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Letter to the Editor

Amoxicillin-induced Kounis syndrome manifesting as late stent thrombosis

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The concurrence of acute coronary syndrome with hypersensitivity and anaphylactic or anaphylactoid reactions constitutes the Kounis syndrome (KS), firstly reported in 1991 [1]. Subsequently, Braunwald [2] described that vasospastic angina can be induced by “mediators such as histamine or leukotrienes”, involved in allergic reactions.

The syndrome can be induced from several causes as many drugs (antibiotics, antineoplastics, and NSAIDs), different conditions (asthma, urticaria, and angioedema) and environmental exposures (bug's sting, latex contact, and shellfish eating) [3]. Bare metal stent (BMS) and drug-eluting stent (DES) struts contain metals usually nickel, cobalt and chromium which are able to induce, as well as the polymer matrix and incorporated drugs, hypersensitivity reactions, leading to destabilization of the plaque with consequent inflammation and thrombosis [4,5].

We report a case of acute myocardial infarction, due to late stent thrombosis of BMS following an urticaria, after exposure to amoxicillin.

A 48-year-old male was referred to our hospital by his general practitioner for an acute inferior myocardial infarction. He had a family history of coronary heart disease and was a heavy smoker. As a child, he was suffered from poliomyelitis, followed by placid paralysis and later by atrophy of the muscles of the right inferior limb. During the last two years he was also hypertensive.

The patient was submitted to coronary angiography which showed a subcritical stenosis of left main, a total occlusion of left anterior descending (LAD) and a distal 90% stenosis of right coronary artery (RCA). After an ineffective attempt of PTCA on LAD, the patient underwent heart surgery performing a coronary bypass on first diagonal (D1) and LAD (left anterior mammary artery sequential) and

on the postero-lateral (PL) ramous of RCA (gastroepiploic artery) without heart-lung machine.

The following year, for reappearance of effort angina, he was again submitted to coronarography which showed a patency of the graft on D1 and LAD, occlusion of PL and a 90% stenosis of distal RCA. This last was treated with implantation of a BMS Coroflex® Delta 3 × 16 mm. The patient was discharged under treatment with simvastatin, aspirin, transdermal nitrates, atenolol and clopidogrel which was discontinued after one month.

After 4 years was readmitted for relapse of NSTEMI, with a peak CK-MB 9.7 ng/ml (normal values <6.6). A BMS (3 × 16 Coroflex® Blue, cobalt chromium) was implanted for an 80–90% stenosis of mid RCA (Fig. 1). The old stent on distal RCA was patent without intrastent stenosis. Clopidogrel was withdrawn after one month.

After 4 months he complained pharyngitis and was treated by general practitioner with amoxicillin (2 g/day). The third day of antibiotic therapy he experienced an urticarial rash on his face, trunk and limbs accompanied by intense itching. An emergency physician administered 20 mg of methylprednisolone IV bolus, but 8 h later the patient felt unwell and was admitted to our hospital for chest pain and intense diaphoresis.

The blood pressure level was 150/80 mmHg, pulse rate was 90/min and regular; findings on cardiovascular, and respiratory examination were normal. The ECG showed elevation of ST segment in inferior leads, and the echocardiogram revealed an akinesis of the inferior, distal postero-lateral wall and distal inferior septum, with EF 40%. A diagnosis of STEMI was made and the patient was immediately transferred to another hospital for primary PCI.

The angiography showed an intrastent stenosis (80%) of mid RCA, followed by a total thrombotic occlusion of the stent implanted four years before, on the distal RCA (Fig. 2, panel A). The graft on D1, LAD was still patent. Therefore the patient underwent implantation of paclitaxel stent (3.0 × 16 mm) in mid and BMS (Vision® cobalt chromium 3.0 × 12 mm) in distal position with good angiographic results (Fig. 2, panel B). Clopidogrel 300 mg loading dose given during the procedure, together with abciximab (19 ml/h for 12 h), was followed by 75 mg daily.

Going out of the cath lab the patient complained relapsing of cutaneous urticarial rash treated with 40 mg of methylprednisolone IV bolus and promethazine 50 mg, (intramuscular injection), followed by oral antihistamines (loratidine). The peak of CK-MB was 23.6 ng/ml and of troponin I was 3.7 ng/ml (normal values <0.04 ng/ml). There was also mild eosinophilia (5.3%, n.v. <5.0%), absent when the patient arrived in our hospital, an increase of C-reactive protein (10.8 mg/dl n.v. <5.0) and increased IgE levels (1000 U.I./ml, normal values <100) while the others

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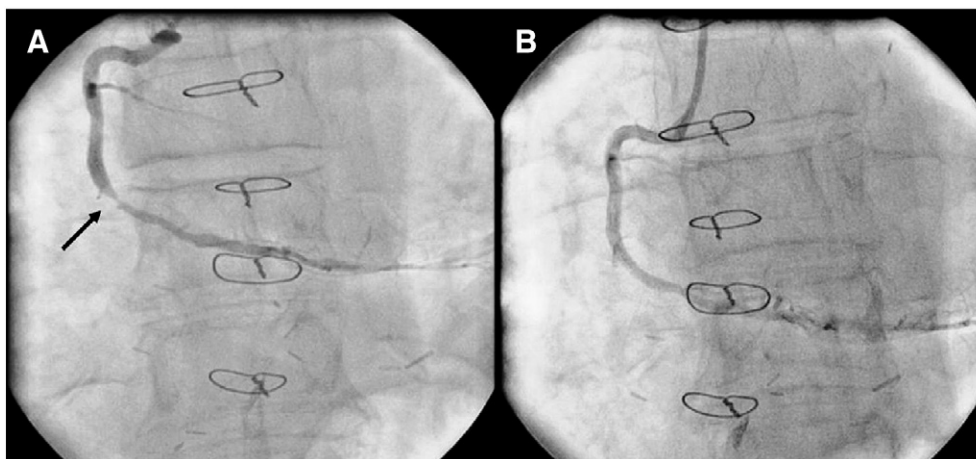


Fig. 1. A. Coronary angiography of RCA showing critical stenosis in the middle tract. B. After implantation of 3 × 16 mm Coroflex® Blue, cobalt chromium stent.

classes of immunoglobulin were normal. The level of sE-selectin was low (21.0 ng/ml, n.v. 29.1–63.4).

The patient was treated with simvastatin, aspirin, atenolol, nitrates and clopidogrel, which was discontinued after one year; loratidine was interrupted 5 days after the hospital discharge. At 30-month follow-up the patient had not any recurrence of acute coronary syndrome.

KS is mainly classified in two variants depending on the pathophysiologic mechanism: vasospasm and atheroma erosion or rupture with consequent thrombosis [3]. Type I (*coronary spasm*) occurs in patients with normal coronaries and represents a manifestation of endothelial dysfunction, and Type II (*coronary thrombosis*) usually in patient with quiescent atherosclerosis. In the second eventuality, the allergic reaction acts as trigger of the thrombosis through the plaque erosion. We would like to propose, herewith, a type III variant (*stent thrombosis*) which would include patients with stent thrombosis in whom thrombus aspiration and hematoxylin-eosin and Giemsa staining reveals the presence of eosinophils and mast cells respectively in the pathology specimens.

Mediators of allergy are released from mast cells. These infiltrate the adventitia of coronary vessels of patients with acute coronary syndromes (ACS), not only in the site of culprit lesion, but also in others plaque prone to rupture [6]. During anaphylactic degranulation, mast cells release several pro-thrombotic and vasoconstrictors

mediators [1,7] such as histamine, neutral proteases (tryptase and chymase), platelet activating factor, prostaglandins and leukotrienes.

Although association previous PCI and KS has been already reported [8,9], this is the first description of the syndrome, induced by an urticaria, due to a very late stent thrombosis. The culprit lesion was the thrombosis of BMS previously implanted. Cellular adhesion molecules such as sE-selectin are a specific product of endothelial cells and are surrogate markers for endothelial damage. The low serum level of sE-selectin means that an endothelial dysfunction (KS Type I) was not implicated in the stent thrombosis of our patient.

The clinical presentation, four years after the procedure, excluded concomitant pro-thrombotic state post PCI. Clopidogrel was withdrawn three months before. Moreover an analogous suspension, immediately after the implant of the stent was not associated to adverse events. Therefore, inadequate therapy cannot be incriminated as pro-thrombotic factor.

The hypersensitivity played a more important role, as indicated by increase of CRP, eosinophilia and by the high IgE levels activating mast cells in order to release the content of their granules [3]. A systemic hypersensitivity reaction seems able to trigger a local chronic, stent-related, allergic inflammation activating the patient inflammatory cell burdens above the level in which smooth muscle contraction and plaque erosion or rupture might occur, inducing thrombosis [10]. The clinical manifestation depends on the local

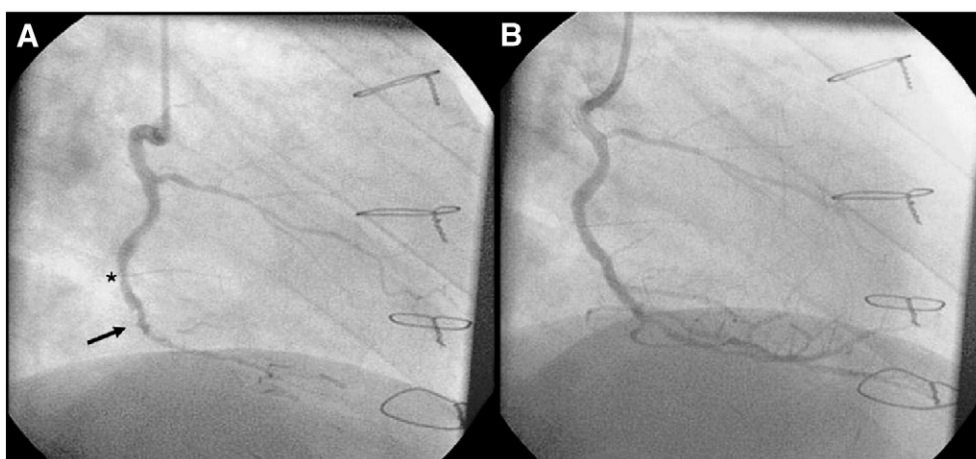


Fig. 2. A. RCA: * intrastent stenosis in the middle tract (asterisk) and occlusion (arrow) as from pre-stent thrombosis in the distal tract. B. After implantation of Taxus® 3 × 16 mm (mid RCA) and Vision® 3 × 12 mm (distal RCA).

concentration of allergens, the inflammatory infiltrates and systemic allergic reaction from different allergens.

It is well known [4], that DES implantation can be followed by systemic and intrastent hypersensitivity reactions. Systemic reactions including rash, itching, hives, dyspnoea, thrombocytopenia, fever, arthralgia and anaphylaxis and often are misinterpreted as related to concomitant drugs. Intrastent reactions can induce coronary spasm, plaque rupture with late thrombosis and death.

Nevertheless, stent-related granulation tissue with eosinophil infiltration was reported in a patient positive for allergic patch-test reactions to the BMS components nickel and molybdenum [11]. These histological findings are similar of those reported in DES thrombosis related to hypersensitivity, showing infiltrates of neutrophils and eosinophils and poor intimal healing [4,12].

The allergenic burden of DES (metal strut, polymer and impregnated drug) is greater, but when allergic reaction is triggered, in either type of stent, it has similar histological and clinical manifestations.

Coroflex® Delta stent, is made from stainless steel 316L which contains nickel, molybdenum and chromium. Blood, saline and mechanical stress can elute metal ions after the stent deposition, starting the hypersensitivity reaction. Adverse reactions have occurred in patients, with implanted intracardiac metal devices and allergy to nickel can be manifested as coronary or cerebrovascular thromboembolism, chest pain, atrial fibrillation, pericardial effusion [13], and signs and symptoms typical for KS. Allergy to nickel occurs in 17.2% of the population and is the most frequent cause of allergic contact dermatitis [14]. Anions eluted from other metals (cobalt, chromium, titanium, and molybdenum) can be also allergic sensitizers.

The use of BMS reduces, but doesn't eliminate the possibility of hypersensitivity reactions resulting in serious clinical consequences, as very late thrombosis. Is important to take a careful history in order to avoid implantation of DES in atopic patient (where BMS are of first choice). When the device is essential skin tests to stent components is mandatory as well as desensitization strategies [15]. Moreover use of corticosteroid and mast cell stabilizers in patients with intracardiac metal devices and concomitant overt allergic reaction could be useful.

Implantation of biodegradable stents, (ecological stents expelled as carbon dioxide in breathing and water in urine), reduce allergenic burden and seem promising.

In conclusion the KS is not a rare clinical entity and must be suspected and excluded when treating allergic reactions associated

with acute coronary syndromes, especially in patients with previous stent implantation.

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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 [16].

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