Letter to the Editor

Letter by Kounis et al Regarding Article, "Sirolimus-Eluting Stents Suppress Neointimal Formation Irrespective of Metallic Allergy"

To the Editor:

In the excellent paper published recently in this journal,¹ the authors found that 14 out of 88 patients (16%) with sirolimus-eluting stent (SES) implantation had positive patch-testing to stainless steel materials without any systemic reaction. Furthermore, SES prevented restenosis, irrespective of this metallic allergy, in all patients as was shown in the follow-up angiography at the 8-month period. However, the authors admitted that this study was limited by the small sample size, and the short follow-up period following the SES insertion. Apart from patch-testing, monitoring of inflammatory mediators, antibody testing, macrophage and T-cell activation studies, would be also helpful in patients with drug-eluting stent (DES) insertion. Although in this group of patients with metallic allergy, systemic involvement was absent; however, intracoronary mast cell activation can not be excluded. DES-activated intracoronary mast cells could release histamine, arachidonic acid metabolites, proteolytic enzymes, as well as a variety of cytokines, chemokines and platelet-activating factor leading to local inflammation, restenosis and thrombosis.

Despite the contrasting mechanisms of obstruction between bare metal and DES, coronary stent implantation, either bare metal or drug-eluting, seems to be associated with the much feared in-stent thrombosis, myocardial infarction and sometimes with paradoxical vasoconstriction. The causality of these events is still speculative and it is not known if they are time limited events. Patients undergoing DES implantation receive 5 different substances that can act as potential antigens. These substances include the metal stent itself which is made from 316L stainless steel containing nickel, chromium, manganese, titanium and molybdenum, 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, patients with implanted stents, receive clopidogrel and aspirin, 2 well known antigenic substances, as antiplatelet agents and these patients can easily be exposed to even more antigenic agents during their everyday activities. Hypersensitivity inflammation is initiated by antigens cross-bridging their corresponding, receptor-bound, immunoglobulin IgE antibodies on the mast cell or basophile cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2,000 out of maximal number of some 500,000–1,000,000 IgE antibodies of the cell surface? It might be possible to accumulate the critical number of bridges by more than 1, non-cross-reactive antigen and its corresponding IgE antibody. Clinical studies indicate that sensitized patients simultaneously exposed to several antigens have more symptoms than mono-sensitized individuals.² A recent study showed that 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.⁴ This data suggest that a possible

sensitization to DES should not be clinically evaluated as a consequence of exposure to a single component but rather viewed as in the context of potential sensitization to multiple DES compounds.

The Kounis syndrome, described 15 years ago, is the concurrence of acute coronary events with hypersensitivity reactions.^{5–8} The existing clinical reports and pathology findings in all patients who have died from coronary stent thrombosis point 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 DES thrombosis is derived from post-mortem and animal studies, and, as such this report is important as far as the SES 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 stent-associated coronary events seems to be of paramount importance for both patients and physicians.

Therefore, this otherwise, excellent study should have been expanded to include more patients with a longer follow-up period and with monitoring of inflammatory mediators, especially arachidonic acid products, together with antibody testing and macrophage and T-cell activation studies. This would enable researchers to establish a definite cause of restenosis and stent thrombosis and would help clinicians to find measures in order to prevent and treat these dangerous stent sequelae.

References

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