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Mast cell disorders: Kids are not just little people

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Abstract Cutaneous mastocytosis is characterized by a pathologic increase in mast cells in the skin and may also involve extracutaneous organs. Symptoms, which are triggered by mast cell degranulation, vary depending on the burden of skin disease and the presence of extracutaneous disease. The clinical presentation, risk of systemic disease, pathogenesis, prognosis, and treatment options differ, largely depending on age at presentation. In the pediatric population, spontaneous remission is typical, generally by puberty, whereas in adults, progression is observed. Extracutaneous involvement and associated hematologic disorders seldom occur in children, as opposed to adults. It is therefore important to avoid overreliance on adult-based approaches to management of cutaneous mastocytosis in the pediatric population. We focus on differences in presentation, workup, and management of pediatric- and adult-onset cutaneous mast cell disorders.

Introduction

Cutaneous mastocytosis is characterized by a pathologic accumulation of mast cells in the skin. Presentation varies from a solitary plaque to widespread cutaneous disease, with or without systemic involvement. A number of classification systems exist, often making it confusing when evaluating patients, especially children with limited skin disease. Characteristic clinical presentations in children include urticaria pigmentosa (UP), solitary mastocytoma, and, less commonly, diffuse cutaneous mastocytosis (DCM). Conversely, telangiectasia macularis eruptiva perstans (TMEP), a common presentation of cutaneous mastocytosis in adults, rarely occurs in children.

The majority of patients with mastocytosis appear to be children (nearly two-thirds of published cases).[1,2] The course of childhood-onset mast cell disease is variable but generally characterized by spontaneous remission by puberty.[3] Adult-onset disease tends to be chronic and may progress to systemic involvement.

Until recently, pediatric mastocytosis was generally thought to be a reactive rather than clonal disease.[4] Evidence in support of this theory included spontaneous clearance of lesions by puberty and absence of adult type c-KIT mutations. More recent evidence, however, suggests otherwise, with pediatric patients expressing c-KIT activating mutations.[5]

How is mastocytosis classified?

Mast cell disease represents a heterogeneous group of disorders that are all characterized by an abnormal proliferation of mast cells in the skin, bone marrow, lymph nodes, liver, or spleen. The heterogeneity in clinical presentation led to the currently accepted World Health Organization classification as cutaneous mastocytosis; indolent systemic mastocytosis; systemic mastocytosis with an associated clonal hematological non–mast cell lineage disease; aggressive systemic mastocytosis; mast cell leukemia; mast cell sarcoma; and extracutaneous

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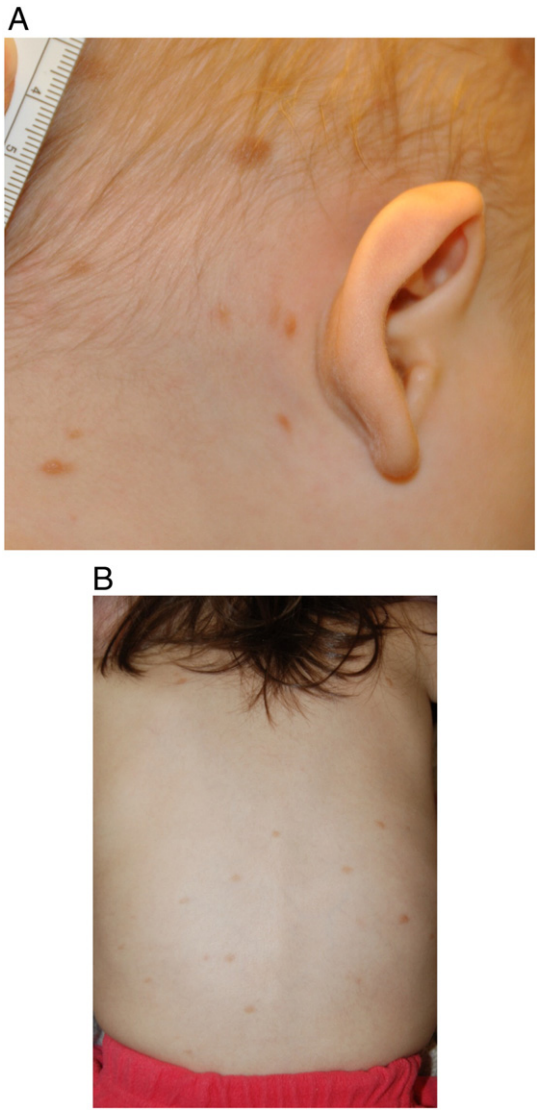

Fig. 1 A, Urticaria pigmentosa in a 2-year-old child. Note the multiple tan-brown papules on the neck. B, Multiple hyperpigmented papules on the trunk of an infant with maculopapular cutaneous mastocytosis (urticarial pigmentosa-type).

mastocytoma.[6] The term *cutaneous mastocytosis* indicates the presence of mastocytosis in skin only and is typical of mastocytosis in the pediatric age group. Advances in laboratory detection of mast cell proliferation have led to the conclusion that the vast majority of patients with adult-onset mastocytosis in skin also have evidence of subclinical systemic disease. Indolent systemic mastocytosis is the most common subtype of systemic mastocytosis, and affected patients have no evidence of extracutaneous organ dysfunction. A small number of patients with indolent systemic mastocytosis may present with only systemic findings and no skin disease. Smoldering systemic mastocytosis is a variant of indolent mastocytosis, which has a higher mast cell burden. For example, hepatosplenomegaly without impaired liver function, ascites, portal hypertension, or hypersplenism is a feature of smoldering systemic mastocytosis. Patients with aggressive systemic mastocytosis

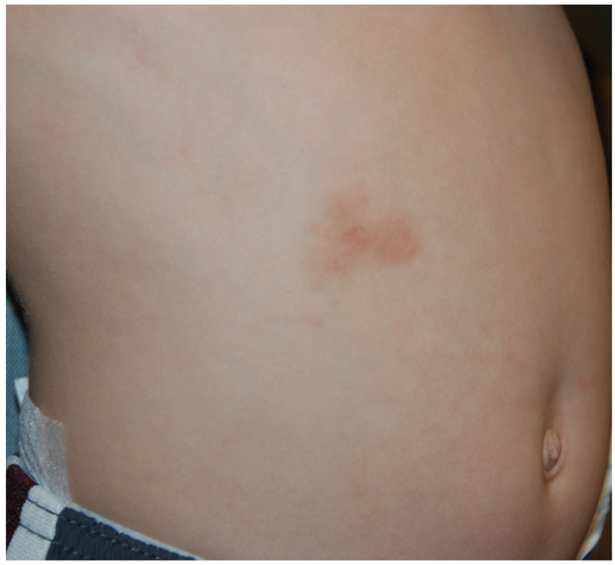

Fig. 2 Solitary mastocytoma on the abdomen of a boy.

have evidence of organ dysfunction but no evidence of mast cell leukemia.[6]

The classification of mast cell disease in children is similar, although some authorities prefer a simpler classification system, excluding mast cell sarcoma and extracutaneous mastocytoma, because these are seldom observed in the pediatric population.[7] Because mast cell disease in children is generally limited to the skin, alternative classification systems have been proposed for childhood disease, largely based on age and clinical features. One proposed classification is based on age at onset of disease: newborn period, infancy (<6 months of age), and childhood (6 months to 16 years).[8] A second proposed pediatric classification is a descriptive one, highlighting the clinical presentation in children: maculopapular cutaneous mastocytosis (MPCM; plaque-variant or UP) (Figure 1A and B); nodular (solitary or multiple mastocytomas) (Figure 2); diffuse cutaneous mastocytosis (Figure 3); and telangiectatic cutaneous mastocytosis. MPCM itself encompasses a spectrum of disease presentation, ranging from small, brown macules and papules (so-called UP) to plaque-type, which is characterized by multiple tan-orange plaques, often several centimeters in diameter. Perhaps, a more simplistic but practical classification in children is cutaneous mastocytosis with or without systemic involvement.

Molecular studies suggest that activating mutations of the c-KIT stem cell factor receptor are expressed in some forms of mastocytosis, mostly in exon 17 (D816 V), particularly in adult patients with systemic involvement. Until recently, c-KIT mutations had not been identified in pediatric patients, except for a small subset with systemic disease. More recent literature suggests otherwise, with the majority of pediatric patients expressing an activating mutation in c-KIT, although not necessarily D816 V. Correlation between genotype and phenotype is not yet apparent. This body of work has led to a proposal that any classification of mastocytosis incorporate molecular genetic analysis, but it seems likely that such a