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Mast cell activation disorders presenting with cerebral vasospasm-related symptoms: A “Kounis-like” syndrome?

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To the Editor,

Kounis syndrome is characterized by acute coronary events occurring throughout anaphylactic or anaphylactoid reactions, even in patients with normal coronary arteries. Clinical manifestations of

this syndrome have been attributed to coronary artery spasm or plaque erosion or rupture induced by acute inflammatory mediators release during these reactions [1–4]. Similarly, vasospasm-related symptoms involving organs other than the heart might also occur in patients with conditions characterized by acute mast cells (MC)-mediator release, as in systemic mastocytosis (SM) and MC activation disorders (MCAD). We report two patients with MC-related disorders who developed transient ischemic attacks while they had previous history of chest pain and Kounis syndrome.

A 54-year-old male suffering from urticaria pigmentosa and indolent SM, diagnosed by bone marrow biopsy suffered from recurrent stress-induced episodes characterized by flushing, angioedema, palpitations, headache, articular pain, paresthesias, fever and increased blood pressure. These episodes were partially controlled with the antimedator and other treatment including disodium cromolyn, ebastine, ranitidine, telmisartan, amlodipine, diazepam, risendronate, calcium carbonate and their frequency decreased when this treatment was initiated. Coinciding with one of these episodes and while his systolic blood pressure was 160 mmHg he developed transient hemiparesis with decreased sensation and muscular weakness of the face. He soon completely recovered (minutes) after

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administration of sublingual ACE inhibitors (75 mg of captopril) which normalized the systolic blood pressure. He underwent ECG, cranial CT scan, cerebral nuclear magnetic resonance, echocardiogram and supra-aortic trunk echography, which were found normal.

A 44-year-old man suffering from chronic urticaria had repeated attacks of chest pain. Two of these episodes were associated with worsening of urticaria, angioedema, dyspnea, palpitations with ECG changes (I and II ST elevation). In the first of these episodes troponin levels were found elevated and this episode coincided with lentil ingestion. These episodes had been diagnosed as type I variant of Kounis syndrome while bone marrow study confirmed the diagnosis of non-clonal mast cell activation syndrome. However, during a recent strenuous work he developed an episode of sudden transient paresis and numbness of his right arm with total spontaneous recovery within 5–10 min. He was hospitalized, but presented a similar episode the next day with the same characteristics. He underwent EKG, thorax X-ray, cranial CT, cerebral nuclear magnetic resonance, cerebral angiography, echocardiogram, transesophageal echocardiogram and supra-aortic trunk echography, which were normal. After neurological evaluation, ischemic or embolic event was ruled out, and acute release of mast cell mediators inducing cerebral vasospasm was suggested. He received antimedator therapy including disodium cromolyn together with H1 and H2 antihistamines without response and, thus, he was included in 2010 in a clinical trial with omalizumab. The frequency of mast cells-mediator release symptoms has decreased since but he still has some episodes of urticaria, angioedema and occasionally chest pain without ECG changes.

Mast cell mediator-related presenting symptoms can widely vary from flushing or pruritus to anaphylaxis in more severe cases. Anaphylactic episodes are a common presenting symptom in systemic mastocytosis and mast cell activation disorders patients [5]. In allergic reactions, aggregation of high-affinity Fc receptors for IgE (FcεRI) on mast cell surfaces elicits the release of preformed granule-associated, such as histamine, neutral proteases, preformed cytokines, and proteoglycans [6]. In SM or MCAD patients, additional pathways of mast cell activation apart from FcεRI have been reported [7]. Thus, acute release of MC-mediators is often elicited without evidence of known triggers. To date, few mediators beyond histamine and tryptase have explored their utility in the diagnosis of anaphylaxis. Recent studies support chymase, carboxypeptidase A3 (CPA) or platelet activating factor as potential markers of anaphylaxis [8]. Mast cell-CPA and chymase convert angiotensin I into angiotensin II, which increases blood pressure by stimulating vascular smooth muscle cells. CPA levels remain elevated longer than total tryptase levels and high levels of CPA have been detected in patients with

anaphylaxis who did not elevate tryptase levels [8]. Unfortunately, its use is currently performed only in research laboratories.

Kounis syndrome has been defined as the concurrence of acute coronary events with allergic or anaphylactoid reactions in patients with normal coronary arteries with or without predisposing factors (type I variant or II, respectively) and in patients with stent thrombosis (type III). These reactions have been attributed to the acute release of inflammatory mediators [1,3]. In the present report, both episodes were also attributed after neurological evaluation, to the acute release of inflammatory mediators. The clinical symptoms, the absence of abnormalities in all the complementary explorations performed – supra-aortic trunk echography, cranial CT and cerebral NMR – and the recovery after the administration of angiotensin-converting enzyme inhibitors, support the hypothesis that the acute release of mast cell mediators might have elicited the vasospasm. To the best of our knowledge there are no data regarding acute release of MC-mediators presenting with cerebral vasospasm. Physicians should take into account vasospasms as presenting symptoms of MC-release and the convenience of maintained antimedator-release therapy in patients with SM and MCAD.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [9].

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