Complex, Persistent, Multi-generational Presentation of Hereditary Alpha Tryptasemia Syndrome Requiring High Dose Omalizumab

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Introduction

Introduction: Hereditary Alpha Tryptasemia Syndrome (HATS) is a rare, complex disorder. The presentation can be intermittent or chronic, with local or multisystem involvement with a baseline tryptase level above >8-10 ng/ml (1,2,3,8). Genetic testing revealing additional copies of alpha-tryptase at TPSAB1 confirms the diagnosis (1,2,3,8).

Case Report

HPI: 67 years old female with a lifelong history of urticaria, she was initially diagnosed with Chronic Spontaneous Urticaria (CSU) and mastocytosis. Her symptoms include itching, hives, and intermittent throat swelling. Her Urticaria Activity Score over Seven days (UAS7) was 30-42, and her Tryptase level was 13.8 ug/L. Genetic testing (5/2019) confirmed three copies of alpha-tryptase (additional copy at TPSAB1) and two copies of beta-tryptase. Her symptoms were exacerbated by IUD, surgeries, and sulfite preservatives, and were refractory to standard regimen to the extent that she had to go to the ER for emergent treatment with steroids and antihistamines.

PMH: Ehlers-Danlos syndrome (EDS), orthostatic hypotension dysautonomia syndrome (POTS), immunodeficiency, drug allergies, rheumatoid arthritis, asthma, chronic bronchitis, Hashimoto's thyroiditis, Sjogren's Syndrome, and Raynaud's Syndrome. **PSH:** Numerous Ob-gyn surgeries.

Initially, she was started on **Xolair (2014) of 300mg q4weeks (for 2 years), thereafter dose titrated to 300mg q2weeks (3 years)** with significant clinical improvement in UAS7 score. Patient was subsequently **diagnosed with HATS (5/2019**) based upon combination of clinical characteristics and laboratory studies. Additionally, given her history of recurrent infections pending further immunodeficiency work-up, she is presently being evaluated for specific antibody deficiency vs. CVID and considered for possible IVIG.

Family History

FH: Two daughters (39-40yo) with similar presentations of urticaria with elevated tryptase (patient reported **16-17 ug/L**) were clinically diagnosed at ages 33 and 35. Given high suspicions, both were started on Omalizumab 300 mg q2wk with good control. One diagnosed with EDS and both with history of recurrent infections.

Allergy Medications

Omalizumab 300mg Q 2 weeks, on **Zyrtec**, 10, BID **Ranitidine**, 150 mg, BID, **Singulair,** 10 mg, daily. **Vit D** 16,000-20,000 IU and **Epi-pen**. (from list of 27 meds)

The EAACI/GA2LEN/EDF/ WAO Guideline (4)	2014 Before Omalizumab	Omalizumab 300 mg q4wk	Omalizumab 300 mg q2wk
Hives (wheals) **0 None** **1 Mild (<20 hives/24 h)** **2 Moderate (20–50 hives/24 h** **3 Intense** **(50 hives/24 h or large confluent areas of hives)**	3	2	1
Itch Severity Score (ISS) **0 None** **1 Mild (present, but not annoying or troublesome)** **2 Moderate (troublesome, but does not interfere with normal daily activity or sleep)** **3 Intense (severe itch, which is sufficiently troublesome to interfere with normal daily activity or sleep)**	3	2	1
Total Score Per day	6	4	2
Total Score Per Week UAS7	42	28	14

Labs	Results
Tryptase Level (2016)	**13.8 ug/L (normal <10-11ug/L)**
Tryptase Level (2019)	**11.8 ug/L (normal <10-11ug/L)**
Genetic testing HATS (5/2019)	**3 copies of alpha-tryptase (additional copy at TPSAB1), 2 copies of beta-tryptase (TPSB2 or TPBAB1)**
Kit D816	**Negative**

Immuno-phenotyping	Results
IgA (Immunoglobulin A Deficiency)	**low**
IgG (Immunoglobulin G) Subclasses	**854 mg/dl (normal 700-1600mg/dl)** **Low Ig3 Ig4**
IgM	Normal
Post Prevnar 13, Pneumovax 23	**Inadequate-poor vaccine response**
Vit D level (supplemented)	Normal

Medical History

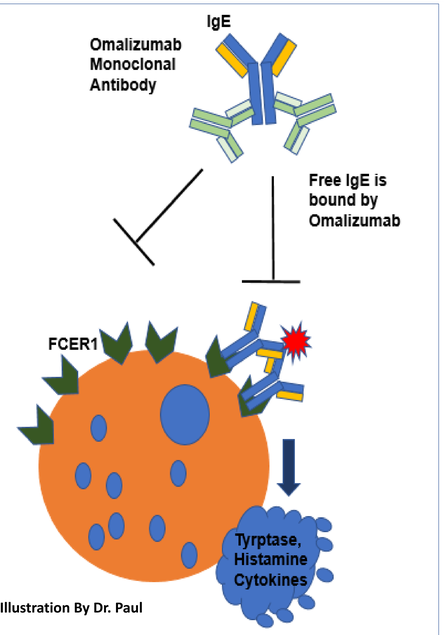
Food and drug allergies: Anaphylaxis to **Sulfites** (Preservatives).
Levaquin: local hives. **Ketotifen:** diarrhea
Fire ants and Yellow Jackets causes Large local swelling
Airway Disease: Asthma, bronchitis, sinusitis, Environmental Allergies

Discussion

When the clinical presentation is consistent with mast cell disorder with multisystem involvement in the setting of elevated tryptase that is refractory to standard treatment, Hereditary Alpha Tryptasemia Syndrome (HATS) should be considered (1-3,7), particularly with a positive family history (of HATS) and Kit D816 negative. Ultimately, genetic testing is required to confirm the diagnosis of HATS.

Omalizumab is a monoclonal antibody and functions by binding to free (non-bound) IgE, and inhibiting its action on the high-affinity IgE receptor (FceR1) on effector cells such as mast cells. Thus, down regulating the FceR1 on mast cells and theoretically on other effector cells as well (5,6,7).

Although the maximum dose of omalizumab approved for CSU is 300mg every month, higher dosing should be considered in difficult to treat and refractory cases. The underlying mechanisms of omalizumab and its benefits/risks continue to be revealed.



Conclusions

We describe a multi-generational presentation of HATS requiring high dose omalizumab for adequate symptom control. When symptoms of CSU remain uncontrolled on standard maximum dose of omalizumab 300 mg q 4 weeks, higher dosing should be considered.

Acknowledgment

We would like to thank the patient for allowing us to present her clinical presentation and family history.

1. Joshua Milner, M.D. Hereditary Alpha Tryptasemia and Hereditary Alpha Tryptasemia Syndrome FAQ. *National Institute of Allergy and Infectious Diseases*. October 17, 2016; https://www.niaid.nih.gov/research/hereditary-alpha-tryptasemia-faq.
2.Lyons JJ & cols. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet*. December, 2016; 48(12):564-1569. https://www.ncbi.nlm.nih.gov/pubmed/27749843.
3. https://rarediseases.info.nih.gov/diseases/13193/hereditary-alpha-tryptasemia-syndrome
4. Table Ref: Zuberbier T, Aberer W, Asero R et al. The EAACI/GA2LEN/EDF/ WAO Guideline for the definition, classification, diagnosis and management of Urticaria. The 2013 revision and update. Allergy 2014; 69: 868–887.
5. Xolair® (omalizumab) US prescribing information 2016. 2014Available from:https://www.gene.com/download/pdf/xolair_prescribing.pdf.
6. Kaplan AP[1], Giménez-Arnau AM[2], Saini SS[3]. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneousurticaria. Allergy. 2017 Apr;72(4):519-533. doi: 10.1111/all.13083. Epub 2017 Jan 4.
7. Payne V[1], Kam PC. Mast cell tryptase: a review of its physiology and clinical significance.Anaesthesia. 2004 Jul;59(7):695-703.
8. Cem Akin, MD, PhD Mast cell activation syndromes. The Journal of Allergy and clinical Immunology. August 2017Volume 140, Issue 2, Pages 349–355
9. https://www.rxlist.com/xolair-drug.htm#indications