Systemic Mastocytosis in Adults: Long-Term Follow up and Real-Life Experience

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ABSTRACT

Systemic mastocytosis (SM) is a rare disease and its clinical presentations and life expectancy are defined in previous studies. However, the real-life experience in SM from developing countries, especially with long term follow up data is limited. Patients who were diagnosed with SM were enrolled and defined as SM subgroups. Indolent SM (ISM)/ smoldering SM (SSM) and advanced SM (advSM) patients were compared according to clinical and laboratory findings. 22 SM patients with the median age was 42 years were evaluated. Eight of 22 (36.4%) patients had ISM, 4/22 (18.2%) had SSM, 5 had aggressive SM (ASM) and the remaining 5 had SM associated with AHN (SM-AHN). Median tryptase level was 61 ng/mL (range 10–200 ng/mL). Alkaline phosphatase level is higher in advSM than ISM/ SSM group (p= 0.003). Anaphylactic events were more frequent in ISM/SSM than advSM group: 9/12 (75%) versus 2/10 (20%), respectively (p= 0.03). Neurological findings are seen more commonly in ISM/SSM (83.3% vs 30%, p= 0.017). Headache and cognitive difficulties were noted in respectively 50% and 32% of patients. Overall survival (OS) was shorter in advASM group; OS at 2-year were 46.7% in advSM and %100 in ISM/SSM patients. Our study highlights the need of collaboration of different disciplines to improve the diagnostic approach and management of SM patients.

Keyorwds: Systemic mastocytosis, Smoldering, Aggressive, Tryptase

INTRODUCTION

Mastocytosis is a heterogeneous group of rare disorders with estimated prevalence 13 per 100.000 cases.[1] In 19th century it was firstly described pathologic accumulation of mast cells in skin and called mastocytosis until a systemic form of mastocytosis with involvement of visceral organs was described in 1949.[2,3] Mastocytosis can be divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM); the latter is commonly seen in adult and characterized by proliferation of neoplastic mast cells (MC) and enhanced release of their mediators in the skin, bone marrow and other organs/systems such as liver, gastrointestinal tract, lymph nodes, spleen, central nervous and skeletal system.[4] MC can play a key role for immune system because of expression of different surface receptors and releasing a wide range of mediators. The release of mediators can cause symptoms, including pruritus, diarrhea, nausea, heartburn, vomiting, bone loss, anaphylaxis, headaches, vertigo, memory/cognitive difficulties and depression.[5]

SM is clinically classified as six following groups; bone marrow mastocytosis (BMM), indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated hematologic (non-mast cell lineage) neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) according to clinical features and extend of disease in the revised 2022 World Health Organization (WHO) Classification of hematolymphoid neoplasms.[6] The latter three types are known as advanced variant of disease with impaired organ function ("C" finding) due to infiltration of pathologic MC.[7] The organ dysfunctions include liver dysfunction (elevated liver function tests, ascites, portal hypertension, cirrhosis), malabsorption (weight loss, hypoalbuminemia), large osteolytic bone lesions and/or fractures, cytopenias.[8] ISM and SSM are most frequent and indolent forms of mastocytosis. ISM can be detected with MC infiltrates in various organs although there is no organ failure or impairment SSM meet diagnostic criteria of SM additional to organomegaly or lymphadenopathy without organ impairment ("B finding) and >30% mast cells infiltration in bone marrow biopsy. In SM-AHN the most common associated hematologic malignancies are chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML), myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS) and nonHodgkin lymphoma (NHL).[9] MCL, diagnosed when percentage of MC increased ≥ 20% in bone marrow aspiration smear, is very rare and poor prognostic form of SM.[10] Advanced SM (advSM) that comprises 3 subgroups: SM-AHN, ASM and mast cell leukemia (MCL). Although patients with ISM/SSM are expected to have a normal lifespan, patients with advSM have significantly shortened survival for now.

The diagnosis of SM still remains challenging and delayed. The patients are usually seen by many disciplines, including allergy/immunology, hematology/oncology, family medicine, internal medicine, endocrinology, gastroenterology, neurology, cardiology and dermatology because of complexity and variety of symptoms and signs. The current study aims to evaluate the prevalence of MC mediator-related symptoms in a cohort of SM patients and compare the clinical, laboratory findings and outcomes between patients with ISM/SSM and advSM.

PATIENTS AND METHODS

This retrospective study included SM patients diagnosed and treated in Departments of Hematology as well as in Allergy and Immunology at Ege University between 2009 - 2020. We identified 27 patients with SM in our center. Of 27 patients, 5 were excluded due to inadequate data. All 22 patients were reevaluated according to the diagnostic criteria of 2016 World Health Organization (WHO) Classification of hematolymphoid neoplasms. The diagnosis is confirmed for 22 patients based on major and minor SM criteria. The major SM criterion is accumulation and/or MCs aggregation in bone marrow BM or another extracutaneous organ (e.g., spleen, liver, bone, LNs, GI tract) biopsy. Minor SM criteria include an abnormal MC morphology, aberrant expression of CD2 and/or CD25 and/or CD30 by MCs, KIT-activating mutation in KIT, and an elevated serum tryptase level >20 ng/mL. All of 22 patients confirmed the major criteria of MC accumulation in bone marrow examination. KIT mutation was evaluated in 5 patients. All patients provided a written informed consent for use of their medical records for research purposes for this study. The research was carried out in accordance with the principles of the Declaration of Helsinki.

We collected the following data at diagnosis; age at diagnosis and disease onset, clinical signs and symptoms (e.g., idiopathic anaphylactic shock, allergy to hymenoptera venom), skin lesions, flushing, gastrointestinal symptoms (diarrhea, nausea, heartburn, vomiting, abdominal cramp) and neurological symptoms (headaches, vertigo), cognitive symptoms (memory loss, cognitive difficulties), psychiatric symptoms (depression, sleep disturbance), organomegaly (spleen and liver), organ dysfunction, prior therapies, bone mineral density (BMD) measured by DXA, T-score and Z-score at the hip and lumbar spine (L1-L4) sites. Osteoporosis defined according to the traditional WHO criteria (bone mineral density, BMD, T-score < –2.5). Apart from serum tryptase level, routine laboratory parameters, including blood counts, chem-

Table 1. Baseline characteristics and laboratory features of patients

		All patients n= 22	ISM/SSM n= 12	AdvSM n= 10
Median age (range)		42 (18-72)	34.5 (23-53)	55.5 (18-72)
Gender	Female n (%)	9	6	3
	Male n (%)	13	6	7
Hb median (range), g/dL		11.6 (7-15.1)	12.95 (7-15.1)	10.4 (7.5-13.7)
Leukocyte count, median (range), X 10^9/L		6.8 (3.6-54.5)	6.3 (4.8-18.9)	11.4 (3.6-54.5)
Neutrophil count, median (range), X 10^9/L		3.8 (1.3-38.1)	3.7 (1.3-11.7)	5.2 (2-38.1)
Eosinophil count, median (range), X 10^9/L		0.9 (0.1-9.7)	0.85 (0.1- 4.7)	1.6 (0.1-9.7)
Platelet count, median (range), X 10^9/L		236.5 (130-415)	268 (93-415)	163.5 (30-332)
Serum tryptase	Mean	89.5	69.28	124
n= 19	Median (range)	61 (10.2-200)	52.25 (10.2-200)	125 (23-200)
Serum alkaline	Mean	143	89.5	208
phosphatase	Median (range)	90.5 (44-489)	87 (44-211)	199 (63-489)
level (u/L)				

istry including alkaline phosphatase (ALP) level and routine coagulation parameters recorded in patients with SM. Bone marrow evaluation and organ involvement seeking were performed for the patients. Reference pathologists (N.O. and D.D) reevaluated all of the bone marrow biopsies for this study. Expression of aberrant phenotype markers CD2/CD25 and CD117 on mast cells was investigated in all patients by immunohistochemical staining in BM biopsy and also by flow cytometry in 4 patients. Patients in our study divided two groups as ISM/SSM and advSM. Both of ASM and HM-AHN SM patients defined as advanced SM (advSM). The clinical and laboratory findings were compared between two groups.

This study was approved by the local ethical committee at the Ege University Medical Faculty (nr: 21-1T/49–07.01.2021).

Statistical Analysis

All statistical analyses considered clinical and laboratory parameters. Categorical variables were presented as percentage and compared with the chi-square test. Normality of distribution were assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median and interquartile ranges. Continuous variables were compared with one-way ANOVA or Mann-Whitney U test according to distribution of normality. Kaplan-Meier analysis was used for evaluation of patient survival. A p value < 0.05 was statistically significant. SPSS (version 21.0.0, IBM Cooperation, Armonk, NY) were used for statistical analysis.

RESULTS

Characteristics of Patients

A total of 22 patients with SM were identified. The baseline of patient characteristics at presentation of these patients are shown in Table 1. Median age was 42 (18-72) years, and 13/22 (59, 1 %) patients were male. Most patients had the major WHO diagnostic criterion (18 of 22, 81%). Eight of 22 (36. 4%) patients had an indolent SM, 4/22 (18. 2%) had a smoldering SM, and 10 had advSM. Of the 10 advSM, 5 had an aggressive SM and the remaining 5 had SM-AHN (Table 1). Two of 5 SM-AHN patients had CMML, one had MPN unclassified, one had myelodysplastic MDS/MPN and the other one had MPN with eosinophilia. Four of 5 patients with SM-AHN were male. The median follow-up of our patients was 31.5 months (range: 2-132 months).

Disease Related Symptoms and Clinical Findings

The median interval from the first symptom to the diagnosis of SM was 3 years (range, 1 to 10 years). The vast majority of patients (72.7%) presented

Table 2. Clinical symptoms and findings at the time of diagnosis

	All patients (n= 22)	ISM/SSM (n= 12)	AdvSM (n= 10)	p
Hepatomegaly&, n (%)	11 (50)	2 (16.7)	9 (90)	0.002
Splenomegaly&, n (%)	8 (36.4)	1 (8.3)	7 (70)	0.006
Skin involvement*, n (%)	7 (31.8)	4 (33.3)	3 (30)	
Urticaria pigmentosa, n (%)	12 (54.5)	8 (66.7)	4 (40)	
Flushing, n (%)	14 (63.6)	10 (83.3)	4 (40)	
Occurrence of anaphylaxis, n (%)	11 (50)	9 (75)	2 (20)	0.03
Gastrointestinal system involvement*, n (%)	2 (9.1)	–	2 (20)	
Neurological symptoms, n (%)	13 (59)	10 (83.3)	3 (70)	0.017

& Detected ultrasonography and/or computary tomography

* proven by skin biopsy. Bold indicates statistical significance (p< .05)

with skin-related symptom or sign, including urticeria pigmentosa (UP) (54.5 %), flushing/pruritis (63.6 %) (Table 2). Skin biopsy was performed in 7 (31. 8 %) patients and cutaneous involvement was confirmed in all of them. Extensive maculopapulose skin lesions which were seen in one of SM-AHN patients are shown in Figure 1 and flushing is seen in Figure 2 in an ISM patient. Anaphylaxis occurred in 50% of all patients, and the occurrence of anaphylactic events were more frequent among indolent SM than advSM patients [9/12 (75%) vs 2/10 (20%) respectively p= 0.03)]. Spontaneous anaphylaxis (i.e., anaphylactic reactions without known triggers) was seen in 5 patients whereas anaphylaxis occurred after an insult in 8 patients (insect venoms, medications, and food in 3, 2 and 1 patients, respectively).

Organomegaly (hepatomegaly and/or splenomegaly) was detected in 12 (54.5 %) of patients. As expected, organomegaly was significantly higher in advanced SM group. Of 10 patients with advSM, 6 had ascites and 4 had portal hypertension. Three patients had gastric symptoms (dyspepsia and weight loss) and colonic mast cell infiltration was documented by endoscopic biopsy in 2 of them.

Neurological findings; headache, memory and cognitive difficulties, depression, sleep disturbances have been questioned and 59% of all patients had at least one neurologic symptom. Neurological findings are more common in ISM/SSM group than advSM group (10/12 (83.3%) vs 3/10 (30%), p= 0.017) as outlined in Table 2. Headache and cognitive difficulties are the most common neurologic symptoms and seen in 50% and 31.8% of patients, respectively.

Skeletal survey was performed in 15 patients, and 7 of them had sclerotic bone lesions. Sclerosis is higher in advSM (4/10 patients, 40%) than ISM/SSM (3/12 patients, 25%) in ISM/SSM, respectively. Bone mineral density (BMD) was performed in 12 patients: half of patients had normal BMD, 4 patients had osteopenia and 2 had osteoporosis.

Laboratory Analysis

Baseline serum tryptase levels were measured in 19 patients with SM and were found to be elevated (> 20 mg/L) in 18 of them (81.8 %) with a median value of 61 ng/mL (range 10-200 ng/mL) (Table 1). Median tryptase level was higher in advSM group than ISM/SSM group (125 vs 52.5 respectively). Median hemoglobin level was 11.6 g/dl (range, 7-15.10) and it was 12.4 g/dl and 10.4 g/dl in ISM/SSM and advSM patients respectively. Hemoglobin level < 10 g/dL in 5 (22.7%) patients, platelet count < 100 × 10^9/L in 6 (18.3%) patients. Six (27.2 %) patients exhibited leukocytosis greater than 12 X 10^9/L and 5 of them had advSM. Serum ALP above the upper normal limit of the reference range in 8 (36.4%) patients. ALP level is significantly higher in advSM group than ISM/SSM group (199 vs 87 u/L p= 0.003) as outlined in Table 1. All 22 patients expressed aberrant marker CD25 while both CD2 and CD25 markers were detected in 10/22 (45%) patients in BM biopsy by immunohistochemical

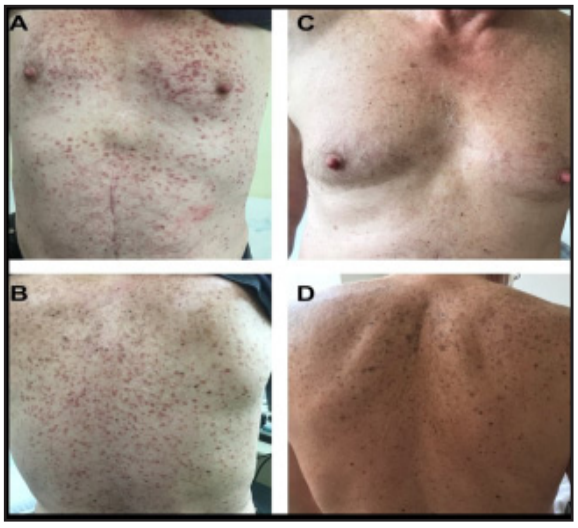

Figure 1. Extensive maculopapulose skin lesions in a patient with SM-AHN. 68 years old male patient diagnosed with systemic mastocytosis with an associated hematologic neoplasm. **A** and **B**: skin lesions at presentation; **C** and **D**: improvement of the lesions after midostaurin treatment

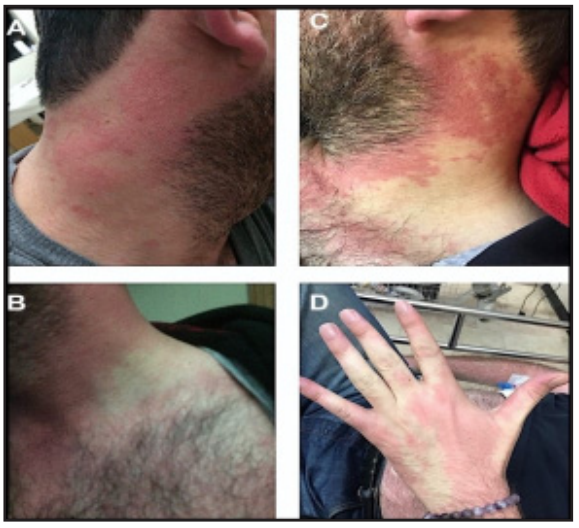

Figure 2. Flushing skin lesions in a patient with ISM. 34 years old male patient diagnosed with indolent systemic mastocytosis presented flushing lesions. **A, B** and **C**: flushing on his neck; **D**: flushing on.

staining and/or flow cytometry. CD2 positivity was similar ISM/SSM vs advSM group (60% vs 44.4%, respectively).

Treatment and Survival

Two years OS rates were %46.7 for advSM patients and 100% for ISM/SSM patients (Figure 3). Five patients died during the study duration: 4 had SM-AHN at a median of 3 months (range, 2-21 months) after diagnosis and 1 ASM (also had chronic hepatitis B virus infection) due to hepatic failure (2 months after diagnosis).

The most common drugs used in ISM/SSM patients were histamine 1 and 2 antagonists (in 8/10 patients). Cladribine was used in a patient with SSM. The patient has been in complete remission for 5 years. Off 5 ASM patients; 3 were treated with midostaurin and all of them had pure clinical response and decreased tryptase level during the treatment. In 5 SM-AHN patients; a 74-year-old male patient with SM-CMML who was treated with 8 cycles of azacytidine and died 5 years after diagnosis. A 73-year-old male with SM-CMML failed to respond to steroid, hydroxyurea. Partial remission was achieved with midostaurin therapy for 8 months but he died from liver failure. A 72-years old female who had SM-MDS/MPN received azacytidine for 12 months after then she progressed to AML and died from AML. A 34-year-old male with SM-MPN NOS was unresponsive to imatinib and interferon therapy and died within 2 months. The fifth patient, a 19-year-old male with SM-MPN/eosinophilia received imatinib from the beginning of diagnosis and he is still in remission with imatinib.

DISCUSSION

In this real-life study, we evaluated our SM patients' symptoms, clinical presentation, treatment and survival outcomes. There are many expected findings: ***a)*** patients with ISM/SSM were younger and had more skin involvement[1,11], ***b)*** patients with SM-AHN had more chronic myeloid malignancies (CMML and MPN)[12,13], ***c)*** patients with advSM had a significantly poorer prognosis.[11,12,14] Although similar to previous studies no gender predilection in ISM/SSM group[9], higher frequency of male patients (7/10) was seen in advSM group in our study. Serum ALP level and sclerotic bone lesions were higher in advSM than ISM/SSM patients. There is a correlation between serum ALP level and symptoms and ALP was significantly higher advanced SM patients in our study ($p< 0.003$) (OR: 1,01 95% confidence intervals (95% CI: 1.00-1.02). Pardanani et al. defined that ALP is an independent risk

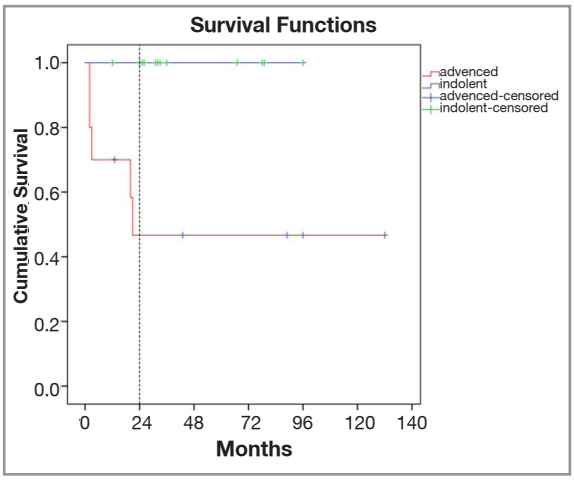

Figure 3. Survival outcomes. Kaplan-Meier survival for patients with advanced systemic mastocytosis (advSM) (red) and indolent/smoldering systemic mastocytosis (ISM/SSM) (blue). Two years overall survival rates were 46.7% for advSM patients and 100% for ISM/SSM patients

factor for survival of SM patients according to retrospective analysis of 580 SM patients from Mayo clinic.[15]

In our study, AdvSM and SSM patients were more common than expected in relative to ISM patients. This emphasize that ISM patients may be under diagnosed or late diagnosed. Related to this point, even in diagnosed patients, diagnosis of SM took a long time. The median time from occurrence of first symptom to diagnosis was 3 years (range, 1 to 10) in our study. Time from appearance of symptoms to diagnosis of SM due to frequent misdiagnosis or delayed diagnosis remains a challenge in clinical practice.

We showed higher prevalence (59%) of neurological findings in SM patients; however, the neuropsychological symptoms are reported one-third of patients with mastocytosis.[16,17] Headache is the most frequent symptom followed by cognitive impairment in our patients. There is no data on the relation of neurological symptoms between SM subtypes yet. Nevertheless, we defined that neurological symptoms are significantly higher in ISM/SSM patients than advSM. According to us, these symptoms are probably underestimated in patients with advSM due to more serious findings such as cytopenias, organ failure and/or underlying hematologic malignancies. Noteworthy, neuropsychological symptoms are not considered as 'C findings' although they are as common as other findings and affect the quality of life in SM.[17,18]

Considering possibility of SM in patients with allergies and anaphylaxis, with bone lesions (sclerotic or lytic) or osteoporosis[19] may be another measure to increase diagnosis of SM. The results of previous studies and clinical observations indicate a strong association between anaphylaxis and mastocytosis, and the prevalence of anaphylaxis has been reported to be 20-56% in adult patients with various forms of mastocytosis[20-22] and 50% of patients had experienced at least one episode of anaphylactic reactions during the study period. Although it was observed that anaphylactic events were higher in males and in patients with skin lesions in some of the previous studies[22] we could not find any gender or symptom differences in the patients presented with anaphylaxis in our study group. However, we found that anaphylactic reactions were more common in patients with ISM/SSM than advSM ($p< 0.003$), in accordance with the earlier reports. SM is a rare cause of osteoporosis but bone manifestations are common symptoms of SM and the real incidence of mastocytosis-related osteoporosis is still unknown.[23] Bone lesions on imaging were detected in 7/15 patients in our cohort and there was no finding of bone fractures despite 2 of them had osteoporosis.

Clearly education is critical to increase awareness of SM in providers and patients. In this regard, using tryptase perhaps as a screening test for patients who have suspicious symptom/sign of SM. A well-established and recommended marker of mastocytosis is the level of tryptase.[12,24] Elevated serum tyrptase levels are usually seen in patients with SM although about 5% of patients with ISM had normal serum tryptase level and mild increased tryptase level can be determined in other diseases such as urticeria, anaphylactic reaction, myeloid neoplasm, myocardial infarction, pregnancy, hepatic failure, hereditary alpha tryptasemia and renal failure.[25-27] Elevated serum tryptase was observed in the vast majority of our patients (median 61 ng/ml). Some of the studies reported tryptase as a possible prognostic indicator of disease stability and/or progression.[28,29] Whereas tyrptase level was higher in advSM group, although we could

not show this correlation statistically in our study group.

Our study had some limitations, it is a single-center study with a small sample size, and therefore most of the findings other than neurological symptoms are confirmed the current knowledge of SM. Additionally, we evaluated the neurological symptoms retrospectively from historical medical record. However, our study is unique in somehow it is the first study which evaluates the neurological features according to SM subtypes. The most striking point of our study is that neurological findings are more common in ISM/SSM patients than advSM patients. Therefore, the confirmation of this results with prospective neurologic evaluation is needed. Even though so many SM patients have been reported from Western countries, this is the second report from Turkey which describe the clinical and laboratory findings of SM patients.

In conclusion, the awareness of SM is very good in allergy and hematology disciplines, but other disciplines where more ISM likely be seen (gastroenterology, dermatology, neurology, cardiology) require more attention to this orphan disease. We believe that if its recognition is increased, diagnosis of SM from our country will be improved and symptoms affecting the other organs especially nervous system will be evaluated more carefully by neurologists.

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