[症例報告]A case report of hyperkeratotic lupus erythmatosus : An electron microscopic study of hyperkeratotic lesion

A case report of hyperkeratotic lupus erythmatosus -An electron microscopic study of hyperkeratotic lesion-

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ABSTRACT

We report a case of hyperkeratotic lupus erythmatosus (LE) occurring on the dorsum of the right hand and the forearm of a 47-year old construction worker. Clinically, the hyperkeratotic LE lesions were scaly, revealing an indurated brownish margin and a wart-like appearance. Histopathologically, marked hyperkeratosis and acanthosis at the epidermis and solar elastosis of the upper dermis were observed. Serum immunoglobulins (IgG,IgA,IgM,) levels were increased, but there was no deposition of the immunoglobulins at the dermo-epidermal junction in direct immunoflourescence examination. Electron microscopically the epidermal basement membrane was thick and partially multilayered, whereas the blood vessel walls were thickened and multilayered at the dermis. The collagen fibers were also thick and abundant, with many fibroblasts present at the upper dermis near the basement membrane zone. From these findings, we concluded that long term exposures to sun light might have damaged the photosensitive skin of LE patient. After repeated damage and repair, the collagen fibers had become thick and abundant with many fibroblasts at the upper dermis. We compared our case with those of Systemic Lupus Erythmatosus (SLE) and Discoid Lupus Erythmatosus (DLE) using electron microscopic and immunohistochemical techniques. We could not determine why some DLE patients show wart-like lesions while others do not. *Ryukyu Med. J., 17(1) 51~56, 1997*

Key words: hyperkeratotic LE, multilayered basement membrane, fibroblasts and UV rays

INTRODUCTION

Hyperkeratotic lupus erythmatosus (LE) is one of the sub-types of discoid lupus erythmatosus (DLE) and also called keratotic LE or verrucous LE. It was first reported by Behcet in 1940. Clinical features of hyperkeratotic LE are scaly and hyperkeratotic lesions with an indurated brownish margin. The lesions shows wart-like eruptions and are commonly observed on the dorsum of the hands and the forearms[1]. Histopathologically, marked hyperkeratosis and acanthosis of epidermis are observed In immunofluorescence staining, deposition of IgG,IgM,IgA and/or complements are often observed at the dermo-epidermal junction[2]. These clinical and histopathological findings are different from other cutaneous LE cases.

Clinically, the lesions of systemic lupus erythmatosus (SLE) are erythema or slightly edematous patches without significant degree of scalling and atrophy. Histopathologically, thinning of the epidermis, liquefaction of the basal cell layer and scattered cell infiltration, comprising mostly lymphocytes at the upper dermis are also observed[3]. Direct immunofluorescence (DIF) in SLE is mostly positive in lesional as well as in uninvolved skin. Cutaneous lesions of discoid lupus erythmatosus (DLE) are well defined, erythmatous, slightly infiltrated discoid patches, some times with adherent thick scales and follicular plugging. These lesions are usually limited to the face. At the sites of the lesion, slight erythmatous pigmentation with scar is often present. Histopathologically, hyperkeratosis, parakeratosis, atrophy of the epidermis, follicular plugging, liquefaction of the basal cell layer and patchy cell infiltration, comprising mostly lymphocytes with some histiocytes at the upper dermis, are observed. Elastic degeneration of the collagen fibers and edema of the upper dermis are observed in light exposed areas[4]. DIF shows linear deposition of immunoglobulins and complements at the dermo-epidermal junction in the lesions, but not in the uninvolved skin. The reason (s) why histological features are different in the skin lesions between hyperkeratotic LE and other cutaneous LE, and why marked changes of

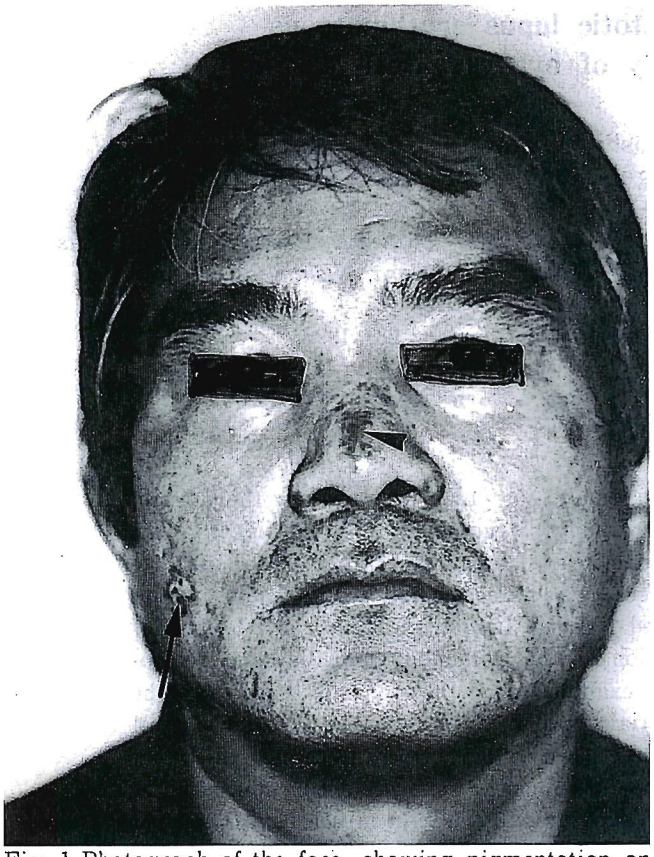


Fig. 1 Photograph of the face, showing pigmentation on the nose (arrow head) and on the right cheek (↑).

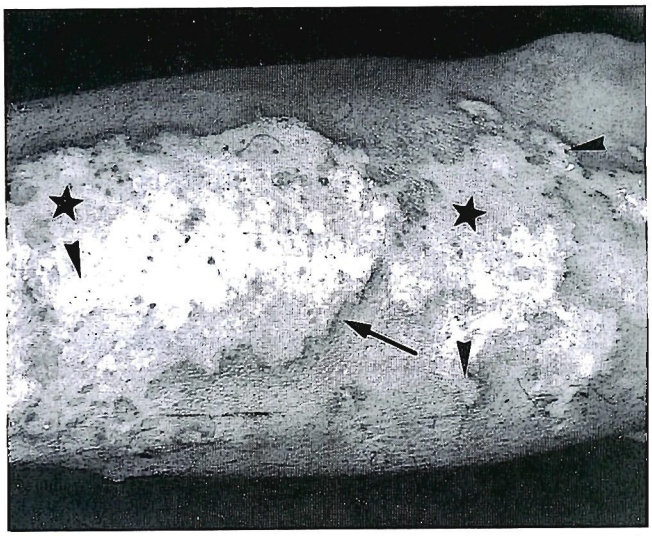


Fig. 2(a) Photograph of the right fore-arm, hyperkeratotic erythmatous lesion with brown margin (↑), Wart-like eruptions (arrow head) and erythma (star), can be seen.

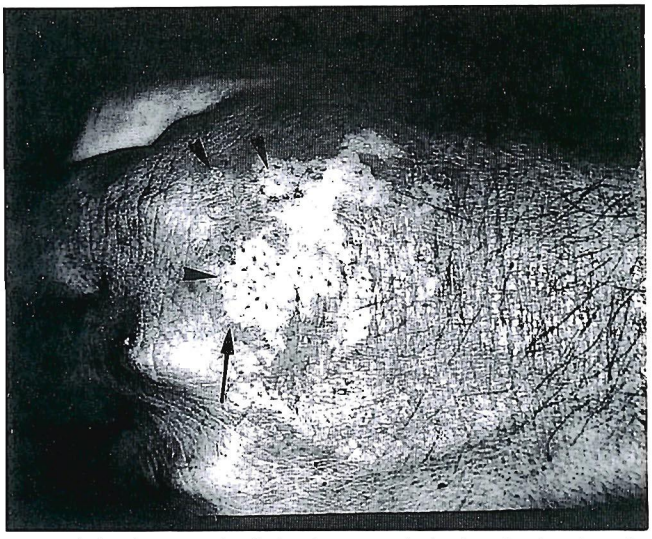


Fig. 2(b) Photograph of the dorsum of the hand, showing the hyperkeratotic lesion with wart-like eruption (arrow head), and brown margin (↑).

hyperkeratosis and acanthosis of epidermis were observed in our LE case, is unclear. This report attempts to investigate the mechanism by which this difference (s) occurs.

CASE REPORT

A 47- year-old construction worker visited our outpatient clinic on 25 January, 1996. The patient had several discoid erythmas, sized 1~2 cm and pigmentation on the nose, right cheek and the ear (Fig. 1) On the right forearm and dorsum of the hand, hyperkeratotic erythmatous lesions with a brown pigmented margin were present, in which some wart-like eruptions were also observed (Fig. 2a,2b). These features had been present for about 10 years however, the lesions became worse in summer. At the age 44 he underwent surgery for pancreatitis, but had not been taking any medication for the last years.

Laboratory data showed that blood and biochemical levels were within normal limits. Serum immunoglobulins (IgG 2128mg/dl, IgA 407mg/dl, IgM 239mg/dl) levels were increased. CH50 was decreased (27U/ml) but complement (C) 3 and C4 were within normal limits. The anti-nuclear antibody was at the upper limit of normal range. The anti-DNA antibody was negative.

A biopsy specimen was taken from the hyperkeratotic lesion of the right forearm for light micro-scopic and electron microscopic examinations and for immunofluorescence staining.

In hematoxylin-eosin (HE) staining, marked hyperkeratosis, parakeratosis, acanthosis and follicular plugging at the epidermis were observed. Liquefaction of the basal cell layer was not clear as compared with the other LE cases. The edematous change was remarkable at the basement membrane zone. An amorphous structure around the blood vessels was also observed, whereas at the upper der mis, much dense cellular infiltration, mainly lymphocytes and some spindle cells, was noted. These spindle cells seemed to be fibroblasts. In the mid dermis, dense cellular infiltration, around the blood vessels was also observed but at the upper and mid dermis, proliferation of the collagen fibers was seen. The collagen fibers were irregular,

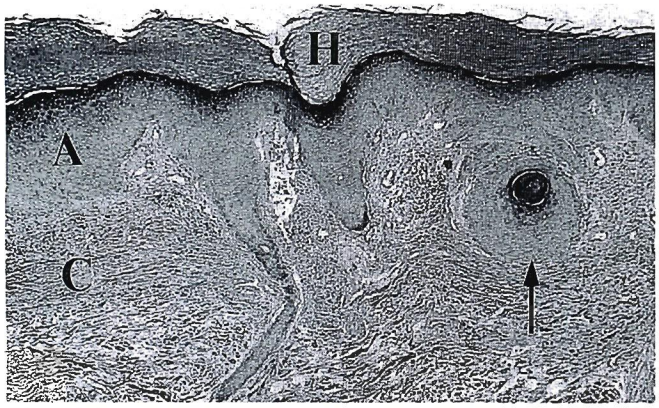


Fig. 3(a) Low magnification view of histopathology showing remarkable hyperkeratosis of the hornylayer (H), marked acanthosis (A), and follicular plugging like change (↑), at the epidermis. C, collagen fibers (HE,×4).

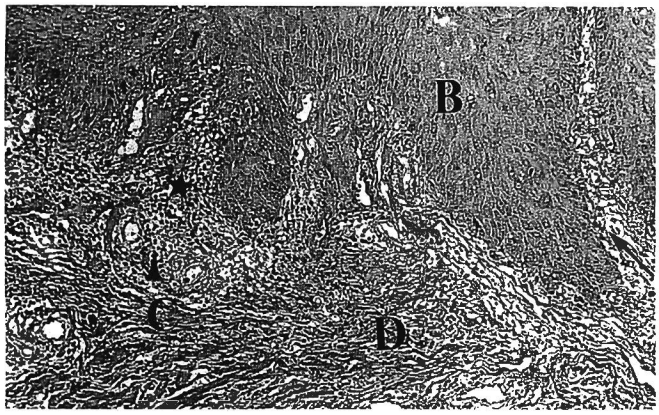


Fig. 3(b) High magnification view showing dense cellular infiltration at the upper dermis (star), and around the blood vessel (arrow head), with edematous change at the basement membrane (↑). Collagen fibers (C) are short and appear proliferated. B, Basal cell layer and D, dermis (HE,×10).

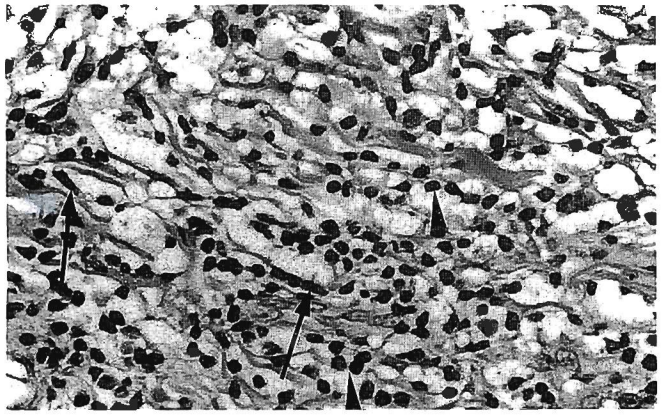


Fig. 3(c) High magnification view at upper dermis showing the cellular infiltration, mostly concisting of lymphocytes (↑). Some spindle cells (arrow head), can also be seen (HE,×40).

short and thick, mostly at the upper dermis (Fig. 3a,3b,3c). Periodic Acid Schif (PAS) stain examination revealed

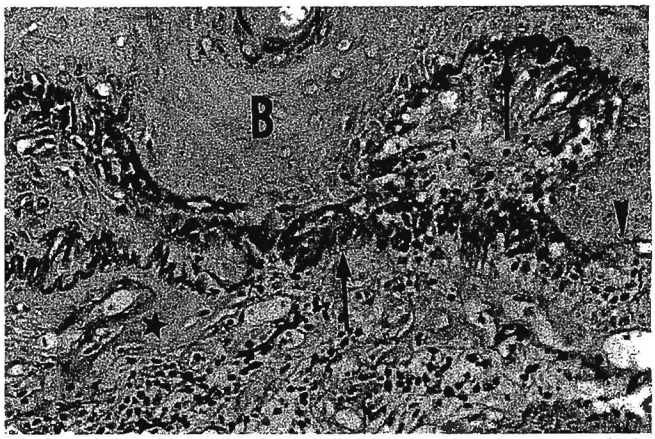
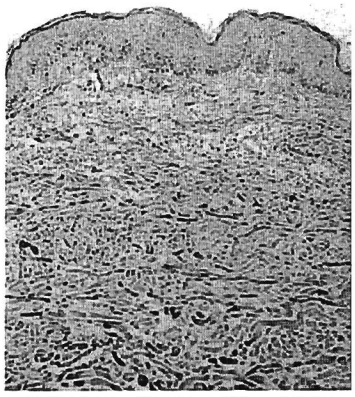


Fig. 4 Multi-layered basement membrane like structure (↑), disappearence of basement membrane (arrow head), and an amorphus structure around the blood vessel (star) are seen. B, Basal cell layer (PAS,×20).



NORMAL SKIN (CONTROL)

OUR CASE (H·L·E)

Fig. 5 Comparison of the normal control with our HLE case. In our case collagen fibers are thick, short and many at the upper dermis (Weigerts,×4).

that the basement membrane at the demo-epidermal junction was thickened and multilayered. In some areas the basement membrane had disappeared. At the papillary dermis the blood vessel walls were thickened revealing an amorphus structure (Fig. 4). In Weigerts staining, the elastic fibers were short, thick and deeply stained at the upper dermis, compared to normal control (Fig. 5). Immunofluorescence stainings showed no positive linear

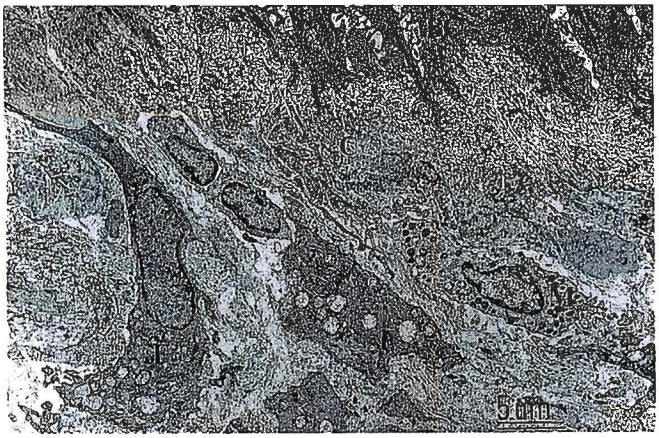


Fig. 6(a) Electron micrograph of HLE, near the basement membranre. The collagen fibers (C) are abundant, fibroblast (F) and mast cell (M), are seen. BC, Basal cell layer (×1500).

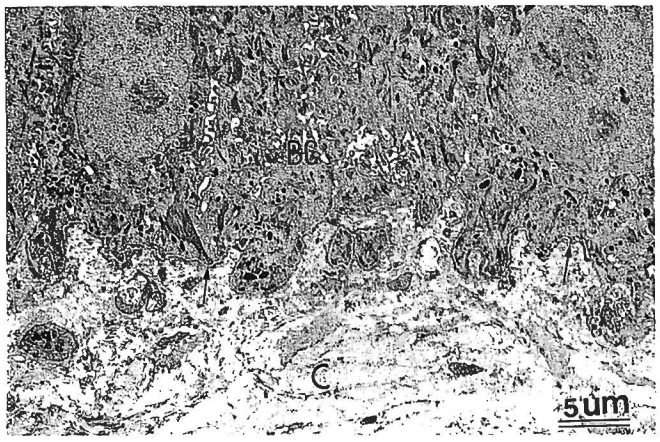


Fig. 6(b) Electron micrograph of the normal control, at the dermo-epidermal junction. Collagen fibers (C), are normal and no fibroblast is seen. Basement membrane (↑); BC, basal cell layer (×1500).

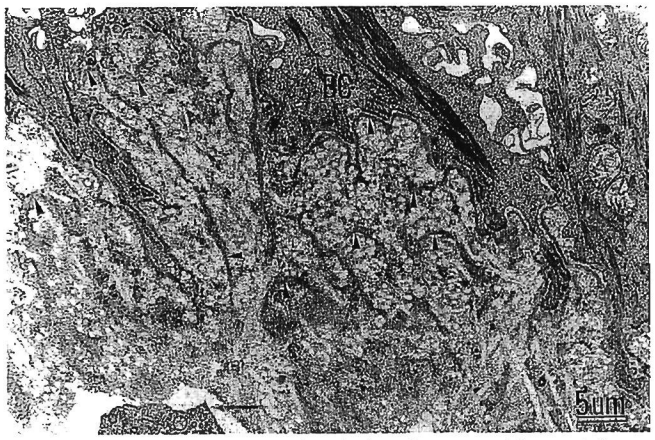


Fig. 7 Electron micrograph of the dermo-epidermal junction showing multi-layered basement membrane (arrow heads) ; BC, basal cell layer (×5000).

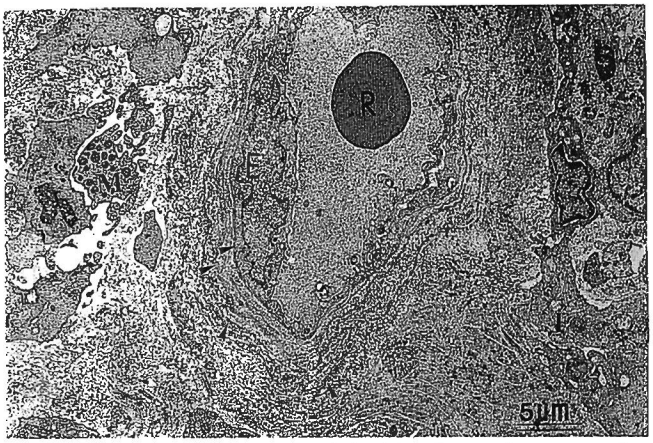


Fig. 8 Electron micrograph of the blood vessel at upperder mis. The wall is thick and multi-layered (arrow heads). Rred blood cell (R), Endothelial cell (E), are present inside the blood vessel. Mast cell (M), fibroblast (F) also can be seen (×1500).

deposition at the basement membrane zone and around the blood vessel walls.

Electon microscopic examination revealed that collagen fibers were abundant and some fibroblasts were seen beneath the epidermal basement membrane at the upper dermis. In comparision to normal skin, the number of fibroblast was striking (Fig. 6a, 6b). The demo-epidermal junction showed several layered basement membrane like- structure similar to basement membrane (Fig. 7). At the upper dermis, the blood vessel walls were thick and multi-layered (Fig. 8). These findings were slightly different from the DLE cases and as a result our case constitute a distinct sub-type. The case was diagnosed as hyperkeratotic lupus erythmatosus, subtype DLE. The patient was treated with Cepharantin 60 mg/day, Vitamin C 1500 mg/day and Antebate (corticosteroid) ointment and he is responding to treatment.

DISCUSSION

Photosensitivity is one of the clinical signs of the various forms of LE. Etiology of the disease is still unknown, but many dermatologists assert that ultra violet (UV) radiations are an important factor in the development of the lesions. Several experiments with single or repeated irradiations of UV rays cause DLE like lesions[5~9]. Experimentally the lesions can be induced in hairless mice by the same methods[10]. Okinawa is located in the sub-tropical zone Therefore the intensity of UV rays is greater than in other regions of Japan. Because of his occupation, our patient had been exposed for a long time to the solar radiation, which resulted in accumulation of UVrays in higher doses. He developed skin lesions, which worsened every summer. Histopathologically ultra violet rays B (UVB) damages the epidermis to a greater extent than ultra violet rays A (UVA), while UVA impairs the dermis to a greater

degree than UVB[10~12]. UVA is less absorbed in the epidermis, and it penetrates deeper into the skin than UVB[11,13,14]. Kumakiri et al. and Hashimoto *et al.* reported that repeated exposures (17-20times) of UVA could cause thick, multi-layered basement membrane at the demo-epidermal junction and blood vessel walls[15~17]. The damage at the epidermis, mostly at the basal cell layer, such as basal cell liquefaction degeneration, hyperkeratosis, acanthosis and parakeratosis, appeared after the irradiation by UVB. The dermal connective tissues were damaged by UVB, which induced solar elastosis[5,10,12,18,19]. Elastosis become severe by the combined effects of UVA and UVB[12,20]. Edema of the upper dermis and dense cellular infiltration, consisting mainly lymphocytes, some monocytes, mast cells and histiocytes, were observed after long term UVA irradiation[10,17,20]. In other cases of cutaneous LE, edamatous change at the dermo-epidermal unction and solar elastosis were not as severe as seen in hyperkeratotic LE. In DIF study, immunoglobulins were shown in linear deposition at the dermo-epidermal junction[2]. It is reported that the damage at the dermo-epidermal junction and the blood vessel walls are caused by immunodeposits. However our hyperkeratotic LE case showed severe solar elastosis and no linear immunodeposits, in comparison with other cutaneous LE. The damage at the dermo-epidermal junction in our case seems to be a result of long term UV exposure. The existence of the multi-layered basement membrane in the electronmicroscopicexamination also supports the idea of repeated solar damage. Electron microscopic examination also revealed that collagen fibers were abundant and many fibroblasts with some mast cells were present at the upper dermis in our case. In 1987, Donald *et al.* observed the proliferation of collagen fibers and fibroblasts beneath the epidermal basement membrane at the upper dermis after 16 weeks of UV-radiation on hairless mice[20]. Fibroblasts together with blood vessels and macrophages move into the wound site as a unit to repair it. The fibroblasts construct new extracellular matrix necessary to support cell growth whiles blood vessels carry oxygen for nutrition[21]. Latkowski et al. reported in 1995 that fibroblasts secrete keratinocyte growth factor (KGF). which is a potent paracrine mitogen, specific for the epidermal keratinocytes[22]. KGF stimulates cell growth through a signalling pathway joined by epidermal growth factor (EGF)[23] and produces and promotes keratinocyte proliferation[24]. KGF secreted by fibroblasts, is in high concentration at the wound site and plays an important role in the migration and proliferation of keratinocytes during the healing process. Increase in proliferation is confined to the basal cell layer, and orthokeratosis is seen in the outer layer[25]. This suggests that KGF can cause parakeratosis and allows the maturation and differentation of the epidermal cells in the healing process[26~28]. It was observed in ourcase that the degeneration of collagen fibers and fibroblasts increase at the upper dermis, near the basement membrane. This histological change caused by solar damage was also reported by Donald *et al.* in their experimental study Increase in fibroblasts at the upper dermis, near the basement membrane zone probably results in secretion of KGF, which stimulates more epidermal cell proliferation.We speculate that the observed remarkable acanthosis and marked hyperkeratosis of the epidermis, may have occurred as a result of fibroblasts proliferation. We also surmise that after repeated damage by UV-rays and subsequent repair, the collagen fi bers becomes thickend and abundant with many fibroblasts at the upper dermis, near the basement membrane. These fibroblasts secrete KGF which cause epidermal cellular proliferation. Hyperkeratotic, wart-like lesions seen in our case, may be the result of excessive KGF production secreted by fibroblasts which causes more epidermal cellular proliferation. It is also likely that hyperkeratotic lesions may have occured after trauma or excessive scratching. However, many cases of DLE do not show hyperkeratotic and wart-like lesions. The differences observed between our case and other DLE cases could not be explained.

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