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LETTER TO THE EDITOR

Anti chimeric antibodies against chimeric monoclonal antibodies may result in Kounis hypersensitivity associated acute coronary syndrome

Dear Sir,

In the very important report published in this journal,¹ a patient suffering from Crohn's disease with recurrent symptomatology and receiving repeated treatment with infliximab developed anaphylactic cardiac symptoms including precordial chest pain, severe dyspnoea, tachycardia and urticaria. The patient was treated with antihistamines and infliximab was replaced by adalimumab. However, adalimumab induced again urticaria symptoms. Measured IgE antibodies were negative but IgG antibodies were present in both instances. The authors characterized these events as acute anaphylactoid and delayed hypersensitivity reaction and commented that their precise mechanism is still not well known. Although cardiological work up was not described, it seems likely that cardiac symptoms induced by infliximab were due to Kounis hypersensitivity associated acute coronary syndrome.² This syndrome is defined, today, as the concurrence of acute coronary syndromes with conditions associated with mast cell and basophil activation, involving interrelated and interacting inflammatory cells and including allergic, anaphylactic and anaphylactoid insults. Three variants of this syndrome have been described so far which include coronary artery spasm, plaque erosion and/or rupture manifesting as acute myocardial infarction and stent thrombosis.

Infliximab is a genetically produced chimeric monoclonal antibody against TNF- α , and consists of 25% murine sequences in the variable region of antibody and therefore, patients develop antichimeric antibodies against infliximab.³ Indeed, such antichimeric antibodies have been found in 14.5–17.1% of patients with Crohn's disease. However, in a recent study,⁴ 11 out of 71 patients, receiving infliximab, developed hypersensitivity reactions such as urticaria, chest tightness, vomiting and oxygen desaturation with IgE, IgM and IgG antibodies against infliximab.

The patient's cardiac symptoms were treated with antihistamines and hydrocortisone. Although the above treatment

is considered appropriate for managing an allergic reaction all above substances namely infliximab, adalimumab, and both antihistamines and steroids² can rarely act themselves as antigens and join forces in order to degranulate basophils and mast cells.⁵

Delayed hypersensitivity reactions to infliximab include atopic dermatitis, acne, allergic contact dermatitis, allergic pulmonary aspergillosis, alopecia areata, atopic dermatitis, cutaneous vasculitis, eruption, erythema nodosum, eczematoid eruption, eczematoid dermatitis, eczematoid-like purpura of Doukas–Kapetanakis, granuloma annulare, lichen planus, necrotizing fasciitis, niacin-like reaction, nummular eczema, psoriasiform eruption, pustular eruption, red man syndrome (striking, “glowing” red discoloration of the skin), serum sickness, urticarial rash and urticarial vasculitis. Acute myocardial infarction (type I variant of Kounis syndrome) has been also reported.⁶

In order to prevent infliximab hypersensitivity reactions and therefore avoid serious cardiac consequences we recommend the following:

- Before drug administration
 1. Careful history of drugs and adverse drug reactions and allergies (atopy)
 2. Both antibody and patch testing, skin prick, intradermal skin testing for the drug
 3. Macrophage and T-cell activation studies
- Monitoring after any cardiac reaction:
 1. Cardiac enzymes and troponins
 2. Total IgE, IgG
 3. Specific IgE and IgG
- Desensitization strategies if it is proved necessary
- Considering the use of mast cell stabilizers in association to steroids and antihistamines

References

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