European Journal of Internal Medicine 30 (2016) 7–10

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Review Article

Kounis syndrome: A concise review with focus on management☆

Filippo Fassio [a,*], Laura Losappio [b], Dario Antolin-Amerigo [c], Silvia Peveri [d], Gianni Pala [e], Donatella Preziosi [f], Ilaria Massaro [g], Gabriele Giuliani [h], Chiara Gasperini [i], Marco Caminati [j], Enrico Heffler [k]

[a] UO Medicina, Ospedale San Jacopo, ASL3 Pistoia, Via Ciliegiole, 97, 51100 Pistoia, Italy
[b] University of Foggia, Viale Pinto, 1, 71121 Foggia, Italy
[c] Servicio de Enfermedades del Sistema Inmune–Alergia, Hospital Principe de Asturias, Departamento de Medicina y Especialidades Médicas, Universidad de Alcalá, Carretera Alcalá, Meco, s/n, 28805 Alcalá de Henares, Madrid, Spain
[d] U.O.s.D. Allergologia, Ospedale Guglielmo Da Saliceto, Via Campagna, 68, Piacenza, Italy
[e] Servizio del Medico Competente, Azienda Sanitaria Locale di Sassari, via Catalocchino 11, 07100 Sassari, Italy
[f] IRCCS Policlinico San Donato, Piazza Edmondo Malan, 1, 20097 San Donato Milanese (MI), Italy
[g] Centro di Ricerca, Trasferimento ed Alta Formazione Denothe, Università di Firenze, Viale Pieraccini, 6, Firenze, Italy
[h] UO Cardiologia, Ospedale San Giovanni di Dio, via di Torregalli 3, 50143 Firenze, Italy
[i] UO Anestesia e Rianimazione, Ospedale San Jacopo, ASL3 Pistoia, Via Ciliegiole, 97, 51100 Pistoia, Italy
[j] UO Allergologia, Azienda Ospedaliero Universitaria Integrata, Piazzale Aristide Stefani, 1, Verona, Italy
[k] Dipartimento di Medicina Clinica e Sperimentale, Pneumologia Riabilitativa e Allergologia, Università degli Studi di Catania, Via Santa Sofia 78, 95126 Catania, Italy

ARTICLE INFO

Article history:
Received 11 January 2015
Received in revised form 7 December 2015
Accepted 13 December 2015
Available online 12 January 2016

Keywords:
Kounis syndrome
Allergic angina
Emergency
Hypersensitivity reaction
Treatment

ABSTRACT

Kounis syndrome is defined as the co-incidental occurrence of an acute coronary syndrome with hypersensitivity reactions following an allergenic event and was first described by Kounis and Zavras in 1991 as an allergic angina syndrome.
Multiple causes have been described and most of the data in the literature are derived from the description of clinical cases – mostly in adult patients – and the pathophysiology remains only partly explained.
Three different variants of Kounis syndrome have been defined: type I (without coronary disease) is defined as chest pain during an acute allergic reaction in patients without risk factors or coronary lesions in which the allergic event induces coronary spasm that electrocardiographic changes secondary to ischemia; type II (with coronary disease) includes patients with pre-existing atheromatous disease, either previously quiescent or symptomatic, in whom acute hypersensitive reactions cause plaque erosion or rupture, culminating in acute myocardial infarction; more recently a type-III variant of Kounis syndrome has been defined in patients with preexisting coronary disease and drug eluting coronary stent thrombosis.
The pathogenesis of the syndrome is discussed, and a therapeutic algorithm is proposed.

1. Introduction

Kounis syndrome (KS) is defined as the co-incidental occurrence of an acute coronary syndrome (ACS) with hypersensitivity reactions following an allergenic event. It was first described by Kounis and Zavras in 1991 as an allergic angina syndrome [1].

Multiple causes for KS have been described so far, including drugs, insect stings, foods, environmental exposures, medical conditions and following the performance of skin prick test to amoxicillin [2–4].

Most of the data in the literature are derived from the description of isolated clinical cases (almost 300) corresponding principally to adults, so the exact pathophysiological mechanisms remain elusive.

An interesting case series of children presenting with KS has also been published [5]. Two of them developed an allergic reaction to amoxicillin/clavulanic acid, and the other two after a hymenoptera sting. All four children developed chest pain associated with ST segment elevation and positive cardiac enzymes, while serum tryptase level was elevated only in one of them.

Hitherto, three different variants of KS have been defined [6–8]:

- Type I (without coronary disease): chest pain during an acute allergic reaction in patients without risk factors or coronary lesions in which the allergic event induces coronary spasm that electrocardiographic

Abbreviations: KS, Kounis syndrome; ACS, Acute coronary syndrome.

☆ This study was conducted without any external financial support.

* Corresponding author. Tel./fax.: +39 0573 994000.
E-mail addresses: fassio.filippo@gmail.com (F. Fassio), losappiolaura@yahoo.it (L. Losappio), dario.antolin@gmail.com (D. Antolin-Amerigo), silvia_peveri@yahoo.it (S. Peveri), giannipalass@libero.it (G. Pala), dpreziosi@libero.it (D. Preziosi), massaroilaria81@gmail.com (I. Massaro), giuliani.gabriele@gmail.com (G. Giuliani), chiara.gasperini@gmail.com (C. Gasperini), m.caminati@gmail.com (M. Caminati), heffler.enrico@gmail.com (E. Heffler).

http://dx.doi.org/10.1016/j.ejim.2015.12.004
0953-6205/

changes secondary to ischemia. The cardiac enzymes and troponins may be either normal or reflect progression toward acute myocardial infarction. The explanation for this type would be endothelial dysfunction and/or microvascular angina have been posit as probable pathophysiological mechanisms.

- Type II (with coronary disease): includes patients with pre-existing atheromatous disease, either previously quiescent or symptomatic, in which acute hypersensitive reactions cause plaque erosion or rupture, culminating in acute myocardial infarction.

- More recently a type-III variant of KS has been defined in patients with pre-existing coronary disease and drug eluting coronary stent thrombosis [9]. In these patients, Giemsa and hematoxylin–eosin staining reveals the presence of mast cells and eosinophils, respectively [10]. Virmani [11] first described in 2004 a case of hypersensitivity vasculitis in a patient with very late drug-eluting stent thrombosis. More recently, the hallmarks of hypersensitivity reactions have been demonstrated in autopsy specimens of patients with very late drug-eluting stent thrombosis, while using intravascular ultrasound in the same patients a high incidence of incomplete stent apposition and vessel remodeling has been demonstrated [12]. Very late stent thrombosis could be another manifestation to be recognized as part of the Kounis syndrome.

This review article is based on scientific publications on Kounis syndrome and the selection of articles has been made searching on PubMed these terms: Kounis syndrome; allergic angina; and acute allergic coronary syndrome. The search was not limited for a time period. As the great majority of literature data come from single case-reports or small case-series, all the published data have been taken into consideration and summarized into this review article.

2. Pathogenesis

Mast cells play a central role in hypersensitivity reactions, and they are necessary for the development of allergic reactions [13]. Mast cells are activated either by IgE-bound antigen cross-linking, anaphylotoxins (C3a and C5a) or a variety of stimuli [14]. Their activation leads to degranulation of preformed inflammatory mediators (e.g. histamine, tryptase, chymase, heparin), increased production of arachidonic acid-derived mediators (e.g. prostaglandin D2, leukotrienes B4 and C4, platelet activating factor (PAF)), and increased gene expression to produce cytokines (e.g. TNF-alfa, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 and GM-CSF) and various chemokines [14]. These mediators are responsible for plasma extravasation and tissue edema, inflammation and leukocyte recruitment, bronchoconstriction and mucus secretion [15].

In heart tissues mast cells are abundant [16,17]: they preferentially locate at sites of coronary plaques [18,19] and might contribute to coronary artery thrombosis [5,20].

Upon mast cell degranulation, histamine is released thus promoting plaque disruption by increasing the arterial hemodynamic stress on the plaque, inducing vasospasm, or both [20,21].

Mast cells are also found extensively in and around thrombi, and could contribute to the destabilization and maturation of thrombi by the anticoagulant effect of heparin- and tryptase-induced degradation of fibrinogen [22].

Coronary microvascular spasm of epicardial coronary arteries has been demonstrated in subjects with vasospastic angina [23], and allergic mediators could have a role in this mechanism as well [24,25].

It is noteworthy that tryptase levels in peripheral blood increase during spontaneous myocardial ischemia but not during a pharmacologically-induced coronary spasm [26], suggesting that mast cell activation in acute coronary syndrome is a primary event and not a result of coronary spasm itself [20].

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 [27]. Moreover, the cardiac mast cell load in the coronary plaques from cardiac patients is up to 200-fold higher than in the coronaries from healthy people [28].

In summary, Kounis syndrome is caused by the effect of pro-inflammatory mediators massively released by mast cells in heart tissue and in coronary arteries and plaques. Because a number of stimuli can trigger mast cell degranulation, primarily IgE-mediated allergic reactions, it is conceivable that any allergic reaction might potentially facilitate coronary spasm or plaque disruption [20].

3. Treatment

Kounis syndrome is a complex acute coronary manifestation which requires rapid treatment decisions aimed not only at myocardium revascularization, but aimed also at treating the concomitant allergic reaction.

Until now, guidelines for the treatment of Kounis syndrome are lacking and most of the evidence on the efficacy of the treatment is based on individual case reports or case series. A recent review by Kounis grants suitable recommendations for each variant [29]. In this context, it has to be assumed that cardiologic management of KS patients should follow the best practices outlined by evidence-based guidelines for the treatment of ACS [30], while management of the severe allergic reaction should follow the anaphylaxis guidelines [31].

Depending on the prevalent initial clinical picture (ACS with chest pain and EKG signs, or allergic reaction with suggestive history of exposure to a known allergen, skin rash, bronchostenosis or other extracardiac involvement) first emergency management of the patient with KS could vary, but both sides – cardiologic and allergic – of the syndrome must be promptly addressed. In the case of a patient with suspected KS referring to a non-cardiologic unit, a cardiologist evaluation must be warranted and, depending on clinical conditions, referral to intensive coronary care or intensive care unit should be taken into account. A putative therapeutic algorithm is proposed in Fig. 1.

3.1. Management of the allergic reaction

Patients with the type I variant may benefit from the treatment of the allergic reaction, which may circumvent further complications.

H1 and H2 blockers, as diphenhydramine and ranitidine, can be used to ameliorate itching, urticaria and angioedema but there are no drugs of choice in initial severe allergic reactions because they do not relieve life threatening respiratory symptoms or shock [31].

Both H1 and H2 antihistamines, such as diphenhydramine (1–2 mg/kg), ranitidine (1 mg/kg) can be used as supportive therapy [29]. Bolus administration of antihistamines can precipitate hypotension and compromise coronary flow; therefore, these drugs should be given slowly [32].

Glucocorticoids, in spite of the non-immediate benefit that they confer, may be used mainly to prevent biphasic anaphylactic reactions. Corticosteroids may also impair wound healing and scar formation which could cause myocardial wall thinning, cardiac aneurysms and cardiac wall rupture [33], but a meta-analysis about corticosteroid treatment in acute myocardial infarction reported no harm and possible mortality benefit with these drugs in acute myocardial infarction [34].

The use of fluids is crucial in a distributive shock as it happens during an anaphylactic reaction. In the case of KS, this intervention should be done cautiously because of the risk of adverse effects such as pulmonary edema. Therefore we suggest that fluids (crystalloid normal saline, rather than a colloid) should be given taking into account the specific clinical conditions such as ejection fraction, hemodynamical instability and the risk of delayed myocardial healing [29].