

Familial Urticaria Pigmentosa: Report of a Family and Review of the Role of KIT Mutations

Nicole M. Fett, MD,*† Joyce Teng, MD, PhD,‡ and B. Jack Longley, MD‡

Abstract: Cutaneous mastocytosis is a rare clinically heterogeneous disorder characterized by mast cell infiltration. Mastocytosis affects both children and adults and has been reported to occur in families. Recent data suggest that mutations in the *c-kit* proto-oncogene are causative of mastocytosis not only in adults but in children and familial cases as well; however, mutation analysis other than D816V is not widely available, making detection of causative mutations problematic. We present the case of a 33-year-old man with a 30-year history of persistent urticaria pigmentosa and his 2 affected children. Sequencing of KIT exons 8, 10, 11, and 17 was carried out on a skin biopsy specimen and mucosal swabs of the incident case and was negative for known KIT mutations. Additional work-up was deferred by the family. Presentation of this familial case of urticaria pigmentosa demonstrates the complexity of genetic evaluation in clinical settings. It suggests that mutations other than those reported in exons 8, 10, 11, and 17 may also result in familial mastocytosis. Presentation of this case also allows for review of the mechanism of action of causative KIT mutations and the recent literature supporting KIT mutations in childhood and familial mastocytosis.

Key Words: mastocytosis, urticarial pigmentosa, *c-kit* proto-oncogene, KIT tyrosine kinase

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INTRODUCTION

Urticaria pigmentosa (UP) is a cutaneous form of mastocytosis that presents as brown macules that urticate with friction (Darier sign). UP usually occurs sporadically. We present herein 3 cases of UP within one family and review the known etiologic mutations in adult, childhood, and familial cases of cutaneous mastocytosis.

From the *Department of Dermatology, Philadelphia VA Medical Center, Philadelphia, PA; †Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, PA; and ‡Department of Dermatology, University of Wisconsin Madison Hospital and Clinics, Madison, WI. The authors declare no conflicts of interest.

Reprints: Nicole M. Fett, MD, Department of Dermatology, University of Pennsylvania, Perelman Center for Advanced Medicine, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104 (e-mail: nicole.fett@uphs.upenn.edu).

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REPORT OF CASES

Case 1

A 3-year-old girl was born with multiple light brown urticating papules that have rapidly increased in number since the age of 2 years. She has no associated systemic manifestations. Physical exam reveals a healthy appearing 3-year-old girl with multiple flesh colored to brown papules scattered over her extremities, trunk, and along her hairline with positive Darier sign (Fig. 1). No organomegaly or lymphadenopathy was appreciated. Complete blood count with differential, assessed during a preceding illness, was normal.

Case 2

Case 1's brother is a healthy 2-year-old boy, who began developing brown urticating macules on his back starting at 10 months of age. He has no associated systemic manifestations. Physical exam reveals a healthy appearing 2-year-old boy with scattered brown macules on his trunk with a positive Darier sign (Fig. 2). No organomegaly or lymphadenopathy was appreciated.

Case 3

A 33-year-old man, father of the cases 1 and 2, who was diagnosed with cutaneous mastocytosis at the age of 3. He presented with erythematous urticating papules on his scalp and later formed similar confluent lesions over his chest, abdomen, and bilateral flanks that have persisted into adulthood. He reports multiple near-syncopal episodes throughout his life. He has loose stools occasionally but does not have problems with swallowing, wheezing, or flushing. Physical exam reveals confluent brown papules on the scalp and trunk with a positive Darier sign (Fig. 3).

No organomegaly or lymphadenopathy was appreciated. Skin biopsy reveals sheets of mast cells (Fig. 4). Serum tryptase level was <20 ng/mL and complete blood count was normal. Sequencing of KIT exons 8, 10, 11, and 17 was carried out on the skin biopsy specimen and mucosal swabs and was negative for known mutations. The patient deferred bone marrow biopsy and additional evaluation for KIT mutations. Cases 1 and 2 did not undergo additional work-up because of parent preference.

COMMENT

Cutaneous mastocytosis is a rare clinically heterogeneous disorder caused by mast cell proliferation, infiltration, and degranulation. Overproduction of mast cells is caused by gain of function mutations in the *c-kit* proto-oncogene,



FIGURE 1. Three-year-old girl with multiple flesh colored to brown papules scattered over her face and trunk with a positive Darier sign.



FIGURE 2. Two-year-old boy with scattered brown macules on his trunk with a positive Darier sign.

resulting in constitutive activation of KIT tyrosine kinase.¹ The KIT tyrosine kinase is made up of 2 identical transmembrane proteins that dimerize in the presence of stem cell factor. Each transmembrane protein of the KIT tyrosine kinase is composed of an extracellular binding domain with 5 immunoglobulin-like motifs (encoded by exons 1 through 9), a transmembrane domain (encoded by exon 10), an auto-inhibitory juxtamembrane domain (encoded by exon 11), and 2 kinase domains (encoded by exons 12 and 13, and exons 16 through 20).² Dimerization of the 2 transmembrane proteins in the presence of stem cell factor activates the KIT tyrosine kinase, decreasing apoptosis and increasing cellular proliferation through downstream signaling via the PI3K/Akt, Jak/Stat, Src, and Ras pathways.³ Two heterozygous activating mutations in KIT (D816V in exon 17 and V560G in exon 11) have been identified in a human mast cell line.⁴ Almost all sporadic adult cases of mastocytosis have been found to carry the D816V mutation⁵; therefore, adult mastocytosis is considered to be a chronic, clonal myeloproliferative disorder caused by a somatic gain of function mutation in KIT.⁶ Historically, sporadic childhood mastocytosis was classified as a reactive disorder based on its clinical behavior (that of spontaneous resolution) and the lack of confirmed KIT mutations. However, recent data have revealed *c-kit*

proto-oncogene mutations with regularity in children with cutaneous mastocytosis as well.^{7–9} Yangihari et al⁸ studied 14 children between the ages of 0 and 16 years and found mutations at codon 816 in 86% of them. Verzijl et al⁹ identified mutations at the 816 codon in 2 of 12 children with sporadic mastocytosis. In the largest series to date, Bodemer et al⁷ studied 50 children with cutaneous mastocytosis aged 0–16 years and found mutations in KIT in 86% of them. Of those children with KIT mutations, 35% had the D816V mutation and 44% had mutations in exons 8 and 9 (corresponding to the fifth immunoglobulin binding area) and exon 11 (corresponding to the juxtamembrane domain).⁷ Thirteen percent of the children studied reported having an affected family member.⁷ In 2 of 4 familial cases, the D816V mutation was found.⁷ These data suggest that sporadic childhood mastocytosis is also a clonal myeloproliferative disorder. What remains unknown is why children seem to have resolution of their disease. In an effort to explain the wide range of clinical phenotypes because of a single gene mutation, Daley et al¹⁰ assessed 36 adult patients with mastocytosis for the Q576R polymorphism of the interleukin-4 receptor. Interleukin-4 is required for the differentiation of mast cell progenitor cells into mast cells. Daley et al¹⁰ found that those patients with the Q576R interleukin-4 receptor polymorphism had less severe disease than those patients with wild-type



FIGURE 3. Thirty-three-year-old man with scattered brown macules on his trunk with a positive Darier sign.

interleukin-4 receptors. Polymorphisms in other mast cell growth factors, such as platelet-derived growth factor (PDGF), interleukin-3, and interleukin-6 may similarly confer differences in disease phenotype.

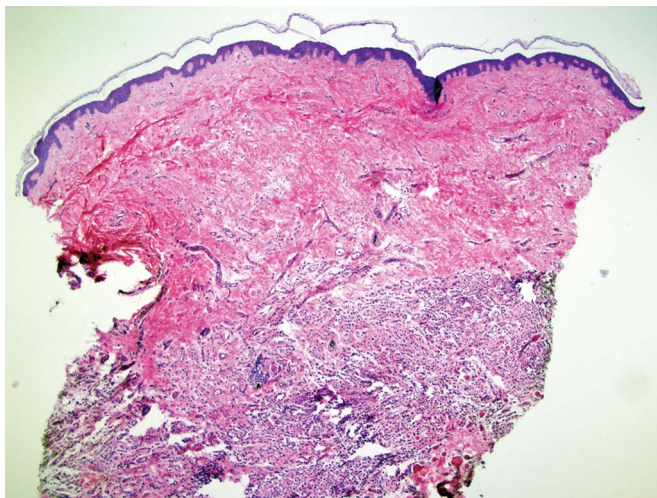


FIGURE 4. Magnification (×20) of hematoxylin and eosin stain reveals sheets of mast cells in the dermis.

Familial cutaneous mastocytosis is being reported with increased frequency. All subtypes of cutaneous mastocytosis (mastocytomas, UP, telangiectasia macularis eruptiva perstans, and diffuse mastocytosis) have been reported to occur in multiple generations in families.^{11–14} The most common inheritance pattern described is autosomal dominance with incomplete penetrance.^{15–18} The etiology of familial mastocytosis is likely a germline mutation in the *c-kit* proto-oncogene, with several mutations described to date.^{7,13,19–21} Germline mutations involve all cells of the body. Germline gain of function mutations in KIT theoretically predispose these families to additional tumors, particularly gastrointestinal stromal tumors, germ cell tumors, and core-binding factor acute myeloid leukemia.² Families with concomitant hereditary mastocytosis and gastrointestinal stromal tumors have been described with mutations in KIT in exon 8 (corresponding to the extracellular juxtamembrane domain) and exon 11 (corresponding to the intracellular juxtamembrane domain).^{19,21} Despite the theoretical increased risk of systemic malignancy in families with mastocytosis, few such concomitant malignancies have been reported to date.^{19,21}

Our increased understanding of the pathogenesis of mastocytosis has led to trials of targeted therapy. Imatinib, a tyrosine kinase inhibitor that targets Bcl-Abl, PDGFR- α and PDGFR- β , and KIT, has been effectively used in treatment of mast cell disease in patients with preserved kinase binding sites (ie, those with mutations that are at sites other than D816 and those that do not affect the kinase site, such as mutations in the juxtamembrane regions).^{20,22} Patients with D816V mutations have altered KIT kinase sites and therefore do not respond to imatinib.²⁰

In conclusion, detection of mutations in KIT in adult, childhood, and familial mastocytosis patients reveal that mastocytosis is a clonal myeloproliferative disease. Similar mutations in KIT result in widely varied clinical presentations, suggesting that other factors affect disease course and prognosis. Additionally, different mutations within the *c-kit* gene may result in similar clinical phenotypes that respond very differently to therapy. Commercially available detection of KIT mutations via allele-specific polymerase chain reaction is currently limited to detection of D816V. Sequencing of commonly involved KIT exons is available in research laboratories and some commercial laboratories. Given the high sensitivity of sequencing of germline mutations, absence of mutations in exons 8, 10, 11, and 17 in the case presented clearly illustrates that other mutations of *c-kit* may cause familial cutaneous mastocytosis. This case highlights the complexity of genetic evaluation and difficulty in genotype–phenotype correlation.

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