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Case report

Severe allergic reaction during angioplasty culminating to fatal acute stent thrombosis: An association with Kounis syndrome

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ABSTRACT

Background: Kounis syndrome is a systemic complication following an allergic reaction, presenting with coronary artery spasm or thrombosis and occasionally with stent thrombosis that can have fatal outcome.
Objectives: Heparins can induce allergic reactions via tissue antigenicity, heparin induced thrombocytopenia and contact system-activating effects of contaminants but allergy bivalirudin has not been reported so far.
Methods: Herein, we describe a patient with fatal acute coronary in-stent thrombosis following an allergic reaction soon after an intra-arterial heparin dose and intravenous administration of bivalirudin during angioplasty.
Results: The patient received intense myocardial infarction protocol treatment including angioplasty and defibillation together with antiallergic therapy but despite all of these efforts and measures, he succumbed 2 h later.
Conclusions: Significant suspicion should be raised that life saving drugs such as heparin and bivalirudin could join forces with concurrent medication acting as antigens and induce fulminant and fatal stent thrombosis as a manifestation of Kounis syndrome

Indroduction

Kounis syndrome was described in 1991 as an acute coronary syndrome attributed to either coronary artery spasm or coronary artery thrombosis following a hypersensitivity reaction. During the first report histamine was considered as one of the major inflammatory mediators able to induce this syndrome.[1] Today, preformed and newly synthesized inflammatory mediators including chemokines, cytokines and arachidonic acid products released during mast cell activation have been incriminated to induce this syndrome. These mediators, apart from histamine, include enzymes such as tryptase, chymase, and cathepsin-D, and arachidonic acid products such as leukotienes, platelet activating factor, thromboxane and prostaglandins. Several causes acting as direct and indirect mast cell degranulators have been incriminated to induce the Kounis hypersensitivity-associated acute coronary syndrome including drugs,[2] various conditions[3] and a variety of environmental exposure factors such as animal stings.[4] Analgesics, anesthetics, antibiotics, anticoagulants, antineoplastics, contrast media, glucocorticoids, non-steroidal anti-inflammatory agents, proton-pump inhibitors, skin disinfectants, thrombolytics and several other drugs have been acting as triggers of Kounis syndrome.[5] Three different types of the syndrome have been described.[6] Type I variant includes patients without atherosclerotic coronary artery disease who experience coronary artery spasm secondary to the acute release of inflammatory mediators. These patients may or may not demonstrate increased cardiac biomarkers but present electrocardiographic abnormalities, most commonly ST segment elevation.[7] Type II variant includes patients with existing atheromatous disease.[8] Finally, type III variant refers to patients with previous percutaneous coronary intervention presenting with in stent thrombosis or stent restenosis following a severe allergic reaction.[9] In the majority of the cases described thus far, the patients experienced minimal complications and recovered fully after the appropriate medical interventions.[10] However, fatal events have been started to appear in the medical literature especially in patients presenting with in stent thrombosis (Kounis Type-III variant).[11] The following report is a unique case concerning a patient who developed type III variant of Kounis syndrome during angioplasty culminating in fatal stent thrombosis.

Case report

A 50-year-old male hypertensive patient suffering from coronary artery disease with stent implantation in the left anterior descending artery 12 years previously was admitted for a routine coronary angiography due to typical angina of one month duration. He had

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undergone 3 coronary angiographies since the first angioplasty because of recurrent chest pain and positive exercise testing. The last angiography that was performed 6 years ago disclosed a patent left anterior descending stent, total occlusion of the right coronary artery and up to 80% diffuse stenosis of the circumflex artery. The patient was managed conservatively with aspirin, clopidogrel, metoprolol, valsartan, mononitrite isosorbite and atorvastatin. He did not describe any previous history of allergy or drug reaction. On admission, the resting electrocardiogram disclosed Q waves at leads II, III and AVF and the echocardiographic left ventricular ejection fraction was 60%. Coronary angiogram, following 50 I.U. of intra-arterial heparin, disclosed a 99% left anterior descending in-stent restenosis, a long 90% distal left anterior descending stenosis, diffuse severe circumflex disease and a total occlusion of the distal right coronary artery (Fig. 1: Ia). The patient denied any surgical consultation and therefore we decided to treat him with angioplasty. An intravenous bivallirudin bolus 0.75 mg/kg injection was administered with maintenance infusion of 1.75 mg/kg/hr and predilatation of the proximal left anterior descending artery stenosis with a 2/20 mm balloon was performed. At this time, the patient experienced severe pruritus, developed an extensive upper body rash covering chest, trunk and extremities and gradually became severely dyspneic, and disorientated. The blood pressure dropped from 125/80 mmHg to 60/30 mmHg with increased heart rate to 130 b/m (Fig. 1: Ib). An oxygen mask of 60% Venturi was placed and intravenous sodium chloride was liberally administered together with 500 mg hydrocortisone sodium succinate and 16 mg of dimetindene. The patient did not respond to this treatment, therefore 0.25 mg (1:10,000 sol) of adrenaline was administered intravenously and dopamine infusion of 20 μg/kg/min was started. Following this, blood pressure stabilized to 95/65 mmHg, with a heart rate of 120 bpm and a 3.0 $\times$ 22 mm drug eluting stent was successfully implanted in the left anterior descending with a TIMI grade-III flow (Fig. 1: Ic). Resuscitation, in the catheterization laboratory, was continued for approximately 45 min, with a second bolus of hydrocortisone, and dimetindene. One hour later the patient developed sudden chest discomfort and subsequently experienced a monomorphic ventricular tachycardia, which rapidly deteriorated to ventricular fibrillation and cardiac arrest. Mechanical chest compressions with the Lund University Cardiac Arrest System (LUCAS^{TM}) system was started, the patient was re-intubated and repeated defibrillations with 200 Joules per second were performed which resulted in institution of spontaneous circulation. The first post resuscitation electrocardiogram showed diffuse severe ST-segment elevation in leads II, III, AVF and V1-6 (Fig. 1: Id). Re-loading with crushed ticagleror through nasogastric tube was done, nor-adrenaline intravenously infusion was started because of low 80/40 mmHg blood pressure and an emergency coronary angiography disclosed an acute stent thrombosis of the left anterior descending coronary artery (Fig. 1: Ie). Baloon angioplasty reinstituted patency of the left anterior descending with a TIMI-II flow (Fig. 1: If) but the echocardiogram revealed a 15% left ventricular ejection fraction. Blood circulating heparin induced thrombocytopenia antibodies were not detected. Unfortunately, despite of all above efforts and measures, the patient succumbed 2 h later. The diagnosis was Kounis syndrome type III variant but the relatives refused postmortem examination.

Discussion

The described patient experienced severe allergic reaction during angioplasty, which was followed by acute stent thrombosis with fatal

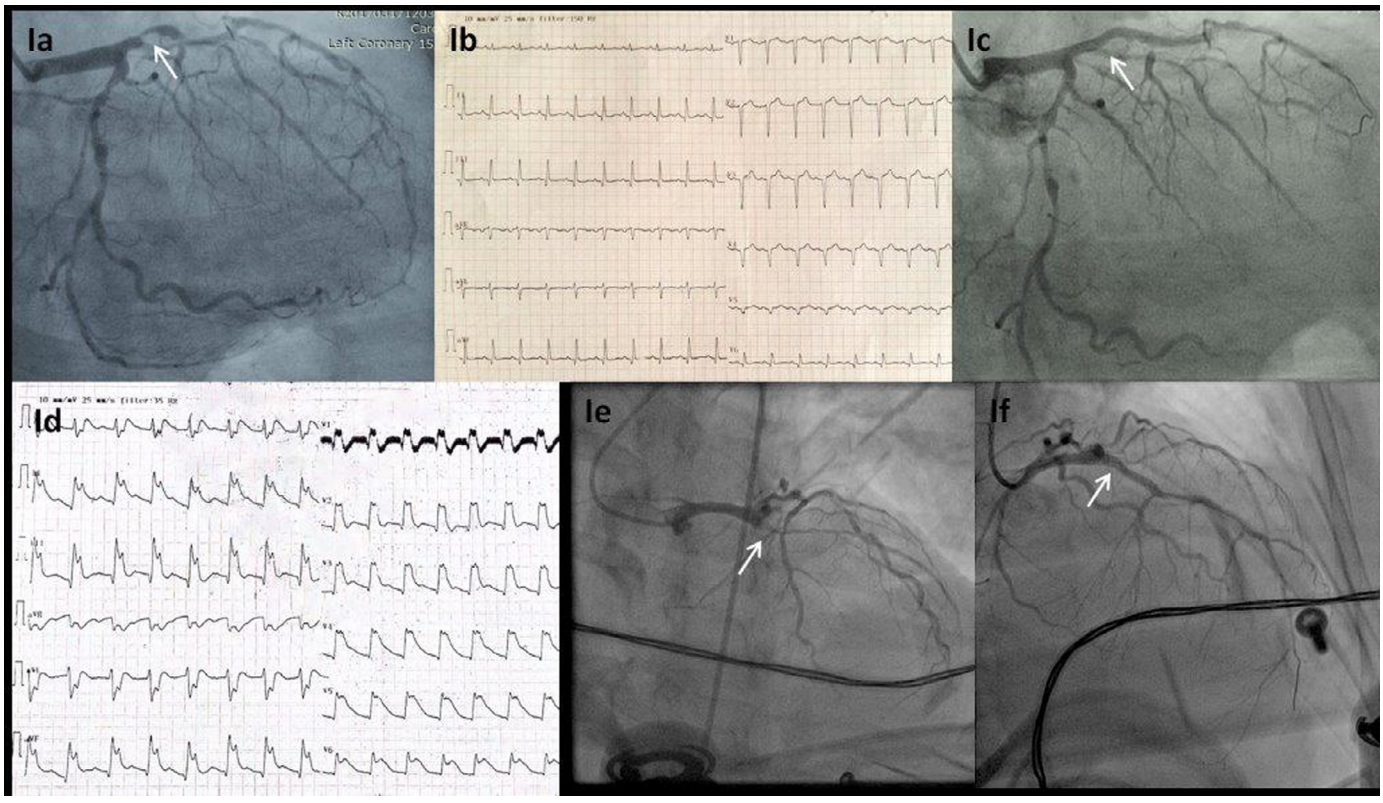

Fig. 1. Panel-Ia: Severe proximal stenosis of the LAD, (arrow). Panel-Ib: ECG following a severe allergic reaction in the cath-lab. Panel-Ic: Angiographic result following implantation of a 3.0/22 mm DES in the proximal LAD, (arrow). Panel-Id: ECG following resuscitation at the CCU. Panel-Ie: Acute stent thrombosis in the proximal LAD, (arrow). Panel-If: Angiographic result following multiple balloon dilatations of the thrombosed DES, (arrow). *Abbreviations:* LAD: Left Anterior Descending artery, ECG: Electrocardiogram, DES: Drug Eluting Stent, CCU: Coronary Care Unit.

outcome; therefore we believe that this case actually represents a Kounis Type-III variant syndrome. As the patient had not any known allergic history and had been undergone to several coronary angiographies in the past, we consider the contrast agent an unlike cause of his allergic reaction. For the very same reason we also consider intra-arterial heparin an unlike cause of the event. However, drug sensitization during the previous angioplasties and procedures can not be excuded. No other medications were administered apart from intravenous bivalirudin in bolus and infusion during angioplasty. As the patient experienced allergic symptoms a few seconds following bivalirudin bolus, it is reasonable to assume that the latter is related to. Bivalirudin, however, is considered as safe and effective anticoagulant agent used during percutaneous coronary interventions.[12] To the best of our knowledge, there are no cases of severe bivalirudin adverse reactions described so far. Similarly, no bivalirudin-induced anaphylaxis has been reported until now. However, the specific product characteristics, clearly states that bilivarudin has been uncommonly connected with hypersensitivity reactions including (hives, generalized urticaria, tightness of chest, wheezing, hypotension and anaphylaxis. In the revised 1/2015-Food and Drug Administration prescribing information highlights, it was reported that among 494 subjects who received bivalirudin in clinical trials and were tested for antibodies, 2 subjects had treatment-emergent positive bivalirudin antibody tests, but without evidence of allergic or anaphylactic reactions. We believe that this issue needs further evaluation. Heparins, on the other hand, are mucopolysaccharides derived from bovine or porcine tissues and can cause anaphylactic reactions not only due to tissue antigenicity but also as a manifestation of the heparin induced thrombocytopenia syndrome and through the contact system-activating effects of contaminants.[13] Heparin induced thrombocytopenia can cause thrombosis, via activation of high and low affinity antibody receptors existing in a subset of 20% of platelets, by heparin-PF4-IgG immune complex formation.[14] In this patient, however, circulating antibodies able to induce heparin thrombocytopenia were not detected. The patient's current therapy was consisting of 7 medications namely aspirin, clopidogrel, metoprolol, valsartan, mononitrite isosorbite and atorvastatin. These medications, in very rare instances, alone or in combination have been incriminated as inducing allergic reactions. Aspirin[15] and clopidogrel,[16] the drugs given to prevent stent thrombosis, have induced Kounis syndrome. Valsatran has induced allergic reaction[17] and metoprolol with angiotensin converting enzyme inhibitors synergistically aggravate anaphylaxis at least partly by decreasing the threshold of mast cell activation.[18] Strangely, hypersensitivity to atorvastatin[19] and even anaphylaxis to nitroglycerin have been reported also.[20] Indeed, sensitized individuals simultaneously exposed to several agents, have more allergic symptoms than monosensitized individuals and IgE antibodies with different specificities can have additive effects and small, even subthreshold numbers of them can join forces and trigger the cells to release their mediators.[21] This can happen when the patient is simultaneously exposed to the corresponding antigens.[22]

Therefore, this case raises significant suspicion that life saving drugs such as heparin and bivalirudin could join forces with concurrent medication and induce fulminant and fatal stent thrombosis manifesting as Kounis syndrome. The Aristotle's (384–322 B.C.) dictum: “Not many is the good, but in the good, the many” (Ouk en to Pollo to ef, but en to ef to poly=OϒK EN TΩ ΠΟΛΛΩ TO Eϒ ΑΛΛΑ EN TΩ Eϒ TO ΠΟΛϒ) should be always brought in mind.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hrtlng.2018.07.015.

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