Original Paper

Cutaneous Toxicity in Oncologic Patients Receiving Epidermal Growth Factor Receptor Inhibitors

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ABSTRACT: Background. In recent years, oncology studies have focused on molecular targeted therapy, based on the development of numerous agents with a role in inhibiting the epidermal growth factor receptor (EGFR). When overexpressed, EGFR plays an extremely important role in the growth of certain tumour cells. Compared to classical chemotherapy, the systemic adverse effects of the molecular targeted therapy are much lower. However, between 80 to 100% of the patients treated with EGFR inhibitors develop a separate class of adverse effects, namely skin reactions. Objectives. Early identification of skin toxicity, dynamic monitoring of patients during EGFRI treatment, correlation of clinical data and their management. Methods. We conducted a prospective study from 2018 to 2021 on patients who had received any EGFRI from all over Oltenia region. We were able to identify 31 oncologic patients who had received EGFRI for metastatic colorectal cancer, lung cancer or head and neck cancer. All of them were completely dermatologically examined, dynamically monitored for each oncological cycle. Results. The dermatological follow-up throughout the study allowed the classification of skin toxicity according to the onset of manifestations after EGFRI treatment, the reporting of serious adverse effects and their management. Within the study group, 29 out of the 31 patients treated oncological with EGFRI therapy experienced at least one cutaneous adverse effect, the majority of which showed clinical polymorphism of lesions. Conclusions. The lack of dermatological treatment often leads to dose reduction or even to the discontinuation of the cancer treatment. Severe forms were also identified and their rapid treatment allowed the continuation of the cancer therapy and increased quality of life for all patients.

KEYWORDS: *Skin toxicity, EGFRI, molecular targeted therapy.*

Introduction

Current oncology studies have focused their attention on the HER gene (ERbB). The epidermal growth factor receptor (EGFR) is part of this HER gene family. EGFR is a tyrosine kinase receptor that when over-expressed plays a role in the development of tumour cells present in several types of solid tumours: colorectal, gastric, pancreatic, head and neck, non-small cell lung, ovarian and prostate.

Also, the over-expression of EGFR is correlated with poorer prognosis and with increased aggressiveness [1-2].

Currently, the inhibition of EGFR activity can be achieved with 2 classes of drugs: monoclonal antibodies (Cetuximab/Erbitux, Panitumumab/Vectibix, Pertuzumab/Perjecta) and tyrosine kinase enzyme inhibitors (Erlotinib/Tarceva, Lapatinib/Tyverb).

Compared to classical chemotherapy, the systemic side effects are rare. However, a special category of adverse effects encountered in patients with EGFRI is represented by cutaneous adverse reactions, which occur either early in the course of the therapy or during the cancer treatment [3].

The early reactions include papulopustular rash (90%), bacterial superinfection (70%) and mucosal damage (conjunctivitis, vulvovaginitis, balanitis).

The late skin reactions include: papulopustular rash/LATE syndrome, skin xerosis, skin ageing, nail changes, hair changes and bacterial superinfection [4-6].

The management of skin toxicity in oncology plays an extremely important role in the patient's compliance to therapy, it also plays an important role in increasing their quality of life.

Material and Method

We conducted a prospective study from 2018 to 2021 on patients who had received any EGFRI from all over the Oltenia region and its surroundings. We were able to identify 31 oncologic patients who had received EGFRI.

All patients were fully dermatologically examined and clinical pictures were taken. Information was also collected on the patients' gender, location of lesions, type of cancer, infusion number, dermatological history, dermatological treatment followed, evaluation of lesions from onset to present.

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The informed consent was signed by every subject prior to the study procedures, and furthermore, the study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

Results

In the study group, 29 out of 31 patients treated with anti-EGFR therapy experienced at least one cutaneous adverse effect, the majority of which showed clinical polymorphism of lesions.

Most patients were undergoing chemotherapy for colorectal cancer (25 out of 31), followed by head and neck cancers (5 out of 31) and lung cancer (1 out of 31).

All patients were on EGFRI treatment, 26 patients were treated with Cetuximab, 4 patients with Panitunumab and 1 patient with Erlotinib.

Taking into account the time of onset of symptoms in relation to the administration of the EGFRI therapy, the adverse cutaneous effects could be classified into 2 categories, as presented in Table 1.

Early reactions	Late reactions
papulopustular rash	papulopustular rash/LATE syndrome
bacterial superinfections	skin xerosis (cracks, eczema, itching)
mucosal damage	facial damage: facial erythema, telangiectasias
	vasculitis
	nail changes
	hair changes: diffuse alopecia, ciliary trichomegaly
	superinfections

The most common dermatological adverse effect of EGFRI was the papulo-pustular rash, identified at 74,19% of the patients, followed up by xerosis and pruritus (48,39%), erosions and cracks (45,16%), telangiectasia (35,48%), erythema (25,81%), hematous meliceric crusts and superinfections (19,35%). 6,45% of the EGFRI patients had also purpura, erytroderma, scales, hyperpigmentation, eczema and vasculitis.

Regulatory abnormalities of hair growth included: localized alopecia (22,58%), trichomegaly of the eyelashes and trichomegaly (12,90%). In term of complications, 3,23% of the patients develop later blepharitis, conjunctivitis (Figure 1), and xanthelasma.

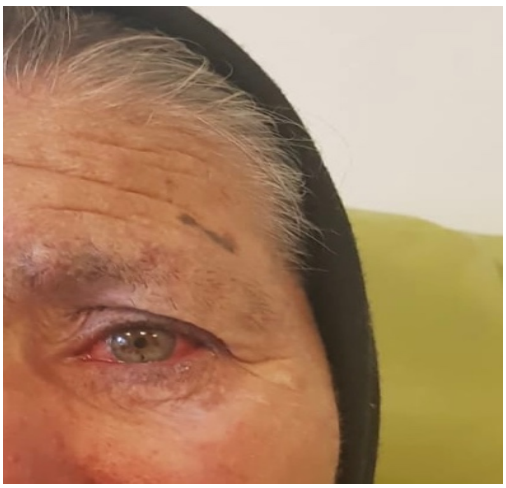


Figure 1. Conjunctivitis, hyperpigmentation, brows change.

The incidence of the nail changes was various: 3,23% of the patients experience onychomycosis and nail haematoma, 9,68% onyxis, 12,90% panaritium, 32,26% paronychia.

Mucosal involvement is characterized by mouth ulcers in 12,90% of the patients.

In patients with colorectal and head and neck cancers treated with EGFRI the frequency of cutaneous side effects is different as presented in Figure 2 and 3.

While in patients with colorectal cancer the most frequent side effects are papulo-pustular rashes (76%), in patients with head and neck cancer the most frequents side effects are erosions and cracks (100%).

Figure 2. Frequency of adverse effects among patients with colorectal cancer.

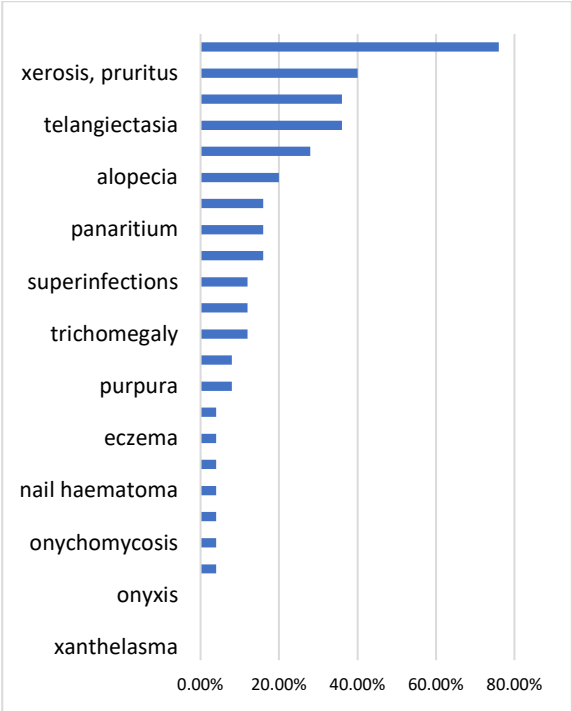
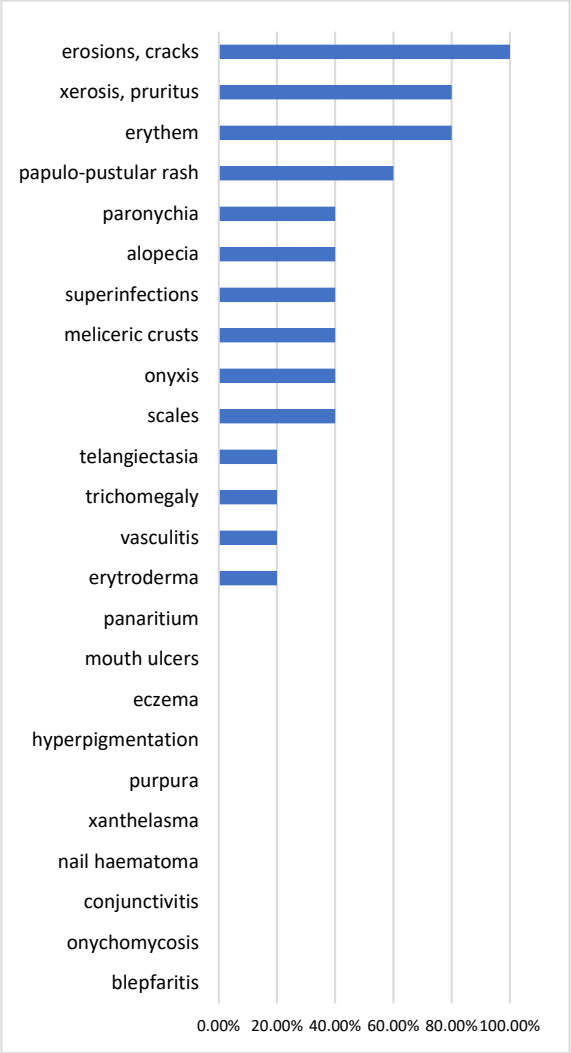


Figure 3. Frequency of adverse effects among patients with head and neck cancers.



The single patient with pulmonary cancer presented cutaneous side effect such as papulo-pustular rash, xerosis, pruritus, telangiectasia, paronychia, superinfections, meliceric crusts, onyxis, eczema, and xanthelasma.

In terms of localization of side effects, the most affected areas are the anterior and posterior thorax, the face and the nails, as presented in Table 2.

Table 2. Dermatological adverse effects localization.

Localization of dermatological adverse effects	
anterior thorax	65,38%
face	61,54%
posterior thorax	61,54%
nail	42,31%
upper limbs	38,46%
lower limbs	15,38%
scalp	15,38%
eyelids and eyebrows	15,38%
generalised	11,54%
abdomen	11,54%

Previous studies mention the sterility of pustules, the microbiological results and cultures are frequently negative and do not show an infectious cause.

Among the severe complications of EGFRI therapy, we report the case of a 62-year-old patient diagnosed with colorectal cancer, with secondary liver metastases, who developed Staphylococcus aureus bacteremia secondary to severe Cetuximab skin toxicity. The patient was operated (left hemicolectomy with left colostomy), treated with chemotherapy and immunotherapy. Located on the trunk, the patient presents a small granular plaque with minimal secretion. Microbial culture was collected from the wound for antibiogram. The bacteriological examination was positive for methicillin-resistant Staphylococcus aureus (MRSA) and antibiotic treatment is instituted with Invanz for 5 days, followed by Tienam for 7 days, then Vancomycin for 8 days with favorable evolution. Over time, the patient presented numerous episodes of acneiform eruptions, xerosis, nail changes, for which he only followed topical treatment. In April 2019, after the 8th treatment with EGFRI the patient presents a generalized papulopustular rash at body level, intense erythema, telangiectasias, intense pruritus, nail and hair changes, baldness, intense skin xerosis. A tissue fragment was harvested from the anterior chest to establish the diagnosis of vasculitis. The histopathological result showed the fragment covered by epidermis with atrophic areas and discrete orthokeratosis, frequent adjacent enlarged capillaries and degeneration of collagen and elastic fibers with discrete hematic infiltrate in-between (Figure 4,5,6,7).

Following the systemic and local treatment, the patient's evolution was favorable, although without remission.

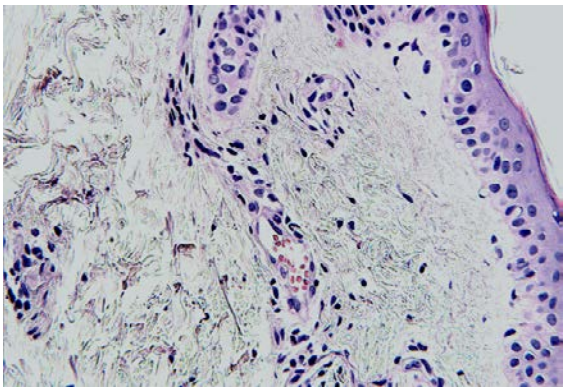


Figure 4. Skin with dilated capillaries, rare extravasated red blood cells, discrete perivascular lymphocytic infiltrate, Hematoxylin-eosin staining, 20×.

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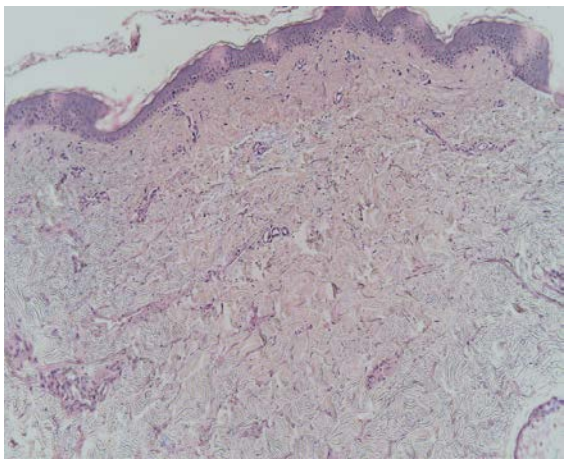

Figure. 5. Skin with dermis fibrosis, fragmented collagen fibers, Hematoxylin-eosin staining, 4×.

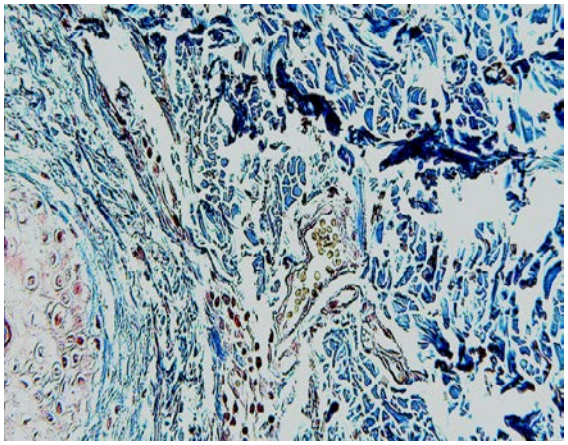

Figure 6. Dermis with intensely fragmented collagen fibers (blue staining), dilated vessels with stasis and extravasated erythrocytes (yellow-brown), Masson trichrome staining, 20×.

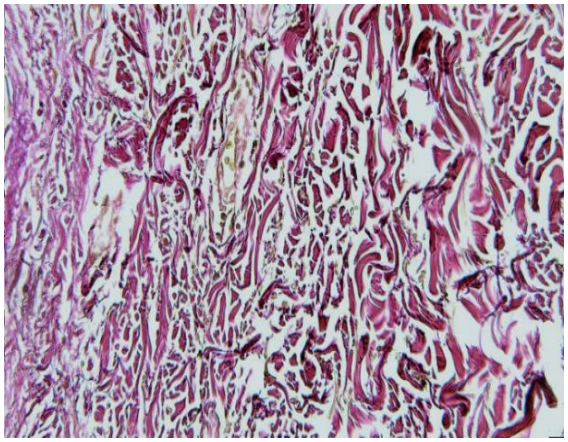

Figure 7. Van Gieson stain, intensely fragmented collagen fibers (red), dilated vessels with extravasated red blood cells (yellow), Van Gieson trichrome staining, 20×.

Discussion

The introduction of molecular targeted therapy has been an extremely important step in increasing the survival among cancer patients.

Compared to classical chemotherapy, the systemic adverse effects are greatly diminished, however the impact generated by the frequency and extent of dermatological manifestations affects patients' adherence to treatment.

The management of EGFRI-induced skin toxicity is of paramount importance in order to continue the cancer treatment and prevent serious adverse effects [7-9].

Papulopustular rash

The most common skin adverse effect reported was the papulopustular rash (Figures 8,9), present in 88.46% of the patients enrolled in this study.

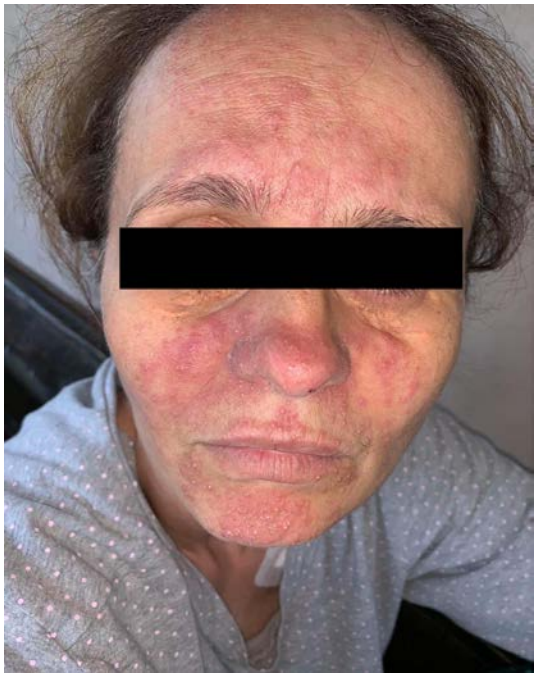

Figure 8. Erythematous papulopustular eruption.

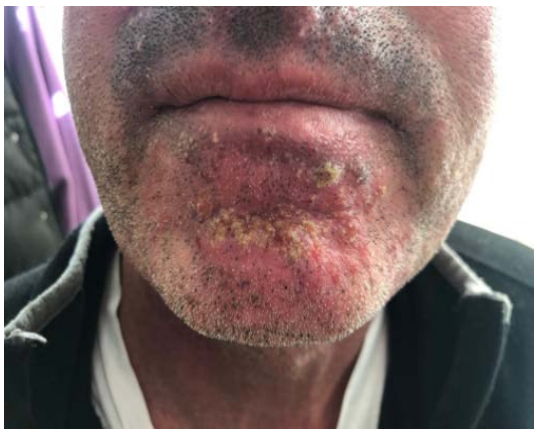

Figure 9. Papulopustular rash, superinfection, meliceric crusts.

The localization varies, being more common on areas rich in sebaceous glands: face, anterior and posterior cervical area, shoulders, arms. The rash may also be present on the legs or abdomen.

The palms and soles are rarely affected. It appears early in 2 or 3 days after the administration of the molecular therapy and it reaches a peak of intensity in 2 or 3 weeks after the treatment [10].

As it is also the case for the study group, the rash starts most commonly with follicular or interfollicular localized papules or pustules [11-12].

In the course of the rash, symptoms such as erythema, oedema, burning sensation on the face are initially described, followed by the subsequent maculopapular rash. The papules formed may evolve into pustules, yellow crusts and in particular cases they may progress to necrosis and skin ulceration. Following the reaction, patients may present residual hyperpigmentation, xerosis, scarring. Some of these hyperpigmentations are the result of self-resolving telangiectasias that occur during eruption and post-eruption [11-13].

The pathological results depend on the intensity of the rash at the time of sampling. Depending on this, the biopsy result varies from a simple infiltrate with dilated T lymphocytes around the follicular infundibulum to suppurative folliculitis [14].

The biopsies taken from the lesions show changes in the stratum corneum, which is much thinner, with focal parakeratosis, loss of basket-weave appearance and dilated follicular infundibula [15-16].

In the case of the biopsy, one can observe structural changes, ectatic capillaries, extravasated red blood cells, discrete perivascular lymphocytic infiltrate. The histopathological appearance suggests the diagnosis of vasculitis.

The pustules are sterile, the microbiological stains and cultures do not show infection, they may superinfect in rare cases. These inflamed pustules and follicular papules create a favorable environment for colonization, proliferation and invasion of S. aureus. The Staphylococcus aureus infection is most commonly accompanied by another dominant symptom, pruritus, which in turn sustains the skin infection. The S. aureus infection can also spread to deep tissues because the skin loses its barrier function [16-17].

EGFRI is also involved in the skin ageing process. This is based on 2 hypotheses: the oxidative stress theory and the cellular senescence theory [18].

The phenomenon of skin ageing (facial erythema, telangiectasia, xerosis) was present in 29 of the 31 cases studied.

Xerosis and Pruritus

The onset of skin xerosis occurs most commonly after the appearance of the papulopustular rash. The skin is dry, dehydrated and it develops an eczematous appearance over time, and the patient also experiences intense pruritus. The superimposition of a secondary infection may lead either to the intensification of the skin rash or to the appearance of meliceric crusts [19].

The damage of the epidermal barrier leads most commonly to superinfection and colonization with resistant bacteria. Cases of interphalangeal ecchymosis and swelling have been reported in the literature [11].

The appearance of cracks in the fingers frequently leads to the limitation of normal activities, patients may experience a burning sensation. Extremely painful perioral cracks of the lips are also described, with impaired quality of life and limitation of normal eating.

Nail Changes

The clinical appearance ranges from pitting, discoloration, paronychia, cracks in lateral folds and cuticles, edema, partial or total nail loss [20].

These are late-onset adverse effects starting 4-8 weeks after the initiation of anti-EGFR therapy. They affect 10-15% of the patients. Cases have been described in which patients may graft infections with pyogenic granuloma, Staphylococcus aureus or Candida albicans (Figure 10) [11].

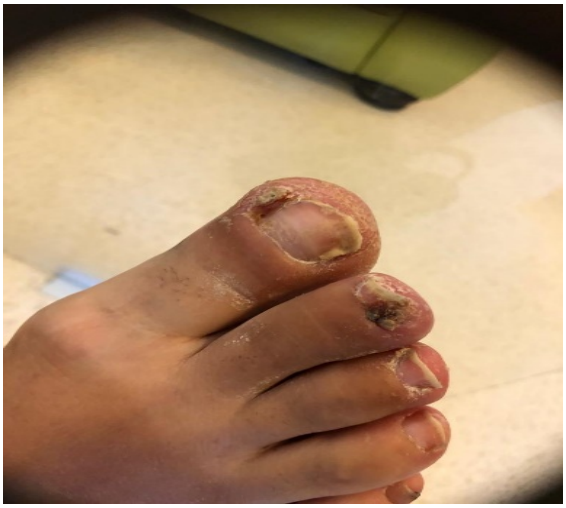

Figure 10. Nail changes: Periungual paronychia and granulation, nail-fold swelling after treatment with Cetuximab.

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Hair changes

The hair changes occur most commonly in 2-5 months after the treatment starts. The clinical appearance ranges from excessive hair growth on the head and/or changes in the texture of the hair on the face and scalp (thin, wavy, brittle hair) (Figure 11,12) [11,21].

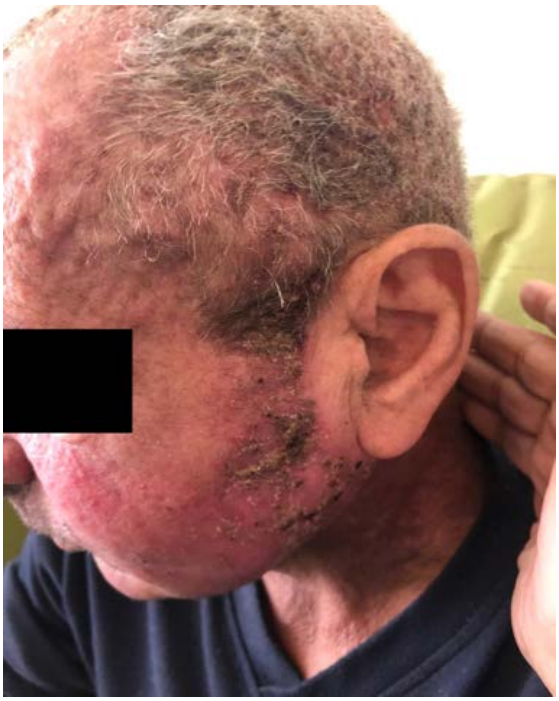

Figure 11. Hair changes: localized alopecia, multiple pustules on the scalp.

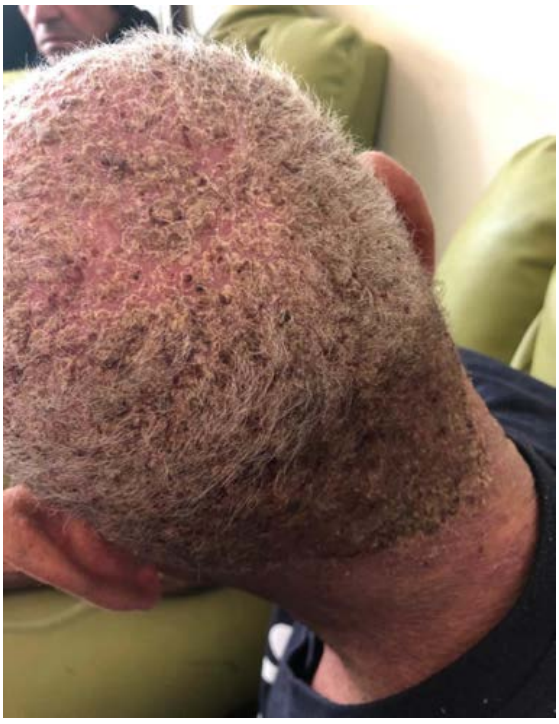

Figure 12. Hair changes: thin, wavy, brittle hair, crusts.

57.68% of the enrolled patients reported changes at the time of the examination, 26% of the patients had alopecia, 15.38% had hypertrichosis and ciliary trichomegaly.

Conclusions

The frequent occurrence of skin toxicity may jeopardize the oncological treatment of patients treated with EGFRI.

Through this continuous follow-up, performed at each oncology treatment, we were able to manage early adverse effects and prevent serious adverse effects that could have led to dose reductions or even discontinuation of the oncology treatment, while emphasizing the importance of a multidisciplinary team.

Conflict of interests

None to declare.

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