

Clinical Communications

Recurrent neurologic symptoms complicating venom immunotherapy in a patient with systemic mastocytosis and severe Hymenoptera allergy

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Clinical Implications

- This case serves as an important reminder of the need to consider an associated mast cell disorder in individuals with hypotensive insect sting reactions. More importantly, it also introduces new areas for exploration pertaining to the observed novel associations of atypical neurologic symptoms, particularly parkinsonism, in the context of mastocytosis and venom immunotherapy.

TO THE EDITOR:

We describe the unusual case of a 49-year-old male landscaper who was stung at work and developed immediate-onset syncope and hypotension, requiring emergency room treatment with epinephrine without neurological sequelae. One year later, the patient again sustained multiple simultaneous Hymenoptera stings but did not have an epinephrine auto-injector with him at the time. He experienced severe anaphylaxis and cardiac arrest, requiring multiple doses of intramuscular epinephrine (time to treatment for which is unknown), with return of spontaneous circulation after 8 minutes. He required an intravenous epinephrine infusion in the critical care unit and regained consciousness after several days. Postarrest neuroimaging demonstrated focal bilateral basal ganglia anoxic/ischemic damage. During the remainder of his hospitalization in the following weeks, he was noted to have a soft and hoarse voice postextubation, and was able to use stairs normally during physiotherapy sessions without any other overt signs of parkinsonism. He was a nonsmoker and was otherwise healthy, on no chronic medications, and with no personal or family history of neurological diseases or allergies. Allergy evaluation demonstrated a positive intradermal skin test result to yellow jacket at 1.0 µg/mL, with additional sensitization detected by specific IgE testing to yellow jacket (1.13 KU/L), wasp (0.82 KU/L), and white-faced hornet (0.68 KU/L).

Venom immunotherapy (VIT) was initiated and maintenance therapy achieved by 3 months (1 mL of 300 µg/mL mixed vespidae and 1 mL of 100 µg/mL wasp). A subsequent sting 1 year later did not result in any signs or symptoms suggestive of an IgE-mediated reaction. However, 48 hours later, acute worsening of parkinsonian features developed including festinating gait, slowed and softened speech, impaired focus and speech initiation, and lethargy. These symptoms slowly improved over the next few weeks before

recurring after his monthly VIT injection. Given recurring symptoms after a series of maintenance injections, VIT was therefore stopped.

Clinical reassessment at this point demonstrated that, in addition, the patient notably had developed urticaria pigmentosa with a positive Darier sign. Serum tryptase level was elevated at 26.3 ng/mL, and subsequent bone marrow biopsy demonstrated spindle-shaped CD25-positive mast cells, with a pathogenic *KIT* D816V mutation. Multifocal aggregates and evidence of associated hematologic neoplasia or myelodysplasia were not seen. Urine 2,3-dinor-11β-prostaglandin-F2α was elevated at 7884 pg/mg Cr (normal, <5205 pg/mg Cr), with a normal histamine level at 0.040 mg (normal, 0.006-0.131 pg/mg Cr). In light of these findings and the presentation, a diagnosis of indolent systemic mastocytosis in association with Hymenoptera hypersensitivity—leading to cardiac arrest, ischemic brain injury, and secondary atypical parkinsonism—was made.

Given the patient's underlying disease, life-threatening reaction history, and high-risk employment, reinitiation of VIT containing only yellow jacket was pursued. However, at a dose of 0.3 mL of 100 µg/mL, his course was again complicated by recurrent acute neurologic deterioration including a flattened, catatonic-like state with decreased verbalization, apathy, and reduced spontaneous motor movements that resolved spontaneously. Despite concomitant therapy with omalizumab and cromolyn, a subsequent attempt using a diluted yellow jacket venom solution (0.1 mL of 1 µg/mL) resulted in recurrent symptoms, ultimately requiring permanent VIT cessation.

Over time, the patient's persistent parkinsonian features stabilized with less severe—but disabling—flattened affect, masked facies, severe hypophonia, rigidity, bradykinesia, and marked freezing of gait. Repeat neuroimaging showed prominent bilateral pallidal cystic changes (Figure 1). The patient remains on cromolyn, montelukast, desloratidine, and omalizumab for his systemic mastocytosis and on venlafaxine and trihexylphenidyl for his parkinsonism. Trials of therapy with levodopa, trazadone, amantadine, ropinorole, and methylphenidate were unsuccessful. Because of his indolent mastocytosis and interdisciplinary consensus that his ongoing neurologic manifestations were unlikely to be related to his mast cell disorder, cytoreductive therapy is not indicated. His tryptase level remained stable.

This case provides a poignant example for the merits of early allergy assessment in patients in whom Hymenoptera hypersensitivity is suspected. The patient's preceding reaction that resulted in isolated hypotension should have merited careful consideration both for the possibility of systemic mastocytosis and for VIT initiation.^{1,2} Unfortunately, he went on to sustain a potentially preventable severe anaphylactic reaction, which resulted in considerable long-term morbidity due to a primary central nervous system insult. This case is particularly novel and intriguing given the recurrent and temporal relationship between worsening of parkinsonian features and VIT initiation, despite the absence of traditional mast cell mediator-related symptoms that might have been expected given the underlying mastocytosis.

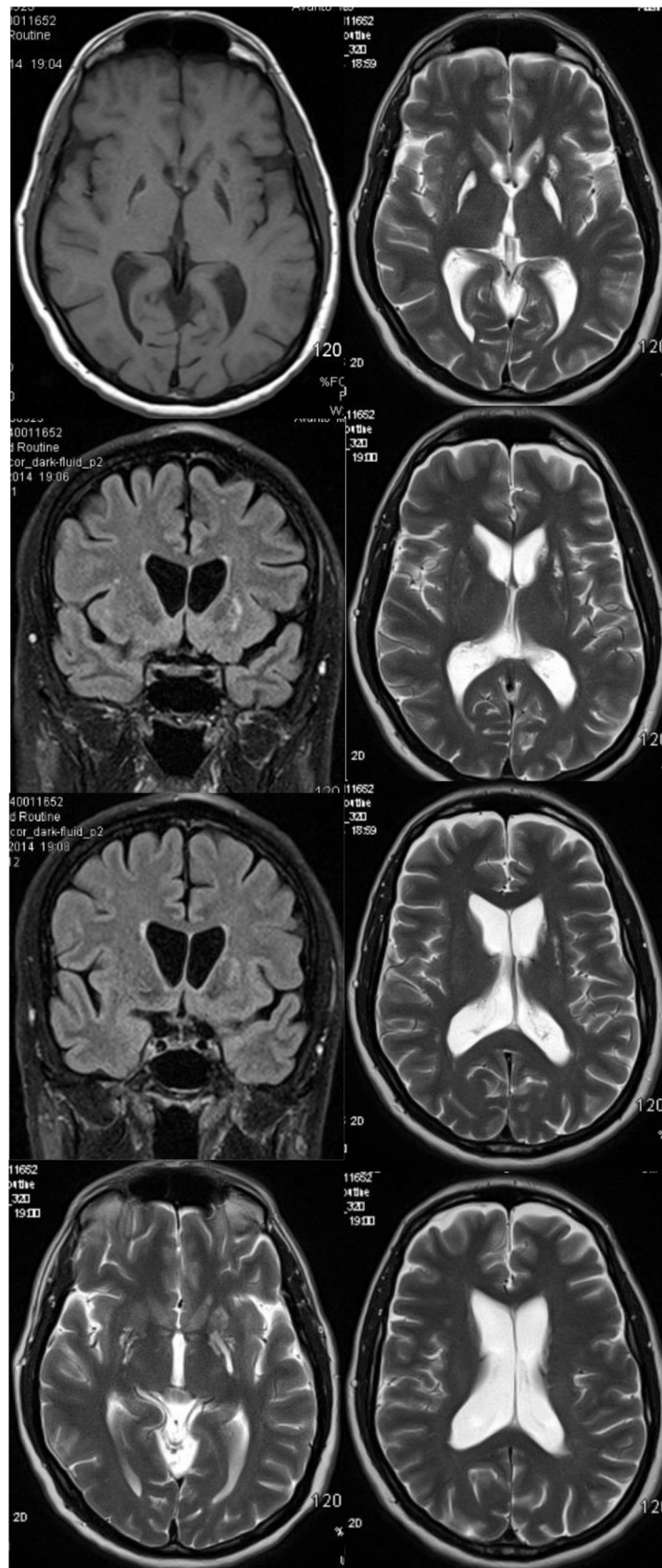


FIGURE 1. T1- and T2-weighted magnetic resonance brain images showing highly focal, persistent bilateral pallidal necrosis as a delayed complication postarrest.

Although there are rare reports of unusual neurologic reactions after Hymenoptera stings, to our knowledge, this represents the first case where unusual neurologic symptoms of this nature are reported in relation to VIT.^{3,4} Moreover, although neuropsychiatric symptoms are commonly reported in individuals with mast cell disease, parkinsonism is generally not thought to be among these features.⁵ Interestingly, histaminergic neurotransmission has been implicated in the pathophysiology of basal ganglia-associated pathology, and, in particular, has been associated with movement disorders such as acute dystonia in a published report in this journal of a patient with systemic mastocytosis.^{6,7} The role of antihistamines in the management of acute dystonic reactions provides further support for the role of histamine in the basal ganglia pathways. In addition, apamin, a toxin present in honeybee venom, has been demonstrated to cross the blood-brain barrier and affect dopaminergic neurons. For this reason, bee venom has been studied for treatment of Parkinson disease.⁸ Although this patient was not honeybee-sensitized, and thereby this was not included in the immunotherapy mixture, it does raise the question whether vespid venoms could have neuromodulatory effects in certain susceptible individuals. Finally, the very focal bilateral basal ganglia (particularly pallidal) necrosis after the patient's cardiac arrest is intriguing, particularly given that no anatomical or cerebrovascular abnormality was noted. Although these regions may be particularly susceptible to anoxic damage, tryptase is known to have several substrates including the alpha chain of fibrinogen and it is possible that the patient's undiagnosed mastocytosis with an unrecognized elevated tryptase level predisposed or contributed to the local fibrosis/necrosis seen on imaging.⁹ This case serves as an important reminder of the need to consider an associated mast cell disorder in individuals with hypotensive insect sting reactions. More importantly, it also introduces new areas for exploration pertaining to the observed novel associations of atypical neurologic symptoms in the context of mastocytosis and VIT.

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