Pediatric Expression of Mast Cell Activation Disorders

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KEYWORDS

• Mastocytosis • Mast cell activation • Mast cell activation disorders • *KIT* mutations • Urticaria pigmentosa • Tryptase • Anaphylaxis

KEY POINTS

- Symptoms in pediatric mastocytosis are often limited to the skin, and presence of skin lesions (urticaria pigmentosa) is the key feature for diagnosis.
- In most affected children, a somatic mutation in the *KIT* gene can be found; however, the *KIT* D816V mutation is only detected in one-third of pediatric patients.
- Extracutaneous symptoms, including anaphylaxis, are rare as opposed to in adult disease and mainly reported in children with very extensive skin involvement, bullous lesions, and high mast cell burden.
- Frequent triggers for exacerbations include friction, heat, fever, and insect stings; however, counseling in regard to avoidance of other potential mast cell activation triggers should be individualized after careful evaluation.
- In approximately 70% to 80% of children, the disease resolves by adulthood and risk for persistent disease may be related to the presence of small, monomorphic skin lesions; disease onset after 3 years of age; detection the *KIT* D816V mutation; high mast cell burden; and systemic disease. Further research is, however, needed including long-term follow-up studies.

Conflicts of Interest: Authors declare no relevant conflicts of interest in relation to this article. Funding: M. Carter is supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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Immunol Allergy Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.iac.2018.04.009
immunology.theclinics.com

INTRODUCTION

Mast cell activation disorders (*MCADs*) is a term proposed to cover diseases and conditions related to activation of mast cells (MCs) and effects of released MC mediators. In its broadest sense, the term, therefore, encompasses a wide range of diseases from allergic asthma to rhinoconjunctivitis, urticaria, food allergy, and anaphylaxis, among many other conditions where MC activation (MCA) may contribute to the pathogenesis.[1]

This article focuses on mastocytosis and gives an overview of its presentations, challenges, and controversies from a pediatric perspective. Mastocytosis is an unusual, heterogeneous group of diseases characterized by the proliferation and accumulation of MCs in body tissues.[2,3] Clinical manifestations depend on the localization of MC infiltration and effects of mediators released from activated MCs, that is, MCA.

The World Health Organization (WHO) classifies mastocytosis into 7 subcategories, including cutaneous mastocytosis (CM)—where MC accumulation is limited to the skin—and systemic mastocytosis (SM)—where internal organs are involved.[3–5] Although most adults (>95%) with mastocytosis are diagnosed with SM when fully investigated, with diverse clinical manifestations ranging from mild to very severe or potentially life-threatening, the disease manifestations in pediatric mastocytosis are typically limited to the skin, that is, CM, and symptoms are often mild (**Table 1**), although gastrointestinal (GI) symptoms are encountered.[6]

Several areas of pediatric mastocytosis are in need of research, including the elucidation of mechanisms involved in the peculiar spontaneous disease resolution observed in approximately 70% to 80% of affected children during adolescence as opposed to adult-onset mastocytosis, which is a chronic disease.[7,8]

EPIDEMIOLOGY

Epidemiologic aspects of pediatric mastocytosis have not been studied in detail. In a population-based study, the prevalence of adult mastocytosis was found to be 10 in 100.000 with a slight female predominance.[9] The incidence and prevalence of pediatric mastocytosis are estimated to be overall similar to or higher than adult mastocytosis.[10] In the adult population, the disease is likely highly underdiagnosed due to a lack

Table 1
Comparison of adult mastocytosis and pediatric mastocytosis

	Pediatric Mastocytosis	Adult Mastocytosis
Most frequent disease category	CM	SM
KIT D816V mutation	20%–30%. Other *KIT* mutations (exons 8, 9, 11) frequent.[14]	>90%–95%
Skin lesions	Always present	May be absent
Typical tryptase level (ng/mL)	<11.4 (normal)	>20, but may be normal
Typical course of the disease	Resolution in 70%–80% before adulthood	Chronic
Symptoms	Often limited to the skin and controllable by anti-MC mediator therapy	Very heterogeneous, may be severe and difficult to control
Extracutaneous manifestations	Rare, but GI symptoms may be encountered	Frequent, including osteoporosis
Risk for anaphylaxis	Low (1%–9%)	High (35%–50%)
Advanced/aggressive disease	Exceedingly rare	5%–10% of patients