Inflammation of Actinic Keratosis During Panitumumab Therapy

Inflamación de queratosis actinicas durante el tratamiento con panitumumab

To the Editor:

Panitumumab is a monoclonal antibody that inhibits epidermal growth factor (EGF) by binding to its extracellular domain. It is approved for the treatment of metastatic colorectal carcinoma in patients who express EGF receptor and wild-type KRAS. Adverse cutaneous effects can occur in up to 90% of patients. We present a case of panitumumab-associated inflammation of subclinical actinic keratoses, an adverse effect not described in the literature to date.

The patient was an 80-year-old woman who in 2007 had been diagnosed with stage IV KRAS wild-type adenocarcinoma with metastasis in the liver, lung, mediastinum, and peritoneum. After progression during several lines of chemotherapy she began intravenous panitumumab monotherapy every 3 weeks. Two months after beginning panitumumab treatment she attended the dermatology department with erythematous-desquamative lesions on the face that were rough to the touch and in some cases erosive (Fig. 1). She had no history of skin problems and was taking no other medication. Dermatoscopy of the lesions showed an erythematous pseudoreticulum with a distinctive strawberry pattern (Fig. 2). Biopsy of one of the lesions revealed the presence of atypical keratinocytes, which were largely confined to the basal layer of the epidermis. Marked solar elastosis, predominantly perifollicular lymphocytic infiltrate, and scattered melanophages were evident in the dermis (Fig. 3). The patient was diagnosed with grade 1 actinic keratosis with inflammation, for which she was treated for 2 weeks with a topical corticosteroid and antibiotics. She received a total of 8 cycles of panitumumab therapy. Five months later the lesions reappeared, leaving a residual pink macula (Fig. 1B).

Cutaneous effects of panitumumab include alterations of the hair and nails, mucositis, photosensitivity, xerosis,

Figure 1  Erythematous desquamative lesions on the patient’s forehead (A) that resolved after 8 cycles of panitumumab therapy (B).

Figure 2  Dermatoscopic image of one of the lesions showing erythema, desquamation, and an erythematous pseudoreticulum with a strawberry pattern.

fissures, and papulopustular eruptions, and may necessitate dose reduction.\textsuperscript{4}

Inflammation of actinic keratosis is common in patients treated with imiquimod, ingenol mebutate, or topical 5-fluorouracil, and its intensity appears to be related to the degree of clinical response.\textsuperscript{3} Subclinical actinic keratosis in the field of cancerization is also frequently observed following treatment with these agents,\textsuperscript{3} and following systemic monotherapy with a variety of chemotherapeutic agents including fluorouracil, capecitabine, doxorubicin, deoxycoformycin, cisplatin, docetaxel, and fludarabine. Inflammation of actinic keratosis has also been reported in patients treated with combination therapies (dactinomycin, dacarbazine, and vincristine, and doxorubicin, cytarabine, and 6-thioguanine),\textsuperscript{2} and with new target therapies, including sorafenib, sunitinib, and erlotinib.\textsuperscript{3} However, we have found no reports linking panitumumab therapy to inflammation of actinic keratosis.

The pathogenesis of this reaction remains unclear. Inflammation of actinic keratosis in patients treated with classical chemotherapeutic agents may reflect a direct cytotoxic effect on atypical keratinocytes or radiation recall in the field of cancerization.\textsuperscript{8} In the case of sunitinib, an antiangiogenic effect on atypical keratinocytes is suspected.\textsuperscript{7}

EGF receptor function is dysregulated in actinic keratosis and squamous cell carcinoma.\textsuperscript{10} It is therefore possible that panitumumab-induced inhibition of this receptor triggered the inflammation of actinic keratosis in our patient. The preferential accumulation of the drug in the follicular infundibulum could favor hyperkeratinization and secondary inflammation of subclinical actinic keratosis, as previously proposed for erlotinib.\textsuperscript{3} It remains unknown whether this cutaneous reaction is associated with a better treatment response, as described for erlotinib.\textsuperscript{9}

In summary, we present the first described case of panitumumab-associated inflammation of subclinical actinic keratosis. While this adverse effect has been previously described for some classic chemotherapeutic drugs and new target therapies, the underlying mechanism remains unknown.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Alopecia Areata and Palmoplantar Pustulosis: Report of 4 Cases

Alopecia areata y pustulosis palmoplantar: informe de 4 casos

To the Editor:

To date, reports on alopecia in patients with palmoplantar pustulosis (PPP) are rarely seen. We herein describe four cases of alopecia in patients with PPP.

During these 10 years, we diagnosed 128 patients with PPP (M:F=1:2) in our department. Among these patients, four patients had PPP and alopecia (3.1%). All of the patients were female, and the age range was from 39 to 56 years old (Table 1). Three patients developed alopecia prior to the onset of PPP, and the remaining patient developed alopecia 10 years after the onset of PPP. Two patients had pustulotic arthro-ostitis. Two patients were smokers, and one was a passive smoker. A metal patch test was carried out in all cases. Three patients showed no reaction, while one patient showed a positive reaction (+) to zinc according to the criteria of the International Contact Dermatitis Research Group. Regarding the type of alopecia, all patients presented with alopecia areata multiplex. Severe types of alopecia involving sites other than the scalp, such as the eyelashes and eyebrows, were not observed. Representative figures are shown in Fig. 1. Laboratory examination did not reveal positive antinuclear antibodies and thyroid abnormalities. Examination of focal infection was performed in all cases, in which dental caries and tonsil hypertrophy were observed each in one case. All cases were conservatively treated for alopecia. Topical immunotherapy with squaric acid dibutylester (SADBE) was applied in one case (Case 1), while the other cases were treated with topical corticosteroid or carpronium chloride lotion. Among four patients, Case 1 was resistant while others were relatively responsive to topical therapies for alopecia.

Thyroiditis, diabetes mellitus, hyperlipidaemia, and psychiatric disorders are sometimes accompanied by PPP. By contrast, there is a limited number of reports on autoimmune skin disorders such as vitiligo and alopecia. Previously, Nakamura et al. reported a patient with PPP, alopecia totalis and Hashimoto's thyroiditis. In their case, the alopecia was severe with involvement of the total scalp, eyebrow, and eyelashes, suggesting immunological interplay among PPP, alopecia, and thyroid disorders. By contrast, our four patients showed a common type of alopecia areata multiplex. Both alopecia and PPP are occasionally associated with autoimmune thyroiditis; however, autoimmune thyroiditis was not detected in any of our patients.

Similar to psoriasis, IL-23/IL-17 inflammatory pathway has recently been suggested to be important in PPP. IL-17 and IL-22 are detected close to or in the acrosyringium of PPP skin lesions, and increased serum levels of both cytokines. The etiology of alopecia areata is complicated, and recent studies have suggested Th1 dominance, Th2 dominance, and Th17 involvement. It is known that psoriasis and alopecia mutually exert exclusive local effects, e.g. the protective effect of psoriatic lesions against hair loss. This Renbok phenomenon is speculated to occur due to a local balance of different Th1/Th2/Th17 subsets which amplify self-sustaining cytokines while suppressing alternative pathways. Most likely, the immune balance may depend on the disease stages, such as initial and progressive phases, or associated diseases such as atopic dermatitis, autoimmune diseases, and connective tissue

### Table 1 Characteristics of four patients with PPP and alopecia areata.

<table>
<thead>
<tr>
<th>Case/Age/Sex</th>
<th>Smoking</th>
<th>Type of alopecia</th>
<th>Precedence</th>
<th>Metal Allergy</th>
<th>Focal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/54/F</td>
<td>+</td>
<td>Areata multiplex</td>
<td>Alopecia</td>
<td>–</td>
<td>Dental caries</td>
</tr>
<tr>
<td>2/39/F</td>
<td>+</td>
<td>Areata multiplex</td>
<td>Alopecia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3/56/F</td>
<td>–</td>
<td>Areata multiplex</td>
<td>Alopecia</td>
<td>Zink</td>
<td>Tonsil hypertrophy</td>
</tr>
<tr>
<td>4/44/F</td>
<td>Passive smoker</td>
<td>Areata multiplex</td>
<td>PPP</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

F: female; PPP: palmoplantar pustulosis

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