Quantifying Diagnostic Delays in Patients With Systemic Mastocytosis

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Background

- Systemic mastocytosis (SM) is a rare clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of cases[1-5] and is characterized by chronic symptoms which can be debilitating[3,6,7]
- Due to the heterogenous and non-specific nature of symptoms, delays from the onset of symptoms to diagnosis can be approximately 6 years[2]
- Data from electronic health records (EHRs) have the potential to train machine learning models to identify patients with undiagnosed SM earlier than the current standard of care
- As a first step towards this goal, we sought to characterize a cohort of patients with SM using EHR data at the University of California, San Francisco (UCSF)

Methods

- EHR data from UCSF (2012–2023) were used to identify patients with diagnosis codes for SM (D47.02) or aggressive SM (C96.21)
- The EHRs of eligible patients were manually reviewed and patients were identified with a definite or probable diagnosis
  - Patients with a definite diagnosis are defined as meeting the WHO 2022 criteria[8], while a probable diagnosis is determined by clinicians
- Structured EHR data (diagnosis codes, medication and laboratory orders) were used to characterize the cohort at the time of their within-system diagnosis
  - Patients were excluded if their within-system diagnosis date occurred prior to the installation date of the EHR system (2012)
- The natural language processing tool, cTAKES, was used to identify the earliest date at which a compatible symptom (based on the Indolent Systemic Mastocytosis Symptom Assessment Form [ISM-SAF][9]) was found in a patient's health record
- The Kaplan–Meier estimator was used to estimate the survival distribution associated with individual features
  - Index date: the first date of a documented SM-compatible symptom
- Groups were compared using the log-rank test
  - Multiplicity was not controlled for (alpha=0.05) due to the exploratory nature of this analysis
- The median differences in the time to diagnosis (in years) between pairs of groups were calculated
- The patients were characterized by their medication use and medical work-up history that cumulatively resulted in a diagnosis
- This study was institutional review board–approved at the UCSF (#22-37116)

Results

- A total of 42 patients with definitive SM were identified at the UCSF (**Table 1**)
  - Median age (interquartile range [IQR]) was 58 years (43–69), 71% were females and 76% were White
- The first diagnosis (within the system) was with indolent SM for 69% of patients
  - Many patients were previously diagnosed outside of the UCSF, but these data are not captured by standard EHR databases
- Most patients were relatively affluent with few comorbidities
- 45% of patients had a skin-based symptom prior to their in-system diagnosis, and 24% of patients were subsequently diagnosed with cutaneous mastocytosis
- At baseline, >50% of patients previously had an abnormal serum tryptase level
- 50% (n=10/20) of patients tested at the UCSF reported a *KIT* mutation
  - This likely reflects a combination of patients who were tested outside the UCSF along with those tested with less sensitive methods (e.g., next-generation sequencing) for *KIT* D816V

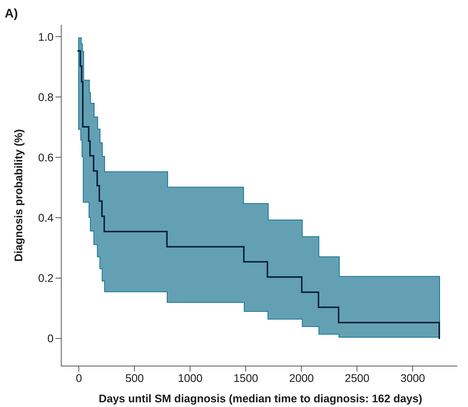
Table 1. Cohort characteristics

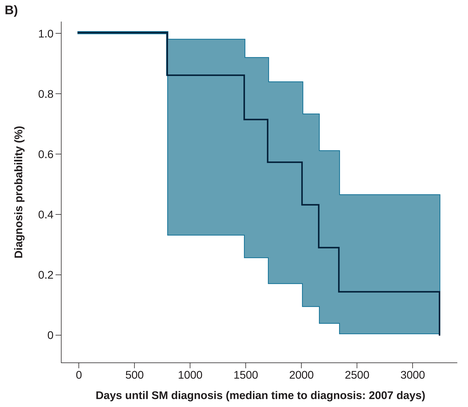
Characteristic	Total cohort, N=42	Patients with time to diagnosis >1 year, n=7
Age (years), median (IQR)	58.0 (43.0–69.0)	46.0 (42.5–62.0)
Female, n (%)	30 (71)	4 (57)
Race/ethnicity, n (%)[a]		
White[b]	32 (76)	4 (57)
Latinx[b]	5 (12)	2 (29)
Asian	3 (7)	1 (14)
Black or African American	1 (2)	0 (0)
Other	1 (2)	0 (0)
SM subtype, n (%)		
Indolent SM	29 (69)	6 (86)
Aggressive SM	3 (7)	0 (0)
Smoldering SM	0 (0)	0 (0)
SM with associated hematologic neoplasm	8 (19)	0 (0)
Mast cell leukemia	2 (5)	1 (14)
Socioeconomic status (ADI)[c], median (IQR)	6.03 (1.90–28.96)	6.03 (1.98–11.22)
Driving distance to the UCSF in miles[b] (IQR)	43.60 (16.80–118.00)	28.40 (9.45–91.90)
CCI, mean (SD)	0.55 (1.06)	1.43 (1.90)
Diagnostic journey, n (%)		
Dermatological symptom prior to diagnosis	19 (45)	7 (100)
Preceding cutaneous mastocytosis	10 (24)	6 (86)
Tested for *KIT* D186V	20 (48)	6(86)
Positive *KIT* D816V test	10 (24)	3 (43)
Abnormal serum tryptase	26 (62)	6 (86)

[a]All racial categories correspond to non-Latinx ethnicity. [b]P<0.05 for distribution vs patients outside subgroup. [c]One patient had a missing address. ADI, Area deprivation index; CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation; SM, systemic mastocytosis; UCSF, University of California, San Francisco.

- The median time from the first presentation of an SM-compatible symptom to a diagnosis was 5.4 months (**Figure 1A**)
- ~60% were diagnosed at the UCSF within 1 year
  - Likely due to carrying an existing diagnosis from another system and being referred for a second opinion, confirmation of SM, or for management
  - To address this, analysis was repeated in the subgroup who remained undiagnosed 1 year after their first year at the UCSF
- ~40% of diagnoses took more than 1 year
  - This may represent a cohort of truly previously undiagnosed patients with SM, which is more representative of a typical patient journey
  - To address this, analysis in this subgroup was repeated, giving a median time to diagnosis of 5.5 years (**Figure 1B**)
- Race and ethnicity may be predictive of the time to diagnosis (**Table 2**)
  - White patients were diagnosed 5.2 years earlier than other ethnicities
  - Latinx patients were diagnosed 6 years later than non-Latinx patients
- Dermatological symptoms affected the time to diagnosis
  - Patients with a skin-based complaint had a median diagnosis time that was 0.4 years longer than those without
- Trends were shown in other predictors, but a larger sample size is required for evaluation of these trends

Figure 1. Time to an SM diagnosis[a] for A) Total cohort with precursor symptoms (n=20) and B) Patients who had a time to diagnosis of >1 year (n=7)[b]





[a]The time to diagnosis after an SM-compatible symptom; abdominal pain, diarrhea, nausea, spots, itching, flushing, brain fog, headache, dizziness, bone pain, fatigue. [b]Ten patients were not included in lead-time analysis as their symptoms were not recorded in their medical notes.

Table 2. Predictors of the time to a diagnosis

	P value	Delta (years)	N
Age >50 years	0.90	–0.3	11
Female	0.23	–2.1	30
Race/ethnicity			
Asian	0.66	4.2	1
Latinx	0.03	6.0	5
White	0.02	–5.2	32
ADI			
<1.90 (top quartile)	0.82	0.1	6
≥1.90, <29.0 (IQR)	0.81	0.0	10
≤29.0 (bottom quartile)	0.97	–0.2	4
Driving distance to the UCSF			
5 miles	0.72	1.9	4
20 miles	0.42	–0.1	8
100 miles	0.33	–0.1	13
Comorbidities			
CCI >0	0.16	0.9	6
Presenting symptoms			
Allergy-related symptoms	0.62	0.1	7
Anaphylatic-like symptoms	0.39	0.2	7
Immune	0.51	0.0	13
Clinical	0.64	0.1	3
Cognitive	0.72	2.2	2
Dermatological	0.00	0.4	19
Emotional	0.16	–2.1	16
Gastrointestinal	0.88	–2.0	16
Musculoskeletal	0.31	0.5	8
Pain-related symptoms	0.54	0.4	13
Respiratory	0.68	0.3	7
Systemic symptoms	0.67	–0.2	17
Urinary	0.35	-0.2	1

- Patients were prescribed a median of two (IQR 1–3) medications post-diagnosis
- The most commonly prescribed medicines were antihistamines (64%)
- 19% of patients had been prescribed a tyrosine kinase inhibitor

Table 3. Medication use after an SM diagnosis

Class	Name	N (%)
	Omalizumab	0 (0)
Tyrosine kinase inhibitors (n=8)	Avapritinib	5 (12)
	Midostaurin	6 (14)
	Imatinib	2 (5)
Chemotherapy (n=5)	Cytarabine/cytarabine	0 (0)
	Azacitidine	2 (5)
	Venetoclax	3 (7)
	Interferon alfa-n3	0 (0)
Antihistamines (n=27)	**H1**	
	Cetirizine	16 (38)
	Fexofenadine	5 (12)
	Loratadine	4 (10)
	Hydroxyzine	3 (7)
	Doxepin	0 (0)
	Diphenhydramine	5 (12)
	H2	
	Famotidine	15 (36)
	Cimetidine	0 (0)
Corticosteroids (n=9)	**Systemic**	
	Prednisone	7 (17)
	Cortisone acetate	0 (0)
	Dexamethasone	2 (5)
	Methylprednisolone	2 (5)
	Prednisolone	2 (5)
	Non-systemic	
	Budesonide	0 (0)

Discussion

- A single-center cohort of 42 patients with SM, a rare clonal disorder of mast cells characterized by non-specific symptoms, was defined
- Accounting for potential out-of-system diagnoses that were verified within the first year, we estimated the median diagnosis time as 5.5 years
- Patients were treated with polypharmacy with the median number of two (IQR: 2–3) prescription medications
- Differences in diagnosis time by ethnicity were uncovered, with White patients being diagnosed earlier than Latinx patients
  - Future work is needed to confirm these findings in other datasets and explore the potential reasons underlying this
- Dermatological symptoms and diagnoses were common in this cohort and were predictive of longer diagnosis times
- This was contrary to prior expectations, as skin-based complaints frequently lead to biopsies and histopathological diagnoses. This may reflect other factors, including:
  - Other skin-based complaints that are pathophysiologically unrelated to SM
  - A lead-time bias effect, where skin-based complaints result in earlier presentations, compared to other symptoms, due to their disfiguring nature
  - SM patients being labeled initially as cutaneous mastocytosis when they did have a systemic disease
    - These findings support previous studies suggesting that adult patients with CM should be fully worked up for systemic disease[10]
- Limitations of this descriptive study include:
  - Small sample size making it challenging to draw meaningful conclusions of subgroups
  - Inability to see a complete patient journey across different healthcare systems
  - Heterogeneous capture of structured data
- Despite the risks of bias due to out-of-system diagnoses, the data captured in EHR systems were rich and could support the training of machine learning algorithms to reduce diagnostic delays
  - The use of manual review to establish absolute diagnosis times (independent of any given health care system), together with the aggregation of data across multiple centers, could enable this kind of method
  - Doing so will be critical to reduce diagnostic delays for SM and other rare diseases, given the non-specific symptoms and the low likelihood that non-specialist providers will recognize this disease and make timely referrals to clinical experts.

Conclusions

- A cohort of patients with SM was identified and their diagnostic journey characterized, highlighting the obstacles patients can experience in the fragmented US healthcare system
- Although this single-center study was limited by small samples, it suggests that both demographic and medical features captured in EHR data can be predictive of the time to diagnosis
- Thus, these data could support the development of predictive models and decision support tools to reduce diagnostic delays in SM and other rare diseases

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