Clinical Impact of Skin Lesions in Mastocytosis: A Multicenter Study of the European Competence Network on Mastocytosis

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Mastocytosis is a rare neoplasm characterized by the expansion and accumulation of mast cells in various organ systems. Systemic mastocytosis (SM) may or may not present with cutaneous lesions. To examine the frequency and clinical impact of cutaneous involvement, data on 1,510 patients with mastocytosis collected in the registry of the European Competence Network on Mastocytosis were analyzed. Cutaneous involvement was found in 1,195 of 1,510 patients (79.1%). Of these, 286 had cutaneous mastocytosis, and 721 had SM with skin involvement. Adult patients with skin involvement who did not have a bone marrow examination (n = 188) were defined as having mastocytosis in the skin. In 315 patients, SM without skin involvement was found. The percentage of cases with cutaneous involvement was higher in indolent SM (100%) and smoldering SM (87.9%) compared to aggressive SM (46.8%) or mast cell leukemia (38.5%). After a median follow-up of 5.6 years, no patient with cutaneous mastocytosis had died, but 2.6% of the patients with mastocytosis in the skin, 5.7% of the patients with SM with skin involvement, and 28.95% of the patients with SM without skin involvement had died. Overall survival was longer in patients with skin involvement (cutaneous mastocytosis and/or mastocytosis in the skin and/or SM with skin involvement) than in patients with SM without skin involvement ($P < 0.0001$). These data argue for a thorough examination of both the skin and bone marrow in adult patients with mastocytosis.

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Abbreviations: ASM, aggressive systemic mastocytosis; BM, bone marrow; BMM, bone marrow mastocytosis; BSA, body surface area; CM, cutaneous mastocytosis; DCM, diffuse cutaneous mastocytosis; ECNM, European Competence Network on Mastocytosis; IQR, interquartile range; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MCM, mastocytoma; MIS, mastocytosis in the skin; MPCM, maculopapular cutaneous mastocytosis; OS, overall survival; PUVA, psoralen plus UVA; SM, systemic mastocytosis; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; SSM, smoldering systemic mastocytosis; WHO, World Health Organization

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INTRODUCTION

Mastocytosis is a rare disease characterized by abnormal growth and accumulation of neoplastic mast cells (MCs) in one or multiple organ systems, including the bone marrow (BM) and skin (Akin and Metcalfe, 2004; Andersen et al., 2012; Metcalfe, 1991; Valent et al., 2003). In general, mastocytosis can be divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM) (Valent et al., 2003, 2001). On the basis of the criteria provided by the World Health Organization (WHO), the disease can further be split into various categories of CM and SM (Akin and Metcalfe, 2004; Hartmann et al., 2016; Horny et al., 2017, 2008; Valent et al., 2001a, 2001b, 2017). In CM, the skin is always affected, but the criteria for SM are not fulfilled (Hartmann et al., 2016; Valent et al., 2001a, 2001b). By contrast, in SM, multiorgan involvement is found, and the skin may or may not be involved.

Whereas all the categories of CM represent indolent neoplasms, this is not the case for SM. Rather, in SM, the clinical course and prognosis range from indolent and stable with normal life expectancy to aggressive SM (ASM) and MC leukemia (MCL) with short survival times (Akin and Metcalfe, 2004; Escribano et al., 2009; Lim et al., 2009; Metcalfe, 1991; Valent et al., 2001a, 2001b, 2003). Whereas most children are affected by CM, most adult patients are suffering from SM (Hartmann et al., 2016; Lange et al., 2013, 2012; Valent et al., 2001a, 2001b, 2003). In contrast to SM, childhood CM can regress shortly before or during puberty (Caplan, 1963; Hartmann et al., 2016).

According to the WHO classification, CM is defined by (i) typical clinical features of skin lesions and additional histological or molecular findings and (ii) the absence of diagnostic criteria sufficient to diagnose SM (Hartmann et al., 2016; Valent et al., 2007b). In adult patients with typical cutaneous lesions, a BM investigation is required to establish or exclude the presence of SM. If no BM studies were performed, the provisional diagnosis of mastocytosis in the skin (MIS) can be established in adults (Valent et al., 2007b). In these patients, the definitive diagnosis (CM or SM) can only be established by BM studies.

On the basis of the WHO classification, CM can further be divided into maculopapular CM (MPCM) (also termed urticaria pigmentosa), diffuse CM (DCM), and localized mastocytoma of the skin (Hartmann et al., 2016; Valent et al., 2001a, 2001b).

SM can further be divided into indolent SM (ISM), isolated BM mastocytosis (BMM, a subcategory of ISM), smoldering SM (SSM), SM with an associated hematologic (non-MC) neoplasm (SM-AHN), ASM, and MCL (Supplementary Table S1) (Horny et al., 2017, 2008; Valent et al., 2001a, 2001b, 2003).

The *KIT* D816V mutation is detectable in most patients with SM but is also found in a subset (about 50%) of cases with CM. Interestingly, childhood CM can also present with other *KIT* mutations (Arock et al., 2015). The extent of the cutaneous disease can be measured by determining the percentage of the involved body surface area (BSA) (Brockow, 2014; Valent et al., 2007a). The diagnostic criteria for cutaneous involvement in patients with SM are typical skin lesions with a positive Darier's sign and increased numbers of MC in biopsy sections of lesional skin and/or a transforming *KIT* mutation (Hartmann et al., 2016).

To get more insights into the impact of skin lesions in mastocytosis, we analyzed patients included in the registry of the European Competence Network on Mastocytosis (ECNM). This registry was established in 2002 and recruited >2,000 patients until 2017 (Valent et al., 2019). The specific aims of our study were to examine the distribution and impact of cutaneous lesions in various categories of mastocytosis and to correlate the presence and absence of skin lesions with clinical and laboratory variables as well as with prognosis.

RESULTS

Diagnostic evaluations to separate CM from SM with cutaneous involvement

Of the 1,510 patients examined, 1,195 (79.1%) presented with skin lesions (Table 1). A BM biopsy was performed in 1,146 of 1,510 patients and was positive in 891 samples (78%), with diagnostic multifocal MC infiltrates detected by immunohistochemistry (Table 1). The *KIT* D816V mutation was found in BM samples in 724 of 946 cases (76.5%). As determined by flow cytometry of BM aspirates, CD2-positive MCs were identified in 435 of 613 samples (71.0%), and CD25-positive MCs were identified in 762 of 854 samples (89.2%). When employing these results and additional minor criteria, the diagnosis of SM could be established in 1,036 of 1,510 patients (68.6%) using WHO criteria (Figure 1 and Table 1). A BM biopsy was not performed in 165 of 1,510 patients (10.9%) who were aged <18 years — these patients were classified as having CM (n = 162) or having MIS (n = 3) following consensus guidelines (Hartmann et al., 2016; Kettelhut and Metcalfe, 1991; Torrelo et al., 2012; Valent et al., 2007a). Only one patient aged <18 years was classified as having SM (Supplementary Table S2). In 188 of 1,510 patients (12.5%) aged ≥18 years, no BM biopsy was performed—in these cases, the provisional diagnosis of MIS was established (Supplementary Table S2). CM was diagnosed in 286 of 1,510 patients (18.9%). The maculopapular variant was found in a majority of these cases (n = 225; 77.3%); 16 patients (7.0%) had DCM, and 45 patients had a mastocytoma (15.7%) (Supplementary Table S3). A well-differentiated morphology of MCs was found in 11 cases — 4 with SM (well-differentiated SM) and 7 with CM. In almost all adult patients with skin involvement (CM or SM), skin lesions were found to be monomorphic and small sized, confirming a previous study (Hartmann et al., 2016; Wiechers et al., 2015). In line with this observation, no disease persistence into adulthood was reported in patients with childhood CM in whom polymorphic skin lesions had been recorded.

Distribution of patients within four defined categories

Patients were divided into four categories: category I, II, and III consisted of 1,195 of 1,510 patients (79.1%) with skin involvement, namely CM (n = 286; 18.9%) (category I), MIS (n = 188; 12.5%) (category II), and SM with skin involvement (SM+) (n = 721; 47.7%) (category III). Category IV included patients with SM without skin involvement (SM−) (n = 315 of 1,510; 20.9%) (Figure 1). Thus, 69.6% (721 of 1,036) of all patients with SM enrolled had typical skin lesions and were

Table 1. Patients' Characteristics

Characteristics	All (n = 1,510)	CM (n = 286)	MIS (n = 188)	SM+ (n = 721)	SM− (n = 315)
Age at first visit, median (IQR)	44.3 (31.5−55.8)	6.0 (1.2−32.6)[1,2,3]	40.0 (31.3−9.6)[2,3,4]	46.3 (36.7−5.3)[1,3,4]	57.2 (45.4−65.5)[1,2,4]
Age at first symptoms, median (IQR)	36.0 (22.6−49.5)	2.5 (0.2−27.9)[1,2,3]	33.2 (23.5−44.6)[3,4]	35.8 (25.2−46.7) [3,4]	52.6 (42.4−63.9)[1,2,4]
Duration of disease, y, median (IQR)	4.0 (0.8 − 10.2)	2.0 (0.5−5.2)[1,2,3]	4.8 (1.0−10.7)[2,3,4]	7.5 (2.4−15.0)[1,3,4]	1.0 (0.3−3.3)[1,2,4]
Male/female	664 (44%)/846 (56%)	136 (48%)/150 (52%)[1,2,4]	63 (34%)/125 (66%)[3,4]	272 (38%)/449 (62%)[4]	193 (61%)/122 (39%)[1,2,3]
Skin involvement	1,195 (79.1%)	286 (100%)	188 (100%)	721 (100%)	—
BM biopsies (n = 1,146)					
MC infiltrates positive[5]	891 (78%)	3 (2%)[6]	0 (0%)	630 (89%)	258 (85%)
No diagnostic MC infiltrates = negative	255 (22%)	124 (98%)[2,3,7]	8 (100%)[2,3]	76 (11%)[2,4]	47 (15%)[3,4]
BM smears (n = 950)					
MC infiltrates positive[5]	669 (70%)	30 (26%)	3 (25%)	442 (78%)	194 (75%)
Negative	281 (30%)	84 (74%)[2,3]	9 (75%)[2,3]	125 (22%)[3,4]	63 (25%)[3,4]
KIT (n = 946)					
Positive	724 (77%)	20 (19%)	6 (43%)	488 (86%)	210 (82%)
Negative	222 (23%)	86 (81%)[2,3]	8 (57%)[2,3]	81 (14%)[3,4]	47 (18%)[3,4]
CD2+ MFC (n = 613)					
Positive	435 (70%)	47 (54%)	4 (50%)	264 (76%)	120 (70%)
Negative	178 (30%)	40 (46%)[1,2]	4 (50%)	83 (24%)[4]	51 (30%)
CD25+ MFC (n = 854)					
Positive	762 (89%)	48 (48%)	4 (40%)	477 (96%)	233 (95%)
Negative	92 (11%)	53 (52%)[2,3]	6 (60%)[2,3,4]	21 (4%)[3,4]	12 (5%)[3,4]
Patient died, n (%)	159/1,044 (15.0%)	0 (0.0%)[1,2,3]	6 (5%)[2,3,4]	67 (13%)[1,3,4]	86 (38%)[1,2,4]
5-year survival		100%	97.4%	93.3%	71.6%
10-year survival		100%	97.4%	87.8%	66.1%

Abbreviations: BM, bone marrow; CM, cutaneous mastocytosis; IQR, interquartile range; MC, mast cell; MFC, multicolor flow cytometry; MIS, mastocytosis in the skin; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement.
[1]Significant ($P < 0.05$) compared with that in MIS; post hoc test: Bonferroni correction.
[2]Significant ($P < 0.05$) compared with that in SM+; post hoc test: Bonferroni correction.
[3]Significant ($P < 0.05$) compared with that in SM−; post hoc test: Bonferroni correction.
[4]Significant ($P < 0.05$) compared with that in CM; post hoc test: Bonferroni correction.
[5]As determined by immunohistochemistry (tryptase staining).
[6]In these patients, a minimal diffuse infiltration of the BM with MCs was seen, but the criteria for systemic mastocytosis were not fulfilled.
[7]In four of these patients, increased MCs with well-differentiated morphology were detectable.

defined as SM+, and 315 of the 1,036 patients with SM (30.4%) without skin lesions were defined as SM− (Table 2).

Demographic differences among the four categories

As shown in Table 1, the four categories showed significant differences regarding age, disease duration, and sex. The median age of patients (at first visit) in the three groups with skin lesions (CM, MIS, and SM+) was significantly lower than the median age of patients with SM− (CM: 6.0 years, interquartile range [IQR]: 1.2−32.6 years; MIS: 40.0 years, IQR: 31.3−49.6 years; SM+: 46.3 years, IQR: 36.7−55.3 years; SM−: 57.2 years, IQR: 45.4−65.5 years; all comparisons $P < 0.001$). The same was found to hold true for the median patient's age at first symptoms (CM: 2.5 years, IQR: 0.2−27.9 years; MIS: 33.2 years, IQR: 23.5−44.6 years; SM+: 35.8 years, IQR: 25.2−46.7 years; SM-: 52.6 years, IQR: 42.4−63.9 years; all comparisons $P < 0.001$). The time from first symptoms to diagnosis was found to be longer in patients with SM+, with a median of 7.5 years (IQR: 2.4−15.0 years) than in those with SM− (1.0 years, IQR: 0.3−3.3 years; $P < 0.001$), in those with CM (2.0 years, IQR: 0.5−5.2 years; $P < 0.001$), and in those with MIS (4.8 years, IQR: 1.0−10.7 years; $P = 0.002$). There was a predominance of male patients in the SM− group (61%) compared with those in the SM+, MIS, and CM groups (38%, 34%, and 48%, respectively; $P < 0.001$).

Skin involvement is more frequent in ISM and SSM than in advanced SM

In the cohort with SM, ISM was diagnosed in 634 of 1,036 patients (61.2%), BMM in 199 patients (19.2%), SM-AHN in 112 patients (10.8%), ASM in 45 patients (4.3%), SSM in 33 patients (3.2%), and MCL in 13 patients (1.2%) (Supplementary Table S3). The percentage of cases with cutaneous involvement in SM (i.e., SM+) was higher in patients with typical ISM (634 of 634; 100%) and SSM (29 of 33; 87.9%) than in those with ASM (21 of 45; 46.7%), MCL (5 of 13; 38.5%), or SM-AHN (32 of 112; 28.6%) (Table 2) ($P < 0.001$). As expected, the Darier's sign was positive in >90% of all the patients with cutaneous involvement, independent of the disease category (I, II, and III) or type of skin lesions.

Differences between CM, MIS, and SM+ variants regarding the percentage of affected BSA

There was a significant difference in the median percentage of the involved BSA when comparing patient subsets (Table 3). In particular, the percentage of involved BSA was higher in patients with SM+ (50.0%, IQR: 25.0−75.0%)

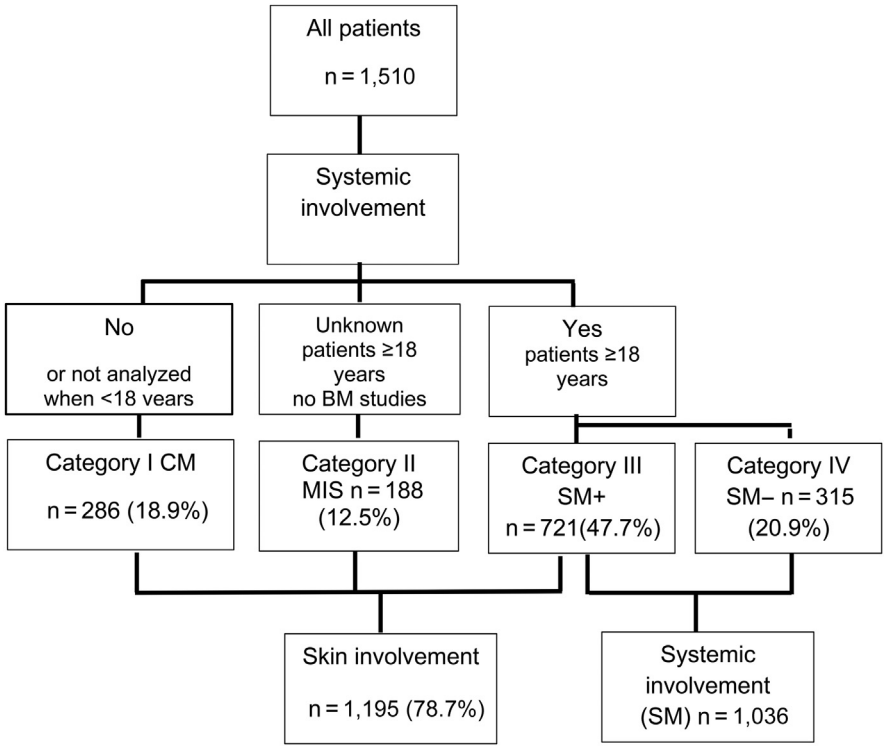

Figure 1. Categories of mastocytosis subgroups among all the 1,510 patients. The figure shows the distribution of the four different categories of mastocytosis and the assignment to mastocytosis types with (n = 1,195) or without (n = 315) skin involvement. BM, bone marrow; CM, cutaneous mastocytosis; MIS, mastocytosis in the skin; SM, systemic mastocytosis; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement.

than in patients with CM (36.0%, IQR: 10.0−64.5%; $P < 0.001$) or MIS (40.0%, IQR: 18.0−60.0%; $P = 0.016$). The CM subtypes also differed significantly from each other regarding the median percentage of BSA: 40.0% (IQR: 20.0−74.5%) in those with MPCM, 45.0% (IQR: 27.5−70.0%) in those with DCM, and 5.0% (IQR: 2.5−5.0%) in those with mastocytoma ($P < 0.001$), and the same was found to hold true when comparing SM subtypes: 50.0% (IQR: 25.0−72.0%) in those with ISM, 70.0% (IQR: 60–80%) in those with SSM ($P = 0.037$), 51.5% (IQR: 14.0−75.0%) in those with ASM, and 50.0% (IQR: 24.0−62.5%) in those with SM-AHN (Table 3).

Skin histology and detection of *KIT* D816V in lesional skin

In a small subset of patients, histological and molecular studies were performed. There was no difference in the percentage of patients with typical histological MC infiltrates in the skin when comparing CM, MIS, and SM+ and also when comparing SM+ subtypes (Table 3). *KIT* D816V was detected in skin biopsies at a similar frequency in patients with SM+ and MIS. The highest incidence of *KIT* D816V positivity was found in patients with SM+ (39 of 42, 92.9%). In the group with CM, the *KIT* D816V mutation was detected in 3 of 4 patients (75.0%).

Evaluation of tryptase levels in the four mastocytosis categories

Tryptase levels were documented in 1,344 patients. As expected, the median serum tryptase level was higher in patients with SM+ (40.9 μg/l, IQR: 22.1−94.0 μg/l) and SM− (37.9 μg/l, IQR: 19.2−98.1 μg/l) than in those with MIS (11.5 μg/l, IQR: 6.4−23.3 μg/l) and CM (7.4 μg/l, IQR: 4.7−13.4) (Supplementary Table S4). Median tryptase levels were comparable between patients with SM+ and those with SM−.

Clinical and laboratory parameters at baseline and during follow-up

Clinical and laboratory results were documented in 913 of 1,301 patients at follow-up visits. We compared the baseline data with data obtained at the last visit. The median follow-up time was 4.2 years (range: 0.5−34.1 years) (Table 4). Overall, the median percentage of involved skin (BSA) decreased over time. This decrease was significant in patients aged ≥18 years (50% [IQR: 30−70%] to 40% [20−72%]; $P = 0.001$) and was also found in patients aged >65 years (data not shown) but was not significant in patients aged <18 years (38% [IQR: 5−60%] to 38% [6−50%]; $P = 0.729$) (Supplementary Table S5), which is probably due to the shorter observation period in the childhood patients. The median percentage of involved BSA decreased not substantially or only slightly in patients with SM+ (50% [IQR: 30−70%] to 50% [IQR: 20−75]; $P < 0.05$) and in patients with MIS (40% [IQR: 19−61] to 36% [IQR: 17−51]; $P < 0.05$) (Table 4).

Supplementary Table S6 shows an overview of therapies given to patients in various categories of mastocytosis, and Supplementary Table S7 shows the clinical course in all the patients. In 43 of 55 patients treated with psoralen plus UVA (PUVA) or UVA and/or UVB with a documented percentage of skin involvement, the percentage of involved BSA was significantly higher at baseline (50%, IQR: 40−70%) than in untreated patients with a documented percentage of skin involvement (40%, IQR: 20−70%; $P = 0.005$). The decrease in skin infiltration in the treated patients was significantly higher than in those without therapy (Supplementary Figure S1; $P < 0.001$). A summary of responses of patients to PUVA or UVA and/or UVB therapy is shown in Supplementary Table S8. Patients receiving cytoreductive therapy had a substantially higher percentage of BSA at baseline (57%, IQR: 40−75%) than untreated patients (40%, IQR: 20−70%). The percentage of BSA decreased

Table 2. SM Subtypes in Patients with SM+ and SM−

All Patients with SM (N = 1,036)	SM+ (n = 721)	SM− (n = 315)
ISM (n = 634)	634 (100.0%)	0
SSM (n = 33)	29 (87.9%)	4 (12.1%)
BMM (n = 199)	0	199 (100%)
SM-AHN[1] (n =112)	32 (28.6%)	80 (71.4%)
ASM (n = 45)	21 (46.7%)	24 (53.3%)
MCL (n = 13)	5 (38.5%)	8 (61.5%)

Abbreviations: ASM, aggressive systemic mastocytosis; ASM-AHN, aggressive systemic mastocytosis with associated hematologic (non-mast cell) neoplasm; BMM, bone marrow mastocytosis; ISM, indolent systemic mastocytosis; ISM-AHN, indolent systemic mastocytosis with associated hematologic (non-mast cell) neoplasm; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with associated hematologic (non-mast cell) neoplasm; MIS, mastocytosis in the skin; SM, systemic mastocytosis; SM+, SM with skin involvement; SM−, SM without skin involvement; SM-AHN, SM with an associated hematologic neoplasm; SSM, smoldering SM.

[1]Patients with SM-AHN included cases with ISM-AHN, ASM-AHN, and MCL-AHN.

significantly in patients receiving cytoreductive therapy ($P = 0.003$) but not in untreated patients ($P = 0.233$) when comparing the baseline data with those of the last follow-up (Supplementary Figure S2).

Serum tryptase levels decreased significantly during follow-up in patients aged ≥18 years (29.3 μg/l [IQR: 16.2−61.5 μg/l] to 26.3 μg/l [IQR: 14.0−57.0 μg/l]; $P < 0.001$) but not in those aged <18 years (5.0 μg/l [IQR: 3.4−6.3 μg/l] to 5.4 μg/l [IQR: 3.0−9.2 μg/l]; $P = 0.638$) (Supplementary Table S5), which may be due to a shorter follow-up in patients aged <18 years. When correlating tryptase levels with the involved BSA by Spearman rank correlation (ρ), there was a rough correlation at baseline ($\rho = 0.137$; $P = 0.001$) and at the last follow-up ($\rho = 0.210$; $P = 0.001$) in patients aged ≥18 years (Supplementary Figure S3).

Disease evolution and survival

Follow-up data were available in 105 of 162 patients with childhood CM (64.8%) and in 97 of 124 patients with adulthood CM (78.2%). Patients with childhood CM and those with adulthood CM showed a 100% overall survival (OS) after 5 and 10 years. In patients with MIS, OS after 5 and 10 years was 97.4%. Survival in patients with SM was shorter than in those with CM, and patients with SM+ had a better prognosis than those with SM− (5-year survival in patients with SM+ was 93.3% vs. 71.6% in those with SM−; 10-year survival in patients with SM+ was 87.8% vs. 66.1% in those with SM−; $P < 0.001$) (Figure 2 and Table 1). OS was longer in patients with skin involvement (CM, MIS, and SM+) than in those with SM− ($P < 0.001$). This was also found to hold true when only adult patients with CM (no childhood patients) were examined. In addition, the absence of skin lesions remained an independent prognostic variable in multivariate analysis (Supplementary Table S9).

Overall, the probability of OS was superior in patients with adulthood CM to that in patients with all other variants of adulthood mastocytosis. In subsequent studies, we also found that OS in patients with SM+ with advanced SM is better than OS in patients with SM− with advanced SM (Supplementary Figure S4). This figure (Supplementary Figure S4) also shows that OS is better in patients with nonadvanced SM without skin lesions (i.e., BMM) than in patients with advanced SM without skin lesions.

Table 3. Differences in Skin Involvement in Patients with CM, MIS, and SM+ Regarding Diagnostic MC Infiltrates and Detectable *KIT* D816V Mutation in Skin Biopsies

Disease Variant	% Involved Skin (n = 723)	Diagnostic MC Infiltrates in the Skin, n/n (%) (814/845)	*KIT* Mutation in the Skin, n/n (%) (49/55)
CM	38.5 (10.0−70.0)[1]	178/181 (98.3)	3/4 (75.0)
Subtypes	Comparison of subtypes: $P < 0.001$	Comparison of subtypes: $P = 0.233$	Comparison of subtypes: $P = 1.000$
MPCM	40.0 (20.0−74.5)	159/162 (98.1)	3/4
DCM	45.0 (27.5−70.0)	7/7	0/0
Mastocytoma	5.0 (2.0−5.0)	12/12	—
MIS	40.0 (20.0-60.0)[1]	138/147 (93.9)	7/9 (77.8)
SM+	50.0 (25.0-75.0)	498/517 (96.3)	39/42 (92.9)
Subtypes	Comparison of subtypes: $P = 0.045$[2]	Comparison of subtypes: $P = 0.774$	Comparison of subtypes: $P = 0.910$
ASM	51.5 (14.0−75.0)	10/10	1/1
ISM	50.0 (25.0−72.0)	455/474 (96.0)	33/36 (94.1)
MCL	—	2/2	0/0
SM-AHN	50.0 (24.0−62.5)	13/13	2/2
SSM	70.0 (40.0−80.0)	18/18	3/3

Abbreviations: ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; DCM, diffuse cutaneous mastocytosis; IQR, interquartile range; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MIS, mastocytosis in the skin; MPCM, maculopapular cutaneous mastocytosis; SM+, systemic mastocytosis with skin involvement; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; SSM, smoldering systemic mastocytosis.

Data are presented as n (%) and median (IQR).

[1]Significantly ($P < 0.05$) different from SM+; post hoc test: Bonferroni correction.

[2]ASM, MCL, and SM-AHN were not included in this analysis because of the low number of cases.

Table 4. Changes in the Clinical and Laboratory Parameters Found when Comparing Baseline Data with Last Follow-Up Data (Median and Range or IQR) in the Four Mastocytosis Categories

Clinical Variable	Measure	Timepoint	All	CM	MIS	SM+	SM−
Years since the first visit	Median (range)		4.2 (0.5–34.1)	3.4 (0.5–34.1)	3.7 (0.5–29.6)	4.8 (0.5–30.5)	3.7 (0.5–19.5)
% of skin involved (n = 239)	Median (IQR)	Baseline	50 (30–70)[1]	48 (25–76)	40 (19–61)[1]	50 (30–70)[1]	—
		Follow-up	40 (18–70)	48 (14–72)	36 (17–51)	50 (20–75)	—
Serum tryptase, μg/l (n = 765)	Median (IQR)	Baseline	28.2 (15.1–58.9)[1]	8.9 (4.7–15.9)	11.5 (6.4–23.3)	40.9 (22.1–94.0)[1]	37.9 (19.2– 98.1)[1]
		Follow-up	25.9 (13.1–56.0)	9.5 (4.5–16.0)	13.1 (7.0–24.5)	38.3 (20.0–74.3)	24.9 (13.0–47.3)
Darier's sign positive (n = 326)	n (%)	Baseline	305/326 (93.6)	60/65 (92.3)	64/73 (87.7)	181/188 (96.3)	—
		Follow-up	295/326 (90.5)	59/65 (90.8)	64/73 (87.7)	172/188 (91.5)	—

Abbreviations: CM, cutaneous mastocytosis; IQR, interquartile range; MIS, mastocytosis in the skin; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement.
[1]Significant changes from baseline to follow-up ($P < 0.05$).

No progression of disease was noted in pediatric patients with mastocytoma or DCM (Supplementary Table S7). In the group with MPCM, 3 of 104 patients developed SM. One patient was diagnosed with MPCM at age 0.7 years and progressed to ISM after 1.5 years. In this patient, a BM investigation showed the presence of spindle-shaped MC that formed small diagnostic clusters and expressed CD2 and CD25 as well as *KIT* D816V. The serum tryptase level at that time was 9.3 ng/ml. The second patient was diagnosed with MPCM at age 43 years and developed ISM after 13.9 years. The third patient had MPCM at age 48 years and developed SM-AHN after 8.4 years. The largest number of progressive cases was recorded in patients with ISM, where 4 of 449 patients developed SSM, 7 developed ASM, and 5 developed SM-AHN. In the cohort with SSM, 1 of 22 patients progressed to ASM, and 2 patients progressed to SM-AHN. An overview of the changes in diagnoses observed is provided in Supplementary Table S6. When comparing patients with childhood CM with patients with adulthood CM, no differences were seen regarding OS, event-free survival, and progression-free survival (Supplementary Figure S4). In the 114 patients with MIS who had a follow-up, 23 underwent a BM biopsy, and in these 23 cases, the final diagnosis was MPCM in 5 patients, ISM in 16 patients, and SSM in 2 patients (Supplementary Table S7).

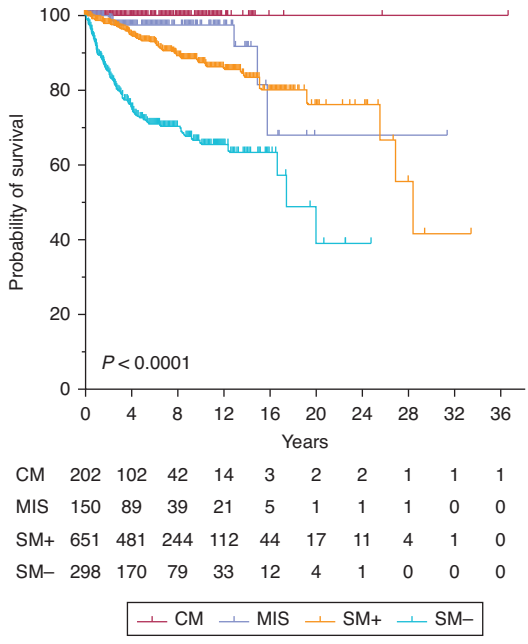

Figure 2. OS of the patients in the four categories (CM, MIS, SM+, and SM−). The medium follow-up of the patients was 4.2 years (range: 0.5–34.1 years). To estimate survival, Kaplan–Meier plots were generated, and the probability of survival of the patients in the various categories of disease (CM, MIS, SM+, and SM−) was compared. The significance levels in differences in survival among the patients' groups were assessed by log-rank test. CM, cutaneous mastocytosis; MIS, mastocytosis in the skin; OS, overall survival; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement.

After a median follow-up of 4 years, no patient with CM had died, but 3.3% of the patients with MIS, 8.1% of those with SM+, and 32.5% of those with SM− had died (Table 1). In 93 patients, the death was related to the disease (advanced SM), whereas eight patients died during stem cell transplantation. In 38 patients, the cause of death was not disease-related and not related to intensive therapy. In 20 patients, the cause of death was not known.

DISCUSSION

Using a large data set of the ECNM registry, we analyzed the frequency and clinical impact of skin lesions in various mastocytosis subgroups and the potential associations between skin involvement and the clinical course and survival. Among the four patient categories examined, SM+ was the most frequent one, followed by CM, SM−, and MIS. More than half of the patients with skin lesions had systemic involvement, which is in line with the notion that most adults with MIS turn out to have SM once a BM study is performed (Brockow, 2014; Escribano et al., 2009; Horny et al., 2008; Valent et al., 2001a; 2001b, 2017). It should also be noted that the vast majority of patients examined were adults, which is explained by the fact that only a few of the participating ECNM centers are specialized in pediatric mastocytosis.

Age, sex, and disease duration showed significant differences when comparing the various categories. In particular, patients with CM were younger, had an earlier onset of the

disease, and had shorter duration than those with MIS, SM+, and SM−. This can be explained by the fact that CM usually occurs in early childhood. Indeed, in our study, 165 of 302 patients with CM (54.7%) were aged <18 years. In the category with SM–, more male patients were identified, and they were older than those with SM+. Similar results were reported by Pieri et al. (2016) in patients with ISM. Patients with ISM− were more frequently males and were older than those with ISM+. The duration of the disease was longest in patients with SM+ with a median time of 7.4 years.

Among the SM subtypes, ISM was the most frequently diagnosed variant. We first asked whether there are differences between CM and SM regarding the type of skin lesions. Whereas maculopapular lesions (MPCM type) were found in about 75% of all patients with CM, this lesion-type was detected in a vast majority (95%) of all the patients with SM+. This observation is consistent with the notion that DCM is more frequently detected in children than in adults and that skin mastocytomas are almost exclusively diagnosed in childhood.

A number of previous and more recent data suggest that in patients with SM, the absence of skin lesions is associated with advanced forms of the disease and a poor outcome (Andersen et al., 2012; Lennert and Parwaresch, 1979; Parwaresch et al., 1985). In a systematic review by Andersen et al. (2012), maculopapular skin lesions were described in 90% of the patients with SM and in 50% of patients with ASM or SM-AHN. In our study, skin lesions were present in all patients with typical ISM and in a vast majority of our patients with SSM, but were only found in <50% of the patients with advanced SM (ASM or MCL or SM-AHN). In addition, our data confirm that the absence of skin lesions is associated with reduced survival in SM. However, there is also one group of patients without skin involvement and low MC burden in whom the prognosis is excellent — these patients have BMM, which is a provisional subset of ISM defined by low tryptase levels, an absence of skin lesions, and an indolent course (Alvarez-Twose et al., 2012; Valent et al., 2001a; 2001b, 2017).

The diagnosis of skin involvement in our study was proven by histology in nearly 70% of the patients. As expected from a registry study, *KIT* mutation analysis was only performed in the skin in a subset of patients (n = 60) and was positive in 88%. Only a few studies have examined the frequency of the *KIT* D816V mutation in lesional skin in various categories of mastocytosis. Kristensen et al. (2013) found the *KIT* D816V mutation in all lesional skin biopsies of 29 adult patients with *KIT* D816V+ SM using a sensitive qPCR technique. We found that the *KIT* D816V mutation is more frequently detected in the skin biopsies of patients with SM+ (95%) than in those of patients with MIS (77%) or CM (71%). However, even when detected in the skin, the demonstration of *KIT* D816V does not necessarily lead to the diagnosis of SM. In addition, *KIT* D816V mutation analysis in skin samples is not well-standardized, and the preanalytical steps and the detection methods vary among centers. On the other hand, several different useful techniques have been developed and applied to detect *KIT* D816V in lesional skin (and in BM) in the past few years (Bodemer et al., 2010; Lanternier et al., 2008). Using these methods, the involvement of the skin with *KIT* D816V+ mastocytosis can be demonstrated in a vast majority of patients with KIT D816V+ disease, including childhood CM and SM.

As expected, serum tryptase levels were significantly higher in patients with SM than in those with CM. However, there was no significant difference in tryptase levels when comparing patients with skin lesions (SM+) with those without skin lesions (SM−). This is best explained by the fact that both groups (those with SM+ and those with SM−) included patients with high and patients with low MC burden and also patients with ISM and advanced SM.

A somehow surprising observation was that tryptase levels as well as skin lesions decreased significantly in adult patients with SM and patients with MIS over time. This phenomenon may be explained by the following: (i) a slight decrease in skin lesions in adults may be part of the natural course of the disease, and indeed, regression and even clearance of MPCM has been described in about 10% of adult patients with SM by Brockow et al. (2002); (ii) the decrease in tryptase and BSA may result from natural organ-aging processes that may create a less permissive microenvironment for MC evolution; and (iii) patients with SM are sometimes treated with antineoplastic therapies reducing MC numbers, which may result in a decrease in skin lesions. This was indeed the case in some of our patients treated with cytoreductive agents or PUVA. In fact, although PUVA therapy is no longer recommended in CM owing to the risk of skin cancer development (Broesby-Olsen et al., 2016), several patients enrolled in the registry had received PUVA therapy. In addition, histamine receptor blockers may also (slightly) counteract MC growth (Hadzijusufovic et al., 2010; He et al., 2005). However, even in untreated patients with SM, both tryptase levels and BSA decrease over time (Brockow, 2014). Even more surprising was the observation that the skin lesions did not decrease in younger patients, which may be explained by the fact that the observation time was rather short and that many of these patients had not yet reached puberty when skin lesions are expected to decrease or even fade away.

During follow-up, changes in diagnoses were noted in 6.8% of the patients. The largest group with a change in diagnosis was the group with MIS (19.8%). BM biopsy proved the presence of SM in 18 of 23 (78.3%) of these patients. Another important observation was that in the cohort with CM (children and adults), no patient died, and only a very few progressed, which is in line with our previous observations (Sperr et al., 2019). In the light of the worse prognosis of SM than that of CM, this observation underlines the need for a BM biopsy in all adult patients with MIS (Valent et al., 2013; Valent et al., 2001a, 2001b). In fact, in CM, the prognosis is excellent, and no patient died in this group. A more detailed description of clinical outcomes in ISM in our ECNM registry has recently been published (Trizuljak et al., 2020). OS was longer in patients with skin involvement than in those without skin lesions, which confirms the available literature (Lennert and Parwaresch, 1979; Parwaresch et al., 1985; Valent et al., 2001a, 2001b, 2007a).

Together, our data show that cutaneous involvement in patients with mastocytosis is a clinically important disease feature that provides diagnostic and prognostic information. In those with SM and high MC burden, the absence of skin lesions is a poor prognostic sign. Whether the slight decrease

in tryptase and skin lesions in adults with SM over time is part of the natural course of the disease or is due to organ aging or therapy effects remains to be determined.

MATERIALS AND METHODS

Patients and clinical examination

Data from 1,510 patients collected in the ECNM registry were analyzed. Diagnoses were established according to the WHO criteria (Valent et al., 2017, 2001). According to these criteria, patients were classified as having CM variants or SM subtypes. All patients with ISM in whom no skin lesions could be detected were classified as having BMM, a provisional WHO subset of ISM (Valent et al., 2017). Skin involvement was diagnosed clinically with or without a proof of monomorphic MC infiltrates by histology and with or without *KIT* D816V mutation analysis. In most cases, the percentage of the involved (lesional) skin relative to the total skin surface area was documented. All patients gave their written informed consent to participate in the ECNM registry project. The registry project has been approved by the local ethics committee of the participating centers, including the Medical University of Vienna (Austria) (ethics committee-number: 1549/2012). Further details are provided in the Supplementary Materials and Methods.

BM studies and serum tryptase measurements

BM biopsies were investigated by immunohistochemistry using commercial anti-tryptase, anti-CD2, and anti-CD25 antibodies. Giemsa-stained BM smears were examined for the presence and percentage of MCs. In a subset of patients, flow cytometry of BM cells was performed to measure the expression of CD2 and CD25 on neoplastic MCs. In a majority of the patients, the *KIT* D816V mutation was examined in BM cells (946 of 1,510, 62.6%). Serum tryptase levels (normal value <15.0 μg/l) were measured by fluoroimmunoenzyme assay.

Follow-up investigations

The median observation time was 4.2 years (range 0.5−34.1 years). During follow-up, an increase or decrease in the involved skin (BSA), tryptase levels, other laboratory parameters, changes in diagnosis (progression to another disease subtype), and survival were captured (Valent et al., 2007a). In case of suspected progression, a re-examination of the BM was performed.

Statistical examinations

Differences in disease-related features between groups were analyzed using Kruskal–Wallis test, chi-square test, or Fisher's exact test (post hoc analysis: Bonferroni correction), and changes from baseline to the last follow-up were analyzed using Wilcoxon signed-rank test or McNemar test. Kaplan–Meier survival estimates were generated and compared among patient groups (CM, MIS, SM+, and SM−) using the log-rank test. $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences 24.0.0 (IBM Corporation; Armonk, NY). Detailed statistical methods are provided in the Supplementary Materials and Methods.

Data availability statement

Primary data that were used to create Figures and Tables in this manuscript will be made available on a reasonable request. However, the complete source dataset (European Competence Network on Mastocytosis registry dataset) cannot be made available on the basis of the European Competence Network on Mastocytosis registry contract.

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CONFLICT OF INTEREST

WRS received honoraria from Novartis, Pfizer, AbbVie, Daiichi Sankyo, Amgen, Thermo Fisher Scientific, Deciphera, Incyte, Celgene, and Jazz. HCKN received institutional financial support from Novartis to perform a phase II trial with midostaurin. BVA received financial support from Novartis for research and is on the advisory boards. ML recieved honoraria from Novartis. CE is on the advisory board of Novartis and Pfizer. VB is on the advisory boards with honoraria from Novartis and congresses with Janssen-Cilag Spa and Sanofi Genzyme. KH received honoraria (advisory board, consultant, and speaker) from ALK-Abelló , Blueprint Medicines, Deciphera, and Novartis. RZ is on the advisory board and received honoraria from Deciphera, Novartis, and Takeda. MT is on the advisory board and received honoraria from Deciphera and Novartis. JG is on the advisory board and received honoraria from Blueprint Medicines, Deciphera, and Allakos and received funding support to conduct clinical trials from Blueprint Medicines and Deciphera. MD has no conflict of interest within this study but received honoraria (advisory board, consultant, and speaker) from Novartis, AbbVie, Janssen-Cilag, Gilead Sciences, and AOP Orphan Pharmaceuticals outside of this study and received research grants from AbbVie, Janssen-Cilag, and Gilead. NVB received honoraria from Novartis and Bristol-Myers Squibb and research funding from Novartis. DF received honoraria from Novartis, Roche, and Pfizer and received a travel grant from Roche. NJ received honoraria from Novartis. JP is on the advisory board and received honoraria from Blueprint Medicines and Novartis; received honoraria from Alexion, Bristol-Myers Squibb, Boehringer Ingelheim, Grünenthal, Merck Sharp & Dohme, Novartis, Pfizer, and Chugai Pharmaceutical; and received funding support to conduct clinical trials from Blueprint Medicines and Deciphera. PV received honoraria (advisory board, consultant, and speaker) from Novartis, Deciphera, Blueprint Medicines, Celgene, and Pfizer and received research grants from Novarts, Celgene, and Pfizer. The remaining authors declared no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: EA, WRS, PV; Data Curation: EA, WRS, AB, AA, EH, HCKN, HOE, BVA, MN, ML, AG, CE, VB, ABF, FC, KH, AI, AR, MJ, PB, RZ, MT, RP, JG, MD, NVB, DF, VS, KB, NJ, JP, PV; Formal Analysis: AA, WRS; Funding Acquisition: PV; Methodology: WRS, PV; Project Administration: PV; Supervision: EA, WRS, PV; Validation: EA, WRS, AB, AA, EH, HCKN, HOE, BVA, MN, ML, AG, CE, VB, ABF, FC, KH, AI, AR, MJ, PB, RZ, MT, RP, JG, MD, NVB, DF, VS, KB, NJ, JP, PV; Writing - Draft Preparation: EA, AB, PV; Writing - Review and Editing: EA, PV

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.12.030.

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