Somatic D816V KIT mutation in a case of adult-onset familial mastocytosis

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To the Editor:

Familial occurrence of mastocytosis is unusual. Most of the clustered cases were pediatric cutaneous mastocytosis without KIT mutations, or presenting uncommon KIT lesions, not yet reported in sporadic cases (ie, A533D or K509I point mutation or deletion of exons 418 and 559-560, in association with familial gastrointestinal stromal tumors). These data suggest that familial mastocytosis comprises a subgroup with a different pathogenesis from the sporadic mastocytosis that is typically associated with the D816V KIT mutation. Here, we report a case of familial systemic mastocytosis (SM) without skin lesions presented in 2 adults, a mother and her son, both carrying the D816V mutation, and associated with systemic reaction to hymenoptera venom. Patients 1 and 2 had no personal or familial history of skin disorders, hematological diseases, gastrointestinal stromal tumor, or other cancer. The unique sister of patient 1 had normal serum tryptase levels and refused any other evaluation. Patient 1 (male, aged 32 years) came to the Allergy Service of Feltre, Belluno (Italy), in 2002 after a systemic reaction (Mueller III) subsequent to a hymenoptera sting, identified as a vespula. Skin prick tests and intradermal tests to Apis mellifera (I1), Vespa crabro (I75), Polistes dominulus (I77), Vespula species (I3), and Bombus terrestris were performed according to the recommendations of the European Academy of Allergology and Clinical Immunology; they evidenced positivity for the I3 venom, which was further confirmed by detection of specific IgE serum antibodies (CAP test, Pharmacia, Uppsala, Sweden). In July 2002, the patient started specific immunotherapy to Vespula species, which is still in course. From 2005 to 2009, he was sometimes stung by a vespid without any reaction. In 2006, a Bombus species field sting caused a Muller IV grade systemic reaction that determined his admission to the emergency room. Skin prick test and detection of specific serum IgE were repeated, and the tests confirmed a sensitization only to Vespula species. Furthermore, serum tryptase level was 12.5ng/mL and he did not show any other mediator-related associated symptoms. Patient 2 (female, 57 years, mother of patient had a history of osteoporosis, which was treated with alendronate 70 mg once a week. In 2002, she was stung by a vespid and had Muller I systemic reaction. Skin prick test and detection of specific IgE serum antibodies were positive for I3 and I4 (Polistes species).

Vespula venom specific immunotherapy was started, but the patient suffered from Muller I systemic reaction after the dose of 20 mg. After a week, the serum tryptase level was 42ng/mL. Some weeks later, she restarted the immunotherapy without any problems. She did not show any other mediator-related symptoms. The history of systemic reactions after hymenoptera sting and persistent raised tryptase serum levels led to the suspicion of SM. Both patients were referred to the Multidisciplinary Outpatients Clinic for Mastocytosis of Verona, Italy, where they underwent physical examination, complete blood cell count, routine biochemistry, abdominal ultrasonography, bone densitometry evaluation with dual-energy x-ray absorptiometry, and bone marrow evaluation with histology/cytology and flow cytometric analysis, performed as previously described. The D816V KIT mutation was demonstrated in both patients on total RNA from bone marrow samples by real-time PCR using mismatched forward primers for both mutated and wild-type sequence to control cDNA quality and by peptide nucleic acidmediated PCR clamping and hybridization probes (the analyses were performed independently in Verona and Salamanca Laboratories). The presence of the D816V mutation was also investigated on genomic DNA from total peripheral blood (PB) and from fluorescence-activated cell sorting–purified populations of PB neutrophils, monocytes, and lymphocytes, by allelespecific real-time quantitative PCR. Genomic DNA from total PB sample of the son showed a slight positivity (2.5%-5%) of the D816V KIT mutation, whereas the mother was negative, which would confirm that it was not a case of germline but somatic mutation. Moreover, analysis of genomic DNA from purified PB cell populations of the son revealed that only monocytes and granulocytes carried the D816V KIT mutation while T lymphocytes were negative for this mutation. Clinical, laboratory, and bone marrow characteristics are reported in Table I. Both patients were diagnosed with indolent SM without skin lesions on the basis of 3 minor criteria (patient 1) or 1 major criteria and 4 minor criteria (patient 2) according to the current World Health Organization recommendations. To the best of our knowledge, this is the first report of a family (mother and son) with adult-onset SM associated with the occurrence of somatic D816V KIT mutation on both patients. Given the rarity of this disease, the simultaneous occurrence on both patients of the D816V KIT mutation by chance is negligible; therefore, SM onset is due to some type of parental inheritance. Nevertheless, the D816V mutation was somatic but not germline, as it has been shown to be restricted to a small part of the myeloid compartment of hematopoiesis. It is generally accepted that unlike familial mastocytosis, adult patients with sporadic mastocytosis usually express activating mutations in exon 17 of KIT, most commonly D816V,2 and this mutation has never been shown to be inherited.1 Indeed, a study performed on 50 pediatric cases showed that despite 36% of the cases being positive for the D816V KIT mutation, they were always somatic, including 2 brothers with a familial form of the disease without any history of KIT-related tumors (other than mastocytosis).

The latter observation is consistent with a case of adult-onset familial SM in monozygotic twins with skin lesions and somatic D816V mutation. Therefore, the report of somatic D816V KIT mutation in familial cases of mastocytosis (either with children or adult onset) suggests the presence of other genetic factors predisposing to the acquisition of somatic-activating KIT mutation. Despite the fact that a great number of growth factor signal transduction pathways are closely related to KIT transduction pathways and may influence mast cell proliferation and survival (reviewed in Orfao et al), and polymorphism of genes encoding for mast cell growth factors and their receptors (eg, IL-13 and IL-4R) is described to influence different phenotypes in mastocytosis, to the best of our knowledge there is still not enough scientific evidence to assume any potential genetic candidate predisposing the development of mastocytosis.

TABLE I. Clinical, laboratory, BM, and PB characteristics of 2 patients at diagnostic of SM

	Patient 1	Patient 2
Sex	Male	Female
Age (y)	37	57
Hemoglobin, median (gr/dL)	16.1	14.2
White cell count, median (X109/L)	5.3	7.0
Platelet count, median (X109/L)	195	212
Tryptase level (ng/mL)	12.4	42.0
Skin lesions	Absent	Absent
Hepatosplenomegaly	Absent	Absent
Lymphadenopathy	Absent	Absent
BM histology		
Cellularity (%)	40	60
Multifocal, dense MC aggregates	Negative*	Positive
BM cytology		
% of atypical type I MC within all nucleated BM cells	<1	<1
(% of BM atypical MC type I of all BM MCs)	75	85
BM flow cytometry		
% of CD251 BM MCs within nucleated BM cells		0.33
0.43		
D816V on BM cDNA	Positive	Positive
D816V on PB gDNA	Positive (2.5%-5%)	Negative
D816V on monocytes gDNA	Positive	–
D816V on granulocytes gDNA	Positive	–
D816V on T-lymphocytes gDNA	Negative	–

BM, Bone marrow; gDNA, genomic DNA; MC, mast cell.
*Small aggregates of atypical MCs.