#691 Systemic Mastocytosis: Shedding Light on A Rare and Complicated Disease

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Introduction

- Systemic mastocytosis (SM) is a rare, clonal mast cell disease driven by the *KIT* D816V mutation ranging from non-advanced, including indolent SM (ISM) and smoldering SM (SSM), to advanced SM (AdvSM), which includes SM with associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL).
- SM is associated with severe and often debilitating symptoms across multiple organ systems, which can lead to morbidity and poor quality of life. The heterogenous and non-specific nature of symptoms can complicate diagnosis, necessitate high healthcare resource utilization (HRU), and is often mis- or under-diagnosed.

Objectives

- Examine electronic medical records (EMRs) to identify and classify patients with SM, describe the natural history of disease and explore mis- or under-diagnosis, HRU pre-/post-diagnosis, and rates of progression and survival of non-advanced and AdvSM.

Methods

- EMRs from adults were manually reviewed from the Kaiser Permanente (KP) Southern California health system with ≥1 SM ICD diagnosis code from Jan 2008-July 2023 in this retrospective cohort study. Three additional patients were added by EMR search for key word “mast cell” in biopsy reports; only patients meeting the 2016 WHO criteria[1] for SM were retained for analysis.
- Patient EMR was manually reviewed by the physician study lead to confirm the SM diagnosis using WHO criteria[1] to calculate the average delay in diagnosis and to determine the average time to progression from non-advanced to AdvSM subtypes.
- Patient demographics and HRU were extracted from KPSC Research Data Warehouse.

Results

- 116 SM patients were confirmed with the following subtypes at initial diagnosis: 77% ISM (n=89); 2% SSM (n=2); 12% SM-AHN (n=14); 9% ASM (n=11); and 0% MCL. **(Table 1)**
- Notably, >40% of the study population was non-white, **(Table 1)** making this study sample the most racially/ethnically diverse sample of patients with SM known to the researchers.
- *KIT* D816V mutation by next-generation sequencing (NGS) was positive in 42 of 92 patients (46%) with test results available. Overall, D816V mutation was reported in 36% of the entire cohort. **(Table 2)**

[1]Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391-405.

[2]Georg G, Gurbisz M, Ratzinger F, Witzeneder N, Simonitsch-Klupp I, Mitterbauer-Hohendanner G, et al. Digital Droplet PCR: Next Generation KIT D816V Testing As Advanced Tool for Diagnosis and Prognostication in Mastocytosis. Blood 2017; 130:2927.

Results continued

- 5 patients were mis-classified with a less advanced SM subtype initially and 3 were completely undiagnosed (missed diagnosis), while meeting WHO criteria.
- The average delay to definitive SM diagnosis (time from first SM code to meeting full WHO criteria) was 58.3±73.1 months.
- Healthcare resource utilization (i.e., hospital admission, emergency department visits, urgent and non-urgent care visits, referrals and treatment of SM patients) generally increased after SM diagnosis. **(Table 3)**

Table 1. Patient Demographics

Patient Demographics	SM Subtype				ALL (N=116)
	ISM (N=89)	SSM (N=2)	SM-AHN (N=14)	ASM (N=11)	
Age					
Median (IQR)	53 (43-64)	71 (68-74)	69 (58-77)	63 (54-77)	56.5 (45-68)
Sex					
Male (N, %)	37 (41.6%)	2 (100)	11 (78.6)	9 (81.8)	59 (50.9)
Race/ethnicity					
Non-Hispanic White (N, %)	55 (61.8)	1 (50.0)	6 (42.9)	6 (54.5)	68 (58.6)
Hispanic (N, %)	20 (22.5)	0	6 (42.9)	3 (27.3)	29 (25.0)
Asian/Pacific Islander (N, %)	6 (6.7)	0	2 (14.3)	0	8 (6.9)
Black (N, %)	3 (3.4)	1 (50.0)	0	2 (18.2)	6 (5.0)
Others (N, %)	5 (5.6)	0	0	0	5 (4.3)

Table 2. SM Patient Cohort Identification (2016 WHO Criteria[1])

SM Assessments	Manually confirmed SM patients (n=116)
Criteria met: One major + at least one minor (N, %)	94 (80.0)
Criteria met: Three or more minor (N, %)	13 (11.2)
Did not meet WHO criteria, but clinically confirmed by historical chart review (N, %)	9 (7.8)
Minor criteria among SM patients	
Spindle-shape cells (N, %)	78 (67.2)
KIT D816V positive, NGS* (N, %)	42 (36.2)
Tryptase positive (>20ng/mL) (N, %)	95 (81.9)
CD2/25/30 positive (N, %)	85 (72.3)
Biopsies performed	
Bone marrow (N, %)	114 (98.3)
Skin (N, %)	29 (24.8)
Colonoscopy (N, %)	14 (11.9%)

**KIT* D816V testing completed in 92 of 116 patients (79%), using NGS, which has lower sensitivity than digital droplet PCR (ddPCR)[2].

Figure 1. Disease Progression (Non-advanced to AdvSM)

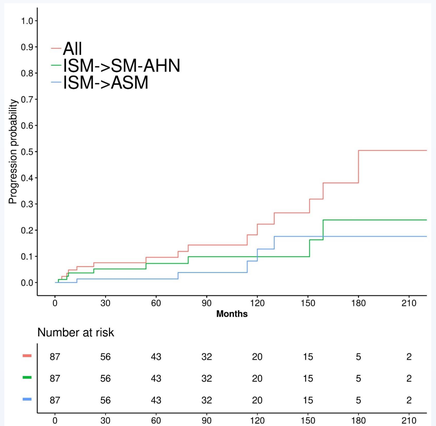

Figure 2. Survival for Non-advanced and AdvSM

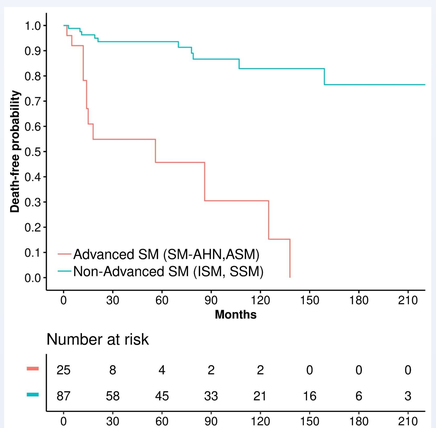

Table 3. Healthcare Resource Utilization (HRU) Pre-/Post-SM Diagnosis

HRU	Before SM diagnosis		After SM diagnosis	
	No. of events	Rate/p-yr (95% CI)	No. of events	Rate/p-yr (95% CI)
Hospital admissions	53	0.1 (0.1, 0.2)	159	0.3 (0.2, 0.3)
ED visits	136	0.3 (0.3, 0.4)	282	0.5 (0.4, 0.6)
Urgent care visits	126	0.3 (0.3, 0.4)	240	0.4 (0.4, 0.5)
Non-urgent visits	4618	11.4 (11.1, 11.7)	9471	16.9 (16.5, 17.2)
Specialty visits				
Hematology/oncology	670	1.7 (1.5, 1.8)	4114	7.3 (7.1, 7.5)
Allergy/immunology	222	0.5 (0.5, 0.6)	939	1.7 (1.6, 1.8)
Gastroenterology	328	0.8 (0.7, 0.9)	636	1.1 (1.0, 1.2)
Dermatology	528	1.3 (1.2, 1.4)	882	1.6 (1.5, 1.7)
Treatments	**No. of dispensings or admissions**	**Rate/p-yr (95% CI)**	**No. of dispensings or admissions**	**Rate/p-yr (95% CI)**
EPIPEN auto-injector	33	0.08 (0.06, 0.1)	152	0.3 (0.2, 0.3)
Epinephrine vials	0	0	12	0.02 (0.01, 0.04)
Systemic steroids	100	0.2 (0.2, 0.3)	514	0.9 (0.8, 1.0)
Inhaled steroids	49	0.1 (0.09, 0.2)	98	0.2 (0.1, 0.2)
H1 antihistamines	114	0.3 (0.2, 0.3)	447	0.8 (0.7, 0.9)
H2 antihistamines	83	0.2 (0.2, 0.3)	615	1.1 (1.0, 1.2)
LTRA and 5-LO inhibitors	45	0.1 (0.08, 0.1)	296	0.5 (0.5, 0.6)
Cromolyn sodium	2	0.005 (0.001, 0.02)	127	0.2 (0.2, 0.3)
Chemo or targeted agents for SM	0	0	450	0.8 (0.7, 0.9)
Osteoporosis meds	122	0.3 (0.3, 0.4)	91	0.2 (0.1, 0.2)
Biologics	0	0	0	0
Proton-pump inhibitors	130	0.3 (0.3, 0.4)	434	0.8 (0.7, 0.8)

Results continued

- 18% of patients with ISM/SSM progressed to a more advanced form of SM based on WHO criteria[1] (mean 88.3 mo; range = 2-295). **(Figure 1)**. ISM to ASM, n=6; ISM to SM-AHN, n=8; SSM to SM-AHN, n=1, ISM to MCL, n=1.
- Survival curves demonstrate that there is an increased probability of mortality once a patient is diagnosed with an AdvSM subtype of any kind. **(Figure 2)**

Conclusions

- SM occurs in more ethnically diverse populations than previously reported
- There is a long delay to definitive diagnosis of SM, which may be improved by physician awareness of SM and with the use of improved diagnostic tools (i.e., assessment of D816V mutation by ddPCR, which has much higher sensitivity than NGS[2])
- Following diagnosis of SM, HRU increased, highlighting the impact of the disease on these patients’ lives
- Continued patient follow-up is imperative as up to 18% of non-advanced SM patients in this retrospective study experienced progression to an advanced form of SM

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