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CASE REPORT

Dermatologic Adverse Events Following Afatinib in a Woman with Non-Small-Cell Lung Cancer: A Case Report

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Abstract: Epidermal growth factor receptor inhibitors (EGFRI) are biological factors used in several types of cancer, including non-small-cell lung cancers (NSCLC). One of the EGFR inhibitors that has been approved for NSCLC is afatinib. Dermatologic adverse events are the most commonly reported and may impair the patient's compliance to the therapy as it causes aesthetic discomfort and significantly impact the patient's quality of life. We report a case of 31-year-old woman diagnosed with stage IV-NSCLC and treated with afatinib since nine months prior to consult who presented with acneiform rash on the face, trunk, both arms and legs; pruritic pustules and waxy scales on the scalp; xerosis and pruritus of the skin; paronychia on both toes; hair changes on the scalp, eyebrows, eyelashes, and hypertrichosis of the face. Microscopic examination with Gram smear from periungual skin showed polymorphonuclear cells (PMNs) and Gram-positive cocci bacteria. Trichoscopy examination of the hair on the scalp revealed tapering hair, pili torti, follicular hyperkeratosis, multiple hair tufts with erythema, and scaling of the skin; the eyebrow and eyelashes revealed pili torti and tapering hair. The administration of afatinib was continued and the patient was treated with moisturizer, sunscreen, and mild cleanser, topical antibiotic, and topical steroid along with oral doxycycline and oral cetirizine for four weeks. Significant clinical improvement and Dermatology Life Quality Index (DLQI) score was seen on the fourth week of observation. Dermatological adverse events present the greatest concern with EGFRIs use because it can lead to infection, pain, depression, and low self-esteem, moreover, misdiagnosis may lead to treatment discontinuation. Recognizing clinical signs, implementing preventive efforts, and appropriate management are important to improve the quality of life and patient compliance for effective therapy of underlying malignancy.

Keywords: afatinib, dermatological adverse effects, EGFR inhibitor, skin toxicity

Introduction

Epidermal growth factor receptor (EGFR) is often over-expressed or overactivated in malignancy, which makes EGFR a key therapeutic target.[1] EGFR inhibitors are a class of biological agents that act on the ErbB family of tyrosine kinases,[2] and are used in several types of cancer, including non-small cell lung cancer (NSCLC), colorectal carcinoma (CRC), pancreatic cancer, head and neck squamous cell carcinoma (HNSCC), and breast cancer.[3,4]

EGFR inhibitors are classified into monoclonal antibodies (mAbs) (eg cetuximab, panitumumab, pertuzumab) and small molecular weight tyrosine kinase inhibitors (TKIs) (eg erlotinib, gefitinib, lapatinib, osimertinib, and afatinib).[3] Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are commonly used for NSCLC with EGFR mutations, one of the possible first-line treatment options is afatinib.[1,5,6]

Previous studies have consistently shown that EGFR-TKIs are well tolerated, however, a few adverse events (AEs) are commonly seen including gastrointestinal tract, liver, lung, and skin.[7] A systemic review and meta-analysis study by Zhao et al[7] shown that 85.4% patients receiving EGFR-TKIs were reported to have at least one systemic adverse effects in all-grade and 33.2% patients have grade three or more adverse effects. The most commonly observed side effect of

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treatment with EGFR-TKIs is dermatological side effects,[1,3,8,9] such as papulopustular (acneiform) rash, xerosis, pruritus, paronychia, hair changes (alopecia, hypertrichosis), and mucositis.[1,9,10]

These adverse effects are mild in most cases, but many patients experience severe discomfort that affects their quality of life and even call reduction in dosage, discontinuation of the treatment, or pharmacotherapeutic intervention resulting in limitation or loss of its effectiveness.[7,11]

Among patients that treated with EGFR-TKIs, afatinib caused the most dermatological adverse events, followed by erlotinib, gefitinib, and osimertinib.[12] Study by Zhao et al[7] show that afatinib had the highest risk of rash, diarrhea, stomatitis, paronychia, and pruritus, but the lowest risk of anemia, constipation, dry skin, and interstitial lung disease. Several studies reported afatinib discontinuation rates between 6–8%.[13–15] A study by Gilardone et al[16] identified significantly more dose reductions in the afatinib group compared to the osimertinib group which could indicate a greater impact on quality of life in the afatinib group compared to the osimertinib group.

Therefore, attention and understanding of EGFR inhibitor-related dermatological adverse events are required to achieve an effective prevention and management,[11,17] because achieving good treatment compliance,[6] achieving maximal patient tolerability, also avoiding treatment delays and interruptions[1,18] are crucial to maintaining a good quality of life.[1,6,18] Herein, we reported one case of dermatologic adverse events and the management following afatinib in a woman with NSCLC.

Case Illustration

A 31-year-old woman was referred to our dermatology department from the department of internal medicine with a history of pruritic erythematous papules on the face, neck, chest, abdomen, both arms and legs accompanied with pruritic pustules and waxy scales on the scalp since eight months prior to the consultation. The patient was diagnosed with stage-IV NSCLC and undergoing treatment with daily administration of oral 40 mg afatinib since nine months prior to the consult. The patient began developing small pruritic erythematous papules within one month of starting oral afatinib. Lesions initially appeared on the face, neck, chest, and upper leg. Individual lesions became confluent and involved 80% of the affected areas. Complaints are accompanied by pruritic pustules and waxy scales on the scalp; dryness, pruritic skin, painful swelling of the periungual skin around bilateral toenails, which sometimes secretes a clear liquid, also excessive growth of eyelashes, eyebrows, and hair on the face. There were no complaints of blisters and skin peeling. Previous history of drug allergy is denied. The Dermatology Life Quality Index (DLQI) in this case report is 16 which indicates very large effects on patient's life.

Physical examination revealed curly, coarse, and brittle hair on the scalp; trichomegaly with thickened and curling eyelashes and eyebrows; and hypertrichosis of the face. Dermatological examination showed generalized xerosis, erythematous papules and pustules on the face (Figure 1A and B), papules with waxy scales on the scalp (Figure 1C), erythematous papules and pustules on the neck, chest, abdomen, back, arms (Figure 1D), and legs (Figure 1E). There were also painful erythematous periunguals with serous crusts on both of the first toes (Figure 1F and G).

Trichoscopy examination of the hair on the scalp revealed pili torti, follicular hyperkeratosis, multiple hair tufts with erythema, and scaling of the skin; eyebrows, and eyelashes revealed pili torti and tapering hair (Figure 2A–D).

Microscopic examination with Gram smear from the periungual skin showed polymorphonuclear cells (PMNs) and Gram-positive cocci bacteria and microscopic examination with 10% KOH solution showed no fungal element. Microscopic examination with 10% KOH solution from the scalp showed no fungal element. Woods lamp examination from the scalp showed no fluorescence.

Based on the history, physical, dermoscopic, and microscopic findings, a diagnosis of afatinib-induced skin toxicities was made.

In this case, general education is provided to patients. For acneiform rash, we gave the patient 1.2% clindamycin gel for the erythematous papules on the face and 0.25% desoximetasone cream for erythematous papules on the chest, back, and upper leg. For the scalp, the patient was given a gentle shampoo, 2% mupirocin cream for the pustules, and 0.05% desonide lotion for the scaly erythematous papules. For the xerosis and pruritus, the patient was given mild moisturizing cream for the face and 10% urea cream for the body twice daily along with broad-spectrum sunscreen. For the

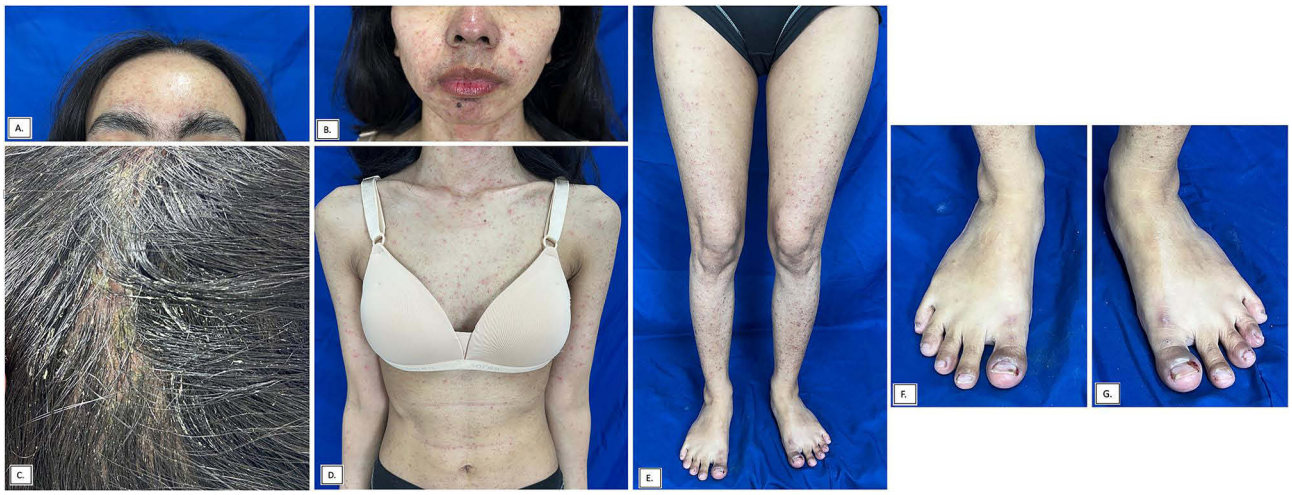

Figure 1 (**A**–**G**) Dermatological examination on admission showed erythematous papules, and pustules on the face (**A** and **B**), papules with waxy scales on the scalp (**C**), neck, chest, abdomen, both arms and both legs (**D** and **E**), and erythematous periungual with edema and serous crust on the both first toes (**F** and **G**).

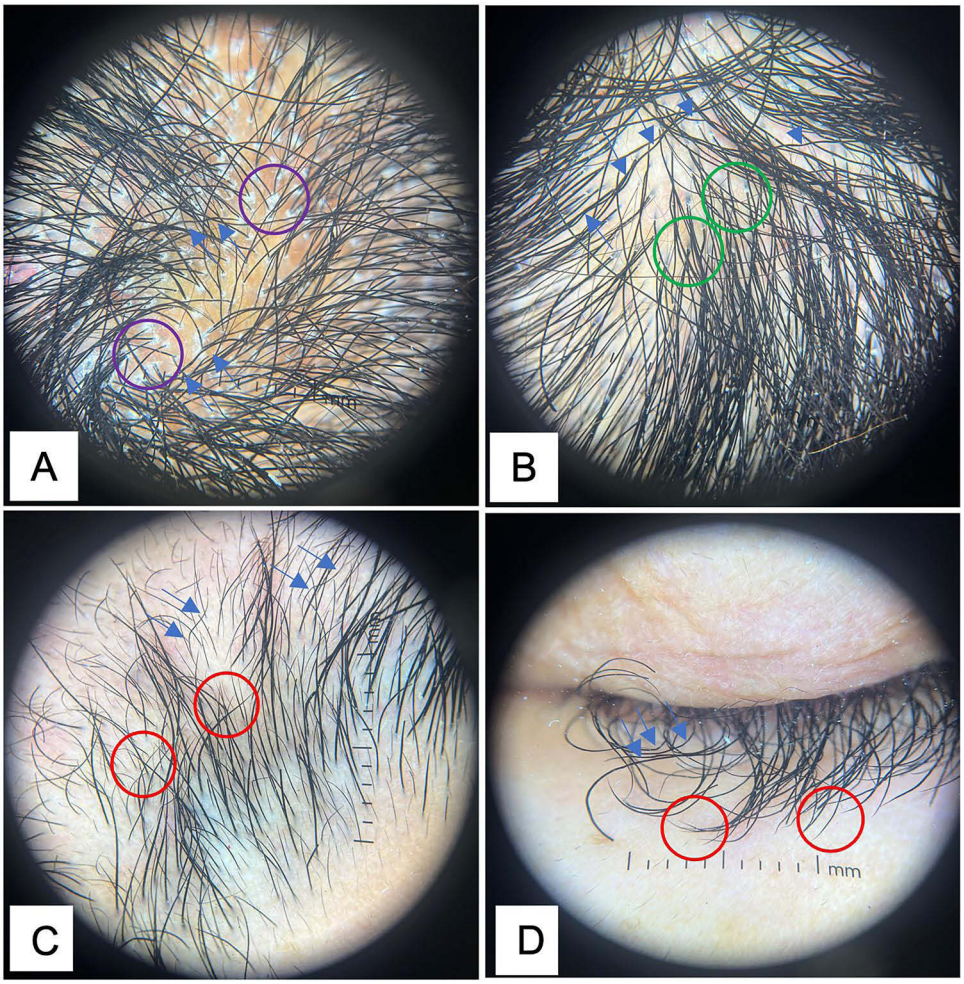

Figure 2 (**A**–**D**) Trichoscopy examination of the hair on the scalp (**A** and **B**) revealed pili torti (blue arrows), follicular hyperkeratosis (purple circles), multiple hair tufts with erythema and scaling of the skin (green circles); eyebrow, and eyelashes (**C** and **D**) revealed pili torti (blue arrows) and tapering hair (red circles).

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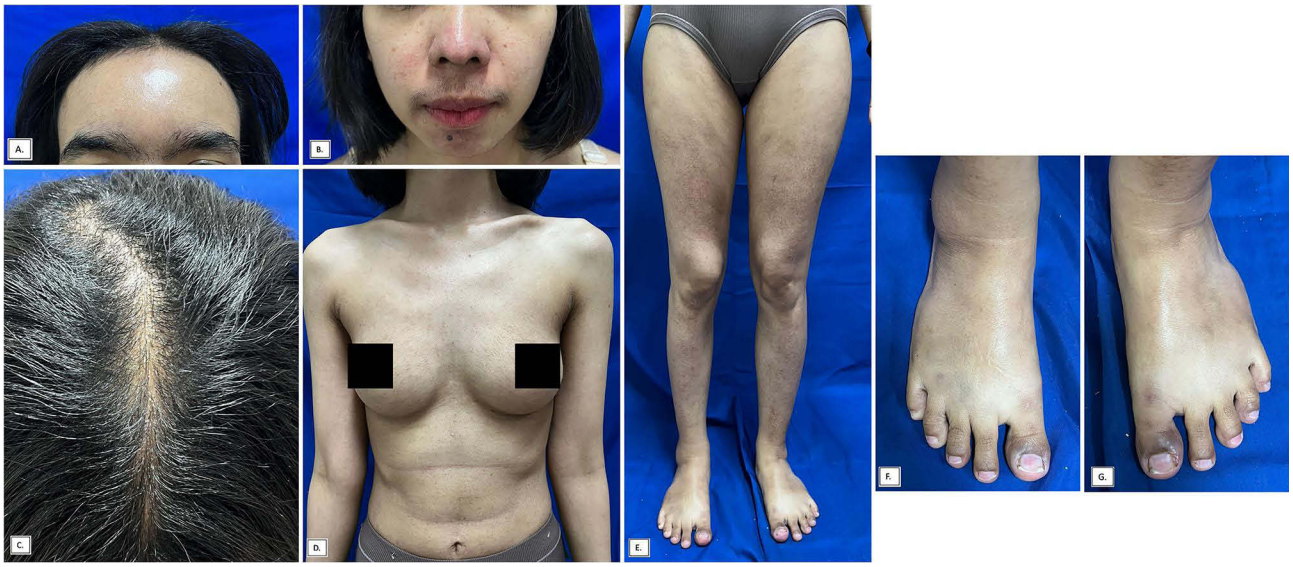

Figure 3 (**A**–**G**) Dermatological examination on week four of observation showed clinical improvement less erythematous papules on the face (**A** and **B**), less papules on the scalp (**C**), neck, chest, abdomen, both arms and both legs (**D** and **E**), and less erythematous and edematous periungual on the both first toes (**F** and **G**).

paronychia, we gave a wet dressing with normal saline and 2% mupirocin cream for the periungual skin on both toes. The patient was also given doxycycline 100 mg twice daily and cetirizine 10 mg once daily for four weeks.

A significant improvement was seen on the fourth week of observation, showing less erythematous papules, and disappearance of pustules on the face (Figure 3A and B), a reduction of pustules and greasy scales on the scalp (Figure 3C), less erythematous papules, and disappearance of pustules on the chest, back, arms (Figure 3D), and legs (Figure 3E) with a reduction of periungual redness and swelling (Figure 3F and G). The DLQI in this patient also decreased from 16 to 5 which indicates small effect on patients life.

Discussion

The dermatologic adverse events related to EGFR inhibitors usually manifested as acneiform rash, xerosis, pruritus, paronychia,[2] hair changes, and mucositis.[1] The overall incidence was acneiform rash (47–100%), xerosis (10–49%), pruritus (8–57%), paronychia (3–25%), hair abnormalities (0–13%), and mucositis (0–44%).[1] A retrospective study by Annunziata et al,[12] in 60 patients with lung cancer treated with EGFR-TKIs reported that the most common skin reactions were rash (63%), xerosis (30%), granuloma (30%), mucositis (18%), psoriasis (8%), fingertips fissures (7%), itching (5%), alopecia (5%), hand-foot syndrome (2%), and trichomegaly (2%). Another study by Napitupulu et al[6] shows that afatinib caused the most skin side effects, ranging from mild to severe, followed by gefitinib and erlotinib. The study also found that patients with stage IV NSCLC had a higher incidence of dermatological side effects, and that women were more likely than men to have mild to severe side effects. Patient in this case is a 31-year-old female diagnosed with stage-IV NSCLC with dermatological adverse effects due to afatinib.

Acneiform (papulopustular) rash is the earliest and most commonly reported adverse event.[3,12] It is generally distributed in the seborrheic areas, where EGFR is more expressed.[12] The National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[19] defines acneiform rash as a disorder characterized by an eruption of papules and pustules, typically appearing in the face, scalp, and upper chest and back. Accurate grading of acneiform rash associated with EGFR inhibitors is essential to ensure timely and appropriate interventions. NCI-CTCAE divided acneiform rash into five grades (Table 1).

The pathophysiology of EGFRI-associated skin rash is not completely understood. It is reasonable to assume that anti-EGFR therapy could interfere with the proliferation, differentiation, migration, and attachment of keratinocytes.[18] Moreover, it may interfere with the epidermal structure, and antimicrobial and inflammatory response, leading to

Table 1 NCI CTCAE V.5.0 Acneiform Rash

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Papule 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 with or without mild symptoms.	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; 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 superinfections with IV antibiotics indicated	Death

Abbreviations: BSA, body surface area; ADL, activities of daily living; IV, intravenous.

dysfunction of normal epidermal barrier and dysregulated cytokines patterns.[20] Since EGFR is highly expressed on epidermal keratinocytes, sebaceous glands, and epithelium of the hair follicle, the inhibition of these receptors can produce characteristic negative dermatologic effects.[18]

Braden RL et al[4] conducted a retrospective study on 157 patients with EGFRI-induced dermatologic adverse events. Papulopustular eruption was observed with a mean time to onset of one and a half weeks after initiation of EGFRIs at the average duration of 9.4 weeks, and eruption mostly involved the face in 97% of patients, followed by the chest (75%), back (61%), abdomen (8%), upper extremity (8%), and lower extremity (4%). Another study reported the onset of acneiform rash is most commonly observed during the first one to two weeks of treatment with an EGFR inhibitor, although the range of onset reported in the literature is between two days and six weeks.[1]

While pustules are generally sterile, secondary infection with bacteria, dermatophytes, or viruses may occur. The severity of the rash waxes and wanes, and typically resolves without permanent scarring within two months of therapy discontinuation, although scarring secondary to bacterial or fungal overgrowth can also occur.[3] In this case, we classified the patient as having a grade two acneiform rash based on NCI CTCAE v.5.0.

In addition to the afatinib-related acneiform rash, the patient in this case also experienced xerosis, pruritus, paronychia, and hair abnormalities (trichomegaly also hypertrichosis of the eyelashes, eyebrows, and facial).

Xerosis is characterized by dryness and roughness of the skin, as well as scaling. The incidence of xerosis in patients treated with EGFR-TKIs ranges from 7.7% to 54%.[10] Xerosis generally occurs late and is usually observed after 15[1] to 60 days of therapy.[1,10] As the condition progresses, fissures appear and the skin becomes itchy and similar to that seen in ichthyosis. The fissures can cause considerable pain,[10] increased susceptibility to injuries whose secondary causes bacterial and viral infections.[1] Deep painful fissures are most often seen in the area of fingertips, heels, periungual skin, and dorsal surface of the interphalangeal joints. Pruritus often coexists with xerosis (50%) and papulopustular rash (62%).[1] NCI-CTCAE divided dry skin/xerosis into three grades (Table 2) and pruritus into three grades (Table 3). In this case, we classified the patient as grade two xerosis and grade two pruritus based on NCI CTCAE v.5.0.

Paronychia is a disorder characterized by an inflammatory process involving the soft tissues around the nail and manifests as dusky erythema around several fingernails and toenails. This results in the formation of painful fissures, swelling, and noninfectious granulation. Bleeding or exudation can result in crust formation.[10] Paronychia frequently

Table 2 NCI CTCAE V.5.0 Dry Skin/Xerosis

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	–	–

Abbreviations: BSA, body surface area; ADL, activities of daily living.

Table 3 NCI CTCAE V.5.0 Pruritus

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	–	–

Abbreviations: BSA, body surface area; ADL, activities of daily living.

Table 4 NCI CTCAE V.5.0 Paronychia

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nail fold edema or erythema; disruption of the cuticle	Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	–	–

Abbreviations: ADL, activities of daily living; IV, intravenous.

accompanies papulopustular rash and develops later on, usually observed after four to eight weeks of therapy.[1] NCI-CTCAE divided paronychia into three grades (Table 4). In this case, we classified the patient as grade two paronychia based on NCI CTCAE v.5.0.

EFGR-TKIs can induce hair changes such as hair loss (scarring or non-scarring alopecia), scalp inflammation, or hirsutism including hair rigidity and curling, trichomegaly, and facial hypertrichosis,[12,21] and eyebrow growth.[21] The incidence of hair changes in patients treated with EGFR-TKIs is <10% within the first three months but increases to approximately 80% after six months of therapy.[10] The EFGR is involved in the development and differentiation of the hair follicle. This receptor is expressed in keratinocytes of the hair follicle and regulates the transformation from anagen to catagen. Its inhibition can stimulate the formation of a disorganized hair follicle with abnormal hair growth.[21] EGFR-TKIs cause androgen-like frontal alopecia with progressive growth of facial hair and eyelashes, which is more evident in female patients.[12] Trichomegaly is usually observed in 10–14 weeks after the therapy.[21]

The trichoscopic findings of hair changes due to treatment with EGFRIs are only reported in a few literature. Kremer et al[22] conducted a cohort study to evaluate the trichoscopic findings in scalp and facial hair on 23 patients treated with EGFRIs. Trichoscopic findings of hair shaft anomalies, including pili torti, affecting scalp hair in 87% of patients, eyebrows in 26% of patients, and eyelashes in 50% of patients. Asymmetric hyperpigmented fusiform widening of hair scalp in 13% of patients, eyebrows in 43% of patients, and eyelashes in 25% of patients. Dermoscopic findings of the peri- and interfollicular skin were scaled, whitish erythematous structureless areas, and branching vessels. Another study by Ena et al[23] reported trichoscopic findings of tufted hairs, follicular hyperkeratosis, and hair casts after three months of lapatinib therapy. A case report by Pirmez et al[24] described two patients treated with erlotinib for one and four years who had trichoscopic scalp hair features of black dots, pili torti, and broken hairs. Fukui et al[25] reported a patient with trichoscopic features of follicular keratotic plugging, milky red areas, white patches, disordered hair shaft, and tapering hair at eleven months after starting therapy with gefitinib. Based on the above literature, these findings are consistent with the trichoscopic features in this patient.

Dermatologists play an important role in patient education and in the prevention and management of EGFR-TKIs-related skin toxicities. The primary goal of the management strategies is to avert any disruptions or premature terminations of the complete EGFR-TKIs treatment course, ensuring patients' quality of life remains tolerable. This is crucial, as discontinuations may limit or compromise the clinical effectiveness of these drugs.[11] Overall management strategy for acneiform rash should be individualized and will depend on the type, severity, location, and need to continue treatment.[1]

Education about general skin care practices to prevent or reduce the severity of acneiform rash, including use of alcohol-free emollients for overall skin moisturization (ie creams, ointments),[3,9,11,18] avoid popping acne pustules and using over-the-counter acne medications, adequately hydration,[3] apply broad spectrum (UVA, UVB) sunscreens before going outdoors and avoid excessive sun exposure,[3,9,11,18] avoid hot water (ie use lukewarm water when showering, washing dishes),[3,11] and avoid tight-fitting clothing or irritating fabrics (eg wool).[3] Dicloxacillin wash (250 mg in 250 mL normal saline) can be used in patients with pustular lesions (grade 1–4).[11] In this case report, apart from being given education about skincare, she is also given mild cleanser for the face and body, alcohol-free moisturizer, and sunscreen.

Lacouture et al[9] recommended topical and systemic treatment for EGFRIs-induced rash according to the severity of the rash. For grade two rash, patients should continue EGFR-inhibitor therapy at the prescribed dose, oral antibiotics for four to six weeks, and topical steroid or topical antibiotics.[3,10] Lu et al[11] recommended oral antibiotics given include oral 100 mg minocycline twice daily or 100 mg doxycycline once to twice daily, oral antihistamine if itchy, and topical medications such as topical antibiotics clindamycin 1–2% or metronidazole 1%, tetracycline 1% or fusidic acid 2%, and topical steroid such as fluticasone propionate 0.05%, betamethasone valerate 0.06%, mometasone furoate 0.1%, desoximetasone 0.25%. In this role, the antibiotics are used for their anti-inflammatory properties and not their antimicrobial effects. If after four weeks of treatment, the rash has not improved or has worsened, patients should be treated for a grade three to four rash. Antibiotic selection for infections should be based on antimicrobial sensitivities.[3]

Chu et al[10] recommend treatments for grade two xerosis, such as continuing EGFR-TKI at the current dose, applying moisturizing cream or ointment to the face and/or body twice daily or more as needed, applying moisturizing cream or vaseline or 10% urea cream to the body twice daily or more as needed, and considering application of topical steroids if eczematous lesions appear. Patients who develop pruritus are suggested to prevent dryness, continue EGFR-TKI at the current dose, and may benefit from topical antipruritics such as chlorpheniramine maleate ointment as needed, or apply pra-moxine 1% or doxepin 5% cream q.i.d.; ice packs, or moisturizers; and administer oral antihistamines.[11]

For paronychia, education should be given to avoid washing their hands frequently, not soak their hands and feet in soapy water for a prolonged period without adequate protection, wear cotton gloves underneath washing-up gloves to protect their hands moisturize and dry their hands and feet regularly, avoid skin irritants and nail trauma/injury, and also wear shoes that protective but loose enough.[10] Special care should be taken when cutting nails. For grade two paronychia, EGFR-TKI may continue at the current dose, oral intervention such as oral doxycycline, minocycline, or cephalexin, topical antibiotics and/or antiseptics such as clindamycin 1%, tetracycline 1%, chloramphenicol 1%, fusidic acid 2%, iodine ointment, and topical β-blocker solution twice daily or administer cryotherapy or other chemical/ electric cauterization if granulation has developed.[11]

For hypertrichosis and trichomegaly, the patients should avoid products that stimulate the scalp, use gentle shampoo, and avoid hair gels, hair dye, and perms. A high temperature should be avoided when blowing hair.[11] If patients develop pustules along with hair changes, the treatment for these pustules is similar to that for acneiform rash. Curly or thick eyelashes may cause conjunctivitis or eye irritation that may require an ophthalmologist consultation.[10]

In this case, afatinib administration is continued according to the previous dose. The patient was given 100 mg doxycycline twice a day and 10 mg cetirizine a day for four weeks. For acneiform rash, we gave the patient topical 2% clindamycin for the erythematous papules on the face and 0.25% desoximetasone for erythematous papules on the chest, back, and upper leg. For the scalp, the patient was given gentle shampoo, topical 2% mupirocin for the pustules, and topical 0.05% desonide lotion for the scaly erythematous papules. For the xerosis and pruritus, the patient was given mild moisturizing cream for the face and 10% urea cream for the body twice daily along with broad-spectrum sunscreen. For the paronychia, we gave a wet dressing with normal saline, and topical 2% mupirocin for the periungual skin on both toes. Significant clinical improvement was seen after four weeks of treatment in the form of less erythematous papules and disappearance of pustules on the face and body, reduced pustules and greasy scales on the scalp, reduced xerosis and pruritus, and reduced periungual redness and swelling. Adverse effects of treatment with EGFR-TKIs can lead to poor drug adherence or discontinuation of the drug, resulting in less than optimal outcomes.

Conclusion

Epidermal growth factor receptor inhibitors (EGFRI)-targeted agents are used in several types of cancer and dermatological adverse events being the most frequently reported. Recognizing clinical signs of EGFRI dermatological adverse events and initiating the therapy as soon as possible is important to prevent patients and physicians from discontinuing EGFRI treatment due to intolerable impacts on the patient's quality of life. Discontinuation may limit or compromise the clinical effectiveness of the drugs, and influence compliance of patients for effective therapy of underlying malignancy.

Ethic Statement

This study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practices, local regulatory requirements, and was approved by the Medical Ethics Committee of Hasan Sadikin General Hospital Bandung (approval number: DP.04.03/D.XIV.6.5/465/2024).

Consent Statement

The authors certify that they have obtained all appropriate patient consent forms. The patient signed a consent form for the publication of the case details and images.

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Disclosure

The authors report no conflicts of interest in this work.

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