Mast cell activation disease

associated with autoimmune thyroid disease: case report and review of literature

Joselyn Rojas, MD, MSc[1,2], María José Calvo Delgado, MD[1], Carmen Chávez, MD[1], Mervin Chávez-Castillo, MD[1], Lidia Mejía, MD[1], Juan Salazar, MD[1], Luis Olivar, Bsc[1], Modesto Graterol-Rivas[3], Sandra Wilches-Duran[3], Julio Contreras-Velásquez[3], Rosemily Graterol-Silva[3], Valmore Bermúdez, MD, MPH, MgSc, PhD[1]*

[1]Endocrine and Metabolic Diseases Research Center. School of Medicine. University of Zulia. Maracaibo, Venezuela.
[2]Endocrinology Department. Maracaibo University Hospital. Maracaibo, Venezuela.
[3]Altos Estudios de Frontera (ALEF) Research Group. Universidad Simón Bolívar, Cúcuta, Colombia.

**Corresponding Author: Joselyn Rojas, MD, MSc. University of Zulia, School of Medicine. Endocrine and Metabolic Diseases Research Center, Maracaibo, Venezuela. Fax: 58-261-7597279. Email: rojas.joselyn@gmail.com*

Abstract

Mast Cell Activation Disease (MCAD) is characterized by abnormal proliferation of mastocytes, where clinical manifestations arise from the excess release of these cells' mediators. This case report concerns a 34-year old male patient who seeks medical attention after 5 months presenting recurring episodes of intense facial flushing with local edema, erythema, and increased volume of the ears and lips, without signs of angioedema. Other symptoms included burning oropharyngeal pain, vascular-type headache and hypotension. These crises occurred predominantly during nighttime and lasted 20-60 minutes, and were often associated with prolonged exposure to sunlight, high temperatures and psychological stress; constituting a clinical picture compatible with MCAD, supported by laboratory findings. Treatment began with ebastine, deflazacort, montelukast, ranitidine and omega-3 fatty acids, without clinical improvement, leading to substitution of this regimen with sodium chromoglycate and initiation of an immunomodulatory diet. This plan achieved satisfactory symptomatic resolution, confirming the diagnosis and highlighting the importance of adequate pharmacologic intervention. During a control consultation, the patient reported nocturnal episodes of tachycardia, palpitations and anxiety unrelated to the flushing crises, which prompted thyroid evaluation, revealing autoimmune thyroid disease with subclinical hyperthyroidism, which was managed with methimazol without complications.

Keywords: Mast cell activation disease, mastocytosis, histamine, facial flushing, autoimmune thyroid disease.

Introduction

Mast cells (or mastocytes) play a fundamental role in the development of immediate allergic reactions by synthesizing, storing and releasing a wide array of mediators upon activation, in a process termed degranulation[1,2]. This may occur due to the classic mechanism involving cross-linking of high-affinity IgE receptors (FcεRI) in response to an allergen; or numerous IgE-independent processes, including stimulation by complement system components, cytokines, opiates, temperature, pressure and vibration[3]. Mastocytes may also be activated by c-KIT ligand (OMIM 184745) binding to its receptor, c-KIT (CD117, OMIM 164920)[4]; an event also involved in these cells' proliferation and differentiation[5,6].

Abnormal proliferation of mastocytes results in a hemopoietic disorder termed mastocytosis or Mast Cell Activation Disease (MCAD), which is most commonly limited to the skin, but may also involve various other tissues, such as the bone marrow, liver, spleen and gastrointestinal tract[7,8]. Excessive release of mediators from mastocytes –histamine, TNF-α, IL-8 leukotrienes, prostaglandins, platelet-activating factor, heparin and tryptase– induces a variety of local and systemic manifestations principally driven by histamine activity: flushing, flares, wheals, pruritus, dyspnea, asthma exacerbations, hypotension, gastroesophageal reflux, peptic ulcers and diarrhea, among others[9-12] (Table 1).

Table 1. Manifestations associated with the release of mastocytary mediators.
Abdominal
Abdominal pain, diarrhea or constipation, nausea, non-*H. pylori*-related gastritis, malabsorption.
Respiratory
Cough, asthma-like symptoms, dyspnea, rhinitis, sinusitis.
Neuropsychiatric
Headache, neuropathic pain, polyneuropathy, impaired concentration and memory, anxiety, insomnia, vertigo, tinnitus.
Cardiovascular
Tachycardia, palpitations, hypotension or hypertension, syncope, flushing.
Cutaneous
Urticaria pigmentosa, pruritus, telengectansia, flushing, angioedema
Musculoskeletal
Myalgia, osteoporosis/osteopenia, ostealgia, migratory arthritis.
Lymphadenopathy
Abnormal mucosal bleeding

Due to the tisular ubiquity of mastocytes and the heterogeneity of the molecules they release, MCAD may present with vastly diverse symptoms, hindering its diagnosis and management. This conundrum has stemmed numerous proposals for their diagnostic criteria and therapeutic approaches, although the topic remains controversial. MCAD can be classificated as shown in Table 2 [13,14].

We report the case of a male patient who attended our department presenting with a diffuse clinical picture, with a constellation of cutaneous, gastrointestinal and neuropsychiatric signs and symptoms over multiple months. These led to repeated consultations in various medical specialties, where clinical and paraclinical findings were interpreted as separate disorders, without reaching a unifying diagnosis.

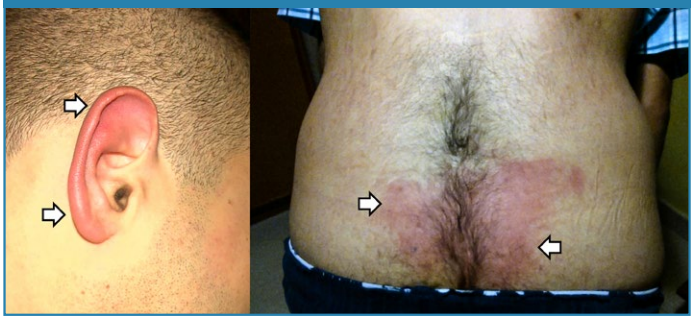
Table 2. Diseases associated with Mast Cell Activation Disordes.
Mast Cell Activation Disorders [13,14]
1. Primary: • **Anaphylaxis with and associated clonal mast cell disorder** • **Monoclonal mast cell activation syndrome**
2. Secondary • **Allergic disorders** • **Mast cell activation with chronic inflammatory or neoplastic disorders** • **Physical urticarias** • **Chronic autoinmune urticaria**
3. Idiopathic • **Anaphylaxis** • **Angioedema** • **Urticaria** • **Mast cell activation syndrome**

Case Report

A 34-year old male from Maracaibo City first seeks medical attention after a period of 5 months presenting recurring episodes of intense facial flushing, with erythema, and edema in the face and neck, beginning at the suprasternal notch, and accompanied by increased volume of the lips and ears, without signs of angioedema. The patient also reports burning pain in the oropharynx, vascular-type headache, and symptoms suggestive of hypotension during these crises. These paroxysms occurred predominantly at night and lasted approximately 20-60 minutes each. Prolonged exposure to the sun or high temperatures, psychological stress and tiredness appeared to be trigger and intensify episodes. The patient reported managing crises by himself with a makeshift mask padded with cold compresses (Figures 1 and 2). No epistaxis, conjunctival injection or other signs suggestive of spontaneous bleeding were apparent during these episodes.

Figure 1. Facial flushing and our patient's makeshift mask padded with cold compresses.

Figure 2. Intense erythema and edema of the right ear and low lumbar area; intensely pruriginous.



These manifestations heavily impaired the patient's daily functioning, particularly at his job as a computer engineer. His typical work day involved 90-minute trips to his workplace and back, prolonged use of computers, mobile phones and other appliances, and occasional on-site inspection of construction areas and platforms. He also reported sleeping only 4-5 hours per night, and described his overall lifestyle as highly stressful. The severity and frequency of the paroxysms –5-7 episodes per day, often associated with occupational exposure to triggering factors– led the patient to suspend his workplace activities from early stages of the disease (February 2013).

He was initially evaluated by the Internal Medicine, Cardiology, Gastroenterology, Neurology, Neurosurgery and Endocrinology departments, undergoing a host of imaging and laboratory tests in order to exclude the presence of a carcinoid tumor, with negative results. Assessment by the Gastroenterology team revealed parasitic duodenitis, severe erosive gastritis, gastroesophageal reflux, peptic esophagus, cholelithiasis, cholecystitis, amoebic rectocolitis and grade I internal hemorrhoids; while the Neurosurgery team found L4-L5 degenerative disc disease.

Because no definite diagnosis was achieved, the patient was referred to the Immunology department of our center (June 2013), where after clinical examination, we requested determination of immunologic laboratory parameters directed to the assessment of the patient's facial flushing, the most prominent feature of his presentation. Relevant findings included positive C-Reactive Protein (9.47 mg/L), slightly elevated serum Immunoglobulin A (435 mg/dL) and normal tryptase levels (2.8 μg/L). The blood sample was taken during an asymptomatic period. Cytometric assessment found low levels of total CD4 and B lymphocytes. Finally, a radioallergoabsorbence test was performed for foods and drugs, revealing the presence of IgE specific for aspirin, piroxicam, ketoprofen, penicillin, ambroxol, iodine, nickel, and latex, and no allergies to foods. Further test results are summarized in Tables 3 and 4.

Table 3. Laboratory tests performed.

Laboratory Parameter	Result
Full Blood Count	
Hemoglobin	13,8
Red Blood Cells	4.730
Hematocrit	47,3%
White Blood Cells	4.690
Neutrophils	52%
Lymphocytes	37,5%
Monocytes	8,9%
Eosinophils	1,3%
Basophils	0,3%
Platelets	215.000
Serum Lipids	
HDL-C	85 mg/dL
LDL-C	136 mg/dL
VLDL-C	26 mg/dL
Total Cholesterol	214 mg/dL
Triacylglycerides	129 mg/dL
Tumor Markers	
α-Fetoprotein	(-)
β-h	(-)
PSA	(-)
Ca125	(-)
Ca19.9	(-)
Ca15.3	(-)
CEA	(-)
Urinary Markers	
5-hydroxyindoleacetic acid	(-)

HDL-C= High-Density Lipoprotein-Cholesterol; LDL= Low-Density Lipoprotein; VLDL-C= Very Low-Density Lipoprotein; β-hCG= Human Chorionic Gonadotropin; CEA= Carcinoembryonic Antigen.

Table 4. Immunologic profile.

Laboratory Test	Result	Reference Range
Immunoglobulin E	0.08	1 - 87 UI/mL
Immunoglobulin G	12.6	7 - 17 g/L
Immunoglobulin M	86	50 - 300 mg/dL
Immunoglobulin A	435	70 - 350 mg/dL
Flow Cytometry		
CD3	53	1500-4000 cells/mm^3
CD3/CD4	510	700-1500 cells/mm^3
CD4/CD8	836	600-1200 cells/mm^3
CD19	118	200-400 cells/mm^3
CD3/CD56	209	200-400 cells/mm^3

Having excluded other flushing-associated disorders, the clinical history of the patient suggests MCAD. The patient also presented many other manifestations well-recognized within the clinical spectrum of MCAD[13,15]: burning pain in the oropharynx, intermittent abdominal pain, gastritis (although the presence of H. pylori has not been excluded), hypercholesterolemia, blood pressure dysregulation, facial flushing, headache, anxiety, insomnia, osteopenia (with vertebral burst fractures found on radiologic examination of the lumbar spine) and environmental sensitivity.

Therapy was started with ebastine 10 mg PO BID for 7 days, and then 10 mg PO OD for 7 days; and deflazacort 15 mg PO OD for 7 days, which was then raised to 30 mg PO OD for the following 2 weeks. At day 15 of treatment, montelukast 10 mg PO OD, ranitidine 300 mg PO OD and omega-3 fatty acids 1000 mg PO OD were added for the following 6 weeks. 21 days after this cycle, the patient denies improvement of symptoms; therefore, we indicated an immunomodulatory diet with restriction of known alimentary triggers for the release of histamine and other vasoactive amines (Tables 5 and 6), along with the use of a second-line drug for inhibition of mastocyte degranulation: sodium chromoglycate 200 mg PO QID, for a total of 800 mg daily.

Tabla 5. Immunomodulatory diet.

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
Breakfast	Baked arepas (corn flour) 2 medium units Shredded beef 6 spoonfuls Chopped vegetables: carrots, red cabbage 4 spoonfuls Pear juice 16 oz	Sweet kernel corn 1 ½ measuring cups Fresh goat cheese or Pecorino cheese (goat or sheep) 4 spoonfuls Milkshake: Bananas and hypoallergenic milk 1 cup	Corn flour buns 2 medium units Shredded chicken, roasted or stewed 6 spoonfuls Chopped vegetables: carrots, red cabbage 4 spoonfuls Peach juice: ripe, boiled, without skin 1 cup	Boiled manioc 3 medium pieces Shredded or minced chicken or beef 6 spoonfuls Apple juice 1 cup	Baked corn flour empanada with minched chicken or beef filling 2 medium units Pear juice 1 cup
Snack	Banana 1 large unit or Apples 2 large units	Apples 2 large units	Red glove grapes 12 units	Crackers 2 units	Peeled nectarine 1 large unit
Lunch	Thick potato and pumpkin soup 2 measuring cups Roast chicken ½ breast White rice 1 measuring cup Salad: string beans, beets, lettuce 6 spoonfuls Kiwi juice 1 large cup	Spinach stuffed chicken 1 breast Boiled potato with onion sauté 1 large unit Steamed broccoli and chard sauté 6 spoonfuls Peach juice: ripe, boiled, without skin 1 cup	Lentil purée soup 1 measuring cup Boiled beet 1 unit Grilled plantain 1/3 large unit Apple juice 1 cup	Grilled beef 200 g Boiled or grilled potato with salt and garlic 1 large unit Salad: Boiled string beans, raw carrots, lettuce 6 spoonfuls Soursop juice 8 oz	Chicken or beef brochette with onions and tomatoes 2 large units Salad: boiled beets, carrots, and potatoes, letttuce; no mayonnaise 6 spoonfuls Boiled or grilled yam with salt and oregano 1 unidad grande Pear juice 1 cup
Snack	Pear 1 large unit	Ripe loquat 1 medium unit	Banana 1 large unit or Apples 2 large units	Pear 1 large unit	Red glove grapes 12 units
Dinner	Baked arepa (manioc and corn flour) 1 medium unit Grilled, shredded chicken 3 spoonfuls Shredded carrots and zucchini 2 spoonfuls Apple juice 1 cup	Rice or mung bean noodles 1 measuring cup Shredded Milanesa beef steak 3 spoonfuls Sauté: String beans, carrots, chayote 3 spoonfuls Jugo de pera 1 cup	Chopped fajita-style chicken ½ breast Colombian potatoes sautéed with salt only 1 measuring cup Chopped carrots and zucchini with olive oil and salt 3 spoonfuls Apple juice 1 cup	Half-ripe plantain, grilled or fried ½ medium unit Shredded chicken, grilled or sewed 3 spoonflus Vegetales: cebolla, cilantro y germinado de lentejas chinas 3 spoonfuls Pear juice 1 cup	Cachapa (Corn tortilla, without eggs) 1 medium unit Shredded beef 3 spoonfuls Chopped vegetables: carrots and coriander 3 spoonfuls Peach juice: ripe, boiled, without skin 1 cup

Table 6. Histamine-releasing foods.

Protein: • Egg whites • Pork • Crustaceans • Fish • Cold meats • Nuts • Milk	**Cereals:** • Wheat **Fruits** • Papaya • Pineapple • Strawberry • Citric fruits **Vegetables:** • Tomatoes • Spinach • Avocado	**Others** • Chocolate • Cocoa • Licorice • Marshmallows • Curry • Food-derived sulphites (e.g. prunes, dates, figs). • Alcohol • Sunflower oil

However, because this agent has not been distributed in our country for the last 8 years, it required importation form Europe, which was delayed for 10 months due to our country's current restrictions on transactions with foreign currency and drug importation. In this interim, the patient suffered a severe 3-hour long crisis (September 2013) which required emergency assistance and granted reinitiation of the first-line management: deflazacort 15-30 mg PO OD, ranitidine 300 mg PO OD and fexofenadine 180 mg PO OD, for 21 days.

In January 2014, the patient complained of unrestful sleep and chronic fatigue with worsening of the crises. After psychiatric evaluation, he was started on mirtazapine, clonazepam, zolpidem and quetiapine, with monthly consultations with this department.

In June 2014, sodium chromoglycate was finally available for our patient, who begins the 800 mg daily regimen. At this point, the patient had been presenting 5-10 flushing episodes per day, which lasted 15-30 minutes each. 2 weeks after starting this medication, he reported less than 5 crises per day, and by August 2014 these had subsided completely, allowing our patient to use mobile phones and undergo exposure to sunlight and high temperatures without problems, thus facilitating reintegration into his workplace.

Nevertheless, in a periodic evaluation with our team (September 2014), the patient reported recurrent episodes of tachycardia and palpitations, of short duration and predominantly during the nighttime, unrelated to the paroxysms of facial flushing. The thyroid was evaluated, revealing decreased size of the gland (Left lobe 4.2 x 1.2 cm, right lobe 4.2 x1.6 cm, isthmus 2.8 cm), with micronodular surface. The laboratory results ascertained TSH 0.1 UI/mL, free T3 4.1 pg/mL and free T4 2.01 ng/mL; with high Anti-TPO antibodies (398 AU/mL, normal value ≤50 AU/mL) and negative Anti-TG antibodies (35 AU/ml, normal value ≤50 AU/mL). With these findings, we diagnosed autoimmune thyroid disease with subclinical hyperthyroidism, and indicated methimazol 10 mg PO OD. With this management, the patient has remained asymptomatic from this point up to the date of submission of this manuscript.

Discussion

Mastocytoses comprise a heterogeneous group of relatively infrequent disorders, with an annual incidence of approximately 5-10 cases per million[16]. Although their etiology remains largely unelucidated, mutations of the c-KIT proto-oncogene appear to play a key role, as they are found in many patients with these diagnoses. This gene, expressed in mastocytes, hemopoietic stem cells and germ cells, codifies a type III tyrosine kinase transmembrane receptor, whose extracellular domain binds mast cell growth factor (stem cell growth factor, c-KIT ligand), which is responsible for the growth, function and survival of these cells[17]. Pediatric patients with the c-KIT mutation tend to develop extensive mastocytosis which may persist into the adult age and may be associated with the clinical onset of Systemic Mastocytosis (SM)[18]. Levels of mast cell growth factor are increased in the cutaneous lesions found in MCAD, being responsible for proliferative stimulation of mastocytes and melanocytes, explaining the hyperpigmentation found in these sites[18]. Anti-apoptotic proteins like BCL-2 are also upregulated in MCAD, suggesting a role for the inhibition of apoptosis in its pathogenesis[19]. Similarly, elevated levels of IL-6 are also found in MCAD and are related to their severity, and may also be in their etiology[20].

On the other hand, the signs and symptoms of MCAD are related to excess tisular infiltration of these cells, and their release of mediators such as histamine, prostaglandins, heparin, proteases and hydrolases. The spectrum of clinical presentations is broad, ranging from asymptomatic to severe cases (SM)[6]. The classification of MCAD includes SM, Cutaneous Mastocytosis, and Mast Cell Leukemia; only the latter is currently considered a rare disease[13], while the cutaneous entities are the most common, particularly urticaria pigmentosa[21]. This subtype affects children mainly, and is characterized by the presence of brownish or reddish macules, papules and plaques, which may appear in any skin area or mucosa, with pruritus, dermographism and positive Darier's sign[6,22].

In most instances, the diagnosis of MCAD can be made solely through non-invasive means, based on the observation of signs and symptoms compatible with the release of mastocyte mediators, identification of the typical skin lesions, and realization of certain ancillary tests; after exclusion of other relevant entities[13].

In the case of our patient, high clinical suspicion of MCAD was raised by his clinical picture: His description of recurring episodes of facial flushing accompanied by burning oropharyngeal pain, intermittent abdominal pain, gastritis, hypercholesterolemia, blood pressure dysregulation, headache, anxiety, insomnia, osteopenia and environmental sensitivity in ensemble constitute a constellation of manifestations compatible with increased mastocyte activity, a finding currently included as one of the major diagnostic criteria for MCAD[13,15].

In order to confirm the diagnosis, the next step is the realization of specific laboratory tests: Tryptase determination car-

ries great value[13], provided that it is quantified both during a crisis and during an asymptomatic period, as the diagnostic criterion demands a 20% increase from the baseline during the crisis[23]. Because we were unable to comply with this requirement, a random tryptase determination was performed, which may explain our finding of normal levels of this enzyme. Other diagnostic criteria include histopathological evidence of mastocytary infiltration in the bone marrow or other extracutaneous organs, as well as detection of genetic alterations in mastocytes from blood, bone marrow or other extracutaneous organs compatible with hyperactivity of these cells[13]. Nevertheless, these were unavailable in our case, and we reoriented our patient's diagnostic management to a more general evaluation of his immunologic profile (Tables 3 and 4).

As has been mentioned before, the manifestations of MCAD result from the degranulation of mastocytes as a consequence of an inappropriate response to specific triggers, including IgE-mediate immune stimuli, bacterial toxins, hymenoptera and ophidic venoms, and, particularly important in MCAD, physical stimuli –e.g. exposure to high or low temperature, sunlight, friction– and drugs, such as aspirin, opiates, polymyxin, amphotericin and others[24]. Therefore, the therapeutic approach is primarily directed towards control of the exposure to environmental factors capable of inducing mastocyte degranulation[13,25,26]. In our patient, the main triggers appeared to be exposure to be work-related exposure to sunlight, high temperatures and psychological stress. Thus, we indicated suspension from his job and initiation of an immunomodulatory diet. Likewise, administration of drugs to act as "anti-mediators" is fundamental in the initial management of subjects with MCAD. Due to ample variety of intermediaries released by mastocytes, pharmacologic intervention should be carefully selected in order to address the clinical manifestations seen in each particular patient[27].

By binding to H1 receptors, histamine is responsible for the cutaneous manifestations –notably, flushing and urticaria–, peripheral vasodilation, edema, headache, mucus production and bronchoconstriction. Thus, first-line treatment for these symptoms features H1 receptor antagonists such as ebastine and cetirizine; while short-term glucocorticoid therapy is indicated in severe or resistant cases[13,28]. Although the latter are considered second-line drugs in MCAD, they are invaluable in most inflammatory and immunologic disorders due to their multiple effects at various levels, including reduced expression of FcεRI, inhibition of mastocyte degranulation through non-genomic mechanisms, inhibition of cytokine and chemokine synthesis, as well as decreased concentration of mastocytes in biopsies of affected tissues[29,30]. Glucocorticoids are also recommended in severe cases of SM, particularly those featuring hepatomegalia[13,30]. Due to the severity of our patient's crises, we began therapy with a mixed approach, with both first- and second-line drugs.

Histamine also binds to H2 receptors, which induces hypersecretion of gastric acid –facilitating the development of dyspeptic alterations– and enhances gastrointestinal motility, favoring the installation of abdominal pain and diarrhea. Therefore, therapeutic guidelines recommend the administration of H2 receptor antagonists, such as ranitidine and cimetidine, from the beginning of treatment; proton-pump inhibitors may also be used in severe cases[13,30].

Following the paraclinical assessment of our patient, the therapeutic plan was modified to achieve adequate control of mastocyte degranulation by adding sodium chromoglycate, a widely-recognized "stabilizer" of these cells' membranes (Table 7). These agents are usually well-tolerated and improve a myriad of symptoms, especially of the gastrointestinal system. Although their mechanism of action remains incompletely elucidated, they have been evidenced to reduce calcium influx in mastocytes, which is necessary for their activation[13,30,31].

Table 7. Mast cell membrane stabilizers.

Drug	Effects
Sodium chromoglycate	Inhibits mast cell degranulation by blocking calcium influx throught the cell membrane. Also inhibits activation of neutrophils, monocytes and eosinophils.
Nedocromil sodium	In addition to its membrane-stabilizing effects, also acts as an H1 receptor antagonist. Also acts on eosinophils.
Lodoxamide	Most powerful membrane stabilizer in the group.

Currently, research efforts are being directed to the pharmacological intervention in MCAD through other target mediators, including prostaglandins, platelet-activating factor and leukotrienes. Receptor antagonists are available for the latter, with accounts of satisfactory responses as coadjutants in MCAD[32]. On the other hand, polyunsaturated omega-3 fatty acids have been demonstrated to modulate mastocyte activity; and in spite of controversial evidence, several authors recommend their use in these disorders[33,34].

In most instances, patients can be successfully managed with first-line agents or combinations, and in refractory cases, other diagnoses should be considered[24]. In patients with favorable responses to treatment, both clinical and laboratory parameters tend to improve substantially and may normalize, although full remission occurs in few cases despite use of multiple medications[27,29]. Our patient experienced satisfactory resolution of symptoms for several months after starting sodium chromoglycate, supporting the diagnosis of MCAD.

Other elements in the clinical spectrum of MCAD include headaches, impaired concentration and memory, fatigue and depressive symptoms, which are present in one third of the adult population with mastocytosis[35]. The pathophysiologic mechanisms involved in this scenario are unknown, although the psychological burden of the disease –with its chronicity

and disruption of daily functioning– may play an essential part; and endocrine factors may be particularly prominent in females. At any rate, in these cases, it is important to include Neurology and Psychiatry specialists in the attending team, who may ponder the addition of neuropsychoactive medication to each particular patient's treatment scheme. Moreover, this interdisciplinary therapeutic group should also include support from nutritionists and psychologists, as well as other medical specialties if required[26].

Autoimmune thyroid disease is a frequent and variable entity, with presentations ranging from hypofunction (Hashimoto's thyroiditis) to hyperfunction (Graves' disease), with predominantly Th1 and Th2 responses, respectively[36]. Nevertheless, the association with MCAD with autoimmune thyroid disease appears to be rare, with scarce published reports. We could only find one case similar to our report in the literature: Benucci et al.[37] described a case of SM associated with osteoporosis in a 57-year old female with history of autoimmune hyperthyroidism.

In conclusion, the hallmark of MCAD is inappropriate activation of mastocytes with release of mediators responsible for a myriad of manifestations which have a powerful impact in the patients' lifestyles. Diagnosis may be accomplished non-invasively with thorough clinical examination and laboratory support. Treatment requires an interdisciplinary assembly of specialists in order to achieve symptom resolution and reincorporation of the patients into their regular day-to-day activities.

DISCLOSURE

The authors have are no conflicts of interest to disclose.

References

1. Galli SJ. New concept about the mast cell. N Eng J Med. 1993;328:257-65.
2. Frieri M, Patel R, Celestin J. Mast cell activation syndrome: a review. Curr Allergy Asthma Rep. 2013;13(1):27-32.
3. Ishizaka K, Ishizaka T. Immunoglobulin E: Biosynthesis and Immunological Mechanisms of IgE-Mediated Hypersensitivity. Cellular, Molecular, and Clinical Aspects of Allergic Disorders. Comprehensive Immunology 1979;(6):153-178.
4. Arinobu Y, Iwasaki H, Akashi K. Origin of Basophils and Mast Cells. Allergology International. 2009;58:21-28.
5. Kitamura Y, Shimada M, Hatanaca K, Migano Y. Development of mast cells forms grafted bone marrow cells in irradiated mice. Nature. 1997;268:442-3.
6. Valent P. The riddle of the mast cell: kit (CD 117)-ligand as the missing link. Immunol Today. 1994;15:11-4.
7. Kutlubay Z, Yardimci G, Engin B, Tüzün Y. Cutaneous Mastocytosis. J Turk Acad Dermatol. 2011; 5(3):1153r1.
8. Zenea A. Mastocitosis una rara afección. Avances Med Cuba 1997;12:40-3.
9. Madendag IC, Madendag Y, Tarhan I, Altinkaya SO, Danisman N. Mastocytosis in pregnancy. Taiwan J Obstet Gynecol. 2010;49:192-196.
10. Briley LD, Phillips CM. Cutaneous mastocytosis: a review focusing on the pediatric population. Clin Pediatr. 2008;47:757-761.
11. Söderholm JD. Mast cells and mastocytosis. Dig Dis 2009;27:129-136.
12. de Giorgi V, Fabroni C, Alfaioli B et al. Solitary mastocytoma: tooth eruption as triggering factor. Int J Dermatol 2008;47:1274-1277.
13. Molderings GJ, Brettner S, Homman J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol. 2011;4:10.
14. Molderins GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup an therapeutic options. J Allergy Clin Immunol. 2010; 126(6): 1099–104.
15. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. J Allergy Clin Immunol. 2011;128(1):147-152. e2
16. Amon U, Hartmann K, Horny HP, Nowak A. Mastocytosis an update. J Dtsch Dermatol Ges. 2010;8:695-711.
17. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocitosis. Leuk Res. 2001; 25:519-528
18. Bulat V, Lugovie Mihie L, Situm M, Buljam M,Blajic I, Pusic J. Most common clinical presentations of cutaneous mastocitosis. Acta Clin Croat. 2009;48:59-64.
19. Xiang Z, Ahmed AA, Möller C, Nakayama K, Hatakeyama S, Nilsson G. Essential Role of the Prosurvival bcl-2 Homologue A1 un Mast Cell Survival After Allergic Activation. J Exp Med. 2001,3; 194(11): 1561–1570.
20. Metcalfe D. Mast cell and mastocitosis. Blood. 2008;112:946-956.
21. Slavkovi-Jovanovi M, Petrovi A, Mihailovi D. Urticaria pigmentosa. A case report. Acta Dermatoven 2008:17(2):79-82.
22. Zenea A. Mastocitosis una rara afección. Avances Med Cuba. 1997;12:40-3.
23. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, Castells M, Escribano L, Hartmann K, Lieberman P, Nedoszytko B, Orfao A, Schwartz LB, Sotlar K, Sperr WR, Triggiani M, Valenta R, Horny HP, Metcalfe DD. Definitions, criteria and global classifications of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int. Arch. Allergy Clin. Immunol. 2012;157:215–225.
24. Carter M, Metcalfe D, Komarow H. Mastocytosis. Immunol Allergy Clin N Am. 2014;34:181–196.
25. Afrin L. The presentation, diagnosis and treatment of mast cell Activation syndrome. Current Allergy & Clinical Immunology. 2014;27(3):146-160.
26. Siebenhaar F, Akin C, Bindslev-Jensen C, Maurer M, Broesby-Olsen S. Treatment Strategies in Mastocytosis. Immunol Allergy Clin N Am. 2014;34:433–447.
27. Akin C. Mast Cell Activation Disorders. J Allergy Clin Immunol Pract. 2014;2:252-7.
28. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluin-Nelemans HC, Hamdy NA, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M,

Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP, Metcalfe DD. Standards and standardization in mastocytosis: Consensus Statements on Diagnostics, Treatment Recommendations and Response Criteria. European Journal of Clinical Investigation. 2007;37(6):435-453.

29. Blackwell Publishing Ltd. Diagnosis and treatment of systemic mastocytosis: State of the art. British Journal of Haematology. 2003;122:695–717.

30. Borriello F, Granata F, Varrichi G, Genovese A, Triggiani M, Marone G. Imunopharmacological modulation of mast cells. Current Opinion in Pharmacology. 2014;17:45–57.

31. Kutlubay Z, Yardımcı G, Engin B, Tüzün Y. Cutaneous Mastocytosis. J Turk Acad Dermatol. 2011;5(3):1153r1.

32. Tolar J, Tope W, Neglia J. Leukotriene-Receptor Inhibition for the Treatment of Systemic Mastocytosis. N Engl J Med. 2004;350:735-736.

33. Gueck T, Seidel A, Baumann D, Meister A, Fuhrmann H. Alterations of mast cell mediator production and reléase by gamma-linoleic and docosahexaenoic acid. Ver Dermatol. 2004;15:309-314.

34. Gueck T, Seidel A, Fuhrmann H. Effects of essential fatty acids on mediators of mast cell in culture. Prostaglandins Leukot Essent Fatty Acids. 2003;68:317-322.

35. El Lateef H. Mast cell activation disease. Egypt J Pediatr Allergy Immunol. 2013;11(2):53-61.

36. Rojas J, Aguirre MA, Cano R, Villalobos M, Berrueta L. La otra cara de Janus y la enfermedad tiroidea autoinmune. Rev Venez Endocrinol Metab 2011;9(3): 89-98.

37. Benucci M, Bettazzi C, Bracci S, Fabiani P, Monsacchi L, Cappelletti C, Manfredi M, Ciolli S. Systemic mastocytosis with skeletal involvement: a case report and review of the literature. Clin Cases Miner Bone Metab. 2009;6(1):66-70.

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