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Review Article

# Dermatologic Adverse Effects Secondary to EGFR Inhibitors Use as Oncological Treatment: Pathophysiology, Clinical Manifestations and Treatment

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**Abstract**

Through the last few years the use of Epidermal Growth Factor Receptor Inhibitors (EGFR) has increased within the treatment of several oncological diseases. Though these drugs offer advantages regarding their systemic adverse events profile, they relate with the appearing of skin lesions among patients. Most frequent are: xerosis, acneiform dermatitis, pruritus, paronychia, and hair alterations. These adverse effects are due to these drugs mechanism of action, and their incidence is a sign of their efficacy.

Regardless the frequency of dermatologic lesions, and the impact these may have on oncological treatment duration, there is still a lack of an established standard treatment or prophylaxis. So far, the treatment is based on antimicrobial agents such as tetracycline and minocycline, topical steroids, anthistaminics, and skin care general measures. This paper reviews dermatologic adverse events of EGFR inhibitors, more common clinical manifestations and different treatments suggested to date.

**Keywords:** Epidermal Growth Factor Receptor Inhibitors (EGFR); Dermatologic adverse effects; Chemotherapy toxicity

## Introduction

Most human epithelial cancers display a marked increase of growing factors, and a particularly high activity of EGFR receptors. When the phenomenon was understood, EGFR became the most important receptor to investigate for researchers, and main therapeutic target for oncological treatment in patients portraying the aforementioned activation [1].

Currently there are two EGFR inhibitor classes for oncological use: monoclonal antibodies and tyrosine kinase inhibitors (TKIs) [1].

Anti EGFR treatments allow for a larger selectivity with better success rates portrayed as response rates, quality of life, progression-free survival, and overall survival, and for lesser adverse events related to chemotherapy agents [2].

Most common side effects with EGFR treatment are those related to skin, since EGFR activation plays an important role for skin's innate immunity, and its inhibition reduces the immunity's integrity. This has been seen in phase II trials with this kind of drugs [3-6] (Table 2).

Although adverse side effects secondary to EGFR inhibition are seldom severe, they do have a high impact on the patient's quality of life, including physical, financial, emotional, and social aspects [7]. A decrease in dose, and a lack of continuity in treatment have been reported in 60% and 32%, respectively, secondary to dermatological adverse effects caused by EGFR inhibitors, which have diminished therapeutic benefits [2]. Joshi *et al* observed that emotional impact and detriment in quality of life is greater in patients younger than 50 years old [8].

## Pathophysiology

EGFR, also known as ErbB1 (HER1) is part of the tyrosine kinase family of Erb receptors, is a transmembrane protein consisting in an extracellular ligand, a transmembrane region, and an intracellular region located in epithelial origin cells. Inhibiting the signal mediated by EGFR can be achieved using monoclonal antibodies (cetuximab, panitumumab) that bind extracellular domain and prevent ligand binding, or using low molecular weight agents (erlotinib, gefitinib, afatinib) that block triphosphate adenosine binding to receptor's

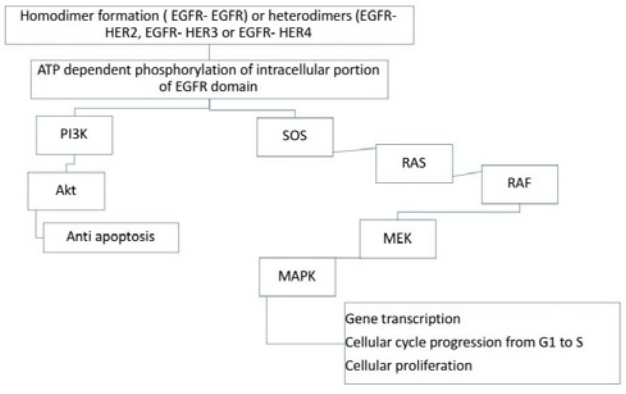


**Figure 1:** EGFR, HER2, HER3, and/or Her4 receptors are activated, homodimers or heterodimers are constitute. This starts a phosphorylation chain ATP dependent of the intracellular domains EGFR specific of tyrosine kinase. This triggers 2 signaling pathways, the fist (left) activates the anti apoptotic cascade, and the second (right) activates RAS, RAF, MEK, MAPK and controls gene transcription from G1 to S and cellular proliferation.




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**Table 1:** EGFR inhibitors and their approved use in oncological treatment.

| Drug | Approved uses |
|---|---|
| Erlotinib | Non-small cells lung cancer<br>Pancreatic carcinoma |
| Gefitinib | Non-small cells lung cance |
| Afatinib | Non-small cells lung cancer |
| Cetuximab | Colon and rectal cancer<br>Squamous cell carcinoma of the head and neck |
| Panitumumab | Colon and rectal cancer |

intracellular portion [9] (Figure 1, Table 1).

When EGFR is activated, different signaling pathways are produced, of which there are 3 main ones: 1) RAS / RAF /MEK / ERK pathway, with repercussion on cell proliferation, cell cycle progression and migration; 2) *Via* JAK/ STAT which also promotes cell proliferation, protects against apoptosis and promotes cell motility and 3) PI3K (phosphoinositol 3 kinase) / Akt which acts by inhibiting apoptosis [10].

EGFR is responsible for several skin essential functions throughout development, like epidermal proliferation, differentiation, migration, repairing and carcinogenesis, keeping keratinocytes in an active and proliferative state, in order to promote motility and apoptosis protection [9,11]. EGFR inhibition stimulates pro-inflammatory cytokines CCL2, CCL5 and interleukins. These are important because they are related to dermatitis onset [12].

EGFR participates in the differentiation and development of epidermal keratinocytes, stimulating their growth, inhibiting differentiation, protecting against UV radiation, inhibiting inflammation, and accelerating wounds repairing. It expresses at follicular and epidermal keratinocytes, at the epidermis basal layer, at hair follicle roots, at sebaceous epithelium, at eccrine epithelium, at dendritic cells and other connective tissues [9,12-14].

This process results in a debridement that causes the loss of hydration, and starts xerosis [15]. It is clear that dermatologic damage mechanism started with EGFR inhibition is related with the effects on proliferation and differentiation of keratinocytes promoting secondary inflammation [13].

The mechanism of the effects of EGFR is explained by the inhibition of EGFR that directly affect keratinocytes by inhibiting growth, promoting apoptosis, decreasing cell migration and stimulating inflammation [16]. Acneiform dermatitis is explained by follicular occlusion that occurs as a consequence of the lack of cellular differentiation of the epithelium and release of cytosines leading to inflammation [17], xerosis by the role that EGFR plays in maintaining the integrity of the epidermal barrier; skin fragility and thinning are related to the action of EGFR in the proliferation, differentiation and survival of keratinocytes [18]. Epidermal changes reflect the altered balance between proliferation and differentiation, which may be responsible for xerosis and desquamation observed in some patients treated with Gefitinib [19].

Cell cultures have shown that inhibiting EGFR increases apoptosis levels up to five times between days 4 and 12, which correlates with the clinical appearing of papulopustular skin lesions among patients treated with these drugs [14].

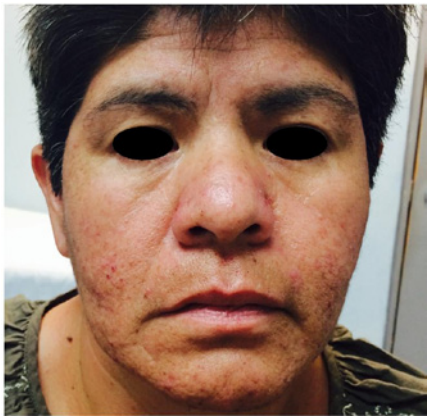

**Figure 2:** Patient with lung adenocarcinoma treated with afatinib. It can be seen localized dermatosis on the face, predominantly on the cheeks, chin and nose with multiple pustules and papules.

## Clinical Manifestations

Different dermatologic adverse effects manifestations have been reported, such as acneiform dermatitis, xerosis, pruritus, hyperpigmentation, eczema, hair damage, paronychia, hand-foot reactions, and even vitiligo [20].

### Acneiform dermatitis

The most common dermatologic adverse effect in patients treated with EGFR inhibition, occurring in up to 85% of patients, with a 10%-20% of them showing severe forms. It has been reported that treatment with monoclonal antibodies and tyrosine kinases inhibitors causes these effects, being most prominent in the first group, particularly with the use of Panitumumab [15,21]. Dermatologic side effects promote treatment cessation in about a 32% of patients, and dose changing in up to 76% of patients [15].

Acneiform dermatitis is characterized by papulopustular lesions, generally accompanied by honey colored scabs and not visible black heads [22]. The most common location is on the face, scalp and upper chest (Figure 2). It has a face flow dissemination, and generally appears during the first month of treatment, and most commonly during first seven to ten days of treatment, though they may appear between days 7 and 42. It generally improves with time, but in only few cases disappears completely while EGFR inhibitors are used [2,23,24]. The lack of open black points distinguishes it from acne; secondary lesions to EGFR therapy are monomorphic, indicating they appeared in a common date [2].

Several risk factors have been identified for development of lesions: no smokers, white race, and male sex. Severe forms are more frequent as a consequence of using monoclonal antibodies, and they appear in 10%-17%, when comparing with tyrosine kinases inhibitors with only 5%-9% [15] (Table 3).

It has not been seen a relationship between severity and a seborrhea, rosacea or acne background, or dermatologic adverse effects; and when used with RT, the effects are dose dependent [23, 25-28].

### Xerosis, pruritus and digital fissures

Xerosis is often observed since the first two months of treatment.

**Table 2:** EGFR inhibitors approved by FDA (2015) and their most common adverse effects [6].

| Tyrosine Kinase Inhibitors | | |
|---|---|---|
| **Drugs** | **Adverse Effects** | |
| Erlotinib | Acneiform dermatitis<br>Diarrhea<br>Asthenia | Cough<br>Dyspnea<br>Anorexia |
| Gefitinib | Non-Specific dermatitis<br>Transaminase elevation<br>Proteinuria | Diarrhea<br>Hepatotoxicity<br>Interstitial lung disease (ILD) |
| Afatinib | Diarrhea<br>Acneiform dermatitis<br>Stomatitis<br>Paronychia<br>Xerosis<br>Anorexy | Pruritus<br>Vomit<br>Dyspnoea<br>Dysphagia<br>Hipokalemia |
| **Monoclonal Antibodies** | | |
| **Drugs** | **Adverse Effects** | |
| Cetuximab | Nausea<br>Anemia<br>Vomit<br>Neutropenia<br>Unspecified dermatitis | Asthenia<br>Diarrhea<br>Anorexia<br>Conjunctivitis<br>Electrolyte disturbances (hypomagnesemia, hypokalemia, hypocalcemia) |
| Panitumumab | Acneiform dermatitis<br>Pruritus<br>Xerosis | Paronychia<br>Erythema<br>Angioedema |

**Figure 3:** Patient with lung adenocarcinoma treated with afatinib. Paronychia at third and fourth singers, as well as nails hyperpigmentation.

At third month, up to a 50% of patients portray it, and at 6 months up to 100% of patients have some degree of xerosis. Skin dryness is usually accompanied by pruritus, which is generalized and present day and night, and it is exacerbated by heat exposition [21]. Elder patients that have received previous therapy with cytotoxic agents and have or have had atopy, usually portray more xerosis [13].

Digital fissures are usually painful, and may impair handy skills [21]. Incidence rate is about 18% in general, and severe forms are about a 3%. Usually they affect finger tips, but they may be seen between fingers, and are related to xerosis [24].

### Paronychia

Its characteristic features are painful, edematous and frequently purulent inflammation at the cuticle that can be seen in hands and feet nails, being more common at first fingers. Traumatism is considered an exacerbating factor [15]. It is present in a 12%-58% of cases [24].

**Table 3:** Dermatologic adverse effects and adverse severe effects by drug group incidence.

| **Overall dermatologic adverse effects Incidence:** | |
|---|---|
| a) Monoclonal antibodies<br>1) Cetuximab<br>2) Panitumumab | a) 80% - 100%<br>1) 88 - 90%<br>2) 100% |
| b) Tyrosine kinase inhibitors | b) 43%-54% |
| **Severe dermatologic adverse effects (Grades 3 & 4)** | |
| a) Monoclonal antibodies: 10%-17% | 10%-17% |
| b) Tyrosine kinase inhibitors | 5%-9% |

**Table 4:** Oral medications recommended for dermatitis acneiform.

| Drugs | Dose |
|---|---|
| Minocycline | 100mg/day |
| Doxycycline | 100mg/day |
| Lymecycline | 300mg/day |

It usually appears after six months. It may affect several nails at once, and can be accompanied by onycholysis and lingual pustules (Figure 3). Pain and discomfort frequently require a dose adjustment of oncological treatment [2,21, 23].

### Hair alterations

Hair manifestations are observed in a 4%-23% of patients, usually appearing after 2-3 months after beginning treatment with EGFR inhibitors. Changes include trichomegaly, facial hair growth, and dry, brittle and fragile hair, as well as no scarring alopecia [21].

### Other

Telangiectasia has been observed, usually on the face, behind pinnae, at thorax and extremities, as well as post-inflammatory hyperpigmentation at the areas where acneiform dermatitis and eczema developed, which gets worse with UV radiation [9,29]. Palmo-plantar erythrodysesthaesia has been reported as specially related to tyrosine kinase inhibition [30].

## Histopathology

At initial stages, inflammatory infiltrate was observed with CD68+ macrophages, CD1+ intraepidermal Lagerhans cells recruitment, and T CD8+ lymphocytes, which usually are not seen in healthy skin. Augmented CD4+ and CD8+ lymphocytes, neutrophil elastase + and mast cells [31].

Similar changes were found at Busam *et al* trial, where patients were treated with cetuximab therapy, and serial biopsies taken. They began with normal skin and, in subsequent biopsies the first changes seen were T lymphocytes infiltrates, surrounding follicular infundibulum; after a week of treatment, surface perifollicular hyperkeratosis, suppurative folliculitis and focal intraepidermal acantholysis with neutrophils infiltrates involving the terminal portion of the sudoriparous duct. At immunohistochemistry, it was observed that after 8 days of treatment there was 3 to 4 times increment of p27 Kip1 at dermal keratinocytes [26].

## Treatment

Side effects importance for treatment resides in the impact of lesions on the patients, since they are cosmetically unpleasant and painful, which jeopardizes both dosing changes and possible

treatment continuation. That is the reason for orienting patients about possible adverse effects before the beginning of treatment and starting prophylactic measures to avoid them. Treatment is based in the type of lesions, as well as their severity and extension [13]. Fortunately, dermatologic lesions treatment does not influence patient's survival [21].

### General measures

Treatment begins with skin care general measures and an adequate solar protection. Patients must be oriented to avoid cleaning products that may promote skin dryness. Emollients use may be used in order to avoid xerosis and fissures, but emollients must not be used on the face and trunk, since these can worsen acneiform dermatitis [32].

### Acneiform dermatitis

Treatment is based on oral antimicrobials. Low potency steroids (1% hydrocortisone. Level of evidence 2A) may help diminishing pruritus, although potent steroids may aggravate the situation [21]. Topical retinoids and isotretinoin are commonly used, whereas their efficacy has not been proved, as it happens with other topic drugs (metronidazole, clindamycin, benzoyl peroxide, salicylic acid) [13,21].

Segaert *et al,* proposed as the basis of treatment drugs as metronidazole topical treatment that can be used at 2% cream, applied twice a day. Oral drugs are reserved (Table 4) for clinical cases with a poor response to topical treatment or according to the extent of injuries [32].

Based on frequency, prophylactic management is recommended unless it is contraindicated. Recommended treatment is topical hydrocortisone at 1%, emollients, sunscreen, and doxycycline 100 mg / 12 hours for 6 weeks. Usually doxycycline is preferred over minocycline because of its greater safety, especially in patients with renal failure. Minocycline has shown same efficacy and it is preferred in patients with greater exposition to UV radiation [15].

### Xerosis, pruritus and dental fissures

It has been used calamine lotion or menthol 1% for the management of pruritus but this can aggravate xerosis. Other systemic agents such as antihistamines or γ-Aminobutyric Acid (GABA) agonists, gabapentin, pregabalin and doxipentinmay help to control itching [21].

Digital fissures treatment may be carried on with urea emollients at 20%. The risk of developing fissures at feet fingers and heel can be reduced by using socks [21]. Low and medium potency steroids can be used with or without salicylic acid at 10%, as well as propylene glycol at 50% concentration in occluding aqueous solutions (30 minutes daily), cyanoacrylate or hydrocolloids [32].

### Paronychia

Prophylactic measures include daily application of topical corticosteroids of medium power in nail folds and baths with antiseptics or diluted chlorine [21]. Paronychia caused by EGFR inhibitors is not infectious, but is very susceptible to become infectious, so it is recommended using at a daily basis creams or soaps with povidone-iodine. Pressure must be diminished by using loose shoes and sox [32].

For established paronychia treatment, it is recommended the use of high potency topical steroids. Systemic antimicrobial must be kept for positive cultures [21].

### Hair alterations

Treatment has not been shown to prevent alopecia; recommended actions are support. For non-scarring alopecia, topical minoxidil can be used; for scarring alopecia, there is not any treatment. According to expert opinion topical hydrocortisone can be used at 2% as preventive management [15].

### Other manifestations

For the treatment of palmar-plantar erythrodysesthesia the use of emollients containing agents, such as urea at 10%, salicylic acid at 3% or 12% lactic acid is recommended; patient must be informed about the importance of avoiding trauma or pressure by using gloves, special shoes and socks, and not wearing tight jewelry. Steroids such as clobetasol at 0.05% or betamethasone every 12 hours for erythema areas [30].

## Conclusions

Adverse effects secondary to EGFR inhibition appear more often on the skin, and affect most of the patients treated with these drugs. This is very important considering patient's quality of life, as well as the risk that these effects might have on oncological treatment continuation. Pathophysiological mechanisms have not explained totally this phenomenon, and it does not matter if there are trials showing a relationship between their appearance and antitumor activity, results are still little conclusive. To date there are not well established clinical guidelines, and that is the reason for requiring -in a near future- the development of controlled trials in order to know therapeutic utility of side effects.

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