Editorial

http://dx.doi.org/10.4070/kcj.2013.43.4.221
Print ISSN 1738-5520 • On-line ISSN 1738-5555

kcj
Korean Circulation Journal

Acute Stent Thrombosis and Heparin Induced Thrombocytopenia: Another Manifestation of Kounis Syndrome?

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Stent thrombosis is regarded today as a multifactorial life threatening condition. Immunological evidence incriminating antigens, such as stent nickel, metal strut, polymer coating and eluted drugs, accompanying the necessary treatment with aspirin and clopidogrel, combined with environmental exposures seems to constitute the most important factor.[1] There are some bizarre, astonishing, peculiar and strange reports according to which patients who developed an inflammatory reaction somewhere else in the human body develop stent thrombosis simultaneously. For example, hypersensitivity reactions to propyphenazone, contrast materials, larvae and insect stings, acemetacine and even clopidogrel were accompanied with thrombosis inside the stent.[2]

In a very important report published in the Korean Circ J,[3] a new antigen, which is more dangerous than the previous ones, seems to exist for the development of stent thrombosis; the 3-component immune complex composed of platelet factor 4 (PF4), heparin and IgG, which serves as the primary antigen able to activate platelets via the Fc receptor (FcγRII) and induce thrombosis. The result of this cascade of events manifests as heparin induced thrombocytopenia (HIT). Kounis syndrome also involves the high affinity and low affinity IgE receptors (FcεRI and FcεRII) situated on the platelet surface, which contribute to platelet activation and aggregation culminating to the development of arterial thrombosis.[4]

The described female patient developed an acute myocardial infarction due to total occlusion of the right coronary and was given aspirin clopidogrel and unfractionated heparin (UFH). Her right coronary artery was found totally occluded with abundant thrombus, and drug eluting stent was implanted with thrombus aspiration. However, despite repeated aspiration, the thrombus extended and progressed proximally to the stented area. She was finally diagnosed to have HIT due to proven new thrombosis and the timing of the onset of platelet fall to 4000/mm^3 in less than 1 day. She was treated successfully with argatroban.

Heparin is one of the oldest and most commonly used anticoagulant drugs; however, it can increase the risk of bleeding, particularly in critically ill patients. Paradoxically, while physicians are cautious for any bleeding side effect, heparins can induce unexpected serious thrombosis when they complicate with type II HIT, which is a severe, life-threatening reaction caused by the antibody to PF4-heparin-IgG complex. Type I HIT is a benign self-limiting non-immune condition which occurs in 10-30% of patients within 4 days after exposure to heparin. HIT affects approximately 5% of adult patients exposed to heparin. In children, the frequency is reported to be 2.3% to 3.7% with a 1% to 3% prevalence in children undergoing cardiac surgery with the use of UFH.[5]

Heparin was first discovered in 1916 by Jay McLean, who was a medical student at Johns Hopkins Medical School.[6] McLean, under the supervision of his professor William Howell, was in search of a coagulant to treat hemorrhage from accidents, war wounds and even childbirth, which, at that time, was a great killer, not for an anticoagulant. McLean's incidental discovery was an extract from a dog's liver, called hepar phosphatid. When he mixed it with a beaker of cat blood, the extract prevented clotting the cat blood for hours. Although heparin alone has very little effect on coagulation, in combination with antithrombin, which is a serine protease inhibitor, it enhances the rate of inhibition of procoagulant proteases, such as

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• The authors have no financial conflicts of interest.

factor Xa and factor IIa (thrombin).

Heparin induced thrombocytopenia is the result of antibody formation against heparin, leading to platelet activation and consequent thrombin production.[7] Following heparin exposure, PF4, which is a highly positive protein present in the a-granules of platelets, quickly binds and neutralizes the heparin. The PF4-heparin complex then serves as the primary antigen to create antibodies, normally of IgG class, which recognizes and binds to the exposed epitopes on PF4.[8] The 3-component antigen-antibody immune complex, composed of IgG, PF4 and heparin, activates the platelets via the Fc receptor (FcγRII) situated on a platelet surface. During activation, the platelets secrete pro-inflammatory (more PF4, platelet derived growth factor, CD154), pro thrombotic (factor V, factor XI, PAI-1), adhesive (thrombospondin, fibrinogen, p-selectin, von Willbrand factor) and chemotactic (ADP, ATP, serotonin, histamine, calcium, magnesium) mediators that propagate, amplify and sustain the thrombotic process.[2] Thrombocytopenia may also be explained by increased platelet consumption due to extensive thrombosis.[9] Furthermore, the 3-component antigen-antibody immune induces endothelial injury by binding to FcγRII receptors on monocytes, leading to tissue factor, thrombin production and promulgation.[7][8] It seems that thrombin generation plays an important role in the pathogenesis of stent thrombosis and thrombosis in general. Treatment of HIT with Argatroban, which is a direct thrombin inhibitor, was provided correctly and successfully by the authors.[3]

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