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Mast Cell Alterations in Chronic Psoriasis Vulgaris: Response to Low-Strength Anthralin Treatment

A transmission electron microscopic study

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ABSTRACT

Mast cell degranulation (MCD) was studied in lesions of chronic psoriasis vulgaris before and during topical treatment with low-strength anthralin. Before the treatment, two forms (A and B) of mast cells with Type I MCD were distinguished in the lesions, in addition to mast cells showing Type II MCD. In Type I MCD, electron-dense mast cell granules in form A mast cells, and electron-dense mast cell granules and vacuoles containing granule matrix in form B mast cells, were released as intact structures by the mechanism of diacytosis. Distinct gaps of the mast cell plasma membranes were observed. Around blood vessels, beneath the epidermal-dermal junction and in the intercellular space of strata basale and spinosum, the mast cell granules appeared partly as intact structures and partly in more or less disintegrated form. In Type II MCD the granule matrix was released into the extracellular compartment by the mechanism of exocytosis.

During treatment with low-strength anthralin, the mast cell changes underwent regression. In macular psoriasis only form A mast cells of Type I MCD were demonstrated, and the released intact mast cell granules were restricted to the immediate neighbourhood of the mast cells. There were no mast cell granules in the epidermis. At the sites with clinically complete clearance of psoriatic lesions, the mast cells displayed no degranulation but distinct gaps were still found in the mast cell plasma membranes.

Low-strength anthralin's mode of action in psoriasis is suggested to involve regression of a series of systems, including prevention of mast cell degranulation, thereby inhibiting release of histamine, proteinase and other mast cell mediators sustaining the psoriatic process.

INTRODUCTION

In recent reports, mast cell degranulation was revealed to be a primary event in the evolution of acute eruptive guttate psoriasis vulgaris following streptococcal pharyngitis (4, 5).

In the continued studies, interest was focused on two questions. The first was if mast cell degranulation occurs only in psoriasis that follows streptococcal pharyngitis, or if it may be observed in psoriasis unrelated to such an infection. The second question was if an improvement of the disease obtained with low-strength anthralin also implied a normalizing of the ultrastructure of the mast cells. This report concerns the mast cell alterations in chronic psoriasis vulgaris before and during topical treatment with low-strength anthralin.

MATERIAL AND METHODS

Subjects

The study comprised 15 patients (11 men, 4 women) aged 19 to 47 years, who had had psoriasis vulgaris for 1 to 5 years. The series was restricted to patients who were sure that neither the initial appearance nor detoriation of their psoriasis was preceded by streptococcal pharyngitis. All had extensive plaque lesions on arms, legs and trunk.

Treatment

In the 4 weeks preceding the low-strength anthralin trial, the treatment of the lesions was with 3 % salicylic acid in petrolatum album in 8 cases and with petrolatum album alone in 7 cases. On the day before the anthralin treatment begun, all the patients were photographed.

Low-strength anthralin treatment. The patients were treated once daily, Monday through Friday, in the out-patient department until the macular stage (2) of all lesions was achieved. At weekends they themselves performed the treatment once or twice daily. Out-patient treatment sessions included bath, but no adjunctives such as oils, Mediterranean salt or liquor carbonis detergens. Nor was ultraviolet light given or antihistamine prescribed. The ointment contained 0.04 % anthralin and 3 % salicylic acid in petrolatum album. The patients were instructed to avoid exposing any part of the skin to unnecessary external trauma, including mechanical removal of scales from the lesions, and apply the ointment in a thin layer, without rubbing it into the skin (2, 3).

During the macular stage, the patients applied the ointment once daily. When the lesions had completely cleared, they used the ointment first once daily and later twice or thrice weekly.

Electron microscopy

Using local anesthesia (Carbocain 10 mg/ml), punch biopsy specimens (3 mm) were taken from arms, legs and trunk: 1) from lesions on the day before anthralin treatment was begun, 2) from macular psoriasis 3 and 5 weeks later, and 3) from clinically completely cleared lesion sites 4 and 12 months after institution of anthralin treatment.

The biopsy specimens were fixed in a 3 % glutaraldehyde solution and

postfixed in a 1 % osmium tetroxide solution. The specimens were dehydrated in graded steps of ethanol and embedded in Epon. They were sectioned on an LKB Ultrotome. After staining in uranyl acetate (1) and lead citrate (10) the sections were examined in a JEOL JEM 100 C electron microscope.

RESULTS

Mast cell alterations before use of anthralin

No difference was found in the ultrastructure of the mast cells between the patients who had been treating their lesions with 3 % salicylic acid in petrolatum album and those who had used petrolatum album alone. Although single mast cells occurred, these were frequently observed in close apposition with cells of other types. In accordance to the observations of acute eruptive guttate psoriasis vulgaris (4), two types of mast cell degranulation, Type I and Type II MCD, were also distinguished in the present material of chronic psoriasis vulgaris before anthralin treatment was begun.

Type I MCD. Based on the ultrastructure of the mast cell granules, two forms (designated A and B) were observed in the lesions from all sites.

The form A mast cells (figs 1 and 2) were similar in ultrastructure to the mast cells of Type I MCD in acute eruptive guttate psoriasis vulgaris following streptococcal pharyngitis (4). The mast cell granules displayed scroll-like figures, parallel lamellae, an amorphous structure and/or a speckled pattern (figs 1B-D and 2A). They were encased in a trilaminar perigranular membrane (figs 1C, D and 2A). The granules were released as intact bodies (figs 1A, D and 2A). At various distances from the mast cells were intact or more or less disintegrated mast cell granules of the same appearance as the mast cell granule material in the form A mast cells (fig 2B). In addition to these earlier observed characteristics (4), the present study demonstrated frequent gaps of the mast cell plasma membrane (fig 1C).

In the form B mast cells (figs 3 and 4A), the granules appeared either as electron-dense structures encased in a distinct trilaminar perigranule membrane or with vacuoles separating the trilaminar perigranular membrane from the granule matrix (figs 3C and 4A). A conspicuous feature of the form B mast cells was the distinctly appearing scroll-like figures, in some granules forming the main component, as well as granules with very densely packed, thin lamellae (figs 3C and 4A). The membrane-bounded vacuoles contained dense and loose granule matrix (figs 3C and 4A). The membrane-encased granules as well as the membrane-bounded vacuoles containing granule matrix were released as intact structures. At various distances from the mast cells, the extracellular space of the dermis was observed to contain membrane-encased mast cell granules, intact as well as disintegrated vacuoles containing dense and loose granule matrix and freely occurring granule matrix of the same ultrastructure as the

mast cell granules and granule matrix in the form B mast cells (figs 3B, C and 4).

Mast cell granules with ultrastructural similarity to those observed in forms A and B mast cells were distinguished in the intercellular space of the strata basale and spinosum (fig 5).

Type II MCD. The mast cells of Type II MCD in this material of chronic psoriatic lesions seemed mostly to be more vacuolized than those in Type II MCD of acute eruptive guttate psoriasis vulgaris following streptococcal pharyngitis (4), even though great variations occurred (figs 6 and 7). Narrow electron-lucent spaces appeared either between the trilaminar perigranular membrane and granule matrix with disintegration of the granule matrix (figs 6A and 7A) or between the inner and outer leaflets of the trilaminar perigranular membrane (fig 6B and C). The vacuolized appearance of the mast cells seemed to be the result of a fusion between adjacent trilaminar perigranular membranes or between the outer leaflets of the adjacent trilaminar perigranular membranes (fig 7). The trilaminar perigranular membranes also fuse with the mast cell plasma membrane (fig 7B), resulting in release of mast cell granule matrix into the extracellular space by the mechanism of exocytosis.

Mast cells in macular psoriasis during low-strength anthralin treatment

In all patients the macular stage was achieved 3 to 4 weeks after low-strength anthralin was begun. In macular psoriasis only form A mast cells of Type I MCD occurred (fig 8). The mast cell granules showed fairly uniform electron density with discernible scroll-like figures and parallel lamellae. They were encased in a trilaminar perigranular membrane. The mast cell granules were discharged as intact bodies through gaps of the cell boundary (fig 8C). Extruded mast cell granules were found only in the immediate neighbourhood of the mast cells (fig 8B). No granules were detected in the epidermis.

Mast cells in clinically completely cleared lesion sites during low-strength anthralin treatment

Clinically complete clearance of the lesions was obtained 2 to 4 months after the institution of low-strength anthralin treatment. The 4-months and 12-months specimens from this skin displayed similar ultrastructure of the mast cells. In the cytoplasm there were few, empty, discrete vacuoles. The mast cell granules had an electron-dense appearance. Scroll-like figures and parallel lamellae as well as a crystalline structure with lattices were distinct (fig 9). The granules were encased in a trilaminar perigranular membrane. Although no degranulation of the mast cells was demonstrable, distinct gaps of the mast cell plasma membrane were still common (fig 9).

DISCUSSION

Studies of the evolution of acute eruptive guttate psoriasis vulgaris following streptococcal pharyngitis revealed mast cell degranulation as a primary event (4, 5). The present study showed mast cell degranulation to be prominent also in the lesions of chronic psoriasis vulgaris. In all the patients selected for the study the psoriasis was neither evoked nor exacerbated by antecedent streptococcal pharyngitis. The results seem to warrant continued investigations to disclose if mast cell degranulation can be triggered when psoriasis is elicited also by other known provoking and exacerbating factors, such as viral infections, phototoxicity, contact dermatitis, drug-induced eruptions and trauma. A recent light and electron microscopic study of early relapses occuring after withdrawal of treatment with a potent topical corticosteroid of plaque type psoriasis revealed mast cell degranulation as a primary event (13).

The present study confirmed the observations in acute eruptive guttate psoriasis vulgaris (4) of two different mechanisms for release of mast cell granule material, referred to as Type I and Type II MCD. In another secretory system, viz. human secretory prostatic cells, electron microscopy showed similar mechanisms for the release of secretory substance (7, 11). In the prostatic cells, the mechanism analogous to Type I MCD was designated diacytosis, while the other mechanism - exocytosis - was characteristic also of Type II MCD.

Clinically and at light and electron microscopy, low-strength anthralin has been demonstrated to normalize the epidermal, inflammatory and vascular changes in the transition of the chronic psoriatic lesions to macular psoriasis and clinically completely cleared skin (2). The epidermal and inflammatory changes responded faster to the treatment than did the blood vessels. In the finally cleared skin, no changes were detected in the epidermis or blood vessels (2). In the present study, regression of the epidermal, inflammatory and vascular disturbances was accompanied by subsidence of the mast cell degranulation. Thus, in the biopsy specimens from macular psoriasis only diacytotic form A mast cells remained and in skin with clinically complete clearance of psoriatic lesion sites, no mast cell degranulation was demonstrated. The general improvement of the disease indicates that the switching from the psoriatic to the normal pathway involves the regression of a series of systems, including prevention of mast cell degranulation.

Patients who were using low-strength anthralin as maintenance treatment were able to keep their skin lesion-free (3). When, however, treatment was discontinued, relapses occurred showing mast cell degranulation as a primary event (unpublished observation). From the observations of mast cell

degranulation as a primary event in acute and relapsing psoriasis and from the finding that in completely cleared skin during low-strength anthralin treatment no mast cell degranulation was detected, it seems reasonable to assume that low-strength anthralin acts via the mast cells, by preventing mast cell degranulation, thereby inhibiting release of histamine, proteinase and other mast cell mediators sustaining the psoriatic process which consequently lies dormant. Whether the distinct plasma membrane gaps of the mast cells here reported in chronic psoriasis vulgaris before and during treatment with low-strength anthralin is of any pathogenetic importance has to be determined.

The importance of antihistamine as an adjunct in low-strength anthralin therapy has been stressed (6, 9). In some, but not in all, patients antihistamine is satisfactory in this respect. A relevant question concerns the extent to which quantitative variations between diacytotic and exocytotic mast cells and between forms A and B of diacytotic mast cells may explain differences in severity of itching and in extent of the lesions, as well as in individual response to treatment.

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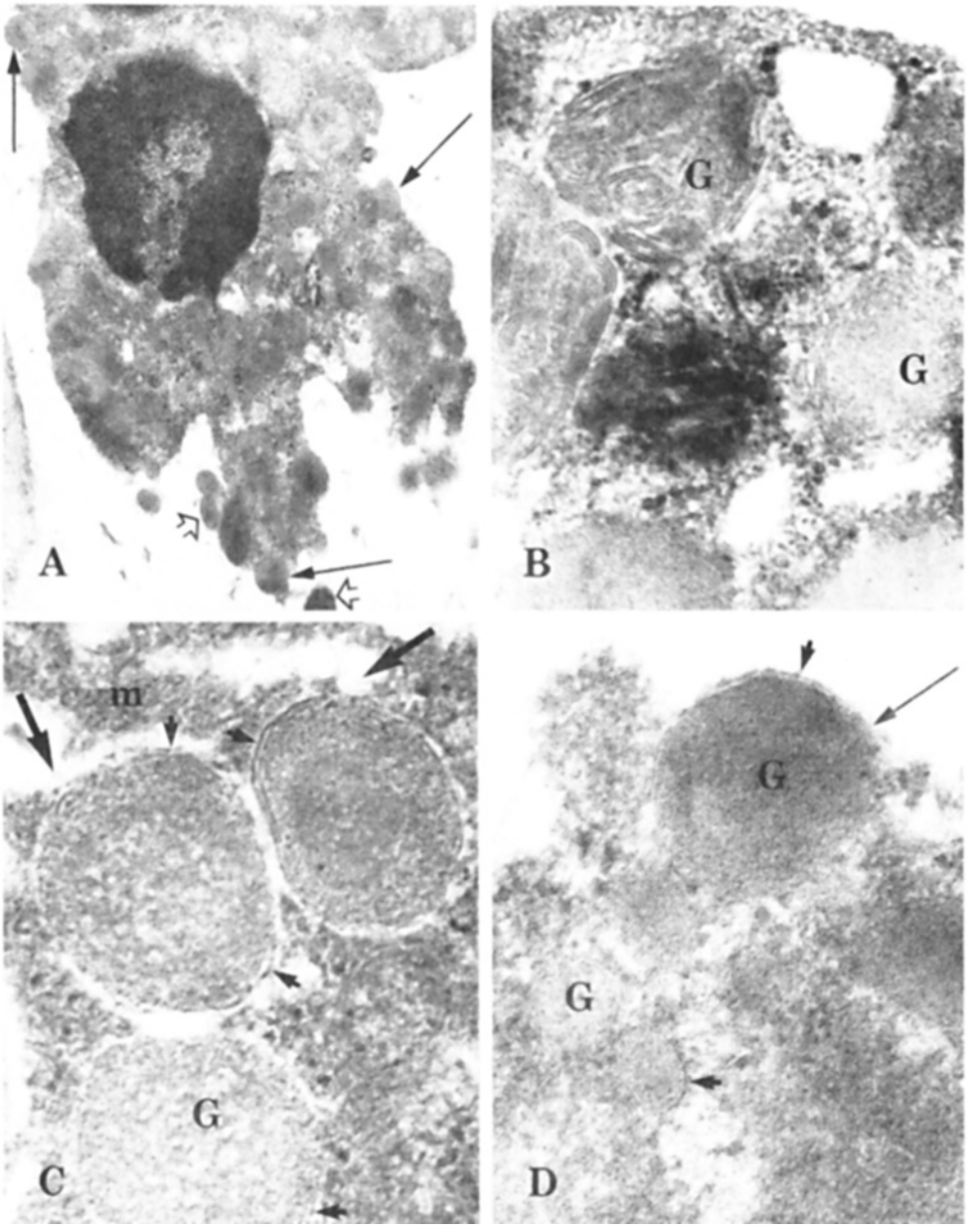

Fig 1. Form A mast cell of Type I MCD in chronic psoriatic lesion before low-strength anthralin treatment showing typical appearance of the granules (G). (1B-D). The granules are encased in a trilaminar perigranular membrane (arrow-heads)(1C,D). They occur in an intermediate position (thin arrows) between the intracellular and extracellular compartments or are completely released (open arrow-heads)(1A,D). Distinct gaps (thick arrows) of the cell boundary (1C). m, microvillus. (mag A x 8 800, B x 53 000, C x 77 000 and D x 84 000).

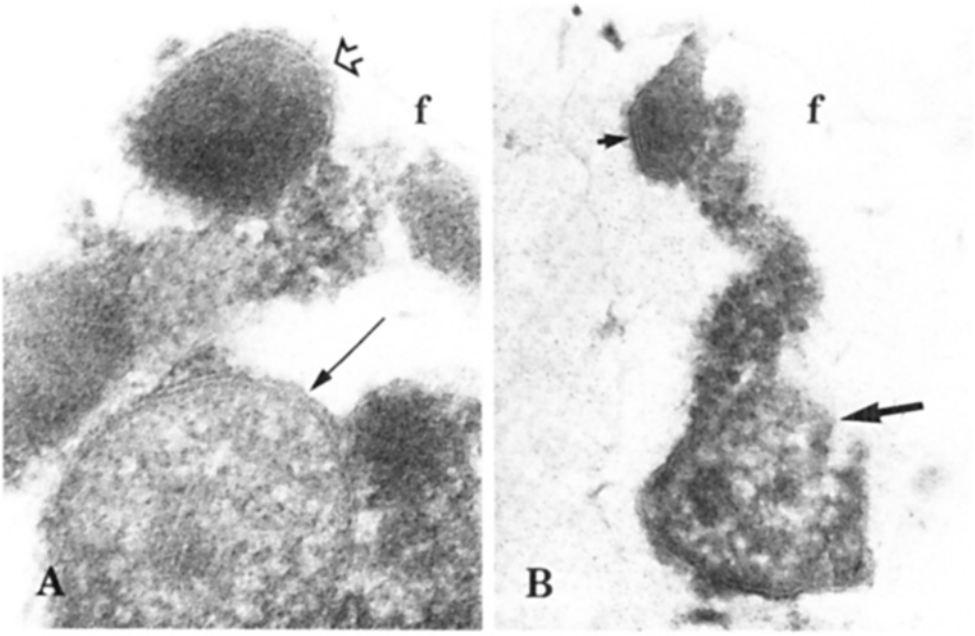

Fig 2. Form A mast cell of Type I MCD in chronic psoriatic lesion before low-strength anthralin treatment. The granule (thin arrow) in intermediate position between the intracellular and extracellular compartments as well as the completely released granule (open arrow-head) are encased in a trilaminar perigranular membrane (2A). In the extracellular space (2B) two mast cell granules show an ultrastructure similar to that of the granules in form A mast cells of Type I MCD. One granule (arrow-head) is intact and bounded by a distinct trilaminar perigranular membrane, while the other granule (thick arrow) is in a state of disintegration. Discharged mast cell filaments (f). (mag A x 120 000 and B x 90 000).

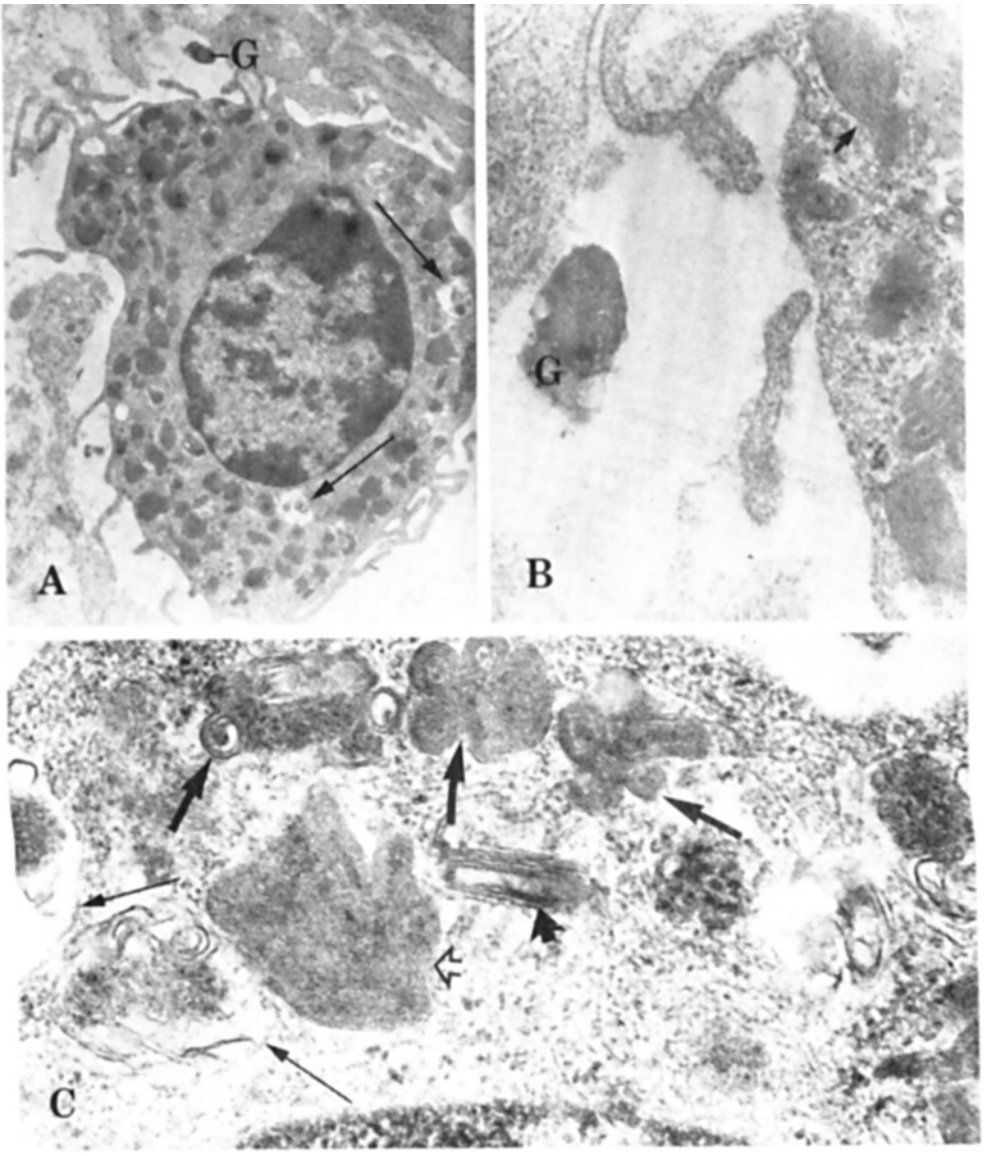

Fig 3. Form B mast cell of Type I MCD in chronic psoriatic lesion before low-strength anthralin treatment. The vacuoles (thin arrows) are bounded by a trilaminar membrane (3A,C). They contain loose and dense mast cell granule matrix. Scroll-like figures (thick arrows), thick lamellae (large arrow-head) and densely arranged, thin lamellae showing a myelin-like structure (open arrow-head) are prominent features of the dense mast cell granules (3C). The discharged mast cell granule (G) displays like the intracellular granule (arrow-head) a myelin-like figure (3B). (mag A x 8 800, B x 51 000 and C x 70 000).

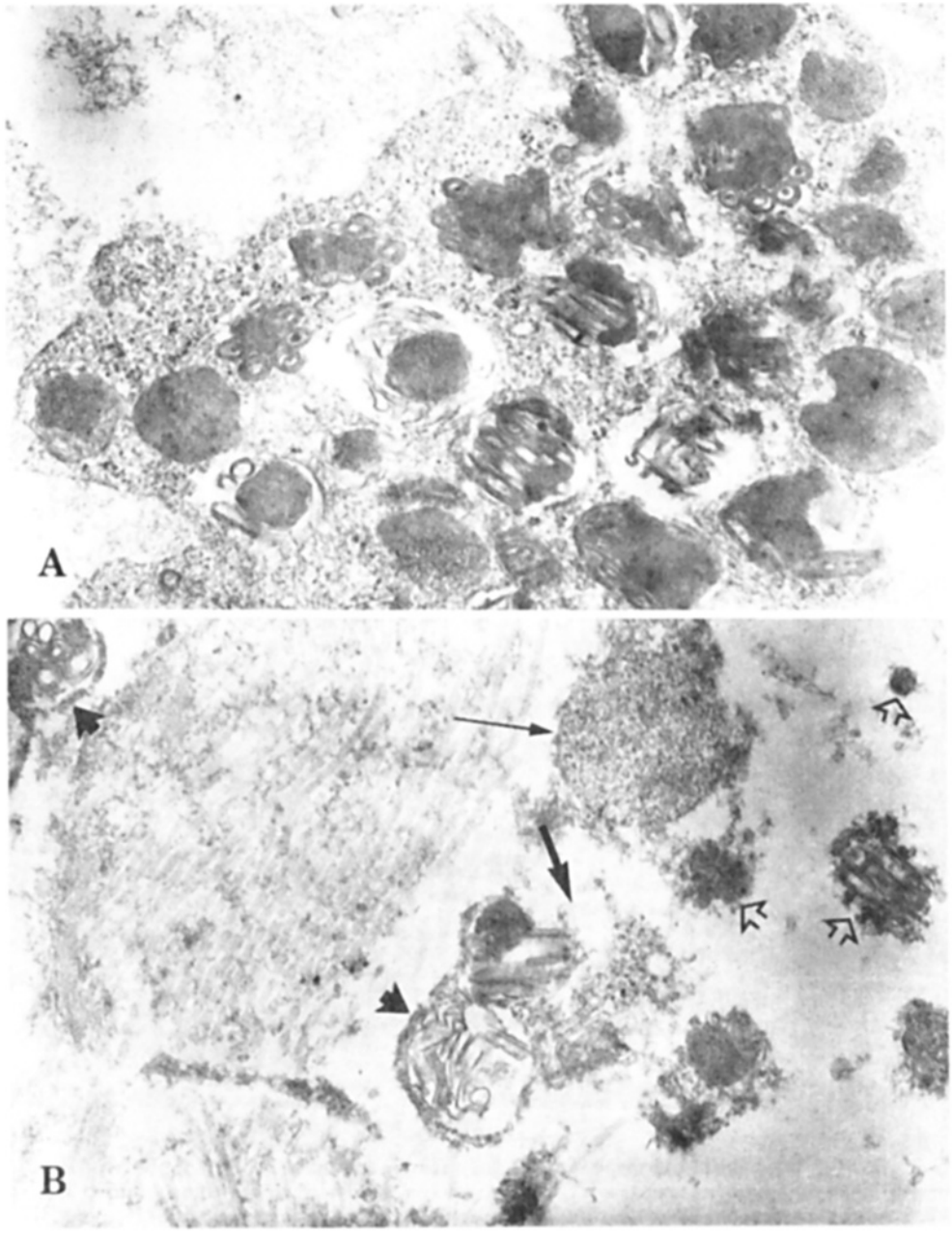

Fig 4. Form B mast cell of Type I MCD in chronic psoriatic lesion before low-strength anthralin treatment. In the dermal extracellular space (4B) is observed an intact mast cell granule (thin arrow) encased in a trilaminar membrane, intact vacuoles (thick arrow-heads) and partially disintegrated vacuole (thick arrow) containing mast cell granule matrix as well as freely occurring mast cell granule matrix (open arrow-heads) similar in ultrastructure to the mast cell granules and granule matrix in the form B mast cell of Type I MCD (4A). (mag A x 32 000 and B x 34 000).

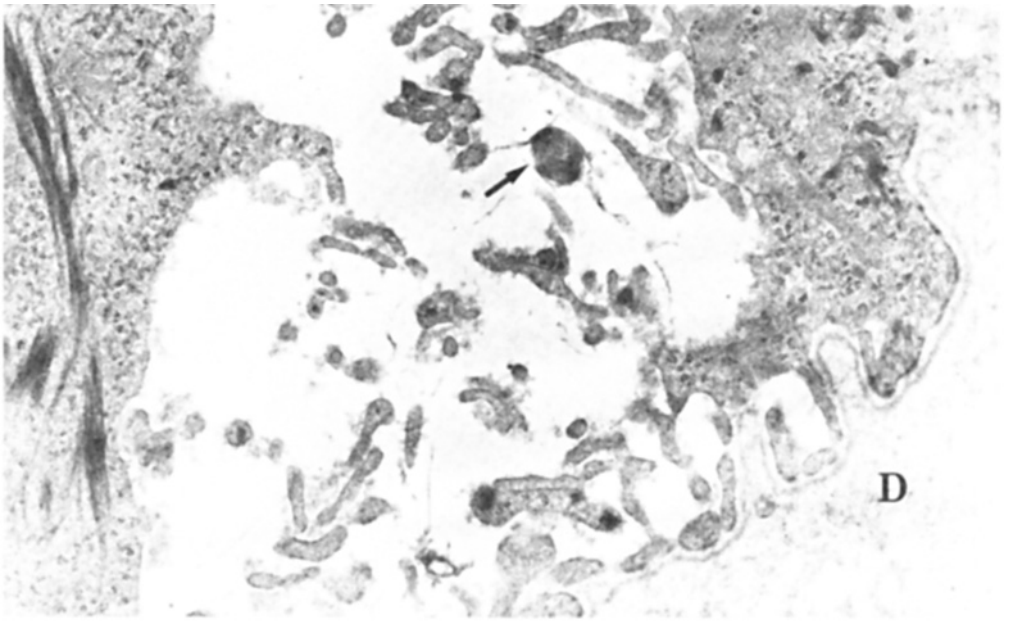

Fig 5. In the widened intercellular space of stratum basale in a chronic psoriatic lesion before low-strength anthralin treatment a granule (arrow) is observed showing a myelin-like figure similar in ultrastructure to granules in form B mast cells of Type I MCD. D, dermis. (mag x 16 000).

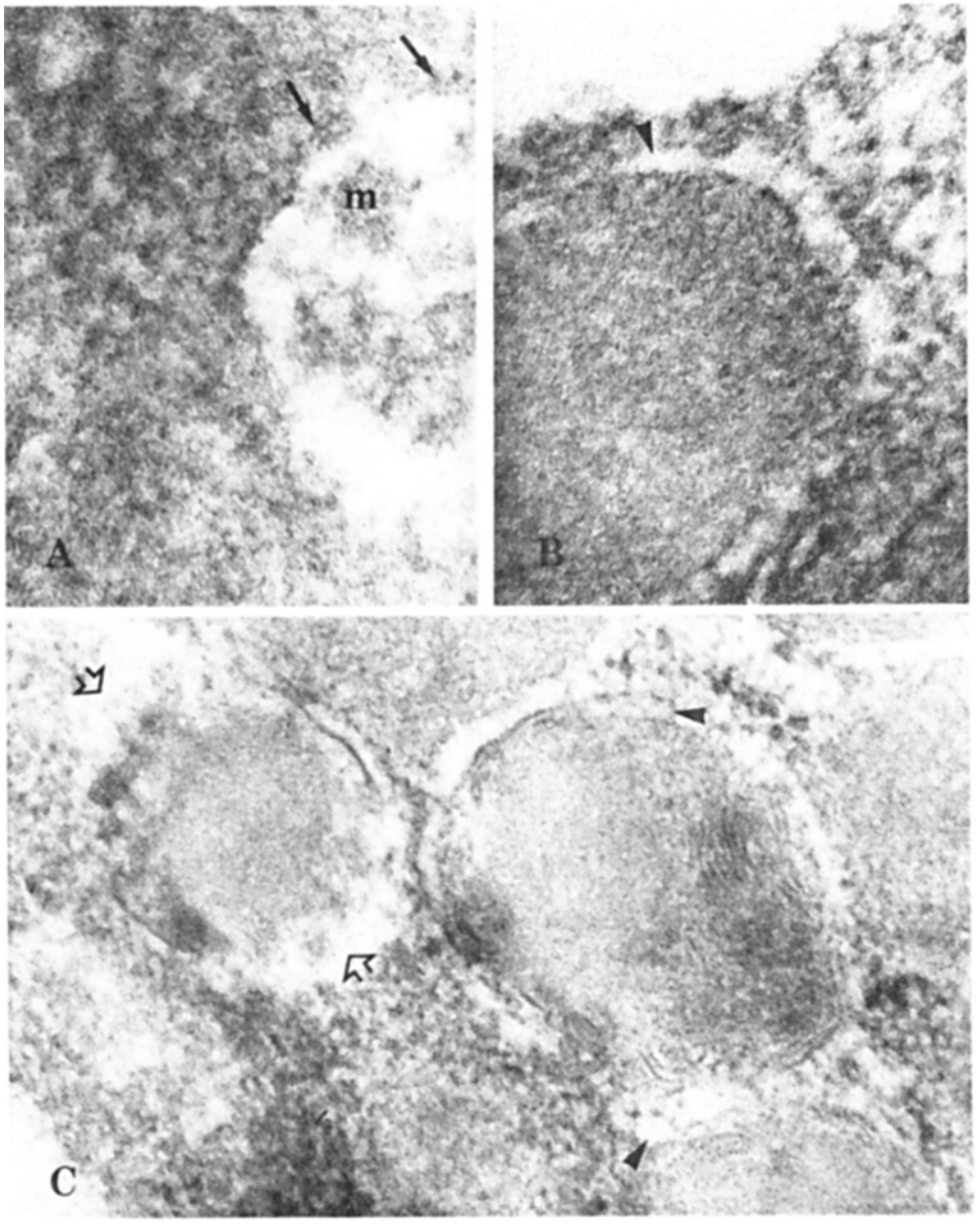

Fig 6. Mast cell of Type II MCD in chronic psoriatic lesion before low-strength anthralin treatment. A narrow electron-lucent area separates the trilaminar perigranular membrane (arrows) from the mast cell granule matrix (m)(6A). In another part a narrow electron-lucent area (arrow-heads) separates the outer and inner leaflets of the trilaminar perigranular membrane (6B,C). The perigranular membrane seems to be partially disintegrated (open arrow-heads) (6C). (mag A x 125 000, B x 160 000 and C x 192 000).

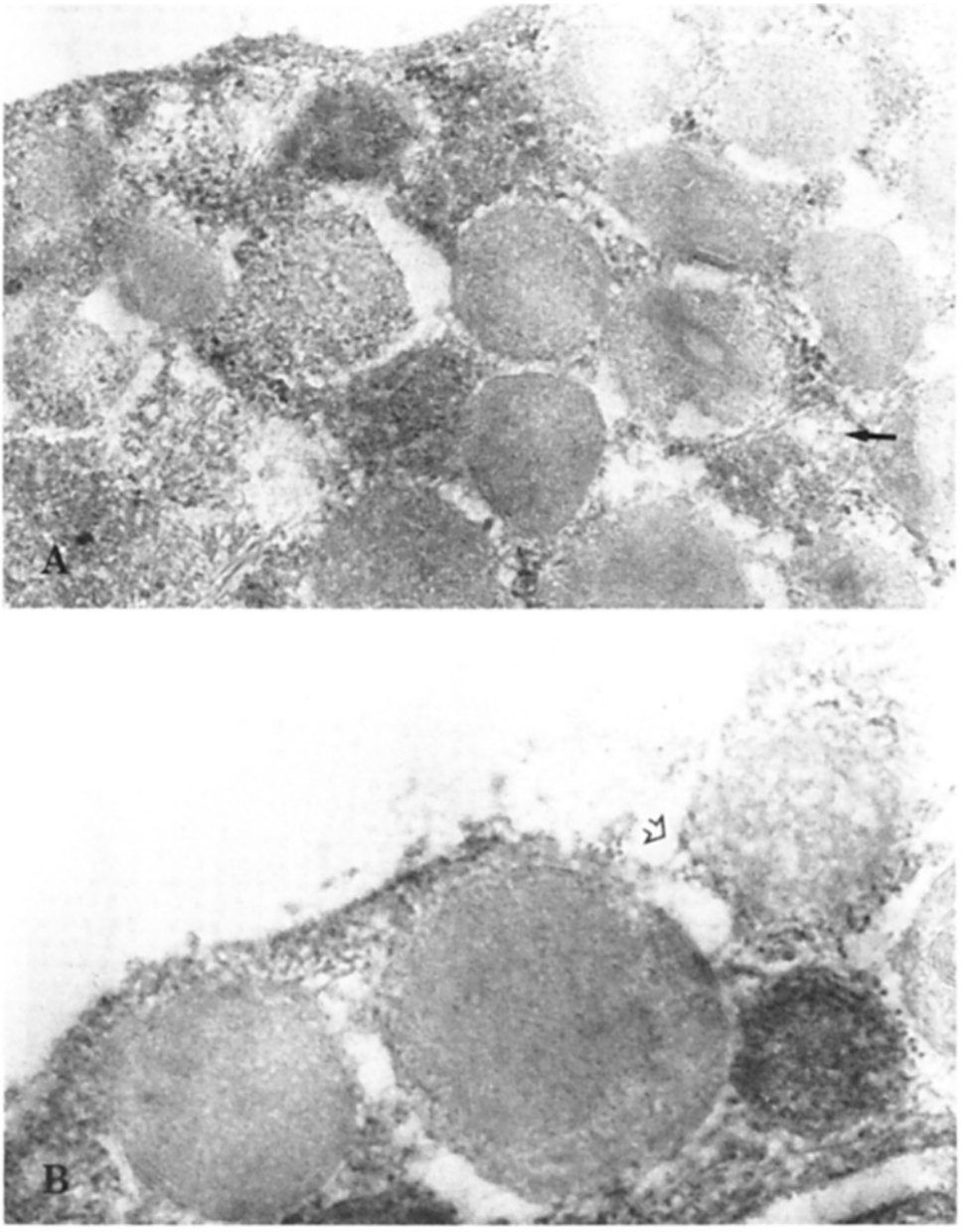

Fig 7. Mast cells of Type II MCD in chronic psoriatic lesion before low-strength anthralin treatment showing a vacuolized appearance. An electron--lucent area (arrow) is separating the perigranular membrane from granule matrix (7A). Mostly the mast cell granules are only bounded by the inner leaflet of the trilaminar perigranular membrane (7A,B) which may fuse with the inner leaflet (open arrow-head) of the mast cell plasma membrane (7B). (mag A x 62 000 and B x 96 000).

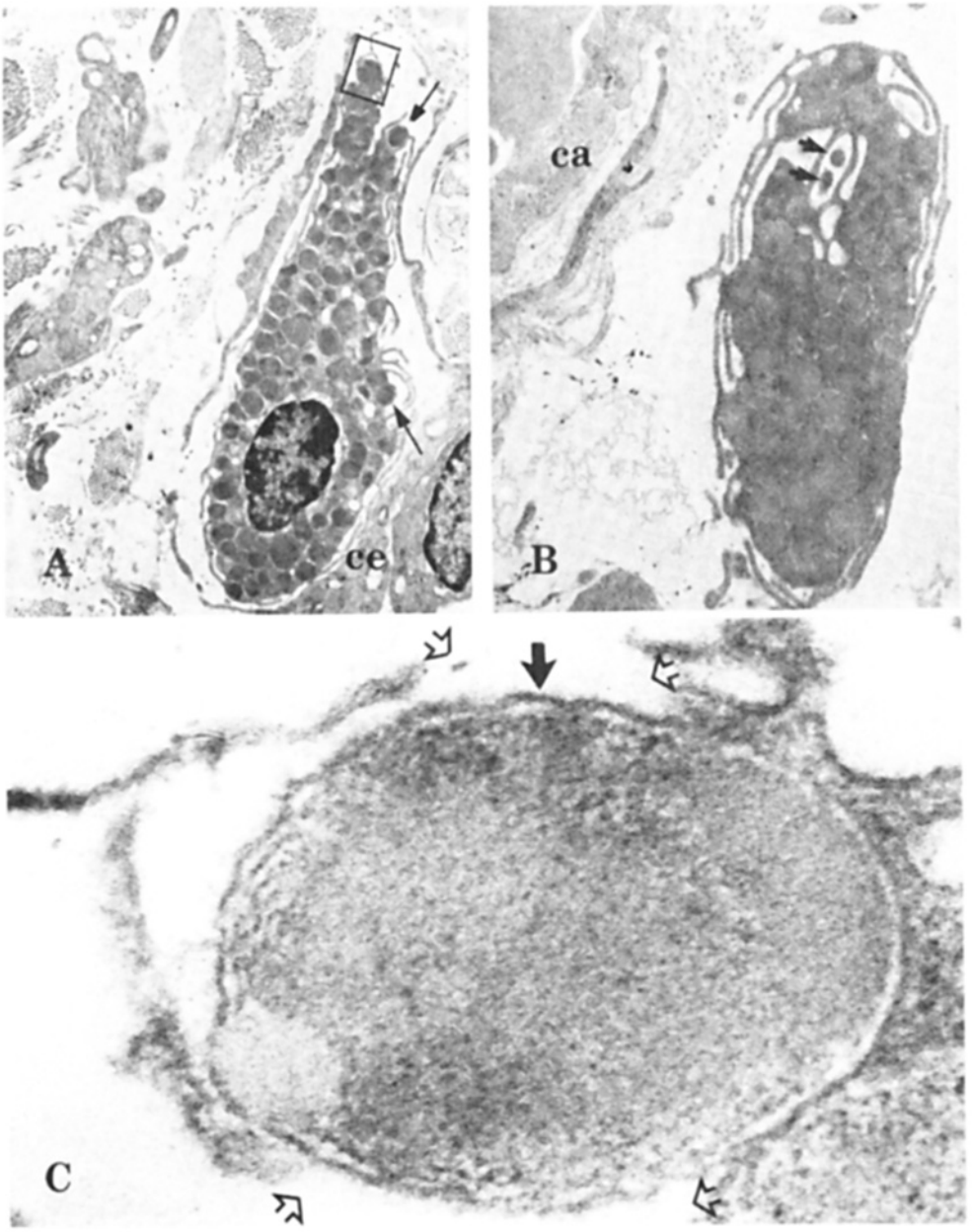

Fig 8. Form A mast cell of Type I MCD in macular psoriasis during low-strength anthralin treatment. A mast cell is in close apposition with another type of cell (ce) (8A). Numerous mast cell granules (thin arrows) are in an intermediate position between the intracellular and extracellular compartments. Enlargement of the area within box (8A) shows that the mast cell granule is encased in a distinct trilaminar perigranular membrane (thick arrow)(8C). The cell boundary exhibits large gaps (open arrow-heads). Discharged mast cell granules (arrow-heads) appear in the immediate vicinity of the mast cell (8B). ca, capillary. (mag A x 12 000, B x 5 800 and C x 134 000).

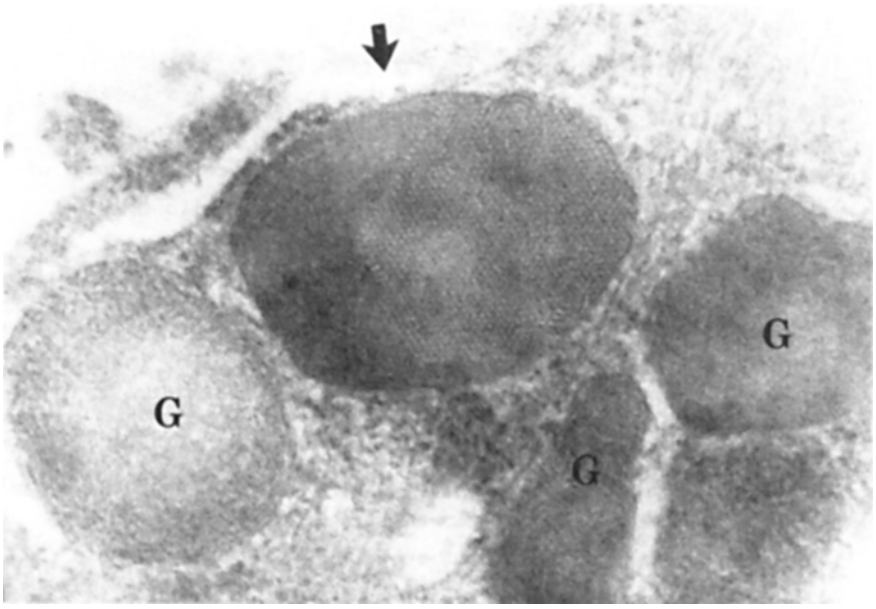

Fig 9. Mast cell in clinically completely cleared lesion site during low-strength anthralin treatment. The mast cell granules (G) are bounded by a trilaminar perigranular membrane. A distinct gap (thick arrow) of the cell boundary is observed. The granule close to the gap shows a crystalline structure with lattices. (mag x 84 000).

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