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Review Article

Cutaneous Adverse Events of Targeted Anticancer Therapy: A Review of Common Clinical Manifestations and Management

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Abstract.

Targeted anticancer therapies, unlike the traditional cytotoxic chemotherapies which lead to systemic toxicities, frequently cause cutaneous adverse events that are symptomatic and manifest in cosmetically sensitive areas. The most common dermatologic toxicities related to epidermal growth factor receptor (EGFR) inhibitors are papulopustular eruption, xerosis, pruritus and paronychia. Vascular endothelial growth factor receptor (VEGFR) inhibitors usually cause hand-foot skin reaction. Reports of dermatologic side effects such as abnormalities of hair growth and mucosal changes also increased.

These events may contribute to poor adherence, dose interruption and discontinuation of the regimens. In addition, psychosocial discomfort causing reduction in the quality of life does occur. However, the presence and severity of cutaneous adverse events has shown to have positive correlation with treatment response.

The management of these side effects can be categorized into prophylaxis and reactive treatment. Systemic antibiotics and topical corticosteroid could possibly prevent or alleviate symptoms caused by EGFR inhibitors. The prevention of sun exposure is recommended to all patients on targeted therapy, and emollients and lubricants can be used to relieve and improve the hand-foot skin reaction.

Keywords **:** targeted therapy, dermatologic toxicities, epidermal growth factor receptor, tyrosine kinase inhibitor

綜合評論

標靶藥物引發的皮膚反應：常見的臨床表現及其處理

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中文摘要

比起化學治療造成的全身性副作用，抗癌標靶藥物更易引起皮膚反應，而這些副作用常發生在影響外觀甚鉅的部位。常見的皮膚反應有上皮細胞生長因子受體抑制劑引發的丘疹樣膿泡型紅疹，乾燥搔癢，以及甲溝炎；血管上皮細胞生長因子受體抑制劑還會引起手足症候群，除此之外也會發現黏膜及毛髮的變化。這些副作用除了會減低病人使用標靶治療的意願，也可能使臨床醫師須調整標靶藥物的劑量，甚至導致治療中斷。對於病人生活品質及心理社會學上都造成不等程度的影響。然而值得注意的是，這些皮膚反應的發生，可能代表標靶藥物在此類病患是有作用的。

皮膚反應的處理可分成預防性及反應性的處理。使用系統性抗生素及外用類固醇藥膏可能某種程度預防副作用的發生或減緩其症狀。所有接受標靶藥物治療的病人都建議做好防曬；使用滋潤保養品則可有效減輕手足症候群的症狀。

關鍵字: 標靶治療、皮膚反應、上皮細胞生長因子受體、酪胺酸激酶抑制劑

INTRODUCTION

Over the last decade, cancer therapy has increasingly shifted toward targeting specific pathways involved in the pathogenesis of malignancy. The agents developed in this effort have improved the ability to target cancer cells and the safety profile compared to conventional chemotherapies. Despite the benefits, treatment with these agents can result in skin adverse events that cause discomfort, restrict activities of daily living, and may lead to poor treatment adherence, dose interruption, and discontinuation of these therapeutic regimens [1,2]. Furthermore, these skin adverse events can increase overall associated treatment costs [3]. Dermatological toxicities are manifested mainly in response to treatment with inhibitors of signal transduction proteins including epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR), KIT (or stem cell factor receptor), RAF (in the Ras-Raf-MEK-ERK pathway), mammalian target of rapamycin (mTOR, in the PI3K/AKT/mTOR pathway), and cytotoxic T-lymphocyte antigen (CTLA) proteins (Table 1).

Although they are not life -threatening, the cutaneous adverse effects resulting from treatment with signal transduction protein inhibitors are symptomatic and can negatively impact patients' quality of life (QoL) [1]. This article aims to provide an overview of the skin toxicities related to cancer target therapy and of the current implications for the management of patients.

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CUTANEOUS COMPLICATIONS WITH EGFR INHIBITORS

Papulopustular Rash

Papulopustular rash, also described as acneiform eruption, is the earliest and most common cutaneous adverse event, which has been reported to occur at rates of 50 to 100% in published clinical trials of EGFR inhibitors [4]. The pathogenesis is different from acne with marked alterations in growth and differentiation of the epidermis leading to altered corneocyte terminal differentiation. Transcriptional effects induced by EGFR inhibitors, including suppressed

Table 1. Summary of targeted therapies and common side effects*

Molecular target(s)	Agent	Class	Cutaneous side effects	Reference
EGFR	Cetuximab	mAb	Papulopustular rash Xerosis, fissures and pruritus Nail and nailfold changes: paronychia, pariungual granulation tissue Hair changes: Alopecia, hypertrichosis, trichomegaly, trichiasis In-field radiation toxicity	4-25
	Panitumumab	mAb		
	Erlotinib	TKI		
	Gefitinib	TKI		
	Afatinib	TKI		
VEGFR, PDGFR, KIT	Pazopanib	TKI	Hand-foot skin reactions Papulopustular rash Xerosis, fissures and pruritus Nail and nailfold changes: paronychia, pariungual granulation tissue Alopecia on scalp Pazopanib, Sunitinib: gray hair	9, 11, 26-32, 43
VEGFR, PDGFR, KIT, RAF	Sorafenib	TKI/STKI		
VEGFR, PDGFR, KIT, RET	Sunitinib	TKI		
VEGFR, PDGFR, KIT, RET, RAF	Regorafenib	TKI		
RAF	Vemurafenib Debrafenib	STKI	Papulopustular rash Hand-foot skin reactions Xerosis, fissures and pruritus Paronychia Keratoacanthoma, cutaneous squamous cell carcinoma Hyperkeratosis	32-39
mTOR	Everolimus Temsirolimus	STKI	Stomatitis/ aphthous ulceration Papulopustular rash	40-42
CTLA	Ipilimumab	mAb	Bumpy red rash Itching Vitiligo and gray hair	57

*Adapted from Abramson RG, et al. Am J Roentgenol 200: 475-483, 2013. [56]
CTLA= cytotoxic T-lymphocyte-associated protein, EGFR= epidermal growth factor receptor, KIT= stem-cell factor receptor, mAb= monoclonal antibody, mTOR= mammalian target of rapamycin, PDGFR= platelet-derived growth factor receptor, STKI= serine-threonine kinase inhibitior, TKI= tyrosine kinase inhibitor, VEFR= vascular endothelial growth factor, VEGFR= VEGR receptor

expression of genes associated with keratinocyte proliferation, attachment and motility, have also been found [5]. The rash usually develops within the first weeks of treatment and can occur as early as 2 days and as late as 6 weeks after EGFR inhibitor therapy is started [6]. Typical presentations are erythematous papules and pustules predominately involving seborrheic-rich areas such as the face and upper trunk (Figure 1). Lesions can be painful and itchy. Comedones, which are characteristic of acne, are not seen in papulopustular rashes [7]. The rash can also involve the lower trunk, extremities, and buttocks (Figure 2) [8].

Table 2. CTCAE grading of selected skin and subcutaneous tissue disorders

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-

Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death

CTCAE = Common Terminology Criteria for Adverse Events, version 4.0; ADL = activities of daily living; BSA = body surface area; IV = intravenous

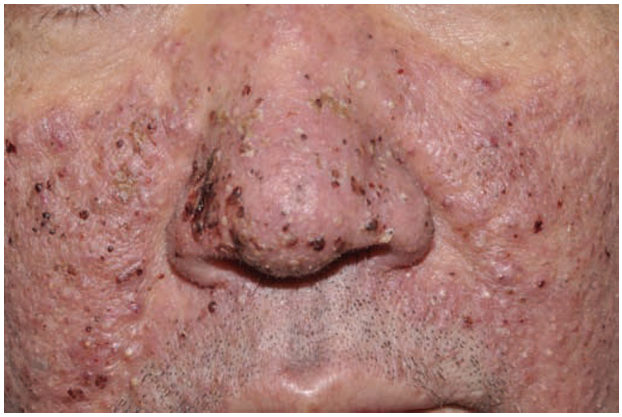

Figure 1. Typical rapulopustular rash on face in a patient taking erlotinib

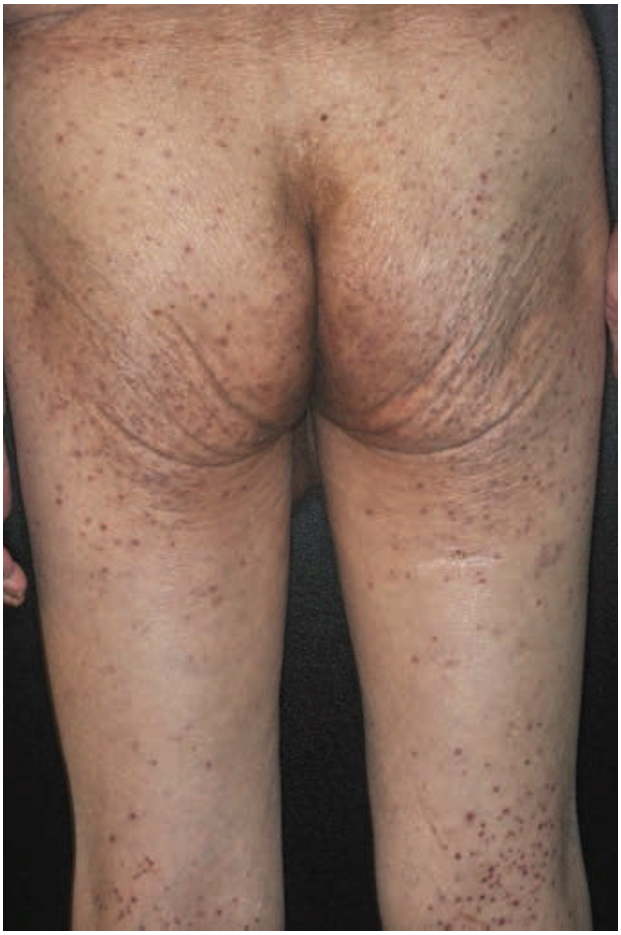

Figure 2. Papulopustular rash on buttocks and lower limbs in a patient on erlotinib

Xerosis and Pruritus

Xerosis is the second most common skin toxicity encountered with EGFR inhibitor use, occurring in over 35% of the patients treated with EGFR inhibitors in most reports [9-11]. It typically occurs following the onset of the papulopustular rash, and presents as dry, itchy, scaly patches, which may progress to painful fissuring and xerotic eczema (Figure 3). Xerosis can affect any site, not only areas where papulopustules have developed [11,12].

Nail Abnormalities

Nail abnormalities are a less common but disturbing side effect of EGFR inhibitor treatment, occurring in 24% of those taking panitumumab, 10–15% of patients on cetuximab, erlotinib and gefitinib, and fewer than 1% of patients treated with lapatinib [10,13]. These changes, with damage to the nail bed (onycholysis, subungual hemorrhage), nail plate (pigmentary changes, brittle nails), or nail fold (paronychia), usually developed after 1-2 months of treatment and sometimes not until after 6 months [12,13]. Initially presenting with erythema, edema, and tenderness of the nail folds, paronychia can affect any fingernail or toenail, which often affects routine activities of daily living. The inflammation can later progress to painful pyogenic granuloma-like lesions over lateral nail fold (Figure 4) [15,16]. Local trauma is not a necessary condition for the development of the lesions but it usually aggravates symptoms of bleeding [17,18]. In severe cases, an ingrown nail or periungual abscess can occur [15].

Hair Alterations

Hair alterations seen with EGFR inhibitor treatment are a late toxicity and usually manifest after 8 weeks [19]. About 5–30% of patients treated for 6 months or longer experience alopecia [7]. Alopecia tends to occur on the scalp and body. Scalp alopecia is typically inflammatory, with both non-scarring and scarring forms having been reported (Figure 5) [20,21]. Mild hair loss can also be seen on the arms and legs [14]. Hair overgrowth, such as hypertrichosis and tri-

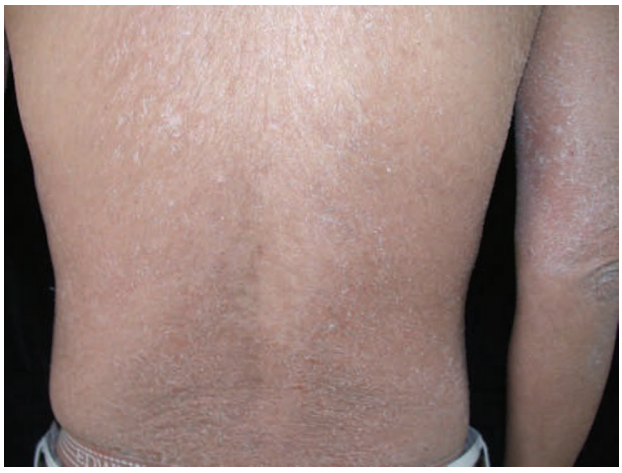

Figure 3. Xerosis accompanied with pruritus in a patient on gefitinib

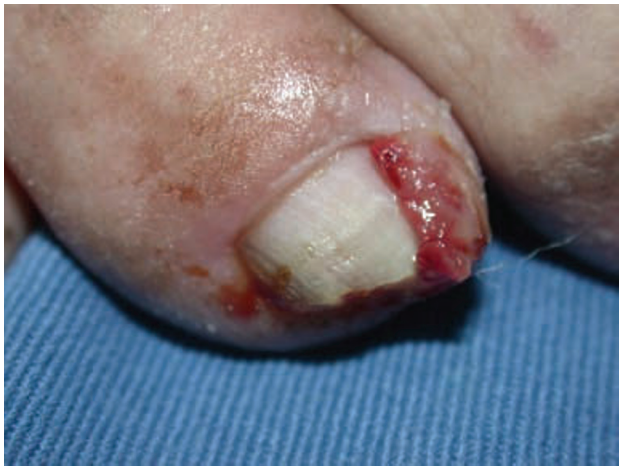

Figure 4. Paronychia with granuloma-like tissue on the toe of a patient taking gefitinib

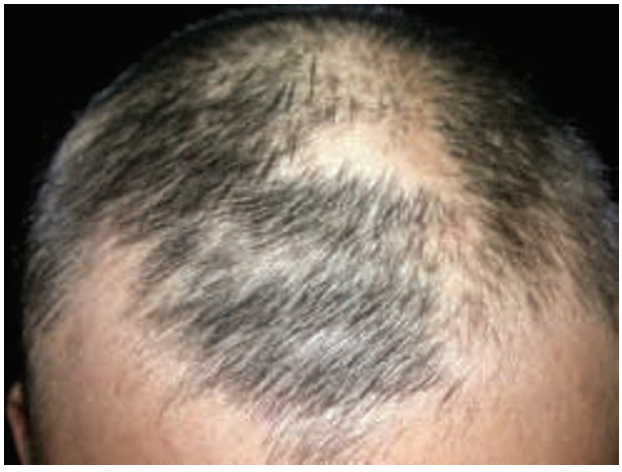

Figure 5. Non-scarring alopecia appeared on a patient taking gefitinib

chomegaly, and hair changes in the texture, growth, or curling usually develop 2-5 months after initiating EGFR inhibitors [19,22,23]. When these alterations occur in the eyelashes, they may lead to corneal irritation and ultimately ulceration [24,25].

CUTANEOUS COMPLICATIONS WITH MULTIKINASE INHIBITORS

Similarly to EGFR inhibitors, multi-targeted kinase inhibitors are also associated with a variety of different dermatologic adverse effects, including papulopustular rash, seborrheic dermatitis-like rash, pruritus, alopecia, modification of hair growth, xerosis and subungual splinter hemorrhage [26].

Palmar plantar erythrodysesthesia or hand–foot skin reactions (HFSR) are commonly associated with multikinase inhibitors targeting VEGFR. Results of recent meta-analyses have demonstrated the incidence of HFSR to be 19% with sunitinib treatment [27] and 34% with sorafenib treatment [28]. A higher frequency of skin and bone marrow toxicities has been noted in Asian countries. In Taiwan, for example, a total of 50% all-grade and 10% grade 3 HFSR has been reported [29]. HFSR often occurs within 6 weeks and usually in the first 2 weeks of starting therapy [30]. HFSR is characterized by painful blistering plaques or by a rash developing on the feet and occasionally on the fingertips (Figure 6). This is frequently most severe at pressure points such as the balls of the feet (Figure 7) and the fingertips, and therefore may impair activities of daily living [27]. The hallmark feature of HFSR is localized lesions with hyperkeratosis or blisters, whereas conventional chemotherapy agents, such as liposomal doxorubicin, fluorouracil, cytarabine, and doxetazel, usually lead to symmetrical erythema and edema in the palms and soles [9].

The most relevant histopathological indication of HFSR is keratinocyte damage, which presents as keratinocyte vacuolar degeneration and confluent keratinocyte necrosis leading to intraepidermal cleavage. Intracytoplasmic eosinophilic bodies resulting

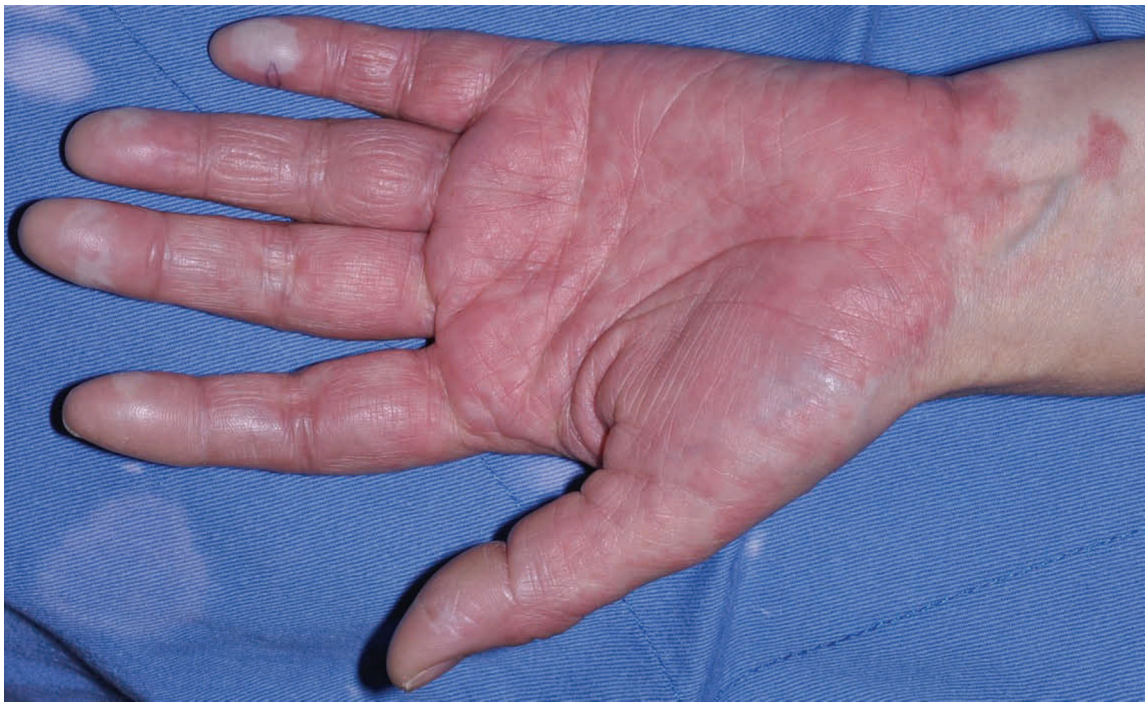

Figure 6. Hand-foot skin reaction due to sorafenib manifesting as tender blisters on fingertips

from necrotic keratinocytes are unique to this entity [9,31]. The pathophysiology of HFSR has not been fully recognized. In a recent pioneer study, Yeh et al found elevated levels of sunitinib and increased expression of FasL in the plasma of HFSR patients, and their concentrations showed strong correlation with one another. The authors demonstrated that plasma of HFSR patients caused keratinocyte death and that this cytotoxicity could be blocked specifically by an anti-FasL antibody. In addition, oral administration of sunitinib to mice increased their skin susceptibility to mechanical pressure. Their data revealed that Fas/FasL interaction mediates keratinocyte death in sunitinib-induced HFSR [32].

OTHER COMMON SKIN SIDE EFFECTS OF TARGET THERAPY

Development of both benign and malignant epithelial tumors, such as inflammation of actinic keratoses, keratoacanthomas and cutaneous squamous cell carcinomas, are observed at higher frequencies among patients receiving agents that target RAF kinase, including sorafenib (6-13.5%) and sunitinib (6.3%) [32-36]. These effects are particularly severe and more common with the selective BRAF V600E inhibitors such as vemurafenib (8-24%) and dabrafenib (6%) (Figure 8) [37-39]. In addition to skin tumors, BRAF inhibitors can induce exanthema (up to 18%), photosensitivity (12%), alopecia (8%), pruritus (7%) and hyperkeratosis (6%) [37].

Oral ulcerations, usually forming within 1-2 weeks after initiation of therapy, are a common dose-limiting toxicity associated with mTOR inhibitors [41,42]. The ulcers generally manifest as painful, discrete, ovoid, superficial ulcers with a well-defined border, a peripheral halo of erythema, and a grayish-white pseudomembrane on the inner aspect of the lips and ventral surface of the tongue and soft palate. The ulcers do not form on gingiva and the dorsal surface of the tongue, unlike viral ulcers which normally do affect keratinized mucosa [40].

Involvement of oral mucosa secondary to EGFR

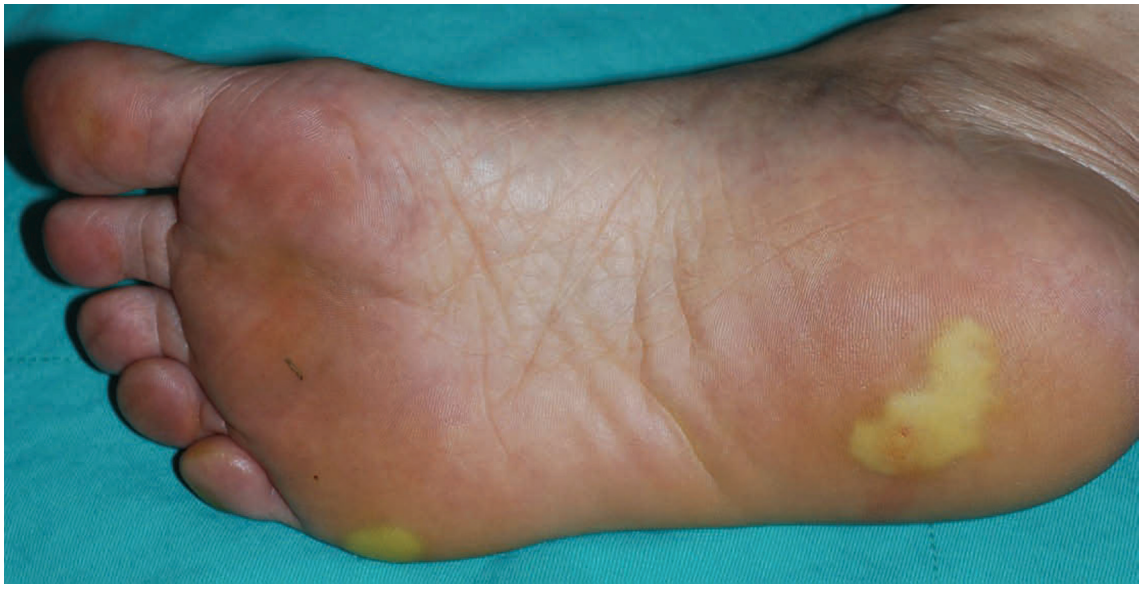

Figure 7. Hyperkeratotic plaques with bullae on soles of patient receiving sorafenib therapy

inhibitors and multikinase inhibitors has also been documented. The clinical presentation reported includes mild to moderate mucositis, stomatitis, and aphthous ulcers, which often resolved without specific intervention [11]. Nasal mucosa ulcers induced by EGFR inhibitors have been reported as well and appear to be related to xerosis and bacterial proliferation in carriers [42]. Both sorafenib and sunitinib may be associated with inflammation of oral mucosa in up to 45% of patients [26]. In a retrospective analysis, Lee et al reported that the onset of stomatitis began before the fourth week in patients treated with sunitinib (81%) and sorafenib (90%) [43].

MANAGEMENT RECOMMENDATIONS

Patient education about potential dermatologic toxicities before initiation of treatment is an essential component of patient care. On initiation of target therapy, although evidence in support of this recommendation is lacking, patients are advised to use sunscreen along with moisturizing cream and gentle cleansers [44,45]. Patients should be instructed to protect their skin, such as by avoiding constrictive footwear, reducing contact with hot water, and wearing gloves and cotton socks to prevent friction or trauma to the hands and feet [6,45]. In order to minimize periungual trauma, patients have to trim their nails regularly [19]. Areas of pre-existing skin damage or hyperkeratosis should be identified and managed before the start of treatment [46,47].

Preemptive Management

Regarding the papulopustular rash induced by cancer target therapy, whether or not to prescribe prophylactic oral antibiotics remains controversial. The administration of tetracycline antibiotics 50 or 100 mg twice per day (tetracycline, minocycline, doxycline, lymecycline) as preventive therapy has been associated with reduced severity of the papulopustular rash and folliculitis as well as improved quality of life (QoL) [48]. Skin toxicity evaluation protocol with panitumumab (STEPP) compared efficacy of reactive and prophylactic treatment with panitumumab, both consisting of a skin moisturizer, sunscreen, 1% hydrocortisone cream, and oral doxycycline. The results showed preemptive management improved QoL and led to a reduction greater than 50%

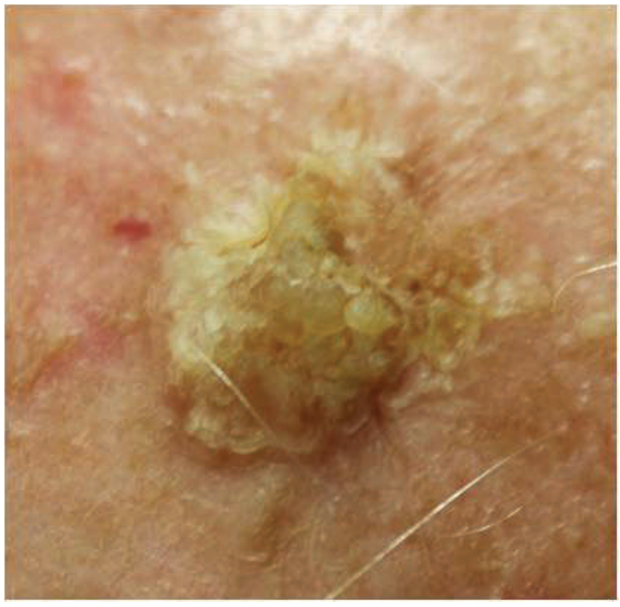

Figure 8. Cutaenous squamous cell caricinoma on right cheek of a patient on vemurafenib

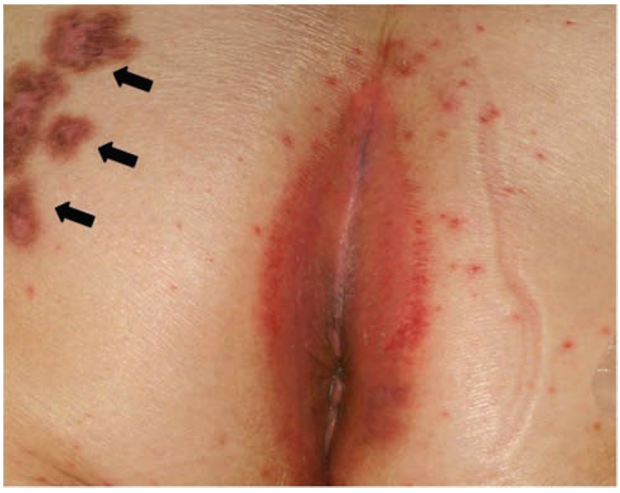

Figure 9. The patient taking gefitinib was found to have cutaneous candidiasis infection on gluteal fold. Scars of previous herpes simplex virus infection were also found (arrow)

in the rate of skin toxicity in comparison to reactive treatment [49]. However, this preemptive management did not reduce the incidence of exanthema [48].

Reactive Management

The standardized National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 grading for skin toxicities (Table 2) is helpful for both oncologists and dermatologists in making treatment decisions [50]. Reassessment of the severity of dermatologic adverse events every other week in order to adjust their management is recommended. However, the NCI-CTCAE may not completely reflect the dermatologic adverse events associated with targeted therapies. The Multinational Association of Supportive Care in Cancer's Skin Toxicity Study Group has therefore developed a modified grading scale specifically for EGFR inhibitor therapy [51].

According to the guidelines for EGFR inhibitor therapy, depending on the severity of the papulopustular rash, topical corticosteroids, antibiotics, or oral antibiotics can be used to alleviate symptoms [47,52]. Low potency topical corticosteroids with or without topical antibiotics are recommended for patients with rash of grade 1. Typical treatment for acne vulgaris may not be beneficial in relieving symptoms caused by EGFR inhibitor therapy since the pathophysiology involved is different [7]. Addition of oral antibiotics twice daily, including doxycycline 100 mg, minocycline 100 mg, or tetracycline 500 mg, should be considered if the severity is more than grade 2 [45,46,53].

Pruritus can adversely affect QoL and sleep [2,6]. Oral antihistamines are helpful for their sedative effects but the symptoms of pruritus are not always relieved. Topical corticosteroids have also been used for scalp itch, and they can be prescribed with moisturizing creams for use once to twice per day to improve xerosis [11,12]. In case of refractory eczema or scaling, a direct microscopic examination of scales prepared with potassium hydroxide to identify the presence of any fungi should be conducted. If fungal infection is detected, additional therapy with antifungal agents is recommended (Figure 9).

Topical agents for inflammatory paronychia in-

clude 4% thymol in alcohol, aluminum acetate, corticosteroid cream, and intralesional triamcinolone. Topical antibiotics or antiseptics can prevent superinfection [15]. Oral doxycycline 100 mg once or twice daily for 6 weeks may help decrease periungual inflammation [53, 54]. Medical intervention, in the form of electrocautery, silver nitrate cauterization, or nail avulsion, is usually required to remove excessive granulation tissue. Although paronychia is often sterile, when increased purulence and pain of the periungual soft tissue occurs, it should be cultured for appropriate antimicrobial selection. The most common pathogens are Staphylococcus aureus, Streptococcus, Enterococcus, Escherichia coli, Klebsiella, Pseudomonas and Candida species [55].

Treatment for inflammatory alopecia should start early with high-potency topical corticosteroid lotions or solutions as first-line therapies [53]. Options for epilation include temporary and permanent hair removal such as shaving, eflornithine, waxing, laser, or a combination of treatments [46,47,53]. Trichiasis can cause corneal ulceration and patients should thus be referred to an ophthalmologist for lash clipping or further treatment [35,46].

Management of HFSR can be started as early as the initiation of target therapy, such as by applying 10% urea cream for moisturization. When treating HFSR of grade 1, topical corticosteroids can minimize inflammation and also soften thickened hyperkeratotic plaques on the hands and feet. For patients with HFSR of grade 2 or 3, dose reduction of the target therapy is another option for reducing bothersome side effects. Non-steroidal anti-inflammatory drugs, such as gamma-aminobutyric acid agonists or narcotics, can also be prescribed for pain control [45,46].

CONCLUSIONS

Despite many published recommendations, universal guidelines for managing dermatologic adverse conditions resulting from treatment with targeted cancer therapy agents are still lacking. Further studies to establish standard evidence-based therapies are needed. Studies of regional consensus should be conducted in the future as well.

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