Kounis syndrome caused by double allergens: the more allergens present, the easier, the quicker, and the more severe the anaphylaxis

Nicholas G. Kounis[1], Ioanna Koniari[2], Panagiotis Plotas[1], George D. Soufras[3], Grigorios Tsigkas[1], Periklis Davlouros[1], George Hahalis[1]

[1]Department of Cardiology, University of Patras Medical School, Rion, Patras, Achaia, Greece;
[2]Electrophysiology and Device Department, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK;
[3]Department of Cardiology, "Saint Andrews" State General Hospital, Patras, Achaia, Greece.

To the Editor: In the very interesting report published in the *Chinese Medical Journal*,[1] a 42-year-old Chinese male patient who had not any previous history of cardiovascular disease, but only bee stings without any sequelae, was stung again while was cycling outdoors. Immediately, he developed sweats, dizziness, headaches, bosom frowsty, shortness of breath, urinary incontinence, hypotension, hypoxygenation, tachycardia, confusion, ST-segment depression in II-III leads, and ST-segment elevation in aVR, eosinophilia, increased cardiac enzymes, but with normal coronary arteries on angiography, compatible with Kounis type I variant progressing to acute myocardial infarction.[2,3] In this patient; however, specific immunoglobulin tests were positive for tree combination (willow/poplar/elm). The patient had complete recovery with anti-allergic medications and fluid replacement.

This case raises important issues on simultaneous exposure of several allergens, the severity of anaphylaxis, and the development of Kounis syndrome.

Immunoglobulin E (IgE) antibodies constitute components of a protein network and are the result of signaling response to antigens/allergens.[4] They are synthesized and released by B lymphocytes as a result of a complex interplay between genes, cytokines, and environmental antigen exposure.

Elevated IgEs are accompanying allergies, infections, and immune conditions. Specific diseases which cause elevation of serum IgE levels include atopic diseases (asthma, allergic rhinitis, atopic dermatitis, urticaria) as well as parasitic diseases, cutaneous diseases, neoplastic diseases, and immune deficiencies. Conditions associated with unusually high serum IgE concentrations (>1000 IU/mL) are allergic bronchopulmonary aspergillosis, allergic fungal sinusitis, atopic dermatitis, human immunodeficiency virus infection, IgE myeloma, lymphoma, systemic parasitosis, tuberculosis, and hyper IgE syndrome.[5] The latter is a rare primary immunodeficiency disease characterized by recurrent skin and pulmonary abscesses and extremely elevated levels of IgE in serum.

Furthermore, elevated IgE levels may be a risk factor for increased cardiovascular mortality[6] and have been found increased in acute myocardial infarction, stable and unstable angina, further correlating with plaque destabilization and severity of acute myocardial infarction.[7]

IgE antibodies are attached on the mast cell or basophil cell surface in specific high affinity FCεRI, FCγRI, and low affinity FCεRII, FCγRII receptors. When a critical number of allergen/antigen molecules cross bridging their corresponding, receptor-bound IgE antibody molecules, then an allergic or anaphylactic reaction takes place.[8]

The critical number of bridged IgE molecules has been estimated to be in the order of 2000, in order to make a total of approximately 1000 bridges that are necessary to trigger the cell out of a maximal number of some 500,000 to 1,000,000 IgE molecules on the cell surface.[9] It might be possible to accumulate the critical number of bridges by more than one, non-cross-reactive allergen and its corresponding IgE antibody.

That is why patients allergic to and simultaneously exposed to several allergens have more symptoms than mono-sensitized individuals. This might be the result of an additive effect of IgE antibodies, with different specificities, initiating the allergic inflammation.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000946

Correspondence to: Nicholas G. Kounis, Department of Cardiology, University of Patras Medical School, Queen Olgas Square, 7 Aratou Street, Patras 26221, Greece
E-Mail: ngkounis@otenet.gr

Chinese Medical Journal 2020;133(15)

Received: 18-02-2020 **Edited by:** Li-Shao Guo

It has been found that a relation exists between the number bound to basophil, and mast cell surface IgE receptors and the number of IgE molecules, some of which are IgE antibodies, in plasma.[9] Consequently, the lower the serum IgE antibody concentration, the more difficult to trigger the mast cell or basophils and the less allergic symptoms.

Indeed, in a relative study[10] it was found that IgE antibodies with different specificities had an additive effect and triggered mast cells and basophils that were sensitized with small, even sub-threshold numbers of IgE antibodies of different specificities. The authors of this study concluded that IgE antibodies with different specificities can join forces and trigger the cells to release its mediator, if the patient is simultaneously exposed to the corresponding allergens.

The patient described by Zhang *et al*[1] had not any previous history of cardiovascular disease or allergic reaction despite the bee stings in the past. However, during his current episode of bee stings he developed severe anaphylactic symptomatology culminating to Kounis syndrome type II (acute myocardial infarction) and was found sensitized to additional allergens namely tree combination (willow/poplar/elm). It seems that all these allergens had joined forces and triggered his current anaphylactic cardiovascular disease.

Cardiologists and emergency care physicians should be always bring in mind that IgE sensitization to an allergen "should not be clinically evaluated on its own but in the possible context of multi-allergen sensitization and exposure."[10]

Conflicts of interest

None.

References

1. Zhang YX, Liu L, Liu LP, Xu H, Li YM. A case of type I Kounis syndrome caused by double allergens. Chin Med J 2020;133:735–737. doi: 10.1097/CM9.0000000000000684.
2. Kounis NG, Koniari I, Chourdakis E, Soufras GD, Tsigkas G, Davlouros P, *et al*. Acute myocardial infarction induced by anaphylaxis in china: the Kounis syndrome. Chin Med J 2018;131:2392–2393. doi: 10.4103/0366-6999.241810.
3. Kounis NG, Soufras GD, Lianas D, Patsouras N. After administration of intravenous epinephrine for bee sting-induced anaphylaxis: Kounis syndrome or epinephrine effect? Chin Med J 2016;129:500–501. doi: 10.4103/0366-6999.176081.
4. Kounis NG, Hahalis G. Serum IgE levels in coronary artery disease. Atherosclerosis 2016;251:498–500. doi: 10.1016/j.atherosclerosis.2016.05.045.
5. Unal D, Gelincik A, Elitok A, Demir S, Olgac M, Coskun R, *et al*. Impact of high serum Immunoglobulin E levels on the risk of atherosclerosis in humans. Asia Pac Allergy 2017;7:74–81. doi: 10.5415/apallergy.2017.7.2.74.
6. Min KB, Min JY. Risk of cardiovascular mortality in relation to increased total serum IgE levels in older adults: a population-based cohort study. Int J Environ Res Public Health 2019;16:4350. doi: 10.3390/ijerph16224350.
7. Guo X, Yuan S, Liu Y, Zeng Y, Xie H, Liu Z, *et al*. Serum IgE levels are associated with coronary artery disease severity. Atherosclerosis 2016;251:355–360. doi: 10.1016/j.atherosclerosis.2016.05.020.
8. Kirshbaum BA, Cohen HB, Beerman H, Pastras T. The basophil degranulation test. A review of the literature. Am J Med Sci 1967;253:473–492.
9. MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, Mckenzie-White J, *et al*. Down-regulation of FceRI expression in human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438–1445.
10. Nopp A, Johansson SG, Lundberg M, Oman H. Simultaneous exposure of several allergens has an additive effect on multisensitized basophils. Allergy 2006;61:1366–1368. doi: 10.1111/j.1398-9995.2006.01211.x.

How to cite this article: Kounis NG, Koniari I, Plotas P, Soufras GD, Tsigkas G, Davlouros P, Hahalis G. Kounis syndrome caused by double allergens: the more allergens present, the easier, the quicker, and the more severe the anaphylaxis. Chin Med J 2020;133:1889–1890. doi: 10.1097/CM9.0000000000000946