



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

Minciullo PL\* and Gangemi S

Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy

## 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- $\alpha$  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

## OPEN ACCESS

### \*Correspondence:

Minciullo Paola Lucia, Department of Clinical and Experimental Medicine, Division and School of Allergy and Clinical Immunology, UOC Allergologia e Immunologia Clinica Policlinico Universitario, University Hospital of Messina, 98125 Messina, Italy, Tel: +39 090 2212049; Fax: +39 090 2217231; E-mail: pminciullo@unime.it

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.

Copyright © 2017 Minciullo PL. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.

## References

- Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract.* 1991;45(2):121-8.
- Clark E. Serum carditis: morphologic cardiac alterations in man associated with serum disease. *J Am Med Assoc.* 1938;110:1098-1100.
- Pfister CW, Plice SG. Acute myocardial infarction during a prolonged allergic reaction to penicillin. *Am Heart J.* 1950;40(6):945-7.
- Lopez PR, Peiris AN. Kounis syndrome. *South Med J.* 2010;103(11):1148-55.
- Biteker M. A new classification of Kounis syndrome. *Int J Cardiol.* 2010;145(3):553.
- Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med.* 2016;54(10):1545-59.
- Kounis NG, Giannopoulos S, Soufras GD, Kounis GN, Goudevenos J. Foods, Drugs and Environmental Factors: Novel Kounis Syndrome Offenders. *Intern Med.* 2015;54(13):1577-82.
- Mirijello A, Pepe G, Zampello P, Criconia GM, Mendola A, Manfrini A. A Male Patient with Syncope, Anaphylaxis, and ST-Elevation:Hepatic and Cardiac Echinococcosis Presenting with Kounis Syndrome. *J Emerg Med.* 2016;51(4):e73-e7.
- Renda F, Landoni G, Trotta F, Piras D, Finco G, Felicetti P, et al. Kounis Syndrome: An analysis of spontaneous reports from international pharmacovigilance database. *Int J Cardiol.* 2016;203:217-20.
- Renda F, Marotta E, Landoni G, Belletti A, Cuconato V, Pani L. Kounis syndrome due to antibiotics: A global overview from pharmacovigilance databases. *Int J Cardiol.* 2016;224:406-11.
- Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome:A review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *Int J Cardiol.* 2017;232:1-4.
- Biteker M, Duran NE, Biteker F, Civan HA, Gündüz S, Gökdeniz T, et al. Kounis syndrome: first series in Turkish patients. *Anadolu Kardiyol Derg.* 2009;9(1):59-60.
- Gázquez V, Dalmau G, Gaig P, Gómez C, Navarro S, Mercé J. Kounis syndrome: report of 5 cases. *J Investig Allergol Clin Immunol.* 2010;20(2):162-5.
- Lombardi N, Pugi A, Maggini V, Lenti MC, Mugelli A, Cecchi E, et al. Underdiagnosis and pharmacovigilance. The case of allergic acute coronary syndrome (Kounis syndrome). *Int J Cardiol.* 2013;168(5):5054-5.
- Kounis NG. Kounis syndrome:an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med.* 2016;54(10):1545-59.
- Kounis NG, Giannopoulos S, Soufras GD, Kounis GN, Goudevenos J. Foods, Drugs and Environmental Factors: Novel Kounis Syndrome Offenders. *Intern Med.* 2015;54(13):1577-82.
- Calco D, de la Hera JM, Lee D. Contrast echocardiography and clinical safety. *Rev Esp Cardiol.* 2006;59:397-401.
- Lonescu A. Bubble trouble: anaphylactic shock, threatened myocardial infarction and transient renal failure after intravenous echo contrast for left ventricular cavity opacification preceding dobutamine stress echo. *Eur J Echocardiogr.* 2009;10(5):707-10.
- Josefsson J, Fröbert O. Losartan-induced coronary artery spasm. *BMJ Case Rep.* 2012;2012.
- van Ginkel AG, Sorgdrager BJ, de Graaf MA, Karalis I, Ajmone Marsan N. ST-segment elevation associated with allergic reaction to echocardiographic contrast agent administration. *Neth Heart J.* 2013;15:725-8.
- 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.
- Shah G, Scadding G, Nguyen-Lu N, Wigmore T, Chenzbraun A, Wechalekar K, 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-e26.
- Luhmann SJ, Sucato DJ, Bacharier L, Allis A, Woerz C. Intraoperative anaphylaxis secondary to intraosseous gelatin administration. *J Pediatr Orthop.* 2013;33:e58-e60.
- Arslan Z, Iyisoy A, Tavlasoglu M. Acute myocardial infarction after prednisolone administration for the treatment of anaphylaxis caused by a wasp sting. *Cardiovasc J Afr.* 2013;24(4):e4-6.
- Kounis NG, Koniari I, Soufras G. Kounis Syndrome after Intake of Levofloxacin: Increasing Incidence of Hypersensitivity to Fluoroquinolones. *J Investig Allergol Clin Immunol.* 2017;27(1):76-7.
- Almeida J, Ferreira S, Malheiro J, Fonseca P, Caeiro D, Dias A, et al. A rare cause of acute coronary syndrome:Kounis syndrome. *Rev Port Cardiol.* 2016;35(12):699.e1-699.e4.
- Bilgin M, Akyel A, Doğan M, Sunman H, Yeter E. Acute coronary syndrome secondary to clarithromycin: the first case and review of the literature. *Turk Kardiyol Dern Ars.* 2014;42(5):461-3.
- Buturak A, Norgaz T, Gorgulu S. Brivudine induced coronary vasospasm as a manifestation of Kounis syndrome:First report. *Int J Cardiol.* 2015;185:4-6.
- Singh Mahal H. Fluconazole-Induced Type 1 Kounis Syndrome. *Am J Ther.* 2016;23(3):e961-2.
- Hamera L, Khishfe BF. Kounis syndrome and ziprasidone. *Am J Emerg Med.* 2017;35(3):493-494.