

Itchy Red-Brown Spots on a Child

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A 5-year-old boy presented with red-brown spots diffusely spread over the body that were present since birth. There were no subjective symptoms, except for rare instances of flushing, itching, and urtication following hot baths and abrasive scrubs. Dermatologic examination revealed widespread brown polymorphic macules and papules of varying sizes on the forehead, neck, torso, and extremities. Physical examination was otherwise normal.

WHAT'S YOUR DIAGNOSIS?

- cutaneous mastocytosis
- histiocytosis X
- LEOPARD syndrome
- neurofibromatosis
- xanthoma disseminatum

PLEASE TURN TO **PAGE 257** FOR THE DIAGNOSIS

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The authors report no conflict of interest.

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doi:10.12788/cutis.0643

THE DIAGNOSIS:

Maculopapular Cutaneous Mastocytosis
(Urticaria Pigmentosa)

A stroke test revealed urtication at the exact traumatized site (Figure). A skin biopsy performed 2 years prior by another physician in the same hospital had revealed mast cell infiltration of virtually the entire dermis. The diagnosis was then firmly established as maculopapular cutaneous mastocytosis (CM) (also known as urticaria pigmentosa) with both the pathology results and a confirmative stroke test, and no additional biopsy was attempted. Serum IgE and tryptase levels were within the reference range. General recommendations about the avoidance of trigger factors were given to the family, and a new-generation H₁ blocker antihistaminic syrup was prescribed for flushing, itching, and urtication.

Mastocytosis is a canopy term for a heterogeneous group of disorders caused by clonal proliferation and accumulation of abnormal mast cells within the skin and visceral organs (ie, bone marrow, liver, spleen, lymph nodes, gastrointestinal tract). Cutaneous mastocytosis, the skin-restricted variant, is by far the most common form of childhood mastocytosis (90% of mastocytosis cases in children)¹ and generally appears within the first 2 years of life.¹⁻⁷ Pediatric CM usually is a benign and transient disease with an excellent prognosis and a negligible risk for systemic involvement.^{2,3,5}

The pathogenesis of CM in children is obscure¹; however, somatic or germline gain-of-function mutations of the *c-KIT* proto-oncogene, which encodes KIT (ie, a tyrosine kinase membrane receptor for stem cell factor), may account for most pediatric CM phenotypes.^{1,3,6} Activating *c-KIT* mutations leads to constitutive activation of the KIT receptor (expressed on the surface membrane of mast cells) and instigates autonomous (stem cell factor-independent) clonal proliferation, enhanced survival, and accumulation of mast cells.²

Maculopapular CM is the most common clinical form of CM.^{2,4,5} In children, maculopapular CM usually presents with polymorphous red-brown lesions of varying sizes and types—macule, papule, plaque, or nodule—on the torso and extremities.¹⁻⁵ The distribution may be widespread and rarely is almost universal, as in our patient.² Darier sign typically is positive, with a wheal and flare developing upon stroking or rubbing 1 or several lesions.¹⁻⁶ The lesions gradually involute and often spontaneously regress at the time of puberty.^{1-3,5-7}

The clinical signs and symptoms of mastocytosis are not only related to mast cell infiltration but also to mast cell activation within the tissues. The release of intracellular mediators from activated mast cells may have local and/or systemic consequences.^{4,7} Erythema,

edema, flushing, pruritus, urticaria, blistering, and dermatographism are among the local cutaneous symptoms of mast cell activation.^{2-4,7} Systemic symptoms are rare in childhood CM and consist of wheezing, shortness of breath, nausea, vomiting, reflux, abdominal cramping, diarrhea, tachycardia, hypotension, syncope, anaphylaxis, and cyanotic spells.¹⁻⁷ An elevated serum tryptase level is an indicator of both mast cell burden and risk for mast cell activation in the skin.^{4,7}

Treatment of pediatric CM is conservative and symptomatic.³ Prevention of mediator release may be accomplished through avoidance of trigger factors.¹ Alleviation of mediator-related symptoms might be attained using H₁ and H₂ histamine receptor blockers, oral cromolyn sodium, leukotriene antagonists, and epinephrine auto-injectors.^{1-3,5} Short-term topical or oral corticosteroids; calcineurin inhibitors (eg, pimecrolimus, tacrolimus); phototherapy; psoralen plus UVA; omalizumab; and innovative agents such as topical miltefosine, nemolizumab (an IL-31 antagonist), kinase inhibitors such as midostaurin, and tyrosine kinase inhibitors such as imatinib and masitinib may be tried in refractory or extensive pediatric CM.^{1,2,5,6}

Although several disorders in childhood may present with red-brown macules and papules, Darier sign is unique to cutaneous mastocytosis. A biopsy also will be helpful in establishing the definitive diagnosis.



The Darier sign was elicited after stroking the skin with a blunt instrument. Bandlike urtication and peau d'orange appearance was noted.

Histiocytosis X (also referred to as Langerhans cell histiocytosis) is the most common proliferative histiocytic disorder. Cutaneous lesions are polymorphic and consist of seborrheic involvement of the scalp with yellow, scaly or crusted papules; eroded patches; pustules; vesicles; petechiae; purpura; or red to purplish papules on the groin, abdomen, back, or chest.⁸

LEOPARD syndrome (also known as Noonan syndrome with multiple lentiginos) is an acronym denoting lentiginos (multiple), electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retarded growth, and deafness (sensorineural). The disorder is caused by a genetic mutation involving the *PTPN11* gene and currently is categorized under the canopy of RASopathies. Cutaneous findings consist of lentiginous and café-au-lait macules and patches.⁹

Neurofibromatosis is a genetic disorder with a plethora of cutaneous and systemic manifestations. The type 1 variant that constitutes more than 95% of cases is caused by mutations in the *neurofibromin* gene. The main cutaneous findings include café-au-lait macules, freckling in axillary and inguinal locations (Crowe sign), and neurofibromas. These lesions may present as macules, patches, papules, or nodules.¹⁰

Xanthoma disseminatum is a rare sporadic proliferative histiocyte disorder involving the skin and mucosa. The disorder may be a harbinger of diabetes insipidus. Cutaneous

lesions consist of asymptomatic, symmetrical, discrete, erythematous to yellow-brown papules and nodules.¹¹

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