



Letter to the Editor

Drug eluting stent-induced Kounis syndrome

Elio Venturini ^{a,*}, Lucia Magni ^a, Nicholas G. Kounis ^b^a Department of Cardiology, Civic Hospital Cecina, Italy^b Highest Institute of Education and Technology, Patras, Greece

Received 16 December 2008; accepted 22 December 2008

Abstract

Kounis syndrome is the concurrence of acute coronary syndromes with allergic conditions like anaphylaxis or anaphylactoid reactions. Cases of hypersensitivity to drugs-eluting-stent (DES) components able to cause serious clinical sequelae, like stent thrombosis have been reported recently. We report a case of a 50-year-old male, allergic to larvae of fly carvaria, who, after exposure to the allergen, developed an acute myocardial infarction due to stent thrombosis, despite optimal medical therapy. To our knowledge this is the first description of intra-stent thrombosis associated with Kounis syndrome. The clinical implications and physiopathology of this association are discussed.

© 2008 Elsevier Ireland Ltd. All rights reserved.

Keywords: Allergic myocardial infarction; Stent thrombosis; Kounis syndrome

1. Introduction

Kounis syndrome (KS) [1] is the concurrence of acute coronary syndrome with hypersensitivity and anaphylactic or anaphylactoid reactions. This syndrome was firstly described in 1991 [2], but only 1998 Braunwald [3] noted that vaso spastic angina can be induced by “allergic reactions with mediators such as histamine or leukotrienes”. Moreover, hypersensitivity reactions to components of DES which, via intracoronary mast cell activation, can induce destabilization of the plaque with consequent inflammation and thrombosis have been reported [4,5]. We report a case of acute myocardial infarction, due to stent thrombosis following an acute allergic reaction.

2. Case report

A 50-year-old male was referred by his general practitioner for chest pain which was started two hours before

presentation. He had a family history of coronary heart disease, hypercholesterolemia and diabetes; was also allergic to larvae of fly carvaria. During examination the pain had been resolved; the blood pressure level was 125/75 mmHg, pulse rate was 78/min and regular; findings on cardiovascular, respiratory, abdominal and neurological examination were normal. ECG and transthoracic echocardiography were normal while the peak of CK-MB was 8.1 ng/ml (<5 ng/ml) and of Troponin I was 0.42 ng/ml (<0.04 ng/ml). A diagnosis of NSTEMI was made. Because of the reappearance of chest pain, the patient was submitted to coronary angiography that showed a 75% stenosis of left anterior descending (LAD) and a 90% stenosis of first and second diagonal branches. Percutaneous coronary intervention (PCI) with implantation of two Cypher stents and one simple balloon angioplasty (for second diagonal), was successfully performed (Fig. 1). The patient was discharged in good general condition on aspirin, statin, bisoprolol and clopidogrel.

Eight months later, while he was on the above treatment, during fishing, he was stung with a hook baited with larva of fly carvaria. He started complaining of dizziness, dyspnoea, glossopharyngeal paraesthesia and was transferred to the emergency room of our hospital. On examination he had broncostenosis, uvula's and periorbital oedema, urticarioid

* Corresponding author. Via Brodolini 27/c, 57023 Cecina (Li) Italy. Tel.: +39 0586614210.

E-mail addresses: vent.elio@tin.it, e.venturini@nord.usl6.toscana.it (E. Venturini).

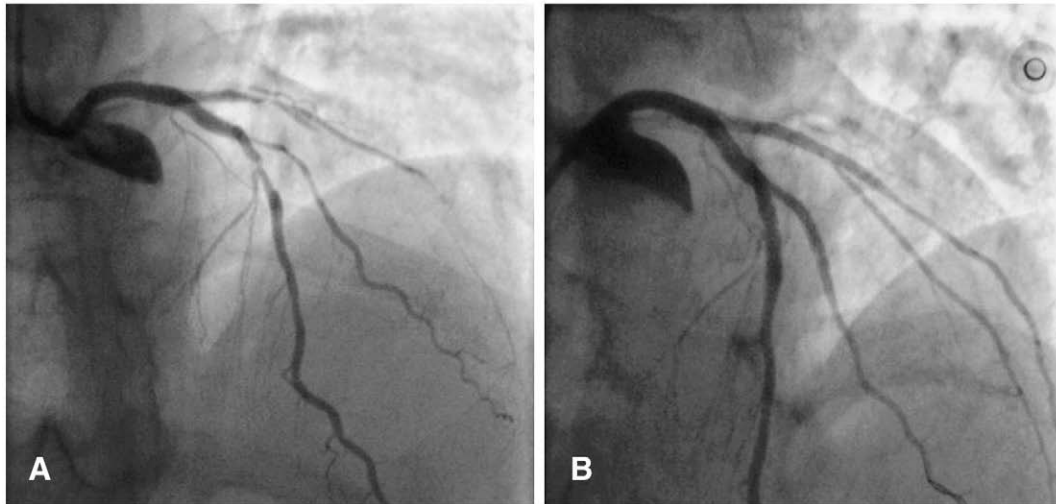


Fig. 1. A. Coronary angiography of left coronary artery showing critical stenosis of LAD in the middle tract and of diagonal branches. B. After implantation of two Cypher stents (2.75 × 23 mm for LAD; 2.25 × 23 mm for I diagonal) and balloon angioplasty.

rash on his trunk and limbs accompanied by intense itching; the blood pressure level was 115/70 mmHg, pulse rate 72/min, the oxygen saturation was 98% in room air. The ECG was normal. The patient was treated with corticosteroids i.v., antihistamines i.m. and adrenaline (0.5 mg in physiological solution 250 ml, at rate 42 ml/h).

After 30 min the patient experienced constrictive chest pain and the ECG showed elevation of ST segment in inferior and antero-lateral leads. The adrenaline was stopped. The echocardiogram revealed an akinesis of the mid septum and lateral, septal and anterior apex. After therapy with verapamil i.v. the ST elevation on inferior lead disappeared, but for the persistence of chest pain, ST elevation on the remaining leads, after treatment with heparin, morphine and lidocaine (for ventricular arrhythmia) the patient was sent for

a new angiogram. Awaiting the procedure the elevation of the ST increased. The coronarography showed an intra-stent thrombosis on LAD and second diagonal branches that were treated with balloon angioplasty (Fig. 2). The peak values of CK level was 4268 U/l (10–190 U/l), of CK-MB > 100 ng/ml and of Troponin I > 100 ng/ml; there was also an increase of leukocytes (17.090/ml) with eosinophilia. The echocardiogram revealed mild reduction of ventricular function (EF 47%) with akinesis of the apex. The patient was discharged under treatment with atorvastatin, aspirin, ramipril, bisoprolol and clopidogrel which was discontinued after one year.

At 18-month follow-up the patient had not any recurrence of acute coronary syndrome, but was admitted twice in our hospital (the first admission was 6 month later) for relapsing pericardial and pleural effusion due to viral infection.

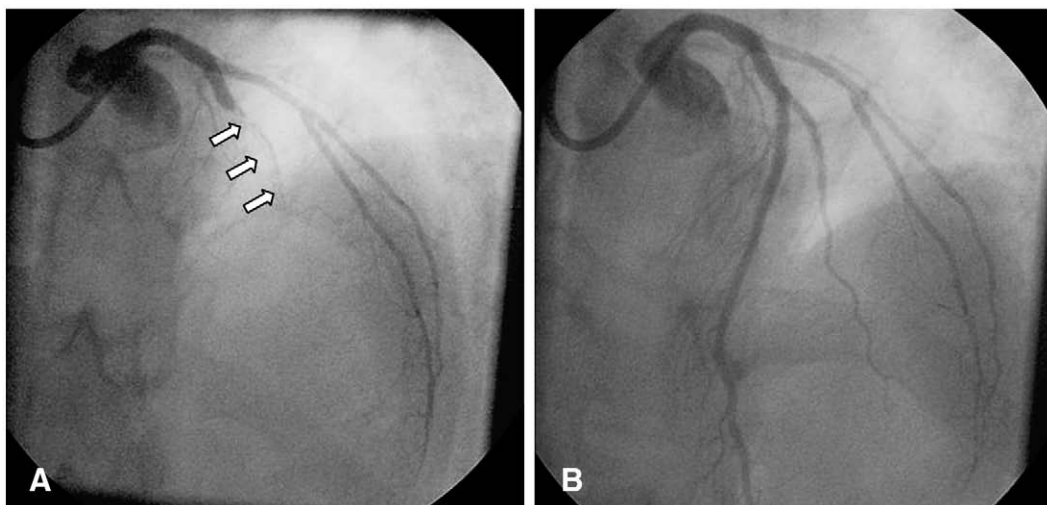


Fig. 2. A. LAD: Occlusion as from intrastent thrombosis B. After balloon angioplasty.

3. Discussion

KS [1] is the concurrence of acute coronary syndromes (ACS) with conditions associated with mast cells activation.

The main mechanisms are coronary artery spasm and/or atheroma erosion or rupture with consequent thrombosis. These are also at the base of the classification of KS in two variants [6]: Type I (*coronary spasm*) in patients with normal coronaries that represent a manifestation of endothelial dysfunction and Type II (*coronary thrombosis*) in patient with quiescent atherosclerosis. In the second eventuality, the allergic reaction acts as trigger of the thrombosis through the plaque erosion.

Mediators of allergy are released from mast cells; these infiltrate the adventitia of coronary vessels of patients ACS, not only in the site of culprit lesion, but also in others plaque prone to rupture [7]. During anaphylactic degranulation, mast cells release several pro-thrombotic and vasoconstrictors mediators [1,6,8]: histamine, neutral proteases (tryptase and chymase), platelet activating factor, prostaglandins and leukotrienes.

All these substances reach high blood levels also in patients with *spontaneous* ACS, that is the result of combined coronary spasm and plaque rupture followed by thrombosis.

There are several causes capable to induce the KS [1]. These include drugs (antibiotics, analgesic, NSAIDs), conditions (asthma, food allergy, urticaria) or environmental exposures (hymenoptera and others stings, shellfish eating, latex contact).

This is the first description of the syndrome by contact with carvaria's larvae. However, association previous PCI and KS has been described [9]. The cause of the ACS, in our patient, was intrastent thrombosis and not simple intrastent stenosis. The clinical presentation, 8 months after the procedure, (and not 4 days) excluded concomitant factors as inadequate level of antiplatelets therapy or pro-thrombotic state post PCI.

Adrenaline which is the standard treatment of anaphylaxis could be the cause of vasospasm-induced myocardial injury even at low-dose [10]. However, there are some differences: the effect begins soon (5–15' min) after the administration and not after 30' as in our patient. In all reported cases, there was not elevation of CK-MB, indicating little loss of myocardial cells and administration of vasodilator drugs induces quickly complete resolution of ST-changes in all leads (and not partial as in our case).

Therefore is unlikely that the ACS has been the consequence of the administration of epinephrine. The latter can be antagonized by verapamil and it is not able to provoke coronary thrombosis. The free interval between beginning of the allergic reaction and the onset of attack was probably due to the attainment of a threshold level of mast cell content that could induce coronary spasm and/or plaque rupture [1].

From the paper of Camenzind [11] the concern of thrombosis of DES is increased. Antiplatelet drug withdrawal is one of the causes, and may be the most important

especially for late thrombosis. Our patient was still in treatment, both with the clopidogrel and with the aspirin, therefore inadequate therapy cannot be incriminated as pro-thrombotic factor.

Instead, the coincidence between allergic reaction and intraluminal thrombus could be due, at least partly, to hypersensitivity to DES. All the components of the stent (nickel strut, polymer and impregnated drug) can induce allergy either separately or synergistically [12]. The use of bare metal stent (BMS) is not associated with allergic reactions. Nebeker et al. [4] conclude that "that DES may be a cause of systemic and intrastent hypersensitivity reactions that, in some cases, have been associated with late thrombosis and death". Systemic reactions including rash, itching, hives, dyspnoea, thrombocytopenia, fever, arthralgia and anaphylaxis often can be related to concomitant therapies like thienopyridines.

When the stent itself appears to be the most probable cause of hypersensitivity, the histological examination in patients died for stent thrombosis demonstrated eosinophilic infiltrates and poor intimal healing [4]; moreover in a brief report of late thrombosis with AMI and occlusion of LAD artery sirolimus-stent, a section of extracted thrombus demonstrated an infiltrate of neutrophils and eosinophils as an allergic hypersensitivity reaction induce by DES polymer [13]. These findings are similar of those of KS and it is not amazing since in both cases an allergic reaction could be involved.

Unfortunately in our patient the thrombus was not submitted to histological evaluation; however, eosinophilia was present.

The KS induced by the contact with carvaria's larvae could have found a *locus minoris resistentiae* in the DES, where the hypersensitivity reaction was severe leading to thrombosis due to presence of inflammatory mediators caused by the DES components. This allowed the level of activated mast cells to reach the threshold able to induce device occlusion from thrombosis.

Therefore the KS is not a rare clinical entity and must be suspected and excluded while treating allergic reactions associated with ACS. The widespread use of DES can increase the possibility of hypersensitivity reactions after their implantation resulting in serious clinical consequences. Is important to take a careful history in order to avoid implantation of DES in atopic patient (where BMS are of first choice). However, when DES are indicated skin tests to DES components and desensitization strategies should be performed [12]. Further studies using corticosteroids and mast cell stabilizers in patients with DES implantation and concomitant overt allergic reaction seem to be necessary.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [14].

References

- [1] Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
- [2] Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991;45:121–8.
- [3] Braunwald E. Unstable angina. An etiologic approach to management. *Circulation* 1998;98:2219–22.
- [4] Nebeker JR, Virmani R, Bennet CL, et al. Hypersensitivity cases associated with drug eluting stent. A review of available cases from the research on adverse drug events and reports (RADAR) project. *J Am Coll Cardiol* 2006;47:175–81.
- [5] Kounis NG, Hahalis G, Theoharides T. Coronary stents, hypersensitivity reactions and the Kounis syndrome. *J Interv Cardiol* 2007;20:314–23.
- [6] Nikolaidis LA, Kounis NG, Grandman AH. Allergic angina and allergic myocardial infarction: a new twist on an old syndrome. *Can J Cardiol* 2002;18:508–11.
- [7] Kaartinen M, Penttilä A, Kovanen PT. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the prediction site of atheromatous. *Circulation* 1994;90:1669–78.
- [8] Kounis NG, Grapsas ND, Goudevenos JA. Unstable angina allergic angina and allergic myocardial infarction. *Circulation* 1999;100:e156.
- [9] Patanè S, Marte F, Di Bella G, Chiofalo S, Currò A, Coglitore S. Acute myocardial infarction and Kounis syndrome. *Int J Cardiol* 2008, doi:10.1016/j.ijcard.2007.12.075.
- [10] Shaver KJ, Adams C, Weiss SJ. Acute myocardial infarction after administration of low-dose intravenous epinephrine for anaphylaxis. *Can J Emerg* 2006;8(4):289–94.
- [11] Camenzind E, Steng PG, Wijins A. A meta-analysis of first generation drug eluting stent programs. Presented at Hotline session I, World Congress of Cardiology 2006, Barcelona September 2–5; 2006. (Abstract).
- [12] Kounis NG, Kounis GN, Kounis SN, Soufras GD, Niarchos C, Mazakaris A. Allergic reactions following implantation of drug-eluting stents: a manifestation of Kounis syndrome? *J Am Coll Cardiol* 2006;48:592–3.
- [13] Barlis P, Virmani R, Sheppard MN, Tanigawa J, Di Mario C. Angiographic and histological assessment of successfully treated late acute stent thrombosis secondary to a sirolimus-eluting stent. *Eur Heart J* 2007;28:1675.
- [14] Coats AJ. Ethical authorship and publishing. *Int J Cardiol* 2009;131:149–50.