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Acrokeratosis paraneoplastica (Bazex syndrome) occurring with acquired ichthyosis in Hodgkin's disease

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Summary We report a patient who exhibited two paraneoplastic skin disorders, acrokeratosis paraneoplastica and acquired ichthyosis, in association with Hodgkin disease. Treatment of the Hodgkin's disease resulted in rapid improvement of both skin disorders, confirming a causal relationship. The simultaneous presence of two paraneoplastic skin disorders suggests a common pathogenetic factor. Transforming growth factor α, produced by tumour cells, may play a part in the aetiopathogenesis of hyperproliferative paraneoplastic skin conditions.

Acrokeratosis paraneoplastica was first described by Bazex in 1965,[1] and is a rare but distinctive paraneoplastic dermatosis. It is associated with malignancies of the upper respiratory or digestive tract, or with cervical or mediastinal lymph node metastases from distant occult neoplasms. Clinically, the syndrome evolves in three stages.[2] The first stage is characterized by erythema and psoriasiform scaling on the fingers and toes, which soon spreads to the bridge of the nose and to the helices of the ears. Nail changes are frequent. In the second stage, a violaceous keratoderma of the palms and soles develops, and the facial lesions spread to the pinnae and cheeks. In the third stage, the eruption extends locally and begins to involve the legs, knees, thighs, arms, trunk and scalp. The dermatosis may antedate the diagnosis of malignancy or appear after its identification.[3] In the most typical cases, the neoplasm begins to produce its first symptoms when the skin lesions have progressed to the second stage.[4] Almost all the tumours associated with acrokeratosis paraneoplastica are squamous cell carcinomas.[5] Exceptions include adenocarcinomas of the lung,[6] oesophagus,[7] stomach[8] and uterus[9] and anaplastic small cell carcinoma of the lung.[10,11]

Associated features of acrokeratosis paraneoplastica include pruritus, vesiculation, sterile paronychia, hyperpigmentation, hypopigmentation, bullous lesions and carpal tunnel syndrome.[12–14] An association with other cutaneous markers of malignancy has been reported in three patients, all of whom had acquired ichthyosis.[8,13,14]

Acquired ichthyosis is a manifestation of lymphoproliferative and non-lymphoproliferative malignancies.[15] It has also been reported in essential fatty acid deficiency,[16] leprosy,[17] renal disease with defects in proline metabolism,[18] hyperparathyroidism,[19] sarcoidosis,[20] systemic lupus erythematosus,[21,22] and after the administration of cholesterol-lowering drugs.[23]

We report a patient with Hodgkin's disease who developed acrokeratosis paraneoplastica and acquired ichthyosis, an association which, as far as we are aware, has not been reported previously.

Case report

A 43-year-old man was referred with a 12-month history of a pruritic, scaly eruption which had started on the fingers and toes, and had subsequently spread to the nose, cheeks, ears and soles of the feet, and eventually to the scalp, trunk and limbs. Physical examination revealed brownish scales on the ears and cheeks, with psoriasiform scaling over the bridge of the nose, nasolabial folds and scalp. The soles of the feet showed a diffuse keratoderma, and the nails showed subungual hyperkeratosis, onychodystrophy and onycholysis (Fig. 1a). All these findings were consistent with acrokeratosis paraneoplastica. In addition, a scaly rash was present on the trunk and limbs (Fig. 2a). Histopathological examination of a skin biopsy from the lower leg revealed hyperkeratosis and acanthosis, with a reduced or absent granular cell layer. The appearance was consistent with ichthyosis vulgaris.

Investigations revealed that he was anaemic and hypothyroid. The erythrocyte sedimentation rate was elevated at 110 mm in the first hour. Computerized tomographic examination revealed multiple enlarged

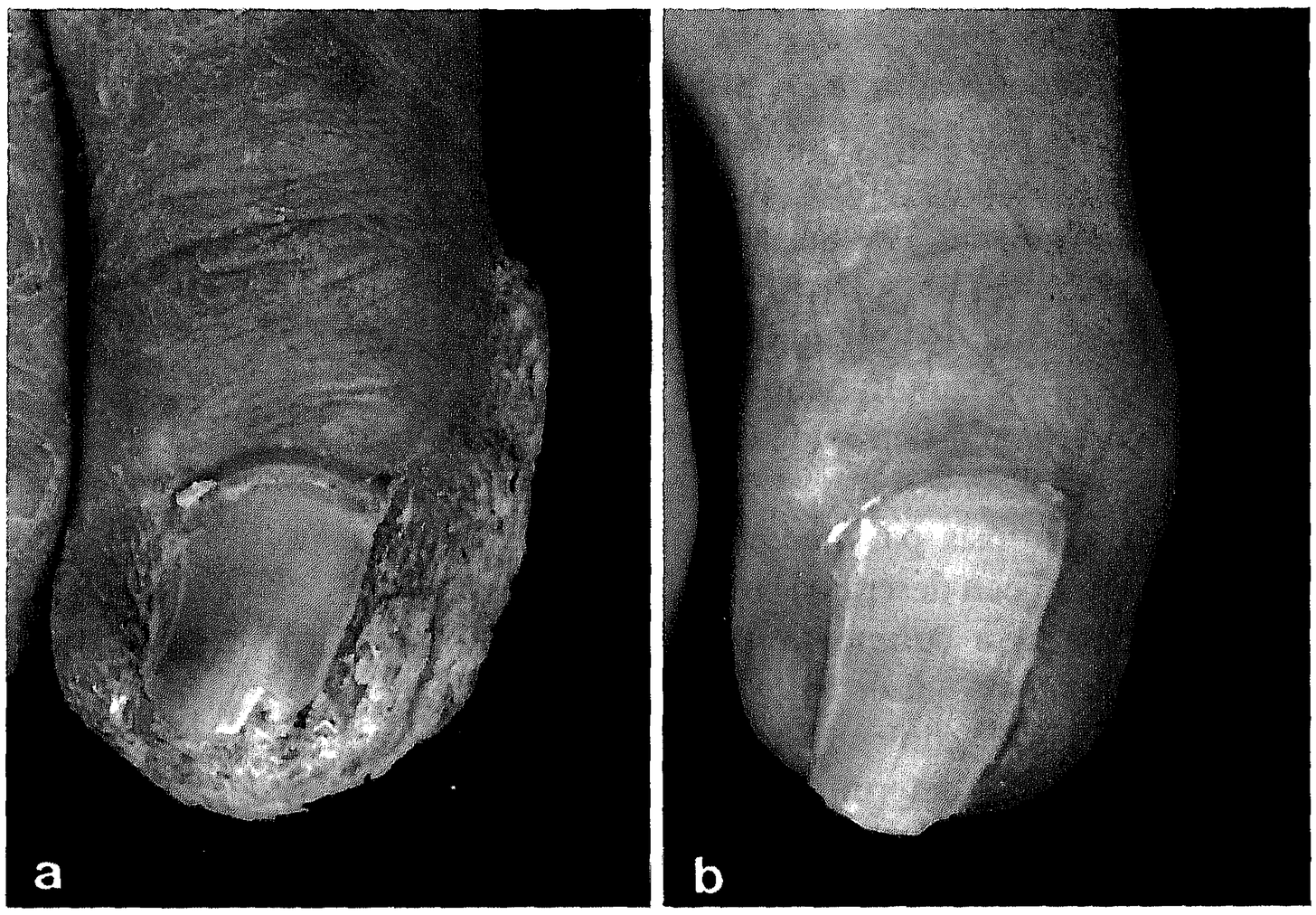

Figure 1. (a) The nail changes of subungual hyperkeratosis, onychodystrophy and onycholysis, before treatment. (b) The nail changes have resolved after chemotherapy.

lymph nodes and multiple tumours (the largest with a diameter of 7 cm) in the abdomen, but no abnormalities in the chest. Echography of the thyroid gland was consistent with hypoplasia. Examination of a sternal marrow aspirate showed increased erythropoiesis and thrombopoiesis. Histology of a temporal artery biopsy was normal. An abdominal mass was biopsied, and the histology was consistent with Hodgkin's disease. As the malignancy was localized beneath the diaphragm, a diagnosis of stage 2b Hodgkin's disease was made.

Chemotherapy was started with a combination of mitoxine, vincristine, natulan and prednisone. The hypothyroidism was treated with thyroxine, and iron supplements were given to correct the anaemia.

On review 2 months later, after three courses of chemotherapy, the skin changes had improved, and both the acrokeratosis paraneoplastica and acquired ichthyosis had virtually resolved (Figs 1b and 2b).

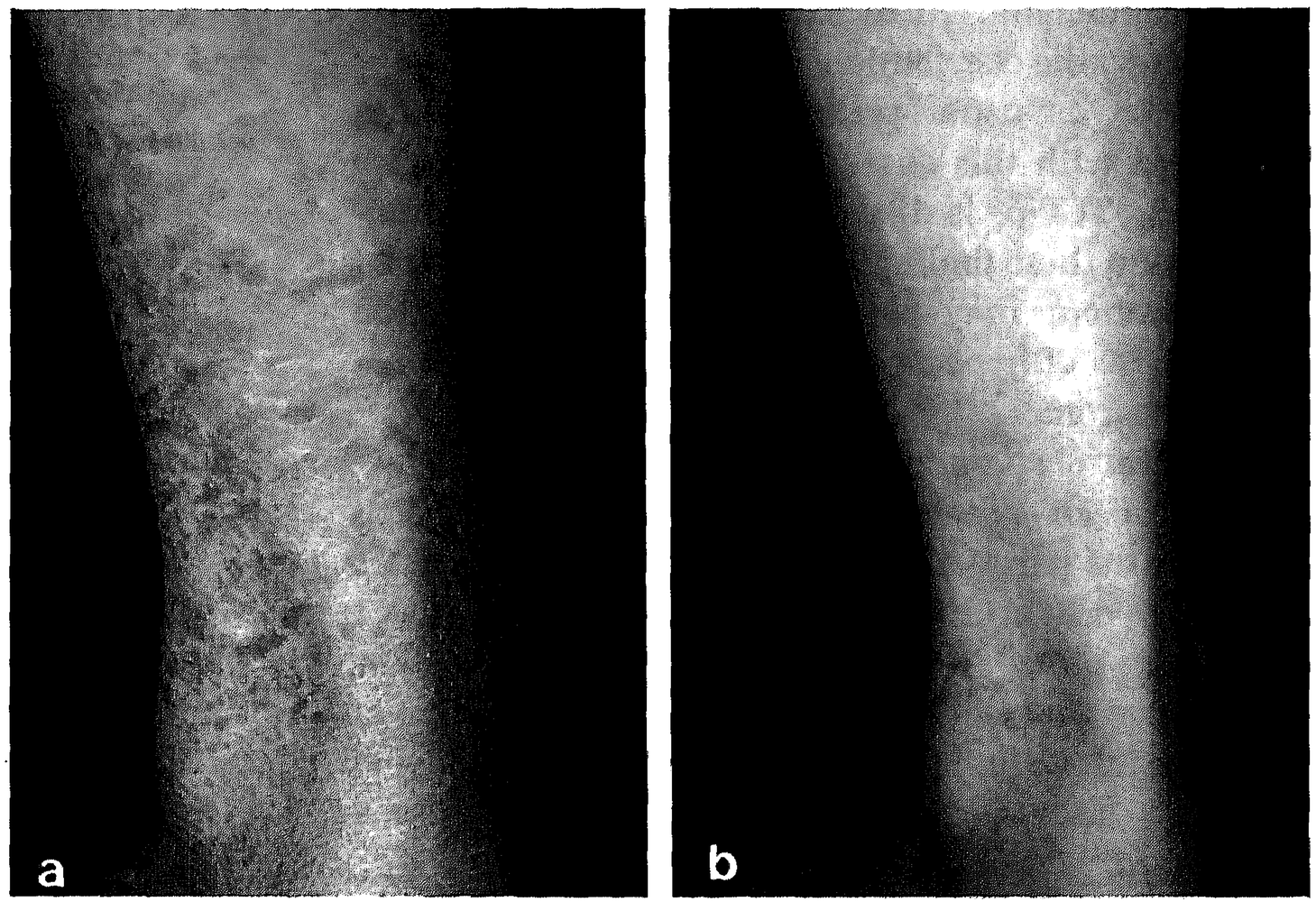

Figure 2. (a) Ichthyosiform scaling of the lower leg before treatment. (b) The appearance of the lower leg has reverted to normal after chemotherapy.

Discussion

Our patient demonstrates the simultaneous presence of two cutaneous markers of malignancy, acrokeratosis paraneoplastica and acquired ichthyosis, in association with Hodgkin's disease. Rapid improvement of both the paraneoplastic dermatoses was achieved by treatment of the underlying lymphoma, confirming a causal relationship. The simultaneous occurrence of acrokeratosis paraneoplastica and acquired ichthyosis has been observed previously.[8,13,14] However, the association of acrokeratosis paraneoplastica with Hodgkin's disease has not been described. Acquired ichthyosis has been reported as a cutaneous marker for underlying lymphoproliferative disorders, especially Hodgkin's disease,[24–28] and is clinically and histologically similar to the genetically determined ichthyoses, especially autosomal dominant ichthyosis vulgaris.[29] Both acrokeratosis paraneoplastica and acquired ichthyosis parallel the neoplasia in its evolution, resolving with appropriate treatment and recurring with relapse. Hence, treatment of the underlying malignancy is the most appropriate therapy. However, when the underlying neoplasm is incurable, cutaneous lesions may respond to topical or systemic corticosteroids[6] or retinoids.[30] The pathogenesis of cutaneous paraneoplastic disorders is uncertain. Expression of transforming growth factor alpha (TGF-α) has been found in tumour tissue from a patient with gastric cancer and acanthosis nigricans maligna.[31] Increased expression of the receptor for epidermal growth factor (EGF), the common ligand for TGF-α and EGF, has been demonstrated by Ellis *et al.*,[32] in the affected skin of acanthosis nigricans maligna. After excision of the underlying malignancy, the distribution of the EGF/TGF-α receptor reverted to its usual predominantly basal location. Coincident with this change, urinary TGF-α was also decreased. TGF-α is highly mitogenic for keratinocytes,[33] and these findings suggest that factors released by the tumour may play an important part in the pathogenesis of hyperproliferative cutaneous paraneoplastic syndromes.

Acrokeratosis paraneoplastica and acquired ichthyosis have been regarded as separate entities, with acrokeratosis paraneoplastica a cutaneous marker for squamous cell and adenocarcinomas, and acquired ichthyosis being related particularly to lymphoproliferative disorders. The simultaneous presence of both conditions as paraneoplastic manifestations of Hodgkin's disease suggests a common pathogenetic mechanism.

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