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

Andreas Trojan*, Emanuel Jacky*, Ferenc Follathb, Reinhard Dummerb

a Division of Oncology, Department of Internal Medicine
b Department of Dermatology, University Hospital Zürich, Switzerland

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/m²) 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 unspecified 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-
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.

Acknowledgement: B. Müller for immunohistochemistry.

Correspondence: Dr. Andreas Trojan
Division of Oncology
Department of Medicine
Universitätsspital
Rämistr. 100
CH-8091 Zürich
E-Mail: andreas.trojan@usz.ch

References
12 Schwartz RA. Glucagonoma and pseudogluca-
15 Sachs B, Romnau AC, von Schmiedeberg S, Ru-
zicka T, Gleichmann E, Schuppe HC. Lamot-
The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors: http://www.smw.ch/set_authors.html

Editorial Board
Prof. Jean-Michel Dayer, Geneva
Prof. Peter Gehr, Berne
Prof. André P. Perruchoud, Basel
Prof. Andreas Schaffner, Zurich
(Editor in chief)
Prof. Werner Straub, Berne
Prof. Ludwig von Segesser, Lausanne

International Advisory Committee
Prof. K. E. Juhani Airaksinen, Turku, Finland
Prof. Anthony Bayes de Luna, Barcelona, Spain
Prof. Hubert E. Blum, Freiburg, Germany
Prof. Walter E. Haefeli, Heidelberg, Germany
Prof. Nino Kuenzli, Los Angeles, USA
Prof. René Lutter, Amsterdam, The Netherlands
Prof. Claude Martin, Marseille, France
Prof. Josef Patsch, Innsbruck, Austria
Prof. Luigi Tavazzi, Pavia, Italy

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch