Etretinate Reduces Connective Tissue Degeneration in Lichen sclerosus et atrophicus

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Retinoids have effects on the metabolism of keratinization and on the metabolism of connective tissue. Recent results have indicated that they may be helpful for treating dermatological diseases which involve marked connective tissue changes such as scleroderma, keloids and actinic skin damage. In addition, retinoids have been shown to reduce the clinical and histological alterations occurring in vulvar lichen sclerosus. For these reasons, etretinate was tried in a patient with extensive lichen sclerosus et atrophicus (LSA). Clinical improvement was seen after three months' treatment, i.e. a decrease in pruritus and softening of the skin. The degenerated zone in the lesional skin was shown by histological analyses to have reduced markedly. The immunohistochemistry, with unaltered staining for type III procollagen and fibronectin, disclosed no signs of enhanced collagen synthesis. Thus the reparation mechanism remained obscure.

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Retinoids, which are extensively used in dermatology, affect cellular metabolism and gene expression (1). The basic molecular mechanisms of their action is unknown, but recent theories suggest that they may act on gene expression in a similar way to steroid hormones (2, 3). Retinoids have been shown to modulate the synthesis of various extracellular proteins in fibroblasts. Retinoids in in vitro fibroblast culture in particular reduce the synthesis of collagen and lower the activity of collagenase, an enzyme capable of degrading collagen (4, 5). Thus, diseases in which alterations in connective tissue are frequently found would be indicated for retinoid treatment. Patients with lichen sclerosus et atrophicus (LSA) of the vulva have recently been treated with etretinate with beneficial results (6), and the same drug has also been tried for treating systemic sclerosis (SS) with promising results (7). We report here on a patient with extensive LSA who was treated with etretinate for three months, resulting in clinical and histological improvement.

CASE REPORT

A 51-year-old woman had had vulvar LSA symptoms for three years and lesions elsewhere in the skin for one year. The vulvar lesions had been treated with oestrogen, hydrocortison and imidazole creams with poor results. Her skin showed small white macules and papules on the upper back, the abdomen and the inner sides of the arms and thighs. These lesions merged to form larger white, indurated areas, especially on the abdomen and around the axillae. She also had depigmented areas under the eyes. Hyperkeratotic follicles were seen on depigmented spots on the upper back. The vulvar mucous membranes were atrophic and a fingertip-sized area of leukoplakia was seen. Both the skin and mucosal lesions were pruritic. Routine laboratory investigations were normal, including negative tests for nuclear and borrelia antibodies.

The patient was treated with etretinate 0.8 mg/kg/day for the first two weeks, after which the dose was reduced to 0.4 mg/kg/day, and because of marked dryness, desquamation and inflammation of the skin ("retinoid dermatitis"), especially in the diseased areas, after another two weeks, to 0.3 mg/kg/day. The patient had also some gastric pains and paronychias at this time. The "retinoid dermatitis" disappeared in three weeks after the etretinate dose was reduced. The treatment was stopped after 3 months as serum triglycerides had risen to 2.29 mmol/l (3× the initial value).

After three months' therapy the pruritus had disappeared entirely from the skin and had decreased markedly in the vulvar area. The lesions were still as white as before, but the indurated areas had softened markedly.

Histological and immunohistochemical methods

Punch biopsy samples for light microscopy and immunohistochemistry were taken from the skin of the abdomen and vulva before and after etretinate treatment. The tissue was fixed in 10% phosphate-buffered formalin, processed routinely, and embedded in paraffin. 5-micron sections were cut and stained with H & E and Verhoeff-van Gieson stains. The thickness of the degenerated dermal zone was determined as a mean value of three to four measurements from H & E sections before and after the treatment using an ocular micrometer.

The sections for immunohistochemistry were deparaffinized and treated with 0.4% pepsin (Chemical Co, St. Louis, Mo) to enhance the availability of the antigens. Endogenous peroxidases were inactivated by exposing the sections to 0.1% hydrogen peroxide, and peroxidase–antiperoxidase staining for type III procollagen and fibronectin was performed according to the method of Sternberger (8). The antibody to pro-III collagen was kindly donated by Drs J. and L. Risteli, Oulu. Purification of the antigen and preparation of the antibody were as described earlier (9). The antifibronectin was obtained from Dako A/S, Copenhagen. Normal rabbit

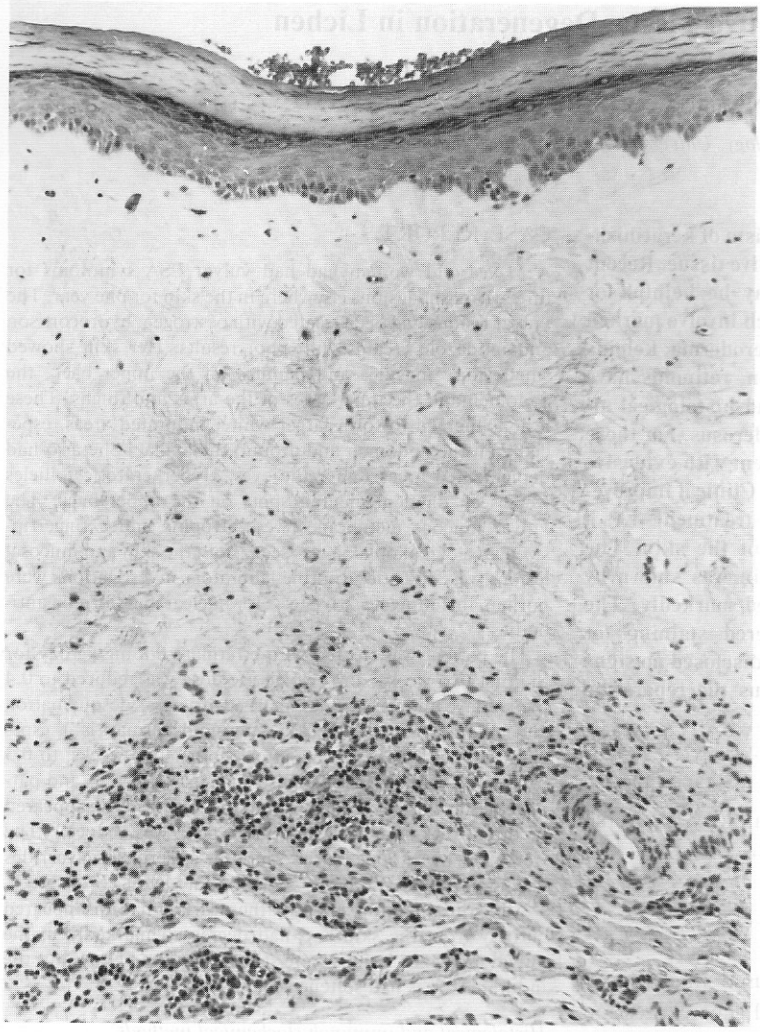

Fig. 1. LM view of a LSA lesion of the vulvar mucosa before etretinate treatment, showing a slightly atrophic, hyperkeratotic and basally oedemic epidermis and a markedly homogenized dermis with moderate numbers of lymphocytes below the degeneration zone. H & E ×140.

serum and phosphate-buffered saline were used for control stainings in place of the primary antibodies.

RESULTS

The light microscopy findings before and after etretinate treatment included homogenization and degeneration of the upper and middle dermis in all specimens and lymphocytic infiltrates in the lower dermis of the samples from the vulva (Fig. 1). The elastic fibres were small, short and few in number in the areas of degeneration before and after the treatment. The epidermis was slightly atrophic and also showed hyperkeratosis and basal oedema in the vulvar skin. The hyperkeratosis diminished after etretinate treatment. The thickness of the degeneration zone in the abdominal skin was 800 microns before the treatment and 490 microns after it. The corresponding figures in the vulvar lesion were 970 microns and 450 microns. No changes in the thickness of the epidermis (except for the reduction in hyperkeratosis) or in the numbers of inflammatory cells were observed.

The antibody to pro-III collagen showed a rather weak staining in the reticular dermis and around pilosebaceous structures but no change after etretinate treatment (Fig. 2). The antibody to fibronectin showed a weak staining over the whole dermis, including the basement membrane areas, but again no changes were seen in the distribution or amount of fibronectin after etretinate treatment.

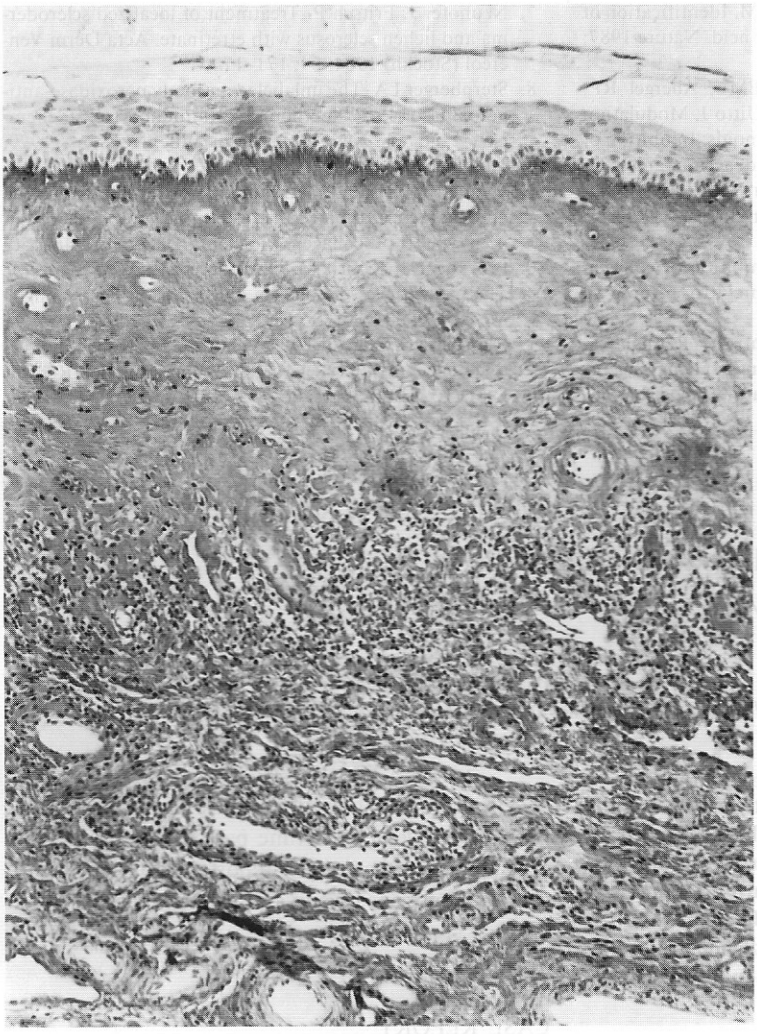

Fig. 2. Immunohistochemical staining of the LSA lesion of the vulvar mucosa for type III procollagen after etretinate treatment shows pro-III collagen in the reticular dermis but not in the degeneration area or below it. The thickness of the degeneration zone and the hyperkeratosis of the epidermis is less compared with Fig. 1. Anti-pro III collagen staining ×140.

DISCUSSION

The most marked histological change involved in LSA is homogenization of the connective tissue, and it was thus very interesting that after three months' etretinate treatment the degeneration zone in the lesional skin seemed to have decreased by almost half. No marked changes could be observed by immunohistochemical methods in either type III procollagen (the minor component of connective tissue) or fibronectin. It has been shown previously that in conditions with increased synthesis of connective tissue type III collagen and fibronectin tend to increase in amount (10, 11). In vitro experiments have shown that retinoids reduce the synthesis of collagen (4), the major component of the dermis, although they have also been shown to reduce the activity of collagenase, an enzyme which degrades collagen (5). The reasons for the discrepancy between the in vitro and in vivo results are currently unknown, but it should be noted that relatively high concentrations of retinoids are required to inhibit collagen synthesis in vitro (4) whereas the concentrations observed in vivo are probably lower.

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Lipodystrophia Centrifugalis Sacralis Infantilis

A 15-year Follow-up Observation

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A unique case of Lipodystrophia centrifugalis sacralis infantilis in a caucasian is reported. This case fulfils all the clinical requirements of the centrifugalis lipodystrophy described in Oriental children by Imamura et al. (1) and usually localized on the abdomen. The 15-year follow-up of this case clearly demonstrates the tendency toward spontaneous remission of the disease after puberty.

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In 1971, under the term "Lipodystrophia centrifugalis abdominalis infantilis" Imamura et al. (1) described a peculiar atrophic skin disease characterized by: (*a*) depression of the skin of the abdomen and of the neighbouring regions, due to the loss of subcutaneous fat; (*b*) centrifugal enlargement of the depressed area; (*c*) presence of an inflammatory border surrounding the entire lesion; (*d*) onset before the age of 3 years; (*f*) absence of abnormalities in other organs. Regional lymph node swelling was noted in about 65% of the patients (2, 3). Thirty patients, out of 55 examined, showed complete or partial spontaneous improvement as time passed (4). Up to now, about 90 cases have been reported in Oriental children and only one case in an English caucasian infant (5).

CASE REPORT

In 1973, a 3-year-old Italian girl was seen at our Department of Pediatric Dermatology for a cutaneous depression of the sacrolumbar region, which had appeared at the age of 1 year as a round patch 3 cm in diameter. The lesion quickly lost its inflammatory features and resolved into a centrifugally enlarging depressed area. No trauma or injection had preceded the appearance of the lesion. On clinical examination the patient showed a large oval depressed area with the larger cross diameter of 11 cm and smaller longitudinal diameter of 6 cm on the sacrolumbar region (Fig. 1). A slightly erythematous border surrounded the entire lesion. The underlying blood vessels were visible through the skin. Regional lymphadenopathy was absent. Laboratory findings and X-ray examination of thorax and bones were all within normal limits. The girl's parents refused histological examination and failed to bring her back for further check-ups.

In February 1988, that is to say 15 years after the first observation, the patient returned spontaneously to our Clinic for a mycologic examination. On that occasion, she asked for a check of the lesion in the lumbosacral region. The patient reported that the lesion had continued to enlarge up to the age