EGFR-induced cutaneous toxicity

Background & Pathogenesis

- EGFR in skin
  - Expressed in basal keratinocytes and around hair follicles.
  - EGFR blockade →
    1. Impaired skin barrier (apoptosis of basal cells)
    2. Neutrophil-mediated inflammation
    3. *Demodex* mite overgrowth
- Predictive biomarker
  - Severity of skin toxicity often correlates with tumor response (1).
- Often surinfection with staphylococci or streptococci (± 40%) (2).
  - **If in doubt, take a swab** (also nasal swab!)
- Acneiform rash develops in 75%-90% (all grades) and 10%-20% (grade 3/4) in patients (3).

Clinical Timeline

Manifestation	Onset	Features
Papulopustular (acneiform) rash	Weeks 1–8	Papules/pustules on face, chest, back, rosacea
Xerosis, eczema, fissures	Weeks 4–12	Dry, scaly skin on limbs → fissures, cracking
Paronychia	After Weeks 8–12	Painful inflammation around nail folds
Pruritus	Variable (1–2 wks)	Intense itching; may become chronic

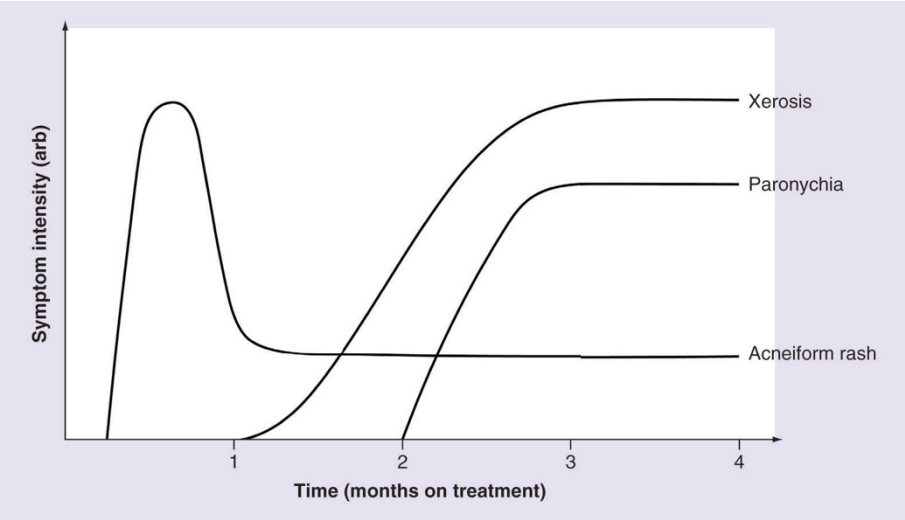

Figure 1: Timeline of most common cutaneous toxicities
From Beech *et al. (4)*

Prevention

1. **Showering**

- Not too long, lukewarm water, once daily.
- Use oil-based cleansers instead of alkaline soaps.

2. **Hydration**
   - Apply emollient creams containing ceramides or urea daily.
3. **Barrier Protection**
   - Wear gloves for wet household tasks (e.g., dishwashing).
4. **Avoid Irritants**
   - Steer clear of alcohol-based lotions, fragrances, harsh detergents.
5. **Sun Protection**
   - Avoid sun exposure; wear sunprotective cloaths; apply sunscreen SPF ≥ 30.
6. **Shoes**
   - Avoid pinching shoes
7. **Profylactic medication**
   - Metronidazole cream 1x/day on the face[1]
   - Minocycline 100mg/day (first 8 weeks, afterwards option to stop or decrease depending on the clinical situation)
   - Start a few days before therapy initation.
8. **Others**
   - Humidifier, avocado, oily fish
   - Vasiline on nailbeds for paronychia

Treatment Strategies

CTCAE grading

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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 with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local 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	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					

[1] Use metronidazole 1% magistral preparation

Papulopustular Rash

- If in doubt of underlying surinfection: swab!
- **Grade 1**
  - Continue profylactic measurements (metronidazole 1-2x/day + minocycline 100mg 1x/day)
- **Grade 2**
  - Increase the dose of profylactic measures
    - Metronidazole 1-2% (1 to 5 times/day)
    - Minocycline 100mg 2x/day
  - In case of surinfection: Flucloxacilline 500-1000mg 3-4dd; or cefuroxime 500mg 2dd (5-10 days)
- **Grade 3-4**
  - Interrupt EGFR-inhibitor until ≤ Grade 1
  - Increase profylactic measures: metronidazole 1-2% 5x/day, minocycline 100mg 2x/day
  - Add compresses with physiologic salt solution 2x15min/day (stop when grade 2)
  - Add momethasone furoaat cream 0.1% or hydocrtisonebutyraat cream 0.1%[2] (max. 2 weeks; stop when grade 2).
  - Refer to dermatology
- !! Be aware of surinfections
  - If surinfection: STOP and switch to flucloxacilline. Afterwards switch back to tetracyclines for anti-inflammatory effect.[3]

Xerosis & Eczema

- Dry eczema: momethasone furoaat cream 0.1% or hydocrtisonebutyraat cream 0.1% 1x/day during 2 weeks, then taper
- Wet eczema:
  - Betamethasonevalerate + fusidic acid 2x/day during 2 weeks, then taper during some weeks
  - Cefurxime 2x500mg/day during 10 days

Fissures

- Always microbacterial swab first (skin, nose always, KNAL if needed)
  - Flucloxacilline 500-1000mg 3-4dd; or cefuroxime 500mg 2dd (5-10 days)
- Fucidic acid (Fucidin®) ointment
- Compounded solutions
  - Propyleneglycol 50%/water 50% (30 min)
    - Fill up the fissures with this solution
  - Vasiline 10% or Fucidin® ointment

[2] e.g. Locoid®

[3] Even if antibiogram show tetracycline resistance.

- Bariéderm® kloven, Xerial® kloven

Paronychia (>8 weeks)

- Gentle nail-fold care; avoid cutting/pulling cuticles, medical pedicurist
- Always swab! But always primary inflammation, thus indication for strong corticosteroids.
- Antiseptic soaks 2x/day
  - Chloramine tablets (5/250 mL)
  - Povidone iodine (1/20)
- "Magistral preparation" 2x/day
  - Clobetasolproprionate 0.05%
  - Chlorhexidine 0.5%
  - Nystatine 10^5 E/g
  - Zinkoxide 10%
  - Base cream (CMC or CNAI)
- Minocycline 100mg/day or other antibiotic
- Other (cryo, surgery, other?)

Pruritus

- Skin hydratation: Xeracalm Avène or Lipikar AP+M La Roche Posay
- Menthol cream and almond oil
  - Zoete amandelolie 5% in AVA Dt/100g
  - Menthol 0,5% in CMC Dt/100g
- Antihistamines (bilastine 1x/day)
  - Can be uptitrated to 2x non-sedating (bilastine) during the day and 2x sedating before sleep ((levo)cetirizine)
- 2nd line: pregabaline
- No UV-treatment

Other

- Hypersensitivity (rare): occurs after few months
- Hypertrichosis:
  - Sometimes need to cut eyelashes due to inwards curling and occular lesions

Further reading

- *ESMO guidelines:* Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. Lacouture, M.E. et al. Annals of Oncology, Volume 32, Issue 2, 157 - 170

- *ASCO educational book:* Alana Deutsch et al. Dermatologic Adverse Events of Systemic Anticancer Therapies: Cytotoxic Chemotherapy, Targeted Therapy, and Immunotherapy. Am Soc Clin Oncol Educ Book 40, 485-500 (2020).

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3. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6(10):803-12.
4. Beech J, Theodora G, Mary J, Nina P, Joanne C, Abigail G, et al. Management and Grading of EGFR Inhibitor-Induced Cutaneous Toxicity. Future Oncology. 2018;14(24):2531-41.