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Squamous Cell Carcinoma in Localized Scleroderma Following Immunosuppressive Therapy with Azathioprine

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A 40-year-old man presented with an ulcerated tumour in a fibrotic plaque on the dorsum of his left foot. Due to severe localized scleroderma, the patient had been treated with azathioprine 10 years earlier. Histopathology of the excised tumour revealed an anaplastic squamous cell carcinoma within a scar of localized scleroderma. The case demonstrates that not only patients with tense scar tissue following burning, congelation, chronic radiodermatitis, lupus vulgaris or lupus erythematosus but also patients who have had localized scleroderma may run a greater risk of developing squamous cell carcinoma. Immunosuppressive therapy has to be discussed as an additional risk factor in our patient. Therefore, narrow clinical follow-up was recommended for early detection of relapse. ***Key words: Tense scar tissue; Immunosuppressive drugs.***

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Squamous cell carcinoma (SCC) is the second most common skin cancer in caucasoid population and occurs frequently in chronic dermatoses and several precursor lesions, e.g. actinic keratoses (1). Accumulative UV dose is suggested to be the most important cause of SCC. However, the well-known association between SCC and tense scar tissue (lupus vulgaris, burns, congelation, radiodermatitis, lupus erythematosus), immunosuppression and other factors (HPV infection, ionizing radiation, arsenic) strengthens the hypothesis that many different pathogenic mechanisms may contribute to the development of SCC (1–5). We report a man with cutaneous fibrosis following severe disabling localized scleroderma (LS), in which a SCC developed 10 years after successful treatment of LS with azathioprine.

CASE REPORT

In 1991, a 40-year-old man presented with an extensive ulcer on indurated fibrotic skin on the dorsum of his left foot. In 1980 and 1981, he had generalized LS with the clinical feature of linear scleroderma on the lower legs. Due to internal involvement of the disease (fever, elevated gamma globulin fraction in the serum electrophoresis, elevated erythrocyte sedimentation rate, arthralgia, destructive joint changes) the disease had been treated with azathioprine (150 mg/day) for about 15 months.

The fibrotic plaques on the dorsa of both feet caused contractures in the ankle joints. In addition, due to the fragility of the skin in this area, inflammatory and erosive lesions developed. In 1985, recurrent verrucous nodules and ulcerations occurred on the dorsum of the left foot. Surgical removal of these lesions was performed three times between 1986 and 1989. Histopathological examination showed LS with secondary ulceration. In 1991, a large bizarre ulcerated tumour, 6 × 4 cm in diameter, with hemorrhagic and putrid secretion developed at the site of the previous lesion. Distal to the tumour a small and approximately 3 mm wide hypertrophic scar extended to the toes (Fig. 1). Contractures of the skin allowed only restricted movement of the ankle joints, the metatarso-phalangeal joints of both big toes and the interphalangeal joints of the fingers. On the trunk slightly indurated areas with de- and hyperpigmentation were present.

Laboratory findings

The erythrocyte sedimentation rate was 15/40 (Westergreen), the C-reactive protein 3.0 mg/100 ml; other routinely performed laboratory investigations were normal. Antinuclear antibodies, antibodies against topoisomerase I and centromere proteins, and antibodies against *Borrelia burgdorferi* were negative.

Chest x-ray, abdominal sonography and computed tomography of the pelvis did not reveal any metastases of SCC.

Histopathology

Histopathology revealed an SCC, Broders' grade 3 to 4. The extended ulcerated tumour showed invasion of the dermis by masses of squamous cells with keratinization in some areas, marked atypia in others and a pronounced inflammatory infiltrate. In the depth were thickened, hyalinized collagen bundles, consistent with scleroderma

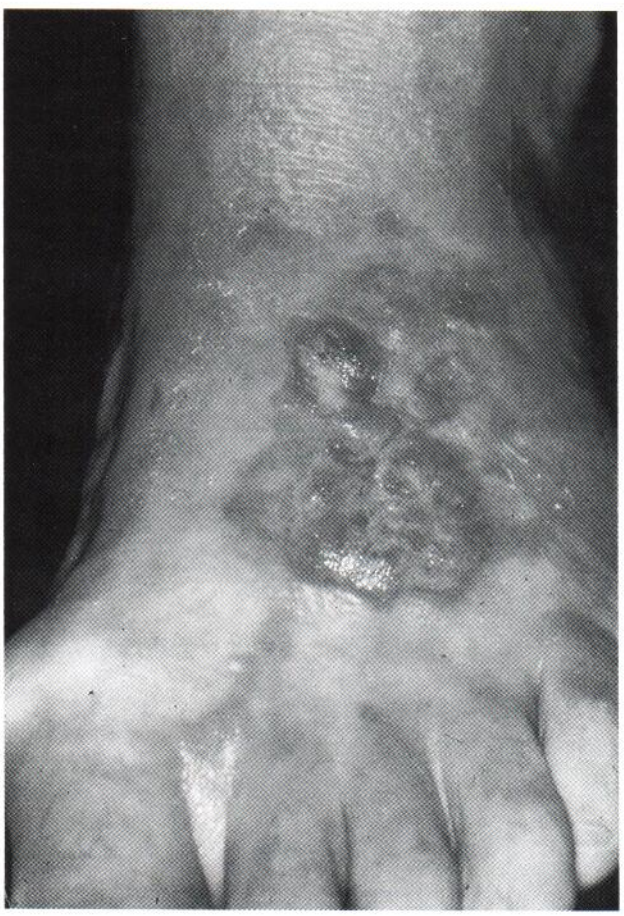

Fig. 1. Ulcerated skin tumour in scar tissue on the dorsum of the left foot.

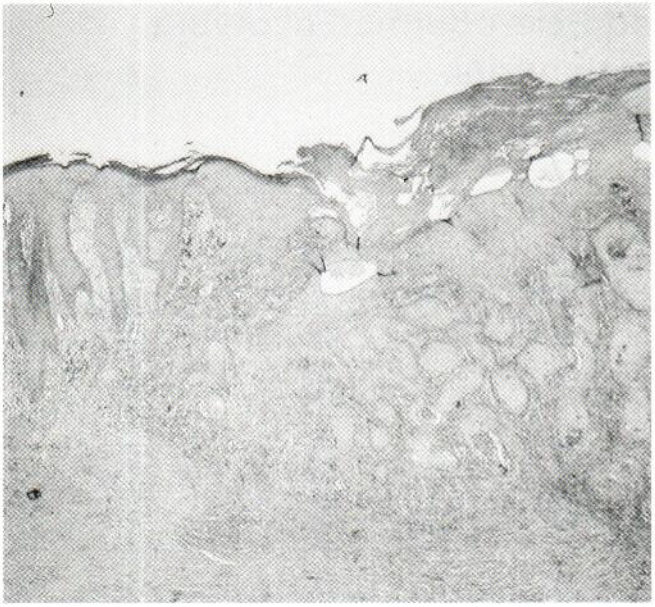

Fig. 2. Squamous cell carcinoma with ulceration within scar tissue. Atypic squamous cells invade the dermis, surrounded by marked inflammatory infiltrate and closely packed collagen fibers in the depth. The cells are characterized by few intercellular bridges, dyskeratosis, eosinophilic cytoplasm, hyperplasia of nuclei, prominent nucleoli and few atypical mitotic figures. The surrounding stroma shows widespread dense inflammatory infiltrate consisting of lymphocytes, histiocytes and eosinophils. There is scar formation in the connective tissue with wide and partially hyalinized collagen fiber bundles (HE stain; ×100).

(Fig. 2). Immunohistochemical analyses (Lu-5 and vimentin) confirmed the squamous cell origin of the tumour (Fig. 3).

Therapy

Complete excision of the tumour with a safety margin of 1 cm was performed in spinal anesthesia, followed by a skin graft from the right thigh. About 10 weeks later a good functional and cosmetic result was achieved.

DISCUSSION

The increased risk for the development of SCC in patients with tense scars following burns, congelation, lupus vulgaris, chronic ulcers and pressure sores, chronic radiodermatitis and, less frequently, lupus erythematosus is well documented in the literature (1–5). However, the development of SCC within a lesion of LS has not been reported so far.

SCC in our patient was based on a chronic, non-healing wound, developing in a fibrotic plaque of localized morphea. The rate of malignancies in chronic inflammatory lesions and sites of repeated mechanical skin irritation is significantly elevated (2). One hypothesis is that chronic inflammation and repeated traumatization select for rapidly dividing and proliferating cells, thus playing an etiologic role in inducing a malignant tumour (1, 2, 5–7). SCC in our patient grew within a site of extended scarring, followed by chronic non-healing ulceration; yet there is some evidence that formation of tense scars alone is sufficient to facilitate the development of malignant tumours (1, 6).

Remarkably, in contrast to other dermatoses exhibiting tense scars (1–8), the occurrence of SCC within scar tissue has not been mentioned as a complication of LS so far.

In our patient, in addition to the fibrosis and the subsequent chronic irritation, another risk factor for the development of SCC has to be discussed, since he had been treated with the immunosuppressive drug azathioprine for 15 months. In a recent review, Younger et al. confirmed that azathioprine facilitates the development of various malignant tumours, e.g. squamous and basal cell carcinomas of the skin, as well as lung and kidney cancer, although the exact role of azathioprine in inducing tumour growth has not yet been completely elucidated (9). Most of the studies demonstrating a tumour-inducing effect of azathioprine have been carried out in allograft recipients (10). Irrespective of the immunosuppressant used, a significant increase in incidence of skin malignancies,

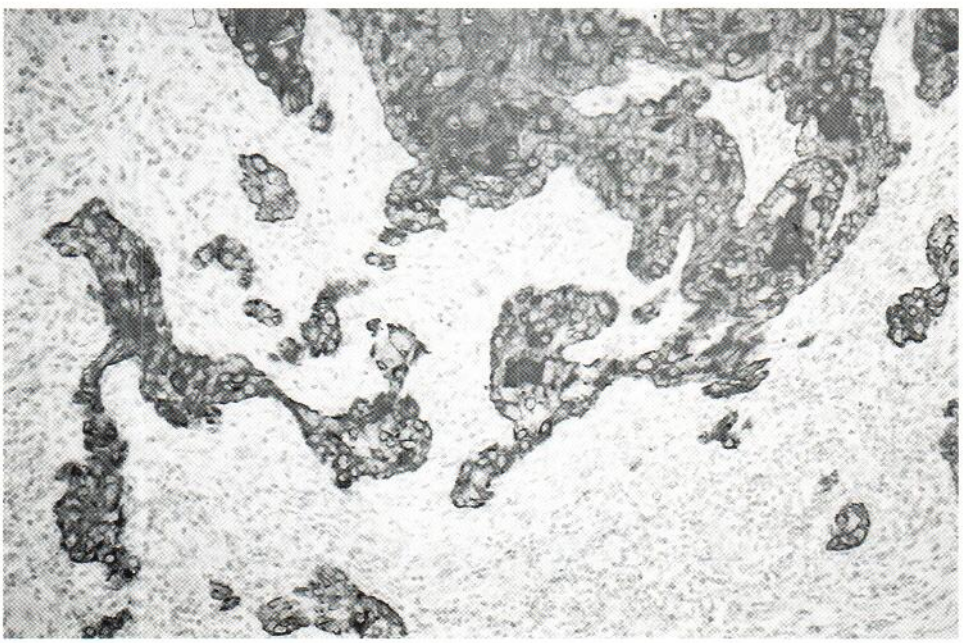

Fig. 3. Immunohistochemical staining demonstrates many of Lu-5 and vimentin positive cells distributed throughout the full thickness of the epidermis and dermis (×400).

as compared with the expected rate of about 0.04 to 0.2 % (depending on the geographic site) was observed in these patients (11–13).

However, whereas it is well documented that azathioprine may enhance the tumour-inducing effect of carcinogens (e.g. ultraviolet radiation), only a few data exist providing evidence that azathioprine may act as an inductor of malignancies by itself (14). Tage-Jensen et al. reported patients with alcohol-induced chronic hepatitis, treated with azathioprine for many years, who had a nearly threefold increased risk for dying from a malignant tumour, as compared with patients who underwent prednisolone therapy (15). Kinlen found a fivefold higher rate of SCCs in patients treated with immunosuppressants for reasons other than organ transplantation, e.g. rheumatoid arthritis, than in a comparable group of non-treated individuals (16). In our patient, the coincidence of scarring following LS, chronic ulcerative changes and the use of azathioprine may explain the fulminant tumour growth. Therefore, treatment with azathioprine or other immunosuppressive drugs should be very carefully considered in patients with LS (17). In patients with long-term aggressive disease complicated by arthralgia, joint contractures or laboratory signs of inflammation requiring aggressive treatment with azathioprine or other immunosuppressants, close clinical follow-up appears to be necessary for detection of SCC at the earliest possible stage.

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