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Syncope as a manifestation of mast cell activation disorder

Anaphylaxis is a potentially fatal systemic allergic reaction that results from the abrupt release of basophil and mast cell mediators, such as histamine and tryptase. The clinical manifestations include skin, respiratory, and cardiovascular symptoms; however, a rapid decrease in blood pressure may be the unique manifestation. The most frequent causes of anaphylaxis are Hymenoptera venom, foods, and drugs.[1] Idiopathic anaphylaxis is considered in case of unknown cause.[2]

Syncope is the abrupt and transient loss of consciousness associated with absence of postural tone followed by a complete and usually rapid spontaneous recovery. The most common causes are vasovagal episodes and heart conditions. In a third of cases, the cause remains unknown. It may be misdiagnosed as a neurologic condition such as epilepsy, a metabolic or toxic disorder, or anaphylaxis.[3]

Tryptase blood levels increase after 30 minutes and remain high for 6 hours, with peak values between 1 and 2 hours after the initiation of the reaction. A high blood level of tryptase obtained after an anaphylactic reaction must be controlled by a baseline determination. The finding of persistent high levels of tryptase is very suggestive of mast cell activation disorders (MCADs).[4] Mastocytosis is considered a primary form of MCAD, caused by an abnormal increase of mast cells in tissues (skin, bone marrow, liver, spleen, and lymph nodes) and associated with somatic mutations in the c-kit gene. The diagnosis of mastocytosis is established by well-defined criteria proposed by the World Health Organizations.

A 42-year-old, white man developed a sudden episode of sweating, dyspnea, wheezing, and stridor while working outdoors. Despite the administration of inhaled bronchodilators, he developed facial cyanosis, blurred vision, and loss of consciousness with absence of postural tone, hypotension (blood pressure, 89/52 mm Hg), tachycardia (142 bpm), hypersalivation, and urine incontinence. He underwent orotracheal intubation performed by the emergency service team and was transferred to the intensive care unit, where he remained stable for 24 hours. Electrocardiography and standard blood test results were normal, but elevations in troponin levels were initially apparent (98.99 ng/L). Chest computed tomography revealed signs of bronchoaspiration but not of pulmonary embolism. The results of head computed tomography were normal.

After 24 hours the patient could be weaned off medications and hospitalized at the Department of Internal Medicine. Neurologic, cardiologic, and respiratory conditions were ruled out by normal or negative physical examination, electroencephalography, echocardiography, ambulatory electrocardiography monitoring, creatinine phosphokinase, and troponin findings. Urine levels of catecholamines, metanephrines, and serotonin were within normal limits.

He reported having repeated similar episodes for the last 5 years. The frequency and severity progressively increased during the last 12 months, always with complete recovery and revealing no findings in any of the complementary tests performed. For the last few months he has experienced persistent palm and sole pruritus, without skin lesions, that did not respond to antihistamines.

Some years before he was referred for an allergy evaluation because of respiratory and skin symptoms. He was diagnosed as having aspirin and other nonsteroidal anti-inflammatory drug (NSAID) intolerance and seasonal rhinoconjunctivitis due to pollens (cypress and olive) and molds (*Alternaria*). The results of a bronchial challenge with methacholine were negative.

A new allergy evaluation, including skin tests with food and airborne allergens, produced similar results, with a total IgE level within the normal range (73.7 kU/L). Repeated baseline tryptase determinations ranged from 23.7 to 25.9 μg/L. The bone marrow aspiration revealed a high percentage of basophils (13%), 11% showing atypical morphologic findings (spindle-shaped) and positive for toluidine blue staining. Mast cells tested positive for $CD25^{+}/CD2^{+}$, but c-kit mutation in exon 17 and 8 tested negative. All these findings were suggestive of MCAD.

We present a case of MCAD in a patient with recurrent episodes of syncope, without skin lesions but showing mast cell infiltration in the bone marrow. Syncope is a common manifestation of systemic mastocytosis, with several reports of patients experiencing recurrent episodes of syncope.[6,7] However, syncope is uncommonly described in other MCAD forms. The differential diagnosis of syncope, especially in cases with other symptoms, such as flushing, abdominal cramping, or diarrhea, should include all forms of MCAD.[8]

MCAD is an uncommon condition characterized by a clonal or nonclonal proliferation of mast cells, infiltrating one or more organs (skin in 99%). According to a recent classification of MCAD,[5] the present case, having only one clonal markers (CD25 expression) but not other criteria of mastocytosis, corresponds to a monoclonal mast cell activation syndrome, a primary form of MCAD.

The most common skin symptom is facial flushing, due to the abrupt release of mast cell mediators, which may provoke hypotension and loss of consciousness (syncope).[7] There are few cases without skin involvement but having mast cell infiltration in organs (gastrointestinal, respiratory, bone, lymph nodes, and neurologic).[4]

Severe recurrent episodes of idiopathic anaphylaxis are a common manifestation of systemic MCAD.[5] Anaphylaxis is more likely when there is a concomitant allergic sensitization (Hymenoptera

Disclosures: Authors have nothing to declare.

venom allergy being the most common one). However, the prevalence of allergic diseases in patients diagnosed as having mastocytosis is similar to the general population (20%–30%).[9] In the reported case, the allergic background of the patient helped to establish the final diagnosis.

The clinical manifestations and prognosis of MCAD depend on the involved organs and the stimulus provoking the release of mediators. A tryptase level greater than 20 μg/L and repeated syncopal events sustained the indication for bone marrow biopsy. Because only one clonality criteria was detected, the patient was diagnosed as having monoclonal mast cell activation syndrome and not mastocytosis.

Because in this case the diagnosis of MCAD was suggested by the finding of a high level of baseline serum tryptase after recurrent episodes of syncope, we proposed the inclusion of tryptase levels in the evaluation of recurrent episodes of syncope. Although tryptase levels constitute a suggestive finding of MCAD and help in the understanding of its clinical features, they lack any prognostic value.

Drugs such as opiates, NSAIDs, muscle relaxants, and radiocontrast media may induce anaphylactic symptoms in patients with MCAD by direct activation of mast cells.[9] In the present case, the patient was previously diagnosed as having NSAID intolerance. We report an uncommon case of MCAD, revealing the possibility of new profiles of presentation of this condition.

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Idiopathic angioedema with F12 mutation: is it a new entity?

In recurrent angioedema attacks without concomitant urticaria or pruritus, bradykinin-mediated angioedema (hereditary and acquired) and angioedema induced by angiotensin-converting enzyme inhibitor are considered. In patients with normal C1 inhibitor (C1-INH) level and function and those with normal C1q antibodies, hereditary angioedema (HAE) with normal C1-INH, angioedema induced by angiotensin-converting enzyme inhibitor, and idiopathic angioedema are possible diagnoses. Idiopathic angioedema is a diagnosis of exclusion and should be considered after a detailed evaluation.[1]

Hereditary angioedema with normal C1-INH was described in 2013 by Sher and Davis-Lorton.[1] This type of HAE is more common in women in their 30s and is related to menstruation, pregnancy, estrogen-containing oral contraceptive drugs, or other high-estrogen conditions. It also can include rare multiorgan attacks and abdominal swelling. Although its etiology is not completely understood, there is evidence showing an association with *F12* gene mutations, which is present in up to 25% of patients in European cohorts and similarly extremely rare in US patients.[1] To be diagnosed as HAE with normal C1-INH, a patient must meet the following criteria: recurrent angioedema without urticaria or a causative medication and with normal or near normal C1-INH antigen and function. The patient also must have normal complement C4 levels during attacks and a positive family history of angioedema and evidence that chronic high-dose antihistamine therapy is ineffective or a disease-associated mutation in the *F12* gene.[2]

Idiopathic angioedema is defined as at least 3 episodes of swelling within 6 to 12 months without a clear etiology after a thorough evaluation. In patients presenting with recurrent swelling without urticaria, the diagnosis is made after the exclusion of acquired angioedema and HAE. In addition, all known causative entities of angioedema should be ruled out. The treatment of idiopathic angioedema remains largely empiric and often is based on the control of clinical symptoms.[1]

We present 2 cases of recurrent angioedema attacks without urticaria, initially considered idiopathic angioedema. However, further evaluation demonstrated mutations in the *F12* gene, suggesting a diagnosis of HAE with normal C1-INH.

A 50-year-old man was referred for recurrent edema attacks on his face, especially on his lips. His attacks began 2 years before the referral and occurred at 15-day intervals with a duration of at least 2 days. He was not taking angiotensin-converting enzyme inhibitors or any other suspicious drugs and attacks were unresponsive to high doses of antihistamines or steroids. C1-INH, C4, C1q levels, F12 levels, and C1-INH function were within normal limits. His initial diagnosis was non-histaminergic idiopathic angioedema and a twice-daily 250-mg dose of tranexamic acid was started. He did not report any angioedema attacks at his 6-month follow-up. Although he did not report a positive family history, an *F12* gene mutation analysis was performed.

A 35-year-old woman was admitted with a 7-year history of recurrent episodes of isolated edema in various locations on her

Disclosure: The authors have declared that they have no conflict of interest.
Funding: No financial support was provided for the study.