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Photochemotherapy-induced Lentigines on a Vitiliginous Patch. Electron Microscopic Observations

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Patients with vitiligo seem to be less prone to the development of lentigines as a side effect of long-term photochemotherapy than do psoriatics. An 8-year-old boy who had a vitiliginous patch on his left thigh, had been receiving photochemotherapy since he was 2 years old. At the age of 3, multiple star-shaped, brownish macules developed at the site of treatment. Photochemotherapy was continued until the patient was 6 years old, at which time no improvement in the vitiligo was seen, so photochemotherapy was discontinued. Now 2 years after treatment the lentigines still persist. On electron microscopic examination, the melanocytes showed two patterns of cell death: coagulative necrosis and apotosis together with atypical cytoplasmic and melanosomal alterations.

Key Words: Vitiligo, photochemotherapy, lentigines, coagulative necrosis, apoptosis

The development of lentigines on the treatment site is a common side effect of long-term photochemotherapy for psoriasis. However, these lesions are very rarely observed in patients with vitiligo (Kanerva and Lauharanta 1985). We describe herein a patient with vitiligo who had been receiving photochemotherapy but has had no improvement and still has multiple star-shaped, brownish macules that have not resolved two years after the discontinuation of PUVA therapy. Using electron microscopy, two patterns of cell death of the melanocytes were demonstrated.

CASE REPORT

An 8-year-old boy who had a vitiliginous patch on his left thigh, had been receiving psoralen and ultraviolet A (PUVA) therapy since he was 2 years old. His vitiliginous skin was exposed to natural sunlight between the hours of 11 a.m. and 3 p.m. 30 minutes after topical application of methoxsalen. The initial exposure to sunlight was 5 minutes, and this was increased by 30 second intervals until the patient developed a moderate erythema 24-48 hours after exposure. He needed only 5-10 minutes of sunlight to produce a moderate erythema throughout the treatment period. This regimen was followed daily by his parents at home; and, if a marked erythema developed, the next treatment was delayed until this erythema subsided. At the age of 3, multiple star-shaped, brownish macules developed at the site of treatment (Fig. 1). But PUVA therapy was continued until the patient was 6 years old, at which time there was no improvement of vitiligo. The PUVA therapy was discontinued and now, 2 years post-treatment, the lentigines still persist.

Histopathologic examination of the lentiginous lesion demonstrated an elongation of the rete ridges and an increase in melanin in the basal cell layer. On staining with DOPA, the melanocytes exhibited an increase in density as well as longer dendritic processes compared with those of normal skin.

Electron microscope studies have been carried out on biopsies taken from the lentiginous and vitiliginous lesions. The melanocytes in the lentiginous lesion were increased in number, and the rupture of the plasma membranes and the vacuolization and loss of cell organells in the cytoplasm were noted. There were aggregations and increased numbers of melanosomes in the adjacent keratinocytes (Fig. 2). The keratinocytes in the PUVA lentigines had large, granular melanosomes, which frequently formed

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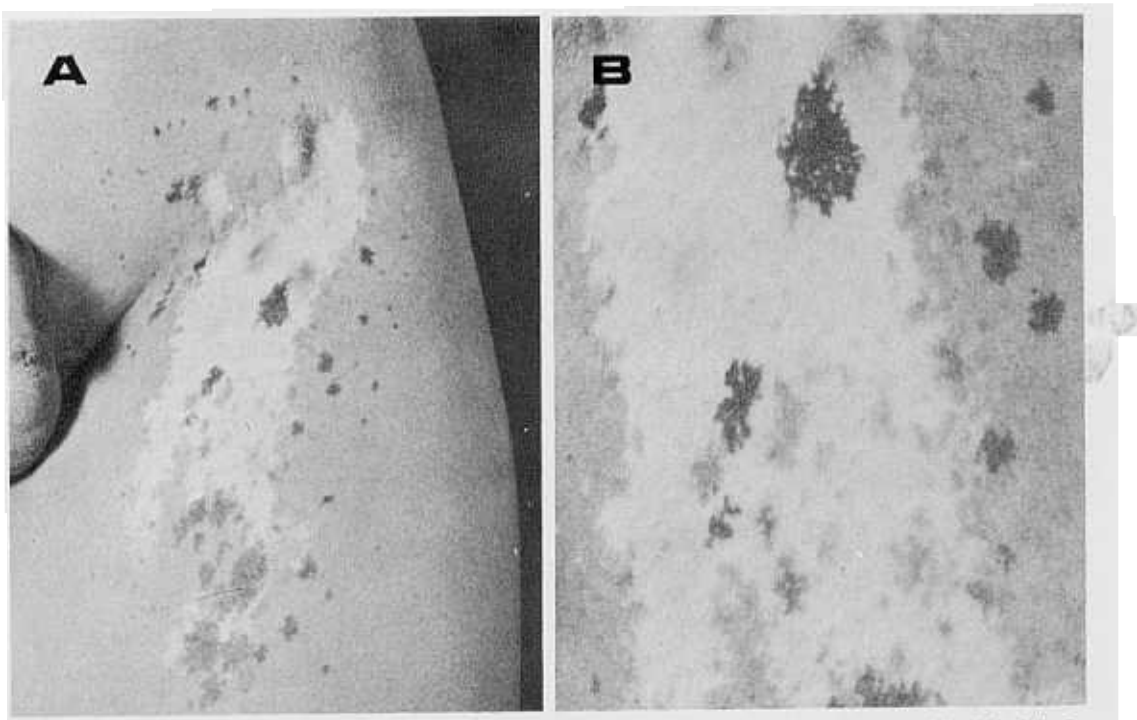

Fig. 1. A, Multiple star-shaped, brownish macules on the vitiliginous and perilesional normal skin of the left thigh. B, Close-up view of the lesions.

macroglobules, compared with those in solar lentigo from the sun-exposed skin of a 67 year-old man having small, not granular, and ellipsoidal melanosomes (Fig. 3). However, melanocytes in the junctional areas were not increased in number, revealed few melanosomes, had minimal shrinkage of the cytoplasm, but had well preserved plasma membranes or organells. The melanocytes were apt to descend into the dermis by pushing on the surrounding viable cells, and the histiocytes were closely apposed to these melanocytes (Fig. 4).

DISCUSSION

Vitiligo is an acquired amelanosis of unknown cause, and is characterized histologically by the disappearance of melanocytes. PUVA therapy is effective in vitiligo (Parrish *et al.* 1976). The mechanism of repigmentation of a vitiliginous lesion is not known. Ortonne *et al.* (1979) suggested that repigmentation of vitiligo induced by PUVA may occur in three phases, first, proliferation of follicular melanocytes followed by migration along the hair follicle to the infundibulum and finally, migration in the adjacent epidermis with centrifugal propagation. Jarrett and Szabo(1956) suggested that there may be a reactivation of DOPA negative melanocytes which persist in the center of the lesions. Bleehen (1976) found that melanocytes were less numerous in the repigmented areas than in the healthy surrounding skin. However, dendrites were more prominent, DOPA oxidase activity was intense, but the size, form and melanization of the numerous melanosomes appeared normal. In our case, no repigmentation of vitiliginous skin was noted despite 4 years of photochemotherapy, but lentigines developed at the site of treatment and still persist. Histopathological findings in this case were quite different from those of vitiligo undergoing repigmentation.

It is well known that patients who have received long-term photochemotherapy may exhibit some side effects, such as skin cancer, epidermal dystrophy, premature aging of the skin, pigmentary changes, and alterations in the immune system (Farber *et al.* 1983). Topical photochemotherapy requires careful monitoring to avoid severe phototoxic erythema or painful

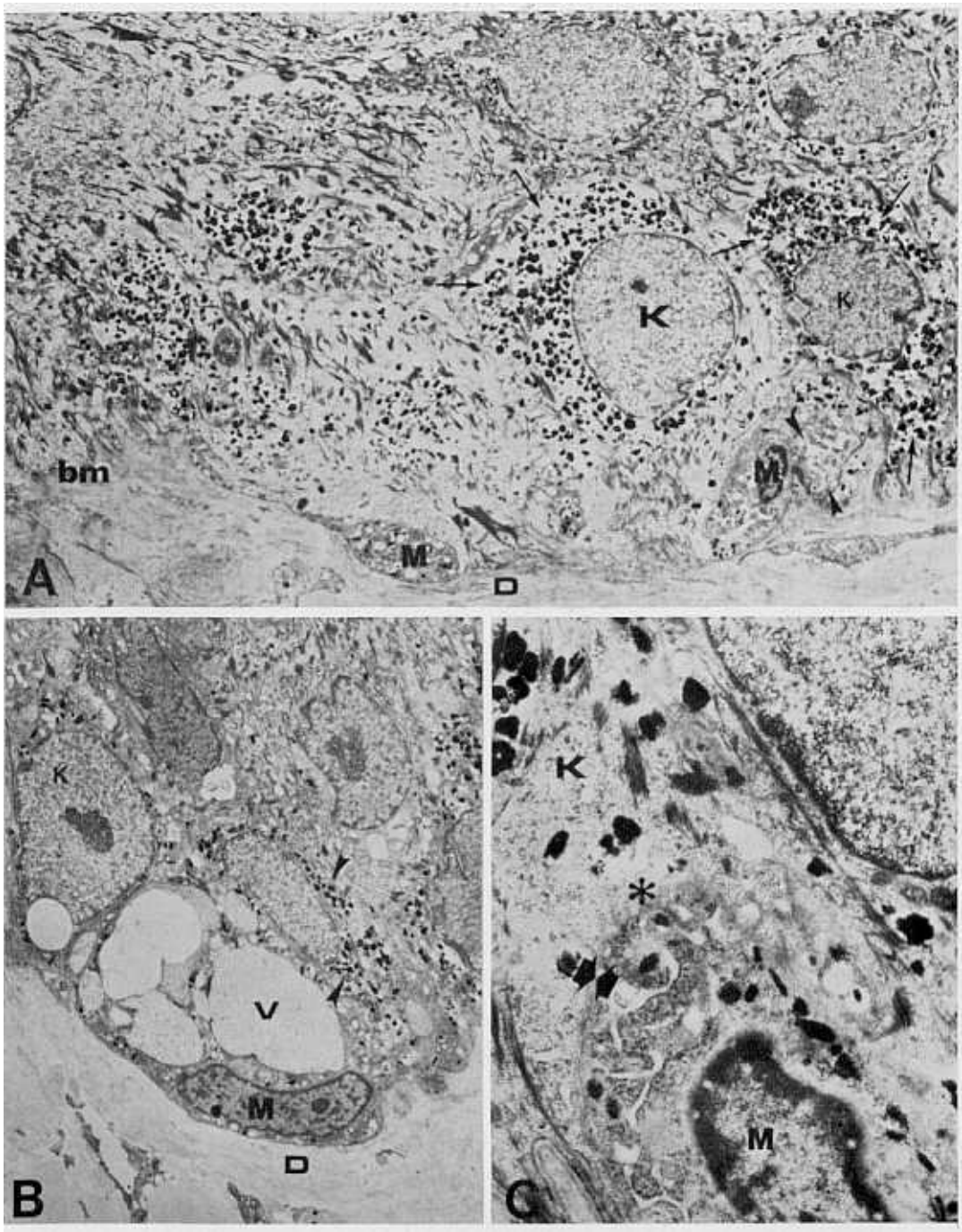

Fig. 2. Electron micrograph of a biospy from a lentiginous lesion. A, Degenerative change in a melanocyte(M) showing vaculoes within the cytoplasm (arrowheads). Basal keratinocytes(K) contain numerous melanosomes (arrows). D=dermis, bm=basement membrane (× 3,750). B, Vacuoles(V) within the cytoplasm of a melanocyte and neighbouring keratinocytes(K) containing numerous melanosomes(arrowheads) (×3,750). C, Melanocytes showing obliteration of the plasma membrane(asterisk) ruptured at the point indicated by the arrows (×15,000).

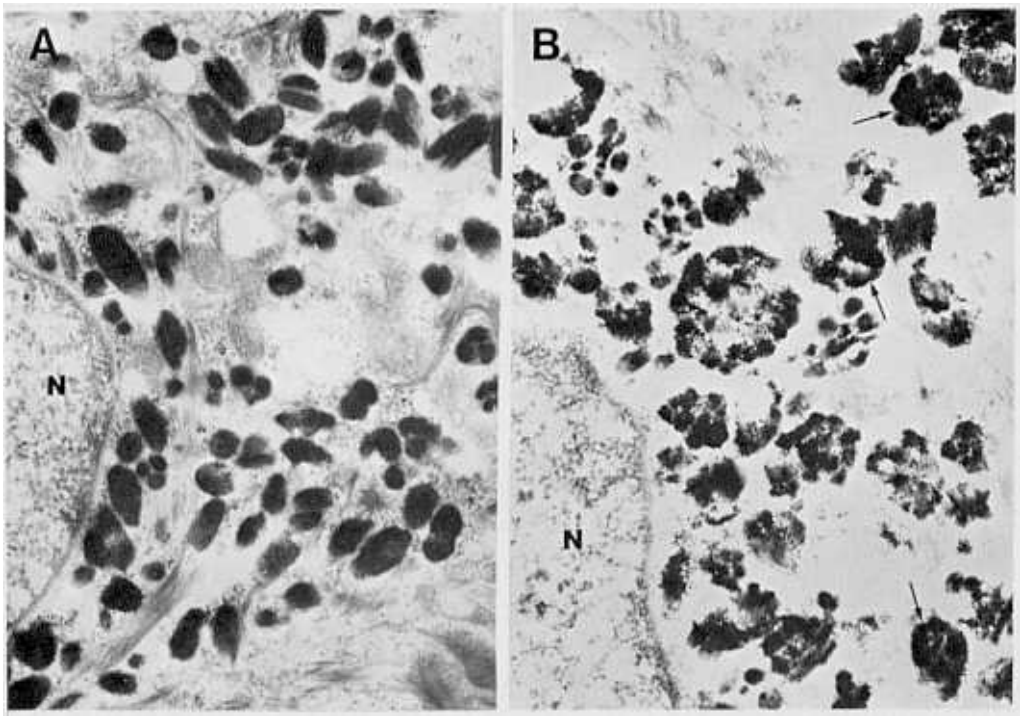

Fig. 3. Comparison of melanosomes in keratinocytes of solar lentigo(A) and PUVA lentigo(B). Note the larger, granular, macroglobular melanosomes(arrows) in (B), compared to the smaller, ellipsoidal melanosomes in (A) (N: nucleus) (×30,000).

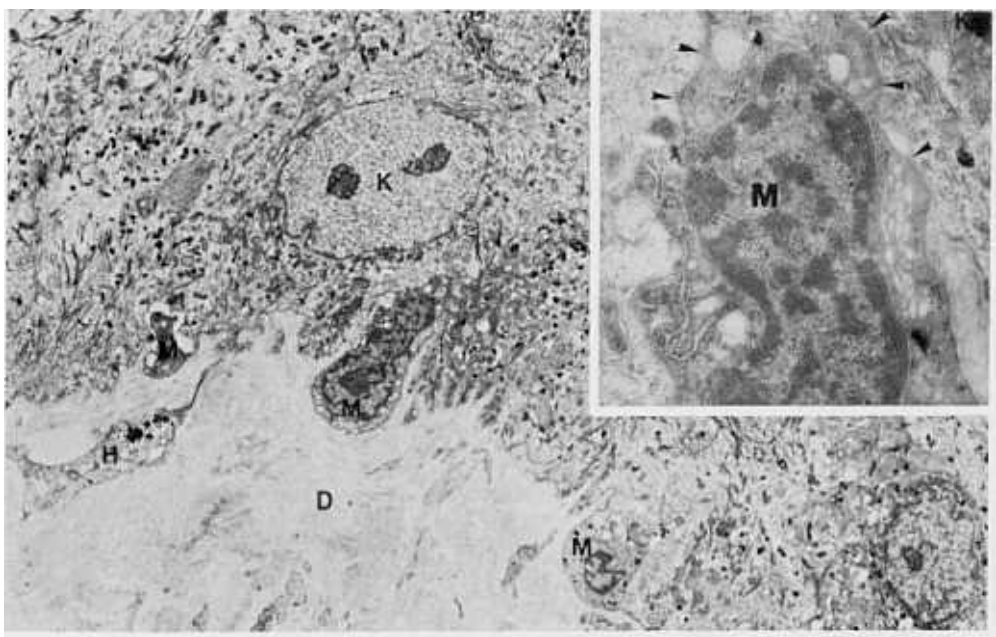

Fig. 4. Melanocytes(M) having dark cytoplasms are apt to descend into the dermis as the histiocyte is apposed to melanocyte (×3,750). Inset, A melanocyte showing few melanosomes, shrinkage of the cytoplasm but well preserved plasma membranes (arrowheads) and cell organells (×20,000).

blistering (Parrish *et al.* 1976). The tumorigenic and mutagenic potential of long-term photochemotherapy is causing concern. Brown macules may develop in patients treated with long-term PUVA. These macules have been called freckles (Bleehen 1978), stellate hyperpigmented freckles (Miller 1982), hyperpigmented spots (Szekeres *et al.* 1981), and star-like hyperpigmented lentigines (Konrad *et al.* 1977). Rhodes *et al.* (1983) reported that these macules were always "lentigines" rather than "freckles", according to current pathological classification from their histopathological investigation. Histologically, PUVA lentigines usually show elongated rete ridges with proliferation of functionally active melanocytes (Rhodes *et al.* 1983).

Recent ultrastructural investigations of PUVA lentigines have demonstrated that basal keratinocytes have a significantly increased frequency of large, single melanosomes, and revealed significantly larger individual melanosomes within compound melanosomes, while the melanocytes show atypical nuclear, cytoplasmic and melanosomal alterations (Rhodes *et al.* 1983; Nakagawa *et al.* 1984; Kanerva and Lauharanta 1985). In our case, ultrastructural findings showed atypical alterations similar to those of other investigators described above. At the present time we do not know whether the abnormal nuclear and cytoplasmic changes in the melanocytes are reversible, or are irreversible and potentially malignant. However, lentigines in our case have persisted for 2 years now after PUVA was discontinued, which indicated that they are at least long-lasting if not irreversible.

The exact mechanism of development of PUVA lentigines is unknown. Kanerva and Lauharanta (1985) suggested that PUVA may influence the different epidermal cell types and a disturbed equilibrium between these epidermal cells could result focally in an increase in melanocytes and formation of elongated rete ridges. The most interesting question in our case is "why only lentigines were developed and persisted but no repigmentation of vitiligo?". Wyllie *et al.* (1980) state that cell death can be classified into two patterns, based on morphological or biochemical criteria. One is "coagulative" necrosis which ruptures the plasma and organelle membranes causing dissolution of the organized structure. The other pattern is "apoptosis" which is characterized by condensation of the cell with maintenance of organelle integrity. This second mode of cell death has been shown in many situations to be under the control of physiological stimuli. Together with atypical cytoplasmic and melanosomal alterations, our morphological observations showed two distinct patterns of cell death: coagulative necrosis and apoptosis which were not reported in the previous literature about PUVA lentigines. These findings led us to consider a possible sequences of events such as this. After PUVA therapy, the inactive melanocytes of adnexal epithelium in the lentiginous lesions were activated, and this resulted in either melanocytic hyperpigmentation, or an increase in the number of active melanocytes, that is melanotic hyperpigmentation, an increase in the size and number of melanosomes which were produced by increasing apocopation or a coagulative necrosis of hyperactive melanocytes, and finally progressed into lentigo. The inactive melanocytes of the adnexal epithelium in the junctional area between the lentiginous lesion and vitiliginous lesion exhibited a course similar to that of lentiginous lesions, but this also may be accelerated in the natural cell death (apoptosis) of inactive melanocytes, which then penetrated into the dermis and were phagocytosed by histiocytes and macrophages, decreasing the number of melanocytes with no progression to repigmentation of vitiligo. However, this hypothesis will need to be further evaluated in similar cases.

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