Case Report

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Grover's Disease Induced by Cetuximab

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Key Words
Epidermal growth factor receptor antagonists · Cetuximab · Grover's disease

Abstract
A 71-year-old man exhibited an acute acneiform rash affecting the face and the upper trunk about 2 weeks after starting cetuximab, an epidermal growth factor (EGF) receptor antagonist treatment for metastatic colon cancer. The skin eruption faded after stopping cetuximab and applying topical corticosteroids. The reexposure to cetuximab 3 weeks later provoked a more extended relapse of the skin rash, which then clinically and histologically corresponded to transient acantholytic dermatosis . While the acneiform cutaneous side effects of the EGF receptor antagonists are interpreted as a result of the direct interference with pilosebaceous follicle homeostasis, in this case an acrosyringium-related pathogenesis might be postulated. Applying topical corticosteroids and emollients, the cetuximab therapy could be pursued.

Introduction

Signal transduction inhibitors targeted at the epidermal growth factor (EGF) receptor, a new class of cancer drugs against solid tumors without the toxic side effects of chemotherapy, often cause pilosebaceous-follicle-related skin eruptions, e.g. for cetuximab in 70–80% of patients [1–8]. Clinically, these eruptions look like a follicular infection or an acneiform rash or even like widespread rosacea. They most often occur in the face, on the upper trunk and the upper arms. Histologically there is a folliculitis with prominent keratin plugs and microorganisms [1–7, 9]. Focal acantholysis has been reported in 2 patients, without further comment [10]. The pathogenesis is believed to depend on the direct interference with the EGF receptor signaling in the skin and the pilosebaceous follicles [1–7, 9]. The optimal treatment modality of this non-immune-mediated side effect, which hampers the use of this promising new treatment approach of solid cancers, has not been defined yet [1–8]. We here report a patient exhibiting a cutaneous side effect of cetuximab, possibly related to another skin appendage, the acrosyringium of eccrine sweat glands, for which a high expression of EGF receptors is also reported [11].

Case Report

In January 2001 the 71-year-old male patient underwent a left hemicolectomy due to advanced, nodal positive colon cancer. Afterwards he received 6 cycles of adjuvant chemotherapy with fluorouracil and leucovorin.

In December 2004 elevated serum levels of carcinoembryonic antigen led to the detection of asymptomatic intrapulmonary metastases. It was decided to treat the patient according to a trial protocol which evaluates the benefit of adding the EGF receptor antagonist cetuximab to a standard chemotherapy regimen with oxaliplatin and oral fluorouracil. The patient was randomized into the group receiving cetuximab (250 mg/m^2 i.v. weekly after a loading dose of 400 mg/m^2 i.v.) in addition to oxaliplatin (130 mg/m^2 i.v. every 3 weeks) and oral fluorouracil (2 × 1,000 mg/m^2 daily for 14 days, repeated every 3 weeks). Four days after the 2nd application of cetuximab the patient exhibited an edematous facial rash followed by an acneiform rash on the trunk 1 week later. Cetuximab was stopped for 3 weeks, and the skin eruptions faded with the application of halometasone (class III topical corticosteroid) cream with triclosan.

Within a few days, the reexposure to cetuximab induced an even more extended rash of discrete, partly coalescent, non-follicular pruritic papules involving the upper parts of the trunk (fig. 1) and the arms, accompanied by low-grade fever and chills. The entire skin showed atrophy and xerosis. Typical of Grover's disease, the biopsy revealed non-follicle-associated irregular mild acanthosis with focal spongiosis and suprabasilar acantholysis covered by a parakeratotic crust together with moderate mixed inflammatory infiltrates containing

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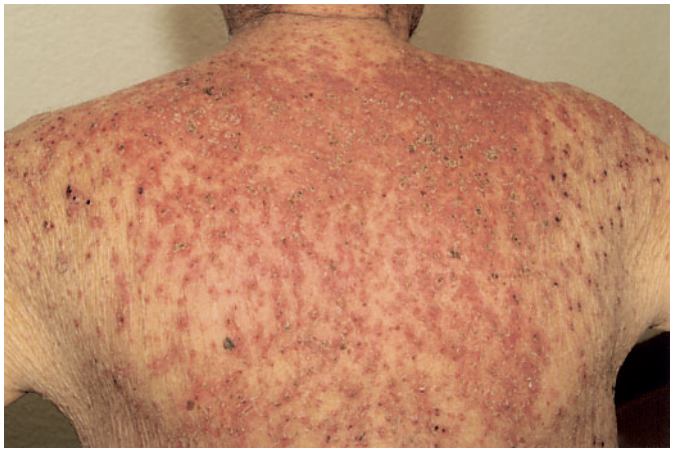

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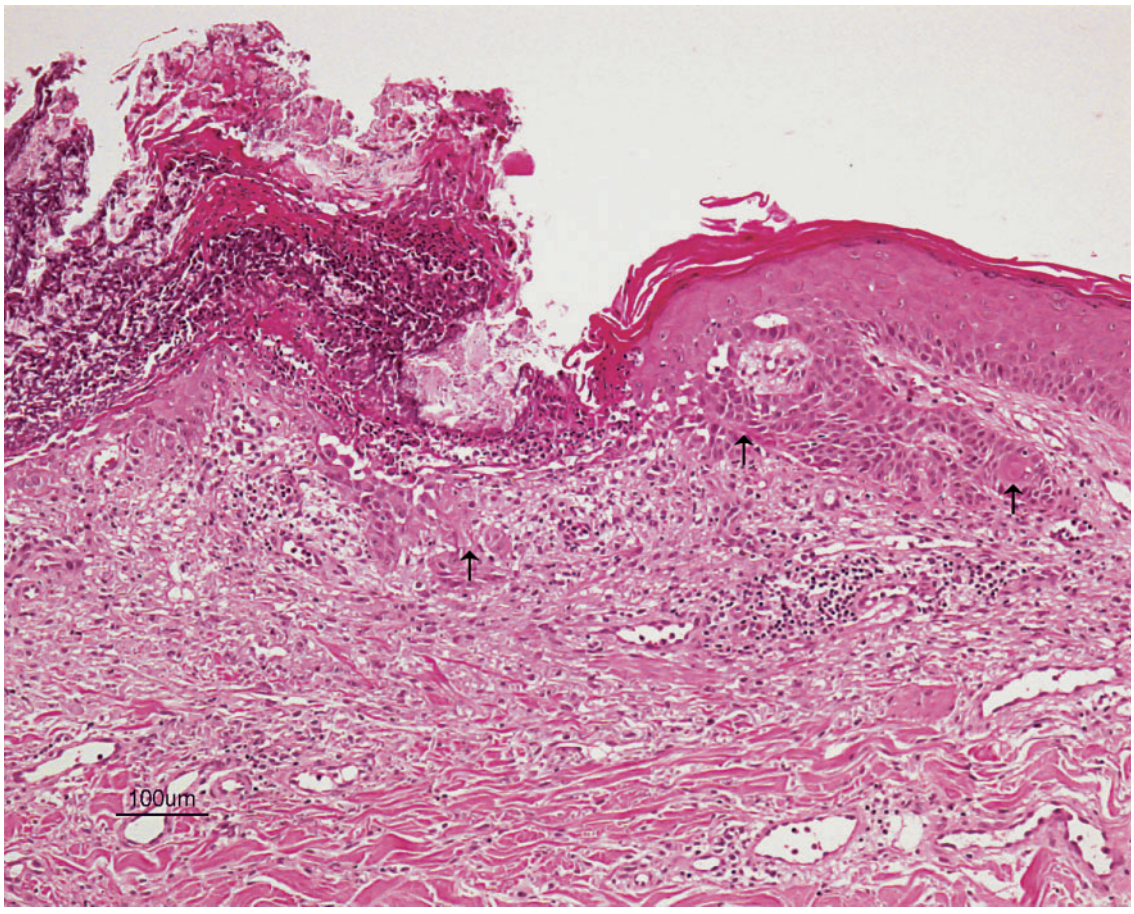

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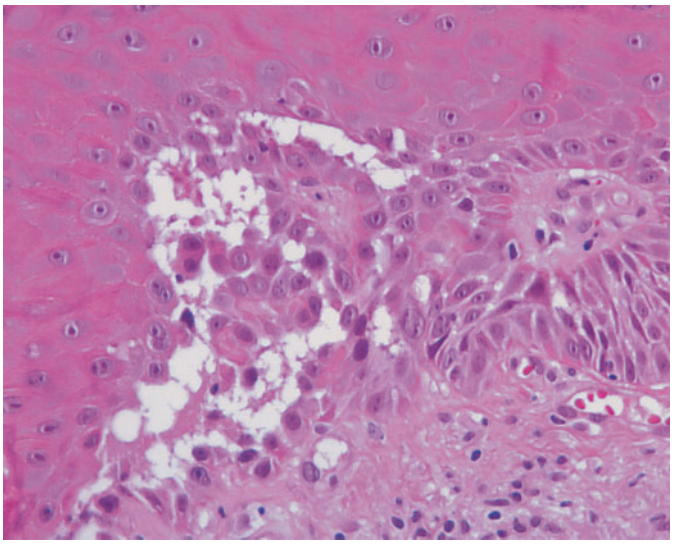

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Fig. 1. Extensive eruption of discrete, partly coalescent and excoriated, nonfollicular papules on the upper back after reexposure to cetuximab.

Fig. 2. Skin biopsy from the upper chest with acrosyringia-associated (arrows) irregular mild acanthosis with focal spongiosis and suprabasilar acantholysis covered by a parakeratotic crust as well as moderate mixed inflammatory infiltrates containing numerous eosinophils in the upper dermis and invading the epidermis. HE. ×100.

Fig. 3. Scattered foci of suprabasilar acantholysis in the skin biopsy from the upper chest. HE. ×200.

numerous eosinophils in the upper dermis and invading the epidermis (fig. 2, 3). Serial sections suggested a correlation with acrosyringia (fig. 2, arrows). The treatment with the same class III topical corticosteroid cream and emollients allowed 6 cycles of the chemotherapy/antibody treatment to be completed within 18 weeks without worsening of the skin condition, the patient showing partial tumor remission.

Discussion

The pathogenesis of transient acantholytic dermatosis (Grover's disease), which is frequent in elderly patients within a hospital setting [12], is still poorly understood. An association with excessive heat, sweating and xerosis is postulated [13], while paraneoplasia is rejected [12]. The predisposing conditions, the site of involvement and the relapsing nature of the disorder may implicate an acrosyringeal dysfunction as the cause [14, 15]. Well-documented induction by drugs has not been reported so far.

Adverse skin reactions are considered a surrogate marker of efficacy in EGF receptor antagonist therapy [1–7]. To the present knowledge they depend on the interference of these compounds with skin homeostasis [1–7, 9], mainly affecting the pilosebaceous follicles (acneiform rash), but on long-term treatment also resulting in cutaneous xerosis, a well-known predisposing factor for Grover's disease. Since the pathomechanisms of these skin reactions are not immune mediated, probably depending on the direct interference with EGF receptor pathways in epidermal keratinocytes, and since there are thus no concerns of progression to a life-threatening reaction such as toxic epidermal necrolysis or hypersensitivity syndrome, the medication is continued whenever possible. There is a lot of debate about which regimen helps best to reduce these often pruritic skin eruptions, anti-acne strategies being rather disappointing [1–8]. In our experience the best results are achieved with medium potency topical corticosteroids with antimicrobial additives in the acute inflammatory phase, combined with a consistent long-term use of emollients to reduce xerosis.

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