subcutaneous tissue simulating celullitis. N Engl J Med. 1950:242: 779-81.
5. Ruiz de Erenchun FR, Vázquez Doval J, Valérdiz S, Serna MJ, Quintanilla E. Inflammatory metastatic carcinoma: a clinical and histopathologic study of three cases. J Dermatol Surg Oncol. 1991; 17:784-7.
6. Tan BB, Marsden JR, Sanders DSA. Melanoma erysipeloides: inflammatory metastatic melanoma of the skin. Br J Dermatol. 1993;129:327-9.
7. Hazelrigg DE, Rudolph AH. Inflammatory metastatic carcinoma. Carcinoma erysipelatoides. Arch Dermatol. 1977;113:69-70.
8. Kamble R, Kumar L, Kochupillai V, Sharma A, Sandhoo MS, Mohanti BK. Cutaneous metastasis of lung cancer. Postgrad Med J. 1995;71:741-3.
9. Hodge SJ, Mackel S, Owen LG. Zosteriform inflammatory metastatic carcinoma. Int J Dermatol. 1979;18: 142-5.
10. Homler HJ, Goetz CS, Weisenburger DD. Lymphangitic cutaneous metastases from lung cancer mimicking cellulitis. Carcinoma erysipeloides. West J Med. 1986;144:610-2.

Acneiform Eruption Secondary to Cetuximab With Pseudomalignant Histopathological Changes

I Vidal-Olmo,[a] J Bassas-Vila,[b] E Herrera-Acosta,[a] and P Umbert-Millet[a]

[a]Servicio de Dermatología, Hospital Universitari Sagrat Cor, Barcelona, Spain
[b]Servicio de Dermatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

To the Editor:

Cetuximab (C225) is an antibody against epidermal growth factor receptor (EGFR) that inhibits cell proliferation.[1] The most commonly reported adverse effect is follicular acneiform eruption.

We present the case of a 69-year-old man with a history of hypertension and type 2 diabetes mellitus. In July 2004, the patient was diagnosed with adenocarcinoma of the sigmoid colon and underwent localized resection. Treatment with cetuximab was started when a computed tomography (CT) scan of the thoracic and abdominal region carried out to assess tumor spread revealed enlarged retroperitoneal lymph nodes. One week after he completed the second cycle of cetuximab the patient presented with a monomorphic erythematous papulopustular follicular eruption that had appeared abruptly on his face, scalp, and back (Figure 1). Examination of the dermis revealed edema and a perivascular and interstitial inflammatory infiltrate composed of lymphocytes, plasma cells, isolated eosinophils, and large cells with a grayish cytoplasm, along with pleomorphism, binucleation, prominent hyperchromatic nucleoli, and the presence of isolated mitotic figures (Figure 3). Immunohistochemistry of these cells was positive for CD-68 and lysozyme and negative for myeloperoxidase, and periodic acid-Schiff staining was negative, confirming their histiocytoid character. The lesion was a cetuximab-induced acneiform eruption that improved after treatment with topical benzoyl peroxide and oral minocycline.

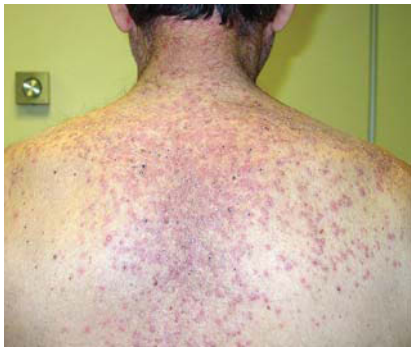

Figure 1. Papulopustular eruptions on the back.

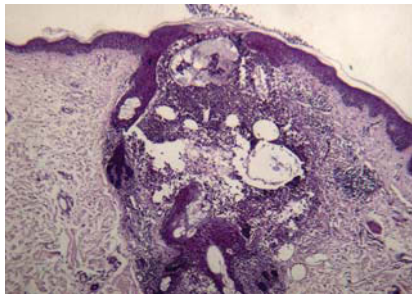

Figure 2. Histology of a papulopustule showing neutrophilic folliculitis with negative periodic acid-Schiff staining. (×25.)

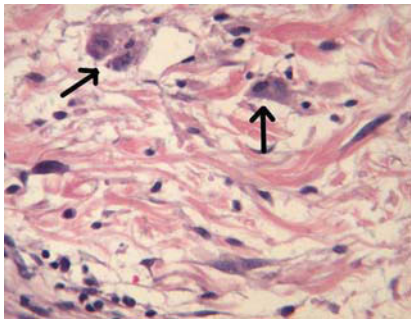

Figure 3. Atypical binucleated histiocytes (arrows). (Hematoxylin-eosin, ×200)

Cetuximab is a chimeric monoclonal antibody that inhibits the EGFR.[2] The antitumor activity of this biologic agent stems from its ability to inhibit cell proliferation, angiogenesis, and the formation of distant metastasis while inducing cell apoptosis. It has been used primarily in the treatment of solid tumors at advanced stages in which EGFR expression has been observed.[3,4] While this chemotherapeutic agent is not associated with any systemic symptoms, cutaneous side effects have been described in several recent publications. While the mechanism involved is poorly understood, various authors have suggested that the EGFR may play a central role in follicular physiology. These EGFR inhibitors interfere with the transition from the anagen to the catagen phase in the hair growth cycle,[2,5] and give rise to infundibular dilatation, hyperkeratosis, and formation of horny plugs, favoring an alteration in local flora that may increase the pathogenic potential of nonpathogenic organisms.[6] However, in all the studies published to date, the results of bacterial and fungal cultures of pustules have been negative.[4] Other authors have suggested that cetuximab may affect the immune system directly giving rise to neutrophil chemotaxis and uncontrolled cytokine production.[4]

After 2 to 6 weeks of treatment with cetuximab, approximately one third of patients present with an acneiform eruption that has not been shown to have any relationship with tumor type, skin phototype, sex, or history of acne or rosacea.[5]

Cutaneous side effects are reversible and dose dependent. Interruption of cancer treatment is usually unnecessary.[5] A positive correlation between cutaneous toxicity and tumor response was initially suggested, but a recently published study failed to confirm this hypothesis.[6]

Histological examination of these eruptions reveals varying degrees of folliculitis—ranging from infundibular dilatation to destruction of hair follicles—caused by a dense, predominantly neutrophilic, infiltrate of polymorphonuclear cells near the skin surface and a predominantly lymphocytic and histiocytic infiltrate in the deeper layers.[4]

In our case, histopathology showed a suppurative neutrophilic folliculitis characterized by large grayish histiocytoid cells characterized by pleomorphism, binucleation, prominent nucleoli, and isolated mitotic figures. Immunohistochemistry of these cells was positive for CD-68 and lysozyme and negative for myeloperoxidase, and periodic acid-Schiff staining was negative. They are probably atypical histiocytes that have not as yet been reported in the context of this type of cutaneous reaction to EFGR inhibitors.

These atypical histiocytes have been observed, and are considered diagnostic, in the acute cutaneous eruptions that appear after administration of granulocyte and granulocyte-macrophage colony-stimulating factors (CSF-G and CSF-GM).[7,8] However, they have also been observed in patients undergoing aggressive chemotherapy who have not received any type of CSF.[9] It has also been suggested that these findings could be specific to cutaneous involvement in leukemia[10] and that these atypical cells could be the result of the proliferation of leukemia cells in the skin. Our patient had not been treated with either CSF-G or CSF-GM and presented no hematological malignancy. After a year of follow-up, the patient developed a metastatic liver tumor without evidence of further complications.

We have presented the case of a patient receiving EFGR-inhibitor treatment for a solid tumor in whom atypical histiocytes were observed infiltrating the dermis. It is probable that some, as yet unknown, mechanism involving EFGR inhibitors is responsible for the appearance of these pseudomalignant cells.

References

1. Herrera-Acosta E, Martín-Ezquerra G, Iglesias M, Umbert P. Erupción acneiforme secundaria a cetuximab. Actas Dermosifiliogr. 2005;96:252-4.
2. Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. Arch Dermatol. 2002;138:129-31.
3. Walon L, Gilbeau C, Lachapelle JM. Acneiform eruptions induced by cetuximab. Ann Dermatol Venereol. 2003; 130:443-6.
4. Jul G, González-de Arriba A, Daudén E. Efectos secundarios de los inhibidores del receptor del factor de crecimiento epidérmico. Actas Dermosifiliogr. 2006;97:296-310.
5. Martínez de Lagrán Z, Ratón JA, Lasa O. Erupción acneiforme por inhibidores del receptor de crecimiento epidérmico. Actas Dermosifilogr. 2005;96: 450-4.
6. Sandwich N. Tolerability in patients receiving treatment in everyday clinical practice. Br J Cancer. 2003;89:S9-S14.
7. Fariña MC, Requena L, Dómine M, Soriano ML, Estévez L, Barat A. Histopathology of cutaneous reaction to granulocyte colony-stimulating factor: another pseudomalignancy. J Cutan Pathol. 1998:25:559-62.
8. Horn TD, Burk DJ, Karp JE, Hood AF. Intravenous administration of recombinant human granulocyte-macrophage colony-stimulating factor causes a cutaneous eruption. Arch Dermatol. 1991:127:49.
9. Valks R, Vargas E, Muñoz E, Fernández-Herrera J, García Díez A, Fraga J. Dermal infiltrate of enlarged macrophages in patients receiving chemotherapy. J Cutan Pathol. 1998:25:259.
10. Yamashita N, Natsuaki M, Morita H, Kitano Y, Sagami S. Cutaneous eruptions induced by granulocyte colony-stimulating factor in two cases of acute myelogenous leukemia. J Dermatol. 1993:20:473.