Familial occurrence of systemic and cutaneous mastocytosis in an adult multicentre series

Mastocytosis represents a group of clonal disorders characterized by abnormal proliferation and infiltration of mast cells in various tissues, particularly skin and haematopoietic organs, ranging from skin-limited diseases to systemic and more aggressive variants.[1] Its clonal nature relies on somatic, gain-of-function mutations in exon 17, causing constitutive activation of the *c*-KIT proto-oncogene and detected in most patients.[2] More than 80% of adult patients with a systemic disease carry a somatic aspartate-to-valine substitution in codon 816 (D816V) of the *KIT* gene.[1] Although it is a putative, non-hereditary disease, familial cases have been reported in paediatric series, with an estimated frequency of 11–13%.[3,4] However, data about the familial occurrence in adults are still lacking.

This retrospective, observational, multicentre study aimed first at assessing the prevalence of familial disease in a large cohort of adult patients with mastocytosis and, second, at describing the clinical and molecular features of familial cases. Our cohort included 1541 adult patients followed by eight Italian Institutions, diagnosed with systemic or cutaneous mastocytosis, according to 2016 WHO criteria.[5] All patients were asked about the occurrence of mastocytosis in relatives. When achievable, KIT mutational status was assessed both in index patients and relatives. Clinical data were collected retrospectively. Informed consent was obtained from participants, according to the guidelines of the local ethics committee Azienda Ospedaliera Universitaria Integrata di Verona.

Among 1541 patients, we identified 23 clustered cases, resulting in an estimated prevalence of 1·5% familial cases. The median age at diagnosis of index patients was 44 years (range 16–70). Diagnosis was systemic mastocytosis (SM) in 16 cases (69·5%) and cutaneous mastocytosis (CM) in four cases (17·4%). Three patients (13·6%) who refused bone marrow biopsy were diagnosed with mastocytosis in the skin (MIS). Ten out of 16 SM patients (62·5%) had indolent systemic mastocytosis (ISM), four (25%) had bone marrow mastocytosis (BMM), one had aggressive SM (ASM) and one had systemic mastocytosis with associated haematological neoplasm (SM-AHN). *KIT* D816V mutation was found in either bone marrow (BM) or peripheral blood (PB) in all but one patient with SM (93·7%).

Relatives with mastocytosis had a median age at diagnosis of 20 years (range 0–70), i.e., they were younger than the index cases. Seven patients (30·4%) had SM (ISM, $n = 3$; SM-AHN, $n = 2$; smouldering systemic mastocytosis (SSM), $n = 1$; BMM, $n = 1$); 13 patients (52·2%) had a cutaneous variant of mastocytosis [maculo-papular cutaneous mastocytosis (MPCM), $n = 7$; cutaneous mastocytoma, $n = 6$] and three patients had a diagnosis of MIS. The *KIT* mutational status was available only in four of seven relatives with SM, and three of them were *KIT* D816V mutated; five relatives with MPCM and one with MIS were negative for *KIT* D816V mutation in BM or PB.

In eight out of 23 clustered cases, the *KIT* mutational status had been assessed in BM in both index patient and relative: concordant results were documented only in four out of eight cases, three D816V mutated and one wild-type. In the remaining cases, the index case carried the D816V mutation, whereas the relative was found to be negative. Finally, the index/relative relationships were: eight out of 23 parent and child (34·8%), eight out of 23 siblings (34·8%) and seven out of 23 other relationship (30·4%).

Index and relative patients' clinical and molecular characteristics are listed in Table I.

In our series, the clinical phenotype was highly heterogeneous, without any clear correlation in the disease presentation among members of the same familial cluster (see Fig 1). Moreover, 11 out of 23 clustered cases (47·8%) had the disease onset during adulthood, whereas in six cases (26·1%) symptoms appeared in childhood. In six families (26·1%) symptoms appeared either in childhood in the index case and in adulthood in relative or vice versa.

Finally, in one case, both the index patient and her sister had an SM-AHN, associated with a triple-negative myeloproliferative neoplasm (MPN) and chronic myeloid leukaemia (CML), respectively. In the index case, the *KIT* D816V mutation was detected in PB, whereas neither the mutational status nor symptoms' age at onset was available for the relative.

To our knowledge, this is the largest report on the prevalence and characteristics of familial mastocytosis in an adult population. Interestingly, in most of our index cases, we identified the *KIT* D816V mutation, which has never been shown to be inherited.

Familial cases described so far were mainly paediatric CM lacking *KIT* lesions or harbouring uncommon *KIT* mutations, often positioned outside the exon 17 (i.e. A533D, K509I).[3] Both somatic and germline *KIT* mutations have been reported in a few familial cases of gastrointestinal stromal tumor and mastocytosis.[6,7] Our group and Broesby-Olsen *et al.* have

Table I. Indices and relatives' clinical and molecular characteristics.

Characteristics	Indices	Relatives
	n = 23	*n* = 23
Sex ratio (M/F)	1·1 (12/11)	1·5 (14/9)
Median age at diagnosis (range), years	44 (16–70)	20 (0–70)
Diagnosis	*n* (%)	*n* (%)
Systemic mastocytosis (SM)	16/23 (69·5)	7/23 (30·4)
Indolent systemic mastocytosis (ISM)	10/16 (62·5)	3/7 (42·9)
Bone marrow mastocytosis (BMM)	4/16 (25)	1/7 (14·3)
Systemic mastocytosis with associated haematological neoplasm (SM-AHN)	1/16 (6·2)	2/7 (28·5)
Aggressive systemic mastocytosis	1/16 (6·2)	0/23 (0)
Maculopapular cutaneous mastocytosis (MPCM)	3/23 (13)	7/23 (30·4)
Mastocytosis in the skin (MIS)	3/23 (13·0)	3/23 (13)
Cutaneous mastocytoma (s)	1/23	6/23 (26)
KIT D816V mutated (BM)	*n* (%)*	*n* (%)*
Systemic mastocytosis	14/15 (93·3)	3/7 (42·9)
Mastocytosis in the skin	ND	ND
Maculopapular cutaneous mastocytosis	0/4 (0)	0/4 (0)
Cutaneous mastocytoma (s)	0/1 (0)	ND
KIT D816V mutated (PB)	*n* (%)*	*n* (%)*
Systemic mastocytosis	11/12 (91·7)	1/1 (100)
Mastocytosis in the skin	0/2 (0)	0/1 (0)
Maculopapular cutaneous mastocytosis	ND	0/1 (0)
Cutaneous mastocytoma (s)	ND	ND

ND, not determined; BM, bone marrow; PB, peripheral blood.
*Number of patients tested or with available molecular data.

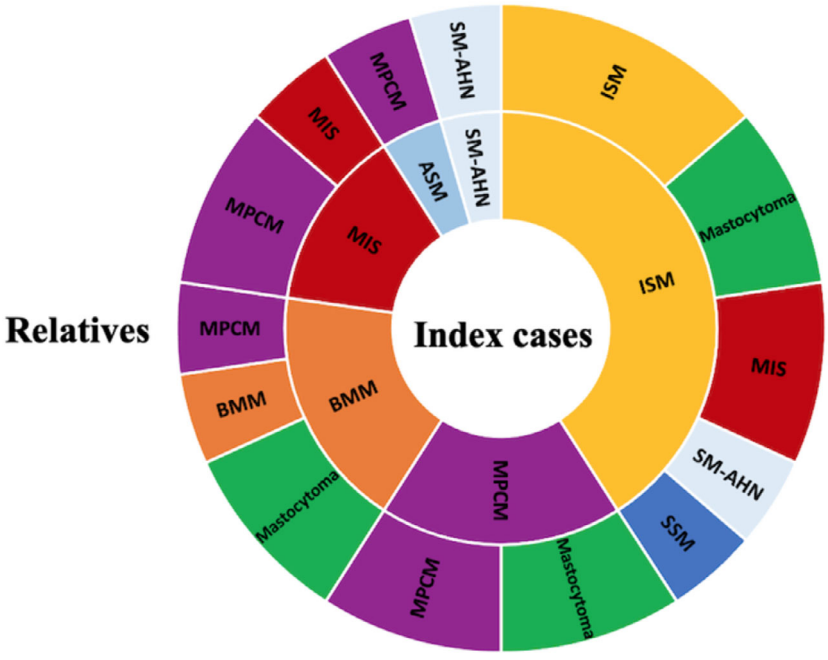

Fig 1. Clinical phenotype of index cases and relatives. ISM, indolent systemic mastocytosis; BMM, bone marrow mastocytosis; MPCM, maculopapular cutaneous mastocytosis; MIS, mastocytosis in the skin; SM-AHN, systemic mastocytosis with associated haematological neoplasm; ASM, aggressive systemic mastocytosis; SSM, smouldering systemic mastocytosis. [Colour figure can be viewed at wileyonlinelibrary.com

previously described two systemic mastocytosis clusters affecting two adult members of the same family, both carrying a somatic *KIT* D816V mutation.[8,9] The same mutation was reported in two paediatric familial cases, one of them harbouring a somatic D816V *KIT* mutation.[3]

Unfortunately, due to the retrospective nature of our study and the higher frequency of pediatric cases, data about relatives' mutational status were limited. Among SM patients, the *KIT* D816V mutation rate was of 93·3% and 42·9% in index cases and relatives, respectively; however,

this mutation was not documented in any tested CM cases. Unfortunately, the *KIT* mutational status was available for both relatives and index cases only in eight families, with concordant results documented in four cases. Since the majority of the relatives had been tested for the *KIT* D816V mutation in other centres, information about the technique used for mutational analysis is lacking. Therefore, we cannot rule out an incidence underestimation related to low-sensitivity methods.

In our series, the different time of onset of the disease, as well as the heterogeneity of mutational status and clinical variants in the same families, suggest the presence of other potential genetic factors favouring the acquisition of a somatic activating *KIT* mutation, such as another *KIT* germline mutation, as well as polymorphisms of genes coding for mast cell growth factors and or their receptors.[10] Future studies of familial cases of CM, including complete sequencing of the *KIT* gene, genetic analyses on skin biopsy samples and exome sequencing could identify new molecular determinants of CM.

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Competing interest

The authors declare that they have no competing interests.

Authors contribution

Ilaria Tanasi designed the research study, collected and analyzed data and wrote the paper. Massimiliano Bonifacio analyzed data and reviewed the paper. Federica Irene Grifoni, Mariarita Sciumè, Chiara Elena, Pietro Benvenuti, Francesco Mannelli, Roberta Parente, Donatella Schena, Luigi Scaffidi, Patrizia Bonadonna, Cristina Papayannidis, Michela Rondoni, Marianna Criscuolo, Alessandro M. Vannucchi, Massimo Triggiani, and Giovanni Martinelli, provided clinical data. Mauro Krampera reviewed the paper. Roberta Zanotti designed the research study, analyzed data and reviewed the paper. All authors read and approved the final manuscript.

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The limited role of comprehensive staging work-up in ocular adnexal extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type (MALToma) with excellent prognosis

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) accounts for 30–90% of ocular adnexal lymphoma, and a majority of ocular adnexal MALT lymphoma (OAML) is stage 1 disease.[1] The role of extensive staging procedures, including positron emission tomography-computed tomography (PET-CT), esophagogastroduodenoscopy (EGD), and bone marrow biopsy, has not been thoroughly investigated for OAML due to its rarity. However, most are commonly performed as there are currently no specific recommendations.[2–4] To evaluate the role of these staging procedures for OAML, we have reviewed data from all the consecutive patients who presented with ocular adnexal mass as the first symptom and were consequently diagnosed with OAML between 2001 and 2015, using a prospective non-Hodgkin lymphoma database.

Data from 130 patients with pathologically confirmed OAML and sufficient medical records were included for analysis (Table SI). The median age at diagnosis was 48 years (range, 20–70), and 45·4% were men. The majority of patients had Ann Arbor stage IE disease with unilateral involvement (n = 90, 69·2%) or bilateral involvement (n = 23, 17·7%), defined as stage IE + IE; stage IV (n = 9, 6·9%) and stage IIE (n = 8, 6·2%) came next. The conjunctiva (n = 108, 83·1%) was the most frequently involved primary site, followed by the lacrimal gland (n = 12, 9·2%), orbit (n = 8, 6·2%), and eyelid (n = 2, 1·5%).

Approximately two-thirds of ocular adnexal lesions were identified by orbit CT (n = 27/38, 71·1%) and magnetic resonance imaging (MRI; n = 33/48, 68·8%), while only 36·7% of primary lesions (n = 44/120) appeared as hypermetabolic lesions on PET-CT, and all of them had already been detected by CT or MRI (Table SII). Regarding staging work-up, more than 90% of patients (n = 120, 92·3%) underwent PET-CT to evaluate systemic involvement of lymphoma, and four of them (3·3%) were upstaged from the stage determined by CT scans covering the neck, chest, and abdomen–pelvis. Conversely, there were no distant lesions found only on CT, but not on PET-CT (Table I). On EGD, 2·4% (2/82) had accompanying gastric MALToma. Bone marrow involvement of MALT lymphoma was observed in only 1·7% (2/120), and none developed clinically significant cytopenia.

The treatment and clinical course of all patients are summarized in Table SIII and Figure S1. Patients with localized disease (stage IE, n = 63/90, 70·0%; IE + IE, n = 20/23, 87·0%) were mainly treated with radiotherapy. Half of stage IIE patients (n = 4/8) and two-thirds of stage IV patients (n = 6/9) received rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). The remaining patients (four with stage IIE, three with stage IV) received radiotherapy to all involved lesions, and there was no relapse requiring further treatment. During a median follow-up of 63·8 months, disease progression or relapse occurred in 10 patients (7·7%); most were local relapse [contralateral eye in three patients and ipsilateral progression in five]. The five-year and 10-year survival rates for all patients were estimated to be 98·5% and 97·1%, respectively, without significant difference according to the stage (stage IV vs others; 100% vs 98·5%, P = 0·695; Fig 1). There were no deaths related to disease progression; one patient died because of small-cell lung cancer and another of rituximab-induced lung injury. There was no transformation to high-grade lymphoma.

In this study, PET-CT detected only about one-third of primary ocular adnexal lesions, which is in line with a previous Australian study that included all histologic subtypes; PET-CT sensitivity, 27% vs CT/MRI, 73%.[5] Moreover, PET-CT was not superior to conventional CT scans covering the