/131 (1.5%)
5–6	2/131 (1.5%)
>6	12/131 (9.2%)
Clinical presentation	
Chest pain	152 (86.8%)
Anaphylaxis	93 (53%)
Rash	47 (26.8%)
Wheezing	25 (14%)
Pulmonary edema	9 (5.1%)
Type of Kounis syndrome	
Type 1	127 (72.6%)
Type 2	39 (22.3%)
Type 3	9 (5.1%)
Troponin	
Elevated	106 (60.6%)
Normal	44 (25.1%)
Not documented	25 (14.3%)
ECG manifestation	
ST elevation	133 (76%)
Inferior leads	89 (66.9%)
Anterior leads	22 (16.5%)
Antero-lateral leads	10 (7.5%)
Lateral leads	7 (5.3%)
Diffuse elevations	3 (2.3%)
Unknown	2 (1.5%)
ST depression	30 (17.1%)
Inferior leads	10 (33.3%)
Anterior leads	10 (33.3%)
Lateral leads	6 (20%)
Antero-lateral leads	4 (13.3%)
Normal	3 (1.7%)
Unknown	9 (5.1%)
Echocardiography	
Abnormal	45/78 (57.7%)
Normal	33/78 (42.3%)
Complications	
Cardiogenic shock	4 (2.3%)
Cardiac arrest	11 (6.3%)
Death	5 (2.9%)
Ventricular fibrillation	2 (1.1%)
Anterior STEMI	2 (1.1%)
Inferior STEMI	1 (0.6%)

STEMI = ST Elevation Myocardial Infarction.

Table 2

Etiology of Kounis syndrome.

<i>Drugs</i>
Antibiotics: Penicillins, Cephalosporins, Metronidazole, Clindamycin, Clarithromycin, Telithromycin, Ciprofloxacin.
Antiviral: Brivudine, Oseltamavir.
Antifungal: Fluconazole
Nonsteroidal anti-inflammatory drugs: Ibuprofen, Diclofenac, Metimazole.
Proton pump inhibitors: Lansoprazole.
Angiotensin Converting Enzyme inhibitors: Enalapril.
Antihistamines: Estimazole.
Anesthetics: Propofol, Etomidate, Midazolam.
Anti-cancer drugs: Cisplatin, Oxplatin, Cyclophosphamide, 5-Fluorouracil, Rituximab
Neuromuscular blockers: Rocuronium, Atracurium
Others: Aspirin, Tramadol, Clopidogrel, Oral contraceptive pills, Propylphenazone, Pseudoephed, Hydrocortisone, Sodium Bicarbonate, Gelofusin
<i>Insects bites</i>
Bee, Wasp, Scorpion, Hymenoptera, Snake, Black widow spider
<i>Foods</i>
Shell Fish, Tuna Fish, Salt fish, Uncooked anchovies, Kiwi
<i>Others</i>
Intravenous contrast material
Latex
Dialysate

All three neutral proteases can induce plaque erosion and rupture [14]. The anticoagulant effect of heparin- and trypsin-induced degradation of fibrinogen can cause destabilization and maturation of thrombi [15]. Chymase, cathepsin-D and leukotrienes are powerful vasoconstrictors [16,17]. There is a threshold level of mast cell activation and mediator release above which the coronary artery spasm and plaque erosion or rupture occurs. This threshold level is closely linked to the body site where the antigen-antibody reaction occurs, the area of exposure, mediator release, and the severity of the allergic reaction [18].

In type I variant (most common variant, 72.6%), the release of inflammatory mediators induces coronary artery spasm with or without increase of cardiac enzymes and troponins. In type II variant (22.3%), the release of inflammatory mediators induces coronary artery spasm together with plaque erosion or rupture manifesting as acute MI. Type III variant (5.1%) includes patients with coronary artery stent thrombosis as a result of an allergic reaction [4].

The diagnosis of KS is based on clinical symptoms and signs as well as on laboratory, electrocardiographic, echocardiographic and angiographic evidence. Careful review of clinical history, including medications and allergies, is always imperative. Our review showed that 25% of the patients have a known history of allergy, mostly to the trigger. Cardiac symptoms include chest pain (most common presentation, 86.6%), palpitations and shortness of breath. Allergic manifestations such as skin rash, hives, and wheezes often happen. Acute pulmonary edema, in the context of acute coronary syndrome, or severe anaphylactic reaction can cause severe hypotension and shock. Laboratory work-up is summarized in Table 3. Histamine has a short half life, approximately 8 min; as such, negative levels do not exclude the diagnosis of KS [19]. The use of IgE levels in the diagnosis of KS remains unclear and the absence of IgE antibodies does not exclude the diagnosis [19]. Cardiac troponin I or T, as well as cardiac enzymes (CK, CK-MB)

Table 3

Diagnostic laboratory work-up in suspected Kounis Syndrome.

Complete blood count (CBC): attention to eosinophils
Cardiac enzymes (CK, CK-MB) and troponin I or T
C-reactive protein (CRP, high sensitivity)
Total and specific immunoglobulin E (IgE)
Histamine, chymase, trypsin serum levels
Arachidonic acid products: thromboxane, leukotrienes, prostaglandins
Tumor necrosis factor (TNF), interferon (INF), interleukin-6 (IL6)

are important to diagnose the myocardium injury associated with the allergic insult. ECG usually shows ST-T changes suggestive of ischemia, with ST elevation MI being the most common presentation. Echocardiogram can also show regional wall motion abnormalities in the distribution of the affected artery [20]. Single-photon emission computer tomography was recently used in the diagnosis of type I variant KS showing severe myocardial ischemia while coronary angiography showed normal coronary arteries [21]. Okur et al. studied 26 patients with known or suspected type I variant KS with cardiac MRI. Delayed contrast-enhanced images showed normal washout in the subendocardial lesion area [22]. Cardiac catheterization may show coronary vasospasm, or stenosis. Our review showed that the right coronary artery was the culprit artery in >50% of the cases.

The major differential diagnosis of KS is Takotsubo, or stress-induced cardiomyopathy, however; these two clinical entities can co-exist. Yanagawa et al. [23] reported a case of a 65-year-old female who developed asthma induced angina, transient left ventricular dysfunction, and life-threatening arrhythmia. The asthma, angina, and arrhythmia resolved after epinephrine and steroid therapy. The left ventricular wall motion progressively improved, as it would be expected in Takotsubo cardiomyopathy. Hypersensitivity myocarditis and coronary allograft vasculopathy are other causes of cardiovascular inflammatory diseases.

Therapeutic management of KS is challenging as it aims for myocardial revascularization as well as treatment of the concomitant allergic reaction. Guidelines for the treatment of ACS are lacking management of KS, and most of the evidence on the efficacy of the treatment is based on individual case reports or case series. In this context, patients presenting with ACS should be treated accordingly based on the ACS guidelines [24].

Patients with the type I variant may benefit from the treatment of the allergic reaction, which, by itself, can resolve the cardiac manifestation. Corticosteroids, such as hydrocortisone at a dose of 1–2 mg/kg/day, cause suppression of arterial hyper-reactivity and alleviation of inflammation and prevent biphasic anaphylactic reactions [24,25].

Both H1 and H2 antihistamines, such as diphenhydramine (1–2 mg/kg), ranitidine (1 mg/kg) can be used as supportive therapy to decrease the allergic manifestations [26]. Patients presenting with distributive shock secondary to severe anaphylactic reaction, require appropriate fluid resuscitation. Epinephrine should be used with caution in KS as it can worsen myocardial ischemia, prolong the QTc interval and induce coronary vasospasm and arrhythmias [24]. The administration of vasodilators such as calcium channel blockers and nitrates can resolve hypersensitivity induced vasospasm [27].

In patients with type II variant, treatment depends on the initial presentation, with conventional therapy for ACS, together with steroids and antihistaminic [4]. The use of beta blockers can exaggerate coronary spasm due to unopposed action of α -adrenergic receptors [28].

In type III variant, treatment should also follow the most recent ACS guidelines. According to the ST elevation myocardial infarction focused update published recently, selective aspiration thrombectomy was downgraded to class IIb, and routine thrombectomy was downgraded to class III (harmful) [29]. In type III variant KS, aspiration of intrastent thrombus is of unique importance as histological examination of aspirated material and staining for eosinophils (Hematoxylin and Eosin) and mast cells (Giemsa) can suggest allergic reaction, with possible subsequent change of the management [4]. In patients who develop allergic symptoms following stent implantation, corticosteroids, antihistaminic and mast cell stabilizers can alleviate the allergic manifestations. If these measures fail, identification of the culprit cause by patch and/or prick skin tests followed desensitization measures should be applied [4,10]. If allergy to nitinol (nickel-titanium alloy) is confirmed by a patch test, with failure of desensitization, removal of the stent might be necessary [30].

Generally, the prognosis of KS is good and complete recovery is expected, in most of the patients, with appropriate treatment. This is mainly driven by the prevalence of type I being the most common

type of KS. In type I KS, vasospasm can be reversed easily by vasodilators. Development of other allergic manifestations, such as wheezes and skin rash, help early identification of the allergic reaction and provoke the appropriate use of corticosteroids and antihistaminic. The good prognosis of type I KS correlates with previous reports of good prognosis of coronary vasospasm in general [31]. Our review showed that serious complications are rare, i.e.: cardiogenic shock occurs in 2.3%, cardiac arrest occurs in 6.3%, and the death rate is 2.9%. Most of these complications happened in males, but the prevalence of KS in males can explain this finding. The mortality rate is similar in both genders [3.0% (4/145) in males and 2.2% (1/45) in females]. An allergic reaction to a medication was the trigger in all of the cases complicated with serious consequences, except for one mortality that was triggered by wasp stings [32].

3. Conclusion

KS is likely an under-diagnosed disease. Knowledge of this syndrome will enable better recognition and appropriate management of these patients. Further studies are required to better understand this disease. Addressing KS as a separate entity in the ACS guidelines is imperative, as the conventional management of patients with ACS might not necessary apply to all patients with KS. In general, the prognosis of KS is better than the “conventional” acute coronary syndrome. This can be explained by several reasons including the known history of allergy to the trigger, the presence of other allergic manifestations and the early administration of the medical therapy which is effective in most of the cases.

Conflicts of interest

The authors report no financial relationships or conflicts of interest regarding the content herein.

Acknowledge

The authors acknowledge Mai Eladly for her help in the preparation of this paper.

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