International Journal of Cardiology 232 (2017) 1–4

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 27 January 2017

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.

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.

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].

☆ 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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http://dx.doi.org/10.1016/j.ijcard.2017.01.124
0167-5273/

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.

Drugs
Antibiotics: Penicillins, Cephalosporins, Metronidazole, Clindamycin, Clarithromycin, Telithromycin, Ciprofloxacin.
Antiviral: Brivudine, Oseltamavir.
Antifungal: Fluconazole
Nonsteroidal anti-inflammatory drugs: Ibuprofen, Diclofenac, Metimazole.
Proton pump inhibitors: Lanzoprazole.
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, Propyphenazone, Pseudophed, Hydrocortisone, Sodium Bicarbonate, Gelofusin
Insects bites
Bee, Wasp, Scorpion, Hymenoptera, Snake, Black widow spider
Foods
Shell Fish, Tuna Fish, Salt fish, Uncooked anchovies, Kiwi
Others
Intravenous contrast material
Latex
Dialysate

All three neutral proteases can induce plaque erosion and rupture [14]. The anticoagulant effect of heparin- and tryptase-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, tryptase serum levels
Arachidonic acid products: thromboxane, leukotrienes, prostaglandins
Tumor necrosis factor (TNF), interferon (INF), interleukin-6 (IL6)