

Case 10.1

A 32-year-old Thai female from Bangkok

Chief complaint: Pustular rashes on the face for 3 weeks

Present history:

The patient was diagnosed with adenocarcinoma of the lung with right tonsil and right upper cervical lymph node metastasis. She was treated initially with carboplatin and paclitaxel. After failure of the previous chemotherapeutic regimen, erlotinib was administered at a dose of 150 mg/day and good response was achieved. During the first 3 weeks of treatment with erlotinib, she experienced papulopustular eruptions on her face, neck, chest, back, and extremities. Swelling and redness of proximal and lateral nail fold developed on her fingers and toes after approximately 6 weeks of therapy. She observed a marked increase in length and irregularity of her eyelashes 3 months after treatment commencement. She had to trim her eyelashes with scissors on a weekly basis. Additionally, dry and itchy skin was noticed.

Past history:

She had neither underlying disease nor other medication.

Family history:

No family history of similar lesions.

Physical examination:

Skin: Multiple discrete erythematous follicular papules and pustules distributed at face, neck, chest, upper back, and extremities. Palms and soles were spared. Generalized mild xerosis was observed. (Fig. 10.1.1, 10.1.2)

Eyelashes: bilateral coarse, excessive curling, and elongated irregular growth of eyelashes (Fig. 10.1.3)

Nails: tender, swelling, erythema, and proliferation of granulation tissue at proximal and lateral nail fold of fingers and toes (Fig.10.1.4)

Other systems: unremarkable



Fig. 10.1.1



Fig. 10.1.2



Fig. 10.1.3



Fig. 10.1.4

Diagnosis: Dermatologic side effects from erlotinib, PRIDE syndrome (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to EGFR inhibitors)

Presenter : Padcha Pongcharoen

Consultants : Vasanop Vachiramom

Treatment :

-2% hydrocortisone cream plus 0.75% metronidazole gel applied to skin lesions

-Muciprocin ointment applied around nails

-Sunscreen

-Trimming of eyelashes

-Treatment interruption for 3 weeks, then erlotinib dosage reduced from 150 mg/day to 100 mg/day

Case 10.2

A 56-year-old Thai male from Sakonnakorn

Present history:

The patient was diagnosed with adenocarcinoma of the lung with liver, lymph node, and adrenal gland metastases. Despite, initial treatment with paclitaxel and carboplatin, the tumor progressed. He developed superior vena cava syndrome, which responded well to radiation therapy. Treatment was switched to a second-line chemotherapeutic agent, erlotinib. Five days after starting erlotinib, he developed multiple erythematous papulopustular eruptions on his face, neck, chest, and upper back. Some lesions progressed to confluent pustules. The oncologist decided to brief discontinue erlotinib treatment.

Past history:

He had underlying hypertension and was treated with amlodipine for several years.

Family history:

No family history of similar lesions.

Physical examination:

Skin: multiple discrete and confluent erythematous folliculocentric papules, papulopustulars, pustules, and nodules involving face, neck, upper chest, and upper back. Some lesions on face had hemorrhagic crusts. (Fig. 10.2.1 and Fig.10.2.2) The rest of skin findings including hair and nails were normal.

Other systems: unremarkable

Pus Gram stain: numerous PMN, no organism

Pus culture: no growth



Fig. 10.2.1



Fig. 10.2.2

Histopathology (S09-10849) (Fig 10.2.3 H&E - Fig 10.2.4 H&E)

- Dense, mixed inflammatory cell infiltrate, predominate of neutrophils, around ruptured hair follicle

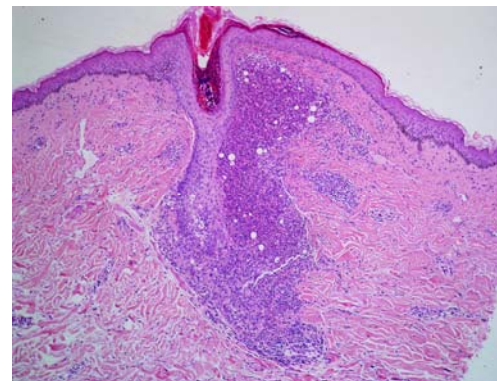


Fig. 10.2.3

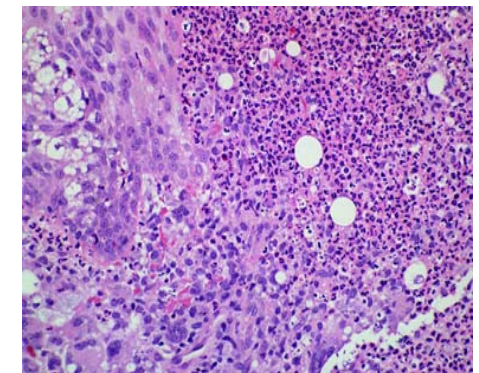


Fig. 10.2.4

Diagnosis :

Dermatologic side effect from erlotinib
(Papulopustular eruption)

Presenter : Padcha Pongcharoen

Consultants : Vasanop Vachiramon

Treatment :

- 0.75%metronidazole gel
- Doxycycline 200 mg/day orally
- Brief discontinue erlotinib

Discussion:

Epidermal growth factor receptor (EGFR) inhibitors are currently in widespread use for the treatment of advanced malignancies. Their chemotherapeutic potential is based on the overexpression of EGFR demonstrated in various epithelial cancers, such as lung, colorectal, breast, head & neck, and pancreatic cancers.¹ Current available EGFR inhibitors are erlotinib (Tarceva[®]), gefitinib (Iressa[®]), cetuximab (Erbix[®]), and panitumumab (Vectibix[®]).

Patients undergoing anti-EGFR therapy frequently present with cutaneous toxicities, which have been observed with all agents and is considered a class effect. The effects of EGFR inhibitors on the skin are directly linked to interference of EGFR signaling. Inhibition of EGFR signaling has been shown to reduce DNA synthesis, arrest growth, induce premature differentiation, and inhibit migration of keratinocytes.^{2,3} A wide spectrum of skin toxicities has been described, including papulopustular eruptions, xerosis, pruritus, paronychia, hair abnormalities, and trichomegaly of the eyelashes. The clinical findings set was proposed in term the PRIDE syndrome (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to EGFR inhibitors).⁴

Acneiform or papulopustular eruption was the most common side effect seen in clinical trials varying from 25%-90%. The median time after initiation of treatment to onset of eruption is 7-10 days, and maximum severity is reach in the second week. It tends to improve over time despite continuing anti-EGFR treatment. The eruption is usually distributed in the seborrheic areas. Less commonly, the

extremities lower back, and abdomen can be involved. Palms and soles are spare. The primary lesions are follicular papules and pustules. Unlike acne, comedones are rarely seen. The lesions may be asymptomatic or accompanied by pruritus. All skin rashes usually resolve within one month after discontinuation of EGFR inhibitors. Histopathologically, the earliest finding is T-cell infiltrate around the follicular infundibulum. Then suppurative folliculitis is seen, with destruction of the hair follicle and subsequent granuloma formation in more severe cases.²

Xerosis is commonly observed, with reported rate of 12%-35% in clinical trials. Xerosis often affects the limbs and areas previously affected by papulopustular rash. Vaginal dryness, perineal dryness, and eye irritation have also been reported.³

Paronychia occurs in 10%-15% of patients and is considered a late event, often arising 4 to 8 weeks after treatment initiation. Complications, such as pyogenic granuloma, and periungual abscess, have been reported.³ Nail changes could persist long after discontinuation of EGFR inhibitors.

EGFR inhibitors can cause variable effects on hair growth, depending on the location on the body. Hair loss occurs in 14%-21%. Scalp hair may become brittle, fine, and curly. Reduced beard growth had been reported, whereas increased growth of eyelashes and eyebrows occurs in 12%-14% of patients after approximately 7 weeks to 5 months of therapy. Eyelashes may appear irregular, coarse, and excessively curly, which can scratch the eye, and lead to ocular problems.^{5,6}

A dose-dependent relationship between both incidence and severity of the skin eruption was observed.⁷⁻¹⁰ Interestingly, number of retrospective studies have found that the presence and severity of rash are indicators of tumor response as well as overall survival.^{11,12} But some studies failed to demonstrate these correlations, possibly due to the small sample size.^{13,14} Future studies are needed to thoroughly

evaluate the value of skin toxicity as a surrogate marker for clinical benefit in prospective clinical trial setting.

Cutaneous toxicities from EGFR inhibitors treatment can cause serious discomfort and have a profound impact on patients' quality of life. Rash led to discontinuation of EGFR inhibitors therapy in 32% of patients, and to treatment interruption in 76% of patients.¹⁵

There is currently no evidence-based treatment guideline to prevent or treat the EGFR inhibitors-associated skin toxicities. Expert panels recommend the use of a grade-based treatment algorithm. (Fig. 10.3)¹⁶

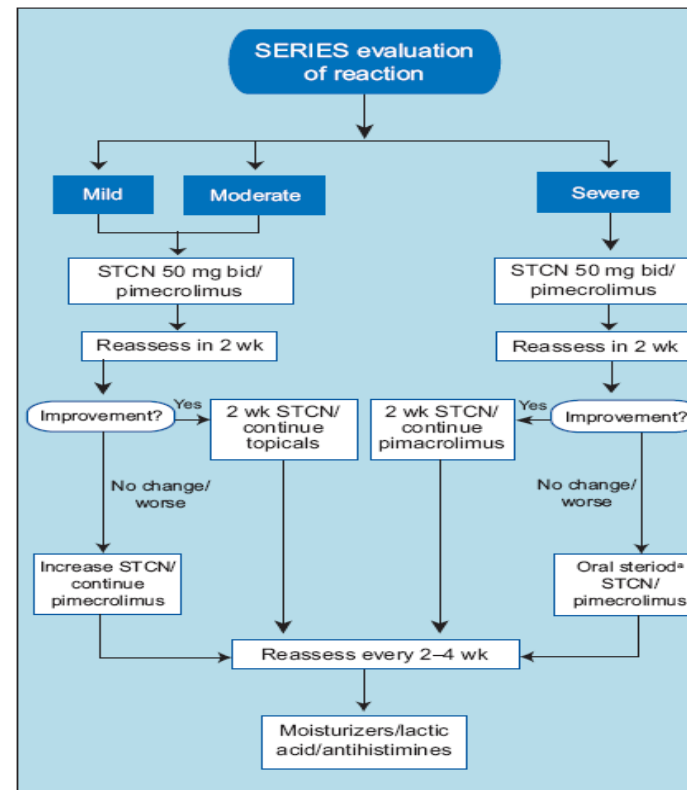


Fig.10.5 : SERIES guidelines– algorithm for management of cutaneous effects of EGFRIs.

National cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

(mild/moderate=NCI CTCAE grade1/2, severe=NCI CTCAE grade3),
STCN=semisynthetic tetracycline (doxycycline or minocycline)

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