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Letter to the Editor

Nickel allergy, Kounis syndrome and intracardiac metal devices

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ABSTRACT

Metal-induced allergic reactions are not rare in every day practice but nickel, cobalt and chromium are the most common offenders. Other metal anions and metal alloys represent also emerging causes for hypersensitivity reaction in humans. The metal struts of endovascular and intracardiac devices are usually alloys containing nickel and constitute causes for allergic reactions with possible intracardiac and intracoronary mast cell activation resulting in the Kounis hypersensitivity coronary syndrome. Newer intracoronary stents avoid nickel thus making them less allergenic. It is advisable that, before any device implantation, careful history of any metal allergy should be taken and efforts should be made for the development of new devices with better biocompatibility.

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1. Introduction

Metals are ubiquitous in the surrounding environment because they are normally present in water, food and generally in the Earth's crust [1]. They constitute an important class of substances that can act as allergens. It is known that metals are constituents in consumer products such as jewellery, cosmetics, paints, dental and body implants as well as endovascular and intracardiac devices. Apart from the well known significance of nickel, chromium, and cobalt in inducing skin hypersensitivity other metals such as aluminium, beryllium, copper, gold, iridium, mercury, palladium, platinum, rhodium, and titanium are emerging human body sensitizers. In the United States [2] nickel, chromium and cobalt induce allergic skin reactions in about 14%, 4%, and 9% while in Europe [3] in about 20%, 4%, and 7% respectively.

Metal anions eluted from nickel, cobalt, chromium, titanium, palladium, and gold are common allergic sensitizers and allergy to nickel occurs in up to 17.2% of the population and is the most frequent cause of allergic contact dermatitis [4]. It is also common that patients are sensitized to multiple metal anions. It is not known whether this is due to concurrent sensitization, cross reactivity or both. However, several studies have shown that sensitization to one metal anion increases the possibility of being sensitized to additional metals [5]. It looks likely that metals “join forces” in order to sensitize individuals.

2. A “device hypersensitivity syndrome”

In a recent report [6], nine patients who had proven symptomatic and instrumental allergy to nickel, as evidenced by cutaneous patch skin tests, and suffering from interatrial shunts preferred to be implanted with full nitinol Amplatzer occluder device and low nitinol Premere closure system. These patients had been previously informed about the possibility to experience some kind of symptomatology after the implantation and were left free to choose alternative therapeutic options [6]. Between the 2nd and 3rd postoperative days, 8 out of 9 patients experienced a short of symptoms which included chest discomfort, exertional dyspnea, asthenia, palpitations, worsening of migraine headache and mild leukocytosis. Interestingly, in the same report, two patients with negative skin patch testing but with occluder system implantation developed atrial fibrillation that resolved with antiarrhythmic treatment. The above symptoms were also treated with prednisone and clopidogrel and were resolved within one week of therapy.

3. The “Kounis hypersensitivity syndrome”

Kounis syndrome was described nearly 20 years ago [7] as the coincidental occurrence of chest discomfort, dyspnea, faintness, nausea, vomiting, syncope, pruritus, urticaria, hypotension, diaphoresis, pallor, palpitations and bradycardia with conditions associated with mast cell activation including allergic, hypersensitivity, anaphylactic or anaphylactoid insults. It is caused by inflammatory mediators released through mast cell activation and involving interrelated and interacting inflammatory cells such as eosinophils, macrophages and T-lymphocytes. Histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines released during

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the activation process are some of the culprit inflammatory agents [8–10]. Interestingly, the same mediators found increased in allergic coronary syndromes are found raised in blood of patients suffering from acute coronary syndromes of non-allergic etiology and a common pathway between these has been proposed [11].

4. Discussion

In their very important report published recently in this journal [12] the authors have used Helex occluder and reported the safety and feasibility of a day case patent foramen ovale closure facilitated by intracardiac echocardiography. They reported no allergic complications in the 53 patients and concluded that intracardiac echocardiography in routine day case patent foramen ovale closure is both safe and feasible with excellent clinical and 3 month echocardiographic results. Only one patient failed same day discharge due to groin haematoma. However, other authors [13] have reported that interatrial shunt closure with devices eluting nickel anions has minimal risk for allergic reactions and these can be prevented if a detailed clinical history has been taken and skin patch testing is performed. Similarly, they emphasized that devices with minimal nickel exposure, like the Helex device, are not associated with allergic reactions and despite the 200,000 Amplatzer devices implanted only few had to be explanted due to allergy. In this series, some patients with pre-procedural known nickel allergy developed chest pain, palpitations, atrial fibrillation and late pericardial effusion. These symptoms and signs were similar to those constituting the “device hypersensitivity syndrome”. Similarly, the above symptoms and signs are characteristics of the Kounis coronary hypersensitivity syndrome.

Amplatzer and Premere atrial septal occluder devices are made from nitinol which is an alloy of nickel and titanium. On the other hand, the majority of intracardiac devices included intracoronary stents that are made from 316 L stainless steel which contains nickel, chromium, and molybdenum. Ions from the above metals are eluted through the action of blood, saline, proteins, and mechanical stress.

It has been already known that allergy and inflammatory reactions have occurred in patients with prosthetic valves and other endovascular prostheses [14]. Allergic reactions to metallic implants have been incriminated for postoperative complications such as loosening or formation of new tissue around the metals [15]. In a patient with aseptic loosening of an orthopaedic chromium/cobalt alloy and positive patch tests to potassium dichromate, peri-implantar tissue examination showed oligoclonal T-cell infiltration and Th1-type cytokine expression [16].

5. Conclusions and future directions

Based on the above, newer intracoronary stent devices e.g. Endeavor with zotarolimus and Xience V with everolimus eluting drugs avoid nickel strut and use cobalt–chromium struts which are less allergenic, according to our previous suggestions [17]. It is advisable that any newer atrial septal occluder devices should comply with these recommendations in order to avoid any metal hypersensitivity. Consequently the

development of new artificial materials with biocompatibility is desirable. Improved properties for better biocompatibility as wet ability and surface free energy can be enhanced using irradiation-modified polymer surface. We currently have a project in designing and testing new materials taking account that release of hydrogen and oxidation of the modified surface layer can cause changes in the physical properties such as mechanical, optical properties, and biocompatibility.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [18].

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