

Novel Skin Toxicity of Epidermal Growth Factor Receptor Inhibitors: A Case of Intertrigo-Like Eruption in a Patient with Metastatic Colorectal Cancer Treated with Cetuximab

Abstract

Over the recent years, targeted therapy has become one of the most important innovations in cancer treatment. Agents targeting the epidermal growth factor receptor (EGFR) are administered in patients with advanced, recurrent, and metastatic malignancy. Skin toxicity is one of the most common side effects of EGFR inhibitors. In this report, we present the case of a 70 year-old male patient with metastatic colorectal cancer who developed an intertrigo-like eruption during molecular target therapy with cetuximab treated with topical corticosteroid. A complete remission was obtained after 4 weeks.

Keywords: *Cetuximab, intertrigo-like eruption, skin toxicity*

Introduction

Targeted therapy has become one of the most important innovations in cancer treatment. Agents targeting the epidermal growth factor receptor (EGFR) are administered in patients with advanced, recurrent, and metastatic malignancy. Skin toxicity is one of the most common side effects of EGFR inhibitors.^[1] We present the case of a 70-year-old male patient with metastatic colorectal cancer who developed an intertrigo-like eruption during therapy with cetuximab.

Case Report

The patient was diagnosed in 2014 and underwent surgery. During 2014, he received adjuvant radiochemotherapy to the surgical anastomosis (total dose = 50.4 Gy/dose per fraction = 1.8 Gy) and to the pelvic lymph nodes (total dose = 45 Gy; dose per fraction = 1.8 Gy), and later chemotherapy according to the folinic acid, fluorouracil, and oxaliplatin scheme for four cycles. In 2016, for disease progression documented by fluorodeoxyglucose-positron emission tomography/ CT, the patient started chemotherapy according to the folinic acid, fluorouracil, and irinotecan scheme in association with Cetuximab 250 mg/sq. m weekly (for 6 cycles). Due to disease

stability, he continued therapy with cetuximab maintenance on a weekly basis, which is still ongoing with partial response to treatment.

During the therapy, he developed multiple, glossy, sharply demarcated erythematous macules involving the bra area (pillar axillary and submammary region), inguinal area, and the scrotum. The lesions caused a burning sensation but did not interfere with normal daily activities (skin toxicity Grade 2 according to NCI/GOG criteria). No other mucosal lesions or palmoplantar involvement was observed. Direct microscopic examination of skin scrapings and fungal cultures were negative. The patient's history suggested the possibility of an intertrigo-like eruption due to cetuximab. A therapy with topical corticosteroid (clobetasol BID for 3 weeks) was introduced. The use of loose clothing, avoidance of sharp objects, and tight shoes was recommended. The lesions responded to treatment with complete remission after 4 weeks [Figure 1]. The case was presented to the oncologists, who decided to continue with the therapy.

Discussion

Cetuximab is an agent targeting the EGFR administered in metastatic or non-resectable colorectal cancer, with expression of the EGFR and without RAS (wild-type) mutations.^[2] Skin reactions are one of the major side effects

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Figure 1: Clinical presentation before and after 4 weeks treatment

associated with cetuximab treatment and they include acneiform rash, xerosis, pruritus, paronychia, hair abnormalities, mucositis, increased growth of eyelashes or facial hair, photosensitivity, and urticarial. These skin manifestations, in association with acneiform eruptions, have been labeled the papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to EGFR syndrome inhibitors.^[1] The most commonly used grading system to define the grade of skin toxicity due to cetuximab is the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 that takes into account the body surface area affected by reaction expressed as a percentage.^[3]

Intertrigo-like eruption has not been associated with cetuximab so far. It is reported as skin toxicity in patients treated with pegylated liposomal doxorubicin.^[4]

The pathogenesis of EGFR inhibitors skin toxicity is unknown. In the epidermis, the EGFR is normally expressed in undifferentiated, actively proliferating basal and suprabasal keratinocytes, outer layers of the hair follicle and pilosebaceous glands. EGFR plays a critical role in maintaining epidermal homeostasis through regulation of keratinocyte proliferation, differentiation, migration, and survival.^[5]

Cetuximab downregulates the level of the phosphorylated EGFR in basal and suprabasal keratinocytes and the outer layer of hair follicles, resulting in diminished proliferation of basal keratinocytes, growth arrest, and apoptosis of keratinocytes. The EGFR inhibitors then induce upregulation of inflammatory chemokines and cytokines such as interleukin-1 and tumor necrosis factor-alpha that recruit macrophages, mast cells, and granulocytes.^[6] The role of EGFR inhibitors on keratinocyte proliferation and inflammation can explain the acneiform eruptions. It is the first case of intertrigo-like eruption in a patient treated with cetuximab. In our opinion, in anatomic regions such as axillary folds, the abdominal belt and inguinal areas, local microtrauma causes vessel damage, extravasation of the molecules in the epidermis and local inflammation with erythema, edema, desquamation, and painful erosions. In addition, EGFR inhibitors play a direct role on keratinocytes.

Skin toxicity represents the most common side effect of EGFR inhibitors.^[1] In patients who develop severe skin eruption (Grade 3), a reduction of dose is indicated. Conservative measures such as moisturizing creams, avoidance of trauma, pressure, and heat exposure are recommended.^[7] Premedications have been described for acneiform eruption. For intertrigo-like eruption, preventive and curative treatments have not been defined. In our patient, the use of topical steroids was necessary to recover the lesions, to alleviate the symptoms, and to improve the quality of life. In our opinion, in patients who have already developed an episode of intertrigo-like eruption, it might be useful to consider the possibility of premedication with corticosteroids.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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