Clinical advances in mastocytosis

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Summary. Mastocytosis is a disease characterized by an abnormal proliferation of tissue mast cells. The events primarily responsible for mast cell proliferation in mastocytosis are largely unknown, but a derangement of the network involving c-kit receptor and its natural ligand (stem cell factor, which promotes mast cell growth and differentiation in man) is likely to have a primary role in this disease. Mastocytosis comprises a wide spectrum of clinical conditions determined by the degree of mast cell proliferation, the organ systems involved, the age at onset and the association with hematologic diseases. Mastocytosis can occur in a pediatric or an adult form. In both groups of patients, the disease may be limited to the skin (cutaneous mastocytosis) or be systemic, involving predominantly the bone marrow and the gastrointestinal tract. The symptoms in patients with mastocytosis are generally related to the increased release of mast-cell-derived mediators, such as histamine, prostaglandin D_2, peptide leukotrienes, platelet-activating factor, heparin and proteolytic enzymes. The measurement of these chemical mediators (histamine, tryptase and prostaglandin D_2 and their metabolites) in body fluids is useful for the diagnosis and the laboratory evaluation of patients with systemic mastocytosis. As little is known about the pathogenesis of the different forms of mastocytosis, the treatment of the majority of these patients is largely symptomatic.

Key words: Mastocytosis – Mast cell – Urticaria pigmentosa – Mastocytoma – Therapy

Introduction

In 1869, the cutaneous manifestations of mastocytosis were described by Nettleship and Tay [1] as an unusual form of urticaria. A decade later Ehrlich [2] described the mast cell, whose tissue density is markedly increased in patients with mastocytosis. Sangster [3] suggested the term "urticaria pigmentosa" (UP) to describe one form of the disease and in 1887 mast cells were documented in the skin lesions [4]. In 1936, Sézary et al. [5] designated UP as "mastocytosis". Ellis [6] noted mast cell proliferation in the skin, liver, spleen, thymus, bone marrow, and lymph nodes in one infant with mastocytosis.

It is becoming increasingly evident that mast cells, traditionally recognized in terms of their primary effector role in allergic diseases, participate in a wide variety of processes in health and disease [7, 8]. They release preformed mediators, such as histamine, proteases, and heparin [9, 10], generate lipid mediators, such as leukotrienes and platelet-activating factor [11, 12], and synthesize various cytokines [13, 14]. Taken together with the strategic localization of mast cells in lymphoid tissues, along nerves and blood vessels [15], throughout connective tissues, and within tissues that interface with the outside environment (i.e., the skin, the respiratory and the gastrointestinal tract), these findings suggest that mast cells play a more complex role in health and disease than previously thought [7, 8].

Mastocytosis is not a single well-defined disorder, but a disease that is heterogeneous in manifestations and prognosis [16]. Patients with indolent forms of the disease may live relatively normal lives with proper medical control of their symptoms. A minority of patients have aggressive forms of mastocytosis, sometimes associated with hematological disorders and a poorer prognosis. The complexity of the pathological process and the heterogeneity of symptoms sometimes provide a difficult diagnostic challenge for the internist, clinical immunologist, pediatrician, or dermatologist, because they are unlikely to see many cases of mastocytosis and to gain a wide clinical experience of the disease.

Classification of mastocytosis

In the past various authors have struggled with the classification of this heterogeneous disorder. Cutaneous mas-
Pathogenetic aspects of mastocytosis

Human mast cells develop from a bone marrow-derived hematopoietic precursor cell CD34+. Normal mast cell development requires an interaction between stem cell factor (SCF) and c-kit receptors expressed by mast cell precursors and by mast cells at various stages of development [20]. SCF stimulates the growth and differentiation of murine and human mast cells in vitro [21, 22] and it also affects mast cells in vivo [23, 24]. SCF exists in a form bound to the cell membrane and in a soluble form; these may have different biological activities in vivo [20, 25]. The soluble form is derived from the cell-bound form by proteolytic cleavage at a protease-sensitive site adjacent to the cell membrane [26]. Thus, production of the soluble form is dependent on both the presence of full-length mRNA for SCF and the activation of a protease. Injection of the soluble form of SCF into the dermis stimulates the proliferation of mast cells [24] and of melanocytes and the production of melanin in humans [27].

The pathogenesis of the various disorders associated with abnormal accumulation of mast cells is still unclear and probably varies in the different forms of the disease. Deregulation or abnormalities of the c-kit receptor or its ligand, or abnormalities involving other mast cell growth factors or their receptors, could produce dysregulated mast cell proliferation or survival [8]. The latter hypothesis is at least in part suggested by an abnormal production of the soluble form of SCF found in the skin of three patients with cutaneous mastocytosis [28]. In particular, it was suggested that this abnormality is due to increased proteolytic processing, since it was not explained by differences in the splicing or sequence of SCF mRNA in the patients examined [28]. Further investigations are necessary to shed light on the pathogenesis of the different forms of this heterogeneous disease.

Skin involvement in mastocytosis

Skin is the most frequent (from 50% to 100%) site of involvement in patients with any form of mastocytosis (Table 1) [17, 29, 30]. Cutaneous manifestations include UP, mastocytoma, and diffuse and erythrodermic mastocytosis.

Urticaria pigmentosa

The most frequent cutaneous lesions in patients with mastocytosis are the red-brown macules and papules of UP (Fig. 1), which occur in a generalized and random distribution. Cutaneous lesions of UP tend to be of highest density on the trunk, whereas palms, soles, face, and scalp are usually free of lesions. Pruritus, dermatographism, and the presence of Darier’s sign (wheat and erythema occurring after a brisk stroke to a lesion) are frequently observed. In infants, a positive Darier’s sign may be accompanied by blister formation with hemorrhage [31]. Flushing has been reported in 17%–36% of patients with UP; 10%–70% of patients with UP had systemic disease [32, 33] with a fo-