Regression of dermal mast cell infiltrates in patients with cutaneous mastocytosis

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ABSTRACT

Background. Fourteen children with urticaria pigmentosa (UP) and two with disseminated cutaneous mastocytosis (DCM) were followed.
Methods. Three skin biopsies were performed: the first one before the age of 2 years, the second one after 1-year treatment and the third 6 years after the second.
Results. The repeated biopsy after the 1-year treatment resulted in a 20-60% regression of the mast cell infiltrates, while the third one disclosed a 70-90% reduction of these infiltrates. In UP patients the mast cell infiltrate changed from vessel unit type >55µm to <55µm. In both the DCM patients the mast cell infiltrate changed into the type >55µm.
In the two nontreated UP patients the mast cell infiltrate type remained <55µm.
Conclusion: The authors observed a spontaneous regression of the mast cell infiltrates in mastocytosis patients during adolescence; the treatment can however essentially influence their reduction.

KEY WORDS

cutaneous mastocytosis, treatment, repeated biopsy, dermal mast cells infiltrate, regression

Introduction

Treatment of mastocytosis requires exact data on the course of the disease, on involvement of a particular organ and the resulting clinical symptomatology. The treatment of mastocytosis is different, that which is good for one patient does not necessarily benefit another one (1).

Retrospective studies have revealed that in half of the cases of cutaneous mastocytosis in children, spontaneous regression of the disease may be expected up to maturity (2,3,4). Therapeutical effect and however its development and clinical symptomatology, have to be monitored, first of all, by recording the number of mast cells in dermal infiltrates and the released mast cells mediators with their impact on target cells (1,5,6,7).

For these reasons we have tried to perform a retrospective study of the evolution of mastocytosis in children related to the treatment, as well as to the age – in the process of adolescence.

Methods

The evolution of dermal mast cell infiltrates were examined by repeated histological investigation of skin biopsies from 14 patients with cutaneous mastocytosis: 12 urticaria pigmentosa cases (UP) and 2 cases of disseminated cutaneous mastocytosis (DCM). In all instances mastocytosis started before the age of two years.

The first biopsies in 12 cases were taken before the age of two years; the second was taken one year after the treatment. Two UP patients were not treated between the first and the second biopsy, because incorrect histological interpretation of the first dermal biopsy,

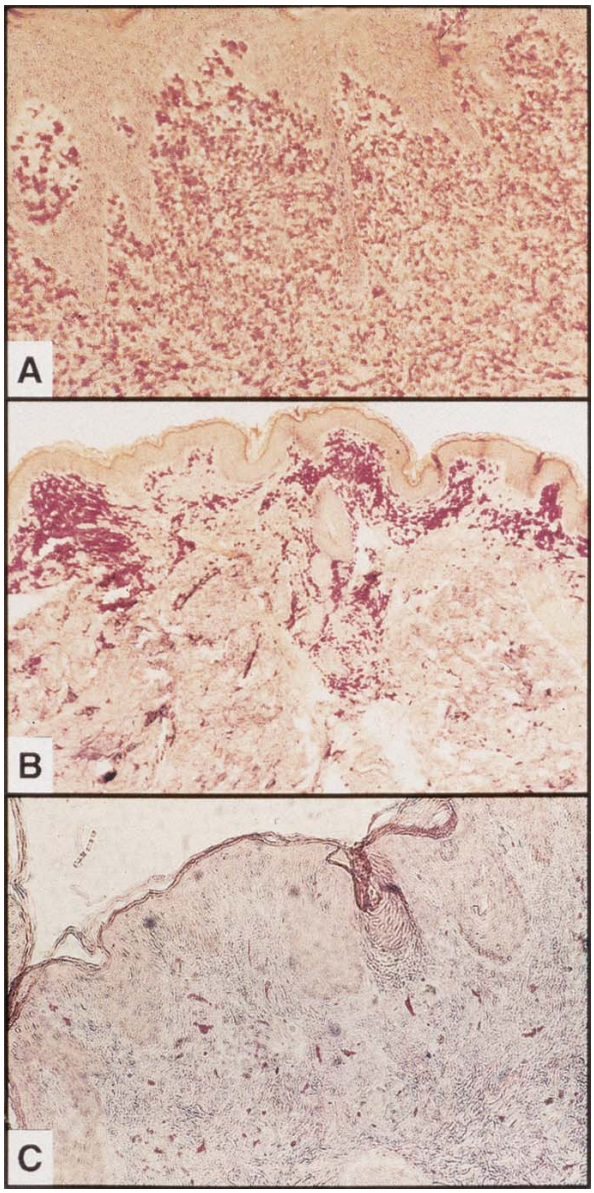

Figure1. A. Disseminated cutaneous mastocytosis. Dermal band-like infiltrates mast of cells, alpha-naphtol-chloracetate esterase staining (CHAE), x 250.
B. Repeated biopsy after one year, the same patient. Dermal mast cell infiltrates, type vessel unit >55µm, CHAE, x 175.
C. Repeated biopsy after 6 years, the same patient. Dermal mast cell infiltrates, vessel unit type <55 µm. Only single perivascular mast cells are seen. CHAE, x 250.

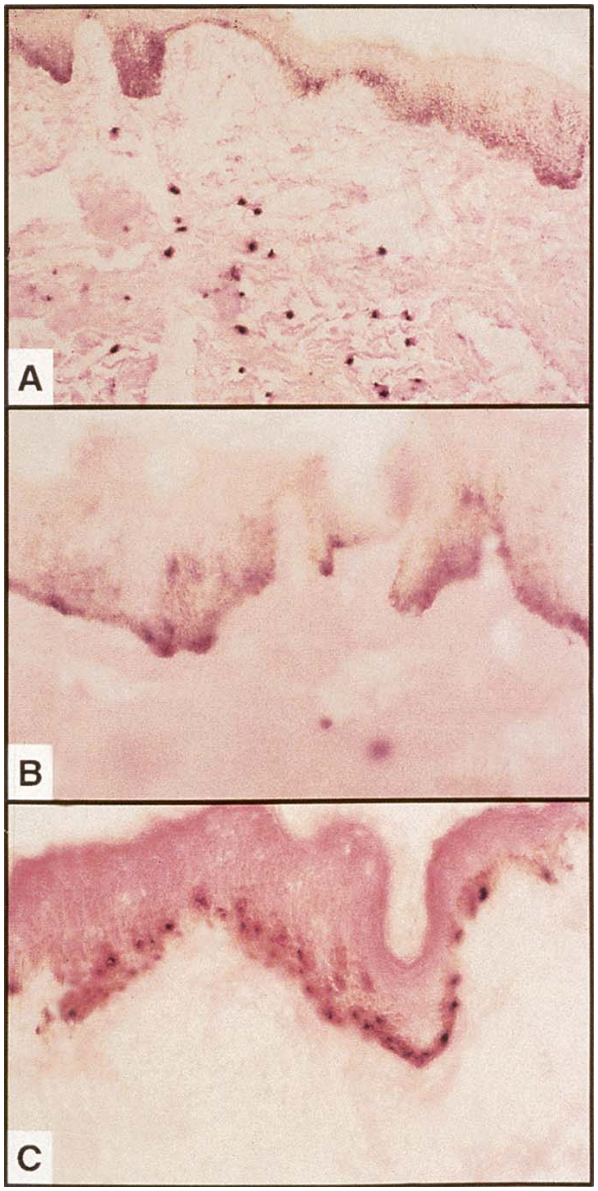

Figure 2. A. Activation of the epidermal melanin unit; thyrosinase activity in melanocytes of the epidermal melanin unit and in melanocytes of the upper and middle dermis; positive L-DOPA reaction, x 175.
B. Biopsy repeated one year later: thyrosinase activity only in melanocytes of the epidermal melanin unit.
C. Biopsy repeated 6 years later revealed similar changes: positive L-DOPA reaction, x 250.

and treatment started after the second skin biopsy. In all 14 UP patients the third skin biopsy was examined after a six-year period following the second biopsy. In the last three-year period before the third skin biopsy, all the patients did not take antihistamines or corticosteroids orally. Antihistamines as well as corticosteroids were applied topically just during the acute exacerbation of the disease (e.g. insect bite), while treatment of these exacerbations lasted approximately 10 days.

Histologic slides were stained with hematoxylin and eosin (H and E), Giemsa, periodic acid Schiff (PAS) and toluidin blue. The biopsies were also examined by Warthin-Starry (W-S) impregnating method (formalin-paraffin embedded material), as well as by detection of thyrosinase (L-DOPA reaction in frozen tissue). The paraffin sections were analyzed using immunohistochemical techniques, like alpha-naphtol chloracetatesterase (CHAE, Sigma) and CD34 (Dakopatts). The samples were also examined with the standard transmission electron-microscopy (TEM) (4,8).

All the patients with UP (12 cases) were treated immediately after the first dermal biopsy for a long time with corticosteroid crèmes or ointments (mostly containing prednicarbate 0,25%, mometasone furoate 0,1%, triamcinolone acetonide) topically applied on the skin lesions once a day. Moreover the patients took ketotifen in combination with H_1 or H_2 antihistamines applied in doses corresponding to the patient's age and body weight (9).

Two patients with DCM were treated with corticosteroids (prednisone) orally, in daily doses 1 mg/kg body weight, gradually decreasing the dose, in combination with H_2 antihistamines (cimetidine, ranitidine) (6,9,10).

Results

The histological band-like pattern of Sweet and Smoller (11), dense coalescent mast cell infiltrates reaching into the deep corium and subcutis, has been observed in two patients with DCM and one patient with UP. In 11 remaining UP cases only histological picture of vessel unit > 55 μm was observed. Here, the mast cell infiltrates were situated perivascularly around dilated capillaries and vessels of the upper, or less frequently of the middle layer of the dermis.

After one-year treatment, repeated skin biopsies in 8 UP cases and 2 DCM cases revealed a 20% - 60% regression of mast cell infiltrates. The mast cell infiltrates, as described by Sweet and Smoller (11), did however not change between the first and second skin biopsies. In 2 UP children with mast cell infiltrates type of vessel unit >55 μm, not treated in the period between the two biopsies, the mast cell infiltrates remained unchanged after one year, in the repeated biopsy appeared to be slightly multiplied (Figure 1). The histological picture of the third biopsy taken after a 6-year interval from the second biopsy, showed in all the cases a 70 – 80% regression of mast cell infiltrates in dermis. With both DCM patients with band-like type mast cell infiltrates, this type

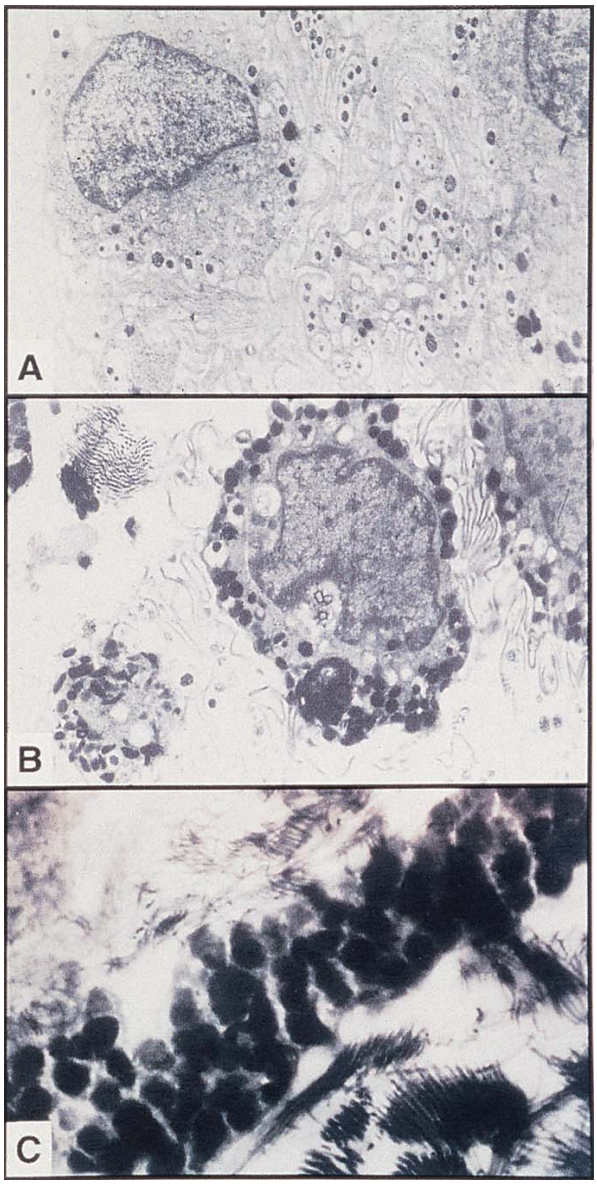

Figure 3. Transmissive electron microscopy (TEM).
A and B. Biopsy and repeated biopsy one year later: similar TEM picture. Atypical dermal mast cells with large oval or bilobated nuclei. The cytoplasmic villi are very long creating a network with electron-dense small and atypical granules, which are dispersed at the periphery of cells and are surrounded by a halo (vacuoles with membranes around them); x 6384.
C. Biopsy repeated 6 years later. Normal dermal mast cell. Cytoplasm is filled with normal electron-dense granules of the same size, without degranulation. Mast cells membrane villi are much shorter. x 8000.

changed to vessel units >55 µm. In 6 UP cases, the vessel unit mast cell infiltrates >55 µm changed to the vessel unit type <55µm (Figure 1). In patients with UP but also with DCM a strong activation of melanogenesis in the epidermal melanin unit could be observed. In the mid dermis dropped off melanocytes (positivity of L-DOPA and W-S) occurred during the first year of the disease. Six years later there was still activation of melanogenesis but only in places of the epidermal melanin unit (Figure 2). Transmission electron microscopy pictures showed in patients with DCM through the first year "atypical dermal mast cells", but six years later their morphology changed into the normal cutaneous mast cells (Figure 3).

Discussion

Spontaneous regression of mast cell infiltrates was classified according the recommended method by Sweet and Smoller (11). This morphometric method was used in assessing dermal mast cell infiltrates in the Giemsa stained sections. They divided dermal mast cell infiltrates in patients with mastocytosis in band-like diffuse dermal mast cell distribution with huge amounts of mast cells and mast cell infiltrates located only like a vessel unit type. A vessel unit (11), was defined as a conglomerate of one or more vascular spaces, thei lumina aligned with endothelial cells, which were located adjacent to each other and were not separated by nonendothelial cells. The vessel units were divided into two groups: (a) < 55 µm and (b) > 55 µm in largest dimensions, using ocular micrometer. The length of the vessel unit was measured from an outer vascular wall of one vessel to the vascular wall of another vessel, located farther away within the same vessel unit.

The synthesis of the mast cell growth factor (SCF), by the epidermal keratinocytes, dermal fibroblasts, or dendritic cells plays a key role (12, 13). There are two SCF forms, the membrane bound and the free, soluble one, which originates from the membrane bound form dissociated by proteolytic proteases and has significant biological effects (14). Mast cells do not produce SCF. On the surface membrane of mast cells there are c-Kit proteins regarded as SCF receptors, in fact they are their ligands (15,16). The above-mentioned receptors of mast cells are product of c-Kit protooncogene being a component of the structural gene known as exon 6 (13,17). Based on comprehensive studies (18, 19), SCF is an important factor with the impact on the number, phenotype and function of mast cells in tissues of healthy people. In mastocytosis SCF mutations, or disturbed metabolism, are to be taken into consideration (16,20). As mast cells (together with eosinophils, monocytes, neutrophils and basophils) derive from CD34 positive multipotent germinal hematopoietic cells in the bone marrow, the pathologic SCF synthesis can under certain circumstances influence even the bone marrow stem cells. It can also be one of the explanations why the diseases of hematopoietic system occur in mastocytosis patients as an accompanying phenomenon. The spontaneous regression of mastocytosis may depend on endocrinologic, immunologic, biochemical, or other processes occurring in human organism during the period of adolescence. The mentioned development may influence the mast cells evolution from expression of c-Kit protooncogene up to production of SCF (21).

In this study SCF was not identified, but the expressivity on mast cells of CD34 was the same as it was the first biopsy or repeated dermal biopsies through or after the treatment of mastocytosis.

Therapeutical effects on mast cell infiltrates of mastocytosis as observed by Kurosawa et al (5) and as confirmed by our study are, also to be taken into consideration. Dermal mast cells infiltrates were through the treatment period less expressed and changed from band-like type to type of vessel- unit or from type of vessel-unit more then 55 µm to vessel-unit less than 55µm.

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