



Letter to the Editor

Kounis syndrome and simultaneous multivessel acute coronary syndromes after successful drug-eluting stent implantation

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1. Summary

Recent reports have shown that implantation of drug-eluting stents (DES) may be associated with simultaneous, multivessel, repeated, remote and peripheral arterial thrombosis. Clinical and pathology findings point towards a possible hypersensitivity reaction to DES manifesting as Kounis syndrome. Prophylactic and therapeutic measures should be undertaken in order to avoid this dangerous complication.

2. Simultaneous multivessel drug-eluting stent thrombosis

In the very interesting report published in the this Journal [1] the authors reported on a patient with cardiogenic shock complicated by acute myocardial infarction due to simultaneous subacute coronary thrombosis occurring 3 days after implantation of two sirolimus stents in the proximal descending coronary artery and in the proximal right coronary artery. Although they did not comment on the possible etiology of this association, they concluded that the use of multiple drug-eluting stents (DES) in multiple coronary artery lesions should be undertaken with great attention in patients having multiple adverse clinical predictors. In another report published also in this Journal [2], concerning

simultaneous multivessel acute DES thrombosis, the authors emphasized the role of more aggressive antiplatelet regimens in higher risk clinical and anatomical situations. Other recent similar reports on simultaneous multivessel DES thrombosis [3,4] have emphasized the role of incomplete or inadequate patient assessment. However, concerns have been raised regarding hypersensitivity reactions with the use of DES.

The Kounis syndrome has been described 15 years ago [5] as the coincidental occurrence of acute coronary syndromes with conditions associated with inflammatory cell activation including hypersensitivity and anaphylactic insults. It is caused by inflammatory mediators such as tryptase, chymase, histamine, arachidonic acid products and a variety of cytokines and chemokines released during this activation.

Current DES components include the nickel strut, the polymer and the impregnated paclitaxel for the TAXUS stent or rapamycin for the CHYPHER stent. All these three components can act as strong sensitizers and allergens and can induce this syndrome [6]. Localized hypersensitivity and very late DES thrombosis resulting in death has been already described [7]. Allergic reactions associated with DES implantation have been described in 17 patients, 4 of whom developed fatal in-stent thrombosis [8]. Today, allergy to DES components is regarded as a real clinical entity [9].

3. DES thrombosis: A much feared stent complication

Thrombosis following successful drug-eluting stent (DES) implantation is a feared complication which may lead to catastrophic consequences including myocardial infarction

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with estimated 30-day mortality ranging from 20–48% [10]. Stent thrombosis has been classified as acute, occurring within 48 hours, subacute, occurring between the 2nd and the 30th day, late, occurring after the first 30 days to 1 year and very late occurring after 1 year of the implantation. The development of stent thrombosis is closely associated with procedural, clinical and angiographic variables such as stent length, supoptimal stent insertion, advanced age, low ejection fraction, brachytherapy, moderate or heavy vessel calcification, multivessel disease, flow disturbances and changes in shear stress, insulin dependent diabetes, withdrawal of clopidogrel and/or aspirin, clopidogrel resistance, delayed endothelialization, totally occluded lesion at baseline, post-procedural TIMI flow <3, and hypersensitivity to stent components [11]. The concurrence of acute coronary syndromes with hypersensitivity reactions has been long ago described and recent correspondence has associated hypersensitivity to DES components with in stent thrombosis [12].

Recently, several meta-analyses of large randomized trials have shown that the overall mortality from DES was increased by 2, 3, and 4 years in comparison with the bare metal stents. A recent study [13] showed that the rate of cardiac death and non fatal myocardial infarction between 7 and 18 months after DES insertion is 4.9% and additional up to 3 years data showed that the rate of mortality and myocardial infarction after sirolimus eluting stent insertion raised to 6.3%. Although, the magnitude of the very late DES thrombosis is not well defined, it seems that is in the range of 0.2% excess events per year after the first year through the fourth year. It is not known whether the very late DES thrombosis continues indefinitely or terminates after 4 years. However, new meta-analysis showed that the very late thrombosis was 5 events per 1000 DES patients with no events in the bare metal stent patients with sirolimus and paclitaxel 3.6 and 5.9 events per 1000 stents respectively [14]. The authors of this meta-analysis also concluded that although the very late thrombosis is low, DES appear to increase the risk of thrombosis. More of this risk is associated with paclitaxel stents but it remains possible that sirolimus stents similarly increase the risk of very late thrombosis compared with bare metal stents.

4. Simultaneous multivessel vasoconstriction following implantation of DES

Abnormal vasomotion with vasoconstriction has been reported in patients with DES during exercise 6 months after implantation [15]. In this study, patients with bare metal stent implantation preserved normal vasomotion with vasodilatation. Severe, diffuse multivessel coronary spasm has been reported in a recent report [16]. Among 13 patients who had implanted DES, 5 developed severe, diffuse and simultaneous spasm involving multiple coronary vessels. Two of them died. Post mortem in one of these patients revealed scattered mast cells in the adventitia of the coronary artery involved suggesting hypersensitivity reaction [17].

5. Repeated, remote and combined stent thrombosis

Acute repeated DES thrombosis has been described in a young woman with severe stenosis of the proximal left anterior descending coronary artery [18]. She presented with acute myocardial infarction and total occlusion of the stent 1 year after stenting while she had discontinued the antiplatelet treatment. She took aspirin and ticlopidin for 9 months thereafter. Two months later, she presented with acute myocardial infarction with re-occlusion at the stent. Blood examination showed no manifest collagen disease or thrombophilia.

Another report describes a patient undergoing stenting for variant angina who developed coronary spasm in another artery following the procedure [19]. This patient, after having a successful stenting of the right coronary artery developed localized spasm in both circumflex and left anterior descending coronary arteries.

Successful angioplasty and stenting of the proximal left anterior descending coronary artery and balloon dilatation of the circumflex coronary artery without stenting was performed in a 40-year-old man [20]. He subsequently developed acute coronary thromboses at both arterial sites and cardiogenic shock as well as peripheral arterial thrombosis requiring repeated therapeutic interventions. However, laboratory tests for thrombophilia revealed the presence of a G20210A prothrombin gene mutation. The authors of this report concluded that inherited thrombophilia should be considered as a possible cause of arterial thrombosis following stent placement.

6. Conclusions

These reports show that DES thrombosis might represent not a local phenomenon but a more general hypersensitivity event involving circulating inflammatory mediators able to induce thrombotic events and/or vasoconstriction as in both variants of Kounis syndrome [21]. Local release of inflammatory mediators seems to elicit a systemic response culminating in mast cell activation [22]. Therefore, in a effort to prevent and treat these disastrous consequences we recommend, especially for atopic patients the following: Monitoring the levels of inflammatory mediators after DES insertion, antibody and skin testing when and where appropriate, desensitization strategies, and careful history of adverse drug reactions and allergies. Others have recommended the measurement of acute phase reactants and periprocedural antiinflammatory therapy [23].

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