Letter to the Editor

Coronary Vasospasm Induced by Cytostatic Drugs: Kounis Syndrome Seems to Be the Most Likely Culprit

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In a very important paper published recently in the Hellenic Journal of Cardiology,[1] the authors described a 52-year-old female patient with no history and no predisposing factors for coronary artery disease, who developed chest pain with electrocardiographic changes suggesting coronary artery spasm following capecitabine administration for colorectal cancer. The authors of this report attributed this reaction to capecitabine cardiotoxicity, endothelial activation, thrombogenic effects and autoimmune phenomena. However, it seems likely that this patient had suffered capecitabine-induced hypersensitivity reaction, culminating in hypersensitivity-associated acute coronary syndrome, the so called Kounis syndrome.[2]

Kounis syndrome and its variants

Kounis syndrome[3] has been described as the coincidental occurrence 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 such as histamine, neutral proteases, arachidonic acid products such as leukotrienes, platelet activating factor and a variety of cytokines and chemokines released during the activation process. A subset of platelets (20%) containing both high (FCεRI) and low (FRεRII) affinity IgE receptors can act like mast and the other inflammatory cells when stimulated by corresponding antigens.[4] This leads to platelet adhesion, activation and aggregation resulting in artery spasm and/or thrombus formation.

Three variants of Kounis syndrome have been described so far:

- Type I variant,[5] which includes patients with normal coronary arteries without predisposing factors for coronary artery disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins, or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. It seems possible that the patient described by Tsiamis et al[1] had suffered a type I Kounis syndrome.
- Type II variant,[6] which includes patients with culprit but quiescent preexisting atheromatous disease, in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac

enzymes and troponins, or plaque erosion or rupture manifesting as acute myocardial infarction.

- In view of recent studies and case reports that have shown coincidence of hypersensitivity reactions following implantation of drug-eluting stents and stent thrombosis, a Type III variant has been described.[7] This type includes patients with stent thrombosis in whom thrombus harvesting and staining with hematoxylin–eosin and Giemsa shows the presence of eosinophils and mast cells, respectively, in the pathology specimens.

Antineoplastic drugs inducing hypersensitivity-associated Kounis syndrome

Antineoplastic drugs that are able to induce acute hypersensitivity-associated Kounis coronary syndromes include[6] the taxanes, such as the antimicrotubule paclitaxel, and the antimetabolite 5-fluoruracil with its prodrug capecitabine, as in the patient described by Tsiamis et al.[1] Apart from back or severe chest pain, other symptoms accompanying Kounis syndrome include dyspnea, flushing, urticaria, hypo- or hypertension, erythematous rashes, and gastrointestinal symptoms. The mechanisms include IgE-mediated hypersensitivity, complement activation or direct mast cell activation. The latter seems possible, because Kounis syndrome can occur with the first exposure to a drug, without IgE sensitization.[7] Tryptase, a product solely secreted from mast cell degranulation, has been found elevated in the serum of reactive patients shortly after the reaction. All types of Kounis syndrome can occur, including the type III variant, because paclitaxel is an agent eluted by drug-eluting stents. The platins, such as the alkaloids cisplatin, carboplatin and oxiplatin, can induce Kounis syndrome, typically type I and/or type II variant, which is accompanied by similar symptoms, like taxanes. However, unlike taxanes, repeated exposures are usually required prior to the onset of hypersensitivity to platins. In one study, 50% of the initial hypersensitivity reactions to platins took place during the 8th course.[8] Monoclonal antibodies are used for the treatment of malignancies, as well as for inflammatory conditions including ankylosing spondylitis and ulcerative colitis. They include infliximab, rituximab, trastuzumab, omalizumab, adalimubad, natalizumab, basiliximab, abciximab and cetuximab. Infliximab, in particular, is a genetically produced chimeric monoclonal antibody against tumor necrosis factor-a, and consists of 25% murine sequences in the variable region of the antibody; therefore, patients develop antichimeric antibodies against infliximab. In this context the paradox phenomenon has occurred: antichimeric antibodies can act against chimeric monoclonal antibodies and can result in Kounis hypersensitivity-associated acute coronary syndrome. Such reports have already been published.[9-12]

Other cytostatic drugs[6] that have been incriminated in inducing Kounis-like syndrome include the interleukin-2 agent denileukin diftitox, the vinca alkaloids, and interferons. Mild to moderate hypersensitivity reactions have also been reported with the use of bleomycin and asparaginase, and these have been mediated by leukotrienes.[13] Leukotrienes are produced *de novo* during allergic or anaphylactic reactions, especially from mast cells, which are a rich source of leukotrienes and constitute the main cells that induce Kounis syndrome. It is possible that some antineoplastic agents could be acting as haptens when attached to the blood proteins. Low molecular weight antineoplastics have been proposed to have haptenic properties.[14]

The capecitabine problem

The main allergic reactions, apart from Kounis syndrome, reported so far during capecitabine administration include acneiform skin rash, linchenoid photosensitive eruption, exudative non-healing scalp, skin reactions, pyogenic granuloma, subacute cutaneous systemic lupus erythematosus, exudative hyponychia dermatitis, and hand–foot syndrome. Indeed, in a recent randomized study[15] of capecitabine, oxaliplatin and bevacizumab administration, among 389 patients receiving combined treatment, 65 (19.27%) developed some kind of allergic reaction. Severe coronary vasospasm similar to type I Kounis syndrome has been reported on several occasions[16-22] with the use of capecitabine, and in a patient with severe and prolonged acute coronary syndrome during treatment with this agent, it was noticed that he had previously developed similar symptoms during treatment with infusion of 5-fluorouracil.[23] In another report, a patient developed ventricular fibrillation following capecitabine-induced coronary vasospasm, necessitating cardioverter-defibrillator implantation.[24]

Can we prevent Kounis syndrome following antineoplastic treatment?

Kounis syndrome has emerged as a life-threatening condition in any case of allergic reaction, independently of its etiology. Therefore, the need to predict

severe consequences and the risk of Kounis syndrome in patients with hypersensitivity episodes is always a challenging issue and one that is of paramount importance for physicians. Hypersensitivity episodes are common following the administration of antineoplastic agents, but only a few patients develop a severe reaction such as chest pain with or without electrocardiographic changes, manifesting as Kounis syndrome, during these episodes. Approximately 30% of patients receiving taxanes, 27% of patients receiving platins and up to 10% of patients receiving monoclonal antibodies are prone to develop some kind of hypersensitivity reaction.[25] We had previously suggested that a threshold level of mast cell content exists,[3] above which it can provoke coronary artery spasm and/or plaque erosion or rupture manifesting as Kounis syndrome. Furthermore, the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody–antigen reaction, the allergen concentration and the route of allergen entrance could be some additional factors. Recent reports have shown that asymptomatic patients with mildly increased serum baseline tryptase are prone to develop an immediate and severe hypersensitivity reaction to hymenoptera sting. Such patients were found to have underlying clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome.[26] In these patients, bone marrow aspiration showed mast cell granulomas and spindle-shaped mast cells; flow cytometric analysis of mast cells revealed mast cells expressing CD2 or CD25 on their surface, and KIT mutation analysis showed KIT mutation at codon 816. KIT is the mast cell receptor for the stem cell factor, which is essential for mast cell development, proliferation, survival, adhesion, and homing. Therefore, patients with serum baseline tryptase greater than normal might have KIT mutations that lower the stimulus threshold for anaphylaxis, and have a hyper-responsive mast cell phenotype resulting in the development of Kounis syndrome. Research efforts into this matter are currently in progress.[26] So far, according to the literature, allergic workup has not been performed in any of the published reports dealing with cardiovascular complications of cancer therapy. However, there are reports showing a relationship between a history of allergic reactions and risk of subsequent hypersensitivity to antineoplastics.[27]

Other reports concerning hypersensitivity reactions to antineoplastic agents have emphasized the role of desensitization strategies.[25] Specific antineoplastic drug therapy is, in the majority of cases, absolutely necessary, despite the development of any hypersensitivity to the particular agent. Therefore, rapid antineoplastic drug desensitization is recommended. This procedure allows temporal clinical tolerance to a drug by gradually giving small doses to complete the total therapeutic dose.[25] This protocol is based on 3 solutions of 1/100, 1/10, and normal dilution of any chemotherapy agent.

Furthermore, we have already recommended several tests, measures and actions (Table 1) before ad-

Table 1. Tests, measures and actions that will help to confirm, prevent and treat cardiac hypersensitivity to antineoplastic agents.

Before antineoplastic 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 the following after any cardiac reaction:
1. Total IgE
2. Specific IgE to administered drug
3. Cardiac enzymes and troponins
4. Neutral proteases (chymase, tryptase)
5. Histamine
6. Arachidonic acid products e.g. thromboxane, leukotrienes, prostaglandins
7. CRP (high sensitivity)
8. Tissue factor
9. TNF
10. IFN-γ
11. IL-6, IL-2, IL-18, IL-10 (with anti-inflammatory activity)

- Rapid desensitization when proved necessary
- Consider the use of mast cell stabilizers in association with steroids, antihistamines and leukotriene modifiers

CRP – C-reactive protein; TNF – tumor necrosis factor; IFN-γ – type II interferon; IL – interleukin.

ministering antineoplastic drugs and following adverse cardiac events.[12]

Cardiac hypersensitivity or cardiovascular toxicity?

There is confusion in the world literature concerning the cardiovascular side effects of antineoplastic drugs. The commonly used term "cardiovascular toxicity" is not appropriate, and denotes dose-dependent action with progressing effects, despite discontinuation of the causative agent, resulting in cardiac fibrosis, histologically confirmed, which has never been proven in the acute cardiac side effects of anticancer agents. The term "cardiovascular hypersensitivity" is more appropriate and should be used instead; this means inflammation and Kounis syndrome, which is not dose-dependent and may arise at any time during or after treatment.

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