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Successful Treatment of Erythema Elevatum Diutinum with 1 alpha, 25-dihydroxyvitamin D_3

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Abstract A 67-year-old Japanese man with erythema elevatum diutinum well responded to treatment with oral administration of 1 alpha, 25-dihydroxyvitamin D_3. Recurrent lesions developed whenever vitamin D_3 therapy was stopped. To our knowledge, this is the first case showing the potential usefulness of 1 alpha, 25-dihydroxyvitamin D_3 modulating the cutaneous leukocytoclastic vasculitis.

Key Words : Erythema elevatum diutinum, Vitamin D_3.

Introduction

Erythema elevatum diutinum is an inflammatory disease with a leukocytoclastic vasculitis and simaltaneously proliferating fibroblasts. Dapsone has been commonly used for treatment of the disease[1]. However, dapsone can cause adverse effects such as hemolytic anemia. We must search for newer effective medications. We report one case of erythema elevatum diutinum with marked improvement after administration of 1 alpha, 25-dihydroxyvitamin D_3 (1α, 25 $(OH)_2D_3$).

Case report

A 67-year-old Japanese man was seen in our Department in September 1989 because of cutaneous lesions and arthralgia. In August 1989, he developed with mild fever and arthralgia of the elbows, followed by painful purpuric-reddish infiltrative erythemas or papules on the upper extremities, buttock and face. He had no serious past history and no previous history of taking drugs. Initially he was treated with oral administration of antibiotic (cefaclor: 1,000 mg/d) for 1 week, without any improvement and treatment was stopped. In September 1989, he was reffered to our Clinic. Physical examination revealed painful, raised, dull reddish colored erythematous, scaly lesions in size of pea to bean, involving the hands, the left elbow and the right cheek, in addition to arthralgia of the elbow joints, but without fever (Fig. 1).

Histological examination of a swollen, painful, erythematous plaque on the dorsum of the left hand revealed a leukocytoclastic vasculitis with mild leukocytoclasis, in addition to proliferating fibroblasts (Fig. 2). Among upper dermis, there are remarkable edema, fibrin deposit, moderate extravasation of red blood cells. Infiltrating cells composed of neutrophils and lymphocytes. Amyloid and lipid stainings were proved negative. Direct and indirect immunofluorescence studies of this specimen for IgG, IgA, IgM and C3 were proved negative.

Laboratory examinations showed an erythrocyte sedimentation rate (42 mm/h); total hemolytic complement concentration (42.0 ; 29-40); C-reactive protein (0.42 mg/dl; normal less than 0.24 mg/dl); IgA (346 mg/dl; normal, 167-300 mg/dl). The following laboratory investigations were either normal or

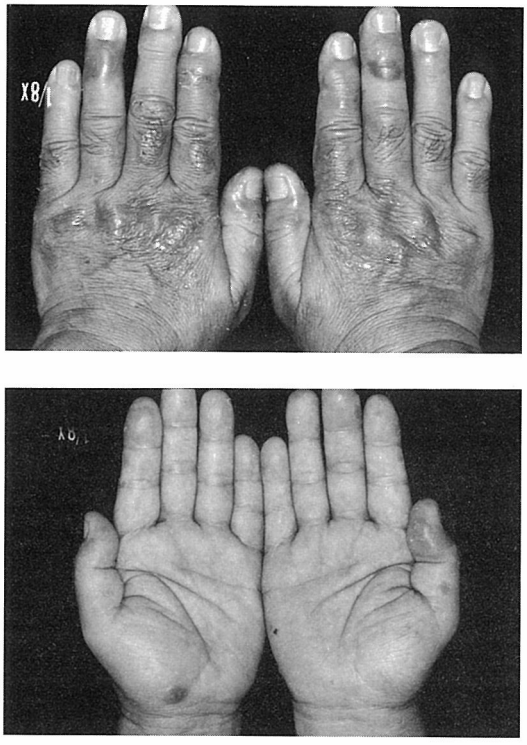

Fig 1. Cutaneous lesions on the hands before treatment with 1α, 25 $(OH)_2D_3$.

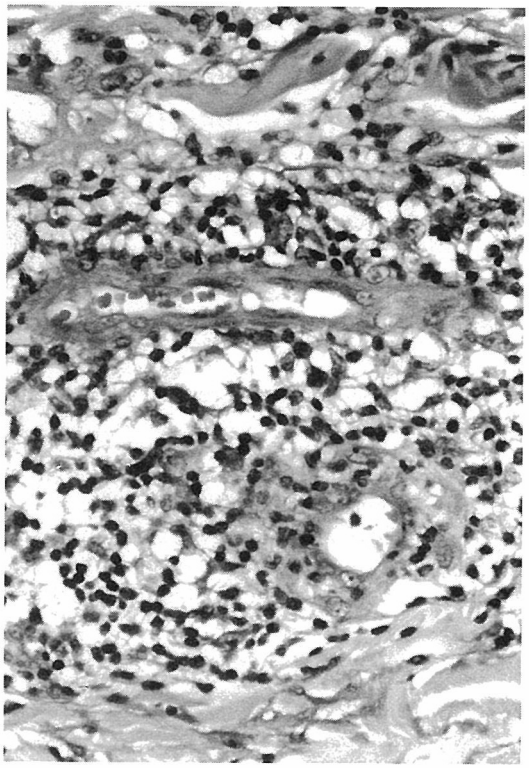

Fig 2. Histopathology of an early erythema on the dorsal hand. There are fibrinoid deposits around and within the vessel walls and abundant lymphocytes, neutrophils and fibroblasts.

negative: complete blood cell count, blood chemistry studies, protein electrophoresis, anti-streptolysin-O titer, anti-nuclear antibodies, rheumatoid factor, cryoglobulins and cryofibrinogens, serum circulating immune complex, urinalysis, and chest x-ray. Bone marrow showed a normally cellular marrow with normal hemopoiesis. Total hemolytic complement concentration (CH_{50}) was variable but usually the level was over the normal upper limit during the development of the eruptions.

The clinical and histological features were consistent with a diagnosis of erythema elevatum diutinum and 1α, 25 $(OH)_2D_3$ of 1 μg was introduced, two weeks later, with remarkable improvement of skin lesions and arthralgia except for some residual hyperpigmentation. The drug did not show any side effect, two weeks later, including laboratory data. The drug was discontinued and the patient was reevaluated. After 3 weeks of discontinuation, the eruption and arthralgia recurred (Fig. 3). Subsequently, 0.5 μg of the 1α, 25 $(OH)_2D_3$ daily was readministered and the symptoms of the eruptions and arthralgia improved in 2 weeks. Biopsy specimen obtained from a withdrawing erythema on the dorsal hand showed moderate infiltrates composed of lymphocytes and histiocytes, without leukocytoclastic vasculitis (Fig. 4). When the drug was stopped, the eruption reappeared. With follow-up periods of 3 years, the patient has been administered 0.25 μg once about every 2 day and well-controlled, without no significant hematological disorders (Fig. 5).

Discussion

The histology of lesions of erythema elevatum diutinum is variable[2]. Early lesions

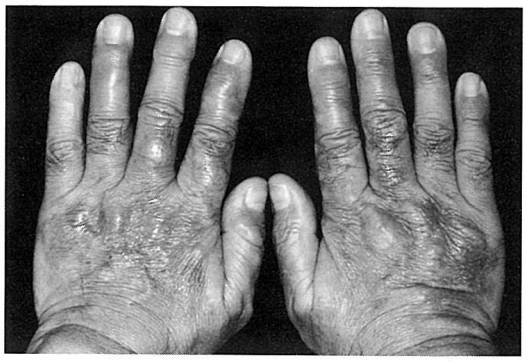

Fig 3. Cutaneous lesions on the hands at re-appearance.

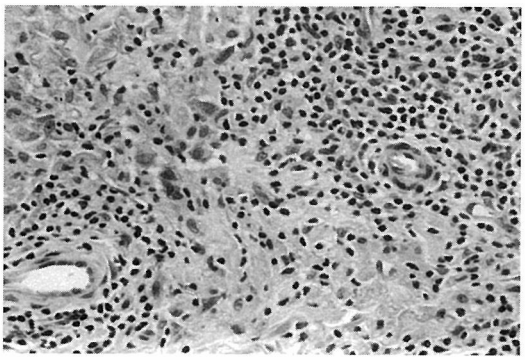

Fig 4. Histopathology after regression of an infiltrative erythema. There are many mononuclear cells and histiocytes, without leukocytoclastic vasculitis.

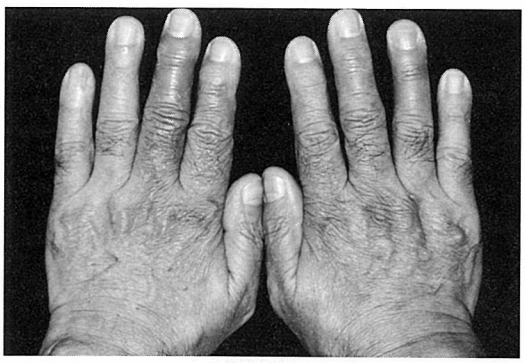

Fig 5. Clinical appearance of the well-controlled hands during medication after follow-up periods of one year.

of erythema elevatum diutinum usually show leukocytoclastic vasculitis with capillary proliferation, whereas late lesions of the disease show fibrosis and areas of granulation tissue. In our patient, the histopathological finding of the biopsied erythematous plaque was an early lesion showing the leukocytoclastic vasculitis. The precise pathogenesis of erythema elevatum diutinum is uncertain[3], although a mechanism due to the deposition of immune complexes, particularly in the wall of small blood vessels, is proposed [4].

1α, 25 $(OH)_2D_3$ in our case was effective for reduction of the damage of vascular endothelial cells and neutrophilic infiltration, whereas mononuclear cells and fibroblasts were spared. Recent studies provide evidence that 1α, 25 $(OH)_2D_3$ has an effect on the regulation of immune responses as well as on hemopoietic cell differentiation and proliferation [5]. 1α, 25 $(OH)_2D_3$ appears to mediate its anti-proliferative effects through both IL-2-dependent and IL-2-independent mechanisms and mediate its anti-inflammatory effects by augumented production of cytokines (Tumor necrosis factor,prostaglandin E_2, interleukin 1). In our case, increased amount of prostaglandin E_2 released from macrophages induced by 1α, 25 $(OH)_2D_3$ may prevent leukocytoclastic vasculitis. Ruzicka et al. reported that induction of leukocytoclastic vasculitis by leukotriene B_4 and 12-hydroxyeicosatetraenoic acid was prevented by prostaglandin E_2[6].

This appears to be the first reported case showing that 1α, 25 $(OH)_2D_3$ is a potent drug for treatment of the cutaneous leukocytoclastic vasculitis. Studies of additional patients may be helpful in evaluating the usefulness of this finding.

References

1) Cream JJ, Levene GM, Calnan CD: Erythema elevatum diutinum: An unusual reaction to streptococcal antigen and response to dapsone. *Br. J. Dermatol.*, **84** : 393-399, 1971.
2) LeBoit PE, Benedict Yen TS, Wintroub B: The evolution of lesions in erythema elevatum diutinum. *Am. J. Dermatopathol.*, **8** : 392-402, 1986.
3) Requena L, Barat A, Hasson A, Arias D,

Gutierrez MC, Martin L, Castro ADE: Erythema elevatum diutinum mimicking porphyria cutanea tarda *Brit. J. Dermatol.*, **124** : 89-91, 1991.

4) Braverman IM, Yen A: Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leukocyto-clastic angiitis. *J. Invest. Dermatol.*, **64** : 105-112, 1975.

5) Rigby WF: The immunobiology of vitamin D. *Immunol. Today,* **9** : 54-58, 1988.

6) Ruzicka T, Burg G: Effects of chronic intracutaneous administration of arachidonic acid and its metabolites: Induction of leukocytoclastic vasculitis by leukotriene B_4 and 12-hydroxyeicosatetraenoic acid and its prevention by prostaglandin E_2. *J. Invest. Dermatol.*, **88** : 120-123, 1987.