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Review

Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors

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ABSTRACT

Inhibitors of epidermal growth factor receptor (EGFR) are commonly used as therapeutic agents in oncology. In contrast to currently used oncological treatments, these inhibitors almost always cause skin- and skin adnex toxicity. About 85% of treated patients develop to a more or lesser extent an acneiform eruption. Xerosis cutis and painful nail disorders occur in, respectively, 35% and 10–15% of all treated patients. Also hair and mucosal changes have been reported, although to a lesser extent. These skin- and skin adnex toxicities are reversible after withdrawal of treatment, but are seldom a reason to stop or interrupt therapy.

This review outlines the classification, the pathogenesis and therapy of these skin, hair, nail and mucosal changes due to EGFR inhibition. Informing the patient and management of these side-effects is very important to reduce discomfort and as such to increase compliance to therapy.

1. Introduction

Epidermal growth factor receptor (EGFR) is overexpressed in many solid tumours.[1] This overexpression is correlated to a progressed stage of cancer and as such to a worsening of the prognosis.[1] Also, EGFR is present in the skin,[2] mainly in the keratinocytes, the follicular epithelium,[3] the sweat- and sebaceous glands and in the endothelium present in the capillaries of the dermis.[4,5] The EGFR signalling cascade is involved in the biology of the keratinocytes in the epidermis and the homeostasis of the hair follicles. Inhibitors of EGFR interfere with this signalling cascade in the epidermis and the adnexal epithelia. Therefore, it is logic that the main toxicity of these inhibitors concentrates on the skin and the skin adnexal structures. These skin- and skin adnexal toxicities arise when inhibiting antibodies to EGFR (cetuximab) as well as tyrosine kinase inhibitors in the EGFR cascade (gefitinib and erlotinib) are administered. Since these therapeutic agents are now commonly used, it is important to acquire insight in the pathophysiological mechanisms of these skin, hair, nail and mucosal toxicities, their clinical presentation and the (therapeutical) management.

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2. Skin toxicities

2.1. *Acneiform eruption*

2.1.1. *Pathophysiological mechanism of the acneiform eruption*

The EGFR signalling cascade plays an important role in the normal differentiation of the keratinocytes present in the epidermis. Activation of EGFR leads to proliferation, migration, keratinisation and survival of the keratinocytes, which are important processes during wound healing and during maintenance of the epidermal barrier.[6] Inhibition of EGFR leads to disruption of the balance between proliferation and differentiation, leading to a thinning of the epidermal thickness.[7–10] EGFR is expressed in the keratinocytes of the hair follicle and the sebaceous glands and therefore inhibition of EGFR leads to disorganisation of the follicles in the seborrhoeic areas of the skin, where mainly sebaceous glands are localised.[5] The presence of a foreign protein (such as cetuximab) bound to the EGFR can also directly lead to an immune reaction and as such to the inflammatory reaction leading to folliculitis. Also, the direct effect of the EGFR inhibitors on the secretion of chemokines contributing to leucocyte chemotaxis and infiltration in the follicles can contribute to the process eventually leading to folliculits.[11] Repeatedly, micro-organisms as a cause of folliculitis have been excluded. Histological examination of the process of folliculitis shows first an influx of T-lymphocytes around the orifice of the follicle,[7,12,13] followed by a widening of this follicular orifice and follicular plugging (micro-comedo). Eventually this will lead to follicular rupture and influx of neutrophilic lymphocytes, leading to destruction of the follicular tube and to superficial folliculitis. In the terminal part of the sweat gland, a neutrophilic infiltrate and acantholysis is present.

2.1.2. *Clinical presentation and management of the acneiform eruption*

Administration of EGFR inhibitors leads after several days in 85% of treated patients to an asymptomatic or itchy erythematous papulopustular eruption in the seborrhoeic areas of the skin.[12,14–16] The eruption mainly involves the T-zone in the face (nasolabial, the forehead and the chin), the neck, and retro-auricular areas. Frequently the shoulders, and the upper part of the back and the chest are involved (Fig. 1A–C). Rarely, the eruption is present on the lower back, the abdomen, the buttocks, the arms, the legs, the scalp and the pubic area.

There are different classifications for the degree of skin toxicity. The classification as proposed by The National Cancer Institute Common Toxicity Criteria, version 3.0 is currently used (Table 1). Skin toxicity grades 1 and 2 most frequently occur (50% and 14%, respectively), followed by grade 3 in 10–18% of patients treated. Rarely a grade 4 reaction occurs. There is no relation between the degree of acneiform rash and a dermatological history of an oily skin, acne, rosacea or skin type. Some clinical studies report a dose-dependent effect of inhibitors of EGFR on the rash, while others contradict this dose-relation.[17,18]

The acneiform rash may have the clinical appearance of acne, although this monomorphic clinical presentation distinguishes itself from real acne by the itchy nature of it, and by the absence of white- and blackhead comedones. Differential diagnostic discrepancy between the acneiform rash and a pustular drug rash (such as that induced by for instance systemic corticosteroid therapy, vitamin B therapy and antiepileptic drugs) can be tricky. Sometimes a diffuse erythema and telangiectasias can be present, which makes the differential diagnosis with rosacea difficult. In some cases, when there are superficial pustules and dried yellow crusts present, the eruption looks like seborrhoeic dermatitis. Occasionally, the

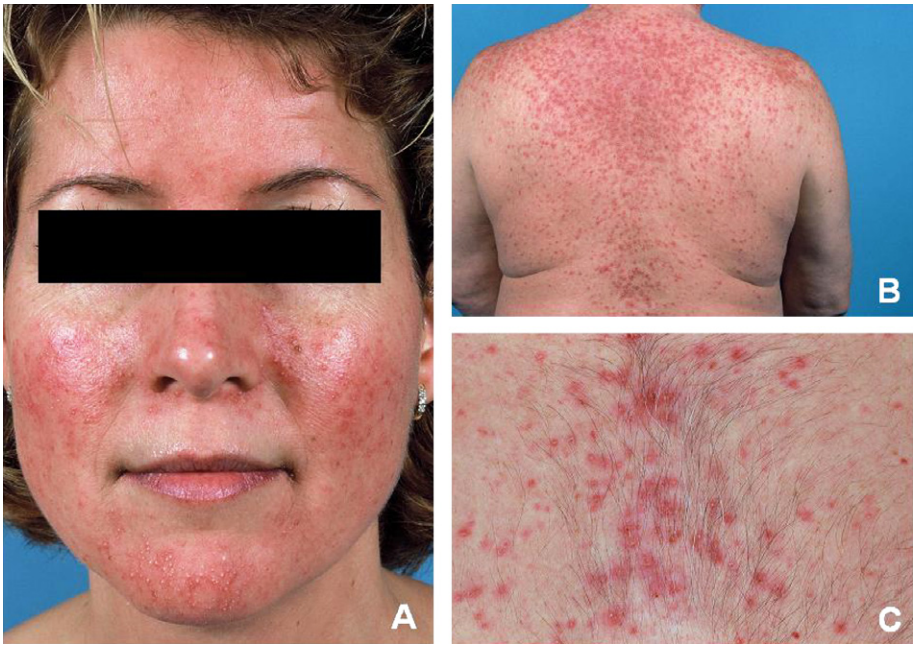

Fig. 1 – Clinical manifestation of an acneiform eruption: *panel A*: pustular eruption localised in the T-zone of the face; *panel B*: extensive pustular eruption localised on the body; *panel C*: details of a follicular pustules, notice the absence of comedones.

Table 1 – Clinical presentation and management of skin and nail disorders

		Clinical presentation	Therapy
Acneiform eruption	Grade 1	• Follicular localised pustules • Asymptomatic	*Local therapy* Metronidazol cream 1% applied twice daily
	Grade 2	• Follicular localised pustules • <50% of the body • Itchy	*Local therapy* Metronidazol cream 1% applied twice daily *Systemic therapy* Minocycline or doxycycline 100 mg once daily *In case of itch or pain* If itchy: antihistamines per os (hydroxyzine or cetirizine) If painful: paracetamol, ibuprofen *In case of infection* Flucloxacillin (500 mg three times daily during 7 days)
	Grade 3	• Follicular localised pustules • >50% of the body • Itchy	*Local therapy* wet wraps (NaCl 0.9% solution), 2–4 times daily during 10 min Metronidazol cream 1% *Systemic therapy* Minocycline or doxycycline 100 mg twice daily Interruption of EGFR inhibitor until skin toxicity is reduced to grade 2 *In case of itch or pain* If itchy: antihistamines per os (hydroxyzine or cetirizine) If painful: paracetamol, ibuprofen *In case of infection* Flucloxacillin (500 mg three times daily during 7 days)
	Grade 4	Exfoliative or ulcerative erythroderma	Stop EGFR inhibitor referral to a burn-wound unit
Xerosis cutis		Itchy, dry skin	Avoidance of excessive exposure to water and soap *Emollients* 5–10% Urea in cetomacrogolcream 20% Soft white paraffin in cetomacrogolcream 20% Soft white paraffin in vanishing cream Antihistamines per os (hydroxyzine or cetirizine) Avoidance of excessive exposure to water and soap
		Fissures	*Emollients* 50% Propylene glycol in cetomacrogolcream 50% Soft white paraffin in paraffin Avoidance of excessive exposure to water and soap
		Pulpitis	*Emollients* 5–10% Urea in cetomacrogolcream Intermittently corticosteroid cream (fluticasone or betamethasone)
		Bacterial surinfection	Flucloxacillin (500 mg three times daily during 7 days)
		Viral surinfection	Valaciclovir (500 mg twice daily during 5 days)
Paronychia			*Local therapy* Preventive measures (wide shoes and antiseptic baths) Highly potent local corticosteroids (clobetasol cream) *Systemic therapy* Minocycline or doxycycline 100 mg once daily *In case of infection* Flucloxacillin (500 mg three times daily during 7 days)

Adapted from Prof. Dr. S. Segaert, Refs. 19,20.

presence of erythema and oedema suggesting facial erysipelas has been reported. In rare cases, the pustules can congregate in pustular lakes which dry into hard yellow adherent crusts. When the papulopustular eruption clears up, it can lead to a post-inflammatory hyperpigmentation and telangiectasias.

It should always be kept in mind that the cutaneous side-effects of inhibitors of EGFR are temporary and diminish in intensity with continued exposure. The rash resolves fully after discontinuation of treatment, and is rarely dose- or treatment-limiting.[16,19,20]

Grade 1 acneiform eruptions not necessarily require treatment (Fig. 1A). If desired it can be treated with local therapy such as metronidazol cream (Table 1). Other anti-acne therapies such as retinoid cream and antibacterial gels and lotions (such as erythromycin gel, clindamycin lotion and benzoyl peroxide gel) may lead to irritation and subsequently dehydration of the skin. This is an additional unwanted side-effect since usage of EGFR inhibitors leads to xerosis cutis. Usage of local corticosteroids should be prevented since they can induce steroid-induced acne, atrophy of the skin, striae and telangiectasias. Although whenever an acneiform eruption with an extensive inflammatory component arises on the scalp, local corticosteroids can be used intermittently (such as hydrocortisone butyrate emulsion).

Grade 2 reactions can be treated with local therapy in combination with oral tetracyclines (Table 1) during 6 weeks to 3 months. Oral anti-acne therapies such as oral isotretinoin should be avoided, although some case reports show a good result. Retinoids can lead to skin- and liver toxicities and to paronychia-like nail disorders, such as reported for EGFR inhibitors. Also, possible interactions between EGFR and the retinoic acid mechanism have been described.[21,22] Antihistamines can be administered in case of complaints of itchy skin.

In case of a grade 3 reaction, EGFR inhibitory therapy should be temporarily discontinued until the acute inflammatory phase has resolved. High dosage of oral tetracyclines in combination with local therapy and wet wraps can accelerate healing.

In case of a grade 4 reactions, which have rarely been reported, the patient should be referred to a burn-wound unit.

2.2. *Xerosis cutis*

Several weeks after start of EGFR inhibitory treatment in about 35% of patients, a dry itchy skin on the arms and legs arises.[14,16] When this condition aggravates, an asteatotic eczema, eventually complicated with a secondary impetiginisation by *Staphylococcus aureus* or *Herpes simplex* infection, can occur. Xerosis cutis and subsequently eczema are more often correlated with an older age, and with an atopic constitution.

If the dry skin is manifested at the hands or feet, it can lead to painful finger and toe-tips (pulpitis sicca) (Fig. 2) and to fissures at the dorsal sides of the interphalangeal joints.

Patient's education with preventive measurements prior to beginning therapy is mandatory. Central in the advice is avoidance of soaps, limiting shower time, the usage of lukewarm water and the frequent use of emollients (Table 1). When present, xerosis cutis should be treated with standard emollients such as 5–10% urea in cetomacrogolcream. Ointments can lead to occlusion of the follicles and as such to folliculitis. Eczema should be treated intermittently with a moderate to potent corticosteroid during several weeks. In case of a wet eczema, a bacterial or viral secondary infection should be excluded or, in case of presence, should be treated with systemic therapy.

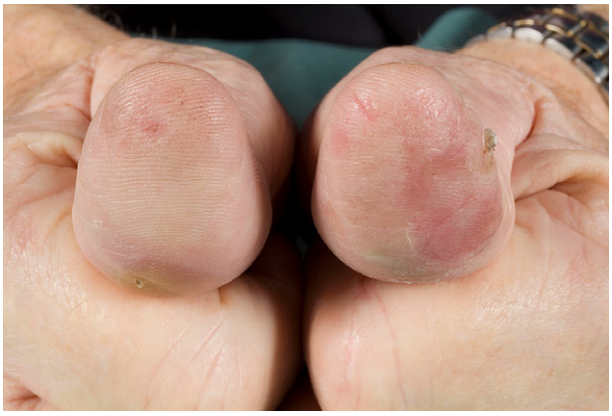

Fig. 2 – *Pulpitis sicca*: at the fingertips there is erythema and desquamation present.

Pulpitis can be treated with emollients (Table 1) frequently applied, possibly in combination with moderate corticosteroid. Since there are no follicles present on the palms of the hand and the soles of the feet, ointments such as liquid paraffin with equal proportions of white soft paraffin can be applied.

The fissures can be treated with propylene glycol in cetomacrogolcream frequently applied.

2.3. *Hyperpigmentation and telangiectasias*

Little is known of the prevalence and the pathophysiological mechanism of these skin reactions. In one study, hyperpigmentation is present in about 10% of patients treated with EGFR inhibitors.[23]

Telangiectasias can develop as a consequence of direct inhibition of EGFR signalling in the endothelial cells in the capillaries in the dermis. Thinning of the epidermis can contribute to the visualisation of these distended capillaries.

Both adverse skin reactions however can also arise secondary to an inflammatory process or as a consequence of excessive sun exposure.

Adequate prevention and management of inflammatory skin conditions such as acneiform eruption and eczema and avoidance of excessive sun exposure can prevent the occurrence of these adverse reactions.

Eventually both skin conditions can fade in time. Cosmetic treatment by laser therapy can be taken into consideration.

3. Hair disorders

3.1. *Pathophysiological mechanism of hair disorders*

EGFR signalling is involved in the normal hair cycle.[6,24,25] A normal hair cycle consists of three phases: the 'growth' phase (the anagen phase), the phase with controlled regression of the hair follicle (the catagen phase) and the 'rest' phase (the telogen phase). EGFR is expressed in the keratinocytes in

the outer sheet of the hair follicle and functions as an on–off switch at the beginning and the end of the anagen phase, and as such plays an important role in the initiation of hair growth.[24] Inhibiting EGFR signalling leads to inhibition of the progression of the anagen to the telogen phase, and results in the formation of a disorganised hair follicle. Disorganisation of the follicle leads to inflammation and as such to follicular necrosis and alopecia.[26]

Disruption of the normal hair cycle can also result in retardation of hair growth and the formation of brittle hair. Contrarily to the expectation, an increased facial hair growth has been reported. This discrepancy can be explained by the fact that the program of hair growth is dependent on the localisation of the body. As such different effects of EGFR inhibition can be expected on different localisations on the body. A possible interaction of EGFR with the androgen mechanism may play a role during the development of vellus hair on the upper lip and in the face of female patients. This theory is further supported by the occurrence of a frontal alopecia, mimicking androgenetic alopecia, in female patients.

3.2. *Clinical presentation and management of hair disorders*

Hair disorders occur only after 2 to 3 months after the start of EGFR inhibitory treatment. Beard hairs and scalp hairs grow more slowly and become brittle, finer and more curly.[14] No adequate therapy is present. Head cooling's, as used for hair disorders caused by chemotherapy, have never been tried. Increased facial hair growth and prominent eyebrows can be epilated or waxed.

Another frequently reported hair disorder is trichomegaly (the occurrence of long, curly eyelashes).[27,28] No adequate therapy, except cutting of the eyelashes, is present.

4. Nail disorders

4.1. *Pathophysiological mechanism of nail disorders*

Paronychia is a superficial inflammation of the epithelium of the lateral nail wall. Most frequently it is caused by an infection, a skin disease, a systemic disease, by pressure or by medication. A similar clinical presentation is seen with chemotherapy treatment such as methotrexate, retinoids[29] and HIV protease inhibitors. Recently EGFR inhibitors have been added to the list of medications causing paronychia. The pathogenesis of EGFR induced paronychia remains speculative. A possible mechanism, as suggested for retinoids, is an increased penetration of nail fragments in the periungual tissue as a consequence of epidermal thinning by inhibitors of EGFR.[7,12,23,29,30] Histological examination shows a reactive granulation formation.

4.2. *Clinical presentation and management of hair disorders*

In 10–15% of treated patients after 4–8 weeks, a painful, erythematous inflammation at the lateral wall of the nail occurs, usually at digit 1 of hands or feet. This can progress into a lateral paronychia-like reaction with granulation tissue formation, which is very painful and presents as ingrown nails (Fig. 3A and B). Secondary impetiginisation, painful fissures and pyogenic granulomas can occur. These nail disorders are highly resistant to therapy. Preventive measures are mandatory and they involve wearing of wide shoes, adequate nail manicure and pedicure and hygienic advice to prevent secondary impetiginisation. Local antiseptics and antibiotic creams can prevent this impetiginisation. When it does occur, oral antibiotics should be advised (Table 1), although these antibiotics will not have an effect on the paronychia as such. Several reports have shown an effect of long-term administration of minocycline or doxycycline in combination with local corticosteroids. Extraction of the nail or coagulation of the granulation tissue can be taken into consideration in cases of very painful and therapy resistant nail disorders.

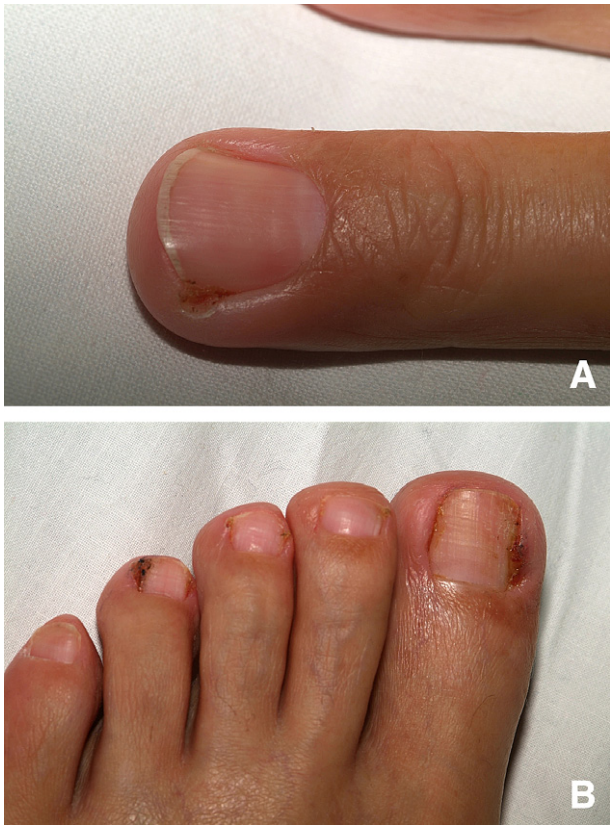

Fig. 3 – *Paronychia*: panel A: an ulcerative area at the lateral wall of the nail of digit II; panel B: an ulcerative erythematous area with exsudative granulation tissue in the edematous nail wall of digits I–II–III and IV.

Nail growth is frequently retarded and nails can become brittle, these nail disorders do not require therapy. Application of nail polish to harden the nails can be done to prevent nail fragmentation.

5. Mucosal disorders

Until now there have been few reports concerning mucosal disorders such as oral and nasal aphthae, and dry anal or

genital mucosa.[7,17] The pathogenesis is unknown and except for symptomatic treatment such as oral gels, nasal and vaginal creams, there are no therapeutic options.

6. Conclusion

Specific adverse skin reactions occur in a large percentage of patients treated with inhibitors of EGFR. Adequate information and simple therapies can increase patient's compliance to therapy, and as such increase the success of these new therapeutic agents.

An acneifrom eruption, which frequently occurs, reacts well to local and oral therapy, such as metronidazol cream and tetracyclines, respectively, and xerosis cutis and eczema are relatively easy to prevent and are treatable with emollients and moderately potent corticosteroids. Extensive hyperpigmentation and telangiectasias can be prevented by avoidance of excessive sun exposure.

Hair disorders usually lead to cosmetic disturbance, but information before start of treatment usually leads to acceptance of these side-effects by patients.

Most of the side-effects are well tolerated and are easily treatable, except for nail disorders, which can be very painful and resistant to therapy.

Conflict of interest statement

None declared.

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