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PRACTICAL APPROACH/CME ARTICLE

EGFR Inhibitors and Cutaneous Complications: A Practical Approach to Management

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ABSTRACT

Epidermal growth factor receptor inhibitors (EGFRIs) are increasingly being used for malignancies of epithelial origin. Though these therapies are better tolerated than conventional chemotherapy, they have unique side-effect profiles that are related to their mechanism of action. Given the function of the epidermal growth factor receptor in the skin, nails, and hair, dermatologic side effects are commonly seen with the use of EGFRIs. This review includes a practical approach to recognizing and treating the most common dermatologic side effects seen with EGFRIs, including papulopustular eruptions, nail changes, xerosis and pruritus, hair changes, mucositis, and radiation dermatitis exacerbations.

Keywords: Cutaneous side effects; Epidermal growth factor receptor; Mucositis; Papulopustular eruptions; Paronychia; Pruritus; Trichomegaly; Xerosis

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INTRODUCTION

Epithelial cancers are characterized by mutations in growth factors and growth factor receptors, giving them the potential for uninhibited cell proliferation, migration, and the promotion of angiogenesis [1]. Epidermal growth factor inhibitors (EGRFIs) are able to inhibit this signaling and treat many different cancers of epithelial origin.

There are two general classes of EGFRIs: anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies (mAb) and small-molecule EGFR tyrosine kinase inhibitors (TKIs) [1, 2]. Anti-EGFR monoclonal antibodies include cetuximab, panitumumab, and necitumumab, which bind the extracellular EGFR inactive receptor, and inhibit the binding of other activating growth factors [1]. The small-molecule EGFR tyrosine kinase inhibitors include gefitinib and erlotinib, and inhibit EGFR signaling by binding the intracellular catalytic domain of the receptor, inhibiting phosphorylation and therefore blocking downstream receptor signaling [1]. Additional small-molecule TKI EGFR inhbitors exist which inhibit multiple receptors, including dual

kinase inhibitors of EGFR and human epidermal growth factor 2 (HER2); these agents include lapatinib, afatinib, and neratinib as well as the multikinase inhibitor vandetanib. EGFR inhibitors are currently approved to treat non-small-cell lung cancer, squamous-cell carcinoma of the head and neck, colorectal cancer, pancreatic cancer, and breast cancer [1, 3].

EGFRIs have proven to have fewer side effects overall and to be less toxic than conventional chemotherapy. Due to their targeted inhibition of growth factor receptors, the side effect profiles of EGFRIs are more specific and are not hematologic, in contrast to conventional chemotherapy [4]. Given the ubiquitous presence of EGFRs in basal cells of the epidermis, hair shaft, sebaceous glands, and the outer root sheath, the side-effect profiles include frequent dermatologic abnormalities [5, 6]. These skin toxicities risk the interruption, reduction, or cessation of these important cancer therapies, in addition to negatively affecting quality of life [7, 8]; therefore, it is important to understand how to recognize and effectively manage these side effects.

An EGFRI-induced rash correlates with better overall survival and progression-free survival in individuals treated with anti-EGFR mAbs and TKIs [9, 10]. Therefore, the presence of these eruptions has been shown to predict tumor response to therapy [10]. EGFRIs are ideally continued despite some skin toxicity, as the cutaneous side effects may be an indication of an effective response.

This study contains a thorough review of the current literature available regarding EGRFI cutaneous toxicities and their management. This article does not contain any new studies with human or animal subjects performed by any of the authors.

PATHOPHYSIOLOGY OF EGFR INHIBITOR SKIN TOXICITIES

EGFRs are required for normal function of the skin and adnexal structures, so it is not surprising that anti-EGFRs induce frequent dermatologic abnormalities [6, 11]. EGFR receptors are localized to basal cells of the epidermis, hair shaft, sebaceous glands, and the hair follicle outer root sheath [5]. EGFR signaling has been shown to be critical to the normal development of skin and hair in human and mouse models [4, 12, 13]. Though the pathophysiology of these eruptions has not been fully elucidated, abnormalities are thought to be due to alterations in EGFR signaling altering cell growth and the promotion of inflammation. As EGFR signaling is critical to normal skin development and regeneration, the inhibition of the EGFR has shown to compromise the integrity of the skin, subsequently causing a weakened stratum corneum, and ultimately leading to xerosis and fissuring of the skin [14].

Various signaling molecules have been suggested to play a role in the pathogenesis of cutaneous anti-EGFR actions, including interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and interleukin-8 (IL-8) [11]. The inhibition of EGFR interrupts cell growth, leading to apoptosis, chemokine signaling, and inflammation [6, 15]. Ultimately, the inhibition of EGFRs causes increased inflammation in the skin and adnexal tissues and thus the various inflammatory side effects we see with EGFR inhibitor use, including papulolopustular eruptions and paronychia.

Infections do not appear to be the drivers of the initiation of papulopustular eruptions or paronychia, but the disruption of the skin barrier can lead to secondary infections as a result [16]. Notably, 38% of individuals with these EGFRI-induced eruptions developed secondary bacterial or viral infections in a retrospective study, most frequently with *Staphylococcus aureus* in 22.6% [17]. These infections may play a role in the late presentations of these eruptions. Studies of erlotinib have shown impairment of the innate immune system activating signaling [15]. Patients receiving EGFRIs have also demonstrated higher densities of demodex in skin affected by papulopustular reactions [18], which is possibly due to impaired host defense mechanisms, and may contribute to the rosacea-like pattern of the typical EGFRI-induced papulopustular eruption.

Given the predisposition for papulopustular eruptions to the face and V-shaped area of the

chest, is it also hypothesized that ultraviolet (UV) radiation is thought to likely play a role in predisposition to EGFR inhibitor side effects. EGFR has found to be upregulated in keratinocytes with UV exposure [6], and EGFR inhibitors have also been shown to increase the risk and severity of radiation-induced dermatitis [19, 20]. Notably, however, there has not been any proven benefit of sunscreen to prevent EGFRI-induced rash [21]. Further study is obviously needed to better fully elucidate the pathomechanisms behind EGFR inhibitor side effects.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

Cutaneous complications are the most frequent adverse side effects of EGFR inhibitors, occurring in up to 90% of patients treated with cetuximab therapy, with grade 3–4 adverse events occurring in 11–18% of treated individuals [22, 23]. The most common dermatologic adverse events caused by EGFR inhibitors include characteristic papulopustular eruptions, dry and itchy skin, hair changes, mucositis, nail changes, and photosensitivity [11]. Diagnoses are primarily clinical, with typical timing and clinical presentations as described below.

The papulopustular eruptions, also referred to as acneiform or acne-like eruptions, are the earliest and most common side effects, typically occurring in the first 2–4 weeks of therapy and affecting 20–80% of patients treated with anti-EGFR therapy [22–25]. The rates of both cutaneous adverse events and papulopustular eruptions due to anti-EGRF therapy tend to be higher with the mAbs than the TKIs, typically occurring in >70% of the individuals treated with mAbs [22]. Additionally, mAbs tend to cause more severe grade 3–4 eruptions (9–10%) than TKIs do (2–4%) [22]. These eruptions are characterized by tender, pruritic, erythematous papules and pustules, favoring areas with high densities of sebaceous glands, including the face, scalp, chest, and upper back (Fig. 1a, b) [25]. Though these eruptions have frequently been described as acneiform or acne-like, in contrast to acne, there are no comedones, itching is a dominant symptom, they improve with topical steroids, and they do not improve with topical retinoids [26].

Nail changes are frequently observed as side effects of EGFRIs, with a reported incidence of 17.2% in a recent meta-analysis [27]. These nail changes include paronychia and pyogenic granuloma-like lesions, with erythema and tenderness of the skin adjacent to the nail (Fig. 2) [28]. Other changes include brittle, thin nails that easily break, as well as onycholysis, with detachment of the nail from the nail bed, and discolored nails due to involvement of the nail matrix (Fig. 3) [11, 28]. These changes can cause significant discomfort for patients as well as interfering with normal activities of daily living due to nail dysfunction.

Xerosis (dry skin) and pruritus are frequent and often significantly bothersome side effects of EGFRIs. These two findings are often clinically interrelated. The xerosis often resembles atopic dermatitis and can have an eczema craquelé ("dried riverbed") appearance (Fig. 4). Xerosis can rarely be complicated by both bacterial infections and reactivation of the herpes simplex virus [29]. Xerosis can also lead to fissuring of the skin with significant associated pain. In a recent study assessing the impact of EGFRI-related dermatologic events on quality of life, xerosis, and pruritus were found to be most significant adverse events reported [30]. All-grade pruritus occurred in 17–58% of EGFRI-treated patients, with the highest frequency occurring in those treated with panitumumab [31, 32].

Hair changes are also frequently seen with prolonged EGFRI therapy (>1–2 months). Patients can develop mild hair loss and changes in hair texture, as well as patchy hair loss in both scarring and non-scarring patterns [33, 34]. Typically, non-scarring hair loss improves after cessation of therapy [25]. Eyelashes can develop trichomegaly, in which they become lengthened, in conjunction with becoming more coarse, curly, and thickened, occasionally causing blepharitis (Fig. 5) [35, 36]. Eyebrow poliosis has also been reported, with loss of eyelash pigment and subsequent white hair development [37, 38]. Hirsutism is also

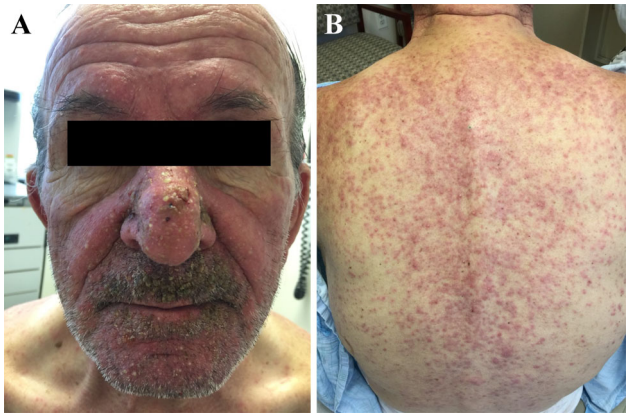

Fig. 1 **a** A typical papulopustular eruption caused by EGFRI therapy, with erythematous papules and pustules focused in the centrofacial region. On closer examination, comedones are notably absent. **b** Erythematous papules and pustules involving the upper back

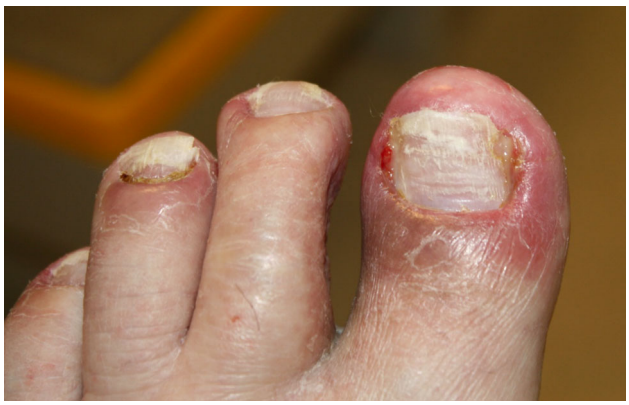

Fig. 2 An example of EGFRI-induced paronychia with periungual erythema, swelling, purulent drainage, and excess granulation tissue

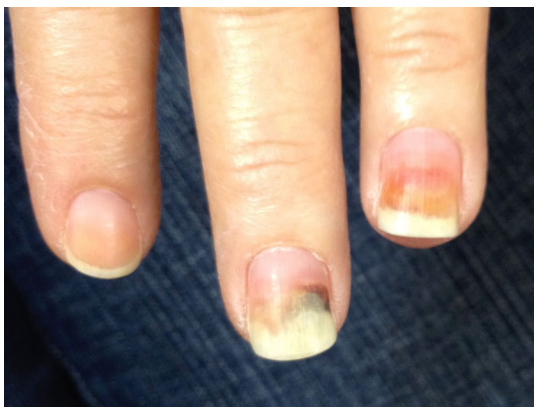

Fig. 3 EGFRI-induced distal onycholysis and subungual hemorrhage

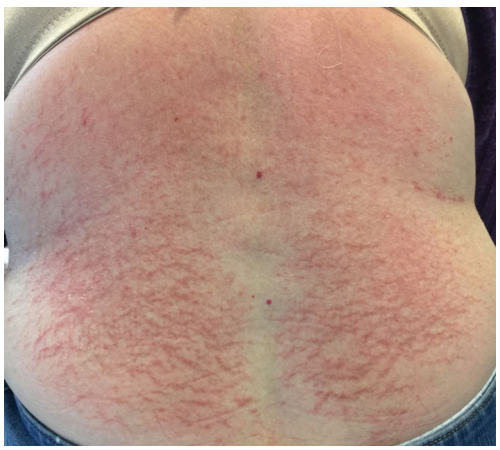

Fig. 4 Significant xerosis with asteatotic eczematous eruption subsequent to EGFRI therapy

Fig. 5 Trichomegaly due to EGFRI therapy

seen, with the excessive hair growth typically occurring on the face [25].

Oral, ocular, and genital mucositis can also be seen with EGFR therapy. Patients may experience multiple oral ulcers or apthae as a consequence of EGFRI therapy (Fig. 6) [16]. It is always important to culture these ulcers for the herpes simplex virus and varicella zoster virus to rule out an infectious etiology. Dry mouth and geographic tongue can also occur [16]. Eye involvement with keratitis and conjunctivitis can occur, and the genital mucosa can be involved, leading to vulvovaginitis and balanitis [11].

Photosensitive eruptions have been observed as a side effect of EGFRI therapy. Interestingly,

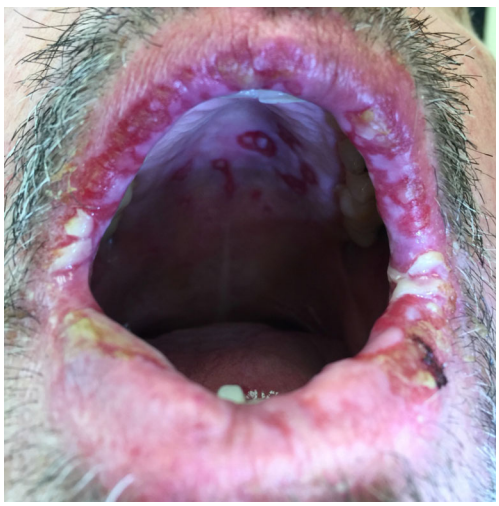

Fig. 6 Significant oral mucositis due to EGFRI therapy with numerous erosions

Table 1 NCI CTCAE v.4

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

ADL activities of daily living, *BSA* body surface area, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

the typical papulopustular eruption tends to favor sun-exposed areas, such as the face and V of the chest [39]. Additionally, radiation dermatitis can be exacerbated or enhanced by concurrent EGFRI therapy and radiation therapy [19, 20, 40].

Fortunately, with EGFRI therapy, severe drug eruptions such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are exceedingly rare, but they have been reported [41, 42]. In a large meta-analysis of 8998 patients treated with EGFRIs, there were no cases of mortality due to rash.

MANAGEMENT OF EGFR-INDUCED CUTANEOUS TOXICITIES

Our management strategies are designed to prevent dose reduction or cessation of cancer therapies. However, for high-grade (grade 4) reactions and any severe life-threatening reactions, dose reduction or cessation is often necessary. When approaching therapies for these reactions, it is first helpful to understand the

Table 2 Dermatologic toxicity management: papulopustular eruptions

Grade	Clinical	Treatment	Level of evidence
Preventative		Topical emollients, topical steroids (class VII), sunscreen (SPF > 30), systemic antibiotics (tetracyclines)	IB [46]
Grade 1	<10% BSA involved	Topical antibiotic; topical steroid (class VI, VII)	III [54, 55]
Grade 2	10–30% BSA involved; psychosocial impact; limiting instrumental ADL	Oral antibiotic (tetracycline)	IB [48]
Grade 3	>30% BSA involved; limiting self-care ADL; associated with local superinfection	Oral antibiotic	IB [46]
		Oral isotretinoin	III [56, 57, 68, 69]
		High-potency class I–II topical steroids	IV [25]
		Systemic corticosteroids	IV [70, 71]
		Aluminum acetate astringent soaks for crusting	IV
		Consider dose reduction or holding chemotherapy	III [54, 55, 72]
Grade 4	Involvement of any % BSA; associated with extensive superinfection; life-threatening consequences	Consider dose reduction or holding chemotherapy	III [54, 55]

Levels of evidence are as follows: *IA* evidence from meta-analysis of randomized controlled trials, *IB* evidence from at least one randomized controlled trial, *IIA* evidence from at least one controlled study without randomization, *IIB* evidence from at least one other type of quasi-experimental study, *III* evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case–control studies, and *IV* evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

ADL activities of daily living, *BSA* body surface area, *SPF* sun protection factor

grading of these reactions. The most common grading system for EGFRI-related adverse events is the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) (Table 1). General recommendations for all individuals undergoing treatment with EGFRIs should include gentle and dry skin care recommendations, as well as adequate sun protection. A cross-sectional survey study concluded that individuals undergoing cancer therapy may benefit from fewer complications by avoiding prolonged hot showers, which should be a part of general dry skin care prevention recommendations [43]. Patients should be advised to use a daily moisturizer, with creams favoured over lotions, as well as sunblock with a sun protection factor (SPF) of at least 30. Any skin care products should be unscented and detergents that are used to wash clothes should be scent-free and dye-free [11, 44].

Papulopustular Eruptions

When approaching therapy for papulopustular eruptions (see Table 2), one should consider a prophylactic treatment approach, especially with the use of mAb EGFRIs (cetuximab and panitumumab), which have a high reported incidence of papulopustular eruptions.

Prophylaxis with doxycycline 100–200 mg daily or minocycline 100 mg daily for ≥8 weeks should be considered if there are no significant contraindications [44]. Prophylactic treatment with tetracycline, minocycline, or doxycycline has been shown to decrease the frequency of grade 2–3 papulopustular eruptions and to improve quality-of-life scores in multiple randomized control trials [26, 45–50], though there are two trials that show a lack of significant benefit [51]. Additionally, a recent RCT has shown a reduction in grade 3 eruptions with both prophylactic therapy and grade-specific reactive therapy, without no significant difference between them [48]. While prophylactic therapy with tetracycline-class antibiotics has generally been shown to reduce the severity of papulopustular skin reactions, it does not necessarily reduce the number of patients affected overall [45, 51] and is not associated with an improved survival benefit [52]. Importantly, tetracycline therapy does not appear to negatively affect tumor response to EGFR therapy [48, 50, 52], and in fact may have beneficial antitumor effects [48, 53].

Treatment of symptomatic papulopustular eruptions depends on the patient's presentation and symptomatology. If the EGFRI needs to be continued, we recommend a treatment algorithm based on the grade of the papulopustular eruption. For grade 1–2 eruptions, treatment should include a topical antibiotic (ex. clindamycin 1% lotion) and a topical steroid of class VI or VII (ex. desonide 0.05% cream, hydrocortisone 2.5% cream; solution or lotion formulations are useful for the scalp) [25, 54, 55]. Itching associated with these eruptions can be managed with topical steroids and antihistamines (ex. cetirizine, fexofenadine, hydroxyzine) [32].

For a grade 2 rash, or a grade 1 rash that has not improved with topical therapy alone, we recommend starting a class VI topical steroid (ex. desonide 0.05% cream) along with an oral tetracycline antibiotic (ex. doxycycline 100 mg twice daily or minocycline 100 mg twice daily). If the eruption contains pustules, we strongly recommend that a swab be taken of one or more of the pustules and sent for bacterial culture. Occasionally, there will be bacterial growth that shows resistance to the tetracycline class of antibiotics. In such cases, a first-generation oral cephalosporin (ex. cephalexin) or trimethoprim/sulfamethoxazole can be used to treat to treat the papulopustular eruption if the bacterial growth shows sensitivity to these classes of antibiotics. It should also be noted that it is important to rule out concurrent viral infections, such as herpes simplex virus, if clinically indicated. Treatment with tetracycline antibiotics improved papulopustular eruptions, including most ≥grade 2 eruptions, in multiple nonrandomized control trials, usually after 1–-4 weeks of therapy [22]. Generally, we recommend treatment for 4 weeks until assessing the response to therapy. For grade 3–4 eruptions, or those that are not responding to first-line therapy, a dermatology consultation should be considered. For grade 3 eruptions, high-potency class I–II topical steroids (ex. clobetasol 0.05% cream, fluocinonide 0.05% cream) can be used for short periods of time, in combination with oral antibiotics, with good efficacy. Alternate treatment options include isotretinoin, and dose reduction should be considered with grade 3–4 eruptions refractory to oral antibiotic therapy [25, 56, 57]. If initiating isotretinoin therapy, all tetracycline antibiotics should be discontinued given the increased risk of pseudotumor cerebri with both medications [58].

In the case that excessive or confluent crusting occurs on top of the papulopustular eruption, as can be seen on the scalp or face, a clinical pearl is to use compresses or wet dressings using aluminum acetate astringent solution. This solution can be found over-the-counter as a powder packet and is ready to use when mixed with water. The patient is instructed to soak a clean, soft cloth in the solution and apply it onto the affected areas for 15 min. The topical steroid cream or solution can then be applied directly onto the skin after the compress is removed, with repeated applications twice a day until improvement is noted.

Nail Changes

Treatment for nail changes associated with EGFRIs (see Table 3) should start with preventative measures. It is important to encourage

Table 3 Dermatologic toxicity management: paronychia

Grade	Clinical	Treatment	Level of evidence
Preventative		Keep hands and feet dry, gentle skin care, avoid nail trauma and injury, nail lacquers	IV [28, 70, 73, 74]
		Prophylactic emollients, sunscreen, hydrocortisone 1%, doxycycline	IIB [46]
Grade 1	Mild; asymptomatic or mild symptoms	Warm water or vinegar soaks, potent topical corticosteroid and antimicrobials	III [73, 75]
		Topical adapalene 0.1%	III [76]
Grade 2	Moderate; limiting appropriate instrumental ADL	Add systemic antimicrobials; tetracyclines or culture driven	III [59, 70, 77, 78]
Grade 3	Severe; disabling, limiting ADL	Systemic antimicrobials as previously noted	III [59, 70, 77, 78]
		Add silver nitrate for excess granulation tissue	III [73, 79]
		Consider holding dose of EGFRI	III [73]

Levels of evidence are as follows: *IA* evidence from meta-analysis of randomized controlled trials, *IB* evidence from at least one randomized controlled trial, *IIA* evidence from at least one controlled study without randomization, *IIB* evidence from at least one other type of quasi-experimental study, *III* evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case–control studies, and *IV* evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

ADL activities of daily living

gentle skin care for the hands and avoidance of trauma and manipulation of the nails and periungual area. This includes the avoidance of biting, manicuring, cutting cuticles, or otherwise traumatizing the area [28]. For brittle nails, the use of nail lacquers can prevent dehydration of the nail and give added strength; both hydroxypropyl chitosan and polyureaurethane 16% are non-drug lacquers that are FDA-approved for this use [28]. Additionally, over-the-counter biotin supplements may be beneficial for added nail strength. Paronychia is initially not infectious, but persistent inflammation may be a sign of infection with organisms such as *Staphylococcus aureus* and *Candida albicans* [59]. Therefore, it is always important to culture the affected area if infection is suspected, particularly in the presence of pustular exudate. Initial treatment of paronychia should include antiseptic soaks (ex. dilute vinegar soaks) and antibacterial solutions as well as a potent topical steroid cream or ointment daily if there is not clear infection. We also recommend the use of oral antibiotics for more severe involvement [28, 59]. For excess granulation tissue, or pyogenic granuloma-like lesions, various topical treatment modalities can be used, including silver nitrate, topical steroids, liquid nitrogen, and electrodessication [28].

Xerosis

Xerosis (dryness of the skin) is a common side effect caused by EGFRI therapy, occurring in up to 35% of individuals [60]. This side effect can be very bothersome, given the resultant itching, fissuring with associated pain, or even bacterial or rarely herpes simplex virus super infection [61]. Xerosis and pruritus are graded separately for severity in the NCI-CTCAE v.4.0, though these cutaneous adverse events often occur simultaneously. Xerosis with any associated pruritus is ≥grade 2. For xerosis, we recommend good dry skin care measures, including avoiding

Table 4 Dermatologic toxicity management: other side effects

Side effect	Clinical	Treatment	Level of evidence
Xerosis	Dryness Fissuring	Use bland emollients and keratolytics (urea, ammonium lactate, salicylic acid, or lactic acid), avoid hot showers, avoid abrasive soaps	III [61, 62, 80], IIB [46]
Pruritus	Prevention	Emollients, hydrocortisone 1%, sunscreen, doxycycline	IIB [26, 46]
	Grade 1	Topical steroids of class IV–V strength	III [25]
	Grade 2	Oral antihistamines	III [25]
	Grade 3	Oral steroids	III [25]
		Oral gabapentin	III [25]
		Consider dose reduction/cessation if refractory	III [25, 32, 62, 81]
Hypertrichosis	Trichomegaly	Eyelash trimming	III [36, 62]
	Hirsutism	Eflornithine	IV [70]
	Alopecia	Laser hair reduction	IV [70]
		Minoxidil 5%	IV [70]
Mucositis	Aphthae	Topical steroids	IV [25]
	Erosions	Antiseptic washes	IV [25]
	Geographic tongue	Anesthetic washes	IV [46]
Photosensitivity	Telangiectasias	Strict sun precautions (hats, SPF > 30)	III [39]
	Hyperpigmentation	Laser (PDL)	IV [11]
	Photosensitive eruption	Bleaching agents	IV [11]

Levels of evidence are as follows: *IA* evidence from meta-analysis of randomized controlled trials, *IB* evidence from at least one randomized controlled trial, *IIA* evidence from at least one controlled study without randomization, *IIB* evidence from at least one other type of quasi-experimental study, *III* evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case–control studies, and *IV* evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

ADL activities of daily living, *SPF* sun protection factor, *PDL* pulsed dye laser

hot prolonged showers and using a moisturizing cream twice daily (Table 4) [62]. Additionally, if there is significant scale, creams with urea, ammonium lactate, salicylic acid, or lactic acid can be used [32].

Pruritus

For pruritus (Table 4) that is associated with either xerosis or other EGFRI eruptions, the most important first step is treating the underlying dermatosis. Next, management can be tailored to the grade of severity of involvement. For grade 1 pruritus, the use of topical steroids of class IV–V in creams or ointments twice daily (ex. triamcinolone 0.1% cream) or a topical antipruritic (pramoxine 1%, menthol 0.5%) is indicated. For grade 2 pruritus, we recommend adding oral antihistamines (cetirizine, hydroxyzine) to help with itching. For grade 3 pruritus,

consider adding oral steroids (0.5 mg/kg daily) or gabapentin/pregabalin, and finally, if these treatments do not work after 1–2 weeks, we recommend considering dose reduction or stopping therapy [32]. Additionally, aprepitant shows promise for the treatment of EGFRI pruritus through neurokinin-1 receptor inhibition [63, 64]. Consulting a dermatologist for severe or persistent pruritus is also recommended, as phototherapy with narrowband ultraviolet B (NBUVB) light can also be used as a tool to treat pruritus.

Hair Changes

For trichomegaly (Table 4) of the eyelashes with EGFRI use, trimming of the eyelashes may be necessary to prevent keratitis and blepharitis. It also helps to brush hair frequently if it is newly kinky or curly [11]. Additionally, trimming of the eyelashes is often required for comfort during EGFRI therapy [36]. For facial hypertrichosis or unwanted hair, eflornithine topically daily can be used. Patients can also consider laser hair removal or electrolysis for permanent hair removal. For non-scarring alopecia, a trial of topical minoxidil 5% daily for women and twice daily for men can be used. Patients frequently prefer the foam formulation over the solution due to ease of use, and it is necessary to wait at least 6 months to see any results with use. This is based on expert consensus and the success of non-scarring alopecia treatment in the general population [25]. For scarring alopecia, we recommend early patient referral to a dermatologist, as initiation of a class I–II topical steroid solution, foam, or lotion daily for the scalp may be considered [25].

Mucositis

Oral mucositis (Table 4) is an uncommon side effect of EGFRI therapy, occurring with much less frequency than in conventional chemotherapy. Given the relatively low frequency of occurrence, therapy for EGFRI-induced mucositis has not been well studied. Recommendations for treatment are extrapolated from treatment studies of mucositis induced by alternate chemotherapy agents. For oral mucositis, typical therapies include topical steroid gels or pastes, antiseptic washes, or anesthetics [25]. For persistent eye irritation, ophthalmology should be consulted to prevent significant ocular side effects [65].

Photosensitivity

A role of sun exposure in worsening EGFRI-induced eruptions is likely given the predisposition for the papulopustular eruption to affect the face and V-shaped area of the chest (Table 4). We regularly encourage our patients to use a sunblock with SPF >30 as well as to practice sun avoidance. Interestingly, however, no clear benefit of sunscreen was observed in a placebo-controlled trial [21]. Further studies are therefore needed to fully understand the relationship between sun exposure and EGFRI-associated eruptions.

Radiation Dermatitis

Notably, radiation-induced dermatitis (RID) induced by cetuximab behaves differently than radiation dermatitis from radiation therapy alone. We recommend good dry skin care and avoidance of unnecessary trauma. Corticosteroid creams are not recommended as preventative therapy, but are recommended for treatment as a response to RID. Hydrocolloid dressings and other advanced dressings can be used as preventative measures for RID. Topical or systemic antibiotics should be used if superinfection is suspected. For grade IV involvement, the radiation or cetuximab dose should be held or reduced, and a wound care specialist should be consulted [66]. For radiation-induced dermatitis, a meta-analysis has shown a reduction in the risk of radiation dermatitis by 87% with Wobe-Mugos E (composed of the proteolytic enzymes papain 100 mg, trypsin 40 mg, and chymotrypsin 40 mg) compared to no medication, but the use of this medication specifically for EGFRI-exacerbated RID has not been studied [67].

For any severe suspected drug eruption, a dermatologist should be consulted.

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