Targeted treatment, unintended breakouts:
A case of epidermal growth factor receptor inhibitor–induced acneiform eruption

Brenda Ngo, Jim Muir

CASE

A male aged 58 years presents with a 1-week history of a widespread pruritic and tender, papulopustular eruption on his face, upper chest and back (Figure 1).

QUESTION 1

What further history would you like to elicit from the patient?[1]

ANSWER 1

Key further features on history would include:

- Natural history of the rash including onset, duration, location, frequency and exacerbating features.
- Associated local symptoms including pain, itching, discharge and bleeding.
- Medication history including use of anabolic steroids, antipsychotics, epidermal growth factor receptor (EGFR) inhibitors, antidepressants, antituberculosis drugs and progestins.
- Past medical history including acne vulgaris, metabolic and genetic disorders or previous and current malignancies.[1]
- Patient perception of disease including psychosocial impact.

CASE CONTINUED

On further history, the patient reports being diagnosed with metastatic colorectal cancer 2 years prior. He had been commenced on cetuximab immunotherapy and 5-fluorouracil (5-FU) chemotherapy. Subsequently he had no biochemical or radiological evidence of disease progression. The patient's pustular rash appeared to specifically coincide with his cetuximab immunotherapy.

This rash had led his oncologist to trial a period of cessation of systemic therapies for 3 months. However, following radiological evidence of disease progression, his oncologist had restarted the treatment. His most recent cycle was 2 weeks prior to this consultation.

He had no history of acne vulgaris, folliculitis or allergies. His other past medical history was only significant for chronic hepatitis B treated long term with entecavir 0.5 mg daily.

QUESTION 2

What is the most likely diagnosis?

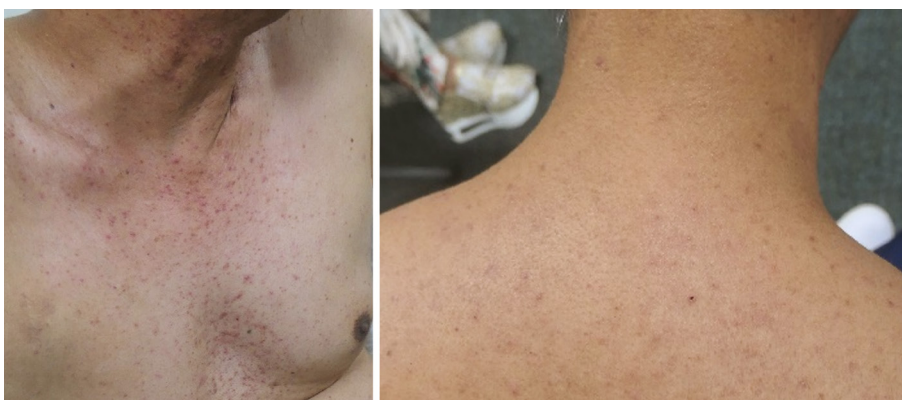

Figure 1. Papulopustular eruption on face, upper chest and back.

Table 1. Summary of epidermal growth factor receptor inhibitors

Class	Drug	Cancers treated
Monoclonal antibodies	Cetuximab	Head and neck Non-small cell lung Non-melanoma cutaneous Colorectal
	Panitumumab	Colorectal
Tyrosine kinase inhibitors	Afatinib	Non-small cell lung
	Erlotinib	Non-small cell lung Pancreatic
	Gefitinib	Non-small cell lung
	Lapatinib	Breast

QUESTION 3

What clinicopathologic features help differentiate acneiform drug eruptions from mimics such as acne vulgaris or bacterial folliculitis?

QUESTION 4

Should the patient's clinician list the drug as an allergy?

QUESTION 5

How would you confirm the diagnosis?

QUESTION 6

How would you manage this patient?

ANSWER 2

The most likely diagnosis is an acneiform eruption associated with cetuximab, an EGFR inhibitor. EGFR signalling pathways are often implicated in tumour growth and proliferation. Therefore, inhibition of this pathway is a common target of immunotherapies for various malignancies. EGFR inhibitors are classed as either monoclonal antibodies or tyrosine kinase inhibitors (Table 1).[2]

Most EGFR inhibitors are well-tolerated and not associated with severe systemic side effects. Nevertheless, dermatological reactions are well documented. A monomorphic papulopustular or 'acneiform rash' develops in 50–100% of patients.[1] This rash differs from acne vulgaris in that it is often pruritic and classically involves the scalp, shoulders, and trunk rather than primarily the face. The rash classically appears within the first 2–4 weeks of commencing treatment with EGFR inhibitors and the severity reduces with each treatment cycle.

Other dermatological side effects of EGFR inhibitors include hair changes, radiation dermatitis enhancement, pruritus, mucositis, xerosis and paronychia. Hair changes are often idiosyncratic. Reports vary from patients developing scalp hair growth or loss, thickening of eyelashes (trichomegaly), alteration of hair from curly to rigid or vice versa and increased brittleness.[1–3]

ANSWER 3

The key differential diagnoses in the case presented are acne vulgaris and bacterial folliculitis. Both might present as a papulopustular rash though have a natural history and clinicopathologic features distinct from an acneiform drug reaction and these are summarised in Table 2.

ANSWER 4

Dermatological side effects of EGFR inhibitors should not be classified as an allergic reaction contraindicating their use for treatment of the patient's malignancy. The EGFR signalling pathway is routinely activated in the normal physiology and development of the epidermis. EGFR is primarily expressed in proliferating keratinocytes in the basal layer of the epidermis. EGFR inhibitors prevent this physiological pathway in the skin thus leading to dermatological sequelae (Table 1).[1–3]

Therefore, the medication's side effects are best conceptualised as an unpleasant side effect of treatment as opposed to a drug allergy.

ANSWER 5

Acneiform reactions to EGFR inhibitors are clinically diagnosed based on careful history and examination. Biopsies and microbial swabs are useful as an adjunct to clarify diagnostic uncertainty. Microbiological stains and cultures typically demonstrate no infective organism. Histopathology typically shows superficial, predominantly neutrophilic suppurative folliculitis with hyperkeratotic follicular infundibula and rupture of the epithelial lining.[4]

ANSWER 6

Management of acneiform rashes resulting from EGFR inhibitors are tailored to the severity of disease (Figure 2). Overarching treatment paradigms include optimising environmental and lifestyle factors, topical therapies, and antibiotics where appropriate.[3] Specific to the case, if isotretinoin therapy was indicated its clinical benefit would need to be balanced against possible exacerbation of the patient's chronic hepatitis B and liver function tests closely monitored.

Patients should be appropriately counselled prior to starting EGFR inhibitors of the high likelihood of developing dermatological side effects and informed that acneiform rashes tend to decrease in severity with further cycles of treatment. If the rash remains persistent despite treatment, a shared decision-making approach should be taken with the patient regarding the risk–benefit calculus of continuing their EGFR inhibitor treatments. This is best achieved as a multidisciplinary discussion involving the patient, their oncologist, general practitioner and or dermatologist.

CASE CONTINUED

In this case, the patient was treated with oral doxycycline 100 mg twice daily for 2 weeks that had failed to resolve the eruption. He was subsequently referred to a dermatology clinic for review. The decision was made to cease the doxycycline, commence isotretinoin 10 mg daily and erythromycin as required concurrently for flares of disease.

Table 2. Comparison of acneiform drug eruptions from epidermal growth factor receptor inhibitors, acne vulgaris and folliculitis

Differential diagnosis	Epidemiology	Pathophysiology	Risk factors or precipitants	Clinical features
Acneiform drug eruption[1–3]	Any age or gender; no gender predisposition 50–100% of patients treated with EGFR inhibitors may have this eruption[1]	EGFR inhibitors trigger growth arrest and premature differentiation of these keratinocytes that subsequently drives downstream inflammation, apoptosis, tissue damage and vasodilation in the epidermis.	Higher doses of EGFR inhibitors are more commonly associated Other medications associated with acneiform drug reaction including: • corticosteroids • anticonvulsants (phenytoin, phenobarbital) • antituberculosis drugs (isoniazid) • antipsychotics (lithium, olanzapine) • antibiotics (penicillins, macrolides)	Onset: Acute onset within 2–4 weeks of starting an EGFR inhibitor Location: Face, neck and trunk Distinguishing features: • Comedones are never present • Predominantly pustular; rare to have a cystic acne phenotype
Acne vulgaris[5]	Adolescents and young adult population affected (M>F)	Sebaceous gland obstruction, infection and inflammation leading to 'comedone' formation Hormonal stimulus drive sebaceous gland obstruction Obstruction leads to superimposed *Cutibacterium acnes* infection → 'comedone' formation	Lifestyle – stress, occlusive clothing or cosmetics, diet Medications – lithium, steroids and anticonvulsants Menstrual cycle Pregnancy Polycystic ovarian syndrome	Onset: Chronic with acute flares Location: Face, arms, trunk and back Distinguishing features: • Multiple clinical subtypes but presence of comedones or 'blackheads' pathognomonic • Acute flares of chronic disease associated with precipitants described
Folliculitis[5]	Any age or gender *Malassezia* folliculitis more common in adolescents	Infection of hair follicle by bacteria/viral/fungal organism with resultant inflammation. Examples of common organisms include: • Bacteria: Staphylococcal Folliculitis most common • Viral: Herpes, Molloscum Contagiosum • Fungal: *Malassezia*	Lifestyle – Hot tubs or pools, frequent shaving/scratching of affected area Prolonged use of antibiotics Immunocompromised status (eg HIV) Topical corticosteroids Diabetes Obesity	Onset: Acute or recurrent acute Location: Any hair bearing surfaces of body Distinguishing features: • Small, well circumscribed, globular, dome-shaped pustules • Pustules often have peri-follicular inflammation associated

EGFR, epidermal growth factor receptor; F, female; M, male.

On review 8 weeks later, it was noted that the acneiform rash had almost entirely resolved. The patient reported no side effects of his isotretinoin treatment. He continued isotretinoin and reported that there was no recurrence of his acneiform rash after his EGFR inhibitor therapy was recommenced.

Key points

- Acneiform drug reactions can be seen with EGFR inhibitors, antipsychotics, antidepressants, antituberculosis drugs, progestins and steroids.
- Patients should be appropriately counselled prior to starting EGFR inhibitors regarding the high likelihood of dermatological side effects.
- Timely rash prevention or management strategies should be initiated in patients treated with EGFR inhibitors to reduce risk of treatment interruption and to preserve quality of life.

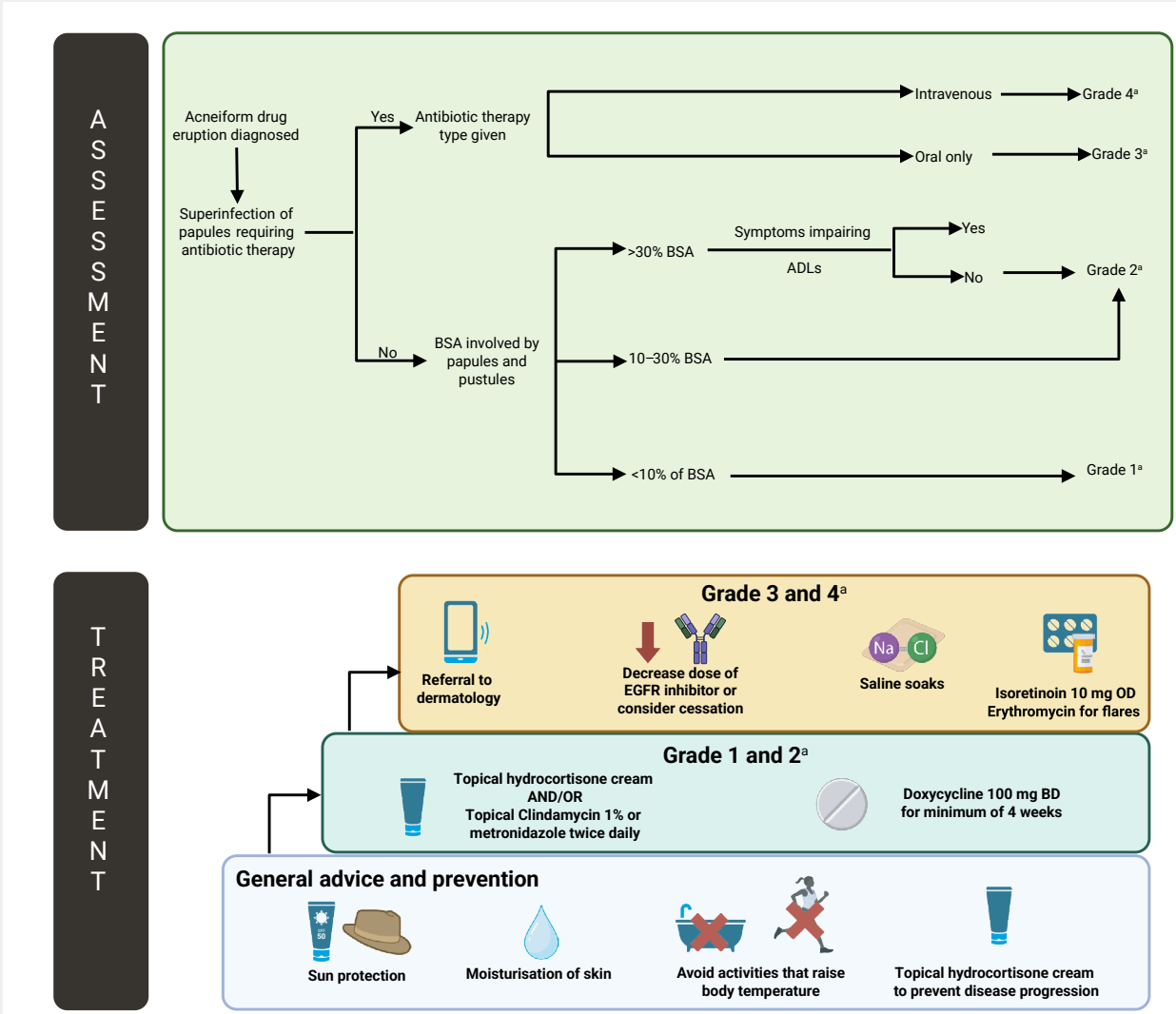

Figure 2. Assessment and treatment pathway for acneiform drug eruptions resulting from EGFR inhibitors.[1,3,6]

[a] Grading as per Common Terminology Criteria of Adverse Events (CTCAE).[6]

ADLs, Activities of Daily Living; BD, twice daily; BSA, body surface area; EGFR, epidermal growth factor receptor; OD, once daily.

Authors

Brenda Ngo MD, Principal House Officer, Dermatology Department, Mater Hospital, Brisbane, Qld

Jim Muir MBBS, FACD, FACRRM (Hon), Consultant Dermatologist, Mater Hospital, Brisbane, Qld; Associate Professor, The University of Queensland, Brisbane, Qld

Correspondence to:
brenda.ngo97@gmail.com

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