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Review

Eosinophilic responses to stent implantation and the risk of Kounis hypersensitivity associated coronary syndrome

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ABSTRACT

The use of drug eluting stents constitutes a major breakthrough in current interventional cardiology because it is more than halves the need of repeat interventions. It is incontrovertible that coronary stents, in general, have been beneficial for the vast majority of patients. A small increase in thrombosis, following DES implantation, is offset by a diminished risk of complications associated with repeat vascularization. However, late and, especially, very late stent thrombosis is a much feared complication because it is associated with myocardial infarction with increased mortality. Despite that stent thrombosis is thought to be multifactorial, so far clinical reports and reported pathology findings in patients died from coronary stent thrombosis as well as animal studies and experiments, point toward a hypersensitivity inflammation. The stented and thrombotic areas are infiltrated by interacting, via bidirectional stimuli inflammatory cells including eosinophils, macrophages, T-cells and mast cells. Stented regions constitute an ideal surrounding for endothelial damage and dysfunction, together with hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances.

Drug eluting stent components include the metal strut which contains nickel, chromium, manganese, titanium, molybdenum, the polymer coating and the impregnated drugs which for the first generation stents are: the antimicrotubule antineoplastic agent paclitaxel and the anti-inflammatory, immunosuppressive and antiproliferative agent sirolimus. The newer stents which are called cobalt–chromiun stents and elute the sirolimus analogs everolimus and zotarolimus both contain nickel and other metals. All these components constitute an antigenic complex inside the coronary arteries which apply chronic, continuous, repetitive and persistent inflammatory action capable to induced Kounis syndrome and stent thrombosis.

Allergic inflammation goes through three phases, the early phase, the late phase and the chronic phase and these three phases correspond temporally with early (acute and sub acute), late and very late stent thrombosis.

Bioabsorbable allergy free poly lactic acid self expanding stents, nickel free stainless steel materials, stent coverage with nitric oxide donors and antibodies with endothelial progenitor cell capturing abilities as well as stents eluting anti-inflammatory and anti-allergic agents might be the solution of this so feared and devastating stent complication.

1. Introduction

Randomized clinical trials have shown a 0.5% to 1% incidence of stent thrombosis yearly [1] for each drug eluting stent and its bare metal stent control, but drug eluting stents (DES) have become a major breakthrough in interventional cardiology because they have reduced, in more than half, the need for repeat intervention compared with bare metal stents (BMS) [2].

However, according to a recent registry from Germany [3] concerning 5842 patients undergoing percutaneous coronary intervention, 3.5% of these developed early and definite stent thrombosis (ST). Furthermore, in a very recent report from Israel [4], the rate of ST, in the real world, was 4.4% after 22 months (very late stent thrombosis) and the fatality rate 36% and the authors of this report commented that this rate was substantially higher than the rates reported in the previous clinical trials. Since it is not known whether very late stent thrombosis is a time limited phenomenon, the problem might increase, if events continue to accrue over time.

Despite that stent thrombosis is thought to be multifactorial, so far clinical reports and reported pathology findings in patients died from

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coronary stent thrombosis as well as animal studies and experiments, point towards a hypersensitivity inflammation. Stented regions constitute an ideal surrounding for endothelial damage and dysfunction, together with hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances. The stented and thrombotic areas are infiltrated by interacting, via bidirectional stimuli, inflammatory cells including [5] eosinophils, macrophages, T-cells and mast cells. Persistent fibrin deposition has been linked to poorer DES endothelialisation [6], while inflammatory cells, particularly eosinophils and mast cells represent an allergic hypersensitivity reaction induced by the DES components [7]. Interestingly, a higher concentration of eosinophils is found to infiltrate DES when compared with BMS [8].

Consequently, in an effort to search for causality, prevention and treatment of stent thrombosis we review the current status of eosinophilic activity following stent implantation, in association with the hypersensitivity coronary syndrome the so called Kounis syndrome [9].

2. The hypersensitivity coronary syndrome: Kounis syndrome

This syndrome, was described 20 years ago as allergic angina and allergic myocardial syndrome [10], and is defined today as the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults [9]. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet activating factor and a variety of cytokines and chemokines released during the activation process. A subset of platelets bearing FCεRI and FCεRII receptors are also involving in the activation cascade [11].

Three variants of Kounis syndrome have been described:

Type I variant [12] which includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins.

Type II variant [12] which includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction.

Type III variant [13] which includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin-eosin and Giemsa demonstrate the presence of eosinophils and mast cells respectively [14].

3. Evidence of hypersensitivity inflammation

3.1. Clinical reports

Recent reports have shown that eosinophilic cationic protein (ECP) which is highly basic, cytotoxic, heparin binding ribonuclease [15] exclusively secreted from eosinophils and constitutes a tool for monitoring hypersensitivity inflammation [16] is associated with the use of bare metal and drug eluting stents. Basal ECP levels are associated with major adverse cardiac events (MACEs) after BMS implantation [17] suggesting that hypersensitivity-mediated inflammation against the metal could explain adverse reactions associated with coronary stenting. Furthermore, pre-intervention ECP baseline serum levels can predict clinical outcomes such as sudden death, stent thrombosis and myocardial infarction following implantation of DES [18].

In a review of available cases from the research drug events and reports (RADAR) project, based on the Food and Drug Administration's manufacturer and user device experience (MAUDE), 262 patients developed hypersensitivity reactions while they had DES implanted (251 CYPHER and 11 TAXUS) and receiving antiplatelet treatment [19]. Seventeen (14 with CYPHER and 3 with TAXUS) were characterized as probable or certain DES-induced hypersensitivity reactions. Presenting hypersensitivity symptoms to all 262 patients were: rash, itching, hives, dyspnea, joint pain or swelling and blisters. Based on MAUDE seriousness codes, these reactions were classified as serious including patients who required emergency treatment with intravenous steroids, hospitalization or cardiac catheterization or resulted in permanent disability or may have contributed to death. Four patients died from coronary thrombosis that extended into the stent. Blood examination from 3 certain cases showed peripheral eosinophilia and raised IgE titers over five times of normal.

In other reports, patients developed intrastent thrombosis contemporarily with generalized allergic reaction, from other causes, showing that stents, like magnet ,attract inflammatory cells and constituted the area of possible intracoronary mast cell and platelet activation activation and development of stent thrombosis. In one such a patient [20], stent thrombosis and acute myocardial infarction coincided with allergic symptoms such as glottis edema, cold sweat, and tongue enlargement followed a flavonate-propyphenasone administration a week after stent implantation. In another patient [21] acute myocardial infarction, in the stented area, coincided with allergic reaction following intravenous administration of the non-anionic contrast material iopromide during a routine excretory urography. Intrastent thromboses have also been reported following insect and larvae sting allergic reaction [22–24].

Serum sickness-like reactions were developed in 2 patients with CYPHER stents the 17th and 18th poststenting day including urticaria-like rash, myalgias and arthralgias [25]. In the first patient, symptoms did not resolve after discontinuation of clopidogrel and substitution with diclopidine. However, symptoms resolved with prednisone. In the second patient, symptoms resolved with prednisone and despite taking aspirin and clopidogrel the patient continued to be symptom free.

Stent are implanted not only in the coronary arteries but also in other body areas including the biliary tracts for biliary strictures. In a patient with recurrent episodes of right-upper quadrant pain, anorexia, fever, thrills and jaundice, the stent was found, after surgery, to be completely occluded with biliary sludge. Pathologic examination of the material revealed infiltration of eosinophils and lymphocytes compatible with nickel allergic reaction [26].

3.2. Thrombus aspiration studies

Although therapeutic thrombus extraction sounds to be useful method for opening the obstructed stents, studies involving routine histological examination of the aspirated thrombus in order to elucidate the cause of intrastent thrombosis have not been carried out so far. Fortunately, few recent studies, evaluating other aspects, have shown infiltration of the harvested thrombus, from very late DES thrombosis, by eosinophils associated with incomplete stent apposition [27]. According to this study, thrombus harvested from implanted sirolimus stents tended to show a higher eosinophil count than those from paclitaxel or zotarolimus stents. Surprisingly, in the same study, histopathological data of aspirated thrombus from spontaneous acute, but not stented myocardial infarction patients, serving as controls, showed also increased eosinophils. Joner et al [28] have reported several pathological mechanisms that may contribute to stent thrombosis, including some factors observed in this preclinical study such as strut malapposition and hypersensitivity reactions. In another thrombus aspiration study [29], between 165 aspirated samples from acute non stented myocardial infarction of non allergic patients, 106 samples were found to be