IL-1RN*2/2, eight of 88 patients for IL-1RN*1/1, and 27 of 88 patients for IL-1RN*1/1. Thus, in our trial, only the frequency of the genotype IL-1RN*2/2 was increased (58% vs. 8%) whereas the frequency of the homozygous genotype IL-1RN*1/1 was even decreased in early-stage gastric cancer (31% vs. 45%). The observed increase of the genotype IL-1RN*2/2 and the simultaneous decrease of the genotypes IL-1RN*1/1 and IL-1RN*1/2 parallels findings in articles on advanced-stage gastric cancer.2-6

Cases with early-stage gastric cancer were selected retrospectively from the tumor bank of one institution led by a coauthor (M.S.), and comprise all accessible cases from 1993 to 2003. In addition, Drs Graziano and Ruzzo mentioned the difference in the average age between controls and patients. We certainly concede an age-dependent probability for the occurrence of gastric cancer. However, the difference between the incidences in both groups is too small to impact the conclusions of our study and similar age differences have also been reported in preceding trials.3,4,6

We acknowledge that the unknown H pylori status of the blood donors might hamper the interpretation of our results. In previous studies,2-6 various linkage disequilibria have been observed between the IL-1B and the IL-1RN loci. In our study, such a linkage disequilibrium was only observed in the subgroup with the intestinal type of early gastric cancer but not in the remainder of patients.

We certainly agree with Drs Graziano and Ruzzo that our data have to await confirmation and extension in independent trials, which should ideally compare early and advanced stages of gastric cancer in a prospective manner to avoid premature and exaggerated conclusions. In our opinion, this precaution is particularly relevant in genetic association studies.

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Abnormal Hair Growth in a Patient With Head and Neck Cancer Treated With the Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Cetuximab

TO THE EDITOR: Cetuximab (C225; Erbitux; ImClone Systems Inc, New York, NY) is a chimeric monoclonal antibody directed selectively against the epidermal growth factor receptor (EGFR).1 Cetuximab has recently been approved for the treatment of patients with EGFR-overexpressing metastatic colorectal cancer. Moreover, in clinical trials cetuximab has shown promising activity in different neoplasms, including head and neck cancer.2,3 Due to the important role of the EGFR in skin homeostasis, cutaneous reactions are a common adverse effect of cetuximab, mainly an acneiform follicular eruption. Other less frequent dermatologic events are small oral aphthous ulcers, seborrheic dermatitis-like eruptions, paronychia, desquamation, pruritus, or one reported case of trichomegaly (abnormally long eyelashes).4,6 In this letter, we report a case of diffuse and abnormal hair growth of the chest apparently related to cetuximab therapy. Based on a biopsy performed in the thoracic skin of this patient, we describe its histopathologic and molecular correlations.

A 66-year-old white man underwent supraglottic laryngectomy due to a stage III supraglottic squamous cell carcinoma. Three months later, the patient developed local progression, and a total laryngectomy plus a modified radical neck dissection was performed. Four months later, the patient presented with a second local relapse. Chemotherapy with carboplatin plus tegafur was administered with no response, and the patient was then included in a clinical trial...
with weekly cetuximab (400 mg/m²/intravenous [IV] followed by 250 mg/m²/IV) plus carboplatin area under the plasma concentration time curve 5 mg · min/mL IV once every 4 weeks. After 1 year of continuous treatment, physical examination revealed abnormally long and thick hair distributed diffusely on the chest. Hormonal serum levels were normal and the patient was not receiving any treatment other than carboplatin plus cetuximab. A punch biopsy of the abnormal hair area revealed disoriented and short inserted hair follicles associated to an irregular architecture in keratinocytes of the inner and outer root sheaths, associated to a faint lymphocytic inflammatory infiltrate (Fig 1A). An immunohistochemical analysis for the phosphorylated form of EGFR showed absence of phosphorylated-activated EGFR in the epidermal keratinocytes and very faint staining in the altered hair follicles, suggesting a major inhibition of EGFR achieved during cetuximab treatment (Fig 1B). After 15 months of treatment, the patient achieved complete response and presented persistent grade 3 folliculitis and abnormal hair growth on the chest. At that time, cetuximab and carboplatin were discontinued. Three months later, the abnormal hair growth and the acneiform follicular eruption resolved.

In previous articles, histopathologic, clinical, and molecular effects of cetuximab and EGFR tyrosine kinase inhibitors have been reported in the skin of patients after a few weeks of treatment. This has been of help to understand the biologic activity of these drugs. However, the clinical and biologic effects of chronic treatment with EGFR-interacting agents are less characterized due to the more limited experience with long-term use of these drugs.

Our patient did not exhibit other known reasons for developing abnormal hair growth. A possible role of carboplatin in this hair abnormality may not be ruled out, however, no reports of a similar nature are available regarding this drug. Furthermore, the disappearance of the excessive hair growth after cessation of treatment further supports cetuximab’s potential role in the growth of abnormal hair. A possible explanation for this abnormal hair growth lies in the role of EGFR in hair cycle regulation. EGFR is a major regulator of the epithelium-mesenchymal interactions and plays an important role in regulating the transformation from anagen or growth phase to catagen or regressive phase. Cetuximab-induced inhibition of the EGFR in hair follicles may alter the growth cycle of the hair follicle and halt the anagen-catagen transformation. This would result in the hair follicles remaining in an aberrant anagen phase, consequently leading to abnormal hair growth. With the increasing use of cetuximab in cancer patients, it will be of interest to see if an effect similar to the one reported in this letter is observed in additional patients.

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Fig 1. (A) Epidermis with a thinner stratum corneum and presence of inflammatory infiltrates with perivascular distribution and affection of the basal layer of epithelium (Hematoxylin-eosin staining x250). (B) Weak expression of activated epidermal growth factor receptor in a hair follicle. Notice the irregular distribution of the keratinocytes in the follicle and the presence of the receptor in cells (DAB x400).


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