Letter to the Editor

Adult-onset systemic mastocytosis in monozygotic twins with *KIT* D816V and *JAK2* V617F mutations

To the Editor:

We present clinical, histopathologic, and mutational findings and clinical course over 30 years in a pair of monozygotic twins with adult-onset systemic mastocytosis (SM) both carrying a somatic *KIT* D816V and Janus kinase 2 (*JAK2*) V617F mutation.

Pregnancy and labor were reportedly uneventful, and the parents were described as healthy. Both twins were healthy during childhood and adolescence.

From the age of 38 (twin A) and 40 (twin B) years, they gradually developed reddish-brown, flat skin elements on the femora and thighs spreading within a few years to the abdomen and arms, with intermittent pruritic exacerbations triggered by friction or heat. In both twins, periodic, colicky abdominal pains and diarrhea were described. No anaphylactic episodes were reported.

At the age of 50 years, a synchronous evaluation was performed. On objective examination, the twins were identical with the same distribution of urticaria pigmentosa (UP) skin lesions. Monozygosity was confirmed by genotyping. Skin biopsies showed mast cell (MC) infiltration consistent with UP. Duodenal biopsies were normal. Bone marrow (BM) biopsies gave at that time no suspicion of SM. However, on recent reevaluation of the BM biopsies with newer immunohistochemical methods, typical findings in SM could be demonstrated in both twins that retrospectively were classifiable as indolent systemic mastocytosis (ISM). Skin and gastrointestinal symptoms improved on treatment with antihistamines (cetirizine) in both twins—and during the next 15 years they did not find the need for hospital contact for their mastocytosis.

Twin A was referred back at the age of 65 years with mild symptoms from the skin. Typical, unchanged UP lesions on the upper arms, abdomen, thighs, and femora were found (Fig 1, *A*). A new BM biopsy revealed classical SM with multifocal infiltrates of tryptase+, $CD117^+$, and $CD25^+$ mainly spindle-shaped MCs. Flowcytometric analysis of BM aspirate revealed that 0.15% of

FIG 1. Photos illustrating identical twins with typical symmetric UP lesions on the legs. **A,** Twin A at age 65 years. **B,** Twin B at age 68 years.

the leukocytes were MCs with abnormal phenotype, with expression of CD25 and CD2. Sensitive flowcytometric analysis of peripheral blood (PB) showed no neoplastic MCs. By using a sensitive and quantitative real-time PCR mutation analysis on genomic DNA,[1] the *KIT* D816V mutation was found in skin, PB, and BM aspirate with an allelic frequency of 3.2%, 4.0%, and 6.0%, respectively. Basal tryptase level was 44 μg/L and stable. A bone mineral density scan few years earlier had revealed osteoporosis. After receiving results from the investigations described below in twin B, the PB was reinvestigated and a *JAK2* V617F mutation with an allelic frequency of 3% was found. No other symptoms or abnormal findings pointing to an SM with an associated clonal hematologic non-MC lineage disease (SM-AHNMD) were found, and twin A was classified as having ISM, fulfilling the major as well as all minor World Health Organization criteria. At the time of writing, the patient is feeling well, and the mild mediator-related symptoms are well controlled on fexofenadine. Twin A has 3 unaffected children aged 48, 46, and 39 years.

Twin B was referred back at the age of 68 years with tiredness and light anemia, thrombocytopenia, and neutropenia. On objective examination, typical symmetric UP skin lesions could be found on the femora, trunk, and upper arms accompanied by teleangiectasias (Fig 1, *B*).

A new BM biopsy showed changes compatible with chronic myelomonocytic leukemia (CMML) type II with 13% blasts in the BM and concomitant SM with accumulation of spindle-shaped $CD25^+$ MCs. Flowcytometric analysis of BM revealed 0.01% $CD25^+$ and $CD2^+$ MCs. Mutation analysis revealed the *KIT* D816V mutation in BM and PB with an allelic frequency of 8% and 3%, respectively. In addition, a *JAK2* V617F mutation could be found with an allelic frequency of 0.25% in BM and 0.06% in PB. Basal tryptase level was 13 μg/L. A bone mineral density scan showed osteopenia.

Thus, twin B was now classified as having SM-AHNMD with a CMML type II developed from an ISM fulfilling the major as well as 3 minor World Health Organization criteria for SM. Treatment with azacitidine for the CMML type II has been commenced. Mediator-related symptoms are minor and well controlled on cetirizine on demand. Twin B has 2 unaffected sons aged 40 and 43 years. Findings in both twins are summarized in Table I.

TABLE I. Findings in both twins summarized

	Twin A	Twin B
Age at onset of UP skin lesions (y)	38	40
Anaphylaxis	No	No
Skin symptoms	Yes	Yes
Musculoskeletal pain	Yes	Yes
Gastrointestinal symptoms	Yes	Yes
Neurologic symptoms	No	No
Basal s-tryptase level (μg/L)	44	13
Bone mineral density *t* score (lumbar spine)	−3.0 (osteoporosis)	−2.3 (osteopenia)
Pathological fracture	No	No
Skin biopsy	UP with $CD25^+$ MCs	UP with $CD25^+$ MCs
Duodenal biopsy	Normal	Normal
BM biopsy at age 50 y	SM*	SM*
BM biopsy present	SM*	SM* + CMML type II
KIT D816V	Positive	Positive
JAK2 V617F	Positive	Positive
FIP1L1-PDGFRA	Negative	Negative
SM classification†	Indolent SM	SM-AHNMD

WHO, World Health Organization.
*WHO criteria fulfilled.
†According to WHO classification.

To our knowledge, this is the first report on twins with SM. SM is normally considered a sporadic, nonhereditary myeloproliferative neoplasia (MPN) related to an activating, somatic *KIT* D816V mutation—and evidence of familial forms of SM is lacking.[2] Familial occurrence of cutaneous mastocytosis is on the other hand well described, including rare case reports in twins.[3,4] In most of these cases, it has not been possible to demonstrate any primary genetic defect and only few reports exist on germline *KIT* mutations in familial cutaneous mastocytosis.[5] Bodemer et al[6] in 2010 reported the finding of somatic *KIT* D816V mutations in 2 brothers with cutaneous mastocytosis without evidence of a germline mutation.

In the present case, both monozygotic twins carry somatic *KIT* D816V mutations with low allelic frequencies and concomitant somatic *JAK2* V617F mutations. The probability that these somatic mutations have occurred as independent genetic events in both twins is negligible; hence, the findings must reflect that a germline mutation in another gene or another genetic mechanism is involved, predisposing the twins to the acquired mutations.

A parallel to this situation is found in the familial occurrence of MPNs, which are traditionally divided into 2 categories.[7] One is the classical hereditary type with simple Mendelian transmission, in which an inherited mutation of a gene directly involved in hematopoiesis leads to single-cell lineage proliferation, for example, the erythropoietin receptor gene leading to hereditary erythrocytosis. The other category of familial MPN is characterized by an inherited predisposition to acquired, somatic mutations leading to an MPN clinically indistinguishable from a sporadic MPN. In several families with clustering of MPNs, the occurrence of somatic *JAK2* V617F as well as somatic *TET2* mutations has been described.[7] The mode of inheritance in these families is complex and with low penetrance, and the primary genetic defect or mechanism is yet to be elucidated.

The mutational findings in the twins described here are compatible with the findings in the latter type of familial MPN. As the parents nor other family members were reported having MPN, there is a possibility that the common genetic change rendering the twins susceptible to somatic mutations may be the result of an acquired mutation at an early embryonal stage. A follow-up of the as-of-yet clinically unaffected offspring will be performed.

While the role of the *JAK2* V617F mutation in several MPNs including polycythemia vera, essential thrombocytemia, and primary myelofibrosis is established, only little is known about its prevalence and role in SM and SM-AHNMD. The mutation has been described in SM patients with concomitant primary myelofibrosis or polycythemia vera.[8,9] It is possible that the occurrence of a *JAK2* V617F mutation in ISM increases the risk of progression into more aggressive forms of SM including SM-AHNMD; however, this has not been investigated systematically. In the actual cases described, it cannot be excluded to be a nonpathogenic epiphenomenon with regard to twin B's development of CMML, since CMML is not typically associated with *JAK2* mutations and since a higher allelic frequency should have been expected if the

CMML clone carries the mutation. Nevertheless, twin A must be anticipated to be at risk for developing SM-AHNMD and will be monitored closely.

Of notice is the only slightly elevated basal tryptase level in twin B. In our experience, tryptase levels below 20 μg/L is not a rare finding in patients fulfilling other World Health Organization criteria for SM. However, the tryptase criterion for SM should anyhow not be applied in the case of SM-AHNMD.

In conclusion, we present a pair of monozygotic twins with adult-onset SM with evolution over a 30-year course into stable ISM (twin A) and SM-AHNMD (twin B). The somatic mutations in *KIT* and *JAK2* found in the twins are probably secondary genetic events resulting from a genetic predisposition to acquired mutations as described in familial cases of MPN.

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REFERENCES

1. Kristensen T, Vestergaard H, Moller MB. Improved detection of the *KIT* D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. J Mol Diagn 2011;13:180-8.
2. Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112:946-56.
3. de la Sotta P, Romero WA, Kramer D, Cárdenas C, González S. Cutaneous mastocytosis in twins: multiple mastocytomas and urticaria pigmentosa in two pairs of monozygotic twins. Pediatr Dermatol 2011;28:585-7.
4. Quaglino P, Mola F, Peroni A, Ortoncelli M, Di Bello C, Savoia P, et al. Adult-onset cutaneous mastocytosis in monozygotic twins. J Am Acad Dermatol 2011;65:680-1.
5. Wasag B, Niedoszytko M, Piskorz A, Lange M, Renke J, Jassem E, et al. Novel, activating KIT-N822I mutation in familial cutaneous mastocytosis. Exp Hematol 2011;39:859-65.
6. Bodemer C, Hermine O, Palmérini F, Yang Y, Grandpeix-Guyodo C, Leventhal PS, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. J Invest Dermatol 2010;130:804-15.
7. Skoda RC. Hereditary myeloproliferative disorders. Haematologica 2010;95:6-8.
8. Sotlar K, Bache A, Stellmacher F, Bültmann B, Valent P, Horny HP. Systemic mastocytosis associated with chronic idiopathic myelofibrosis: a distinct subtype of systemic mastocytosis associated with a clonal hematological non-mast cell lineage disorder carrying the activating point mutations *KIT*D816V and *JAK2*V617F. J Mol Diagn 2008;10:58-66.
9. Thachil J, Hawkins S, Woodcock B. JAK-2 positive myeloproliferative neoplasm co-existing with systemic mastocytosis. Br J Haematol 2011;152:675.

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