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Editorial

Coronary stent thrombosis: Beware of an allergic reaction and of Kounis syndrome

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During their everyday practice, physicians are encountering some unexpected, peculiar, bizarre, strange, surprising, extraordinary and astonishing events that need quick explanation and emergency treatment. According to these events, patients with coronary stent implantation who accidentally developed an allergic reaction elsewhere in the human body from various causes developed, contemporarily, the much feared intrastent thrombosis. For example, acute myocardial infarction, in the stented area, has coincided with allergic reaction following intravenous administration of the non-anionic contrast material iopromide during a routine excretory urography.[1] Stent thrombosis has been associated with allergic symptoms such as glottis edema, cold sweat, and tongue enlargement following a flavonate-propyphenazone administration a week after stent implantation.[2] Intrastent thromboses have also been reported following insect and larvae sting-induced allergic reactions.[3] Late drug eluting stent thrombosis defined as type III variant of Kounis syndrome[4] has occurred following an allergic reaction to non steroidal anti-inflammatory agent acemetacine.[5] The astonishing event is that even an allergic reaction to clopidogrel,[6] the drug that is given to prevent stent thrombosis, itself has induced stent thrombosis! An additional report published in *Indian Heart Journal*[7] was referred to a 60-year-old male patient with stent implantation for critical left anterior descending coronary artery stenosis who developed stent thrombosis following a snake bite. This patient was thrombolysed and his coronary angiogram, 5 days later, revealed patent stent with TIMI III flow and no evidence of thrombus.

All above reports were concerning patients who were receiving multiple medications, known to induce allergic reactions, following stent implantation. Therefore, one can assume that stents, like magnet, attract inflammatory cells and constitute the area of possible mast cell and platelet activation.

1. Snake bites and IgE-mediated hypersensitivity reactions

The described patient[7] developed severe central chest pain and hypotension few hours after he was bitten by snake. His electrocardiogram showed ST segment elevation in the anterior chest leads with echocardiographic wall motion abnormalities in the area of stent implantation. Administration of inotropes and volume expansion did not improve symptoms and the patient was successfully treated with thrombolysis. This case raises some important questions concerning the etiology of snake bite-associated stent thrombosis, the inadequacy of inotropes and volume expansion, the cause of snake bite-induced myocardial injury and the preference of the myocardial event to that particular stented territory. Although the exact mechanism of snake bite-induced myocardial injury still remains unclear, direct cardiotoxicity, hypercoagulability, toxic myocarditis from envenomation, vasospasm from panic and sarafotoxin and hypovolemia have been suggested as possible causes. However, in this case with stent implantation, IgE-mediated allergic reaction seems possible. The venom of snakes contains a mixture of proteins such as amino acids, toxic peptides, metalloproteins, proteolytic enzymes, peptide hydrolases, phospholipase A2, hyaluronidase and phosphodiesterase. All these ingredients either themselves or as haptens attached to serum proteins can induce allergic or anaphylactic reactions. Indeed allergic or

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anaphylactic symptoms such as hypotension, shock, urticaria, localized angioedema and asthma have been reported and have been attributed to mast cell mediators including histamine.[8] Several reports associate snake bites with allergic or anaphylactic reactions[9–14] and Kounis syndrome.[15] In another study[16] seven of the eight patients with systemic snake bite reactions had both positive skin tests and snake venom-specific immunoglobulin E antibodies. Therefore, in the described patient, with stent implantation acting as antigenic complex inside the coronaries,[17] the development of stent thrombosis should be regarded as manifestation of Kounis syndrome.

2. Stent thrombosis: a hypersensitivity process

The bare metal stents have platform made of stainless steel, which contains nickel, chromium, titanium, manganese, and molybdenum, and the currently used drug eluting stents or second generation stents have platforms of cobalt-chromium and platinum-chromium that contain also nickel and other metals. Their polymer coating, eluted drugs, aspirin and thienopyridines which the stented patients are exposed to together with any inadvertent environmental exposure are acting all as strong antigenic complex able to induce an allergic reaction and stent thrombosis.[17] Stent thrombosis is the result of serial adhesion, activation and aggregation of platelets.[18] Platelet adhesion starts when shear forces induce extensions in platelet membrane (tethers) which bind transiently to the injured coronary intima in an "on and off and start and stop" fashion via interaction of the glucoprotein (GP) Ib receptor with Von Willebrand Factor (VWF). This process is called tethering and it is followed by platelet rolling which is the result of interaction between GP VI receptor and collagen.

Platelet activation takes place with stimulation of receptors for adenosine diphosphate, thromboxane, thrombin, serotonin, epinephrine and some less known receptors such as receptors for platelet activating factor, for histamine, for high affinity and low affinity IgE receptors known as FCεRI and FCεRII. During their activation platelets change shape from discoid to spiculated form and release granules which contain, proinflammatory, prothrombotic, adhesive and aggregatory mediators. Platelet aggregation is the result of binding of GP IIb/IIIa receptor with fibrinogen and interaction with VWF. Thrombin converts fibrinogen to fibrin which serves as a stable láttice for the creation of thrombus.

Therefore, receptors for hypersensitivity mediators are also participating in platelet activation and these mediators are derived from the allergic unit of eosinophils and mast cells.[19] This can explain why patients, as the described one, can develop stent thrombosis during an allergic episode.

3. Inadequacy of inotropes and volume expansion to treat severe anaphylaxis

Experimental studies with ovalbumin-sensitized guinea pigs[20] have shown that soon after antigen administration, electrocardiogram shows signs of acute myocardial ischemia, cardiac output is decreased by 90%, left ventricular end-diastolic pressure rises indicating pump failure and arterial blood pressure increases. Blood pressure starts declining steadily after 4 min. The authors of these experiments have concluded that the rapid increase in left ventricular end-diastolic pressure suggests that volume loss due to an increase in vascular permeability and decreased venous return were unlikely to have been the primary causes of the documented depression in cardiac output. The view that the registered anaphylactic cardiac damage might be due to peripheral vasodilatation should be definitively excluded.[20] Similar findings have been reported by other authors.[21,22] Furthermore, other experiments have shown that severe impairment of the cerebral blood flow takes place during anaphylactic shock which could not be explained by the level of arterial hypotension and this was attributed to early and direct action of anaphylactic mediators on cerebral vessels. In the clinical setting, there are reports of patients with anaphylactic cardiac shock who do not respond to intravenous fluid administration and antiallergic therapy but require treatment for acute coronary event.[23] In some patients, the administration of inotropes worsened hypotension and eliminated cardiac output!.[24] This shows that in hypersensitivity, allergy and anaphylaxis the heart and especially the coronary arteries are the primary target and physicians should focused their attention on this matter.

The same had occurred in the patient described in this Journal in whom inotropes and blood expansion did not improve his clinical symptoms, hemodynamics and electrocardiographic changes but he needed thrombolysis and myocardial infarction therapy.

4. Conclusion

Despite that life saving coronary stent implantation has become the most frequently performed therapeutic procedure in medicine,[25] stented patients, are occasionally facing problems during their everyday life. These patients are exposed to foreign substances inserted and being in direct touch with the coronary intima. The most feared complication of stent insertion is stent thrombosis with death rate up to 40%. Although stent thrombosis is regarded as multifactorial complication, procedural, clinical and angiographic variables have been incriminated. Hypersensitivity to stent components and to drugs the patients are taking after stent insertion together with any environmental exposure seem to be some of the main causes of stent thrombosis. Such exposures include any allergy reactions, atopic diathesis and drugs. Venoms from all the major snake families have been implicated in the causation of allergic reactions.[10] Stent manufacturing companies have already taken protective and defensive means by issuing official warnings and detailed information, emphasizing the indications and contraindications for stent implantation. Physicians should read and notice, before stent implantation, warnings of manufactures' information sheets enclosed in the commercial stent packages of new generation stents.[26]

REFERENCES

1. Kogias JS, Papadakis EX, Tsatiris CG, et al. Kounis syndrome: a manifestation of drug-eluting stent thrombosis associated with allergic reaction to contrast material. *Int J Cardiol*. 2010;139:206–209.
2. Patanè S, Marte F, Di Bella G, Chiofalo S, Currò A, Coglitore S. Acute myocardial infarction and Kounis syndrome. *Int J Cardiol*. 2009;134:e45–e46.
3. Greif M, Pohl T, Oversohl N, Reithmann C, Steinbeck G, Becker A. Acute stent thrombosis in a sirolimus eluting stent after wasp sting causing acute myocardial infarction: a case report. *Cases J*. 2009;2:7800.
4. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. *Clin Ther*. 2013;35:563–571.
5. Akyel A, Murat SN, Cay S, Kurtul A, Ocek AH, Cankurt T. Late drug eluting stent thrombosis due to acemetacine: type III Kounis syndrome: Kounis syndrome due to acemetacine. *Int J Cardiol*. 2012;155:461–462.
6. Karabay CY, Can MM, Tanboğa IH, Ahmet G, Bitigen A, Serebruany V. Recurrent acute stent thrombosis due to allergic reaction secondary to clopidogrel therapy. *Am J Ther*. 2011;18:e119–e122.
7. Satish R, Kanchan R, Yashawant R, Ashish D, Kedar R. Acute MI in a stented patient following snake bite-possibility of stent thrombosis – a case report. *Indian Heart J*. 2013;65:327–330.
8. Persson H. Clinical toxicology of snakebite in Europe. In: Meier J, Julian White, eds. *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Boca Raton, FL: CRC Press Inc.; 1995:413–432.
9. Schmutz J, Stahel E. Anaphylactoid reactions to snakebite. *Lancet*. 1985;2:1306.
10. Wadee AA, Rabson AR. Development of specific IgE antibodies after repeated exposure to snake venom. *J Allergy Clin Immunol*. 1987;80:695–698.
11. Kopp P, Dahinden CA, Müllner G. Allergic reaction to snake venom after repeated bites of *Vipera aspis*. *Clin Exp Allergy*. 1993;23:231–232.
12. Prescott RA, Potter PC. Hypersensitivity to airborne spitting cobra snake venom. *Ann Allergy Asthma Immunol*. 2005;94:600–603.
13. de Medeiros CR, Barbaro KC, Lira MS, et al. Predictors of *Bothrops jararaca* venom allergy in snake handlers and snake venom handlers. *Toxicon*. 2008;51:672–680.
14. Forbes T, O'Donnell R. Anaphylactoid reaction to facial adder bite. *Arch Dis Child*. 2011;96:822.
15. Frangides C, Kouni S, Niarchos C, Koutsojannis C. Hypersensitivity and Kounis syndrome due to a viper bite. *Eur J Intern Med*. 2006;17:215–216.
16. Reimers AR, Weber M, Müller UR. Are anaphylactic reactions to snake bites immunoglobulin E-mediated? *Clin Exp Allergy*. 2000;30:276–282.
17. Kounis NG, Mazarakis A, Tsigkas G, Giannopoulos S, Goudevenos J. Kounis syndrome: a new twist on an old disease. *Future Cardiol*. 2011;7:805–824.
18. Mehta SR, Yusuf S. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. *J Am Coll Cardiol*. 2003;41:79S–88S.
19. Minai-Fleminger Y, Levi-Schaffer F. Mast cells and eosinophils: the two key effector cells in allergic inflammation. *Inflamm Res*. 2009;58:631–638.
20. Felix SB, Baumann G, Berdel WE. Systemic anaphylaxis separation of cardiac reactions from respiratory and peripheral vascular events. *Res Exp Med*. 1990;190:239–252.
21. Tosaki A, Koltai M, Braquet P, Szekeres L. Possible involvement of platelet activating factor in anaphylaxis of passively sensitised, isolated guinea pig hearts. *Cardiovasc Res*. 1989;23:715–722.
22. Zavecz JH, Levi R. Separation of primary and secondary cardiovascular events in systemic anaphylaxis. *Circ Res*. 1977;40:15–19.
23. Davidson J, Zheng F, Tajima K, et al. Anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension. *Shock*. 2012;38:429–435.
24. Shah G, Scadding G, Nguyen-Lu N, et al. Peri-operative cardiac arrest with ST elevation secondary to gelofusin anaphylaxis – Kounis syndrome in the anaesthetic room. *Int J Cardiol*. 2013;164:e22–e26.
25. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med*. 2012;366:54–63.
26. Kounis NG. Drug-eluting coronary-artery stents. *N Engl J Med*. 2013;368:1558.