Epidermal Growth Factor Receptor Inhibitors and Associated Cutaneous Drug Eruptions: Mechanisms, Recognition, and Management

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Epidermal growth factor receptor (EGFR) inhibitors are being used to treat several malignancies involving the head and neck, breast, lung, kidney, prostate, pancreas, and brain. EGFRs are overexpressed in malignancies and usually correlate with a poor prognosis, especially in patients with non–small cell lung cancer. Two categories of EGFR inhibitors are available: monoclonal antibodies and small receptor tyrosine kinase inhibitors. Abrupt onset of a cutaneous eruption is commonly seen in patients treated with these agents. This article discusses the significance of EGFRs, presents an illustrative case report with description of the characteristics of the cutaneous eruption associated with inhibiting agents, and assesses management of affected patients.

Epidermal growth factor receptor (EGFR) inhibitors are being used to treat several malignancies involving the head and neck, breast, lung, kidney, prostate, pancreas, and brain.[1] EGFRs are overexpressed in malignancies and usually correlate with a poor prognosis, especially in patients with non–small cell lung cancer.[2] There are 2 categories of EGFR inhibitors that are currently used: monoclonal antibodies and small receptor tyrosine kinase (TK) inhibitors. Abrupt onset of a cutaneous eruption, which has been described as acneform, is commonly seen in patients treated with these agents. We present a case of a patient who developed a cutaneous eruption after initiation of therapy with panitumumab, a fully humanized chimeric monoclonal antibody that was approved in September 2006 by the US Food and Drug Administration (FDA) for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma. This article also discusses the significance of EGFRs, the characteristics of the cutaneous eruption associated with EGFR inhibitors, and management of affected patients.

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CASE REPORT

A 64-year-old man undergoing treatment of stage IV metastatic colorectal adenocarcinoma presented to the office with an eruption involving predominantly the face (Figure 1) and scalp, with scattered upper trunk, upper extremity (Figure 2), and lower extremity lesions also

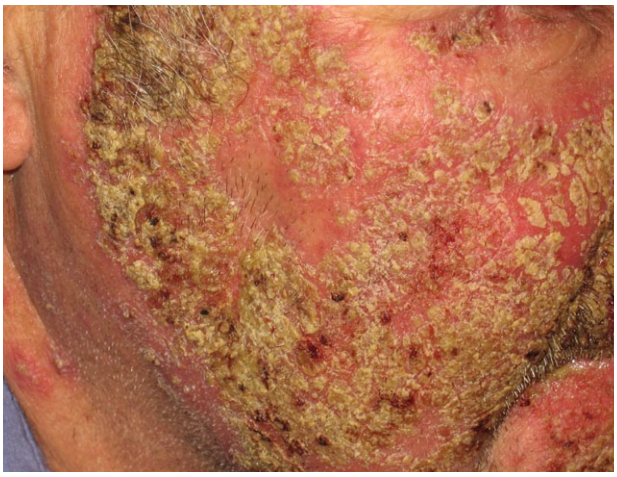

Figure 1. Confluent erythema and crusting noted diffusely on the face.

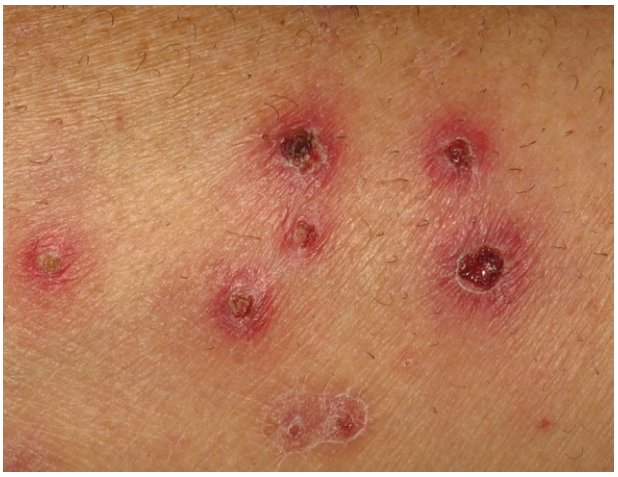

Figure 2. Crusted and superficial eroded erythematous papules on the forearm.

noted. His colorectal cancer was initially diagnosed and treated in July 2004 with partial colectomy and subsequent chemotherapy and radiation. He also underwent an abdominal perineal resection in February 2005. Recurrent tumor in the pelvis was noted on a whole body positron emission tomography scan in September 2005, and he subsequently received 6120 cGy in 34 fractions. A computed tomography scan in March 2006 revealed an enlarged left inguinal lymph node that was biopsied and confirmed as a metastatic colon adenocarcinoma. He was started on a combination chemotherapy treatment with panitumumab, oxaliplatin, leucovorin, bevacizumab, and 5-fluorouracil in May 2006.

He presented with multiple crusted papules and pustules located diffusely with confluence on the scalp and face, with concomitant scattered lesions noted on the upper trunk and bilaterally on the upper and lower extremities. The palmar and plantar surfaces were spared. Mild skin tenderness and hair thinning were reported. His past medical history was remarkable for a personal history of eczema. The review of systems was negative for any fevers, chills, cough, night sweats, and recent bacterial or viral infections.

The patient observed that the eruption occurred after 5 months of therapy with panitumumab, and a dermatologic consultation was requested within 2 weeks of this eruption. Grading of his cutaneous eruption according to the National Cancer Institute Common Toxicity Criteria for Adverse Effects (NCI CTCAE) version 3.0 scale (Table) on the head and neck revealed a rating of severe (grade 3).[3,4] The eruption on his upper and lower extremities was rated in severity as grade 1.

Panitumumab was discontinued by his oncologist after onset of the skin eruption approximately 2 weeks before his dermatologic evaluation. His eruption was treated with oral tetracycline 500 mg twice a day along with application of triamcinolone 0.1% ointment twice a day. A mild cleanser and moisturizer were also recommended along with instructions to follow up in one month. At follow-up one month later, his eruption was completely resolved.

COMMENT

Epidermal Growth Factor Receptors

The EGFR is a 170-kDa protein that belongs to the ErbB family of tyrosine kinase proteins that are important mediators of cell growth, differentiation, and survival.[5] HER2/neu (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4) comprise the remainder of this family of proteins. All 4 proteins in this family are composed of an extracellular domain that is involved in recognizing and binding ligands, a lipophilic transmembrane domain, and an intracellular TK domain with a regulatory carboxy terminal segment.[5-8] There exists a high degree of homology in the TK domain among members of the ErbB family.[9,10]

The EGFR is activated by binding of a ligand. Several ligands have been identified, including EGF, transforming growth factor-α, epiregulin, amphiregulin, heparin-binding EGF-like growth factor, and betacellulin.[11] Upon binding of the ligand, the EGFR binds to another EGFR or another member of the ErbB receptor family, forming a homodimer or a heterodimer, respectively.[5] The intracellular TK domain is activated upon formation of the dimer and results in activation of various downstream signaling effector pathways that ultimately control important processes such as cell proliferation and differentiation, apoptosis, angiogenesis, adhesion, and motility.[5,7] Mutations, gene amplification, autocrine ligand expression, or overexpression in the EGFR can lead to dysregulation, resulting in uncontrolled cell growth and proliferation, angiogenesis, inhibition of

National Cancer Institute Common Toxicity Criteria[3,4]

National Cancer Institute Common Toxicity Criteria for Adverse Effects version 3.0

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash: acne/acneform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	–	Death
Rash: desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area	Severe generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering ≥50% of body surface area	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Nail changes	Nail changes	Discoloration; ridging (koilonychia); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with activities of daily living	–	–
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	–	–
Dry skin	Dry skin	Asymptomatic	Symptomatic; not interfering with activities of daily living	Interfering with activities of daily living	–	–

National Cancer Institute Common Toxicity Criteria for Adverse Effects version 2.0

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash: desquamation	–	None	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface area or localized desquamation or other lesions covering <50% of body surface area	Symptomatic generalized erythroderma or macular, papular, or vesicular eruption or desquamation covering ≥50% of body surface area	Generalized exfoliative dermatitis or ulcerative dermatitis

apoptosis, resistance to chemotherapy and radiotherapy treatment, invasion, and metastasis.[5-8,11]

Inhibition of EGFRs

Several potential anti-EGFR targeting strategies have been reported in the literature, including monoclonal antibodies that interfere with ligand binding, low-molecular-weight TK inhibitors, antisense oligonucleotides or ribozymes that block receptor translation, and monoclonal antibodies serving as carriers of radionucleotides, toxins, or prodrugs.[8] Most of the EGFR inhibitors can be classified into 2 categories: monoclonal antibodies that bind the extracellular domain, thereby blocking ligand-binding TK activation, and small receptor TK inhibitors that block receptor phosphorylation by binding to the TK portion of the receptor.[8,12,13]

Monoclonal Antibodies—Cetuximab is a chimeric human/murine monoclonal antibody that has been approved by the FDA for the treatment of EGFR-positive metastatic colorectal carcinoma as monotherapy in patients who are intolerant of irinotecan-based chemotherapy or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.[8,14] Cetuximab is also approved by the FDA for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck as monotherapy in patients who are not responsive to standard chemotherapy or in combination with radiation therapy in patients with unresectable squamous cell carcinoma of the head and neck.[8,15]

Panitumumab is a fully humanized chimeric monoclonal antibody approved for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with disease progression on or following chemotherapy regimens containing fluoropyrimidine, oxaliplatin, and irinotecan.[16] Matuzumab, inotuzumab, and cimazumab are monoclonal antibodies that are currently under evaluation in clinical studies.

TK Inhibitors—Gefitinib, an orally administered EGFR reversible TK inhibitor, is approved by the FDA for the treatment of non–small cell lung cancer. The FDA has limited gefitinib prescriptions at this time to patients currently receiving and benefiting from the agent, patients who have previously received and benefited from gefitinib, and previously enrolled patients or new patients in non–Investigational New Drug clinical trials approved by an institutional review board prior to June 17, 2005.[17]

Erlotinib is a reversible TK inhibitor indicated as monotherapy for patients with locally advanced or metastatic non–small cell lung cancer after failure of at least one prior chemotherapy regimen. Erlotinib is also indicated in combination with gemcitabine in patients with locally advanced, unresectable, or metastatic pancreatic cancer.[18]

Lapatinib is another reversible TK inhibitor that is currently under investigation.[8,18] EKB-569 and canertinib are irreversible TK inhibitors that are currently under investigation.[8,18]

Cutaneous Reactions Associated With EGFR Inhibitors

Several cutaneous adverse effects have been reported, including an acneform eruption, xerosis, paronychia, telangiectasia, hyperpigmentation, small ulcers of oral or nasal mucosa, urticaria, and trichomegaly (lengthening of the eyelashes).[7,11,18-20]

Acneform Eruption—A cutaneous eruption, initially termed *acneform eruption*, is seen in more than half of patients treated with EGFR inhibitors, with a more severe reaction seen in patients treated with monoclonal antibodies.[21,22] Cetuximab and panitumumab have been associated with an acneform eruption in 75% to 100% of patients.[23-29] Saltz et al[25] noted an eruption in 86% of patients, with 18% of these eruptions being severe as graded by the NCI CTCAE version 3.0 scale. Acneform eruptions have also been seen with the use of gefitinib (66%)[28] and erlotinib (75%, 5% grade 3).[27]

The degree of eruption correlates with the dosage and duration of treatment with EGFR inhibitors. This form of eruption has been observed more commonly in patients receiving 500 mg/d of gefitinib than with the 250-mg/d approach.[29] An association has been noted between the severity of the eruption and tumor/treatment response.[30,31]

The eruption described as acneform is usually located in seborrheic areas such as scalp, face, neck, upper trunk, postauricular region, and shoulders, while sparing palmar and plantar surfaces.[11,15,32] In fact, the term *acneform* is not truly accurate, based on histologic evaluation and also clinical presentation in many cases. The eruption presents as erythematous papules and pustules, which may be associated with pruritus. A rosacealike eruption has also been observed, consisting of diffuse erythema with follicular papulopustules and telangiectasia.[33] Although the cutaneous eruption may sometimes resemble acne vulgaris clinically, an important distinction is that it is not associated with comedones or cysts, nor does it resemble acne vulgaris pathologically.[31,34] Also, in many cases, the lesions tend to be predominantly monomorphic or demonstrate a greater confluence of lesions, both of which are not characteristic of acne vulgaris. There is no alteration of the sebaceous glands in patients treated with EGFR inhibitors, which is in contrast with findings in patients with acne.[31]

The onset of eruption ranges from 2 days to 6 weeks, with an average of 1 week after commencement of therapy with EGFR inhibitors, and is usually maximal after 3 to 5 weeks.[11,18,23,35] The delay in onset of the eruption seen

in our case was unusual as compared to the typical onset that has been reported. The eruption usually resolves within 4 weeks of stopping EGFR-inhibitor treatment but may recur once therapy is resumed. Resolution of the eruption is also seen with withdrawal of treatment or reduction in dose.[32] Spontaneous and progressive resolution has been reported despite continuation of the same dose of gefitinib.[5,32,36]

Adverse effects due to EGFR inhibitors are classified based on either NCI CTCAE version 3.0 or NCI CTC version 2.0.[3,4] The criteria are shown in the Table.[3,4] Severe skin reactions (NCI CTCAE grade 3 or higher), including abscesses, sepsis, and death, have been observed in 12% of patients treated with panitumumab.[26]

Pathogenesis of Cutaneous Eruptions

EGFRs are normally expressed in basal epidermal keratinocytes, sebaceous glands, eccrine glands, outer root sheaths of hair follicles, and endothelial cells.[37,38] EGFRs play an important role in the differentiation, keratinization, and proliferation of keratinocytes and normal differentiation and development of hair follicles.[11,39] EGFR activation also leads to epidermal hyperplasia and hyperkeratosis.[40] Activation of EGFRs in the epidermis causes a reduction in basal keratinocyte differentiation while promoting differentiation in the suprabasilar keratinocytes.[28,41]

No clear evidence exists on the pathogenesis of the cases described as acneform eruption. Several hypotheses exist, but none is clearly accepted as the definitive explanation. Cutaneous side effects caused by EGFR inhibitors are thought to be due to inhibition of EGFR signal transduction in epidermal and follicular epithelium.[42] Cetuximab was noted by Busam et al[23] to upregulate p27Kip1, a negative growth regulator that binds to and inactivates cyclin-dependent kinase-2, causing cell cycle arrest. Gefitinib has also been shown to upregulate p27Kip1.[28] The upregulation of p27Kip1 in epidermal keratinocytes is thought to play a role in the acneform eruption by altering follicular and epidermal homeostasis, but the exact mechanism is unknown.[23] Follicular hyperkeratosis followed by plugging, ostial obstruction, eventual follicle rupture, and subsequent inflammatory response has been suggested to play a role in the acneform eruption caused by cetuximab.[29,31]

EGFR inhibitors may also affect the immune system, either directly or indirectly, by reversing the suppression of chemokine production, causing leukocyte chemotaxis and infiltration of the skin.[33] Alexandrescu et al[24] suggested that cutaneous eruption seen with EGFR inhibitors may be produced by effects on intracellular downstream pathways and not by the blockade of the EGFR. It has also been suggested that EGFR inhibitors may cause changes in skin microflora by altering follicular growth, thus causing an inflammatory reaction.[43]

Histology

Histologically, earliest changes involve an infiltrate of T lymphocytes surrounding the follicular infundibulum.[23] After one week of therapy, patterns ranging from superficial perifolliculitis to florid suppurative folliculitis are usually seen.[23,24,42]

Treatment

The acneform eruption has been noted to resolve after reduction in dose or discontinuation of EGFR inhibitors. Benzoyl peroxide and retinoids, both topical and oral, have been reported to be effective based on case reports.[26,44]

Low-dose oral isotretinoin 20 mg daily for one month followed by administration every other day was effective in a case reported by DeWitt et al.[44] The mode of action of isotretinoin is thought to involve normalization of follicular epithelium and differentiation, inhibition of neutrophil chemotaxis, reduction in sebaceous gland function, or all of these mechanisms.[26]

Oral antibiotics such as minocycline 100 mg twice daily, dilute acetic acid soaks to the crusts followed by mupirocin 2% cream 3 to 4 times daily, and salicylic acid shampoo have also been reported to be of benefit.[44]

Other Adverse Cutaneous Effects

Nail Changes—Nail changes are seen in 10% to 15% of patients treated with EGFR inhibitors, with paronychia being the most common presentation.[23,33,45-47] Paronychia is usually seen after 1 to 4 months of therapy.[25,45] Erythema, tenderness, swelling, fissuring of lateral nail folds, and distal finger tufts have also been seen.[23,33,45] Recalcitrant paronychia, with *Staphylococcus aureus* being the most common pathogen, has been seen in patients treated with erlotinib.[18] Fissures on the hands and feet and cracking of the nail plate and eponychium have been reported.[34] The pathogenesis of paronychia and other nail toxicities associated with EGFR inhibitors is unknown.

Treatment of nail changes, seen in patients treated with EGFR inhibitors, involves oral and topical antibiotics, bland emollients, and symptomatic relief using soaks and cushioning.[34,23,45-47]

Xerosis—Xerosis, fissuring, and cracking of the skin are adverse effects seen with EGFR inhibitors. Advanced age, atopic diathesis, and previous therapy with EGFR inhibitors increase the occurrence of these events.[33] A compromised epidermal barrier also serves as a source of entry for bacteria and viruses, such as *S aureus* and herpes simplex virus, resulting in secondary infections.[9,18,30]

Hair Changes—Trichomegaly is the most common hair change noted with EGFR-inhibitor therapy.[18,48-52] Bouché et al[48] reported a case of trichomegaly with no associated hypertrichosis in a patient treated with cetuximab. Trichomegaly completely regressed after one month of

stopping cetuximab. Curling of the scalp hair has also been reported.[18] Irregular aberrant eyelash growth can be treated with regular epilation and eyelash trimming, with reversal to normal texture also reported with the discontinuation of the EGFR inhibitor.[18,48-51]

SUMMARY

EGFR inhibitors are a major advance in the treatment of multiple malignancies. The presence of EGFRs in multiple locations in the skin appears to be associated with the common development of cutaneous eruptions after administration of these agents. The most common cutaneous eruption associated with EGFR inhibitors is described as an acneform eruption, although clinically and histologically the eruption is not consistent with acne vulgaris. Although discontinuation of the inciting drug leads to prompt resolution, it may be optimal to continue the EGFR inhibitor at a lower dose, discontinue it temporarily, or initiate treatment with low-dose oral isotretinoin, which appears to be beneficial. Further studies are needed to better understand the pathogenesis and management of this unique cutaneous drug reaction.

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