

# Acneiform lesions secondary to ZD1839, an inhibitor of the epidermal growth factor receptor

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## SUMMARY

Drugs that inhibit the epidermal growth factor receptor, such as ZD1839 or C225, are being used increasingly in the treatment of solid tumours. This has led to the appearance of new secondary effects. We describe the case of a patient who presented with an acneiform eruption secondary to the administration of ZD1839. These lesions healed in a few days after stopping the drug.

## REPORT

Novel chemotherapeutic agents may produce cutaneous side effects. Monoclonal antibodies to the epidermal growth factor receptor (EGF-R) and EGF-R-specific receptor tyrosine kinase inhibitors are in use in clinical trials for the treatment of solid tumours. Among available anti-EGF-R antibodies the most advanced in clinical development is C225 (Cetuximab). Furthermore there is a large number of inhibitors of the EGF-R tyrosine kinase under clinical development. Gefitinib, also known as ZD1839 (Iressa<sup>TM</sup>, Astra-Zeneca, Wilmington, DE, USA) is a low-molecular weight quinazolin derivative that inhibits the activation of EGF-R tyrosine kinase through competitive binding of the ATP-binding domain of the receptor. It has recently been approved by the Food and Drug Administration as monotherapy for the treatment of patients with locally advanced or metastatic nonsmall-cell lung cancers (NSCLCs) after failure of both platinum-based and docetaxel chemotherapies.<sup>1</sup>

We present the case of a 50-year-old male diagnosed with lung adenocarcinoma in 1997. He received surgical treatment (lobectomy) and chemotherapy (paclitaxel, cisplatin, gemcitabine, irinotecan, vinorelbine, docetaxel, oxaliplatin, at different periods), and adjuvant radiotherapy for successive disease recurrences. In December 2001, the patient started treatment with ZD1839 at 200 mg daily. Seven days after starting this treatment, the patient presented with pustules and erythematous papules on the face, trunk, back and presternal area. The patient continued with the treatment and after 2 months, because his lesions still persisted, he came to our department. Physical examination revealed a papulopustular eruption, located on the seborrhoeic areas of the face (Fig. 1a) and on the anterior and posterior aspects of the trunk (Fig. 1b), with no comedones or cysts. Bacteriology and mycology cultures of these lesions were negative. During this period the patient was not receiving any other drugs. A biopsy from an active lesion revealed orthokeratotic hyperkeratosis of the stratum corneum, lymphocyte

exocytosis in the basal layer of the epidermis, with basal layer hydropic degeneration. A dense inflammatory infiltrate of lymphocytes and neutrophils was observed in the dermal papillae. Furthermore, there was a perifollicular dense aggregate of multinucleated giant cells and macrophages (Fig. 2). Direct immunofluorescence was negative for immunoglobulins, fibrinogen and complement. The patient was diagnosed as having an acneiform eruption secondary to ZD1839 administration. The drug was stopped, and the skin lesions resolved over a 2-week period.

Blocking the EGF-R inhibits keratinocyte proliferation and migration<sup>2</sup> and induces apoptosis.<sup>3</sup> The EGF-R has also been implicated in keratinocyte differentiation.<sup>4</sup> Drugs that inhibit the EGF-R could also possibly be useful in the treatment of other diseases where EGF-R is implicated, such as psoriasis,<sup>5</sup> or epithelial skin tumours.<sup>6</sup>

In some histologic studies of patients treated with ZD1839 or C225, keratin plugs and microorganisms have been found in dilated infundibula.<sup>7-10</sup> These changes are probably secondary to an aberrant differentiation of suprabasal keratinocytes, caused by EGF-R inhibition, which results in an acneiform eruption. Infundibular necrosis together with alopecia were observed in EGF-R knockout mice, suggesting a central role for EGF-R also in hair follicle biology.<sup>11</sup>

EGF-R inhibitors are being increasingly used in the treatment of solid tumours. Side effects described include acneiform lesions as in our patient,<sup>7,8</sup> seborrhoeic dermatitis, paronychia<sup>12</sup> necrolytic migratory erythema-like lesions<sup>13</sup> acute interstitial pneumonia<sup>14</sup> and gastrointestinal symptoms. Busam et al.<sup>7</sup> studied a series of 10 patients with metastatic renal carcinoma treated with C225 for 1 week: all 10 patients developed a follicular rash in an acneiform distribution. This was accompanied by pain and fissuring of the distal finger tips. No infectious cause was found in these patients. Two patients had oral ulcers of 2–3 mm, with negative cultures for herpes virus. Our patient did not have oral or finger tip lesions. Furthermore, Van Doorn et al.<sup>8</sup> recently described an acneiform eruption in three patients receiving treatment with ZD1839. These patients presented with follicular papules and pustules in an acneiform distribution together with generalized cutaneous xerosis and scaling and altered hair growth. Bacteriologic and mycologic cultures were performed in all three patients, and *Propionibacterium acnes* was found in one patient. In summary, we describe a further case of a florid acneiform eruption secondary to ZD1839. Many of the novel anti-inflammatory and chemotherapeutic agents target the EGF-R or related signalling pathways. Dermatologists need to be aware of these agents and their cutaneous side effects.

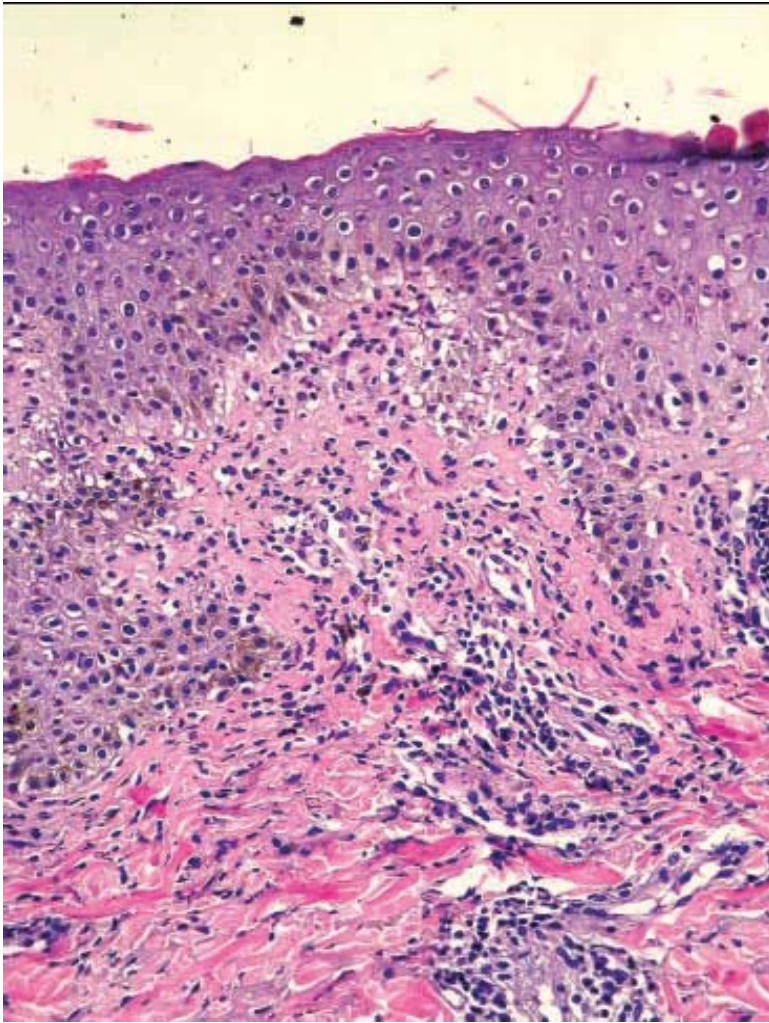
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**Figure 1.** (a) Papular–pustular lesions on the seborrhoeic areas of the face; (b) Papular–pustular lesions also present on the patient’s back.



**Figure 2.** Orthokeratotic hyperkeratosis and lymphocytic exocytosis with hydropic degeneration of the basal layer. There is a dense inflammatory infiltrate in the dermal papillae and a perifollicular aggregate of multinucleated giant cells and macrophages.