INTRODUCTION

The epidermal growth factor receptor (EGFR) is a member of the type 1 receptor tyrosine kinase (TK) family. It is a 170 kD transmembrane glycoprotein that binds EGF, transforming growth factor (TGF)-α, and many other ligands. Upon binding, it dimerizes, and TK on the intracellular side of the receptor is activated to initiate the intracellular signaling cascade. The EGFR is physiologically expressed in epithelial tissues and hair follicles. Inhibition of EGFR can produce a range of cutaneous adverse effects, the most frequent being a characteristic acneiform skin eruption. As the latter is associated with good anti-neoplastic responses, the onset of EGFR-inhibited acneiform skin eruption is typically viewed as a positive sign by patients and physicians. It can usually be treated well with standard acne drugs, but in rare cases, the skin eruption can be so severe that systemic therapy and/or interruption of EGFR treatment are required. One of the severest forms of EGFR-inhibited skin eruption occurring on the head and neck area resembles folliculitis decalvans. Here, we discuss the management of such a case seen in our department. In addition, we present an analysis of tumor necrosis factor-α, interleukin-1β (IL-1β), and IL-17A expression based on immunohistochemical stains and qPCR.

Key words: Epidermal growth factor receptor-inhibitor, folliculitis, folliculitis decalvans, interleukin-17A, interleukin-1β, tumor necrosis factor-α

Extreme Phenotype of Epidermal Growth Factor Receptor Inhibitor-induced Destructive Folliculitis

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ABSTRACT

Due to the increasingly widespread use and side effect profile of epidermal growth factor receptor inhibitors (EGFRIs), cutaneous side effects of these drugs are frequently encountered. The EGFR is expressed on keratinocytes and fibroblasts. Inhibition of EGFR can produce a range of cutaneous adverse effects, the most frequent being a characteristic acneiform skin eruption. As the latter is associated with good anti-neoplastic responses, the onset of EGFR-inhibited acneiform skin eruption is typically viewed as a positive sign by patients and physicians. It can usually be treated well with standard acne drugs, but in rare cases, the skin eruption can be so severe that systemic therapy and/or interruption of EGFR treatment are required. One of the severest forms of EGFR-inhibited skin eruption occurring on the head and neck area resembles folliculitis decalvans. Here, we discuss the management of such a case seen in our department. In addition, we present an analysis of tumor necrosis factor-α, interleukin-1β (IL-1β), and IL-17A expression based on immunohistochemical stains and qPCR.

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serous crusts. EGFR-induced acneiform eruptions can be distinguished from acne vulgaris by the absence of comedones. The pathophysiology of EGFR-induced skin eruptions and alopecia is incompletely understood. Inhibition of EGFR inhibits proliferation, differentiation, and adhesion of keratinocytes, which may favor the uncontrolled growth of opportunistic bacteria thriving in areas rich in pilosebaceous units. It has been reported that EGFR inhibition causes the release of inflammatory cytokines by keratinocytes.

As the hair follicle, or pilosebaceous unit, is the focal point in acneiform skin eruptions, it is not unexpected that hair growth can be affected as well, resulting in either increased facial hair growth or trichomegaly of eyelashes or impairment of hair formation resulting in curly, brittle hair, and alopecia. Erlotinib and gefitinib have been associated with inflammatory nonscarring alopecia and severe forms of scalp involvement include folliculitis decalvans (FD), scarring alopecia, or erosive pustular dermatosis of the scalp. Here, we report on the manifestations and management of a severe form of EGFR-associated scarring alopecia.

CASE REPORT

A 51-year-old physically challenged man was treated with the EGFR inhibitor cetuximab 500 mg and the alkylating agent cisplatin 75 mg for a stage 4 HNSCC. He was referred to our clinic for cutaneous side effects, occurring 1 month after cetuximab therapy had been initiated. The patient presented at that time with pustules, erosions, tufted hair, and golden crusts on the cheeks, nose and front, neck, and throat [Figure 1a]. At 6 weeks after treatment onset, the entire scalp was involved, and only few remaining longer hair residues were visible [Figure 1b]. Bacteriology performed on a pustule on the scalp revealed *S. aureus*, and a biopsy of the scalp showed dystrophic hair follicles surrounded by perifollicular inflammatory infiltrate with plasma cells. Direct immunofluorescence was negative.

Based on the above features, we retained the diagnosis of EGFR-induced FD, and initiated treatment with topical class III steroids and antiseptics. Within 3 weeks of treatment, the skin lesions had completely resolved [Figure 1c] and somewhat to our surprise, given the condition’s severity. The scarring alopecic areas were transformed into a status compatible with noninflammatory Brocq’s pseudopelade. Cetuximab was continued during the dermatological treatment.

In case a systemic treatment would have been required, we performed immunohistochemical stainings for tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-17 of a scalp biopsy. Compared to normal skin, increased expression was observed for IL-17 and TNF-α in lymphocytes and nonspecifically in plasma cells [Figures 2a-c and 3]. The findings were confirmed at the mRNA level using qPCR [Figure 3]. IL-17 was more than 150-fold elevated compared to healthy skin samples (n = 2). TNF-α was about 80-fold increased, while IL-1β was more than 5 times overexpressed.

DISCUSSION

The presented case is instructive considering the pronounced clinical presentation of EGFR-induced destructive folliculitis of the scalp, and the surprisingly efficient treatment response to topical steroids and antiseptics. In this case, extensive hair loss was seen, which can cause a considerable decrease in the quality of life.

EGFR has been reported to elicit numerous types of hair loss including alopecia areata, erosive pustular dermatosis, and FD. While there are data on the expression of cytokines in alopecia areata, there is very little known about cytokine expression in FD. Alopecia areata is associated with increased serum concentrations of TNF-α, IL-6, IL-17A, as well as IL-21 and IL-22. IL-1β has been shown to inhibit hair growth *in vitro* and in a genetic analysis, IL-1β single-nucleotide polymorphisms have been shown to be associated with alopecia areata. It has also been suggested that the IL-17 GG genotype is associated with an increased susceptibility for AA. An IL-17RA gene polymorphism possibly contributes to an increased susceptibility to alopecia areata. Erosive pustulosis is another disease of the scalp that can be induced by EGFR, and it is otherwise primarily seen in elderly people with atrophic Sun-damaged skin. It is characterized by follicle-destroying pustules on the scalp. There have been no studies performed regarding the association of TNF-α and any ILs in patients suffering from EGFR-induced skin eruptions.

Our patient suffered from FD, a scarring form of alopecia. It has been published that TNF-α is weakly to moderately expressed in FD. In our case, however, TNF-α was highly expressed, at least 80 times more than in healthy skin samples at the mRNA level [Figure 3]. There is no data on IL-17A and FD, and only one paper reported the expression levels of IL-1β in FD, showing a weak-to-moderate level.
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of IL-1β expression, comparable with our findings. Our data suggest that an increased expression of IL-17A, with a more than 150-fold increase, may contribute to the pathogenesis of EGFRI-induced FD [Figure 3].

Since we report here a single case, these findings should be taken with caution and confirmed in the future. If TNF-α or IL-17A should prove to play an essential role in the pathomechanism of FD, associated or not to EGFRI, TNF-α blockers, such as infliximab, etanercept, adalimumab or ustekinumab, as well as the IL-17-inhibiting monoclonal antibody, secukinumab, may be the treatment options for severe cases.

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Conflicts of interest

There are no conflicts of interest.

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