Peer reviewed article

Necrolytic migratory erythema (Glucagonoma)-like skin lesions induced by EGF-receptor inhibition

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ZD1839 (Iressa®) is an orally active, selective epidermal growth factor receptor (EGF-R) tyrosine kinase inhibitor that blocks signal transduction pathways involved in cell proliferation [1]. In many human malignancies, application of the ZD1839 alone or in combination with chemotherapy has already demonstrated both effectiveness and tolerability as well as probably dose related side effects, e.g. diarrhoea [1–3]. Despite the fact that EGF-R is also expressed in various structures of the human skin [4, 5], besides rash and acne-like skin lesions, severe skin toxicities under treatment with ZD1839 are rare [6, 7]. However, the histopathological consequences of EGF-R inhibition in the human skin in patients with a history of concurrent skin diseases have not been characterised.

Here we describe a 55-years old patient with non-small cell lung cancer who developed a grade 4 skin toxicity after commencing a monotherapy with ZD1839. Initially she had received total brain irradiation (20 Gray) for symptomatic cerebral metastases. Intercurrent chemotherapy with Gemcitabine (weekly 1000 mg/m^2) was stopped after stable disease was assessed. Two months later oral monotherapy with ZD1839 (compassionate use, Astra Zeneca®) was initiated at 250 mg/day to treat progressive cerebral metastases. At the same time the patient's antiepileptic therapy with carbamazepine (400 mg/day) was changed to sodium valproate (300 mg/day), based on data reporting an anti-tumour activity for this substance, mediated by a potential effect upon histone deacetylases inhibition [8, 9]. Six weeks later the patient presented with metastatic infiltration of three vertebral bodies. Following immediate local irradiation (8 Gy) the patient's condition rapidly improved. Due to the rapid appearance of painful, necrolytic, migratory, erythema-like skin lesions in the lower trunk and most prominently on both legs in addition to a pre-existing livedo reticularis (figure 1a, b) a skin biopsy was taken. Histology revealed necrosis of the epidermal layer and an unspecific vasculopathy. Immunological and laboratory parameters however revealed no evidence for a systemic collagenosis, activated coagulation, paraneoplastic glucagonoma [10, 11] or pseudoglucagonoma syndromes (e.g. hepatitis, liver cirrhosis, pancreatitis, malabsorption, danazol therapy and heroin abuse) [12, 13]. Immunohistochemistry demonstrated strong expression of EGF-R (Chemicon mAb) in the epidermal layer. Morphologically no changes in the eccrine or sebaceous glands, assumed to result from EGF-R mediated inhibition of migration and apoptosis [14] (figure 2a) were found and no positive staining for EGF-R expression in oc-

Figure 1

Characteristic net-like pattern of cyanotic mottled discoloration of the skin (pre-existing livedo reticularis) and erythema combined with erosions after superficial vesicles in the intertriginous areas. a: overview; b: detail.

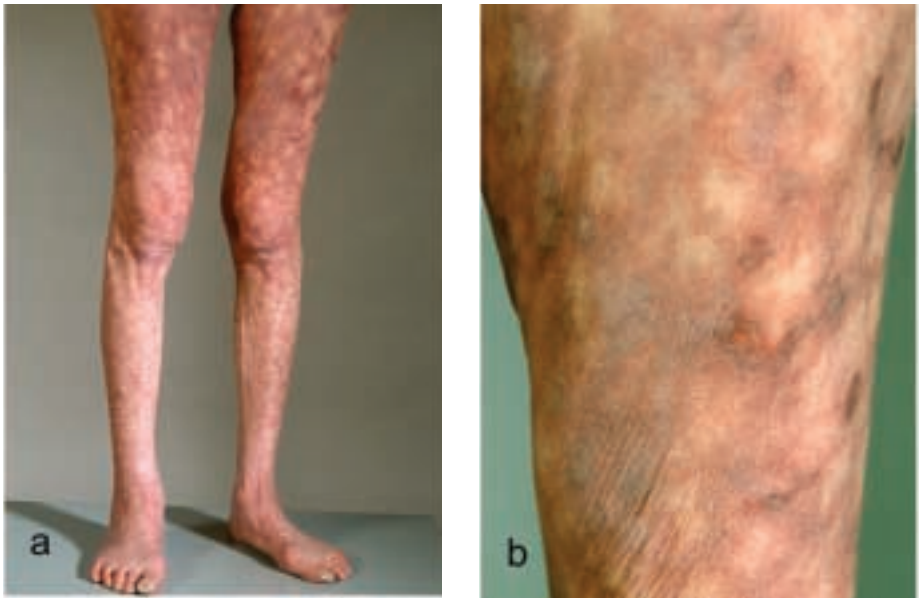
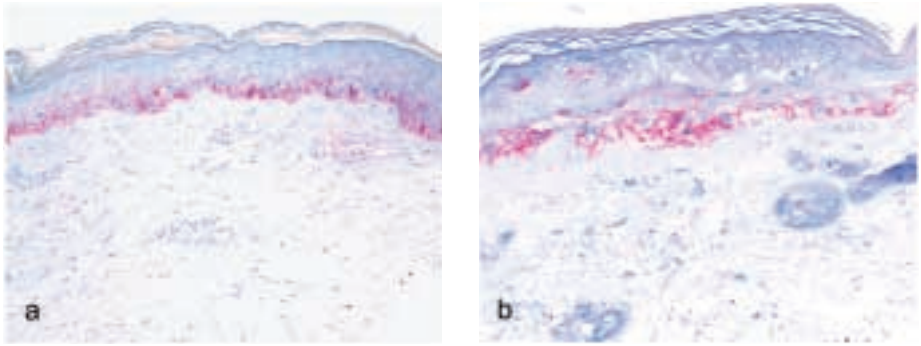


Figure 2

a. Prominent EGFR expression in the basal layer of the interfollicular epidermis, and in the outer root sheath of hair follicles as well as the eccrine glands (during ZD1839 therapy); capillaries were filled with erythrocytes. Eosinophils were not present.
b. High magnification (x400) revealed an increased number of apoptotic cells in the stratum corneum, but no EGFR expression in the endothelial cells of the dermal capillary plexus.



casional (1% to 3%) endothelial cells [1] of the dermal capillary plexus was noted (figure 2b). After ZD1839 withdrawal (sodium valproate at confirmed therapeutic serum level was maintained) and oral steroid therapy the patient's skin gradually improved.

In this patient exceptionally severe alterations of skin homeostasis due to EGF-R inhibition alone or as an adverse and potential synergistic event in combination with sodium valproate [15, 16] were observed. The possibility that these lesions were triggered by a pre-existing livedo reticularis cannot be excluded.

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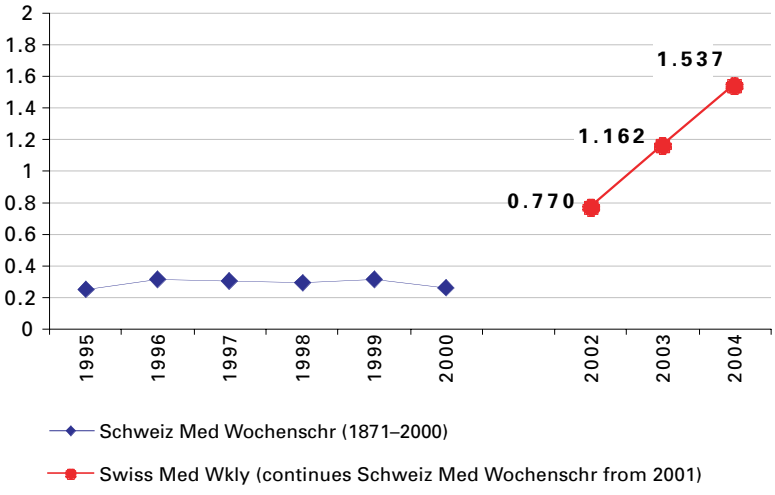

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