Development of a Clinical Scoring System to Identify Conditions of Mast Cell Proliferation in a Community Setting

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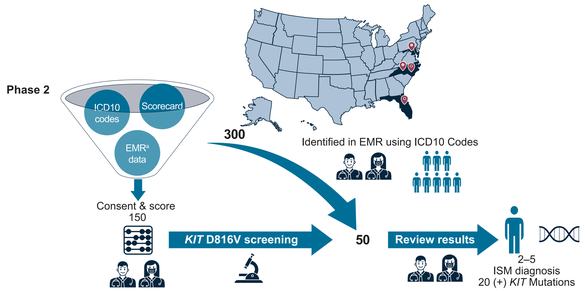
Rationale

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease primarily driven by the *KIT* D816V mutation[1,2]
- Systemic mastocytosis (SM) is estimated to affect 1 in 10,000 adults[3]
- The phenotypic presentation of ISM is highly individualized and non-specific, with many patients experiencing chronic debilitating symptoms across multiple organ systems. Accumulation and activation of abnormal mast cells can lead to symptoms including maculopapular lesions with Darier's sign, flushing, hypotensive anaphylaxis, diarrhea, nausea/vomiting, and brain fog, amongst others.[4–7] These symptoms commonly result in polypharmacy and a poor quality of life[4–7]
- In a real-world allergy community setting, distinguishing ISM, a clonal, mast cell disease from non-clonal mast cell activation syndrome (MCAS) remains challenging. Patients with ISM, are often underdiagnosed due to the generalized presentation, prolonging diagnosis, and treatment.[4,8] Diagnosis is further complicated by patients often presenting to a diverse range of healthcare specialists, the necessity for bone marrow biopsy, and limited sensitivity of available molecular testing[5]
- The current World Health Organization (WHO) diagnostic criteria may not fully characterize the total phenotypic spectrum of ISM[9-11]
- Here we describe the observable objective findings readily accessible in the community practice setting SM criteria that were retrospectively collected and analyzed to develop a scoring system with the purpose of assisting clinical decision-making to determine ISM diagnosis in the community allergy practice setting

Methods

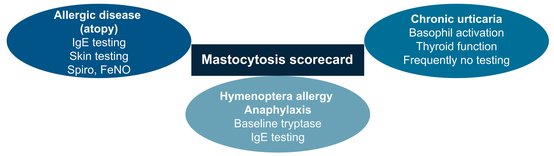
- Data from electronic medical records (EMR), including total immunoglobulin E (IgE) and serum tryptase, from 4 Consortium of Independent Immunology Clinics (CIIC) community allergy sites were retrospectively collected and analyzed (**Figure 1**)
- The study population comprised 20 patients with ISM
- Patient data were trended against frequently co-existing conditions, and a weighted scoring system was developed based on these correlations (**Figure 2**)

Figure 1. Map of CIIC community allergy sites – FL, NC (2) and MD and data collection



CIIC, Consortium of Independent Immunology Clinics; EMR, electronic medical records; FL, Florida; ICD10, International Classification of Diseases 10th Revision; ISM, indolent systemic mastocytosis; MD, Maryland; NC, North Carolina.

Figure 2. Systemic mastocytosis scorecard

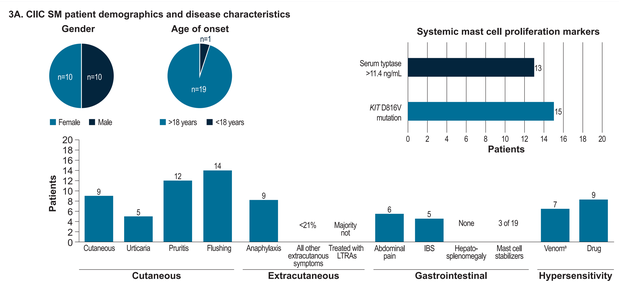


IgE, immunoglobulin E; spiro, spirometry; FeNO, fractional exhaled nitric oxide test.

Results

- Patient demographics (n=20) are shown in **Figure 3**
- Many patients lacked comprehensive testing
- Mediator-driven symptoms outside of anaphylaxis lacked specificity in predicting ISM
- Hymenoptera venom hypersensitivity had the highest frequency, with definite correlation of increased severity of anaphylaxis grade to presence of clonal disease
  - Prolonged anaphylaxis or anaphylaxis with loss of consciousness may be a stronger indicator than elevated tryptase, but not all SM patients have been stung
- Total IgE >100 IU/mL (n=2) and absence of atopic disease (n=5) suggested ISM
- Serum tryptase was highly variable (7.7–242 ng/mL) and correlated with cutaneous involvement but not with bone marrow mast cell burden
  - Serum tryptase during anaphylaxis was recorded in a minority of patients
  - Grade ≥3 anaphylactic reactions were suggestive of proliferating disease even in the absence of serum tryptase >20 ng/mL, a WHO minor criterion
  - In women with antihistamine-responsive flushing, severe anaphylaxis was a better predictor for *KIT* D816V than serum tryptase
  - Recent use of a high-sensitivity droplet digital polymerase chain reaction (ddPCR) test in the peripheral blood identified 4 patients with ISM with low tryptase
- Two distinct ISM phenotypes were identified: Phenotype 1 (n=7) favored male patients and was related to severe anaphylaxis from Hymenoptera envenomation, whereas Phenotype 2 (n=16) had severe, but also frequent symptoms of allergic reactions (**Figure 4**)

Figure 3. Patient demographics (n=20)



[a]Hymenoptera venom hypersensitivity had the highest frequency. IBS, irritable bowel syndrome; LTRA, leukotriene receptor antagonists.

Figure 4. Identified ISM patient phenotypes

Phenotype 1

- Favored male patients
- Severe anaphylaxis from Hymenoptera envenomation
- Prolonged, severe (hospitalization), and multisystem/loss of consciousness
- Threat to life, and the high severity in this group even when serum tryptase was below 20 ng/mL
- Number of patients: 7

Phenotype 2

- Frequent and severe symptoms of allergic reactions
- Overall, lower serum tryptase but higher regular burden on quality of life (unquantified)
- 1 out of 16 checked had serum IgE >100 IU/mL, 6 out of 16 were undetectable
- Number of patients: 16

- Patient vignettes for 2 patients are shown in **Figure 5**. Study period began March 2022 and completed October 2022

Figure 5. Patient vignettes

Patient 1
61-year-old man

- Patient at clinic since 2019
- Initially seen for anaphylaxis to Hymenoptera
- Bone marrow biopsy was negative for *KIT* D816V (5–10% threshold)
- Serum tryptase varied from 30–34 ng/mL
- Receiving venom therapy and 1 daily antihistamine
- During study period, peripheral blood was positive for *KIT* D816V for 0.6% MAF of cells checked by high-sensitivity ddPCR (detection level >0.03%)

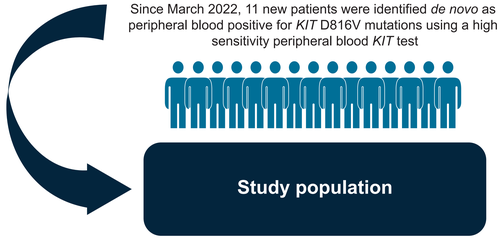
Patient 2
57-year-old female

- Following completion of study was seen in November 2022 in routine follow-up for mastocytosis
- Bone marrow biopsy completed in 2021 was negative for *KIT* D816V mutation
- Peripheral blood was positive for *KIT* D816V mutation in 2022 follow-up, albeit at a low percentage (0.47%)

ddPCR, digital droplet polymerase chain reaction; MAF, mutant allele frequency.

- Since March 2022, 11 patients were previously underdiagnosed and have been correctly diagnosed with ISM based on positive *KIT* D816V detection in blood (**Figure 6**)
- In 20 cases, no abnormal mast cell morphology was noted outside the bone marrow

Figure 6. Previously underdiagnosed patients



Conclusions

- Due to the heterogeneity and wide-ranging clinical presentation of ISM, it remains challenging to separate clonal from non-clonal activation syndromes[4,8]
- Select WHO criteria for classifying ISM require tests which may not be readily accessible in the real-world practice setting, relying on pathology of skin, gut, and bone marrow biopsies
- In this patient population, mediator-driven symptoms outside of anaphylaxis did not correspond to all WHO criteria
  - The level of serum tryptase observed in testing did not appear to correlate with the severity of symptoms and corresponding burden on quality of life
- WHO minor criteria include serum tryptase >20 ng/mL, but presence of Grade ≥3 anaphylactic reactions can be suggestive of clonal disease even in the absence of that finding
- Following prospective validation, set to start from 2023 and last through to Summer 2024, the CIIC scorecard can help inform clinical decision-making in a community allergy setting, specifically regarding appropriate molecular testing and recommendation for comprehensive diagnostic workup

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