

Letter to the Editor

Kounis syndrome and hypersensitivity reactions associated with endovascular devices

Dear Sir,

In their important review published in the July issue of this journal (1) concerning hypersensitivity to endovascular devices, the authors correctly concluded that, at the moment, preprocedural evaluation of patients for allergy is inadequate. However, they have omitted to refer to pathophysiology and possible causes for the much feared in-stent thrombosis and to newly described 'device syndrome' after patent foramen ovale (PFO) closure.

Although vasospasm associated with cardiac interventions is a known phenomenon, different from delayed-type reactions, and the probability of contact sensitization is independent of enhanced immunoglobulin E (IgE) delayed responsiveness (2), various authors have emphasized the association of Kounis syndrome with allergy to stent components (3–6). This syndrome is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators released during the activation process (7). Two variants of this syndrome have been described recently (8). Type I variant concerns patients with normal coronary arteries and is associated with coronary artery spasm which, if prolonged, could progress to acute myocardial infarction. Type II variant concerns patients with culprit but quiescent pre-existing atheromatous disease and is associated with either coronary artery spasm or acute myocardial infarction.

There are few clinical reports and reported pathology findings, and all patients died from coronary stent thrombosis, pointing towards an allergic reaction with infiltration of inflammatory cells including eosinophils, mast cells, macrophages and T cells. Much of what is currently known relating to the histopathological features of drug-eluting stent (DES) thrombosis is derived from post-mortem and animal studies, and as such, this review is important as far as the metallic allergy is concerned. Persistent fibrin deposition

has been linked to poorer DES endothelialization, while inflammatory cells, particularly eosinophils, represent an allergic hypersensitivity reaction induced by the DES components.

This subject has not received any serious attention so far; therefore, the search for causality and application of prophylactic and therapeutic measures for endovascular device-related allergic events seems to be of paramount importance for both patients and physicians.

Patients undergoing stent implantation receive multiple substances, which can act as potential antigens. These substances include the metal stent, which is made from 316L stainless steel containing nickel, chromium, manganese, titanium and molybdenum, and for DES include the polymer coating and the impregnated drugs which for today are the antimicrotubule, antineoplastic agent paclitaxel and the anti-inflammatory, immunosuppressive and antiproliferative agent rapamycin. Additionally, these patients receive antiplatelet therapy with clopidogrel and aspirin, two well-known antigenic substances, and could easily be exposed to more antigenic agents during their everyday activity. Allergic inflammation is initiated by antigens cross-bridging their corresponding receptor-bound IgE antibodies on the mast cell or basophil cell surface. According to a recent study, IgE antibodies with different specificities can have an additive effect, and even small amounts of corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them (9). It might be possible to accumulate the critical number of bridges by more than one non-cross-reactive antigen and its corresponding IgE antibody (10).

On the other hand, a newly observed syndrome (11), resembling Kounis syndrome, has been described in 9 (19.5%) of 46 patients undergoing PFO closure with a full-nitinol (nickel–titanium alloy) Amplatzer Occluder (Cribiform, ASD Occluder; AGA Medical Corporation, Golden Valley, MN) and a low-nitinol Premere Closure System (St Jude Medical Inc., GLMT, St Paul, MN). This syndrome consisted of chest discomfort, exertional dyspnoea and mild leucocytosis. The syndrome was treated with prednisone

and clopidogrel, and in all patients was resolved after 1 week of therapy. Interestingly, none of the patients without nickel allergy (tested with patch skin technique) developed postclosure symptoms. In another report (12), acute chest pain with ST elevation (type I Kounis syndrome) was observed during PFO closure.

We advocate, therefore, measurement of inflammatory mediators such as total IgE, specific IgE for drugs and device components, chymase, tryptase, histamine, arachidonic acid products (thromboxane, leukotrienes and prostaglandins), tissue factor, cytokines and chemokines (tumour necrosis factor, interferon, interleukin-6 (IL-6), IL-2, IL-18, IL-10], as well as immunological evaluation and hypersensitivity techniques regularly after DES insertion and PFO closure with metal devices in order to predict and prevent Kounis syndrome. Additionally, new DES and closure devices combining drugs with antiallergic and anti-inflammatory actions that may also be disease modifying might be the solution of this problem. For example, mast cell stabilizers may be used because the latter have stabilized allergic reactions clinically and have abrogated thrombotic events experimentally (13).

Nicholas G. Kounis, George Hahalis,
Sophia A. Kounis and George N. Kounis
Department of Medical Sciences,
Patras Highest Institute of
Education and Technology
Queen Olga Square, 7 Aratou Street,
Patras 26221, Greece
Tel/Fax: +30-2610279579
e-mail: ngkounis@otenet.gr

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