



Letters to the Editor

□ KOUNIS SYNDROME AND ACUTE MULTI-VESSEL CORONARY STENT THROMBOSIS

□ To the Editor:

We have read with interest the very important report published recently in this journal concerning a patient who developed acute multi-vessel coronary stent thrombosis 24 h after uncomplicated implantation of two coronary stents (1).

The authors of this report ruled out arterial damage, stent malapposition, and hypercoagulability, and considered clopidogrel resistance as a likely cause for the simultaneous stent thrombosis. However, this patient received three drugs during the procedure, namely clopidogrel, aspirin, and bivalirudin. Although the brands of stents were not described, the current drug-eluting stents are composed from 316L stainless steel alloys containing nickel, chromium, manganese, titanium, and molybdenum; the polymer cover and the impregnated drugs, which, for today, are the antimicrotubule, antineoplastic agent paclitaxel, or the anti-inflammatory, immunosuppressive, and antiproliferative agent rapamycin. Therefore, the patient was under the influence of *six* potential antigens, all of which are known to cause allergic inflammation and, consequently, intracoronary mast cell activation. The agents clopidogrel, aspirin, bivalirudin, nickel, paclitaxel, and rapamycin have been incriminated to induce numerous hypersensitivity reactions (2–5).

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, constitutes the Kounis syndrome (6). This syndrome 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. For example, a novel action of histamine is the induction of tissue factor expression and activity (7). Tissue factor is a key enzyme in the activation of coagulation. It binds activated factor VII, which in turn activates factor X, leading to thrombin formation. Elevated tissue factor antigen and activity have been detected in plasma and in atherectomy specimens of patients with

unstable angina, denoting that tissue factor is involved in the initiation and propagation of acute coronary syndromes (8). This effect of histamine is completely abolished by H1 receptor antagonists. Two variants of this syndrome have been described: Type I variant includes patients with 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 (6). Type II variant 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 plaque erosion or rupture manifesting as acute myocardial infarction. Although overt hypersensitivity symptoms were not present in this patient, intracoronary mast cell activation could not be excluded. It is known that these events may be more common than suspected and is hard to document them, unless they become systemic (9). The described patient had an uncomplicated 24-h hospital course and was asymptomatic at discharge, but within few hours of arrival home after discharge, developed stent thrombosis. The development of “acute” stent thrombosis supports the assumption that this was an immunoglobulin E (IgE)-mediated allergic inflammation involving intracoronary release of inflammatory mediators. Coronary “subacute,” “late,” and “very late” stent thrombosis seem to be lymphocyte-mediated or “irritation” allergic inflammation.

According to a recent report, simultaneous exposure of several allergens has an additive effect on multi-sensitized mast cells and basophils (10). Other clinical studies indicate that such patients have also more symptoms than mono-sensitized individuals (11). Ideally, to elucidate the exact cause of stent thrombosis, measurement of the following inflammatory mediators would have been advisable: total IgE, specific IgE for drugs and device components, chymase, tryptase, histamine, arachidonic acid products (thromboxane, leukotrienes, prostaglandins), tissue factor, cytokines, and chemokines (tumor necrosis factor, interferon, interleukin-6).

Based on findings that mast cell stabilization with corticosteroids and mast cell stabilizers have relieved

allergic reactions clinically and have abrogated thrombotic events experimentally, we have already proposed impregnation in the stent polymer such agents to prevent the so-much feared intra-stent coronary thrombosis (12). Some of our suggestions have been incorporated in current protocols (13).

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