A 60-year-old woman with recurrent episodes of flushing, urticaria, and angioedema

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ABSTRACT

Recurrent episodes of flushing, urticaria, and angioedema raise suspicion for many conditions with a wide differential diagnosis. The diagnostic approach involves consideration of allergic, cardiovascular, gastrointestinal, endocrine, infectious, neurologic, dermatologic, and drug-related causes. We describe a unique case of recurrent episodes of flushing, urticaria, and angioedema that has gone into remission after a novel therapeutic intervention.

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A 60 year-old woman with recurrent episodes of flushing, urticaria, and angioedema presented to the allergy clinic for follow-up after an emergency department (ED) visit for “total body flushing” about an hour after eating wheat crackers, cheddar cheese, and decaffeinated tea. She had previously presented to a local ED with “flushing” involving her arms, legs, torso, neck, and face. She denied gastrointestinal symptoms at that time, but she reported previous similar episodes that were associated with abdominal discomfort and diarrhea. In the ED, she was treated with epinephrine, diphenhydramine, and steroids with resolution of her symptoms.

Her medical history included asthma, fibromyalgia, osteoarthritis, migraine headaches, hypothyroidism, and hyperlipidemia. Her medications included albuterol as needed, sumatriptan, fexofenadine, levothyroxine, and fluoxetine. Her allergy history included hives when exposed to tetracycline, gastrointestinal upset, and a syncopal episode when exposed to smells of eggs and popcorn and local swelling to stinging insects.

PHYSICAL EXAMINATION

She was a comfortable-appearing woman. Her vital signs were temperature 36.7°C, heart rate 68 beats per minute, blood pressure 120/72 mm Hg, and respira-

tory rate 16 breaths per minute. Head, eyes, ears, nose, and throat exam was unremarkable. Lungs were clear to auscultation bilaterally. Cardiac exam revealed a regular rate with no murmurs. Skin exam revealed no flushing, urticaria, angioedema, eczema rashes, dermatographism, or urticaria pigmentosa lesions. The remainder of the physical examination was unremarkable.

INITIAL LABORATORY FINDINGS

Laboratory studies had shown normal complete blood count and differential, mildly elevated transaminases attributed to hepatic steatosis, and normal thyroid stimulating hormone. Immunoglobulin E (IgE) Radioallergosorbent testing of suspected allergens included egg white, egg yolk, ovalbumin, ovomucoid, honey bee venom, yellow jacket wasp venom, paper wasp venom, white face hornet venom, yellow face hornet venom, and corn were less than 0.35 kU/L (reference range, less than 0.70 kU/L). Total IgE level was 54 kU/L (reference range, 0–150 kU/L).

QUESTION 1

What is the differential diagnosis of this patient's episodes of flushing, urticaria, and angioedema?

- 1) IgE-mediated allergies to foods, drugs, and a variety of other allergens
- 2) Hereditary angioedema
- 3) Mastocytosis
- 4) Monoclonal mast cell activation syndrome (MCAS)
- 5) Idiopathic MCAS
- 6) Idiopathic chronic urticaria, angioedema, or anaphylaxis
- 7) Carcinoid syndrome
- 8) Pheochromocytoma

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Table 1. Two recently proposed criteria for the diagnosis of mast cell activation

First criterion

- 1) Typical clinical symptoms: flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, hypotension, or diarrhea
- 2) Increase in serum total tryptase by at least 20% above baseline plus 2 ng/mL during or within four hours after a symptomatic period
- 3) Response of clinical symptoms to histamine receptor blockers or mast cell targeting agents, *e.g.*, cromolyn

Second criterion

Major criteria

- 1) Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (*e.g.*, gastrointestinal tract biopsies; CD 117, tryptase, and CD25 stained)
- 2) Unique constellation of clinical complaints as a result of pathologically increased mast cell activity (mast cell mediator syndrome)

Minor criteria

- 1) Mast cells in bone marrow or other extracutaneous organ(s) showing an abnormal morphology (>25% in bone marrow smears or histologies)
- 2) Mast cells in bone marrow express CD2 and/or CD25
- 3) Detection of genetic changes in mast cells from blood, bone marrow, or extracutaneous organs, for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved
- 4) Evidence of a pathologically increased release of mast cell mediators by determination of the content of
  - 1) Tryptase in blood
  - 2) N-methylhistamine in urine
  - 3) Heparin in blood
  - 4) Chromogranin A in blood
  - 5) Other mast cell-specific mediators (*e.g.*, leukotrienes, prostaglandin D₂)

Source for first criterion, Ref. 2; source for second criterion, Ref. 8. The diagnosis of mast cell activation syndrome is made if both major criteria or the second criterion and at least one minor criterion are fulfilled.

QUESTION 2

What additional investigations might be useful?

- 1) Skin-prick testing to suspected allergens
- 2) Food challenges of suspected allergens
- 3) Tryptase during an episode
- 4) Baseline tryptase
- 5) Bone marrow biopsy
- 6) Complement component 4 (C4) and C1 inhibitor levels
- 7) Urine 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin
- 8) Urine vanillylmandelic acid/metanephrines
- 9) Platelet activating factor
- 10) C-kit D816V mutation, which is the resulting substitution of aspartate (D) to valine (V) at position 816 in the kinase domain that leads to autoactivation of the KIT receptor tyrosine kinase.
- 11) Twenty-four-hour urine collection for N-methylhistamine or prostaglandin-D2 or its metabolite 11 β -prostaglandin F_{2 α}

DISCUSSION OF THE DIFFERENTIAL DIAGNOSIS

She then underwent skin testing to corn, egg, stinging insects, and annatto, which was negative with ap-

propriate controls. She had denied graded food challenges, but she reported challenging herself with eggs without incident. Baseline serum tryptase level was 20.6 ng/mL (reference range, less than 11.5 ng/mL). Repeat tryptase level one month later was 17.9 ng/mL.

Additional diagnoses, such as carcinoid syndrome, pheochromocytoma, and hereditary angioedema, were less likely with negative urine 5-HIAA level, negative urinary catecholamines, and negative C4 and C1 inhibitor functional assays respectively. Due to her symptoms in the setting of elevated serum tryptase at the time of the events, she was referred for bone marrow biopsy for work-up of mastocytosis. The bone marrow biopsy showed 0.001% mast cells that were negative for cluster of differentiation 2 (CD2)/CD25 coexpression or the KIT D816V mutation. MCAS was favored as the diagnosis.

CLINICAL COURSE CONTINUED

Our patient was treated with cetirizine 10 mg nightly and given an epinephrine autoinjector with an anaphylaxis action plan. She was instructed to avoid mast cell activators and any substances that disagreed with her. She continued to have similar episodes approximately two to three times per year. She had an episode at work after preparing her usual tea and granola without any

other previous ingestions or exposure to smells. Within minutes, she experienced abdominal discomfort, diarrhea, flushing, hives, and swelling of her hands, neck, lips, cheeks, and ankles. She felt like she was going to lose consciousness but did not. She was given epinephrine and diphenhydramine at work and was taken to the ED by emergency medical services. Her vital signs on presentation were unremarkable. She ultimately received three doses of epinephrine, prednisone, and ranitidine. Tryptase level was not drawn at that time. She was discharged on a prednisone taper and ranitidine 150 mg two times daily. Her cetirizine dose was then increased to 20 mg nightly. She again had similar episodes concerning for anaphylaxis, which required similar management in the ED, with tryptase up to 38.3 ng/mL after an episode. These episodes had occurred approximately 12–24 hours after her nightly cetirizine doses. She had also reported periods of constant flushing of her skin and three to five loose bowel movements daily. Montelukast 10 mg daily was then added. Ketotifen or cromolyn were not added. Between episodes her tryptase level remained elevated between 13.2 and 20.9 ng/mL (reference range, less than 11.5 ng/mL). Histamine skin test was also performed and showed a blunting of histamine response on cetirizine. The addition of montelukast had not significantly changed the frequency of her episodes.

Subsequent outpatient work-up also revealed severe vitamin D deficiency with vitamin D₂₅-hydroxy level of 6 ng/mL (reference range, 25–100 ng/mL). She was treated with ergocalciferol 50,000 IU weekly with repeat vitamin D₂₅-hydroxy level 47 ng/mL approximately 12 weeks later. She was then decreased to ergocalciferol 50,000 IU every other week. Over the next year, she had not had any episodes of flushing, angioedema, or anaphylactic reactions. At that time, she reported only intermittent erythematous blanching lesions and intermittent self-limited flushing, but she otherwise reported improved diarrhea and no epinephrine use for over a year.

DISCUSSION

Our patient had clinical findings that appeared due to mast cell activation not associated with mastocytosis or an allergic or inflammatory reaction. Symptoms can be mild with headache, fatigue, nausea, or insomnia to symptoms of an immediate type allergic reaction, including urticaria, flushing, abdominal cramping, and diarrhea. More severe cases may present with respiratory symptoms, hypotension, and anaphylaxis.¹

Mast cell activation disorders are classified into three broad categories, primary, secondary, and idiopathic MCAS. Primary MCASs are due to monoclonal mast cell disorders and include systemic mastocytosis (SM) and monoclonal mast cell activation disorder (only one

Table 2. Differential diagnosis in patients with suspected MCAS

Cardiovascular
Myocardial infarction
Endocarditis/endomyocarditis
Aortic stenosis with syncope
Pulmonary infarction
Endocrinologic
Acute hypothyroidism
Acute hypoglycemia
Adrenal insufficiency
Hypopituitarism
Gastrointestinal disorders (with diarrhea + dehydration)
Acute inflammatory bowel disease
VIP-secreting tumor (VIPoma)
Acute episodes of Morbus Crohn or colitis ulcerosa
Food intoxication
Infectious diseases
Severe bacterial or viral infections ± septic shock
Acute gastrointestinal infection with dehydration
Acute encephalitis/meningitis
Acute parasitic diseases (e.g., acute Chagas disease)
Neurologic/CNS disorders
Epilepsy
CNS tumors
Other CNS diseases
Intoxication
Psychiatric conditions
Skin diseases
Hereditary or acquired angioedema
Pemphigus vulgaris
Acute lupus erythematoses
Acute toxic dermatoses
Hematologic malignancies
Acute leukemia
Myelodysplastic and myeloproliferative disorders
Myeloma
Hodgkin and non-Hodgkin lymphomas
Hematologic, acute anemia ± hypovolemic shock
Acute gastrointestinal bleeding
Massive hypermenorrhea
Drug-induced side effects
Drug-induced hypoglycemia
Drug-induced hypotension
Drug-induced diarrhea
Drug-induced CNS damage

MCAS = mast cell activation syndrome; CNS = central nervous system. Source Refs. 1 and 12.

or two minor World Health Organization criteria for SM fulfilled).² When working up primary disorders, recent research has shown many patients with MCAS harbor mutations in KIT other than D816V, which has important implications because current clinically avail-

able testing for mast cell clonality related to KIT alterations is limited to probing by polymerase chain reaction for only the specific KIT-D816V mutation.³ In mastocytosis, mast cell aggregates may be distributed in a patchy fashion, and a single bone marrow biopsy may fail to show findings of SM in about one-sixth of cases.⁴

Secondary MCASs are due to conditions that produce the symptoms and signs of mast cell activation and include allergic disorders, physical urticarias, and chronic autoimmune urticaria.⁵ When investigation for primary or secondary MCAS does not reveal an underlying cause of suspected MCAS, the diagnosis of idiopathic MCAS is made.^{2,5} Idiopathic urticaria, angioedema and anaphylaxis are associated variants of mast cell activation disease and must be supported by objective physical findings and tryptase levels for idiopathic anaphylaxis when possible.⁶ Idiopathic MCAS is diagnosed per specific criteria when criteria for idiopathic anaphylaxis are not met. Two recently proposed criteria for MCAS are presented in Table 1. When idiopathic MCAS is suspected, it is important to consider a broad differential diagnosis that may cause similar symptoms as presented in Table 2.

Treatment options are directed toward mast cell mediators. Options include histamine I and II blockers (*i.e.*, diphenhydramine, cetirizine, loratadine, and ranitidine), leukotriene receptor antagonists (*i.e.*, montelukast), and mast cell membrane-stabilizing medications (*i.e.*, cromolyn sodium) and avoiding triggers.^{7,8} The general approach involves adding medications sequentially. Signs of improvement in symptoms with any specific therapy may be seen within four weeks.⁸ Specifically with respect to our case, it is possible that more frequent dosing of histamine type 1 (H1) blockers, combined H1/H2 receptor blockade, or more frequent dosing of montelukast could have led to improved control of her symptoms.

In patients with suboptimal responses to standard therapies, it is important to consider additional factors. Recent literature has shown that vitamin D and its metabolites may affect mast cell activation. Yip *et al.* performed studies that showed vitamin D3 metabolites suppressed IgE-induced mast cell mediators *in vitro* and reduced IgE-mediated passive cutaneous anaphylaxis reactions *in vivo*.⁹ Studies in chronic urticaria patients have shown trends toward lower urticaria symptom severity scores when high dose vitamin D3 was used as add-on therapy to antihistamines and leukotriene receptor antagonists.¹⁰ Additionally, studies in children from birth to age four years old showed higher epinephrine prescription rates and anaphylaxis

admissions in southern Australia compared with Northern Australia implicating the potential role of less sunlight exposure and vitamin D deficiency as contributors to anaphylaxis.¹¹

FINAL DIAGNOSIS

MCAS exacerbated by vitamin D deficiency.

CONCLUSION

Idiopathic MCAS is becoming an increasingly recognized condition. One must consider a broad differential and exclude primary or secondary causes of mast cell activation disorders before the diagnosis is made. Recent studies have suggested vitamin D may play a role in suppression of mast cell activation and have an immunomodulatory effect. With MCAS, one may consider vitamin D deficiency when patients' symptoms continue despite traditional therapies targeting mast cell mediator release.

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