Dermatology 2009;219:87–88

DOI: [10.1159/000205017](https://doi.org/10.1159/000205017)**Drug-Eluting Coronary Stents: Hypersensitivity Reactions to Paclitaxel and the Risk of Kounis Syndrome***George D. Soufras^a, George N. Kounis^b, John A. Chiladakis^c, Sophia A. Kounis^b, Georgia V. Gouvelou-Deligianni^b, Maria Batsolaki^b, Nicholas G. Kounis^b*^aDepartment of Cardiology, Agios Andreas State General Hospital, ^bMedical Sciences, Patras Highest Institute of Education and Technology, and ^cDepartment of Cardiology, University of Patras Medical School, Patras, Greece**Key Words**

Drug-eluting stents • Hypersensitivity • Kounis syndrome • Paclitaxel

In a very important paper published recently in this journal [1], the authors reported on a patient who developed disseminated wheals, itching, asthma-like breathing, acute sinovitis and night sweats 2 weeks following paclitaxel-eluting coronary stent insertion for critical coronary disease. His dermatological symptoms were urticaria covering the extensor surface of the arms and neck, the back of his feet and swelling of palms and soles. There was leukocytosis, with elevated C-reactive protein and lactate dehydrogenase. A skin prick test showed a late reaction after 24 h to two paclitaxel dilutions in concentrations of 1.00 and 10.0%.

Although the authors correctly emphasized the serious sequelae of paclitaxel-stent-induced allergic reactions, they have omitted to refer to hypersensitivity coronary syndrome or Kounis syndrome as a consequence of allergic reactions to stent components [2]. Kounis syndrome has been implicated in the pathogenesis of the much feared in-stent thrombosis [3]. Stent thrombosis may lead to catastrophic consequences including myocardial infarction with an estimated 30-day mortality ranging from 20 to 48%, and hypersensitivity to stent components is regarded as one of its causes [4]. 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 reactions. It is caused by a variety of inflammatory mediators released during the activation process including histamine. Histamine can induce tissue factor expression and activity which is the key factor for coagulation. Two variants of this syndrome have been described [5]. Type I variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease. Type II variant includes patients with culprit but quiescent preexisting atheromatous disease.

The authors of this report anticipated that the allergic symptoms of urticaria, asthma and arthralgia as well as the late skin prick reaction to paclitaxel may indicate type III serum sickness disease. These symptoms have appeared 2 weeks after stent implantation, and this time lag may also indicate immunological sensitization. It is known that paclitaxel is eluted completely within 4–6 weeks after stent implantation. Since paclitaxel-specific IgE binding was not detected, the authors thought that these reactions may be related to toxic or pseudoallergic effects of paclitaxel.

However, this patient with paclitaxel-eluting stent implantation was under the influence not only of a sole antigen, but he had received 5 different substances which could have acted as potential antigens. Furthermore, this patient could easily have been exposed, thereafter, to more antigenic agents during his everyday

Table 1. Allergic reactions to drug-eluting stent components

Paclitaxel	Angioedema Atrioventricular block Bronchospasm Cutaneous flushing Diaphoresis Kounis syndrome Left bundle branch block Ventricular tachycardia Urticaria
Polymers	Allergic conjunctivitis Allergic rhinitis Allergic stomatitis Facial angioedema Generalized anaphylactic reaction Generalized urticaria Interstitial asthma Neurodermatitis Stomatitis venenata Sarcoid granuloma (delayed hypersensitivity)
Nickel	Allergic contact dermatitis Baboon syndrome Bronchial asthma Dependent edema Diffuse exanthema Fever Flexural dermatitis Itching erythema Pericarditis Pompholyx formation Rosacea

activity. Drug-eluting stents are composed of the nickel strut, the polymer coating, the eluted drug plus aspirin and clopidogrel. The patient's symptoms started 2 weeks after stent implantation which makes them unlikely to be IgE-mediated reactions.

Paclitaxel is eluted completely within 4–6 weeks after stent implantation, while nickel and polymer remain for life in the patient's coronaries. Therefore, there is persistent, continuous and repetitive exposure of the coronary intima to both antigenic substances which can lead to chronic allergic inflammation [6]. Chronic allergic inflammation is characterized by the presence of many innate adaptive immune cells at the affected sites as well as substantial changes in the extracellular matrix and changes in the number, phenotype and function of structural cells [6] which can lead to thrombosis and/or restenosis.

Paclitaxel itself, as well as the polymer coating and the nickel strut antigens, have induced many allergic reactions (table 1). Paclitaxel belongs to a distinct type of antineoplastic drugs which in micromolar concentrations, easily achieved in patients, inhibit microtubule assembly (M phase of the cell cycle) resulting in dissolution of the mitotic spindle structure, thereby inhibiting proliferation of cells. Most cytostatic drugs have been reported to induce allergic reactions [7]. There are several reported instances of hypersensitivity reactions, mainly of anaphylactic type (type I), but also types II, III and IV [8]. According to a recent report [9], up to 42% of patients receiving systemic paclitaxel for treatment of various types of cancer experience some kind of hypersensitivity reactions, and up to 2% of the patients developed serious allergic reactions. So far, there are several reports associating type I and type II variants of Kounis syndrome with paclitaxel systemic administration [10].

Therefore, the following suggestions that have been proposed and incorporated in current protocols [11] for patients undergoing stent implantation should be applied in order to avoid hypersensitivity reactions and hypersensitivity coronary events. These include: detailed history taking regarding allergies and drug hypersensitivity reactions, patch and prick testing, antibody testing when and where appropriate, macrophage and T-cell activation studies, monitoring the levels of inflammatory mediators after implantation, desensitization strategies when and where applicable, and considering the use of corticosteroids and mast cell stabilizers since the latter have experimentally abrogated late thrombotic events [12].

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