



Kounis Syndrome due to Drugs: Increasing Awareness of a Still under Diagnosed Condition

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Editorial

It has been more than 25 years since Kounis and Zavras first reported “the concept of allergic angina” to describe the concomitant appearance of an allergic reaction and an acute coronary syndrome [1], later defined as “Kounis syndrome” (KS). However, the association between cardiovascular symptoms and signs with allergic and anaphylactic reactions has been reported several years before as arteritis and carditis after anti-pneumococcus serum [2] and acute myocardial infarction associated with urticaria secondary to penicillin therapy [3].

Up to now three variants of the syndrome have been described: coronary vasospasm in normal coronary arteries (type I), acute coronary thrombosis in patients with preexisting coronary lesions (type II) and thrombosis of drug-eluting stents with thrombi infiltrated by mast cells and eosinophils (type III) [4,5].

Several are the factors or substances reported to trigger KS, mainly drugs, and their number is continuously increasing. Recently, new and atypical etiological factors have been reported, such as food [fruit, vegetable, fish, shellfish], scombroid syndrome, helminth infection (*Anisakis simplex*, *Echinococcus granulosus*), insect sting or bite (Hymenoptera, jellyfish, scorpion, fly) [6-8].

Among drugs, antibiotics and NSAIDs are the most involved classes [9-11]. Renda and coworkers extrapolated 51 cases of KS from the international pharmacovigilance database VigiBase™, the global World Health Organization database for Individual Case Safety Reports [9]. In this report the most frequent trigger drugs were NSAIDs (31 cases, 60.7%), followed by drugs for cardiovascular disease (10 cases, 19.6%), antibiotics (9 cases, 17.6%) and anesthetics (5 cases, 9.8%). The involved antibiotic classes were penicillins, beta-lactamase inhibitors, quinolones, nitroimidazoles. However, more than one drug was suspected for some patients [9]. From the same pharmacovigilance database together with another database, EudraVigilance, the authors retrieved 16 cases of antibiotic-induced KS and 6 of them were related to amoxicillin/clavulanic acid [10]. It is interesting to note that in the first work of Renda, even if the period of search was 2000-2014, the first report of KS was in 2010 and approximately one half of cases were reported in 2014 [9]. Likewise, in the other work of Renda about KS due to antibiotics, although the period of analysis was 2001-2016, the first case was reported in 2011 and the reports increased in the following years [10]. Abdelghany and coworker, instead, reported the data from a MEDLINE search on KS. Until March 2016 they found 175 cases of KS mainly caused by drugs, insect bites and foods [11]. In this Review the most reported drug class was antibiotics (48 cases), represented by penicillin's and cephalosporin's. NSAIDs are present among the other classes of involved drugs; however, the numbers of cases are not reported [10]. In other previous case series with a limited number of patients with KS, drugs were the most frequently suspected agents (11 out of 14 patients) and the most common drugs were antibiotics (penicillin's and cephalosporin's) in 7 cases, NSAIDs in 3 cases and omeprazole in 1 case [12-14].

Other categories of drugs have been reported as causative agent of KS, such as, angiotensin II receptor- α antagonist losartan, ultrasound contrast agents, gelofusin and gelatins and corticosteroids [15,16]. All those cases, but two on ultrasound contrast agents [17,18], have been reported from 2012 onwards [19-24].

In the last years the reports on KS, especially those caused by drugs, are rapidly increased and several are the suspected drugs. In addition to penicillin's and cephalosporin's, other categories of antibiotics such as quinolones (levofloxacin and ciprofloxacin) [25,26] and macrolides (clarithromycin) [27] have been associated to KS. Among other classes of drugs, antiviral [28], antifungal [29] and antipsychotic drugs [30] are examples of novel causes of KS.

Therefore, reports on KS due to drugs are constantly increasing and more cases are expected to

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Received Date: 20 May 2017

Accepted Date: 26 May 2017

Published Date: 30 May 2017

Citation:

Minciullo PL, Gangemi S. Kounis Syndrome due to Drugs: Increasing Awareness of a Still under Diagnosed Condition. *Remed Open Access*. 2017; 2: 1061.

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be reported in the next years. This rise reflects increased consciousness of such a serious and potentially fatal condition which is probably still under diagnosed.

It is advisable that physicians, allergists and cardiologists in particular, take in account KS in the differential diagnosis of allergic reaction and acute coronary syndrome respectively. Furthermore, it is important to highlight that all drugs are potential trigger factors of KS.

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