Cutaneous Mastocytosis in Adults and Children

New Classification and Prognostic Factors

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KEYWORDS

• Mastocytosis • Mast cell • Cutaneous mastocytosis • Urticaria pigmentosa • Classification • Prognosis • WHO

KEY POINTS

- Cutaneous mastocytosis is a highly heterogeneous subtype of mastocytosis. Heterogeneity mainly depends on the age at disease onset and the clinical form of presentation.
- The classification of cutaneous mastocytosis has recently been redefined by the World Health Organization and an international consensus task force.
- A subset of children with mastocytosis shows persistence of the disease into adulthood, usually as the classic indolent systemic mastocytosis or as well-differentiated systemic mastocytosis.

INTRODUCTION

Mastocytosis is a heterogeneous disease characterized by the clonal expansion and accumulation of mast cells (MCs) in different organs and tissues.[1–3] The clonal nature of the disease can be established by the demonstration of activating mutations of the c-kit gene in most patients, provided that highly sensitive diagnostic methods are used.[4–7] This proto-oncogene encodes for a receptor in the membrane of MCs called *KIT*, a tyrosine-kinase protein that regulates growth and differentiation of MCs. In mastocytosis, *KIT* mutations induce a ligand-independent hyperactivation state of the receptor that leads to an increased survival of MCs, resulting in their accumulation in tissues.

Depending on the sites of organ involvement, 2 main forms of mastocytosis are recognized: (1) cutaneous mastocytosis (CM), when the skin is the only tissue affected, and (2) systemic mastocytosis (SM), characterized by MC infiltrates in

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extracutaneous organs, mostly the bone marrow (BM), with or without concomitant skin involvement.[1,8–10] The heterogeneity of mastocytosis is evidenced by the fact that the disease can develop both in children, supposedly as CM that tends to spontaneously regress by adolescence, and in adults, in whom mastocytosis is often systemic and shows a chronic course. More rarely, mastocytosis can exhibit an aggressive behavior with high cell proliferation rates and shortened survival.

In this article, we focus on the dermatologic aspects of mastocytosis, including a brief review through the different terminologies, concepts, and classification approaches that have been used along the history, with special emphasis on the most modern vision of the disease.

HISTORIC OVERVIEW

In 1869, Nettleship and Tay[11] described the case of a 2-year-old girl who presented with what looked like a rare form of chronic urticaria leaving brownish stains, which is widely thought to be the first case of mastocytosis reported in the literature, 10 years before the discovery of MCs by Paul Ehrlich.[12] The term *urticaria pigmentosa* (UP) was coined in 1878 by Sangster[13] to refer to a skin eruption found in a child that was described as "an anomalous mottled rash accompanied by pruritus, factitious urticaria and pigmentation." Nine years later, Unna[14] documented the presence of MCs in skin lesions of UP, but it was not until 1936 when the term mastocytosis was first used.[15]

Early attempts for classification of CM date from the first quarter of the twentieth century. At that time, 3 main forms of UP were already distinguished:

1. Macular
2. Nodular (xanthelasmoid form)
3. Mixed type (maculonodular)[16,17]

Later, more uncommon forms of UP with peculiar characteristics, such as bullous UP,[18,19] diffuse erythrodermic mastocytosis,[20,21] and *telangiectasia macularis eruptiva perstans* (TMEP)[22] were described, becoming rapidly recognized as novel cutaneous variants of UP.

By the mid-twentieth century, the systemic nature of mastocytosis was first established on the basis of histopathological findings in an autopsy carried out in a fatal case of UP that showed MC infiltrates not only in the skin but also in internal organs.[23] Within the following years, the concept of mastocytosis as a systemic disease in nature was rapidly spread out in parallel to increasing numbers of reports showing extracutaneous involvement,[24–29] but also cases purely restricted to the skin were described,[24,25] a dual vision of the disease that still remains today.

In the 1960s, Caplan[26,27] proposed to classify UP cases into 3 categories according to the number of skin lesions and the age at disease onset:

1. Solitary lesion (group I)
2. Multiple lesions appearing in infancy and early childhood (group II)
3. Multiple lesions appearing in late childhood, adolescence, and adulthood (group III)

Noteworthy, this classification provided pioneer information in terms of prognosis of the different categories of the disease. Thus, whereas solitary lesions tended to involute completely with time, some cases in group II and most cases in group III seemed to persist indefinitely; moreover, a correlation was found between late onset of skin lesions (group III) and the existence of a systemic MC disease.

The first comprehensive classification of mastocytosis in which both CM and SM were incorporated together was developed by Lennert and Parwaresch in 1979.[28]