LETTERS TO THE EDITOR

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Rectosigmoid ischemia and cerebral coma following gadolinium-induced anaphylaxis: A new manifestation of Kounis syndrome presented as devastating complication

Gadolinium-based contrast mediums are the most commonly used agents in magnetic resonance imaging for both angiography, and brain tumor enhancement due to their association with the degradation of the blood–brain barrier. When oxidation is removed from gadolinium medium and gadolinium salts, a silvery-white metal anions remain that are able to induce allergic reactions and anaphylaxis. Whereas such reactions are not common, other reactions including nephrogenic systemic fibrosis and acute kidney injury due to primary excretion of gadolinium from the kidneys and various cardiac arrhythmias including QTc electrocardiographic prolongation are occasionally encountered [1,2]. Despite that gadolinium-based contrast mediums are characterized as benign agents, in some occasions they can lead to life threatening conditions and Kounis syndrome [2-5]. The concurrence of acute coronary syndromes such as coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation involving other interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults constitute 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 degranulation process of these inflammatory cells. Platelets bearing specific fragment crystallizable region receptors are also involved in the activation cascade [7]. All these inflammatory cells participate in an inflammatory cycle and activate each other via multidirectional signals.

The coronary arteries, the heart and the entire arterial system seem to be vulnerable to allergic, hypersensitivity, anaphylactic, and/or anaphylactoid events and physicians should be alert for their consequences. The incidence of Kounis syndrome [8] ranges from 1.1% to 3.4%. Kounis syndrome was initially thought to be a rare condition but seems rather to be an under diagnosed disease. Three variants of this syndrome have been described so far. They include the type I variant in patients with coronary artery spasm but with normal or nearly normal coronary arteries and no predisposing factors for coronary artery disease, the type II variant in patients with quiescent preexisting atheromatous disease who present with acute myocardial infarction and the type III variant in patients with coronary stent implantation who develop stent thrombosis (subtype a) or stent restenosis (subtype b) due to allergic inflammation [9].

Recent research has shown that Kounis like syndromes can affect not only the coronary arteries but also the cerebral arteries [10,11] and the mesenteric arteries [12].

In the very important *report* by Juliani et al in *Annali Italiani di Chirurgia*[13], a 72-year-old woman suffering from anal squamous cell carcinoma and receiving mitomycin and fluorouracil chemotherapy and then radiotherapy, developed anaphylactic reaction to Gadolinium during regular magnetic resonance imaging, with shock and cardiac arrest, that lasted about half an hour before she was successfully resuscitated. Following this event the patient developed massive digestive bleeding that was successfully treated with Hemospray and passage of stool from the vagina due to the presence of a recto-vaginal fistula. The patient became comatose for about 30 days, during which she was uncontactable. Colonoscopy revealed rectosigmoid ischemia with total necrosis of the posterior rectal wall with exposition of presacralis fascia. This report raises important issues concerning anaphylactic shock and cardiovascular collapse, and also anaphylactic shock and coma.

The sigmoid colon derives its name from a Greek letter sigma and constitutes a hindgut structure that receives its blood from the sigmoidal branches of the inferior mesenteric artery and collateral blood supply from the left colic artery and inferiorly from the superior rectal arteries. Both these branches also originate from the inferior mesenteric artery. The rectosigmoid junction is a major watershed zone known as Sudeck's point, which is prone to ischemia in states of decreased perfusion. Therefore, the question which arises in the case described by Juliani et al [13], is whether systemic vasodilation or mesenteric vasoconstriction was the cause of a such devastating result during gadolinium-induced anaphylaxis. Indeed, systemic vasodilation can induce plasma leakage, volume loss due to increased vascular permeability, and reduced venous return resulting in mesenteric hypoperfusion. On the other hand, the mediators release during

anaphylaxis (histamine, chymase, tryptase, cathepsin D, leukotrienes, thromboxane, platelet activating factor) can cause rectosigmoid ischemia with total necrosis of the posterior rectal wall with exposition of presacralis fascia.

In particular, the above mediators released during anaphylactic shock apply the following actions [14]: Histamine can induce coronary vasoconstriction via the H1 receptors, chymase and cathepsin-D convert angiotensin I to angiotensin II which are major vasoconstrictive substances, tryptase activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin that can promote plaque disruption and induce pericellular matrix degratation (basophils have about 500-fold lower levels of tryptase than mast cells). Indeed, leukotienes acting as powerful vasoconstrictors, thromboxane promoting platelet aggregation and vasoconstriction and platelet activating factor can further induce vasoconstriction.

As far as the coronary arterial tree there are experiments and clinical events that have shown the followings during anaphylaxis: In ovalbumin sensitized guinea pigs within 3 min post ovalbumin administration it was observed that[15]: Cardiac output decreased by 90%, left end ventricular diastolic pressure increased significantly by 35%, indicating pump failure, arterial blood pressure increased significantly by 35% and started declining steadily after 4 min and the electrocardiogram revealed signs of acute myocardial ischemia. The conclusion was that "the idea that the registered anaphylactic damage might be due to peripheral vasodilatation can be definitely excluded". In addition, the rapid left end ventricular diastolic pressure increase suggests that decreased venous return and volume loss due to vascular permeability increase are unlikely to be the primary causes of the documented cardiac output and blood pressure depression.

Moreover, in the clinical setting there are studies demonstrating that, in anaphylaxis, cardiac biomarkers denoting myocardial injury are raised [16]. Additionally, there are also clinical reports of patients with anaphylactic cardiac collapse and Kounis syndrome with increased serum troponin, who did not respond to intravenous fluid administration and inotropic support and required coronary syndrome treatment protocol [17].

In the described case [13], the gadolinium induced anaphylactic shock, that was associated with cardiac arrest and coma, could had been the result of both mesenteric vasoconstriction causing ischemia and systemic vasodilation inducing mesenteric hypovolemia.

In a recent study [18], it was found that anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension. The authors of this paper concluded that, in anaphylactic shock, severe impairment of the cerebral blood flow takes place, which could not be explained by the level of arterial hypotension.

Indeed, cerebral coma from irreversible diffuse hypoxic-ischemic encephalopathy has been described in a female patient following bee-sting induced Kounis syndrome an she is still in a vegitable state mechanically ventilated in the intensive care unit after 6 months [8]. In another patient, with Kounis syndrome, from Spain, anaphylactic reaction to amoxicillin-clavulanic acid under general anesthesia induced severe, irreversible and subsequently fatal encephalopathy of ischemic origin as a result of low blood pressure affecting the cerebral arterial system[19].

Furthermore, transient cerebral ischemic attacks were developed in 2 patients with mast cell-related disorders while they had previous history of chest pain and Kounis-like syndrome [20]. The first patient developed transient hemiparesis with decreased sensation and muscular weakness of the face and the second developed episodes of sudden transient paresis and numbness of his right arm following strenuous work that was re-developed during hospitalization.

All of the above show that the mesenteric and cerebral and arteries can be affected via the same mechanism as the coronary arteries through the action of anaphylactic mediators that can induce vasoconstriction, hypo-perfusion and thrombosis. Therefore, mesenteric and cerebral ischemia following anaphylactic shock could be due to direct action of anaphylactic mediators on the cerebral arterial system and not solely due to hypovolemic hypotension. Surgeons and physicians should be aware of the various manifestations of Kounis syndrome in order to apply prompt and appropriate therapeutic measures

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