

Systemic mastocytosis in the elderly

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“Later onset” of systemic mastocytosis (SM) has been associated with a poorer prognosis. We examined clinical and laboratory findings, associated disorders, and survival in an older mastocytosis population. After receiving Mayo Clinic Institutional Review Board approval, we identified 42 patients aged 70 years and older at the time of diagnosis of SM. Associated disorders, cytogenetic abnormalities, laboratory findings, and survival were recorded. Only 10 patients had no associated hematologic disorder. Single or multiple chromosomal abnormalities, exclusive of the *KIT* Asp816Val mutation, were detected in eight patients (19%). *KIT* Asp816Val mutation was present in 14 patients, negative in three, and not tested in 25. Slight to marked bone marrow hypercellularity was observed in 33 patients (79%). Concurrent hematologic abnormalities included chronic myelomonocytic leukemia ($n = 7$), acute myelocytic leukemia ($n = 1$), myelodysplastic syndrome (MDS; $n = 7$), eosinophilia ($n = 7$), myelofibrosis ($n = 1$), myeloproliferative disorder ($n = 1$), multiple myeloma ($n = 1$), B-cell lymphoma ($n = 1$), and thrombocytopenia ($n = 4$). Eight patients had a hematologic disorder that preceded the diagnosis of SM. Tryptase levels were elevated in 38 of 39 patients tested. Survival from the diagnosis of SM was poor for patients with associated thrombocytopenia, leukemias, and MDS. In conclusion, patients with SM diagnosed at age 70 or older have an increased risk of secondary hematologic disorders and abnormal laboratory findings. Cytogenetic abnormalities are common, and survival is short in many SM patients with associated leukemias, MDS, or eosinophilia. *Am. J. Hematol.* 88:406–408, 2013. © 2013 Wiley Periodicals, Inc.

Introduction

The prognosis for patients newly diagnosed with systemic mastocytosis (SM) remains an important consideration when decisions concerning treatment arise. For SM patients (without associated hematologic disorders), clinical features associated with a worse prognosis from the time of referral to a hematologist include hepatosplenomegaly, increased serum alkaline phosphatase (SAP) level, bone marrow mast cell content 10% or higher, and anemia [1]. In addition, SM patients with an associated clonal nonmast cell lineage hematologic disorder (SM-AHNMD) have lower 5-year survival rates than do patients with SM alone (17% vs. 75% [2]; 28% vs. 61% [3]). Laboratory variables associated with aggressive SM at the time of referral include increased bone marrow mast cell burden, eosinophilia on bone marrow aspirate, and increased SAP [1].

However, among variables that increase the risk of death in SM, late-onset disease has been recognized for more than 20 years as one of the most significant factors (univariate analysis, $P < 0.002$; multivariate analysis, $P < 0.004$) [4,5]. P values for late-onset symptoms were considerably lower than those of any other variable such as absence of cutaneous mastocytosis lesions, lower platelet count, higher serum lactate dehydrogenase (LDH) value, lower hemoglobin level, higher total bone marrow cellularity, and many other variables [4]. Independent predictors of overall survival in patients with indolent SM (ISM) include age at diagnosis of at least 60 years, increased SAP, and development of an associated clonal nonmast-cell lineage hematologic disorder (AHNMD) [6].

No consensus has been reached about the definition of “late onset.” However, in one large review of SM, patients categorized in three age groups (17–49 years, 50–64 years, and ≥ 65 years) had progressively worse survival as age range increased (compared with expected survival) [7]. In other demographic studies of SM, “advanced age” has been defined as 65 years and older [5]. In this study, we examined the clinical and laboratory features of SM patients who were 70 years and older when SM was diagnosed.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. Patients aged 70 years and older seen at Mayo Clinic (Rochester, Minnesota) from January 1, 2000, through July 31, 2012, with a new diagnosis of SM, were identified through institutional electronic databases. Medical records were thoroughly reviewed to confirm the diagnosis of SM. The following findings were documented and SM classified according to accepted criteria [8]: sex, bone marrow cellularity, presence of additional hematologic disorder(s), tryptase level, eosinophil count, SAP, LDH, presence of splenomegaly and of skin lesions, *KIT* Asp816Val mutation, and any other cytogenetic abnormalities.

Results

Forty-two patients (26 men, 16 women) were identified who met the age and diagnostic criteria. The average age was 75.7 years (men, 75.2 years; women, 76.1 years). The most common presenting signs and symptoms included diarrhea ($n = 6$), weight loss ($n = 6$), stomachache or abdominal pain ($n = 3$), headache ($n = 3$), anaphylaxis ($n = 3$), and anemia ($n = 3$); however, multiple concerns were common. Twenty-seven patients (63%) had an

Abbreviations: AHNMD, associated clonal nonmast cell lineage hematologic disorder; ISM, indolent systemic mastocytosis; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; SAP, serum alkaline phosphatase; SM, systemic mastocytosis; SM-AHNMD, systemic mastocytosis associated with a clonal nonmast cell lineage hematologic disorder

Additional Supporting Information may be found in the online version of this article.

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TABLE I. Incidence of Splenomegaly and Urticaria Pigmentosa and Duration of Survival of Elderly Patients With Systemic Mastocytosis, Stratified by Hematologic Disorder

Hematologic disorder	Splenomegaly, No. (%)	Urticaria pigmentosa, No. (%)	Survival, mo
Thrombocytopenia (n = 4)	2 (50)	0 (0)	35 ^a ; 22 ^a ; 20 ^a ; 5+
Leukemias (n = 9) ^b	7 (78)	1 (11)	18 ^a ; 16+; 6 ^a ; 6 ^a ; 5 ^a ; 4 ^a ; 1 ^a ; <1 ^a
Myelodysplastic syndrome (n = 7) ^c	5 (71)	2 (29)	87; 41 ^a ; 12 ^a ; 5 ^a ; 1 ^a
Eosinophilia (n = 7) ^b	5 (83 ^d)	0 (0)	>115; 48 ^a ; 39+; 17+; 7 ^a ; 2 ^a
Other hematologic or immune disorder (n = 5)	3 (60)	2 (40)	77; 52 ^a ; 48+; 26+; 1 ^a
None (n = 10) ^b	0 (0)	4 (40)	>104; 79; 35; 21 ^a ; 18+; 17+; 8+; 5; 3

^a Deceased.^b One patient was lost to follow-up.^c Two patients were lost to follow-up.^d One patient was status post splenectomy.

associated hematologic disorder that fell into one of the following categories: thrombocytopenia ($n = 4$), leukemias ($n = 9$), myelodysplastic syndrome (MDS; $n = 7$), or eosinophilia ($n = 7$). In addition, five other hematologic disorders, immune disorders, or isolated chromosomal abnormalities were found, including myeloproliferative disorder ($n = 1$), B-cell lymphoma ($n = 1$), sclerosing mesenteritis ($n = 1$), myelofibrosis ($n = 1$), and trisomy 8 without associated diagnosed hematologic disorder ($n = 1$) (Table I). In 10 patients, no hematologic or immunologic disorder was identified; patient characteristics in this group were consistent with a classification of ISM in nine of 10. Survival data are shown in Table I. Short survivals, with death within the first 6 or 7 months after diagnosis, were common in the patients with associated leukemias, MDS, or eosinophilia. Overall, the diagnosis was ISM for 15 patients, SM-AHNMD for 22, aggressive SM for four, and smoldering SM for one. There were no patients with mast cell leukemia.

Bone marrow hypercellularity was noted in 33 patients (79%), normocellular bone marrow in six (14%), and hypocellular, variable cellularity, or indeterminate cellularity in one each (7%). Other hematologic diagnoses preceded the diagnosis of SM in eight patients (Supporting Information Table SI). The main hematologic disorders associated with SM in our elderly cohort are listed in Supporting Information Table SII, along with secondary hematologic findings. Patients commonly had more than one hematologic finding. Bone marrow was positive for the *KIT* Asp816Val mutation in 14 patients and negative in three patients; testing was not performed in 25 patients. In addition, other cytogenetic abnormalities occurred in eight patients (19%). These abnormalities and associated hematologic disorders are listed in Supporting Information Table SIII.

The average eosinophil count was highest among the "eosinophilia" group (6,508/mm³; reference range, 50–500/mm³), followed by patients with leukemias (1,017/mm³), no hematologic or immunologic disorders (698/mm³), MDS (323/mm³), thrombocytopenia (53/mm³), and "other" hematologic or immunologic disorders (12/mm³). The average LDH value was highest for the leukemia group (489 U/L; reference range, 122–222 U/L), followed by patients with eosinophilia (220 U/L). Average LDH values in the remaining patient groups were normal. Fig. 1 shows the average serum tryptase values and SAP values. Serum tryptase levels (data available in 39 patients) were increased (>11.5 ng/mL) in 38 and affected all patient groups, whereas SAP values were markedly elevated only in the thrombocytopenia,

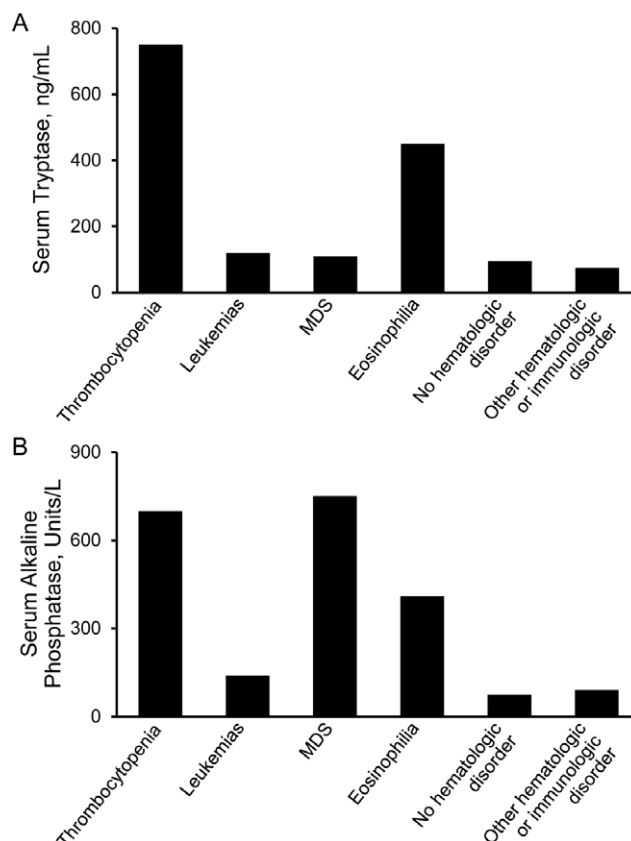


Figure 1. A: Average serum tryptase values for each patient group (the reference range is <11.5 ng/mL). B: Average SAP values for each patient group (the reference range is 45–115 units/L).

MDS, leukemia, and eosinophilia groups. Supporting Information Table SIV summarizes patient classification, presence of skin lesions, *KIT* Asp816Val mutation status, presence of "B" findings (organ enlargement without dysfunction) and "C" findings (organomegaly-related dysfunction), minor criteria (including tryptase levels), and response to nonsymptomatic therapy.

Discussion

This review of 42 elderly patients with SM (≥ 70 years at diagnosis) reinforces the poor prognosis, especially if SM was associated with another hematologic neoplasm. Twenty-seven patients (63%) in our cohort had a hematologic diagnosis in one of five broad categories, and five (14%) had less common hematologic or inflammatory disorders or a chromosomal abnormality. Additionally, eight patients had a hematologic abnormality that preceded SM by a variable length of time, in one case by 20 years and in others by 10 and by 4 years.

Our findings of poor prognosis of elderly patients with SM were consistent with that reported by Lim et al. [5], who showed that patients with ISM who were younger ($P < 0.001$) or had a longer duration of symptoms before diagnosis ($P < 0.001$) had superior survival compared with patients in the other SM groups. Other factors previously documented to be negatively associated with survival include an elevated serum LDH level, splenomegaly, bone marrow hypercellularity, circulating mast cells, coexisting additional hematologic disorder, elevated alkaline phosphatase level, thrombocytopenia, anemia, and absence of cutaneous lesions of mastocytosis [3,4,9]. Many of these findings can indicate a high burden of mast cells or organ

damage by mast cells, and they are thought to indicate aggressive disease [10].

The absence of urticaria pigmentosa in patients with aggressive SM has been reported in several series [11,12]. In the current study, the group lacking associated hematologic or immune disorders had the highest percentage of patients with urticaria pigmentosa. For patients with ISM, the presence of *KIT* mutations involving hematopoietic lineages other than mast cells has been reported to be significantly higher among patients with skin lesions compared with patients lacking skin lesions [13]. The presence of the Asp816Val mutation in all hematopoietic lineages ($P=0.02$) with the serum $\beta 2$ -microglobulin level ($P=0.003$) was the best combination of independent parameters for predicting disease progression. The reason for the favorable association between skin lesions and prognosis of SM in adults remains unexplained.

In a recent review of 342 consecutive adults with SM, about 40% had SM-AHNMD [5] and patients in that category had the second-shortest survival (median, 24 months). Only patients with mast cell leukemia had shorter survival (median, 2 months). It remains possible that the high number of patients with SM-AHNMD in our series could be attributable to referral bias. Only 10 of our patients did not have another associated hematologic or inflammatory disorder, with 62% categorized as having aggressive SM or SM-AHNMD and the remainder having ISM or smoldering SM. Nearly 17% of our patient group had eosinophilia, with an average total eosinophil count greater than $6,500/\text{mm}^3$ (hypereosinophilic range). Peripheral blood and bone marrow eosinophilia have been reported in patients with SM [14,15]; however, the clinical outcome was similar in patients with SM and myeloproliferative neoplasms, with and without eosinophilia [16]. The association of SM with hypereosinophilic syndrome with cardiac involvement appears, however, to be rare [17]. The “mast cell-eosinophil axis,” whereby each cell type produces cytokines and chemokines that support the survival, activation, and signaling of the other, may explain the common, mutually supportive, association of these two cell types in SM and other disorders [18]. Moreover, eosinophil granule proteins have been detected in HMC-1 cells, an immature mast-cell line derived from a patient with mast-cell leukemia [19]. Both solid and hematologic malignancies have been reported to be associated with SM [20–22]. In one report, the statistical analysis did not indicate that risk for malignancies increased after the diagnosis of SM [22].

Patients of advanced age at the time of the diagnosis of SM will commonly have an associated AHNMD and can have short survival from the time of diagnosis. In our review, we found that fewer patients with SM who lacked

an associated hematologic abnormality died within 6 months of diagnosis compared with the groups with leukemias, MDS, or eosinophilia. This fact should be considered when discussing treatment options with these patients.

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