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Mastocytosis among elderly patients

A multicenter retrospective French study on 53 patients

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Abstract

Mastocytosis is a heterogeneous group of diseases with a young median age at diagnosis. Usually indolent and self-limited in childhood, the disease can exhibit aggressive progression in mid-adulthood. Our objectives were to describe the characteristics of the disease when diagnosed among elderly patients, for which rare data are available.

The French Reference Center conducted a retrospective multicenter study on 53 patients with mastocytosis >69 years of age, to describe their clinical, biological, and genetic features.

The median age of our cohort of patients was 75 years. Mastocytosis variants included were cutaneous (n = 1), indolent systemic (n = 5), aggressive systemic (n = 11), associated with a hematological non-mast cell disease (n = 34), and mast cell leukemia (n = 2). Clinical manifestations were predominantly mast cell activation symptoms (75.5%), poor performance status (50.9%), hepatosplenomegaly (50.9%), skin involvement (49.1%), osteoporosis (47.2%), and portal hypertension and ascites (26.4%). The main biological features were anemia (79.2%), thrombocytopenia (50.9%), leucopenia (20.8%), and liver enzyme abnormalities (32.1%). Of the 40 patients tested, 34 (85%), 2 (5%), and 4 (10%) exhibited the *KIT* D816V mutant, other *KIT* mutations and the wild-type form of the *KIT* gene, respectively. Additional sequencing detected significant genetic defects in 17 of 26 (65.3%) of the patients with associated hematological non-mast cell disease, including *TET2, SRSF2*, *IDH2*, and *ASLX1* mutations. Death occurred in 19 (35.8%) patients, within a median delay of 9 months, despite the different treatment options available.

Mastocytosis among elderly patients has a challenging early detection, rare skin involvement, and/or limited skin disease; it is heterogeneous and has often an aggressive presentation with nonfortuitous associated myeloid lineage malignant clones, and thus a poor overall prognosis.

Editor: Lydia Eccersley.

AR and AA contributed equally to the study. OH and SG-L codirected the study.

The authors report no conflicts of interest.

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Medicine (2016) 95:24(e3901)

Received: 18 May 2015 / Received in final form: 17 May 2016 / Accepted: 18 May 2016

Published online 1 May 2016

http://dx.doi.org/10.1097/MD.0000000000003901

Abbreviations: AGS = alteration of general status, ASM = aggressive systemic mastocytosis, CEREMAST = Centre de Reference des Mastocytoses (= mastocytosis reference center), CM = cutaneous mastocytosis, HMG = hepatomegaly, HSMG = hepatosplenomegaly, ISM = indolent systemic mastocytosis, MCAS = mast cell activation symptoms, MCL = mast cell leukemia, MCS = mast cell sarcoma, MDS = myelodysplastic syndrome, MGUS = monoclonal gammopathy of undetermined significance, MPN = myeloproliferative neoplasm, PHT = portal hypertension, SM-AHNMD = systemic mastocytosis with associated clonal nonmast cell lineage disease, SMG = splenomegaly, TMEP = telangiectasia macularis eruptivans perstans, UP = urticaria pigmentosa, WT = wild type.

Keywords: *ASLX1*, elderly, *KIT*, mast cell, systemic mastocytosis, *TET2*

1. Introduction

Mastocytosis is a heterogeneous group of disorders characterized by abnormal growth and accumulation of mast cells (MCs) in 1 or more organ systems.[1] The most commonly affected tissues are the skin, bone marrow (BM), and gastrointestinal (GI) tract, whereas the liver, spleen, and lymph nodes are less commonly involved.[1,2] The WHO 2008 classification of hematopoietic malignancies has defined several variants including cutaneous mastocytosis (CM), extracutaneous mastocytoma, indolent systemic mastocytosis (ISM), systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (SM-AHNMD), aggressive SM (ASM), mast-cell leukemia (MCL), and mast cell sarcoma (MCS).[1] The clonal proliferation of MCs in different variants of matocytosis is usually related to an acquired gain-of-function mutation in the *KIT* gene, which encodes for a transmembrane tyrosine kinase receptor for stem cell factor, namely KIT/CD117.[3] KIT is expressed on maturing MC progenitors and on mature MCs. Most adults with mastocytosis present with the *KIT* D816V mutation (>90%), but additional genetic lesions involving epigenetic regulation, RNA splicing, and/or transcription have been recently described and are thought to contribute at least in part to the aggressiveness of the disease.[1,4–7] Of note, clinical manifestations of mastocytosis are variable and are either related to the release of MC mediators or to pathological MC infiltration, or both.[1] It has previously been described that the disease among children is usually benign, but the clinical and genetic presentations among elderly patients have not often been studied.[4,5,8]

Little data are available on mastocytosis in the elderly, in which age is also the background for additional mutations and clonal features for both mast-cell and other myeloid cell lineages. Indeed Lim et al and Brockow et al found that the late onset of the disease and an age at diagnosis >60 years is one of the most significant risk factors for death in systemic mastocytosis (SM) with a shorter overall survival (OS), as reported in a multivariate analysis; indeed, the cumulative probability of death in patients with ISM was 2.2% at 5 years and 11% at 25 years; and Lim et al showed that patients with SM-AHNMD and ASM display a life expectancy between 41 and 24 months compared with ISM patients that have the same life expectancy as healthy people.[9,10] Most other publications on mastocytosis patients >70 years of age are case reports showing a broad spectrum of clinical presentations in elderly patients, and underlining the challenge represented by the establishment of a positive diagnosis in such cases. Only 1 report has focused on a cohort of elderly patients, aged 70 years and older at the time of diagnosis.[11] In this study, 42 patients displayed a high rate of associated hematological disorders: *KIT* D816V mutation was present in 14 patients, negative in 3, and not tested in 25, and no report was available on additional mutations.[11]

Thus, given the limited amount of data available in the literature for such patients, the aims of our present study were therefore to systematically analyze clinical, biological, and genetic features encountered in mastocytosis in our nationwide cohort of 53 elderly patients (>69 years of age), and especially to report on the different complex genetic backgrounds and clinical presentations of the disease at diagnosis at this age.

2. Patients and methods

2.1. Patients

The diagnosis of mastocytosis was established in accordance with the current WHO criteria for mastocytosis.[1,12] Fifty-three consecutive patients referred to the National Reference Center for Mastocytosis, Paris, France, and to regional centers of excellence in France were retrospectively enrolled in this multicenter study on the criteria of diagnosis over 69 years old. All patients gave their written informed consent. The study was approved by the local Ethics Committee of the Necker Enfants-Malades Hospital, and was carried out in accordance with ordinances of the Helsinki convention. This cohort consisted of 32 men and 21 women, with a median age of 75 years of age (range 70–90). The mastocytosis categories were as defined by the WHO criteria. In addition to BM biopsy establishing the diagnosis of systemic disease in all patients, liver, gastrointestinal, and cutaneous biopsies were performed for specific organic involvement confirmation respectively in 10 (18.9%), 12 (22.6%), and 27 (27.9%) patients. The treatments were retrospectively collected.

In our French mastocytosis reference center, 565 patients are followed, including 448 who are between 18 and 69 years old. In this cohort of young adults including 61% women, the median age at diagnosis is 38 years old.

3. Methods

3.1. Serum tryptase measurement

Total serum tryptase level (protryptase + β-tryptase) was determined using a fluorescent enzyme-linked immunoassay (Unicap, Pharmacia).[13] The limit of detection of this assay is 1 ng/mL, and in healthy controls, serum tryptase levels ranged from <1 to 15 ng/mL, with a median of 5 ng/mL.

3.2. KIT mutational status and analysis of additional genetic defects

The *KIT* mutational status was analyzed as previously described using a highly sensitive technique.[14,15] In addition, mutation analyses were performed to detect *TET2, SRSF2, ASLX1, CBL, IDH2, JAK2, NRAS, and U2AF1* as already described.[13–17]

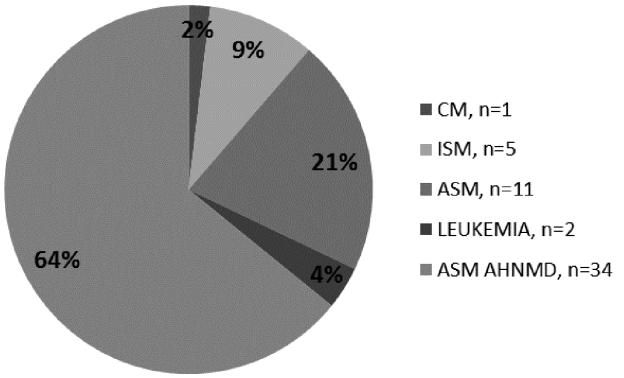

Figure 1. WHO classification of the cohort of 53 elderly mastocytosis patients.

4. Results

4.1. Clinical presentation

Among the 53 elderly patients, the variants of mastocytosis were indolent SM (ISM, n=5; 9.4%), aggressive SM (ASM, n=11; 20.8%), ASM with associated hematologic non-MC lineage disease (ASM-AHNMD, n=34; 64.2%), cutaneous mastocytosis (CM, n=1; 1.9%), and mast cell leukemia (MCL, n=2; 3.8%) (Fig. 1). The main clinical and biological features of the elderly patients are depicted in Table 1. The clinical presentation was very heterogeneous. A total of 50.9% (n=27) of the patients displayed poor performance status, 75.5% (n=40) presented with mast cell activation symptoms (flush n=17, pruritus n=19, diarrhea n=12, abdominal pain n=14); 24.5% (n=13) had lymphadenopathy, 50.9% (n=27) had hepatosplenomegaly, including 4 patients with only hepatomegaly and 6 patients with only splenomegaly. Ascites or other signs of portal hypertension-related disturbances were observed in 26.4% of patients (n=14). Skin involvement was observed among 49% (n=26) patients, mostly urticaria pigmentosa (UP) (n=24) or less frequently telangiectasia macularis eruptiva persistans (TMEP) (n=2). Forty-seven percent (n=25) of patients displayed osteoporosis, including 12 of 25 (48%) patients with fractures (mostly at vertebral sites). Few patients (11.3%) displayed B findings as defined by the WHO classification, whereas C findings were documented in almost all patients (88.7%). Two patients affected by chronic eosinophilia ($>1.7 \times 10^9$/L) exhibited specific patterns

Table 1

Main features of the overall study population of 53 elderly mastocytosis patients subdivided into 3 groups: indolent forms (CM and ISM), aggressive forms (ASM, MCL, MCS), and ASM-AHNMD.

Features	CM/ISM N=6	ASM/MCS/MCL N=13	ASM-AHNMD N=34
Age (median, y, range)	73.5 (70–90)	78 (70–90)	74.5 (70–85)
Sex M (%)	2 (33.3%)	6 (46.15%)	24 (70.6%)
Death (n, %)	0	6 (46.15%)	13 (38.2%)
Clinical features			
Alteration of general status (n, %)	2 (33.3%)	7 (53.85%)	18 (52.9%)
Mast cell activation symptoms (n, %)	5 (83.3%)	7 (53.85%)	28 (82.3%)
Cutaneous symptoms (n, %)	5 (83.3%)	7 (53.85%)	14 (41.2%)
Osteoporosis (n, %)	5 (83.3%)	6 (46.15%)	14 (41.2%)
Fracture (n, % in osteoporotic patients)	1 (20%)	4 (66.7%)	7 (50%)
Hepatosplenomegaly (n, %)	0 (0%)	9 (69.2%)	18 (52.9%)
Lymphadenopathy (n, %)	0	3 (23.1%)	10 (24.9%)
Ascites/portal hypertension (n, %)	0	3 (23.1%)	11 (32.35%)
B findings (n, %)	6 (100%)	0	0
C findings (n, %)	0 (0%)	13 (100%)	34 (100%)
Biological features			
Anemia (n, %)	0 (0%)	11 (84.6%)	31 (91.2%)
Hemoglobin (median, g/dL, range)	13.7 (13–14)	10,6 (7.7–13.8)	10,1 (6.8–14.8)
Leucopenia (n, %)	0	2 (15.4%)	9 (26.5%)
White cells (median, /mm^3, range)	5500 (4700–5400))	5800 (4100–22700)	6550 (1900–70000)
Neutrophils (median, /mm^3)	3100 (2900–4000)	3100 (741–17700)	3815 (481–58000)
Thrombocytopenia (n, %)	0	6 (46.15%)	21 (61.8%)
Platelets (median, /mm^3)	20 (183–230)	77 (28–226)	85 (20–528)
Tryptase (median, ng/mL)	25,5 (5.45–63)	200 (95–800)	182 (22–1077)
Eosinophils (median, /mm^3)	200 (200)	100 (100–2120)	685 (191–2500)
Hepatic abnormality (n, %)	0	5 (38.5%)	12 (35.3%)
Albumin (median, g/L)	40.5 (38–43)	33 (25–42)	37 (23.8–45)
Genetic features			
Sequencing (n, %)	2 (33.3%)	9 (69.23%)	29 (85.3%)
D816V mutation (n, %)	2 (100%)	7 (77.8%)	25 (86.2%)
Other mutation (n, %)	0 (0%)	1 (11.1%)	1 (3.5%)
Wild type (n, %)	0	1 (11.1%)	3 (10.3%)

ASM = aggressive systemic mastocytosis, ASM-AHNMD = ASM with associated hematologic non-mast cell lineage disease, CM = cutaneous mastocytosis, ISM = indolent systemic mastocytosis, MCL = mast cell leukemia, MCS = mast cell sarcoma, TMEP = telangiectasia macularis eruptiva perstans, UP = urticaria pigmentosa.

Skin symptoms: UP, Darier sign or TMEP. Mast cell activation symptoms: flush, pruritus, diarrhea, and abdominal pain. B findings ("borderline benign"): signs that are reflective of the involvement of several myeloid cell lineages in the disease process or of a massive increase in the number of mast cells without impairment of organ function. B findings reflect a smoldering state with uncertain clinical course for the future. C findings ("consider cytoreduction"): signs that are always alarming and are possible indicators for requiring therapy using cytoreductive agents. Neutropenia (neutrophils <1.500/μL). Liver abnormalities: increase of liver enzymes or bilirubin to at least 1.5 times the upper limit of normal.

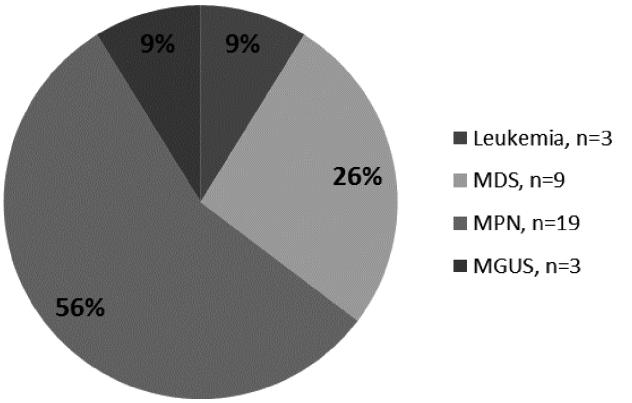

Figure 2. Details of the 34 patients with ASM-AHNMD according to type of associated clonal non-mast cell lineage disease. ASM, aggressive systemic mastocytosis; ASM-AHNMD, ASM with associated hematologic non-mast cell lineage disease.

of cardiac and pulmonary involvement, respectively. Considering the clinical history and the onset of characteristic signs displayed by patients, the median time to diagnosis was estimated at 9 months, with extremes ranging from 3 to 12 months from the beginning of systemic signs, because some patients displayed cutaneous lesions for many years that were not linked to mastocytosis.

Thirty-four (64.2%) patients displayed SM-AHNMD. The distribution of associated non-mast cell hematological diseases is shown in Figure 2. The most frequent associated non-MC malignancies were myeloproliferative neoplasms in 19 patients (55.9%), followed by myelodysplastic syndrome (MDS) in 9 patients (26.5%) and acute leukemia in 3 patients (8.8%). Moreover, monoclonal gammopathy of undetermined significance or indolent myeloma were found in 3 (8.8%) patients.

When comparing the 3 subgroups of patients (Table 1): indolent (CM/ISM) versus aggressive (ASM, MCL), versus AHNMD, we observed the following features:

1. Indolent forms displayed more often mast cell activation symptoms and cutaneous localization and no deaths.
2. Aggressive forms displayed the worst performance status and more often had hepatosplenomegaly and C findings.
3. AHNMD also displayed C findings, but more often portal hypertension and mast cell activation symptoms.

4.2. Biological features

Seventy-nine percent (n=42) of the patients displayed anemia with a median hemoglobin level of 10.5 g/dL (range 7.7–14.8); 50.9% (n=27) had thrombocytopenia with a median platelet count of 91×10^9/L (range 20–528×10^9/L), and 20.8% (n=11) had leucopenia with a median PolyNuclear Neutrophils (PNN) count of 3.5×10^9/L (range 0.74–58×10^9/L) and a median total white blood cells count of 6×10^9/L (range 1.9–70×10^9/L) for the 53 patients. Abnormal liver function tests were present in 32.1% of the patients (n=17). The median serum tryptase level was 176 ng/mL (range 5.45–1077, normal <15 ng/mL). The median blood albumin level was 37.5 g/L (range 23.8–45).

When comparing the different subgroups (Table 1), patients with aggressive forms more often had cytopenia and had higher tryptase levels.

4.3. KIT mutations and other genetic defects

The entire coding regions of *KIT* were sequenced in 40 of the 53 patients (75.5%). When a mutation was detected, it was mostly the *KIT* D816V. Indeed, this mutation was retrieved in 34 of the 40 tested patients (85%), whereas 2 patients (5%) presented another *KIT* mutation, (p.(Phe504_Asn505delinsLeuLysPheLysThr) and p.Ser501_Ala502dup), and 4 patients (10%) displayed wild-type *KIT*. For 26 patients, including 1 ISM, 2 ASM, 21 SM-AHNMD patients, and the 2 patients with MCL, sequencing data for additional genetic defects were available and are shown in Table 2. Seventeen (65.3%) of them (including 14 SM-AHNMD, 2 ASM, and 1 MCL patient) exhibited *TET2* (n=12), *SRSF2* (n=8), *IDH2* (n=3), *ASLX1* (n=4), *CBL* (n=1), *U2AF1* (n=2), and/or *NRAS* (n=1) mutations. Ten patients had at least 2 mutations, mostly patients with SM-AHNMD variant (n=9). No patient, even those with eosinophilia, exhibited the FIP1L1/PDGFRA mutation.

4.4. Treatment

All patients received at least symptomatic treatments with antihistamines (anti-H1R and anti-H2R) or proton pump inhibitors, low doses of corticosteroids (oral or local; n=11), or best supportive care in some cases (bisphosphonate and/or transfusion regimen). For most patients, specific treatment was not proposed due to the patients' poor general condition and/or associated malignant hematological disease with no available treatment options due to the patients' advanced age. The type of chemotherapy regimen proposed was available and well documented in 17 patients with the systemic and aggressive forms of the disease. Nineteen patients received either cladribine (n=11), velcade (n=1), interferon α (n=3), or thalidomide (n=5). Six other patients, for whom chemotherapy regimens containing ARA-C and fludarabine failed, received midostaurin (PKC 412) in a context of high-risk advanced-stage myeloproliferative or

Table 2

Types of additional mutation found among 26 late-onset systemic mastocytosis patients.

	ASLX1	CBL	IDH2	JAK 2	SRSF2	TET 2	U2AF1
MDS	2	0	1	0	2	3	1
MPN	2	1	2	3	5	6	0
ASM	0	0	0	0	1	2	1
LEUK	0	0	0	0	0	1	0

ASM = aggressive systemic mastocytosis, LEUK = leukemia of non mast cell disease, MCL = mast cell leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasm.
Additional genetic defects were found in 26 patients, including 1 ISM, 2 ASM, 21 ASM-AHNMD patients, and 2 with MCL. Seven patients displayed 2 mutations and 3 patients displayed 3 or more mutations. These findings had no effect on prognosis in our cohort.

Table 3

Main features of the 53 patients.

Patient	Age on inclusion	Sex M/F	WHO classification	Main clinical features	Main biological features	Reason for bone marrow biopsy	Positivity of bone marrow	Tryptase serum rate	*KIT* mutation	Death (D)	B or C fin-dings	Cutaneous lesions	Additi-onnal mutations
1	90	M	ASM	AGS, HMG, SMG	An, Th	Cytopenia	Yes	800	NA	D	C	No	SRSF2 TET2
2	90	F	ISM	MCAS, TMEP, Os	no	Stag	Yes	5.45	ND	ND	B	Yes TMEP	ND
3	86	M	ASM	HMG	An	Cytopenia	Yes	176	ND	D	C	No	ND
4	85	M	AHNMD-MDS	MCAS, UP, Os+F	An	Stag	Yes	143	D816V	ND	C	Yes UP	TET2
5	84	F	AHNMD-MPF	SMG,	An	Cytopenia	Yes	NA	D816V	ND	C	No	None
6	83	F	AHNMD-MDS	AGS, HMG, SMG	An, Th	Cytopenia	Yes	212	D816V	ND	C	No	TET2
7	83	M	AHNMD-MPF	AGS, HMG, SMG, PHT	An, Th	Cytopenia	Yes	1077	NA	D	C	No	None
8	83	F	AHNMD-MPF	MCAS, HMG,	An, Th	Cytopenia	Yes	33	D816V	NDS	C	No	TET2
9	82	M	AHNMD-MPF	UP, MCAS, HMG, SMG, PHT	An, Th	Stag	Yes	235	NA	D	C	Yes, UP	None
10	82	M	AHNMD-MDS	MCAS, AGS UP, Os+F	An, Th, leuc	Stag	Yes	22	D816V	ND	C	Yes UP	IDH2 U2AF1
11	81	M	AHNMD-MGUS	AGS, MCAS, UP, OS+F, HMG	An, Leuc, Th	Stag	Yes	370	D816V	D	C	Yes, UP	None
12	80	M	MCL	AGS, MCAS, Os, SMG, PHT	An, Th, Leuc	Cytopenia	Yes	426	NA	D	C	No	TET2
13	80	F	ASM	MCAS, HMG, SMG	An	Cytopenia	Yes	190	D816V	ND	C	No	ND
14	79	M	AHNMD-MPF	AGS, MCAS, HMG, SMG, PHT	An, Th	Cytopenia	Yes	169	D816V	D	C	No	IDH2 JAK2 ASLX1 NRAS SRSF2
15	79	F	ASM	UP, Os+F, HMG, SMG, Adp	An	Cytopenia	Yes	297	D816V	ND	C	Yes up	ND
16	79	F	ASM	AGS, MCAS, UP, Os+F	no	Stag	Yes	104	501–502 dup	ND	C	Yes UP	ND
17	79	M	AHNMD-MPF	AGS, MCAS HMG	An, Th	Cytopenia	Yes	140	D816V	ND	C	No	ND
18	78	M	AHNMD-MPF	AGS, MCAS, HMG, SMG, PHT	An, Th	Cytopenia	Yes	355	D816V	D	C	No	SRSF2 TET2
19	78	M	ASM	AGS, UP, Os, HMG, SMG, PHT	An, Th	Stag	Yes	233	WT	D	C	Yes, UP	ND
20	77	M	ASM	AGS, UP, HMG, SMG, OSf	An, Th	Cytopenia	Yes	579	D816V	ND	C	Yes UP	ND
21	77	F	AHNMD-MPF	MCAS, HMG, SMG	An	Cytopenia	Yes	131	NA	ND	C	No	TET2
22	76	F	ASM	MCAS, HMG, SMG	An	Cytopenia	Yes	174	NA	D	C	No	TET2 U2AF1
23	76	M	ASM-AHNMD	AGS, Os, HMG, SMG, PHT	An, Th	Cytopenia	Yes	200	NA	D	C	No	None
24	76	F	ASM	MCAS, SMG	An, leuc	Cytopenia	Yes	131	D816V	ND	C	No	ND
25	75	F	MCL	AGS, MCAS, HMG	An, Th	Cytopenia	Yes	465	D816V	D	C	No	None
26	75	F	AHNMD-MPF	MCAS,	Th	Cytopenia	Yes	28	ND	ND	C	No	ND
27	75	F	AHNMD-MPF	MCAS	An, Th	Cytopenia	Yes	200	ND	ND	C	No	ND
28	75	M	AHNMD-MPF	AGS, Os+F, HMG, SMG, Adp	An, Th	Cytopenia	Yes	29	D816V	D	C	No	ND
29	75	M	AHNMD-MPF	AGS, MCAS, UP	An, Leuc, Th	Cytopenia	Yes	23	D816V	ND	C	Yes, UP	ND
30	74	M	ASM	AGS, MCAS, UP, HMG, SMG,PHT	An, Th	Cytopenia	Yes	200	D816V	ND	C	Yes UP	ND
31	74	M	AHNMD-MDS	AGS, MCAS, UP, Os, HMG, PHT	An, Leuc, Th	Cytopenia	Yes	700	D816V	ND	C	Yes UP	ASLX1 SRSF2 TET2
32	74	M	AHNMD-MPF	AGS, MCAS, SMG	An, Th	Cytopenia	Yes	331	D816V	ND	C	No	CBL IDH2 JAK2 SRSF2

Patient	Age on inclusion	Sex M/F	WHO classification	Main clinical features	Main biological features	Reason for bone marrow biopsy	Positivity of bone marrow	Tryptase serum rate	*KIT* mutation	Death (D)	B or C fin-dings	Cutaneous lesions	Additi-onnal mutations
33	74	F	AHNMD-MGUS	MCAS, UP, Os+F,	no	Stag	Yes	430	D816V	D	C	Yes UP	ND
34	74	M	ISM	AGS, MCAS, UP, Os	no	Stag	Yes	63	ND	ND	B	Yes UP	ND
35	74	F	ISM	MCAS, Os	no	Stag	Yes	13.6	D816V	ND	B	No	ND
36	74	M	AHNMD-Leukemia AML	AGS, MCAS, UP, Os+F, HMG, Adp, PHT	An, Leuc	Cytopenia	Yes	38	WT	ND	C	Yes UP	ND
37	73	F	AHNMD-MGUS	AGS, MCAS, Os, UP	An	Cytopenia	Yes	178	D816V	ND	C	Yes UP	ND
38	73	M	AHNMD-MPF	MCAS, AGS, SMG, HMG	An, Th	Cytopenia	Yes	350	P504L	D	C	No	SRSF2 TET2
39	73	F	ISM	MCAS, UP	no	Stag	Yes	29	ND	ND	B	Yes UP	ND
40	72	M	AHNMD-MDS	MCAS, HMG,	An,Leuc	Cytopenia	Yes	NA	D816V	D	C	No	ASLX1 SRSF2
41	72	M	AHNMD-MDS	MCAS, HMG, SMG	An	Cytopenia	Yes	95	WT	D	C	No	ND
42	72	M	AHNMD-MPF	AGS, MCAS, HMG	An	Cytopenia	Yes	200	D816V	ND	C	No	JAK2
43	71	M	AHNMD-MPF	AGS, MCAS, UP, Os, HMG, PHT	An	Stag	Yes	186	D816V	ND	C	Yes UP	ND
44	71	M	AHNMD-MDS	MCAS, SMG	An	Cytopenia	Yes	73	D816V	ND	C	No	ND
45	71	F	AHNMF-MPF	MCAS, SMG,	An	Cytopenia	Yes	822	D816V	D	C	No	ASLX1 TET2
46	70	M	AHNMD-MDS	MCAS, SMG	An, Th	Cytopenia	Yes	73.4	WT	ND	C	No	None
47	70	F	AHNMF-MPF	AGS, MCAS, UP, OS, HMG, PHT	An, Th	Cytopenia	Yes	164	D816V	D	C	Yes UP	ND
48	70	M	AHNMD-MDS	MCAS, UP, HMG	An	Stag	Yes	228	D816V	ND	C	Yes UP	ND
49	70	M	AHNMD-MPF	MCAS, UP, HMG, PHT	Th, leuc	Stag	Yes	330	D816V	D	C	Yes, UP	SRSF2 TET2
50	70	M	AHNMD-HCL	UP, Os	An	Cytopenia	Yes	62	D816V	ND	C	Yes UP	ND
51	70	F	ASM	UP, Os+F	no	Stag	Yes	95	D816V	ND	C	Yes UP	ND
52	70	M	ISM	AGS, MCAS, UP, Os	no	Stag	Yes	43	D816V	ND	B	Yes UP	None
53	70	F	CM	UP, Os+F	no	Stag	No	22	ND	ND	B	Yes UP	ND

Leuk = leukemia, Adp = adenopathy, AGS = alteration of general status, AHNMD = associated clonal non-mast cell lineage disease, AML = acute myeloid leukemia, An = anemia, ASM = aggressive systemic mastocytosis, CM = cutaneous mastocytosis, D = dead, D816V = *CKIT* mutation D816V, F = fracture, HSMG = hepatosplenomegaly, ISM = indolent systemic mastocytosis, Leuc = leucopenia, MCAS = mast cell activation symptoms, MCL = mast cell leukemia, MDS = myelodysplastic disorder, MGUS = monoclonal gammopathy of undetermined significance, MPN = myeloproliferative neoplasm, Os = osteoporosis, NA = not available, ND = not dead, NDone = not done, NF = not found (but sequencing done), PHT = portal hypertension, Th = thrombopenia, TMEP = telangiectasia macularis eruptivans perstans, UP = urticaria pigmentosa, WT = wild type. Reason for bone marrow biopsy: Stag = staging of mastocytosis.

myelodysplastic syndromes (n=4), an aggressive form of mastocytosis (n=1) or a mast cell leukemia (n=1).

4.5. Prognosis and outcome

After a median follow-up of 17 months (range 7–50 months), death occurred in 35.8% (n=19) of the patients. Considering the time to diagnosis, death occurred after a median time of 26 months from disease onset (range 10–62 months). Approximately one-third (n=6) of the 19 deaths were related to the rapid progression of the AHNMD. Two-thirds (n=12) of the deaths were related to the progression of mastocytosis and/or to the toxicity of the chemotherapy regimen, including both patients with respectively MCS or MCL. Fatal toxicities were as follows: BM failure with severe neutropenia and septic shock (n=1), refractory thrombocytopenia and hemorrhage (n=3) and refractory anemia (n=2); specific organ involvement with liver (n=3), heart (n=1) or pulmonary (n=2) failures. The remaining death was related to sudden heart failure of unknown origin.

When comparing the 3 different subgroups (Table 1), patients with aggressive forms of the disease displayed the worst prognosis.

5. Discussion

To our knowledge, this study reporting 53 elderly mastocytosis patients with a focus on additional mutations besides *KIT* is the largest published on elderly adults in the literature so far. The Table 3 summarizes the principal features of the 53 patients. Of note, data of our study point to several differences in the initial presentation between our elderly patients and patients with the "classical" disease mainly described in infancy and young adulthood. Indeed, elderly patients usually present with extremely poor performance status, symptoms of mast cell activation, hepatosplenomegaly, and sometimes ascites or osteoporosis with fractures, associated with cytopenia. Diagnosis of this rare disease in elderly patients is often long delayed, probably because gerontologists are less aware of the typical signs of the disease than the cutaneous symptoms, which is all the more frequent ad evocative when occurring at a younger age, as confirmed by our data. Indeed we found a relatively low frequency (less than half of cases) of urticaria pigmentosa (UP) in this cohort, contrasting with the high frequency of UP (up to 85%) reported for younger patients with systemic mastocytosis, and for whom UP constitutes a major diagnostic sign.[20,21] On the other hand, cutaneous involvement is found in about 90 percent of patients in the general mastocytosis population without an AHNMD, and about one-third of this population first develop characteristic lesions in adulthood; this form of the disease represents only 1.9% of our elderly population, while 88.7% of our patients exhibited C findings and almost 1 or more hematologic organ impairment.[8,18,19]

Besides *KIT* mutations found recurrently in SM, we were able to detect mutations in *TET2, JAK2*, or *SRSF2* genes, which are usually found in myelodysplastic/proliferative disorders. In the study by Schwaab et al,[5] 27 of 39 patients (69.2%) with different forms of systemic mastocytosis also exhibited some of these additional defects. In our study, we found almost similar rates. Indeed, we observed at least one of these additional mutations in 17 of 26 (65.3%) of our patients tested who had associated hematological malignancies. The finding of common molecular neoplastic mechanisms and/or a common hematopoietic progenitor cell origin for both mastocytosis and myelodysplastic/myeloproliferative disorders should be therefore of great interest. We have recently reported that *TET2* deficiency has the ability to affect *KIT* D816V+ MCs, and therefore promote more severe forms of the disease.[15] In our cohort of elderly patients, we found a frequency of 46.2% of *TET2* mutations, which is higher than that (20%) reported in the literature.[6,7,9,15,17] Patients with *TET2* mutations harbored the following variants of mastocytosis: ASM (n=2), ASM-AHNMD (n=8), ISM (n=1), and MCL (n=1). By contrast, *SRSF2* mutations were observed in 8 patients (30.8% of our cohort), including 7 affected by a severe AHNMD form, a frequency that is similar to that reported in the literature (24%–37%).[6,14,17]

The mortality rate is high in the cohort (35.8%), but this is somewhat expected since most of the patients are classified as SM-AHNMD and because elderly patients usually display more comorbidities than young patients. According to the literature and to our results, the OS was worst among patients with additional genetic defects compared with those where the *KIT* D816V mutation was the sole defect identified.[17] Taken together, these results underline the critical need to sequence not only *KIT* but also additional genes to better characterize mastocytosis and the frequently associated AHNMDs, these latter malignancies playing a major role in the poor prognosis of the elderly. Indeed, the *KIT* mutant D816V may disappear in some advanced forms of the disease which is best explained by selection and transformation of more malignant subclones derived from a more primitive neoplastic stem cell compartment where *KIT* D816V is not expressed.[7] Therefore, new treatments such as kinase inhibitors targeting both mast cell and other myeloid cell malignant proliferation could open up interesting therapeutic prospects in the context of elderly patients displaying mastocytosis.[22,23]

In conclusion, the clinical and prognostic profiles described herein confirmed the variable presentation of mastocytosis in elderly patients. Indeed, besides the dominant patterns of limited and/or self-limited benign cutaneous disease in infancy, and mostly indolent systemic disease with frequent neuropsychological features in young adulthood, elderly patients in our cohort exhibit a more severe aggressive outcome, less frequent skin involvement and/or limited disease, but frequent nonfortuitous association with other myeloid malignancies, probably due to the high frequency of aggressive and AHNMD forms of mastocytosis in the ageing population.[8,24–28] A better knowledge of *KIT* and other additional myeloid lineage mutations should help improve therapeutic differential targeting of this heterogeneous disease.[5–7,9,14,15,17,29]

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