To the editor:

WHO subvariants of indolent mastocytosis: clinical details and prognostic evaluation in 159 consecutive adults

The 2008 World Health Organization (WHO) proposal recognizes 2 provisional indolent systemic mastocytosis (ISM) subvariants: smoldering systemic mastocytosis (SSM) and isolated bone marrow (BM) mastocytosis (BMM).[1] SSM is characterized by a high burden of mast cells (MCs; Table 1), whereas BMM is defined by BM involvement without concurrent skin involvement or presence of multiorgan visceral lesions. To date, prognostic relevance of the proposed ISM subclassification has not been validated by primary data.

In the current study, we reviewed clinical/BM data for 159 ISM patients drawn from a previously reported larger study of 342 adult SM patients,[2] ensuring that patients were accurately classified into ISM subgroups per the WHO proposal. The current study was approved by the Mayo Clinic institutional review board, and mutational (*KIT*D816V and *JAK2*V617F) and statistical analyses were performed as previously described.[2,3]

Twenty-two patients (14%) had SSM, 36 (23%) had BMM, and the remaining 101 (63%) did not fit either category and were designated as "ISM-other" (ISMo; Table 1). Age at presentation was significantly higher in SSM than in BMM or ISMo (median 64, 45, and 48 years, respectively; $P < .01$). SSM patients also displayed significantly higher incidence of constitutional symptoms (45%; $P < .01$), anemia (55%; $P < .01$), and MC mediator levels. The latter correlated with BM MC burden ($P < .01$) but, interestingly, not with MC mediator symptoms, which were more frequent in BMM (86%; $P = .03$). Of the 55 (35%) patients studied, only 1 patient (ISMo) exhibited an abnormal karyotype (46,XX,fra(10)(q25)). Fifty-nine (37%) patients were screened for *KIT*D816V and *JAK2*V617F. JAK2V617F was universally absent, and KITD816V distribution was as follows: SSM (n = 7; 100%), BMM (n = 13; 92%), and ISMo (n = 39; 69%). At a median follow-up of 27 months (range, < 1-417 months), 26 deaths (16%) were recorded: ISMo 14 (14%), SSM 10 (46%), and BMM 2 (6%). The combined median survival was 198 months: ISMo 301 months, SSM 120 months, and BMM not reached ($P < .01$). In a multivariable analysis, advanced age was the primary determinant of inferior survival and accounted for the marked difference in survival between SSM and the other 2 groups. Causes of death were available for 14 of the 26 deaths (Table 1); transformation to acute leukemia was seen in 1 patient (SSM) and aggressive systemic mastocytosis (ASM) in 4 patients (3 SSM and 1 ISMo).

We recently showed that overall, ISM patients have a life expectancy that is not significantly different from the control population.[2] Here, we show that SSM and BMM are not as rare as previously believed and may constitute approximately one-third of all ISM cases. Furthermore, we found no significant association between the incidence of MC mediator symptoms and the level of MC mediators. In fact, there was a strong positive correlation between MC mediator levels and BM MC burden ($P < .01$). Finally, SSM may be distinct from both BMM and ISMo in terms of age distribution and risk of disease transformation. However, given the small number of SSM patients, additional studies are required to clarify the age-independent survival impact of SSM.

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Contribution: A.P. designed the study, collected and analyzed the data, and wrote the paper; K.-H.L. collected and analyzed the data; T.L.L., C.M.F., and R.F.M. did sample preparation and/or molecular analysis; C.-y.L. reviewed the bone marrow histology; and A.T. designed the study, analyzed the data, and wrote the paper.

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Table 1. Comparison of demographic, clinical, and laboratory characteristics between ISM subgroups

Characteristic	No. (%) of patients	Median (range)	ISM-other, no. (%)	BMM, no. (%)	SSM, no. (%)	*P*
Total no. of ISM	159	—	101 (63)	36 (23)	22 (14)	
Demographic characteristics						
Male	69 (43)	—	39 (39)	21 (58)	9 (69)	NS
Age, y	—	49 (19-84)	48 (21-84)	45 (19-77)	64 (38-78)	< .001
Time from symptoms to SM diagnosis, mo		72 (0-516)	72 (0-516)	48 (0-204)	114 (1-372)	.005
Clinical characteristics						
Urticaria pigmentosa	100 (63)	—	86 (85)	n/a	14 (64)	n/a
Cutaneous symptoms*	119 (75)	—	79 (78)	26 (72)	14 (64)	NS
Constitutional symptoms*	30 (19)	—	15 (15)	5 (14)	10 (45)	.003
Mediator-related symptoms*	110 (69)	—	68 (67)	31 (86)	11 (50)	.01
Idiopathic and/or recurrent anaphylactoid reaction*	53 (33)	—	21 (21)	28 (78)	4 (18)	< .001
Musculoskeletal symptoms*	48 (30)	—	36 (36)	7 (19)	5 (23)	NS
Gastrointestinal symptoms*	113 (71)	—	70 (69)	26 (72)	17 (77)	NS
Hepatomegaly	22 (14)	—	10 (10)	0 (0)	12 (55)	n/a
Splenomegaly (n = 157)	26 (17)	—	11 (11)	0 (0)	15 (68)	n/a
Lymphadenopathy†	22 (14)	—	13 (13)	0 (0)	9 (41)	n/a
B-findings						
BM MC > 30% or serum tryptase > 200 ng/mL	23 (14)	—	8 (8)	0 (0)	15 (68)	n/a
Hypercellular BM or dysmyelopoiesis, without cytopenias	13 (8)	—	2 (2)	0 (0)	11 (50)	n/a
Hepatosplenomegaly and/or LNP without functional impairment	41 (26)	—	21 (21)	0 (0)	20 (91)	n/a
Laboratory characteristics						
Hemoglobin, g/dL	158 (99)	13.9 (8.1-16.7)	13.9 (10.6-16.7)	14.4 (8.6-16.3)	12.4 (8.1-15.2)	< .001
White blood cell count, $\times 10^9$/L	157 (99)	6.6 (1.6-19.3)	6.8 (1.6-15.2)	6.3 (2.8-9.9)	6.7 (2.9-19.3)	NS
Platelet count, $\times 10^9$/L	152 (96)	260 (39-570)	270 (39-563)	273 (160-500)	218 (73-570)	NS
Serum tryptase, ng/mL						
< 11.5	90 (57)	54 (11.4-1410)	66.3 (13.1-440)	25.9 (11.4-60.5)	212.5 (106-1410)	< .001
≥ 11.5	89 (99)	—	54 (100)	23 (96)	12 (100)	NS
≥ 200	11 (12)	—	3 (6)	0 (0)	8 (67)	< .001
Urine histamine, μg/g Cr/24 h						
< 35	34 (21)	49 (17-986)	61 (17-581)	30 (18-82)	208 (198-986)	.002
≥ 35	21 (62)	—	16 (76)	2 (20)	3 (100)	.004
Urine N-methylhistamine						
30-200 μg/g Cr	51 (32)	335 (33-4156)	502 (52-2376)	208 (33-515)	2208 (141-4156)	< .001
> UNL	41 (80)	—	28 (90)	8 (53)	5 (100)	.006
Urine beta PG-F2α						
≤ 1000 ng/24 h	72 (45)	1880 (119-13 100)	2409 (119-13 100)	1132 (159-7477)	8838 (465-12 633)	.007
> UNL	50 (69)	—	31 (78)	13 (52)	6 (86)	NS
BM % MC	141 (89)	10 (1-90)	10 (1-60)	5 (5-20)	40 (8-90)	< .001

ISM indicates indolent systemic mastocytosis (SM); SSM, smoldering SM; BMM, isolated bone marrow mastocytosis; BM, bone marrow; MC, mast cell; LNP, lymphadenopathy; PG, prostaglandin; UNL, upper normal limit; Cr, creatinine; NS, not significant; n/a, not applicable; and —, unknown or not done. SSM is defined by the presence of 2 or more "B-findings" (ie, BM MC > 30% or serum tryptase > 200 ng/mL, BM hypercellularity or dysmyelopoiesis without cytopenias, and organomegaly and/or lymphadenopathy without functional impairment). Causes of death were available for 14 of the 26 deaths: disease transformation (n = 4; all SSM), cardiovascular (n = 3; all ISMo), solid tumor (n = 4; 3 ISMo and 1 BMM), complications of MC mediator release (n = 2; 1 each SSM and ISMo), and infection (n = 1; SSM).

*As defined in Lim et al.[2]

†Either palpable or detected by imaging studies.

To the editor:

Both permissive and nonpermissive HLA-DPB1 mismatches can induce polyclonal HLA-DPB1 specific immune responses in vivo and in vitro

Clinical studies have indicated that human leukocyte antigen (HLA)–DPB1 functions as a classical transplantation antigen in allogeneic stem cell transplantation (SCT). Mismatching for HLA-DPB1 was associated with an increased risk of graft-versus-host disease (GVHD) but also a decreased risk of disease relapse.[1,2] However, some studies showed that specific HLA-DPB1 mismatches were associated with poor clinical outcome.[3] It was suggested that this unfavorable effect was caused by differences in immunogenicity between HLA-DPB1 alleles. An algorithm defining permissive and nonpermissive HLA-DPB1 mismatches was developed based on cross-reactive T-cell reactivity patterns. It was suggested that permissive mismatches would not result in T-cell

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