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Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab

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The concept of mast cell activation syndrome (MCAS) has evolved over the last several decades to describe cases involving evidence of profound mast cell degranulation without an obvious trigger or evidence of aberrant mast cell proliferation.[1] In 2010, Akin, et al. proposed a set of diagnostic criteria including: 1) absence of evidence of primary or secondary causes of mast cell activation (including mastocytosis); 2) episodic symptoms consistent with mast cell mediator release affecting ≥2 organ systems; 3) evidence of an increase in a validated urinary or serum marker of mast cell activation; and 4) a decrease in severity of symptoms with anti-mediator therapy including histamine 1 and 2 receptor antagonists, leukotriene antagonists, or mast cell stabilizers.[1] Treatment of MCAS involves the use of one or more of the aforementioned classes of medications,[2] while prednisone, cyclosporine A, methotrexate, and azathioprine are alternatives when treatment with more conservative therapy fails.[2] Treatment of refractory cases presents a difficult dilemma for the clinician. We present a case of the successful use of omalizumab (monoclonal antibody to IgE) in the treatment of a pediatric patient who met the proposed diagnostic criteria for MCAS.

Our patient is an 11 year old male with a history of eczema and viral-induced wheezing who presented in September 2010 for evaluation of presumed anaphylactic reactions to both cherries and blackberries. Symptoms included hives and breathing difficulty. He had an additional episode with similar symptoms for which a trigger was not identified. In the weeks preceding these events, he reported headache, flushing, abdominal pain, diarrhea, and fatigue. Percutaneous skin prick testing using common aeroallergen extracts and cherry was negative. Complete blood count showed a white blood cell count of 12,500/μL with a lymphocyte predominance and normal numbers of eosinophils, basophils, and monocytes. Serum tryptase was 15.8 μg/dL (normal 0.4–10.9 μg/dL). A monospot was positive, which was potentially significant as the presence of heterophile antibodies can increase tryptase levels.[3] Total IgE was 26 IU/mL. The child was counseled on avoidance of cherries and blackberries, prescribed an epinephrine auto-injector, and started on oral cetirizine at 10 mg twice daily.

Over the next four months, he continued to experience frequent abdominal pain, diarrhea, urticaria and flushing, as well as episodic anaphylactoid reactions requiring the use of epinephrine several times per month. Tryptase levels remained elevated (17.8 μg/dL; 19.8

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μg/dL). Histamine-1 receptor blockade was increased to twice daily cetirizine plus twice daily loratadine ("4× therapy") with continuation of twice daily ranitidine. Symptoms improved but persisted, and bone marrow biopsy was obtained to exclude systemic mastocytosis or monoclonal mast cell activation syndrome (MMAS). Normal marrow morphology was noted with the absence of a large population of mast cells or spindle-shaped mast cells. CD25 staining was negative. Additionally, a chronic urticaria index, which tests for presence of autoantibodies to the high-affinity IgE (FcεRI) receptor, was within normal limits. Polymerase chain reaction for the KIT (D816V) mutation commonly found in systemic mastocytosis and MMAS was unable to be performed due to lack of amplifiable nucleic acid in the specimen. Upper and lower endoscopy did not show the presence of mast cell aggregates in the bowel wall.

The patient improved on a prolonged course of oral corticosteroids, but symptoms increased after their discontinuation and he was started on omalizumab as a steroid-sparing agent in April 2011. He continues to receive omalizumab 150 mg subcutaneously every 4 weeks. He had rapid improvement in symptoms and has had one episode of urticaria with shortness of breath in the 10 months on omalizumab therapy. The patient continues on H1 receptor blockade with twice daily cetirizine and loratidine and H2 receptor blockade with twice daily ranitidine.

This case supports the potential efficacy of omalizumab for MCAS in children not responding to maximal anti-histamine therapy. Molderings, et al. recently reported benefit with omalizumab therapy in 1 of 2 patients with monoclonal mast cell activation syndrome.[4] There have been other reports of successful treatment of systemic mastocytosis with omalizumab.[5,6]

The mechanisms underlying the symptomatic improvement of patients with MCAS treated with omalizumab are not fully understood. The binding and inactivation of IgE by omalizumab leads to a decreased level of IgE available for binding to mast cells, leading to downregulation of FcεRI.[7] Others have proposed that omalizumab may interfere with mast cell mediator release.[8] In sum, omalizumab may be an efficacious therapy for treatment resistant MCAS, and further studies are needed to ascertain what factors lead to improvement in MCAS patients receiving omalizumab.

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