



Letter to the Editor

Kounis syndrome: A manifestation of drug-eluting stent thrombosis associated with allergic reaction to contrast material

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Abstract

Stent components acting as potential antigens and promoting intracoronary mast cell activation can lead to catastrophic intrastent thrombosis. Patients with drug-eluting stent (DES) implantation are prone to hypersensitivity reactions from five potential antigens namely, nickel strut, polymer coating, eluted drug, as well as, concomitant drugs clopidogrel and aspirin. These events may be more common than suspected because it is hard to document them, unless they become systemic, in which case they manifest themselves as the Kounis syndrome characterized by the concurrence of acute coronary events with hypersensitivity reactions. This report concerns of a patient with implanted DES who developed an acute myocardial infarction in the stent area following an allergic reaction to contrast material.

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1. Introduction

Acute myocardial infarction following stent implantation is an emerging serious clinical problem in patients treated with DES [1]. Recent data have shown that a small but increasing number of patients, with implanted DES, may develop simultaneous, multivessel, repeated, remote and peripheral arterial thrombosis [2]. Clinical and pathology findings point towards a possible hypersensitivity reaction to DES components manifesting as Kounis syndrome [3]. Current DES components include the metal stent itself which is made from 316L stainless steel containing nickel, chromium, molybdenum, the polymer coating, and the impregnated drugs which for today are: the

antimicrotubule, antineoplastic agent paclitaxel and the anti-inflammatory, immunosuppressive and antiproliferative agent rapamycin. For Endeavor zotarolimus-eluting stent which is a newly synthesized sirolimus analogue and received FDA approval recently long results and side effects from its use have not been established [4]. Other agents such as everolimus, biolimus, tacrolimus pimecrolimus etc. are currently undergoing safety and efficacy trials either impregnated in metal stents or used in transplant recipients in order to prevent rejection. All these agents either separately or synergistically seem to be able to induce hypersensitivity reactions and hypersensitivity coronary events [4]. Additionally, patients we implanted stents, receive clopidogrel and aspirin, two well known antigenic substances, as antiplatelet agents.

We report a patient who developed acute myocardial infarction, in the stented coronary area, following allergic reaction to an additional antigenic agent (a non-anionic contrast material) during radiographic examination.

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2. Case report

A 48-year-old heavy smoker man was referred for investigation for recurrent renal colic and low back pain. During his admission routine laboratory investigation revealed no abnormality and he was scheduled for abdominal contrast-enhanced CT-scan and intravenous urography. The patient did not recall any previous history of drug allergy, rhinitis, eczema, dermatitis, bronchial asthma and diabetes mellitus.

However, six months previously he had been admitted to another hospital for an acute anterior myocardial infarction. Coronary angiography, at that time, had shown 60% narrowing of the anterior descending coronary artery, and 90% narrowing of the circumflex coronary artery for which successful coronary angioplasty with a CYPHER (Cordis Corp.) stent implantation had been performed. The patient's current medication included clopidogrel 75 mg daily and aspirin 325 mg daily.

The patient was transferred to the radiology department where an infusion 50 mL of non-anionic contrast material Iopromide (Ultravist, Scepta, Inc.) was started for the procedure of the intravenous excretory urography.

The procedure was uneventful, but 10 min later the patient felt unwell, became pale, weak and dizzy, started sweating with retrosternal discomfort. He also started complaining for pain and numbness in both arms with

generalized itching. His pulse was 100 beats/min regular and the blood pressure was 110/80 mm Hg. He was given intravenously 500 mg of hydrocortisone sodium succinate, 30 mg of diphenhydramine and 50 mg ranitidine and was transferred to the cardiology department. An electrocardiogram performed there (Fig. 1 Panel A) showed slightly elevated ST segment in I, AVL and acute T waves in the precordial leads compatible with acute anterior myocardial infarction involving the target-vessel territory in view of the previous stent implantation in the circumflex artery. Pulse oximetry showed an oxygen saturation (SpO₂) of 85%. The patient was given a further dose of 500 mg of hydrocortisone sodium succinate and was treated with bolus heparin 5000 IU with maintenance dose of 1000 IU/h and nitroglycerin infusion 40 µg/min. Blood was taken for cardiac enzymes, troponins, histamine, tryptase, immunoglobulins, complement proteins C₃ and C₄ and blood count estimation.

The following 4 h the patient's symptoms started to subside and the new electrocardiogram (Fig. 1 Panel B) showed T-wave inversion in I, AVL and left precordial leads. The results of blood tests showed increased troponin I with peak of 11.39 ng/ml (normal value 0.00–0.15 ng/ml) and increased cardiac enzymes thus confirming the diagnosis of an acute myocardial infarction. Serum tryptase was 30 µg/L (normal value 5.6–13.5 µg/L) suggesting an allergic reaction. Subsequent daily serum tryptase estimations were

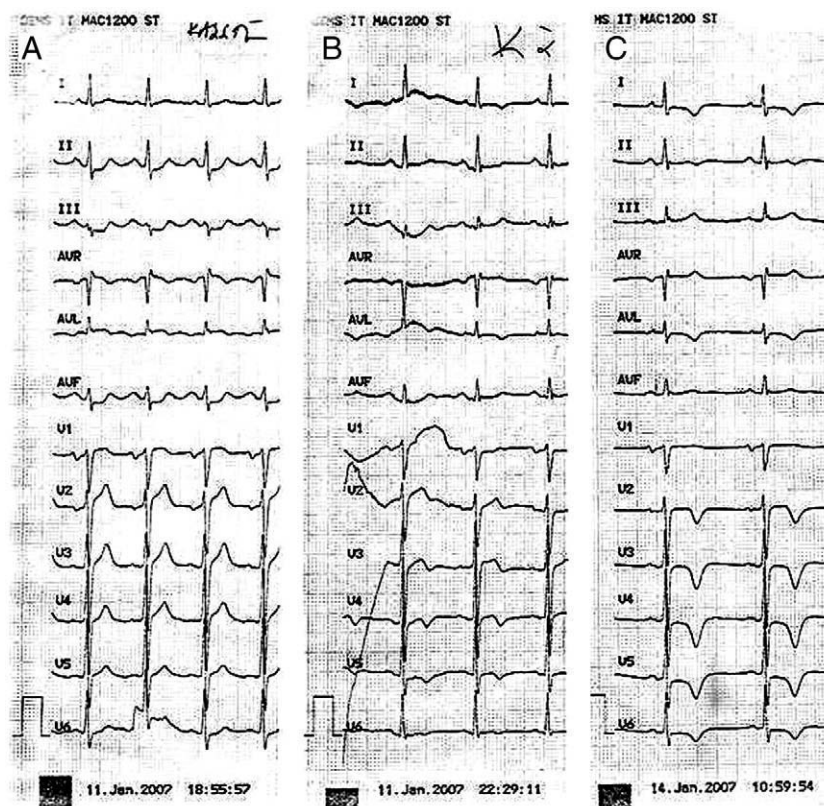


Fig. 1. Sequential electrocardiographic changes in the stented area following allergic reaction to contrast material.

within normal limits. Blood histamine and complement proteins were normal. Subsequent electrocardiograms (Fig. 1 Panel C) showed giant T-wave inversion in the left precordial leads.

Cardiac catheterization in the University Hospital revealed a significant circumflex coronary artery intrastent stenosis with apical aneurysmal formation. Percutaneous transluminal coronary angioplasty was performed with successful stent implantation.

3. Discussion

Patients undergoing DES implantation receive five different substances which can act as potential antigens. These substances include the nickel strut, the polymer, the eluted drug, plus aspirin and clopidogrel. Hypersensitivity inflammation is initiated by antigens cross-bridging their corresponding, receptor-bound, immunoglobulin IgE antibodies on the mast cell or basophile cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2000 out of maximal number of some 500 000–1,000 000 IgE antibodies of the cell surface [5]. It might be possible to accumulate the critical number of bridges by more than one, non-cross-reactive antigen and its corresponding IgE antibody [5]. Clinical studies indicate that sensitized patients simultaneously exposed to several antigens have more symptoms than mono-sensitized individuals [6]. A recent study showed that IgE antibodies with different specificities can have an additive effect and even small amounts of corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them [7]. This data suggest that a possible sensitization to DES should not be clinically evaluated as a consequence of exposure to a single component but rather viewed as in the context of potential sensitization to multiple DES compounds.

The described patient received intravenously additional antigenic substance, a non-anionic iodinated contrast material, for the procedure of the excretory urography, thus making six potential antigenic substances into his body. Consequently, hypersensitivity reaction occurred and intracoronary mast cell degranulation took place into the stented coronary area resulting in Kounis syndrome. This syndrome is caused by mediators released from mast cell degranulation which can constrict the coronary arteries and promote plaque erosion and rupture [8–13].

Although the introduction of low-osmolar non-anionic contrast materials has diminished the side effects significantly to 2.1%, some symptoms still encountered and include fever, purpura, skin reactions, convulsions, dyspnea, renal damage, and hypersensitivity reactions including Kounis syndrome [3,14]. Non-ionic and dimeric contrast molecules bind to circulating proteins to a lesser extend than ionic and monomeric contrast molecules making them less toxic. However, several conditions and co-medication have been identified as risk factors for the occurrence of side effects

Table 1

Risk factors to iodinated contrast material

Conditions	Drugs
–Allergic disease	–Allergic, nephrotoxic, neuroleptic drugs
–Bronchial asthma	(metformine, NSAIDs, diuretics,
–Cardiovascular disease	aminoglycosides, vassopressors,
–Cerebrovascular disease	antidepressants, analeptics, MAO-inhibitors)
–Dehydration	–Drug addiction
–Diabetes mellitus	–Drug allergy
–Epilepsy	–High osmolar contrast material
–Homocysteinouria	–High dose contrast material (>100 ml)
–Hyperuricaemia	–Intra-arterial drug injection
–Hyperthyroidism	
–Liver disease (cirrhosis)	
–Multiple myeloma	
(Morbus Kahler)	
–Old age > 70 years	
–Pheochromocytoma	
–Renal disease	
–Sickle cell anemia	

of iodinated contrast materials (Table 1). In the described case, the patient had previous coronary artery disease and co-medication (five allergens). Physicians should be aware of these factors and side effects in order to take prophylactic measures such as sufficient hydration, pre-heating of the contrast fluid in order to reduce its viscosity and preference to low-osmolar material.

Myocardial infarction and stent thrombosis seems to be manifestation of Kounis syndrome especially in susceptible patients, and prophylactic and therapeutic measures should be undertaken and should include [2,3]: Careful history of adverse drug reactions and allergies, monitoring of inflammatory mediators after stent insertion, antibody and skin testing when and where appropriate, macrophage and T-cell activation studies, desensitization strategies, considering the use of mast cell stabilizers and steroids, measuring of acute phase reactants, peri-procedural anti-inflammatory therapy. New stents combining drugs with anti-inflammatory and anti-allergic properties that may also be disease modifying might be the solution of the problem.

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