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# Acneiform Eruption Induced by Cetuximab

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**SUMMARY** Cetuximab is a recombinant human/mouse chimeric monoclonal antibody that targets the extracellular domain of the epidermal growth factor receptor (EGFR). Cetuximab is approved by the US Food and Drug Administration for the treatment of EGFR-expressing metastatic colorectal cancer as monotherapy in patients who are intolerant to irinotecan-based chemotherapy, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy. Due to the important role of the EGFR in skin homeostasis, cutaneous reactions are a common adverse effect of cetuximab, mainly as acneiform follicular eruption seen in almost 85% of patients. We report on a 46-year-old female Caucasian patient with metastatic colorectal cancer, referred to our department for acneiform eruption induced by cetuximab in combination with irinotecan. Four days after the first infusion the patient developed intense acneiform eruption consisting of erythematous follicular papules and pustules spread to the face, neck and upper part of the trunk, accompanied by intense pruritus and fever (38.0 °C). There were no comedones. Biopsy specimen revealed superficial and florid neutrophilic suppurative folliculitis. She was treated with erythromycin tablet 600 mg, three times a day for 1 month, and topical clindamycin solution 3%. After 1 month of treatment, the lesions consistently faded, and the patient continued receiving immunochemotherapy.

**KEY WORDS:** cetuximab, acneiforn eruption, treatment

## INTRODUCTION

Novel biologically targeted therapies that interfere with specific molecular pathways affecting cancer evolution have been developed as potential treatment options for patients refractory or intolerant to conventional chemotherapy (1). The epidermal growth factor receptor (EGFR), also called HER-1, is a transmembrane glycoprotein that binds specific ligands, epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-$\alpha$), initiating a cascade of intracellular signaling that ultimately regulates cell proliferation, migration, adhesion, differentiation and survival. The EGFR is constitutively expressed in many normal epithelial tissues, including skin and hair follicle. Aberrant signaling through the EGFR is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis and angiogenesis. EGFR is expressed by 30% to 100% of solid tumors (2). Some tumor cells that overexpress this receptor also produce a high level of EGFR ligands, creating an autocrine activation loop that is thought to promote independent

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tumor growth. Indeed, increased EGFR activity has been correlated with worse prognosis in patients with various types of cancer, including head, neck, colorectal, lung, renal and pancreatic cancers (3). The chimeric antibody cetuximab alone and in combination with irinotecan has shown a consistent therapeutic activity in EGFR-expressing refractory colorectal cancer (CRC) (4-6). Indeed, cetuximab is approved by the US Food and Drug Administration for the treatment of EGFR-expressing metastatic colorectal cancer as monotherapy in patients who are intolerant to irinotecan-based chemotherapy, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy. EGFR inhibitors are generally well tolerated and do not have severe systemic side effects of cytotoxic drugs. However, due to the important role of EGFR in skin homeostasis, cutaneous reactions are a common adverse effect of cetuximab, mainly as acneiform follicular eruption seen in almost 85% of patients (7-9). Other less frequent dermatological adverse events are xerosis, small oral aphthous ulcers, seborrheic dermatitis-like eruptions, paronychia, desquamation and pruritus (10).

## CASE REPORT

We report on a 46-year-old female Caucasian patient with metastatic CRC, referred to our department for acneiform eruption induced by cetuximab in combination with irinotecan. Previuosly, she was unsuccessfully treated with eleven cycles of polychemotherapy consisting of fluorouracil/leucovorin plus irinotecan (FOLFIRI), followed by eight cycles of another combination of chemotherapy (fluorouracil/leucovorin plus oxaliplatin, FOLFOX); however, the lung and liver metastases continued progressing. Capecitabina, a third-line chemotherapy, was then administered in 4 cycles, with no improvement. The last cycle of FOLFOX was then administered to the patient as the last chance, with no success. Biopsy specimen immunophenotyping revealed 10% of neoplastic cells to be EGFR positive. Therefore, the patient underwent a first cycle of intravenous immunochemotherapy with cetuximab 600 mg (400 mg/m$^2$) and irinotecan 290 mg (180 mg/m$^2$). Four days after this first infusion, the patient developed intense acneiform eruption consisting of erythematous follicular papules and pustules spread to the face, neck and upper part of the trunk, accompanied by severe pruritus and fever (38.0 °C) (Fig. 1A). There were no comedones. Biopsy specimen revealed superficial and florid neutrophilic suppurative folliculitis. A dense monomorphic infiltrate of neutrophils and eosinophils was constantly distributed around the infundibula (Fig. 1B). She was treated with erythromycin tablet 600 mg, three

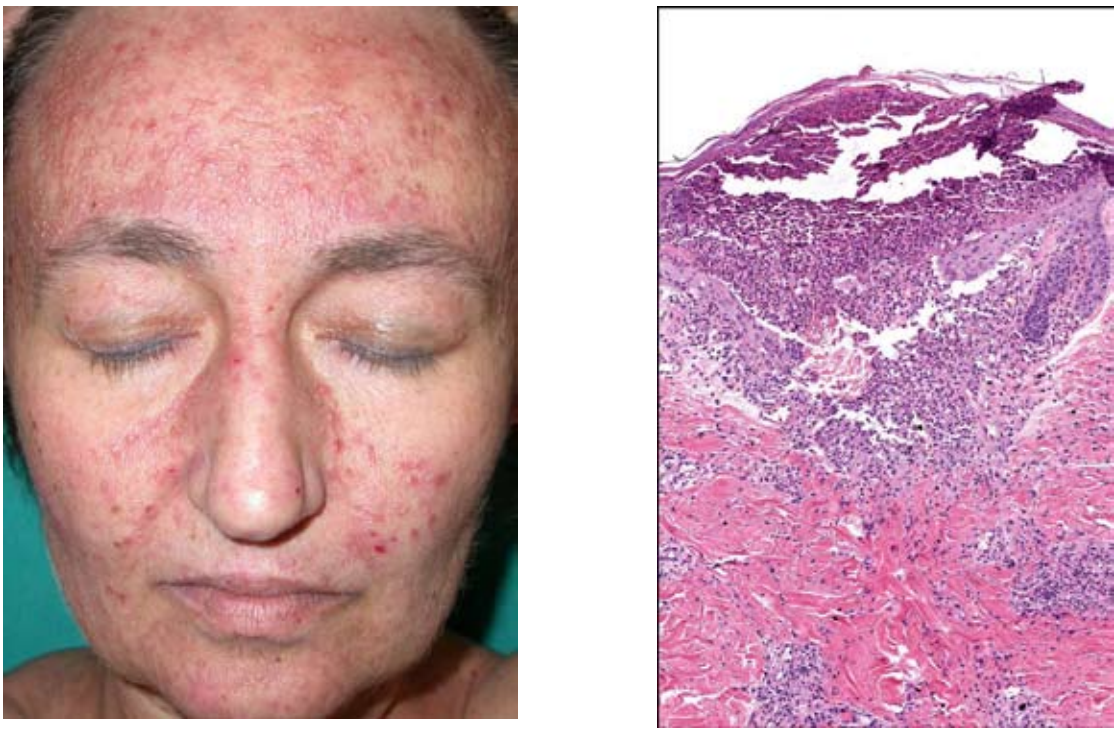

**Figure 1.** (A) Erythematous follicular papules and pustules; (B) Superficial and florid neutrophilic suppurative folliculitis with a dense monomorphic infiltrate of neutrophils and eosinophils around the infundibula.

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times a day for 1 month, and topical clindamycin solution 3%. After 1 month of treatment, the lesions consistently faded and the patient continued receiving immunochemotherapy. Eight months after cetuximab/irinotecan therapy, the progression of metastasis was arrested.

## DISCUSSION

A classic case of acneiform eruption in a female patient receiving cetuximab for metastatic CRC resistant to conventional chemotherapy is reported. Acneiform eruption is a common side effect of EGFR inhibitors as biological drugs, which is observed in 75%-100% of patients. The eruption is generally confined to the seborrheic areas, shoulders and upper trunk, whereas sometimes it may involve the abdomen, buttocks and even the arms and legs. The skin lesions consist of itchy erythematous follicular papules that may evolve into pustules. The pustules may merge into lakes of pus that dry out with the formation of yellow crusts. The follicular skin lesions are not preceded by visible comedones and can therefore not be considered as true acne. The acneiform eruption arises after a few days up to 1 week of treatment and reaches maximum intensity after 2 to 3 weeks following the beginning of therapy. Rarely, the rash occurs in a delayed way after the first three weeks of treatment. Data from a large number of clinical trials suggest that there is a relationship between the rash incidence and response/survival rate, indicating rash as a possible marker of effective target inhibition and activity of EGFR-targeted agents (8,11). Rash does not affect all patients and there is a high inter-individual variability. Current data indicate that both the onset and severity of rash are related to drug exposure, although its etiology remains unclear. It has been reported that EGFR inhibition of keratinocytes *in vitro* increases the levels of chemoattractants including CCL2/MCP-1, CCL5/RANTES, CXCL10/IFN-γ-inducible protein/10 leading to stronger recruitment of inflammatory cells, possibly favoring cutaneous pustular reactions (12). Clear guidelines for rash management are warranted, since cetuximab is to be largely and for longer periods used in the near future.

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