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Case Report

Anaphylaxis is not Always Synonymous of Allergy – A Recurrent Presentation

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Abstract

This case report presents a 9-year-old previously healthy female who experienced recurrent episodes of anaphylaxis without identifiable triggers. Her initial episode included sudden nighttime awakening, abdominal pain, vomiting, diarrhea, bilateral plantar itching, followed by a generalized pruritic rash, facial erythema, and labial edema. After treatment with intramuscular adrenaline, antihistamines, and corticosteroids, the symptoms resolved rapidly. However, over the next six weeks, she experienced four additional anaphylactic crises with similar gastrointestinal and cutaneous symptoms, and one episode with respiratory involvement. Laboratory investigations revealed elevated tryptase levels during crises, suggesting mast cell activation. Extensive allergological and etiological testing, including screening for clonal mast cell disorders, was negative. A diagnosis of Mast Cell Activation Syndrome (MCAS) was considered, supported by her response to mast cell stabilizers, sodium cromoglicate, and ketotifen. This report highlights the challenges in diagnosing MCAS, particularly in pediatric populations, where its prevalence remains unclear. The case emphasizes the importance of excluding other potential causes of anaphylaxis and the need for personalized treatment, which in this case significantly improved the patient's symptoms and quality of life. The patient continues to have a controlled emotional state, with no further episodes following initiation of preventive therapy.

Keywords: *Anaphylaxis, Mast Cell Activation Syndrome, Pediatrics*

Introduction

Anaphylaxis is defined as a systemic hypersensitivity reaction, potentially fatal, with an acute onset and rapid evolution, usually triggered by exposure to certain agents.[1,2] Idiopathic anaphylaxis (IA) is characterized by the absence of a specific trigger factor.[3] Usually, in IA there is multisystemic involvement with hypotension, hypoxia, diarrhea, urticaria and upper respiratory tract impairment, resulting of excess mast cells activation.[3] When activated, mast cells release a variety of vasoactive mediators such as tryptase and histamine, responsible for signs and symptoms of allergic reactions.[1]

There was a recent proposal to classify mast cells (MC) activation disturbs. Primary MC disturbs are associated with clonal MC proliferation and KIT D816V mutation and/or anormal expression of CD25 into MC. Secondary MC disturbs are associated with other allergies or connective tissue disorders (via IgE, for example). Idiopathic are classified as nonclonal MC proliferation without trigger factors, and this group includes MCAS.[3,4]

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The criteria for MCAS were first proposed in 2010, but only accepted in international consensus in 2012.[1,3] Three criteria must be met to diagnose MCAS: presence of typical symptoms of MC activation; laboratory evidence of MC activation, by increased tryptase compared to baseline levels; and good response to MC inhibitory therapy.[3,4]

Case Presentation

A 9-year-old female child, previously healthy and with no allergies known, presented to the Emergency Department (ED) in a first episode of sudden nighttime awakening, colicky abdominal pain, vomiting, diarrhea, and bilateral plantar itching. The symptoms progressed half an hour later to generalized pruritic maculopapular rash, facial erythema, and labial edema, without dyspnea, pharyngeal tightness, or lipothymia. Parents denied previous context of illness, infectious contacts, or recent medication intake. Last meal was 4 hours before admission, without introduction of new foods. After evaluation at ED, she was treated with intramuscular adrenaline, systemic antihistamine, and corticosteroids, resulting in rapid resolution of symptoms.

Subsequently, 3 days after discontinuing the treatment with oral antihistamines, she returned to the ED after a sudden episode of dry and irritative cough after dinner accompanied by pharyngeal tightness, stridor, watery rhinorrhea, facial erythema, abdominal pain, vomiting and diarrhea.

She experienced repeated anaphylactic crisis with the same characteristics requiring ED visits, with a sum of four episodes in six weeks. All episodes involved gastrointestinal and cutaneous symptoms (diarrhea, abdominal pain, vomiting, facial erythema/ pruritic maculopapular rash) and one included respiratory symptoms. The patient did not have hypotension associated with the crisis described. In all the crises, there was a positive response to intramuscular adrenaline.

Initial laboratory workup revealed an elevated tryptase level during the crisis (19 ng/mL), without other alterations. The patient was referred to the Immunoallergology consultation for further investigation. In outpatient care, she was medicated with rupatadine and montelukast, maintaining episodes with the same characteristics. Additional allergology study performed was negative. Further etiological investigation showed normal basal tryptase (5 ng/mL), normal complement activity, negative autoimmunity investigation, normal serum catecholamines and urinary metanephrines (excluding pheochromocytoma) and negative 5-hydroxyindoleacetic-acid assay (excluding carcinoid syndrome). Given the presented findings, the hypothesis of Mast Cell Activation Syndrome (MCAS) was considered and oral sodium cromoglicate and ketotifen were initiated, with clinical improvement. The patient had negative KIT D816V mutation and was referred to Hematology consultation. The disease was a source of anxiety for the for the sociofamilial context, and therefore the child was referred to a Psychologist maintaining follow-up due to the impact of the crisis.

After beginning the preventive therapy with mast cell stabilizing medication (sodium cromoglicate and ketotifen), no further anaphylactic episodes or symptoms interfering with her daily routine were reported resulting in more controlled emotional stress.

Discussion

The criteria for MCAS were first proposed in 2010, but only accepted in international consensus in 2012.[1,3] Three criteria must be met diagnose MCAS: presence of typical symptoms of MC activation; laboratory evidence of MC activation, by increased tryptase compared to baseline levels; and good response to MC inhibitory therapy.[3,4]

MCAS includes a heterogeneous group of diseases, with unknown prevalence in pediatric population, characterized by episodes of spontaneous activation and degranulation of MC, with anaphylaxis as the extreme example of this inappropriate activation, causing significant familiar anxiety.[5-7]

Patients usually have a variable clinical phenotype affecting multiple organs. However, there is a key characteristic of systemic anaphylaxis recurrent episodes with simultaneous involvement of at least two organs, similarly to presentation of the described clinical case.[6] Symptoms, especially in patients with MCAS, can vary between urticaria, flushing, itching, angioedema, nasal congestion, wheezing, headache, hypotensive syncope, tachycardia, abdominal pain, diarrhea and vomiting.[4,8]

For MCAS diagnosis, the presence of an elevated MC biomarker is essential. The crucial biomarker is serum tryptase, or in more rare cases, it is possible to use other markers such as histamine, leukotrienes and prostaglandin.[6] Serum tryptase is a reliable blood test and should be evaluated in all situations of clinical MCAS suspicion or in the presence of anaphylaxis and severe allergic reactions.[6] In the clinical case described, the tryptase evaluation was performed during one of the episodes in ED context, showing increased tryptase levels greater than the baseline value – in crisis 19 ng/mL (more than 20% + 2 ng/mL above the baseline value of 5 ng/mL).[4]

In MCAS the symptoms are compatible with MC activation, although there is no clonal proliferation.[8] In cases where there is clonal proliferation, it occurs typically due to activation of somatic mutations in the proto-oncogene KIT, with D816V mutation being the most frequent.[8] In the case previously described, there was no evidence of this mutation in the investigation performed, supporting the diagnosis of MCAS.

In patients who present severe hypotension and anaphylaxis, differential diagnosis includes cardiovascular disturbances such as orthostatic hypotension or paroxysmal arrhythmias; endocrinological emergencies such as pheochromocytoma, medullary thyroid carcinoma, insulinoma, carcinoid syndrome; psychological illnesses such as anxiety, panic attacks, somatic symptom disorder; neurologic diseases like migraine, seizures, stroke; or serious infections and adverse drug reactions.[5,8]

Therefore, the first step for prompt guiding of patients with suspected MCAS is to exclude disorders that can mimic this condition.

Generally, symptoms associated with MCAS can be controlled by blocking receptors for mediators (H1 and H2 histamine antagonists or leukotriene blockers), inhibiting mediator synthesis (aspirin), inhibiting mediator release (sodium cromoglicate), anti-IgE therapy or, as in the clinical case above, through a combination of different approaches.[8] Sodium cromoglicate has shown evidence in cases of MCAS with significant skin, gastrointestinal, and neuropsychiatric involvement.[8] Complementing these treatments, it is essential for patients with severe presentations, like anaphylaxis, to carry auto-injectable adrenaline pens.

In clinical practice, diagnosing MCAS is a real challenge, as we are faced with very variable and nonspecific symptoms, nevertheless this diagnostic should be considered whenever a triggering factor is not identifiable.[6] Since the beginning of MCAS diagnose and case identification, the number of suspected patients has increased significantly.[4] The clinical presentation of these patients is variable and nonspecific, despite the significant impact on quality of life. Moreover, the MCAS response to treatment still remains poorly defined.[4]

Therefore, the related MC disturbs are complex clinical entities, more frequent than previously predicted, but still underdiagnosed.[6]

Conclusion

Anaphylaxis is an extreme example of mast cell inappropriate activation. Mast Cell Activation Syndrome (MCAS) was first proposed as a distinct idiopathic clinical entity in 2010 and diagnosis is made in the presence of multiple episodes of multisystemic symptoms, increase of crisis tryptase and good response to mast cell stabilizing medication. Treatment must be individualized and may include oral sodium cromoglicate and antihistamines. Prompt diagnosis and detailed knowledge allow disease control and are essential to improve quality of life and manage the family's anxiety.

Conflicts of Interest

The authors declare no conflicts of interest.

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