

Dystonia as an unusual presentation of systemic mastocytosis: Possible link between histamine release and movement disorders



Alexandra Phillips, PA-C, MPH^a, Flavia C.L. Hoyte, MD^{b,c}, and Donald Y.M. Leung, MD, PhD^{a,d}

Clinical Implications

- Mast cell mediators have numerous effects on various organ systems.
- Histamine may play a role in movement disorders, specifically acute dystonia.
- Efficacy of treating status dystonicus with diphenhydramine may be due to antihistaminergic effects as opposed to sedating effects.

TO THE EDITOR:

We present the interesting case of an adolescent female with dopamine-responsive dystonia and symptoms concerning for systemic mast cell mediator release. Mastocytosis refers to a rare group of cutaneous and systemic disorders in which mast cells accumulate in one or multiple tissues.¹ Clinical symptoms of mastocytosis result from mast cell mediator release and, in systemic mastocytosis (SM), extracutaneous tissue infiltration.² The effects of mast cell mediator release are wide ranging and can include symptoms consistent with acute anaphylaxis as well as chronic abdominal pain, flushing, diarrhea, fatigue, and musculoskeletal pain.² Mutations in the stem cell factor receptor, c-KIT, have been implicated as the major contributor to the pathogenesis of both cutaneous and systemic disease.¹

Dystonia conditions, particularly dopamine responsive dystonia (DRD), are rare disorders that are clinically and genetically heterogeneous.³ DRD typically arises in childhood with symptoms including sustained or intermittent muscle contractions, specifically limb rigidity and bradykinesia. The hallmark of DRD is response to low-dose dopamine therapy.⁴

A potentially life-threatening manifestation of DRD is status dystonicus (SD), which is characterized by frequent or continuous severe generalized dystonic spasms.⁵ SD triggers include infection, adjustment in medications, stress, anesthesia, and pain.⁵ SD treatments are largely supportive in nature and based on case reports/series.⁵ Antihistamines such as diphenhydramine have been used effectively, pointing to a possible role of histamine dysfunction in the movement dysregulation of dystonia.⁶

A 17-year-old girl with DRD, scoliosis, and cutaneous mastocytosis (CM) presented to National Jewish Health in Denver, Colo, for evaluation and management of possible SM.

Past medical history included mild eczema and asthma during childhood, as well as scoliosis diagnosed at age 12. At age 15, the patient noticed small hyperpigmented skin lesions that would intermittently get red and itchy on her extremities (Figure 1). She also began having painful jerking, posturing, and twisting movements of her neck and limbs. Neurologic evaluation

confirmed significant truncal posturing, asymmetry on examination, increased tone, restricted range of motion, and worsening scoliosis. Workup for genetic and metabolic causes of her dystonia was unremarkable. She was initiated on carbidopa/levodopa, which significantly improved her symptoms, yielding a diagnosis of DRD.

Dermatologic evaluation of her skin lesions demonstrated a positive Darier's sign. Skin biopsy was consistent with monomorphic maculopapular cutaneous mastocytosis (MCM) (Figure 2, A). She was placed on 5 mg daily Claritin without improvement in symptoms. In addition to her baseline MCM and dystonia, the patient was experiencing daily and acute systemic symptoms following this general progression: hives, nausea, acute abdominal pain, lightheadedness, difficulty getting air in, cloudy thinking, and worsening dystonia. Occasionally, the patient's systemic symptoms would progress to SD lasting 1 to 2 hours with 2 to 3 days of subsequent joint stiffness and fatigue. Diphenhydramine resolved acute symptoms. Epinephrine had never been used. Triggers varied and included certain foods, medications, hot temperatures, friction, vibration, and stress. She did not have a history of food allergies, but was avoiding many, including dairy, because of the possible association with past symptoms. In addition, she complained of chronic abdominal pain, weight loss, and musculoskeletal pain. On examination, the patient was thin with appreciable scoliosis and numerous lesions consistent with MCM over her face, upper chest, and extremities. She again demonstrated a positive Darier's sign.

Laboratory evaluation showed elevated baseline tryptase (15.5 mcg/L, normal <11), mildly elevated urinary N-methylhistamine (296 mcg/g, normal 30-200), normal urinary 2,3-dinor-11beta-prostaglandin F2 alpha (3610 pg/mg, normal <5205), unremarkable urinary leukotriene E4 (66 pg/mg, normal <104), normal whole blood histamine, negative peripheral blood c-KIT D816V mutation, and undetectable



FIGURE 1. Monomorphic maculopapular cutaneous mastocytosis lesions on the patient's left arm.

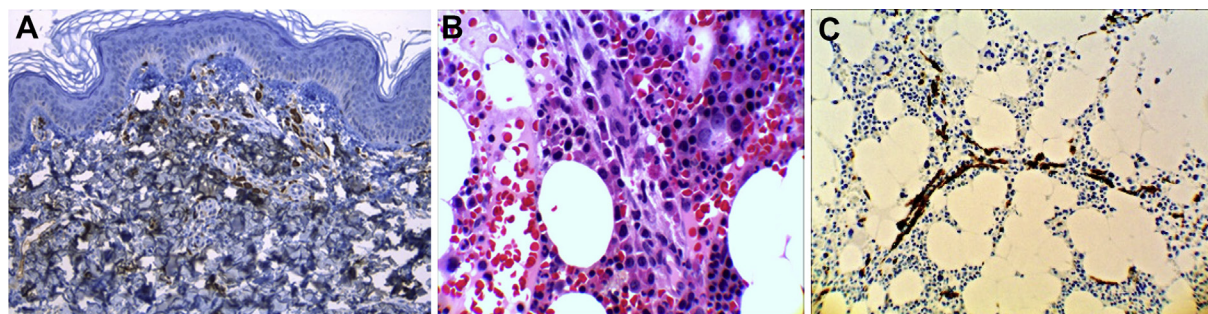


FIGURE 2. **A**, Skin biopsy stained for mast cells and tryptase indicative of cutaneous mastocytosis. **B**, Hematoxylin and eosin staining of bone marrow biopsy revealing the presence of atypical spindle-shaped mast cells. **C**, Bone marrow biopsy stained for the mast cell marker CD117, showing >25% atypical spindle-shaped mast cells, consistent with systemic mastocytosis.

ImmunoCAPs to foods and environmental allergens. Bone marrow biopsy confirmed the diagnosis of SM by demonstrating 3 minor criteria as defined by the World Health Organization¹: (1) greater than 25% atypical mast cells by morphology (Figure 2, B and C), (2) positive c-KIT (D816V) mutation by allele-specific PCR, and (3) aberrant mast cell expression of CD25 and CD2 by flow cytometry (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). She also had a positive methacholine study with clinical improvement in chest pain after albuterol administration.

A milk challenge was performed in an effort to liberalize her diet. During the challenge, the patient experienced an episode of SD that responded to IV diphenhydramine. No hives, angioedema, wheezing, nausea, or vomiting occurred. Epinephrine was not given. Comprehensive metabolic panel (CMP) and creatine kinase (CK) labs remained normal. The patient had subsequent fatigue and joint stiffness for 48 hours. She reported similar symptoms the last time she ingested dairy 1 year earlier.

The following therapies were initiated: oral cromolyn, which improved her abdominal pain and appetite, leading to weight gain; low-dose fluticasone propionate and salmeterol, which improved her chest pain; and an enhanced antihistamine and mast cell stabilization regimen of ketotifen, fexofenadine, ranitidine, and montelukast, which have helped decrease her hives and the intensity/frequency of systemic symptoms. If these therapies were insufficient, we would consider the use of omalizumab, which has been reported to be beneficial in a case series of patients with SM.⁷ Although she has continued experiencing intermittent dystonic symptoms, she is stable on carbidopa/levodopa.

SM has not been previously linked to dystonia. However, there is evidence suggesting a role of histamine dysfunction in movement disorders and various other neuroinflammatory conditions.⁸ Treatment of acute dystonia with antihistamine medications is usually rapidly effective in an emergency setting.^{9,10} The target histamine receptor is not known, but histamine receptors are present in the brain or there may be off-target effects by diphenhydramine. This may explain the partial response of dystonia symptoms to first-generation H₁-antihistamine. However, van't Groenewout et al⁸ demonstrated that mice with dystonia were effectively treated with both non-sedating and sedating antihistamines, suggesting that antihistamines are effective through a mechanism other than sedation. Mice with induced torticollis were treated with various therapies

including diphenhydramine and cimetidine, 2 antihistamines, which were more effective than anticholinergics in alleviating dystonia.⁸ In addition, researchers demonstrated injecting histamine itself into the red nucleus of the brain-induced torticollis, which was attenuated with antihistamines.⁸

Mast cell mediators, including histamine, have been linked to a variety of multiorgan system symptoms, including neuropsychiatric and muscular symptoms. Headache, syncope, "brain fog," and even symptoms resembling multiple sclerosis have been reported.² Of the mast cell mediators, histamine seems most suspect in the pathophysiology of SD in our patient, as treatment with diphenhydramine therapy was rapidly effective. Also, histamine contributes to pruritus, gastric hypersecretion, bronchoconstriction, and increased vasopermeability, symptoms our patient sometimes exhibits during her dystonic episodes. Histamine dysfunction has been implicated in the pathophysiology of various neurological conditions involving movement abnormalities such as Parkinson's disease, epilepsy, and Tourette's syndrome. SM may be another condition where histamine dysfunction results in atypical movements such as dystonia.

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^aDivision of Allergy and Clinical Immunology, Department of Pediatrics, National Jewish Health, Denver, Colo

^bDivision of Allergy and Clinical Immunology, Department of Medicine, National Jewish Health, Denver, Colo

^cDepartment of Medicine, University of Colorado School of Medicine, Aurora, Colo

^dDepartment of Pediatrics, University of Colorado School of Medicine, Aurora, Colo
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Corresponding author: Donald Y.M. Leung, MD, PhD, National Jewish Health, 1400 Jackson Street, Room K9261, Denver, CO 80206. E-mail: leungd@njhealth.org. 2213-2198

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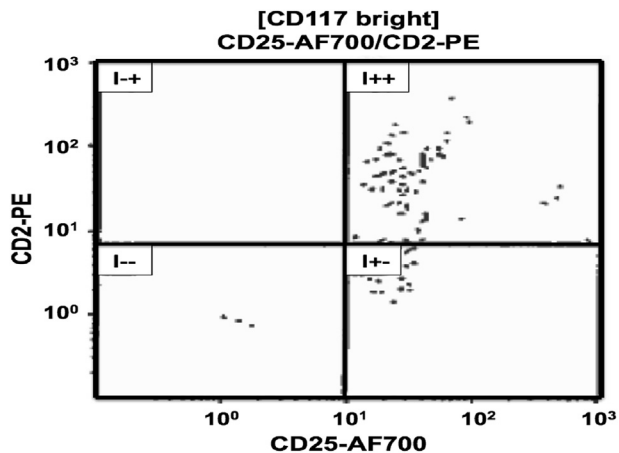


FIGURE E1. Bone marrow aspirate, flow cytometric analysis demonstrating CD117 bright mast cell gates for CD25 and CD2. The majority of cells were positive for CD25/CD2 indicative of an aberrant mast cell population.

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