A new germline mutation in KIT associated with diffuse cutaneous mastocytosis in a Chinese family

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Summary

Diffuse cutaneous mastocytosis (DCM) is an extremely rare disease characterized by massive proliferation of mast cells infiltrating the entire skin. We report a Chinese family with indolent DCM, and detection of a new germline KIT mutation located in the fifth immunoglobulin-like loop of the KIT protein, which probably results in a gain-of-function effect and consequent overactivation of mast cells. Our report expands the knowledge of correlations between the genotype of KIT mutations and the phenotype of DCM.

Report

The proband was a 35-year-old man of Chinese Han origin. He was born to nonconsanguineous healthy parents after an uneventful full-term pregnancy. At 5 months of age, he was reported to have intermittent blistering around his neck induced by scratching. The bullous lesions later spread and became generalized to involve his whole trunk and limbs thereafter. These mostly resolved by the time he was 2 years of age, followed by diffuse thickening of the skin with a reddish-brown colour and a ‘grained-leather’ appearance. By the time he reported us, apart from repeated pruritus and weals induced by hot stimuli or exercise, the patient experienced blistering only after hard friction or severe trauma.

On physical examination, the patient was found to have several vesicles on his proximal upper arm, and large coalesced plaques with a grained-leather appearance on his trunk (Fig. 1a,b). Cutaneous hyperpigmentation was seen in the flexure areas. A positive Darier sign or dermographism was detected all over his body. The patient denied a history of anaphylactic shock, recurrent headache, diarrhoea, nausea or wheezing.

On histological examination of a biopsy taken from a plaque on the patient’s trunk, a dense infiltration of mature mast cells was seen in the superficial and mid dermis (Fig. 1d). Bone-marrow biopsy was not performed. Laboratory investigations found no abnormalities in the patient’s full blood profile or serum biochemical
profile. Chest radiography and abdominal ultrasonography also gave normal results.

The patient reported that his 8-year-old son experienced nearly identical symptoms, whereas the patient’s parents and his daughter appeared healthy (Fig. 1c). The patient was started on treatment with oral antihistamine agents, which partially controlled the symptoms.

It was decided to carry out genetic studies, which were approved by the Clinical Research Ethics Committee of Peking University First Hospital, and informed consent for participation and sample collection was obtained from all participants.

Peripheral blood leucocytes were obtained from the proband and his family members, and genomic DNA was extracted. We sequenced all exons of the KIT gene, and identified a heterozygous mutation c.1352C>G in exon 9 (Fig. 2a), which results in the substitution of a cystine for a serine at codon 451 (p.S451C). The mutation was also present in the patient’s affected son but not in his unaffected daughter or parents, or in 200 unrelated ethnically matched normal individuals. The S451 residue is highly conserved across species.

DCM is an extremely rare, clinically heterozygous disease that accounts for < 10% of all cases of mastocytosis. Two clinical variants of DCM in infants have been described in the literature: the large haemorrhagic bullous variant and the infiltrative small vesicular variant. Onset of DCM is usually within the first 6 months, with extensive bullous lesions being the most frequently reported initial symptom. Infants with DCM at this stage were often misdiagnosed as having epidermolysis bullosa, impetigo bullosa or staphylococcal scalded skin syndrome. However, in DCM, the blistering has a tendency to cease with time after 2 years, followed by the distinctive appearance of a grained-leather texture of the skin. In addition, a positive Darier sign or dermographism, as well as mediator-related symptoms, including itching, flushing, diarrhoea, hypotension or even anaphylactic shock, are highly indicative of mastocytosis. Histopathological findings of dense infiltration of mature mast cells help to exclude other differential diagnoses.

Because it is a generalized and severe form of CM, whether DCM will finally progress to SM and involve various internal organs, or remain indolently restricted to the skin is uncertain. In spite of several reported cases of SM presenting with diffuse cutaneous involvement, none of the 10 cases of DCM in a study with a follow-up of up to 8 years progressed to SM. In another study reporting a family with DCM affecting three generations of five individuals, only one adult patient had mild and static mast-cell infiltration of the appendix and bone marrow, whereas the other four had no systemic involvement. Consistent with these studies, our proband, as well as his affected son, showed partial remission of the symptoms without any evidence suggestive of SM, which may suggest a favourable prognosis for DCM.
The proto-oncogene KIT, encoding a tyrosine kinase receptor for stem cell factor (SCF), is mainly expressed in a small spectrum of cells including mastocytes and melanocytes. KIT contains five immunoglobulin-like loops in the extracellular domain, as well as a transmembrane domain, a juxtamembrane autoinhibitory domain, and a tyrosine kinase domain. The S451 residue is located in the fifth immunoglobulin-like loop, which plays a role in stabilizing SCF-induced KIT dimers and in proteolytic cleaving of the dimers from the cell surface. The mutation p.S451C may possibly result in inability of proteolytic cleaving of KIT dimers, leading to persistent activation of KIT and subsequent increased proliferation of mast cells in the patients. To our knowledge, only four mutations in the KIT gene have been reported in DCM to date, which comprised three somatic mutations (p.D816Y, p.D816I and p.D816V) in sporadic cases and one germline mutation (p.A533D) in one family (Fig. 2b); the mutation reported in the current study (p.S451C) is the second germline mutation reported.4,10 Because of its rarity, the exact correlation between the genotype of KIT mutations and the phenotype of DCM remains largely elusive, and our report, together with other studies in the future, will help to, at least in part, clarify this issue.

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Learning points
- Most sporadic cases of CM are caused by somatic mutations in the KIT gene, while familial cases were attributed to germline KIT mutations.
- Despite the widespread infiltration of mast cells in skin, DCM can remain indolent until adulthood without systemic involvement.
- Nevertheless, careful examination is necessary in patients with DCM to rule out involvement of the internal organs.

References
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