Epidermal Growth Factor Receptor Inhibition Induces Trichomegaly

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Case report. The epidermal growth factor receptor (EGFR) is important for normal skin development and function (1–3). Binding of the ligands EGF or TGF-α induces dimerization of the receptor and activation of the intracellular tyrosine kinase, resulting in downstream activation of different signalling pathways including MAP-kinases. EGFR expression is upregulated in several malignancies and therapies targeting EGFR are now under development. Strategies include antibodies inhibiting ligand-binding and low molecular weight compounds inhibiting the intracellular tyrosine kinase.

In this case report we describe growth of eyelashes (trichomegaly) in a 26 year-old female treated with irinotecan and Cetuximab (chimeric antibody against EGFR, Imclone) (see Fig. 1). The patient was diagnosed with colon cancer with liver metastases and received treatment with irinotecan (350 mg/m2 every 3 weeks) for several months. Owing to progressive disease, Cetuximab was added to the irinotecan treatment. As seen in most patients on irinotecan treatment, our patient developed alopecia grade II that was unaltered on the combined Cetuximab–irinotecan treatment. After the first week of treatment, the patient developed the typical acneiform erythematous rash commonly described in patients on Cetuximab and other EGFR inhibitors (4). She observed a marked increase in the length of her eyelashes and eyebrows after about 10 weeks of treatment. The photograph was taken after 20 weeks of treatment. Owing to the grade II acneiform erythematous rash, the patient began treatment with tetracycline (300 mg/day) starting in week 19. The patient had a clinical, radiological and biochemical response to Cetuximab treatment with a reduction in tumour size of 47% and plasma CEA levels were decreased from 432 to < 5 (normal range). A skin biopsy taken at 28 weeks after start of treatment showed histopathological findings as previously described in patients on EGFR inhibitors (4), with reduced Ki-67 expression compared to normal skin biopsies. There was no evidence of androgen-stimulated hair growth. Plasma sex hormone levels and elevated SHBG were in the range normally seen in young females taking contraceptive pills. The patient did not use any other medication.

Similar trichomegaly was also observed in another female patient with metastatic colon cancer who was treated with Cetuximab monotherapy after progression on irinotecan treatment. Because of the marked and inconvenient increase in the length of her eyelashes, she resorted to using scissors to trim her eyelashes.

Fig. 1. Growth of eyelashes and eyebrows in a 26-year-old female treated with irinotecan (350 mg/m2 every 3 weeks) and Cetuximab (chimeric monoclonal antibody against EGFR, 250 mg/m2 once a week). The picture was taken after 20 weeks of treatment.
Previous studies have shown that EGFRs are located in keratinocytes and hair follicles, especially the outer root sheath of the hair follicles (1, 4). In experimental studies EGF and TGF-α have been shown to induce auditory hair cell replacement (5). Histopathological examinations of skin biopsies obtained from patients treated with EGFR inhibitor (Iressa) have shown markedly thinner stratum corneum, reduced keratinocyte proliferation, increased apoptotic index and maturation (4). One might speculate that EGFR inhibition results in increased terminal differentiation (maturation) causing the observed trichomegaly. Others have reported that interferon alpha-2b treatment causes trichomegaly (6). Interferon has been shown to inhibit EGF-mediated events (7). Our observations suggest that the mechanism regulating the growth of hair may differ in different parts of the body, since these two patients experienced stimulation of the growth of the eyelashes and eyebrows at the same time as they had the typical irinotecan-induced pronounced general hair loss (alopecia grade II). Imatinib Mesylate (STI 571), another tyrosine kinase inhibitor used with considerable success in patients with CML (chronic myelogenous leukemia) has been reported to induce hair repigmentation (8). In conclusion, inhibition of different tyrosine kinases may regulate hair growth and pigmentation.

REFERENCES