Dermatologic Emergencies in the Hospital

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Disclosures

- I have no financial interests to disclose.

Overview

GOAL:

Improve our recognition of three different *drug-induced T-cell mediated* dermatologic emergencies that occur in hospitalized patients:

- Stevens-Johnson syndrome (SJS)
  Toxic epidermal necrolysis (TEN)
- Drug reaction with eosinophilia and systemic symptoms
  Drug-induced hypersensitivity syndrome (DRESS/DIHS)
- Acute generalized exanthematous pustulosis (AGEP)

Cutaneous Adverse Drug Reactions (ADRs)

- 90% of cutaneous ADRs are mild and self-limiting
  - Morbilliform drug eruption
  - Fixed drug-eruption
- Severe cutaneous ADRs (SCAR), often life-threatening, occur in 1 per 1000 to 1 per 10,000 hospitalized patients
  - SJS/TEN
  - DRESS/DIHS
  - AGEP

Cutaneous Adverse Drug Reactions (ADRs)

- It's important to have a *working knowledge* of…
  - Culprit drugs (common ones)
  - Timelines of drug exposure for developing rash
  - Morphology (appearance) of rash
  - Associated clinical signs & symptoms

Common drugs…

Major Cutaneous Adverse Drug Reactions (ADRs)	Implicated Drugs*
Mild and self-limiting	
Morbilliform drug eruption (MDE), also called an exanthematous eruption or maculopapular eruption (MPE)	penicillins, allopurinol, sulfonamides, cephalosporins, anticonvulsants
Fixed drug eruption (FDE) Multifocal fixed drug eruption, also called a generalized fixed drug eruption	sulfonamides, tetracyclines, NSAIDs, aspirin, sedatives, pseudoephedrine
Potentially life-threatening SCAR	
Acute generalized exanthematous pustulosis (AGEP)	β-lactam antibiotics, macrolides, calcium channel blockers, terbinafine
Drug reaction with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome (DIHS), or hypersensitivity syndrome (HS)	anticonvulsants, sulfonamides, allopurinol, minocycline
Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN)	sulfonamides, anticonvulsants, allopurinol, NSAIDs, barbiturates, nevirapine

*For any of the above cutaneous ADRs, the list of implicated medications is *not* complete and contains only the more commonly reported medications.

Table compiled using information available references (3, 7, 8, 11, 12, 14, 15).

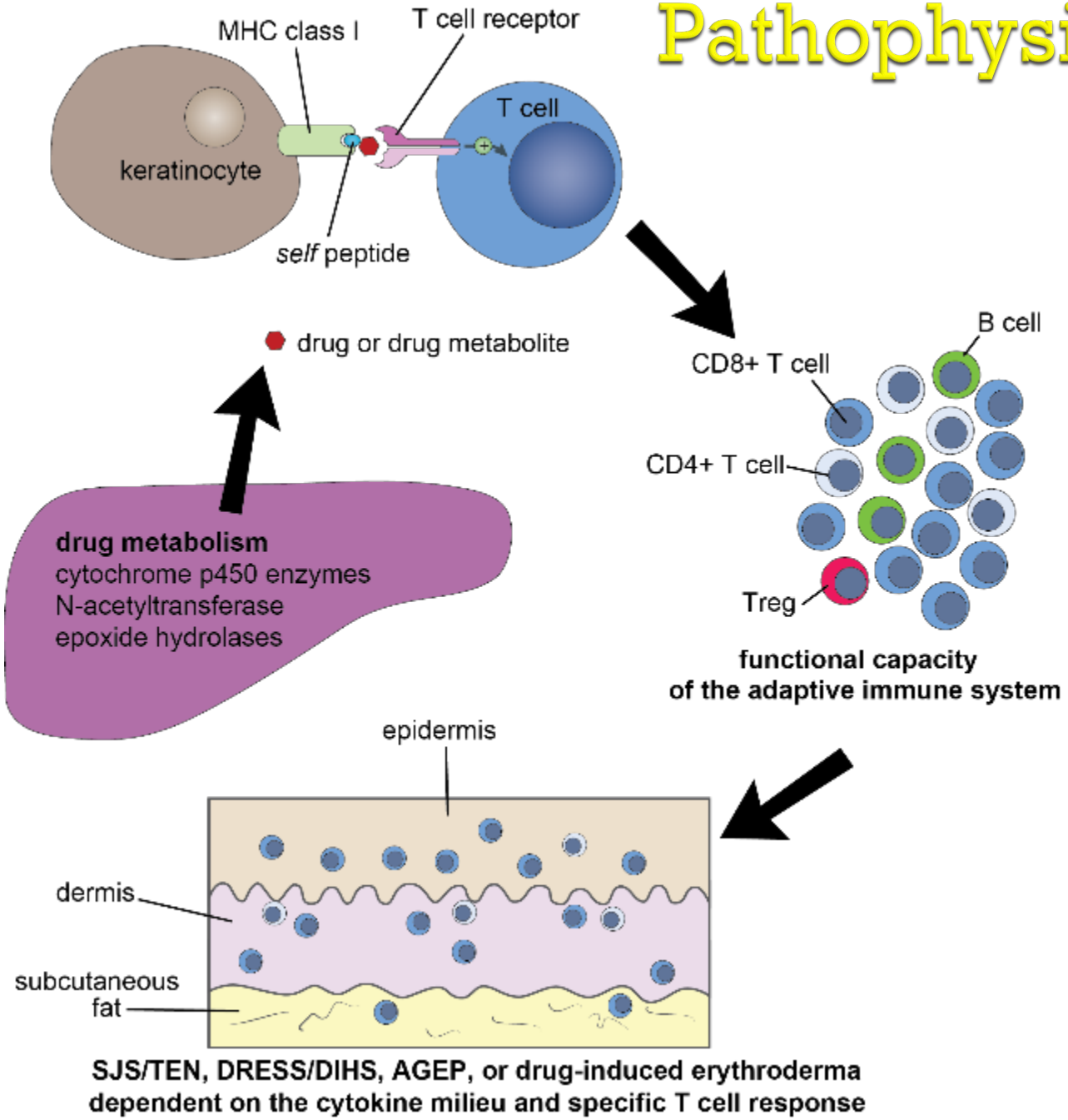
Timelines…

Major Cutaneous Adverse Drug Reactions (ADRs)	Time Interval*
Mild and self-limiting	
Morbilliform drug eruption (MDE), also called an exanthematous eruption or maculopapular eruption (MPE)	4-14 days
Fixed drug eruption (FDE) Multifocal fixed drug eruption also called a generalized fixed drug eruption	*First* exposure: 7-14 days *Repeat* exposure: 1-2 days
Potentially life-threatening SCAR	
Acute generalized exanthematous pustulosis (AGEP)	1-4 days
Drug reaction with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome (DIHS), or hypersensitivity syndrome (HSS)	14-40 days (2-6 weeks)
Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN)	7-21 days

*Time interval between drug exposure and the onset of the skin rash.
For any of the above cutaneous ADRs, the time interval is typically much shorter for repeat exposures.

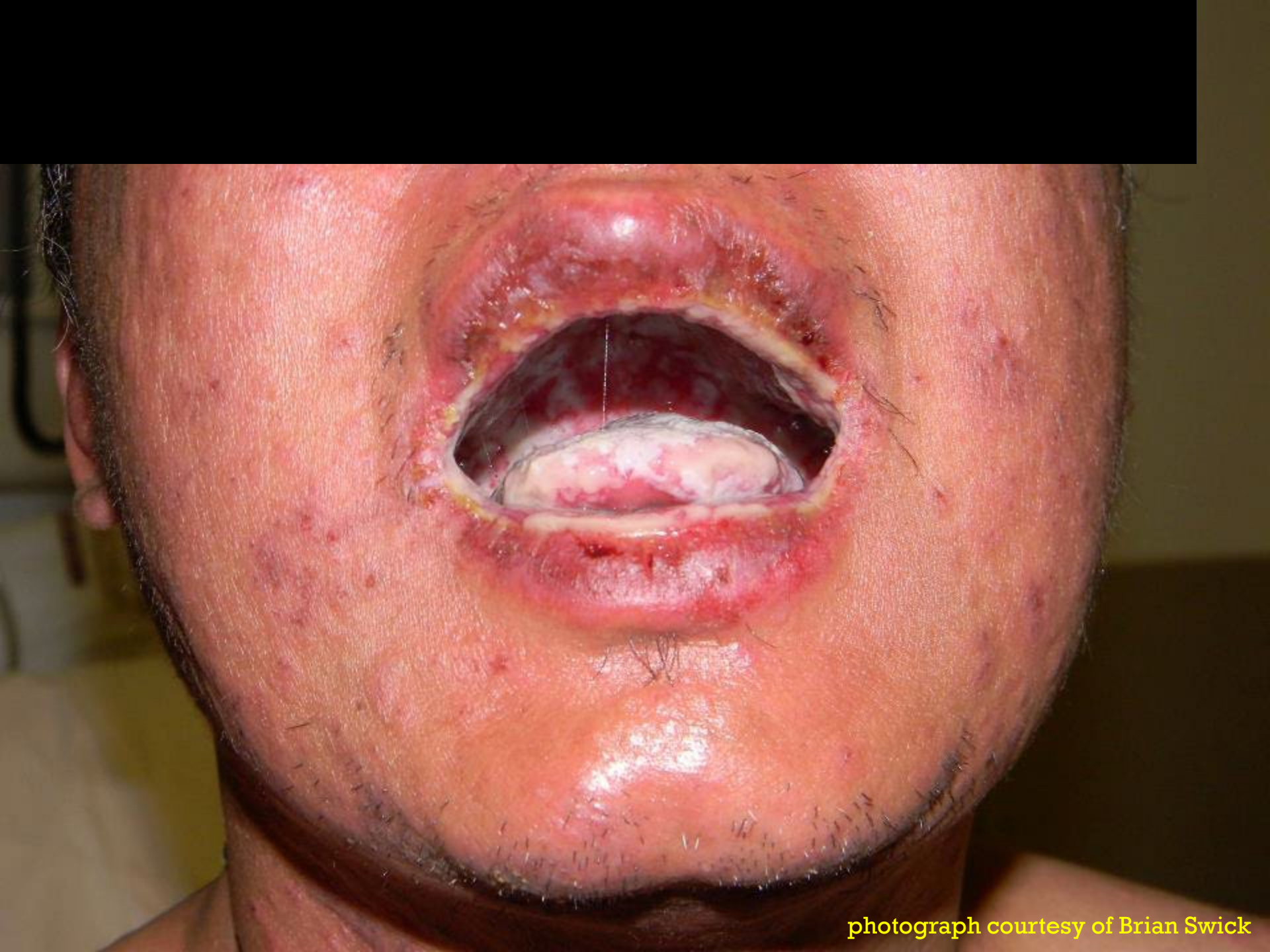
Table compiled using information available references (3, 7, 8, 11, 12, 14, 15).

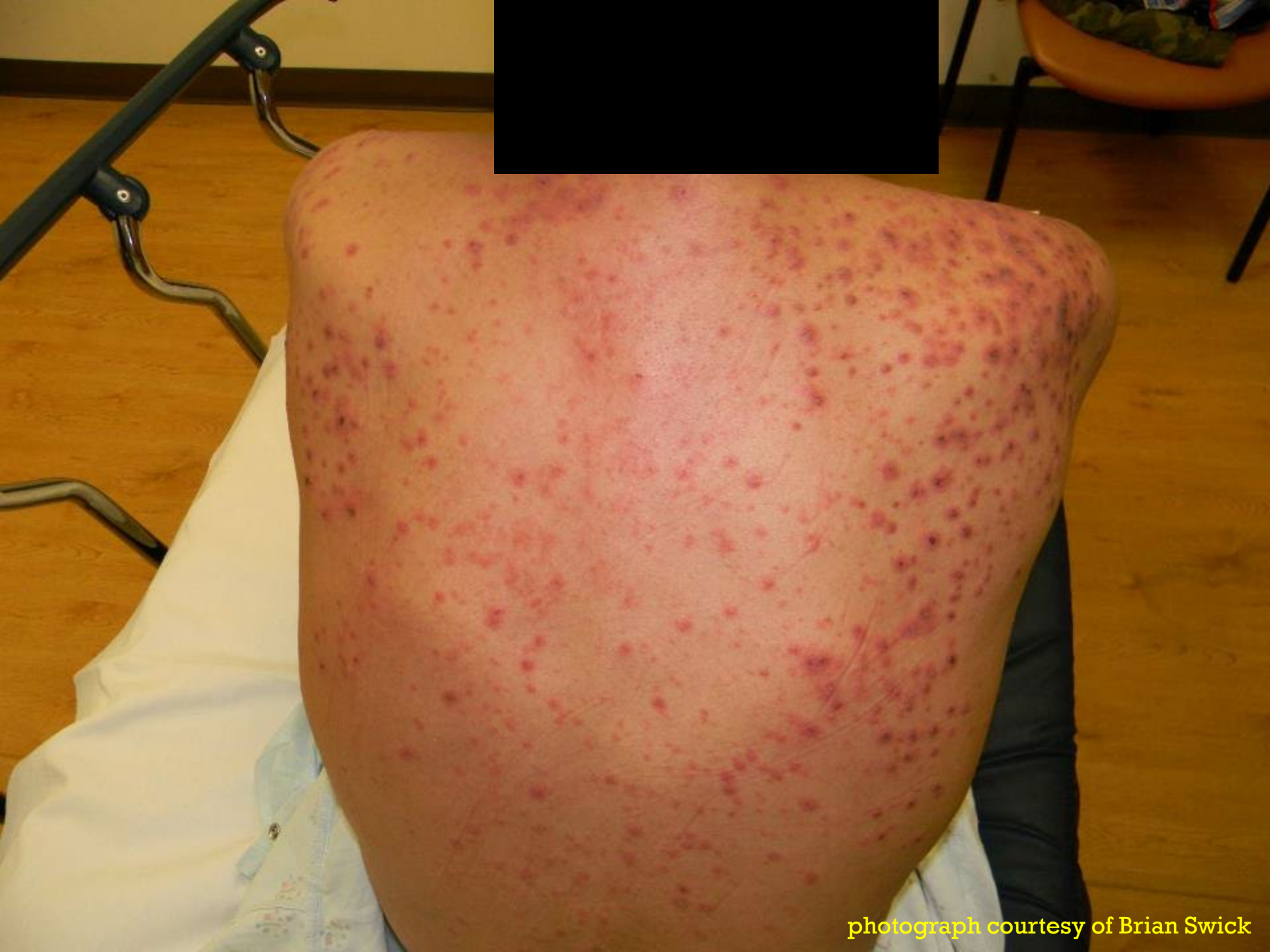
Pathophysiology



Pathophysiology

- SJS/TEN, DRESS/DIHS, and AGEP
  - T-cell mediated *delayed hypersensitivity reactions*
    - Genotypic variations
      - Enzymes of drug metabolism
      - Major histocompatibility complex I proteins (HLA types)
      - T-cell receptors
    - Functional capacity of the immune system
      - Collective behaviors of the various specialized populations of T cells, B cells, and antigen presenting cells
    - Clinical appearance of the rash is determined by the cytokine milieu and specific T cell response


photograph courtesy of Brian Swick


photograph courtesy of Brian Swick


Stevens-Johnson Syndrome
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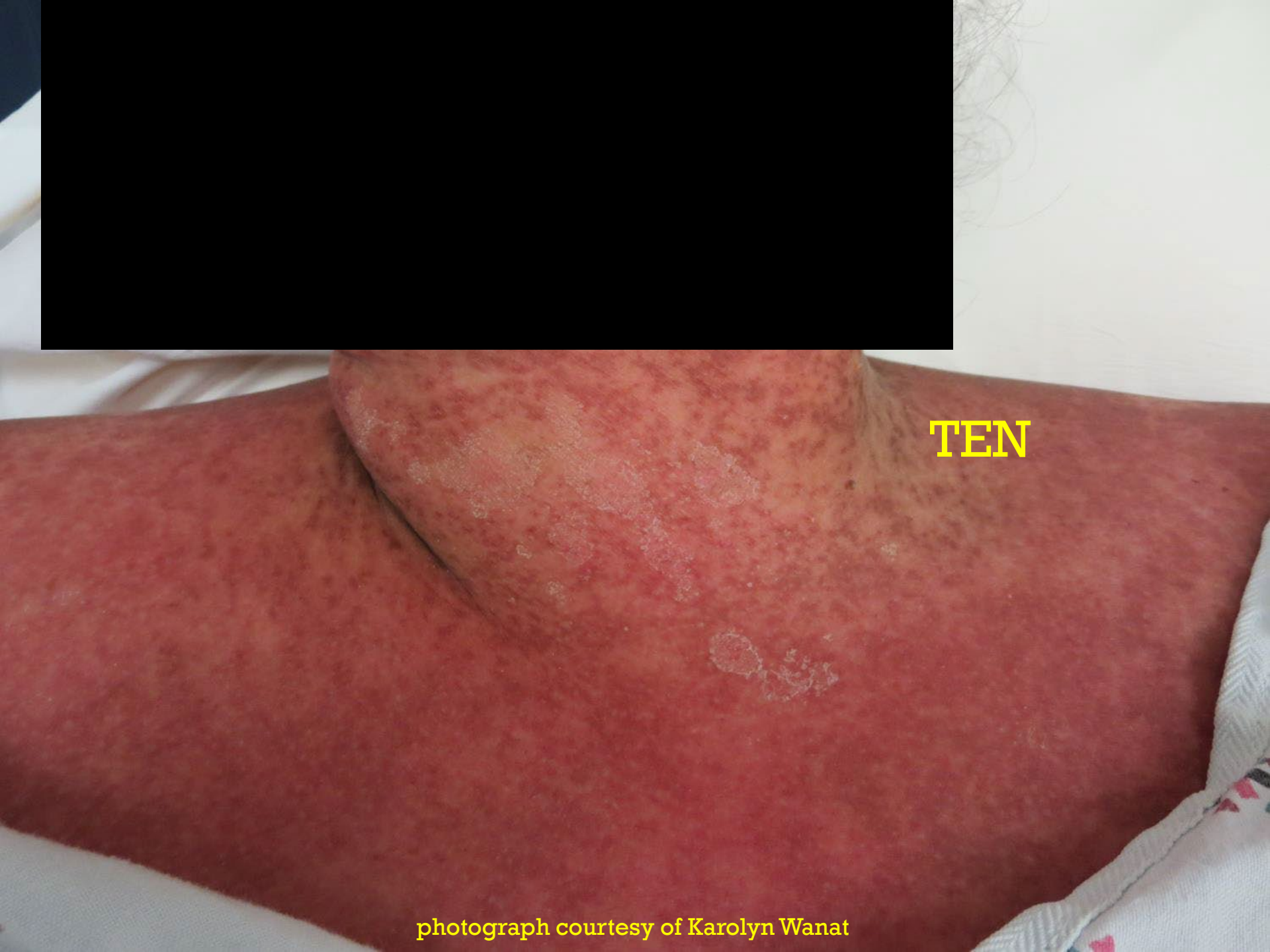

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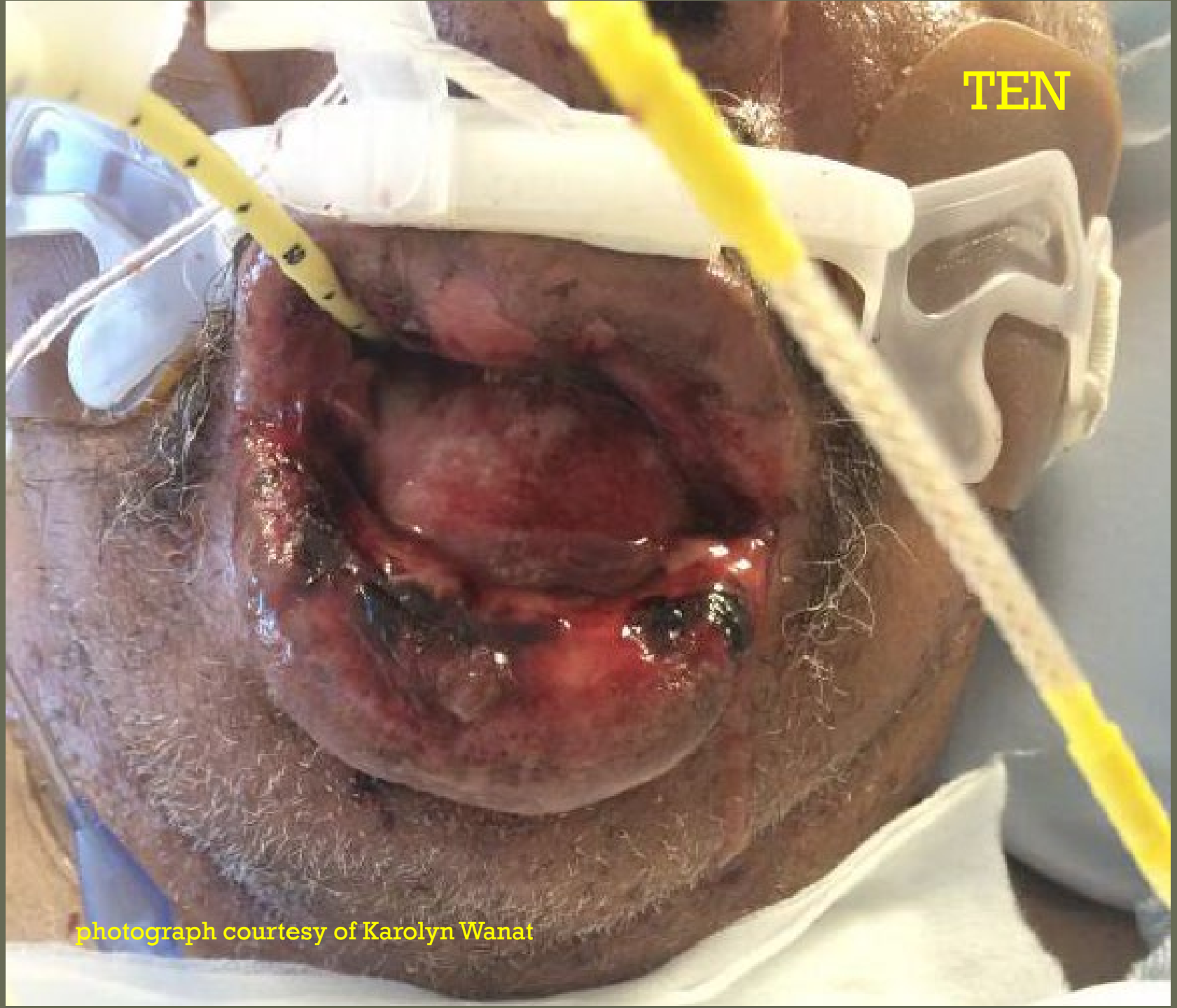
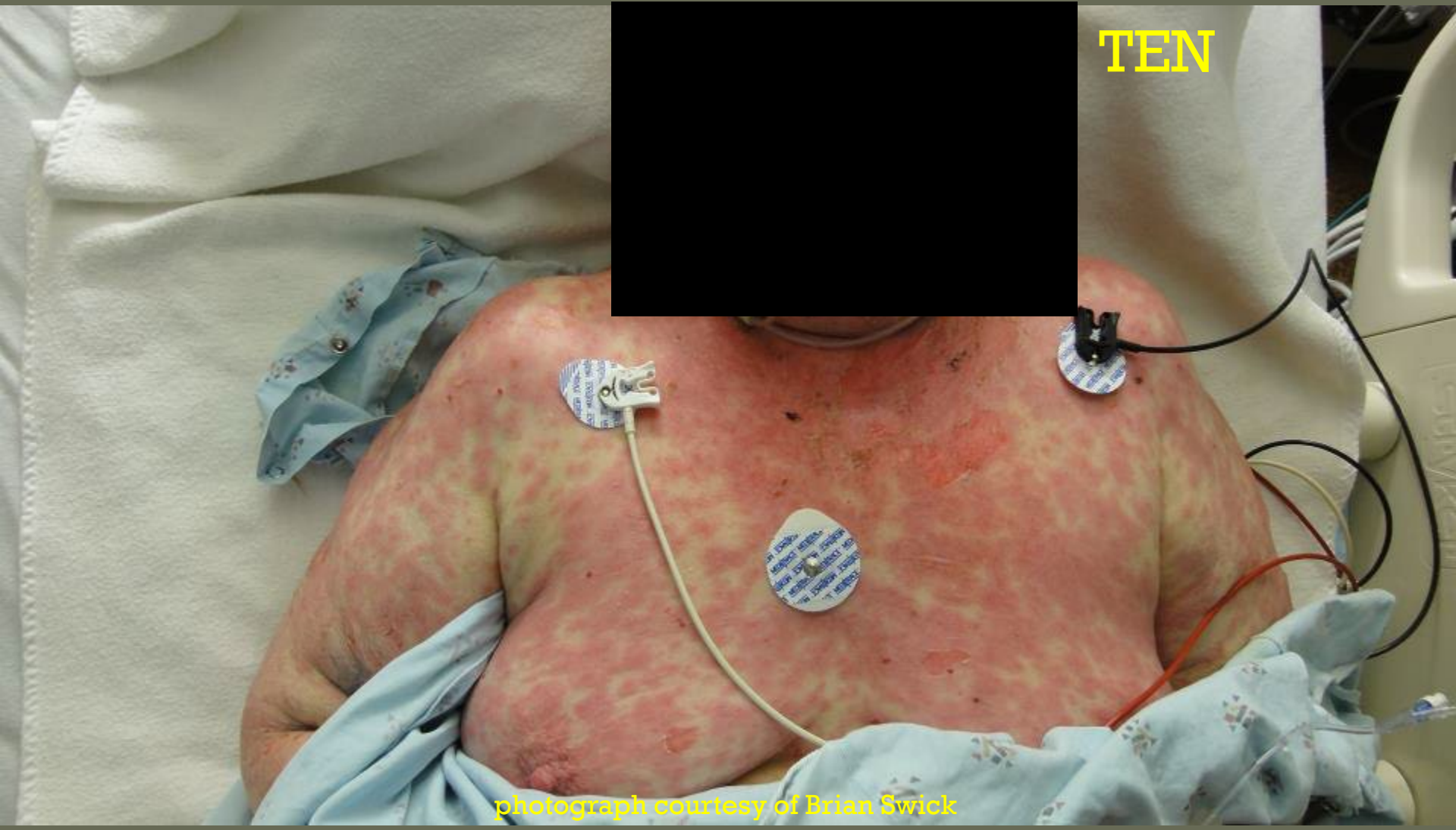
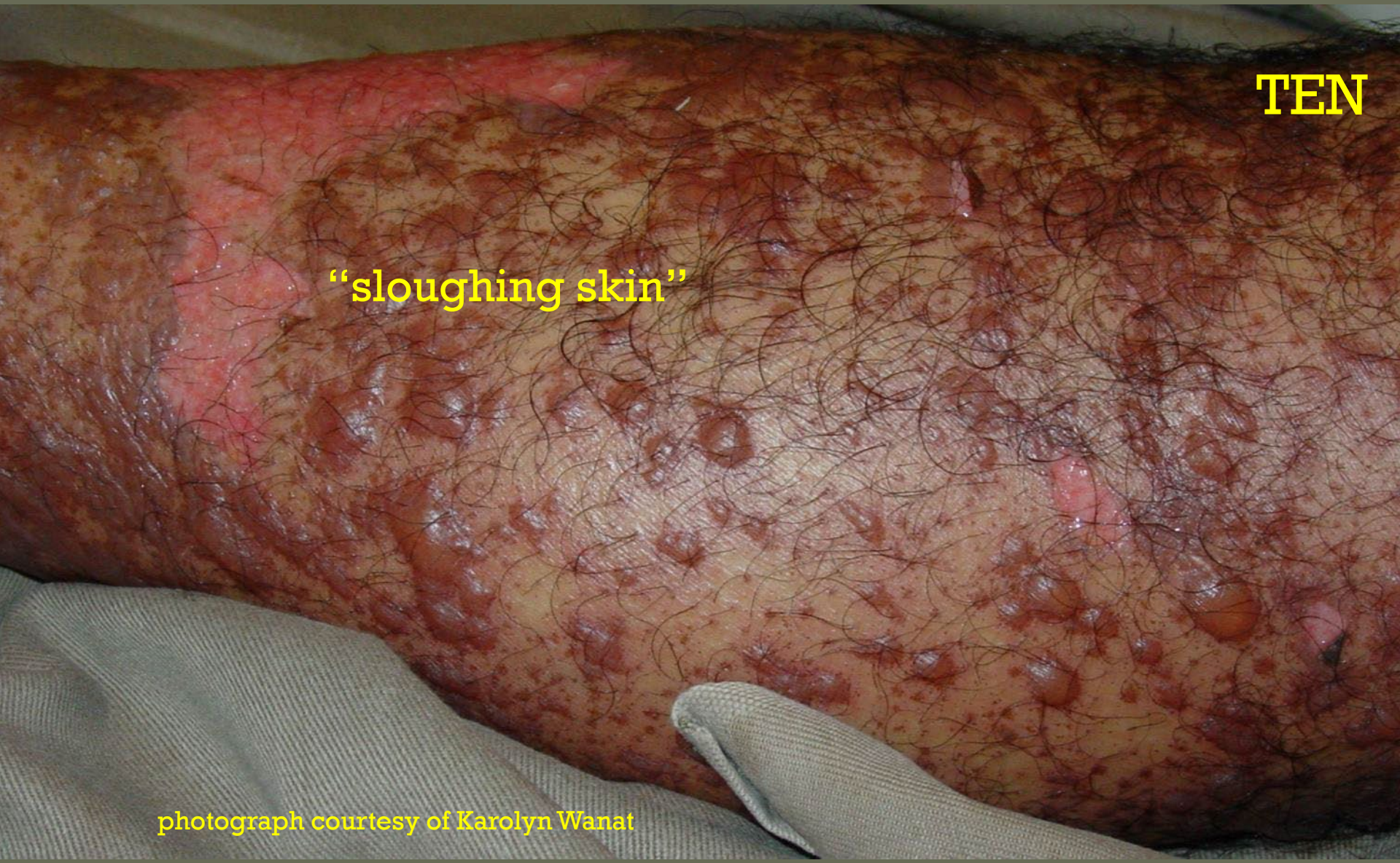
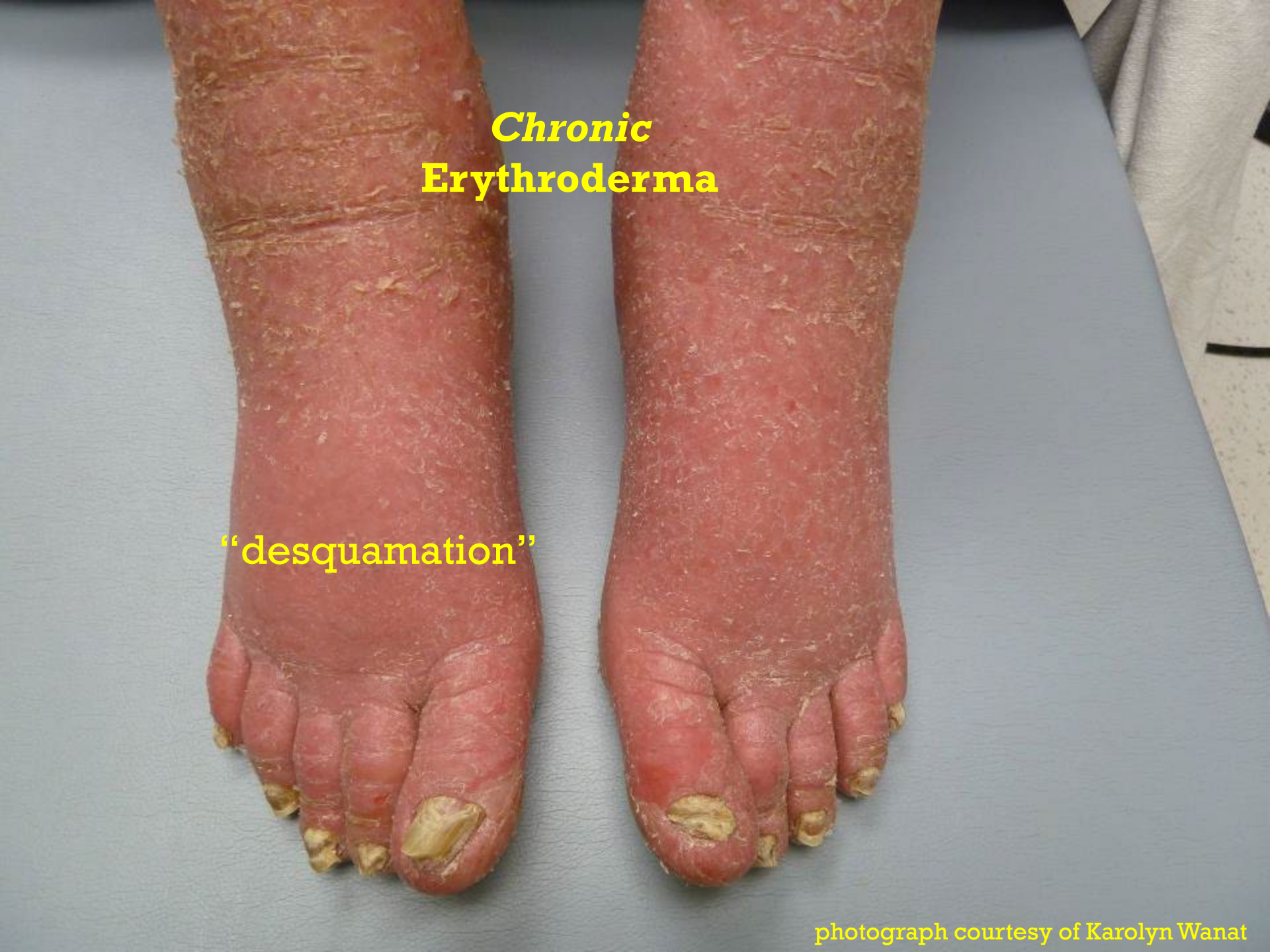

TEN
photograph courtesy of Karolyn Wanat


TEN
photograph courtesy of Brian Swick


TEN
“sloughing skin”
photograph courtesy of Brian Swick


TEN
"sloughing skin"
photograph courtesy of Karolyn Wanat



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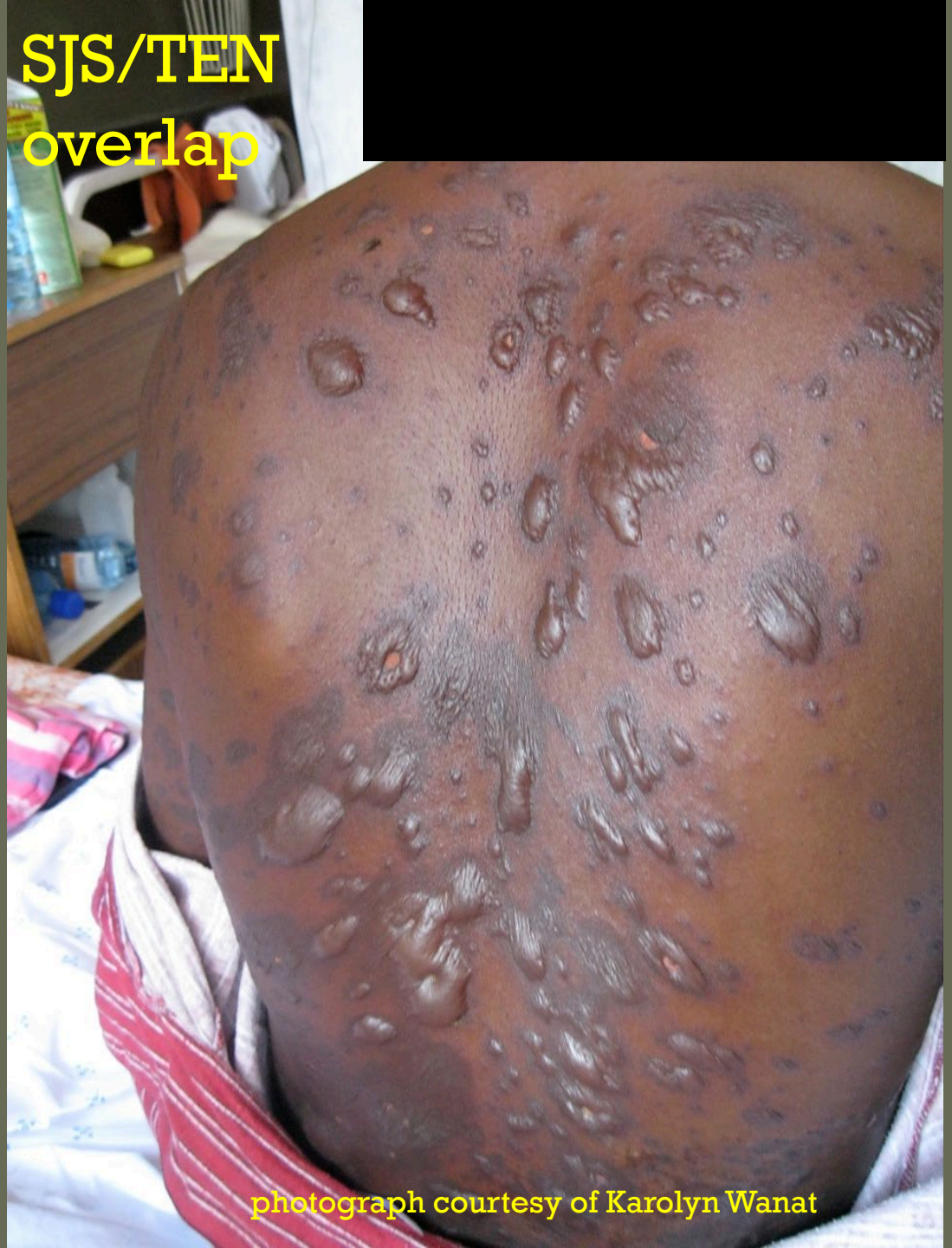
SJS/TEN overlap



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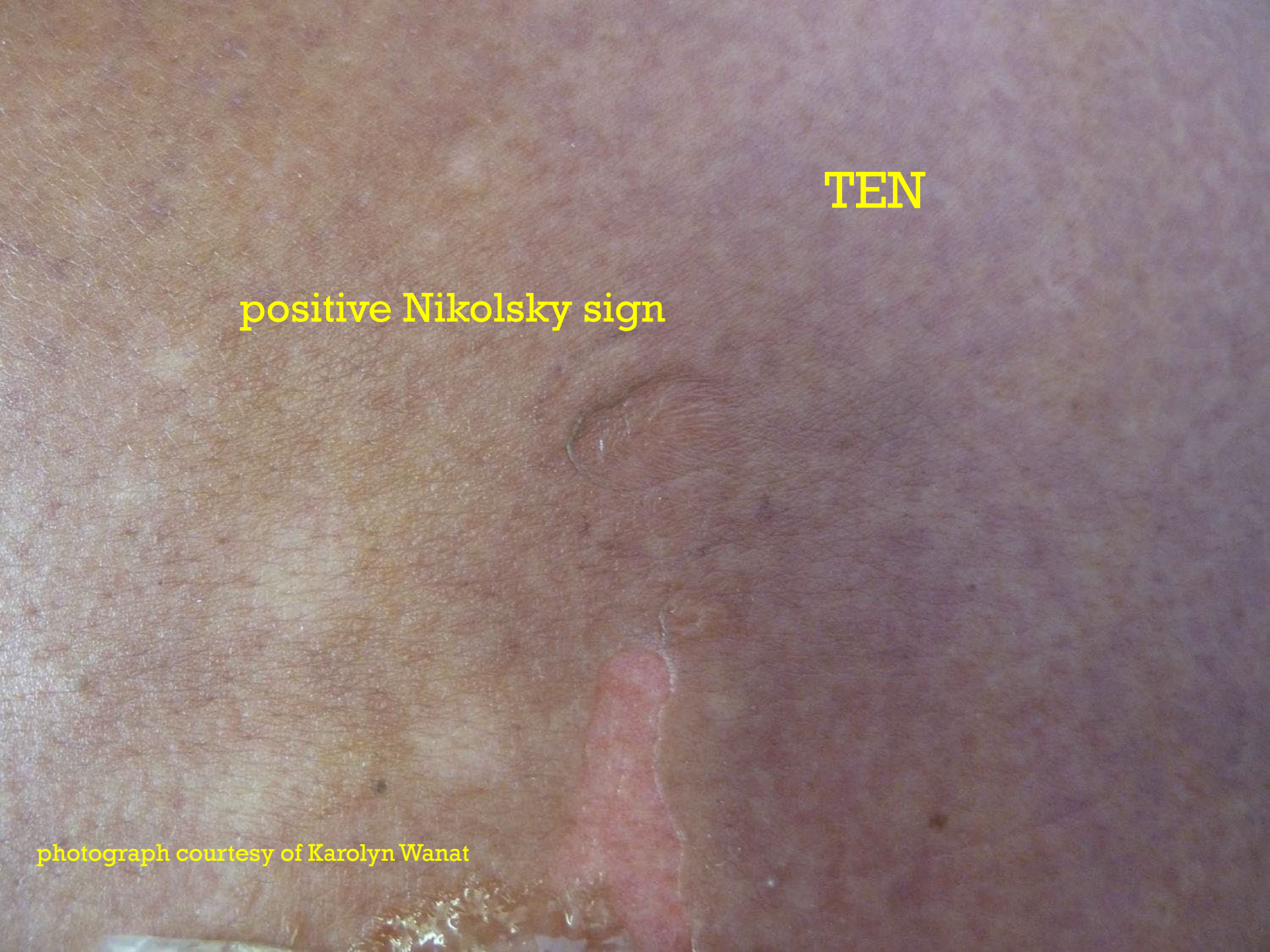
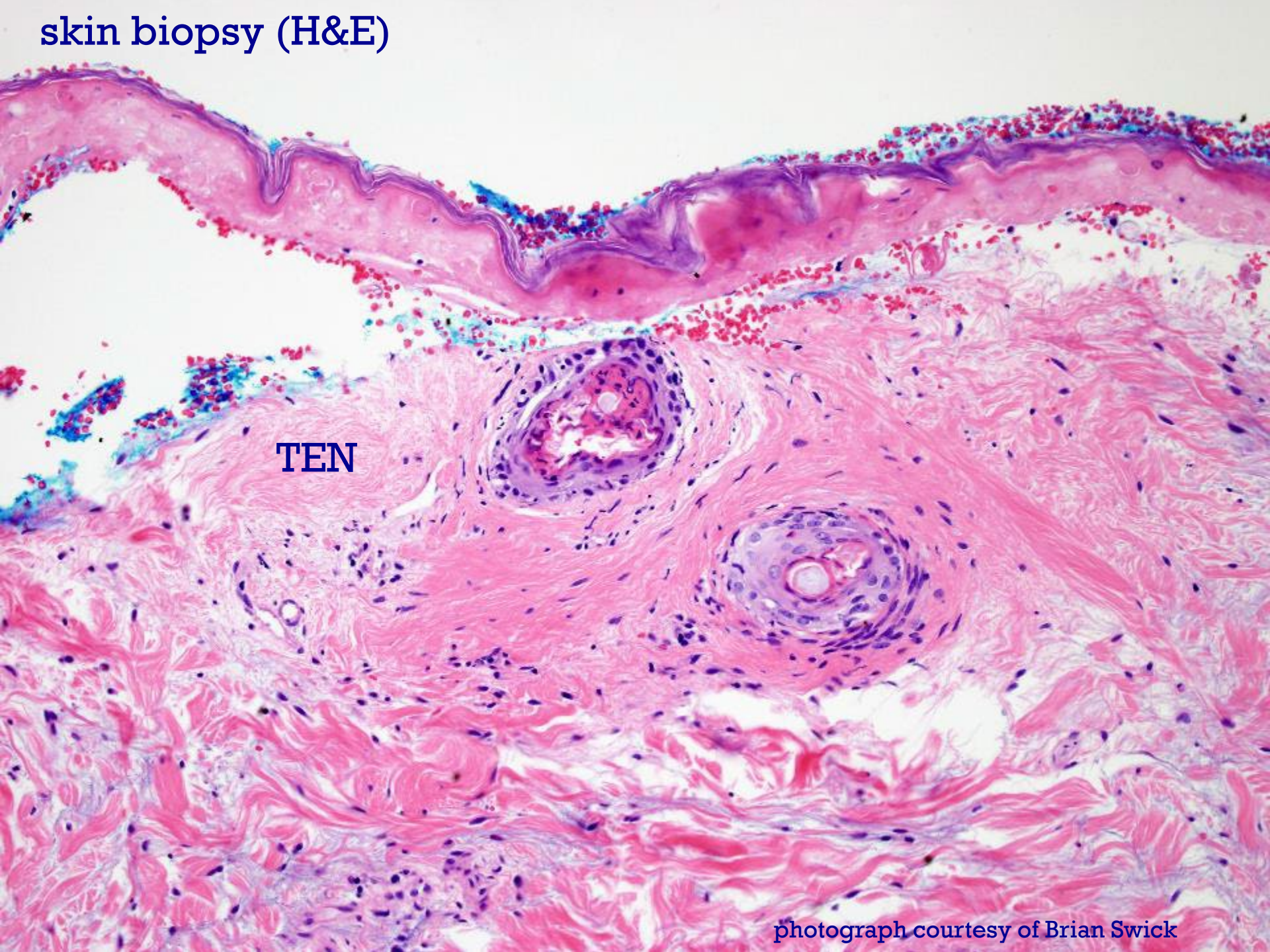

TEN
positive Nikolsky sign
photograph courtesy of Karolyn Wanat

skin biopsy (H&E)



photograph courtesy of Brian Swick

SJS/TEN

- *Acute* and *life-threatening* mucocutaneous eruption
  - Spectrum of severity:
    - Stevens-Johnson Syndrome (SJS) with <10% BSA
    - SJS/toxic epidermal necrolysis (TEN) overlap with 10-30% BSA
    - TEN >30% BSA
- Triggers
  - *Drugs*
    - sulfonamides, nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, sulfasalazine, allopurinol, aminopenicillins, cephalosporins, quinolones, minocycline, NSAIDs (-oxicams)
  - *Infections*
    - Dengue virus, CMV

SJS/TEN

- Associated clinical signs & symptoms
  - *Dusky red initially flat lesions* that can develop bullous epidermal detachment appearing on the trunk > extremities (+Nikolsky sign)
  - Mucosal involvement >80% of cases involving >2 sites, including the oral cavity, nasal cavity, conjunctivae, and genitals
  - Prodrome 1-3 days prior to onset of rash: fever, malaise, myalgias, photophobia, conjunctival itching/burning, odynophagia, dysphagia
  - Skin rash develops 7-21 days following drug exposure, typically associated with burning and pain
  - Bacterial sepsis often results from loss of cutaneous barrier function
  - Survivors can have mucocutaneous scarring

SJS/TEN

- Risk factors
  - Slow acetylator phenotypes
  - Specific human leukocyte antigen (HLA) alleles for MHC class I:
    - HLA-B*1502 allotype in Han Chinese exposed to carbamazepine
    - HLA-A*3101 in all patients exposed to carbamazepine
    - HLA-B*5801 allotype in patients exposed to allopurinol
    - HLA-B*5701 in patients exposed to abacavir
  - Immunocompromised status (e.g. HIV/AIDS)

SJS/TEN

- Prognosis by the SCORETEN

Criteria	Value at *initial* presentation	Value
Age	>40 years	1
Heart rate	>120 beats per minute	1
Malignancy?	Yes	1
Epidermal detachment*	>10% body surface area	1
Blood urea nitrogen	>28 mg/dL (>10 mmol/L)	1
Glucose	>252 mg/dL (>14 mmol/L)	1
Bicarbonate	<20 mEq/L (<20 mmol/L)	1

*Sum of detached and detachable epidermis.

SCORTEN Total	Mortality Rate
0-1	~3.2%
2	~12.1%
3	~35.3%
4	~58.3%
≥5	~90%

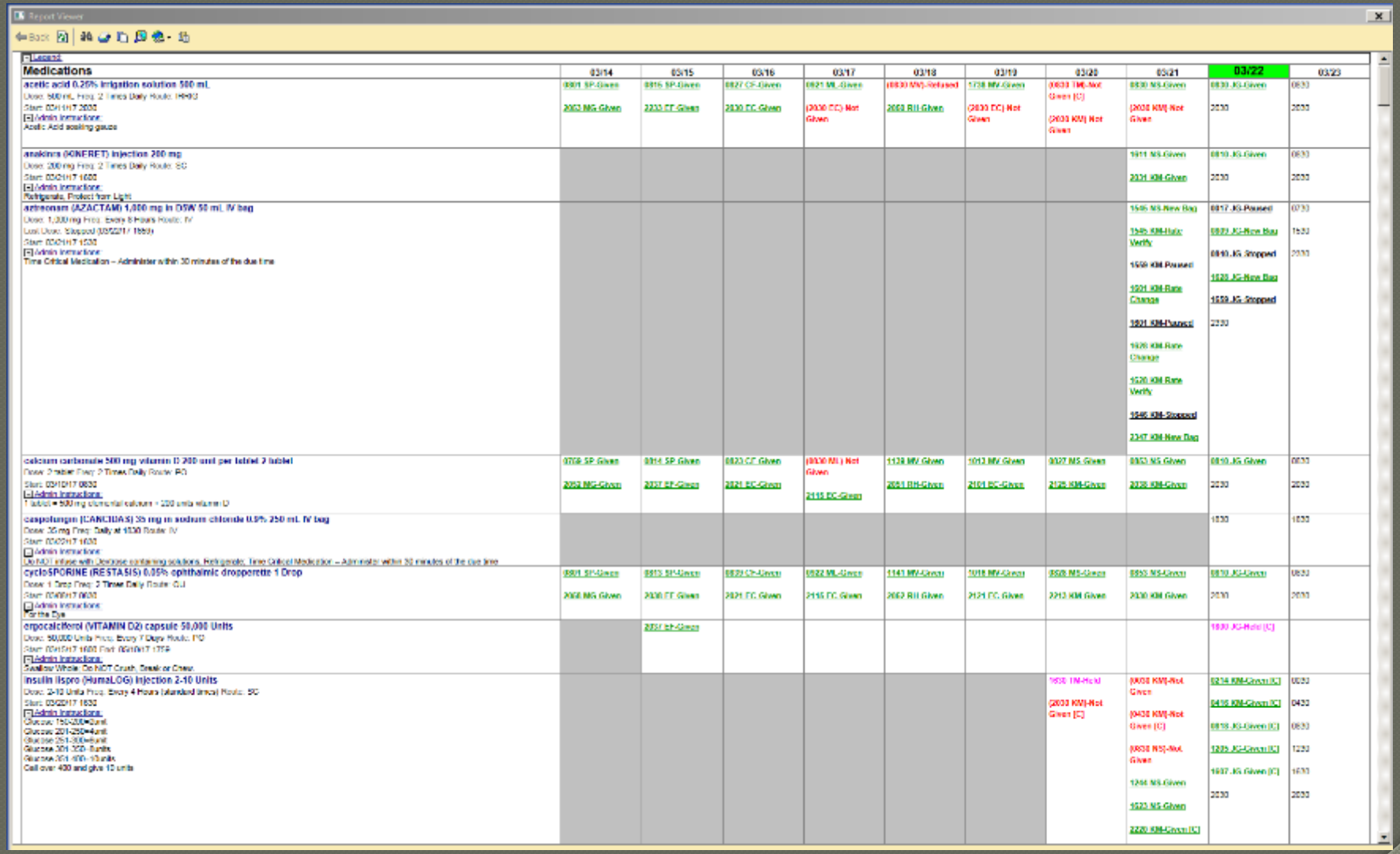
SCORTEN predictions are typically calculated within the first 24 hours following hospital admission, but they have been shown to be roughly valid for up to the first 5 days of hospitalization [18].

SJS/TEN

- Differential diagnosis
  - EM major, staphylococcal scalded skin syndrome, drug-induced linear IgA dermatosis, AGEP, DRESS/DIHS, paraneoplastic pemphigus, acute graft-versus-host disease (GVHD), acute syndrome of apoptotic pan-epidermolysis, morbilliform drug eruption
- Work-up [no evidence-based guidelines]
  - Skin biopsy- specimens for frozen section and permanent mounts
  - Detailed timeline of drug exposures to identify potential culprit drug(s)
  - No definitive laboratory test for identifying the culprit drug
    - Lymphocyte transformation testing
    - Cutaneous patch testing

SJS/TEN

Electronic medication administration reports are helpful!



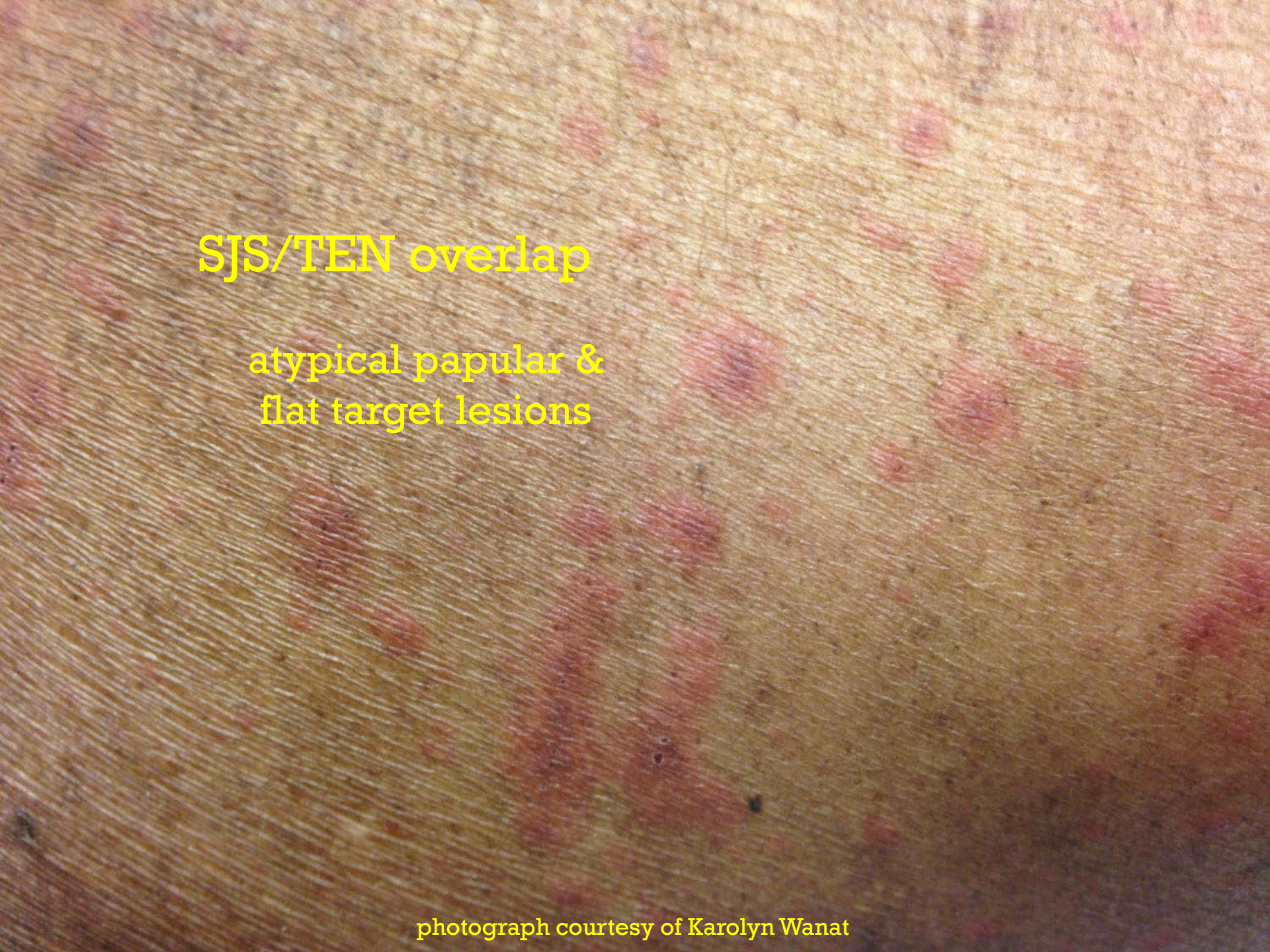
Medications	03/14	03/15	03/16	03/17	03/18	03/19	03/20	03/21	03/22	03/23
acetic acid 0.25% irrigation solution 500 mL Dose: 500 mL Freq: 2 Times Daily Route: IRRIG Start: 03/14/17 2000 [+] Admin Instructions: Acetic Acid soaking gauze	0801 SP-Given 2002 MG-Given	0815 SP-Given 2233 CF-Given	0827 CF-Given 2030 CC-Given	0821 ML-Given (2030 CC) Not Given	(0830 KM)-Refused 2003 RH-Given	1138 MV-Given (2033 CC) Not Given	(0833 TM)-Not Given [C] (2033 KM) Not Given	0830 NS-Given (2033 KM) Not Given	0830 JG-Given 2030	0830 2030
anakinra (KINERET) injection 200 mg Dose: 200 mg Freq: 2 Times Daily Route: SC Start: 03/14/17 1600 [+] Admin Instructions: Refrigerate. Protect from Light								1911 NS-Given 2031 KM-Given	0810 JG-Given 2030	0830 2030
aztreonam (AZACTAM) 1,000 mg in D5W 50 mL IV bag Dose: 1,000 mg Freq: every 8 Hours Route: IV Last Dose: Stopped (03/22/17 1559) Start: 03/14/17 1600 [+] Admin Instructions: Time Critical Medication – Administer within 30 minutes of the due time								1545 NS-New Bag 1545 KM-Hold: Verify 1559 KM-Paused 1601 KM-Rate Change 1601 KM-Changed 1626 KM-Rate Change 1630 KM-Rate Verify 1646 KM-Stopped 2347 KM-New Bag	0817 JG-Paused 0823 JG-New Bag 0840 JG-Stopped 1520 JG-New Bag 1559 JG-Stopped 2330	0730 1530 2030
calcium carbonate 500 mg-vitamin D 200 unit per tablet 2 tablet Dose: 2 tablet Freq: 2 Times Daily Route: PO Start: 03/15/17 0830 [+] Admin Instructions: 1 tablet = 500 mg chemical calcium + 200 units vitamin D	0709 SP-Given 2002 MG-Given	0814 SP-Given 2037 EF-Given	0823 CF-Given 2021 EC-Given	(0830 ML) Not Given 2115 EC-Given	1128 MV-Given 2003 RH-Given	1013 MV-Given 2101 EC-Given	0927 NS-Given 2125 KM-Given	0953 NS-Given 2038 KM-Given	0810 JG-Given 2030	0830 2030
caspofungin (CANCIDAS) 35 mg in sodium chloride 0.9% 250 mL IV bag Dose: 35 mg Freq: Daily at 1030 Route: IV Start: 03/20/17 1030 [+] Admin Instructions: Do NOT infuse with Dextrose containing solutions. Hold orders: Time Critical Medication – Administer within 30 minutes of the due time									1030	1030
cyclosPORINE (RESTASIS) 0.05% ophthalmic dropperette 1 Drop Dose: 1 Drop Freq: 2 Times Daily Route: OU Start: 03/20/17 0930 [+] Admin Instructions: For the Eye	0801 SP-Given 2002 MG-Given	0815 SP-Given 2030 EF-Given	0827 CF-Given 2021 EC-Given	0822 ML-Given 2115 EC-Given	1141 MV-Given 2003 RH-Given	1018 MV-Given 2121 EC-Given	0908 NS-Given 2213 KM-Given	0953 NS-Given 2030 KM-Given	0810 JG-Given 2030	0830 2030
ergocalciferol (VITAMIN D2) capsule 50,000 Units Dose: 50,000 Units Freq: Every 7 Days Route: PO Start: 03/15/17 1600 End: 03/15/17 1759 [+] Admin Instructions: Swallow Whole. Do NOT Crush, Break or Chew		2037 EF-Given							1630 JG-Held [C]	
insulin lispro (HumaLOG) injection 2-10 Units Dose: 2-10 Units Freq: Every 4 Hours (standard time) Route: SC Start: 03/20/17 1630 [+] Admin Instructions: Glucose 150-200=2unit Glucose 201-250=4unit Glucose 251-300=6unit Glucose 301-350= 8units Glucose 351-400= 10units Call over 400 and give 10 units							1630 TM-Held (2003 KM)-Not Given [C]	(0430 KM)-Not Given (0430 KM)-Not Given [C] (0530 NS)-Not Given 1246 NS-Given 1521 NS-Given 2220 KM-Given [C]	1214 KM-Given [C] 0416 KM-Given [C] 0838 JG-Given [C] 1235 JG-Given [C] 1637 JG-Given [C] 2030	0030 0430 0830 1230 1630 2030

SJS/TEN

- **Management**
  - *STOP THE OFFENDING DRUG*
  - Transfer to ICU, burn unit, or other specialty unit capable of providing intensive nursing support focused on:
    - Reconstitution of the epidermal barrier
    - Restoration of fluid balance
    - Minimization of potential of ocular complications
    - Monitoring & prevention of infection
  - No evidence-based guidelines for adjunctive therapies
    - IVIg
    - Steroids
    - Cyclosporine
    - TNF-α inhibitors

    } Maybe some low-level evidence of benefit…

photograph courtesy of Karolyn Wanat



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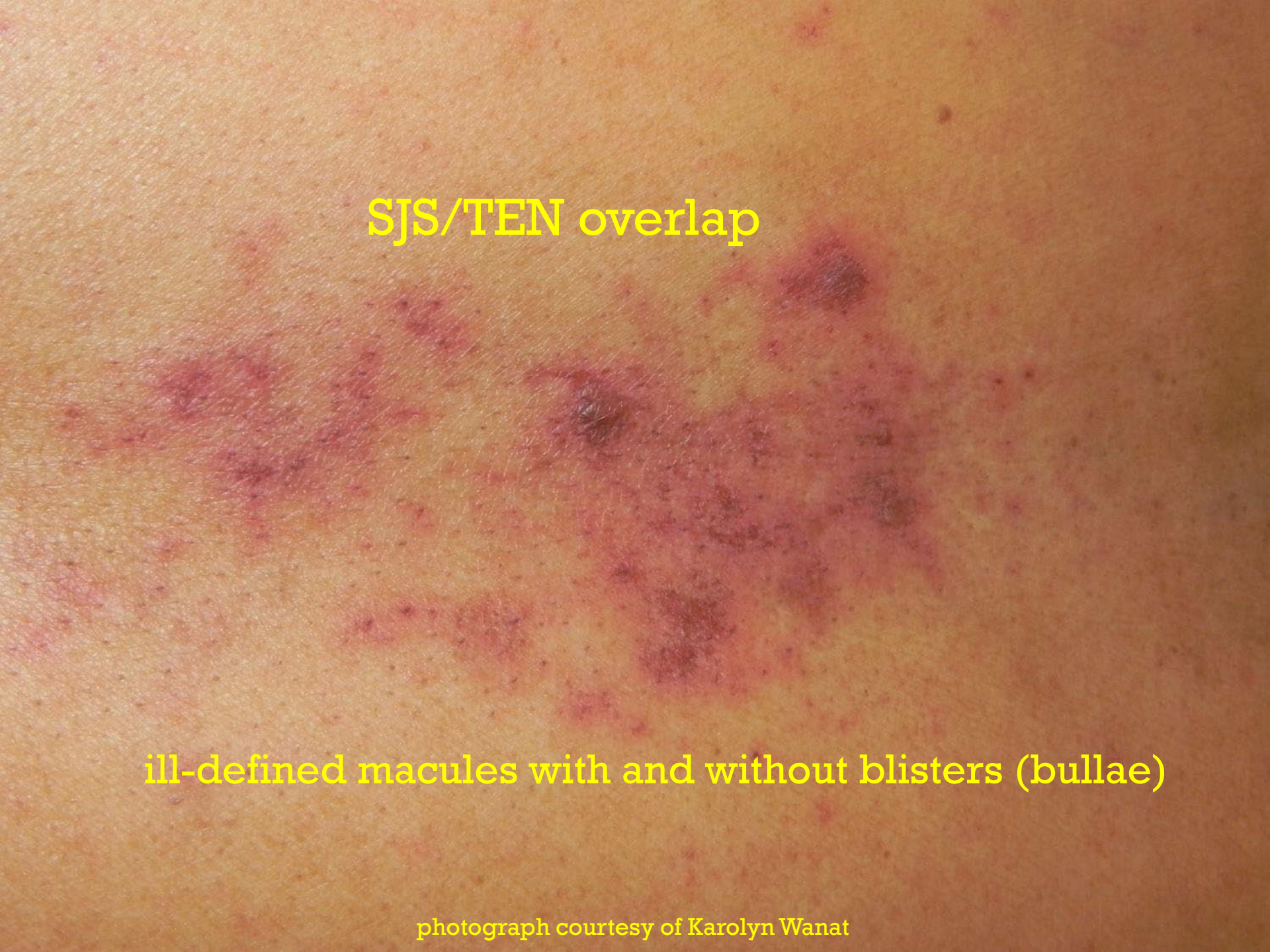
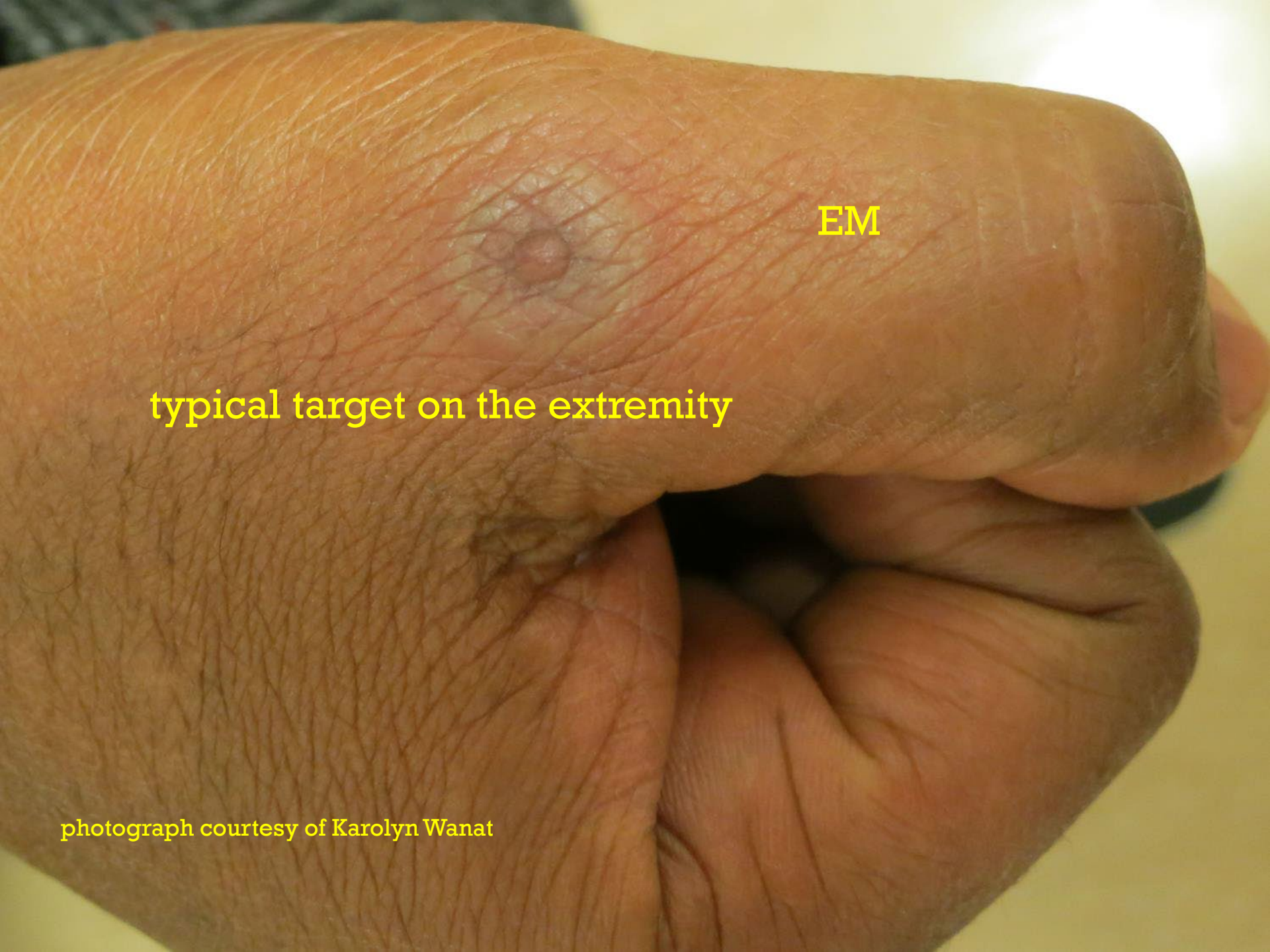
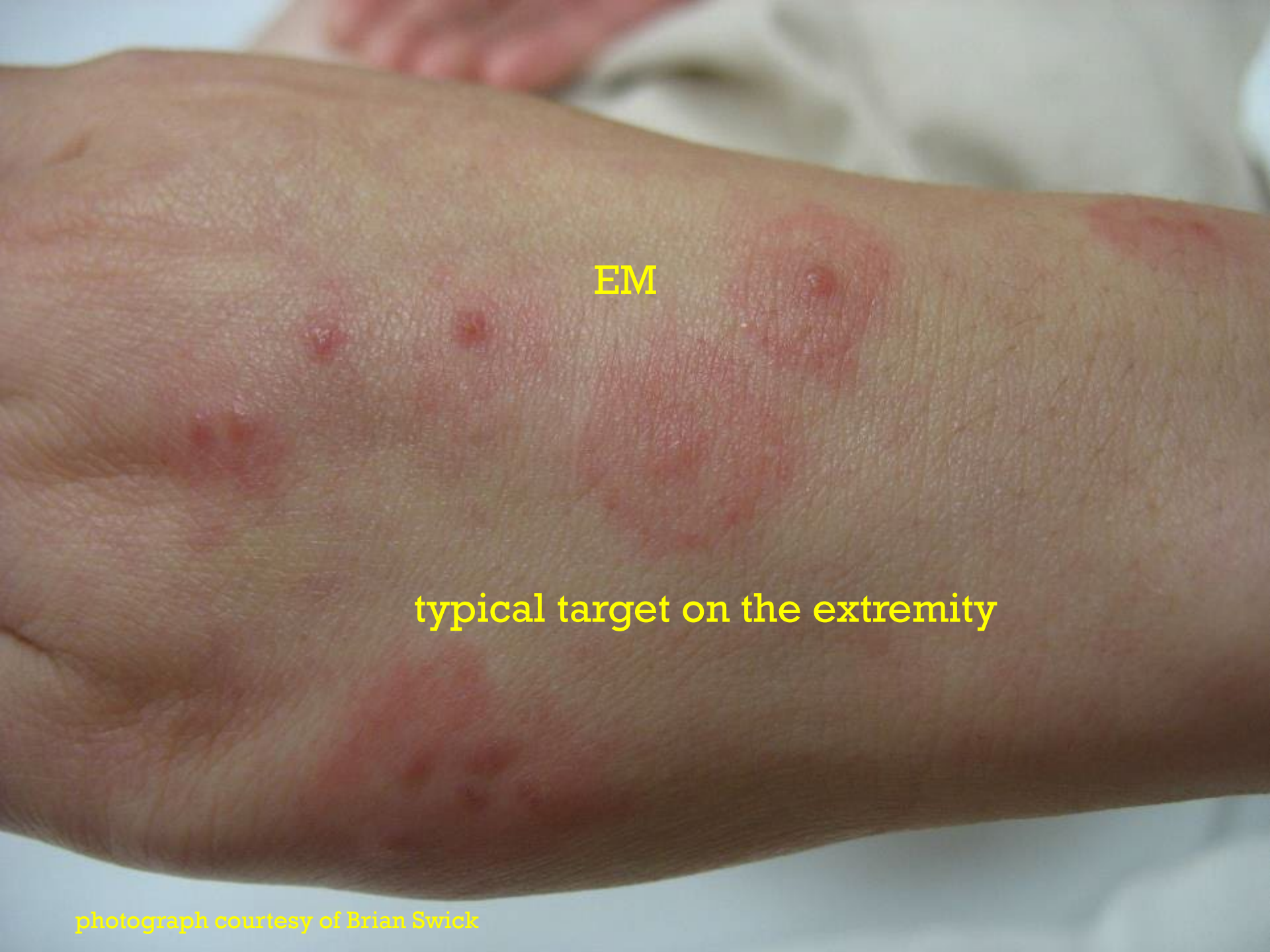

SJS/TEN overlap
ill-defined macules with and without blisters (bullae)
photograph courtesy of Karolyn Wanat


EM
typical target on the extremity
photograph courtesy of Karolyn Wanat

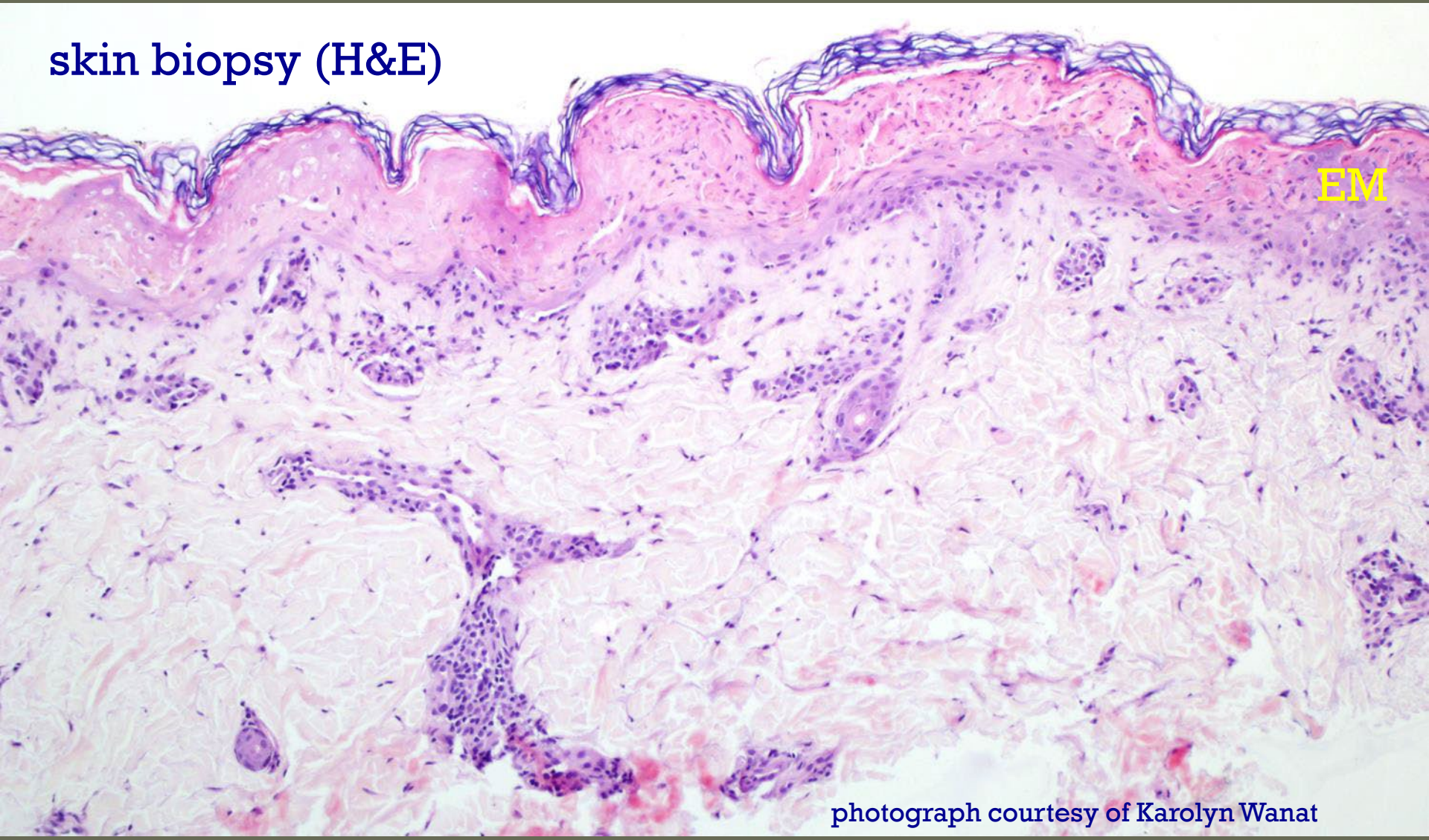


photograph courtesy of Brian Swick

SJS/TEN overlap

photograph courtesy of Brian Swick

skin biopsy (H&E)



photograph courtesy of Karolyn Wanat

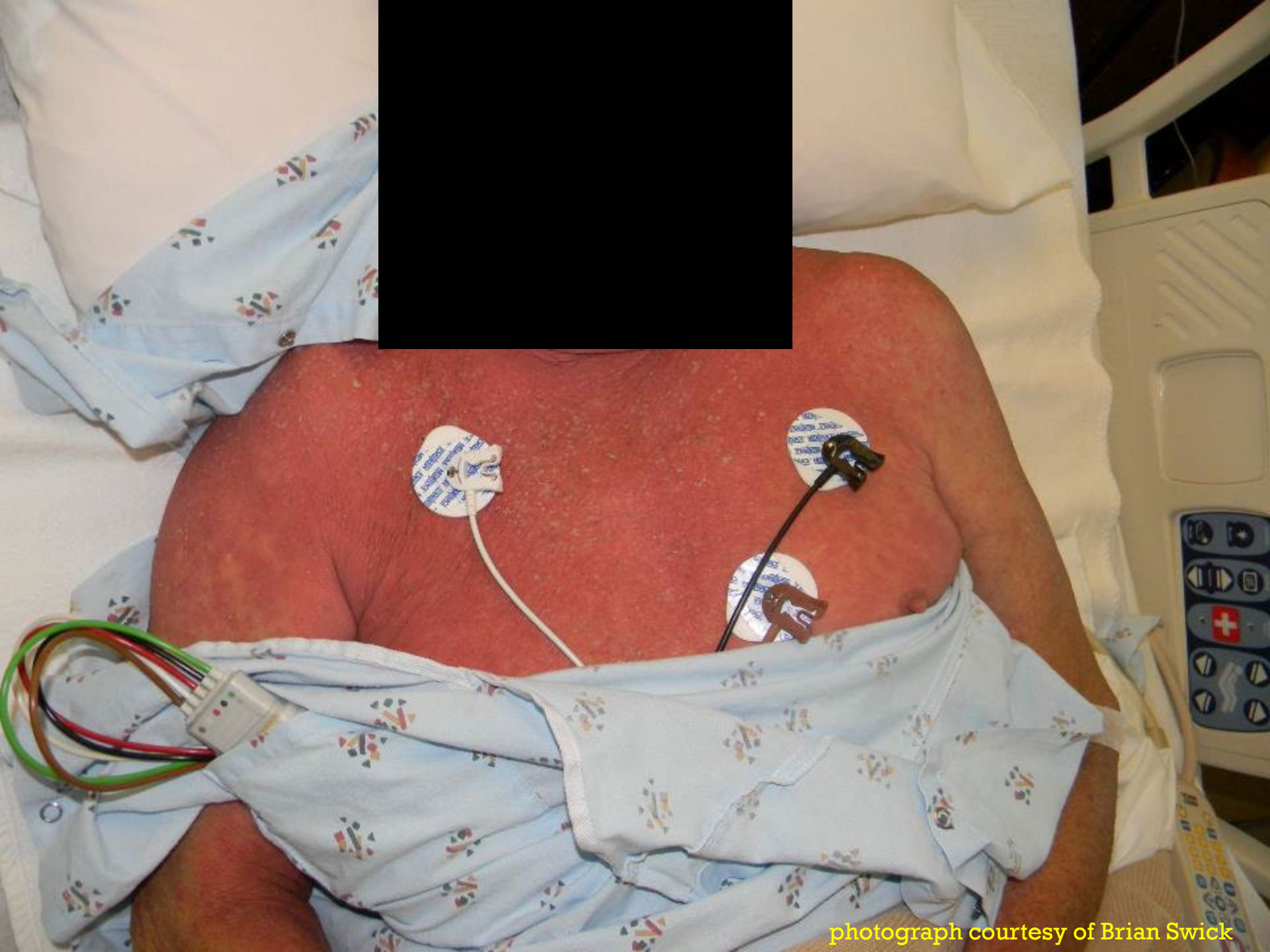
Biopsy is <u>not</u> always helpful in distinguishing between EM and SJS/TEN

SJS/TEN or Erythema Multiforme (EM)?

- Significant overlap in clinical and histopathologic findings
- Historically thought to represent one *spectrum* of disease
- Based on consensus diagnostic criteria, epidemiologic studies have since suggested:
  - EM is a distinct disease triggered by *infection*
  - SJS/TEN is a disease spectrum triggered by *drug exposure*
- Distinguishing between EM and SJS/TEN has important implications with regards to clinical treatment & prognosis
  - EM *is not* typically life-threatening
  - SJS/TEN *is* life-threatening

SJS/TEN Clinical Pearls

- SJS/TEN versus Morbilliform Drug Eruptions (MDEs)
  - MDEs are not painful (usually itchy)
  - MDEs have no signs of active or impending epidermal detachment
  - MDEs will *not* be associated with prodrome or fever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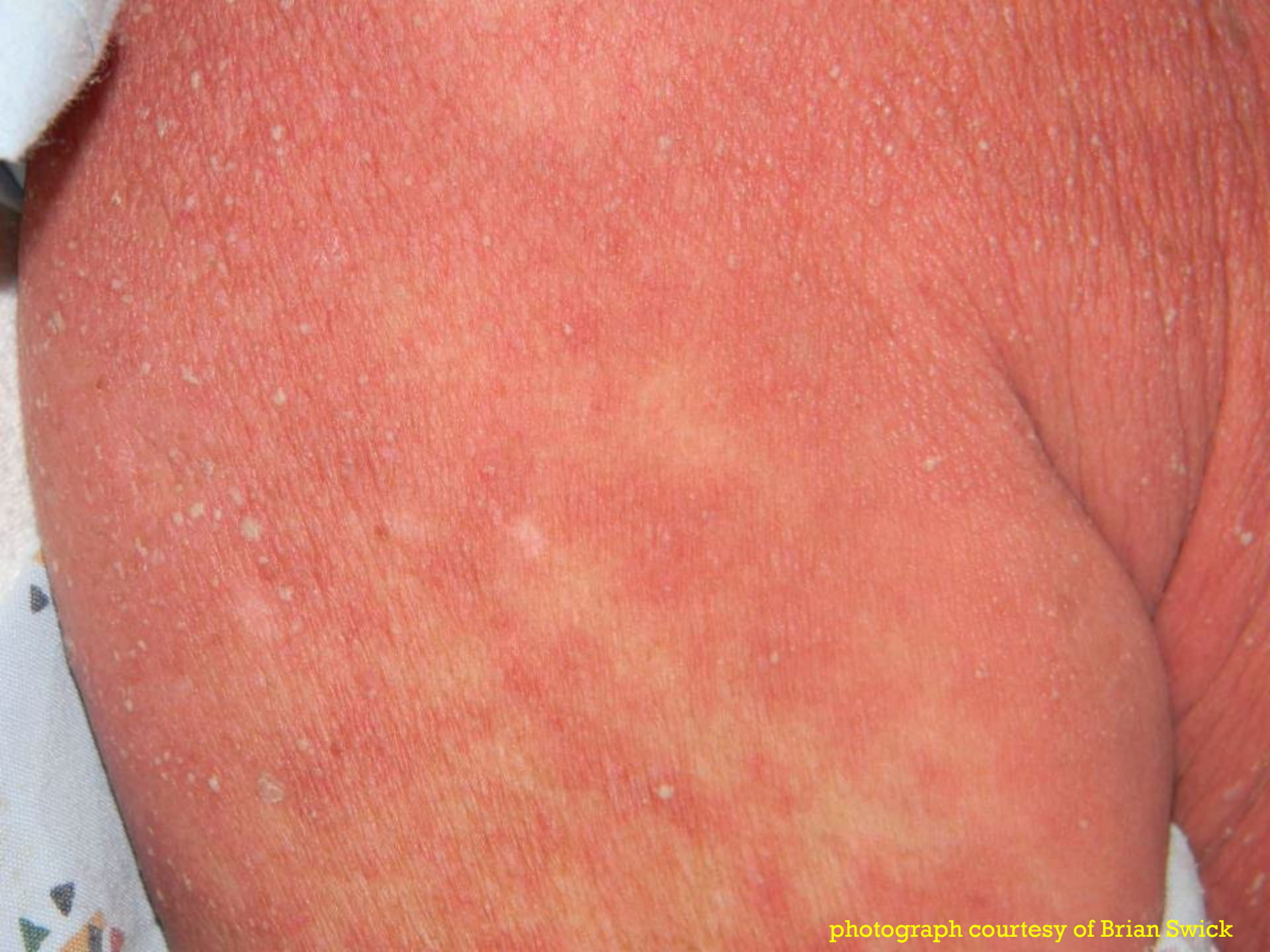
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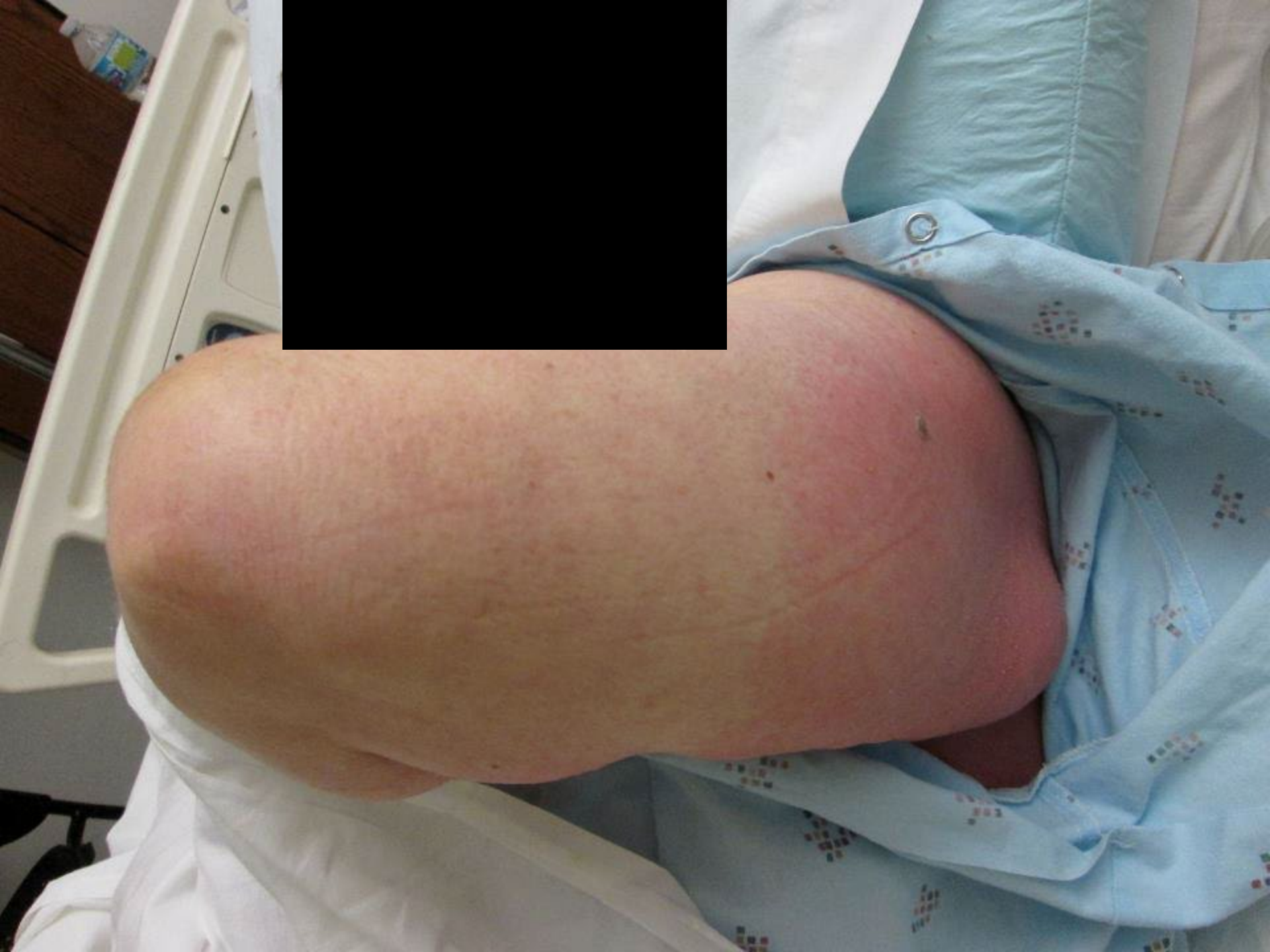
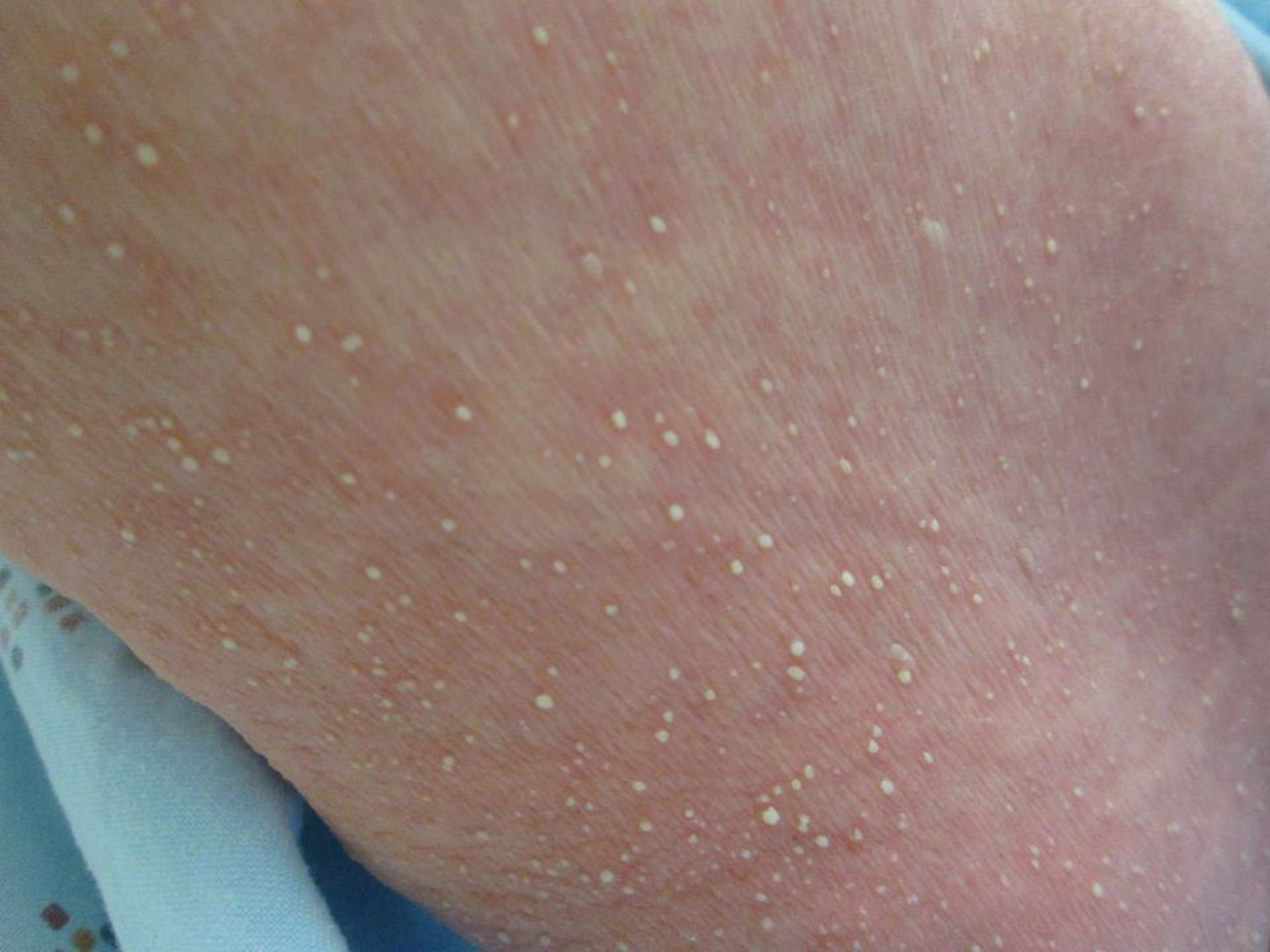
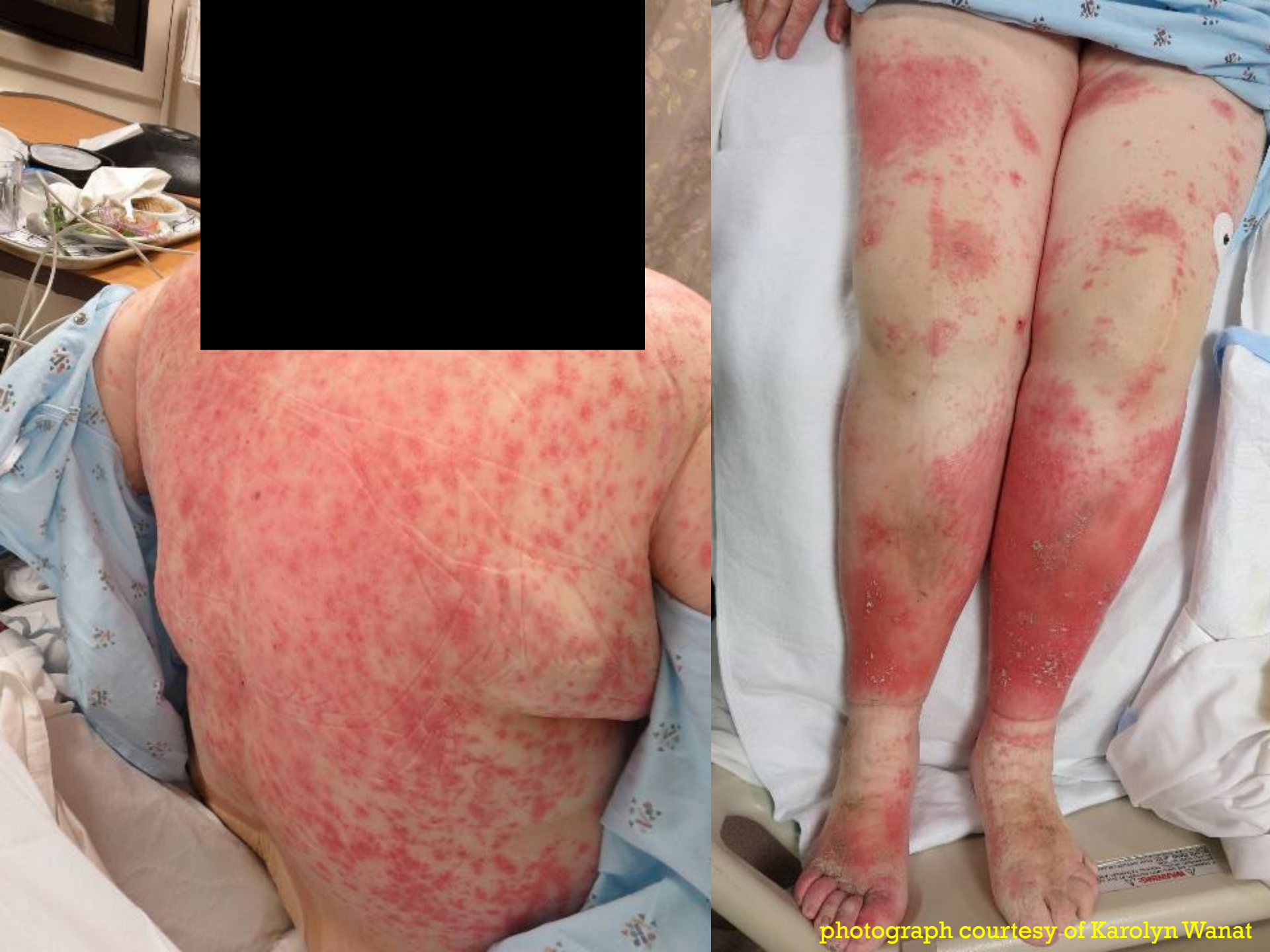
Acute Generalized Exanthematous Pustulosis (AGEP)

photograph courtesy of Brian Swick



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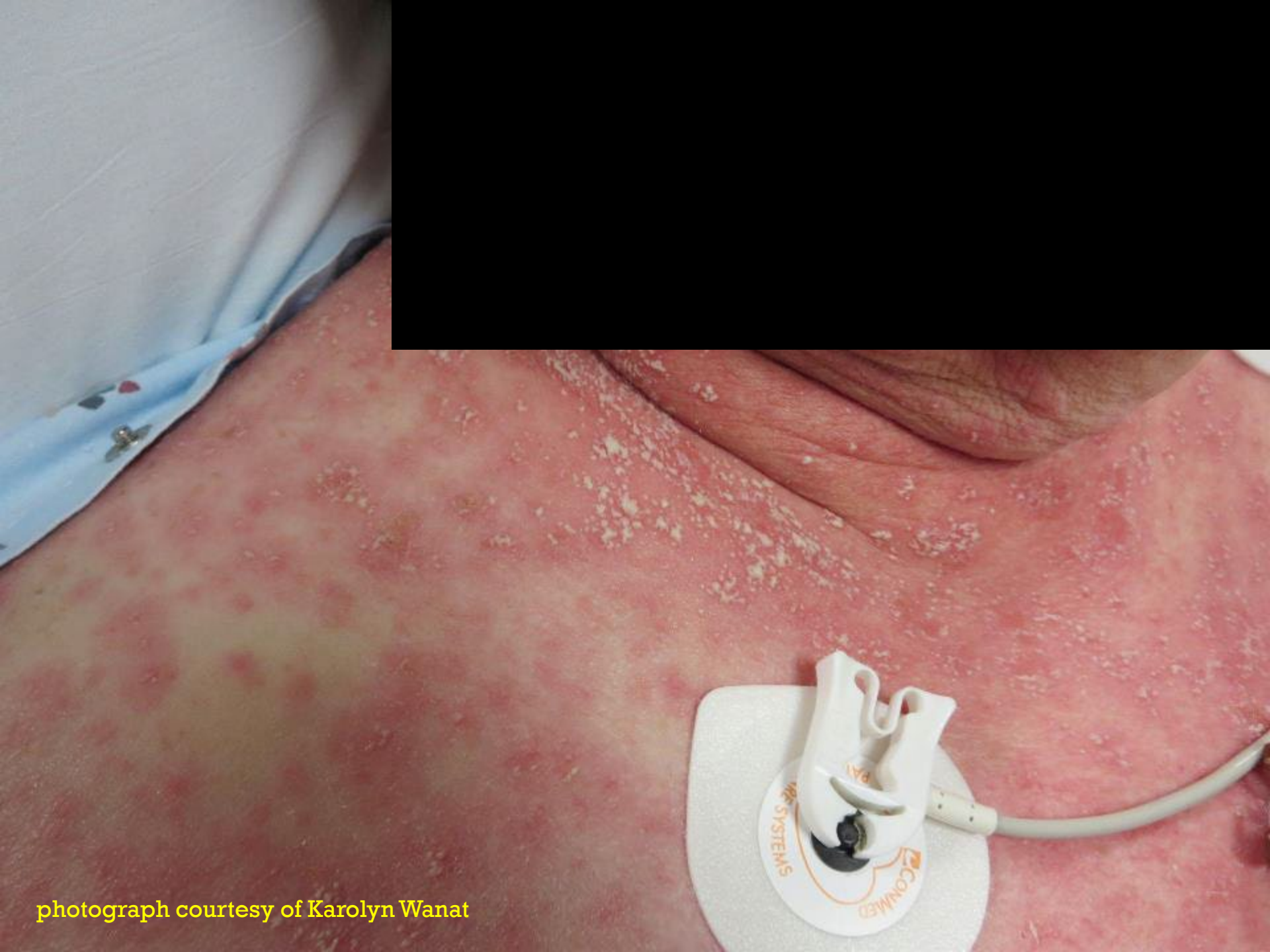

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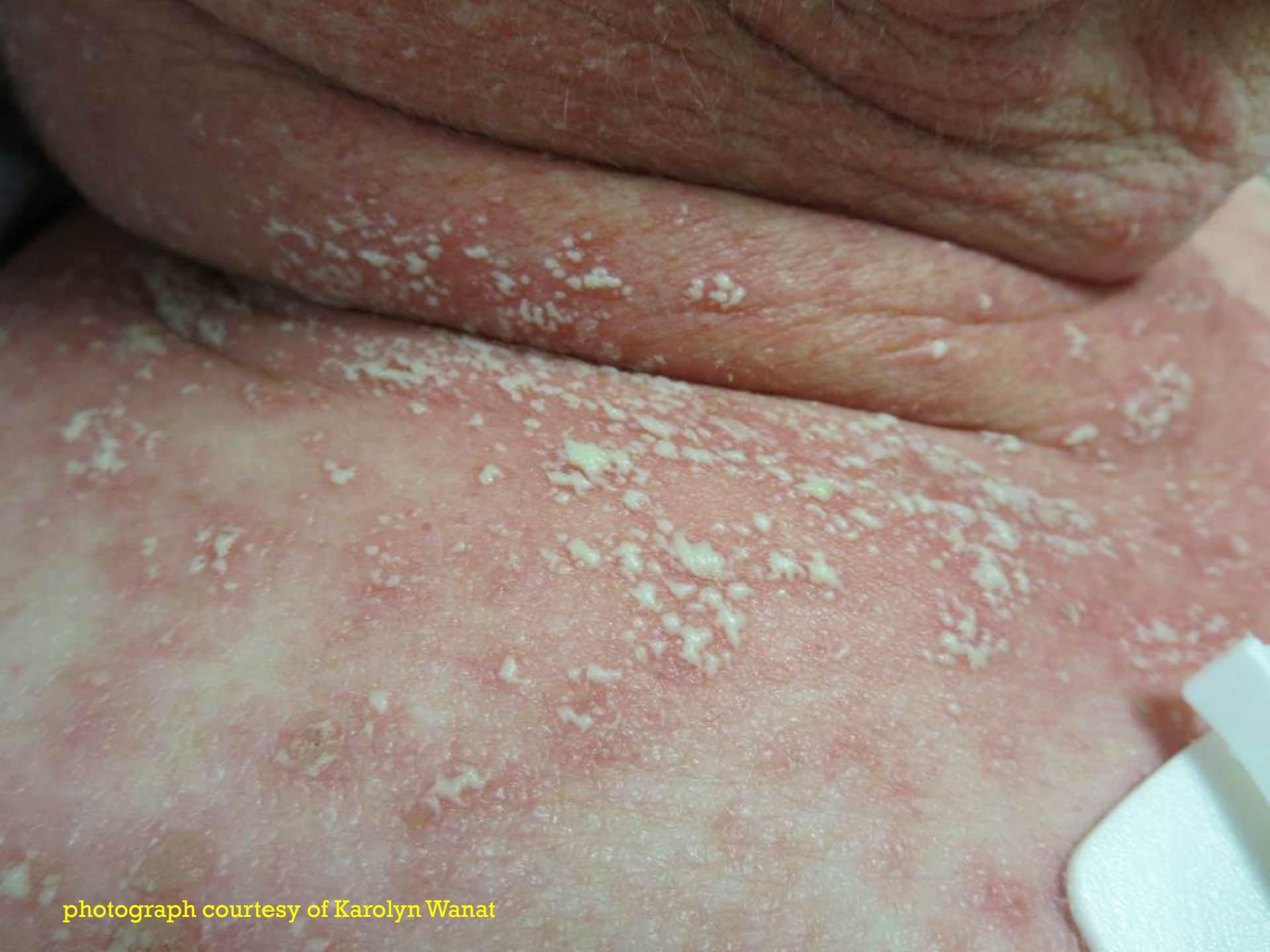

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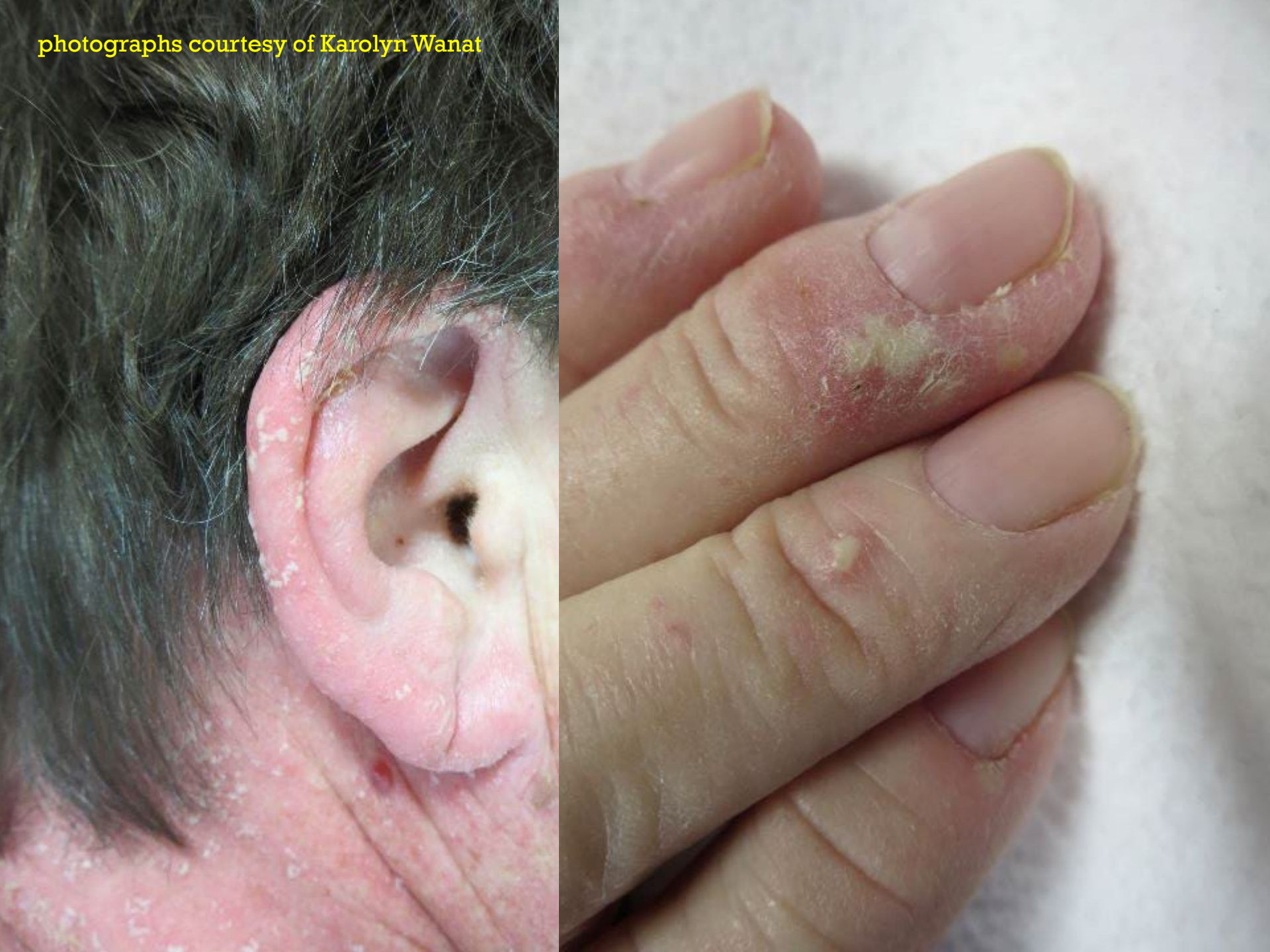

photographs courtesy of Karolyn Wanat

AGEP

- *Acute* and potentially *life-threatening* cutaneous eruption
- Triggers
  - ***Drugs***
    - *Antimicrobials*:
      aminopenicillins, penicillins, cephalosporins, macrolides, quinolones, sulfonamides, terbinafine, ketoconazole, fluconazole, metronidazole, isoniazid, vancomycin
    - *Calcium channel blockers*: diltiazem
    - *Antimalarials*: hydroxychloroquine
    - *Others*: acetaminophen, carbamazepine
  - ***Infections***
    - *Viral*: EBC, CMV, enterovirus, adenovirus, parvovirus
    - Bacterial: chlamydia pneumoniae

AGEP

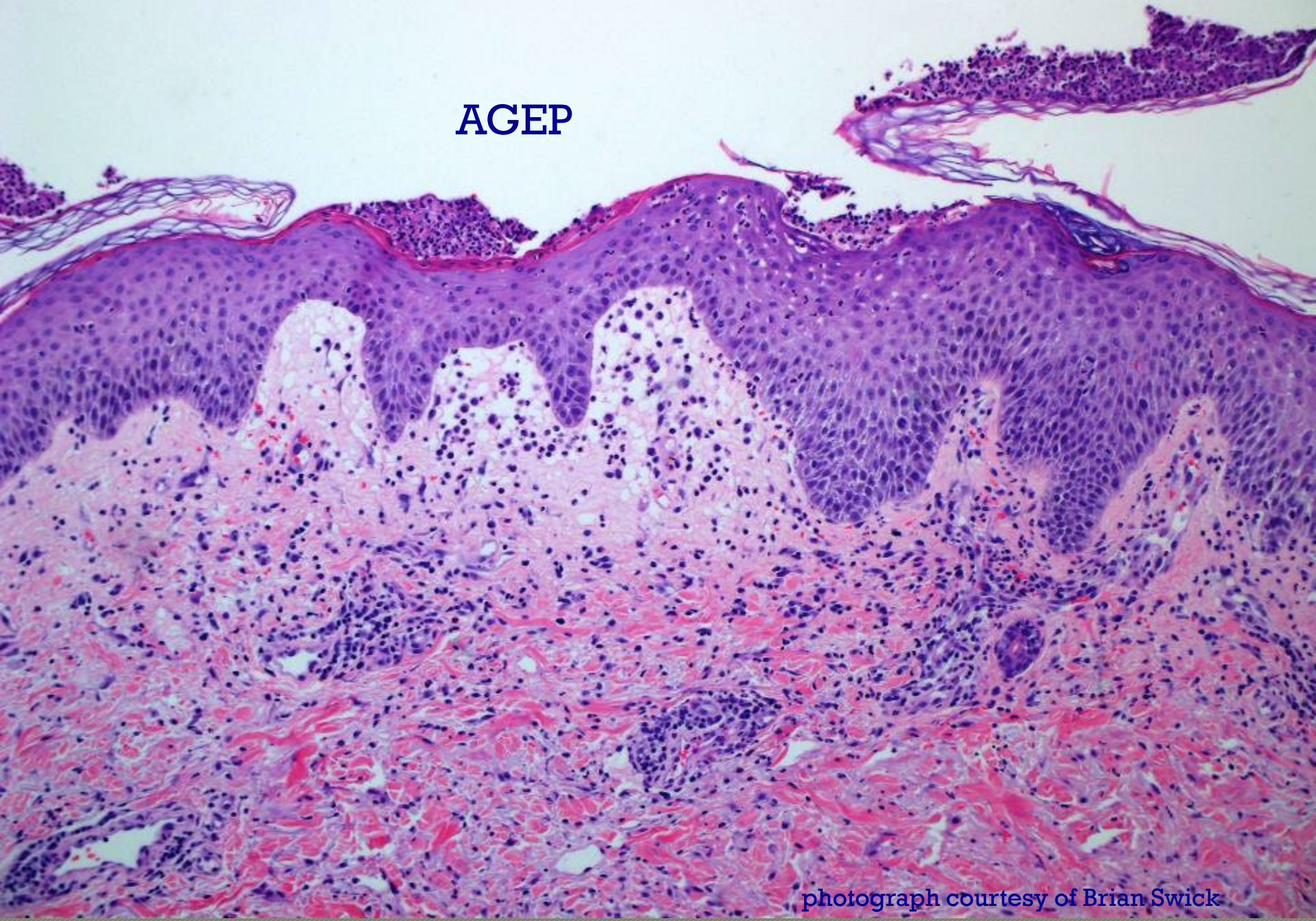
- Associated clinical signs & symptoms
  - CHARACTERISTIC MORPHOLOGY
    Sterile non-follicular pustules on an erythematous background that develop symmetrically within the body folds (intertriginous areas)
  - Rash begins ~48 hours following drug exposure, associated with fever >38°C and pruritus or mild burning sensations of the skin
  - No specific prodrome
  - *Rare* mucous membrane involvement
  - Rash resolves within 4-15 days following discontinuation of the offending drug, accompanied by superficial *desquamation*

AGEP

- Associated clinical signs & symptoms
  - Hematologic (common)
    - leukocytosis with neutrophilia
    - transient eosinophilia (~20-30% of cases)
  - Renal insufficiency (rare)
  - Pulmonary dysfunction (rare)
  - Hemodynamic instability (rare)
- Risk factors
  - Mutations in the IL-36 receptor antagonist
  - Markedly elevated CRP levels and neutrophil counts may carry an increased risk for internal organ involvement

skin biopsy (H&E)

AGEP



photograph courtesy of Brian Swick

Diagnosis: EuroSCAR criteria

AGEP

Variable	Score
Morphology	
Pustules	
Typical	+2
Compatible with disease	+1
Insufficient	0
Erythema	
Typical	+2
Compatible with disease	+1
Insufficient	0
Clinical course	
Mucous membrane involvement	
Yes	-2
No	0
Acute onset	
Yes	0
No	-2
Resolution within 15 days	
Yes	0
No	-2
Fever ≥38°C	
Yes	+1
No	0
Neutrophils ≥7000 cells/μL	
Yes	+1
No	0
Histopathology	
Other disease	-10
Not representative of AGEP	0
Exocytosis of neutrophils	+1
Subcorneal and/or intraepidermal pustules NOS with or without papillary edema	+2
Subcorneal and/or intraepidermal spongiform pustules with papillary edema	+3

NOS: not otherwise specified

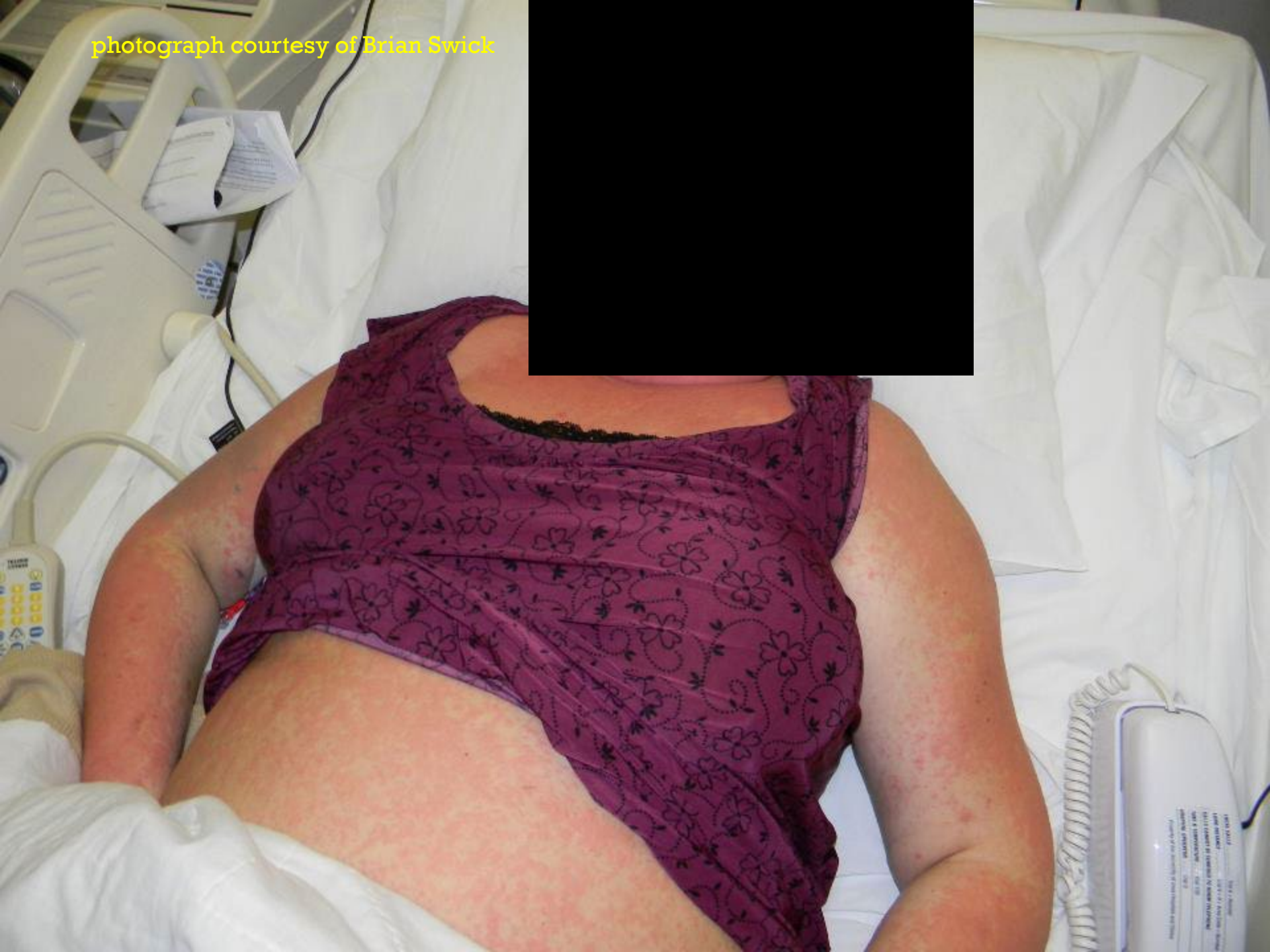
Total score:
≤0 non-diagnostic
1-4 possible AGEP
5-7 probable AGEP
8-12 definitive AGEP

AGEP

- Differential diagnosis
  - follicular and acneiform pustular eruptions like bacterial or pityrosporum folliculitis; steroid acne; impetigo; cutaneous candidiasis; tinea corporis; neutrophilic eruptions like Sweet's syndrome; staphylococcal scalded skin syndrome; pustular psoriasis; subcorneal pustular dermatosis; DRESS/DIHS; SJS/TEN
- Work-up [no evidence-based guidelines]
  - CLINICAL DIAGNOSIS, but skin biopsy can be supportive
  - Detailed timeline of drug exposures to identify potential culprit drug(s)
  - No definitive laboratory tests for identifying the culprit drug
    - Lymphocyte transformation testing
    - Cutaneous patch testing

AGEP

- Management [no evidence-based guidelines]
  - *Immediate withdrawal of the culprit drug*
  - Symptomatic treatment:
    - Antihistamines
    - Antipyretics
    - Mid-potency topical steroid (triamcinolone 0.1% ointment/cream)
    - Emollients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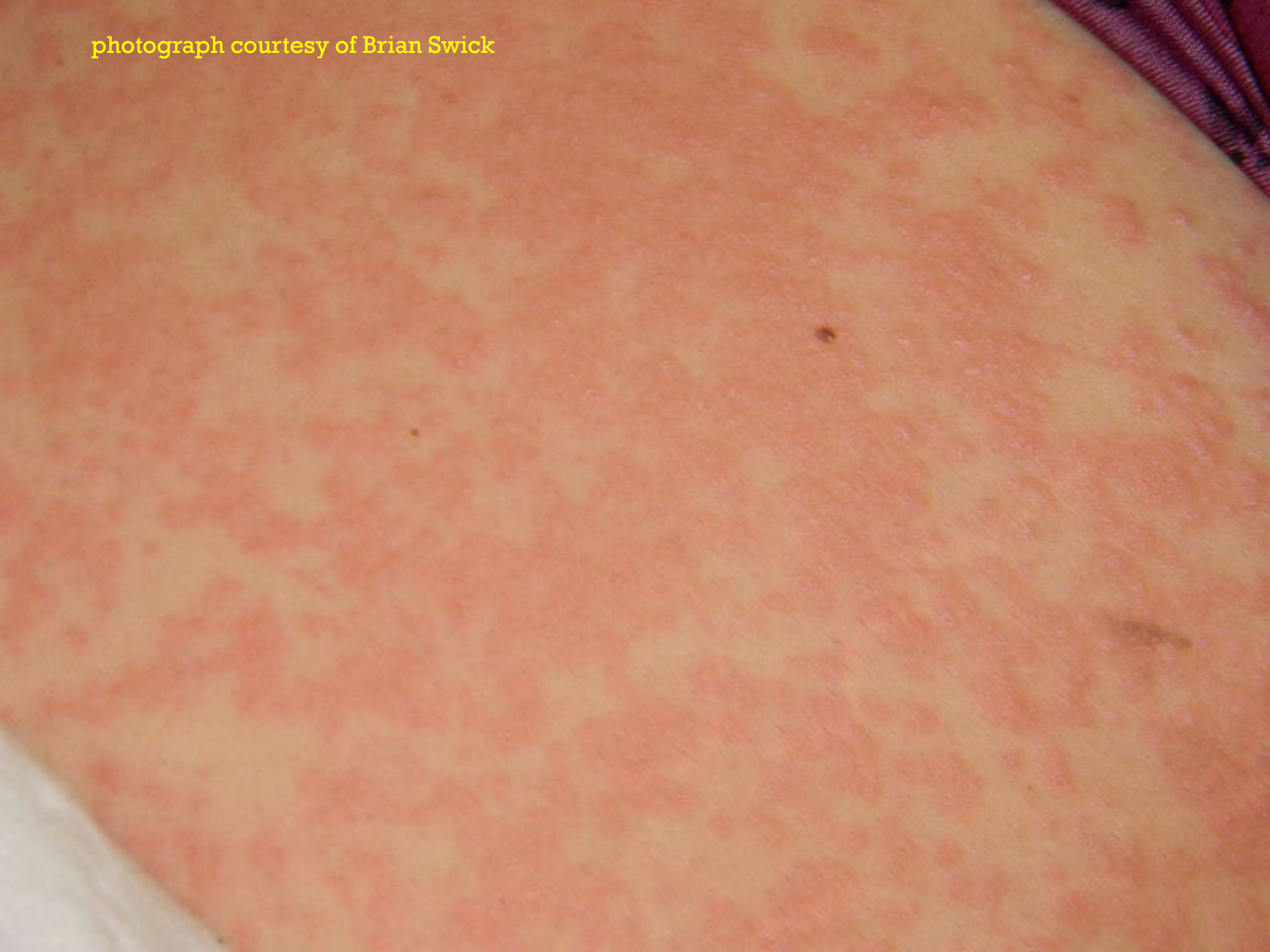
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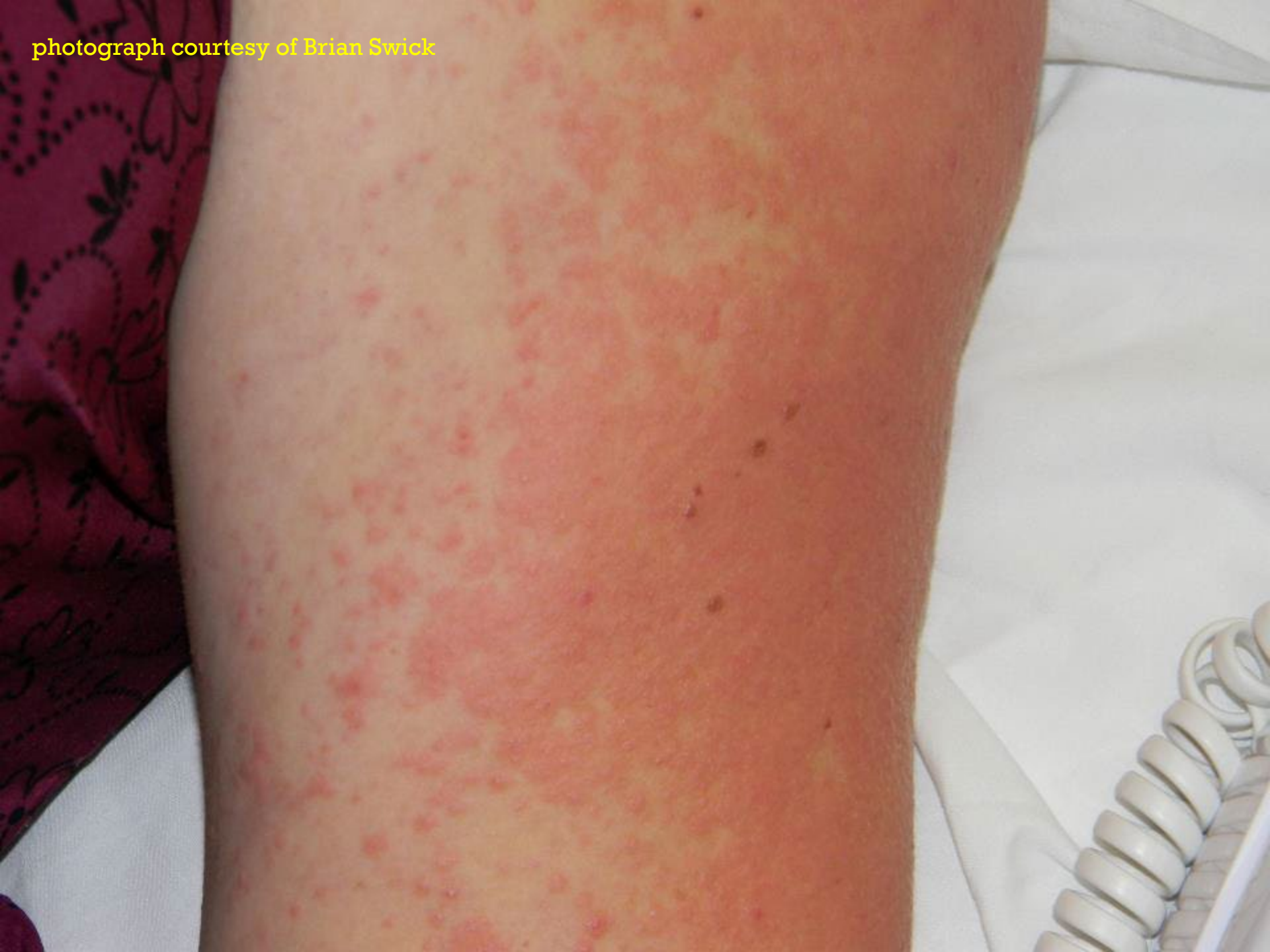
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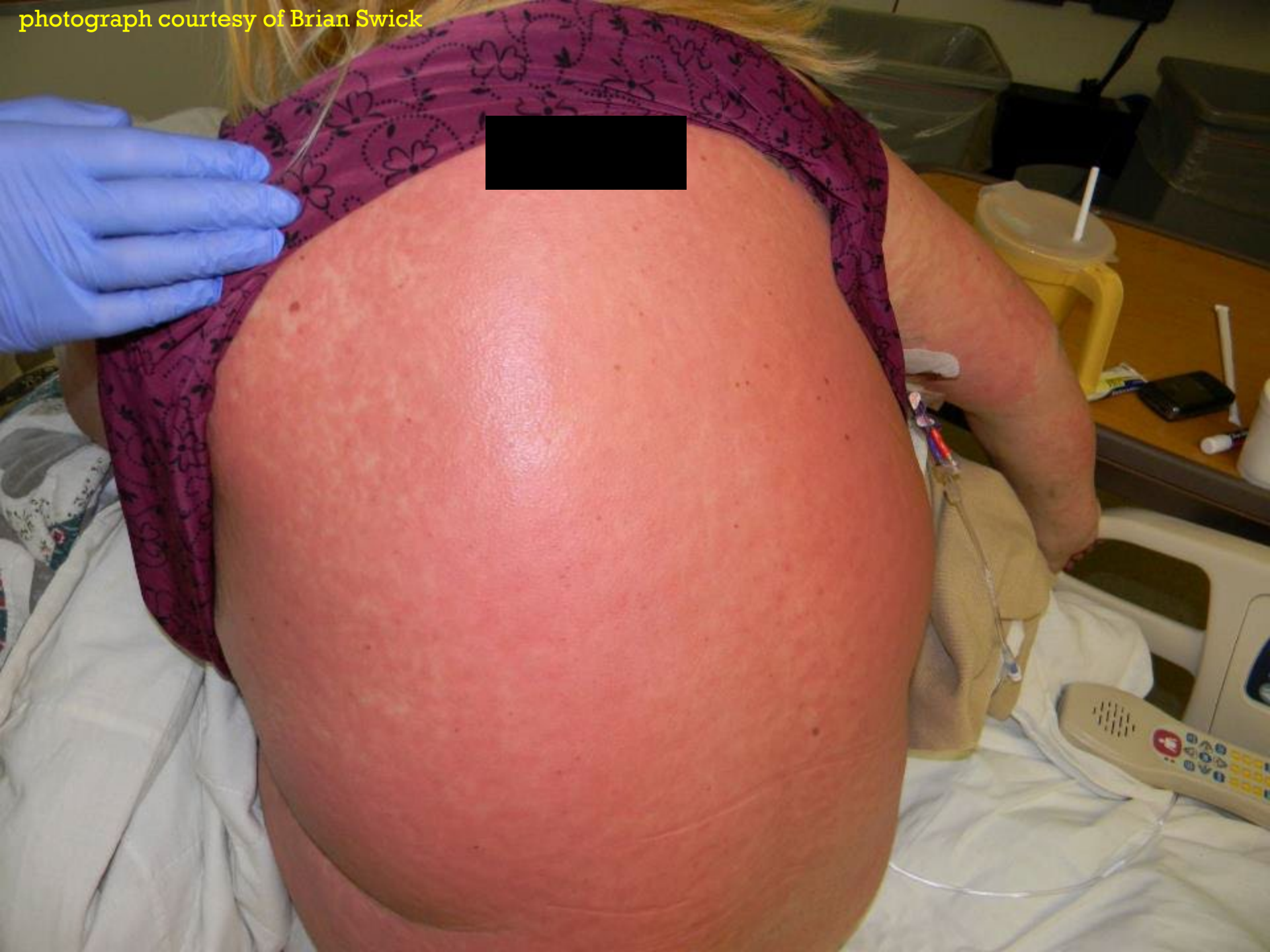
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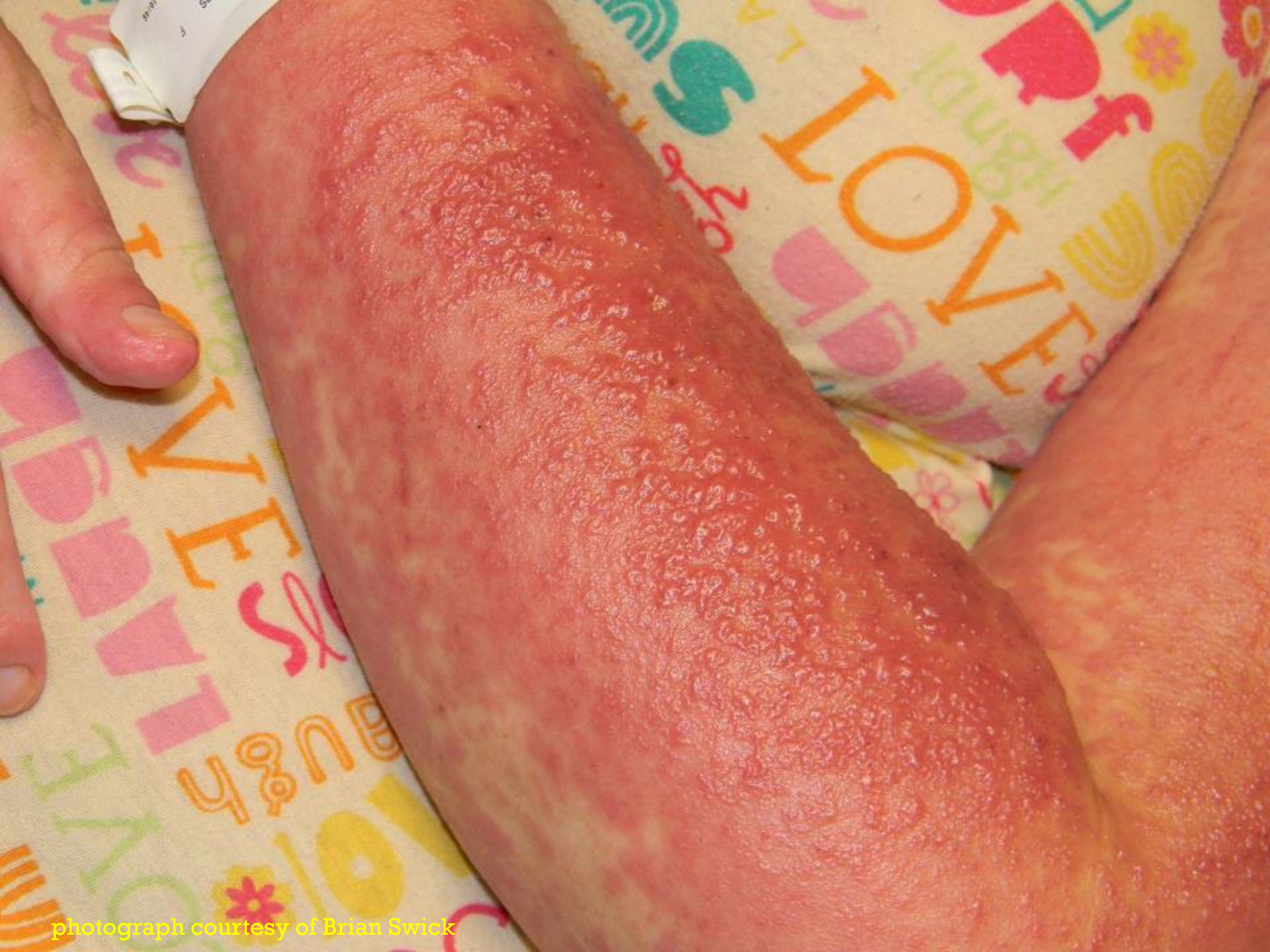

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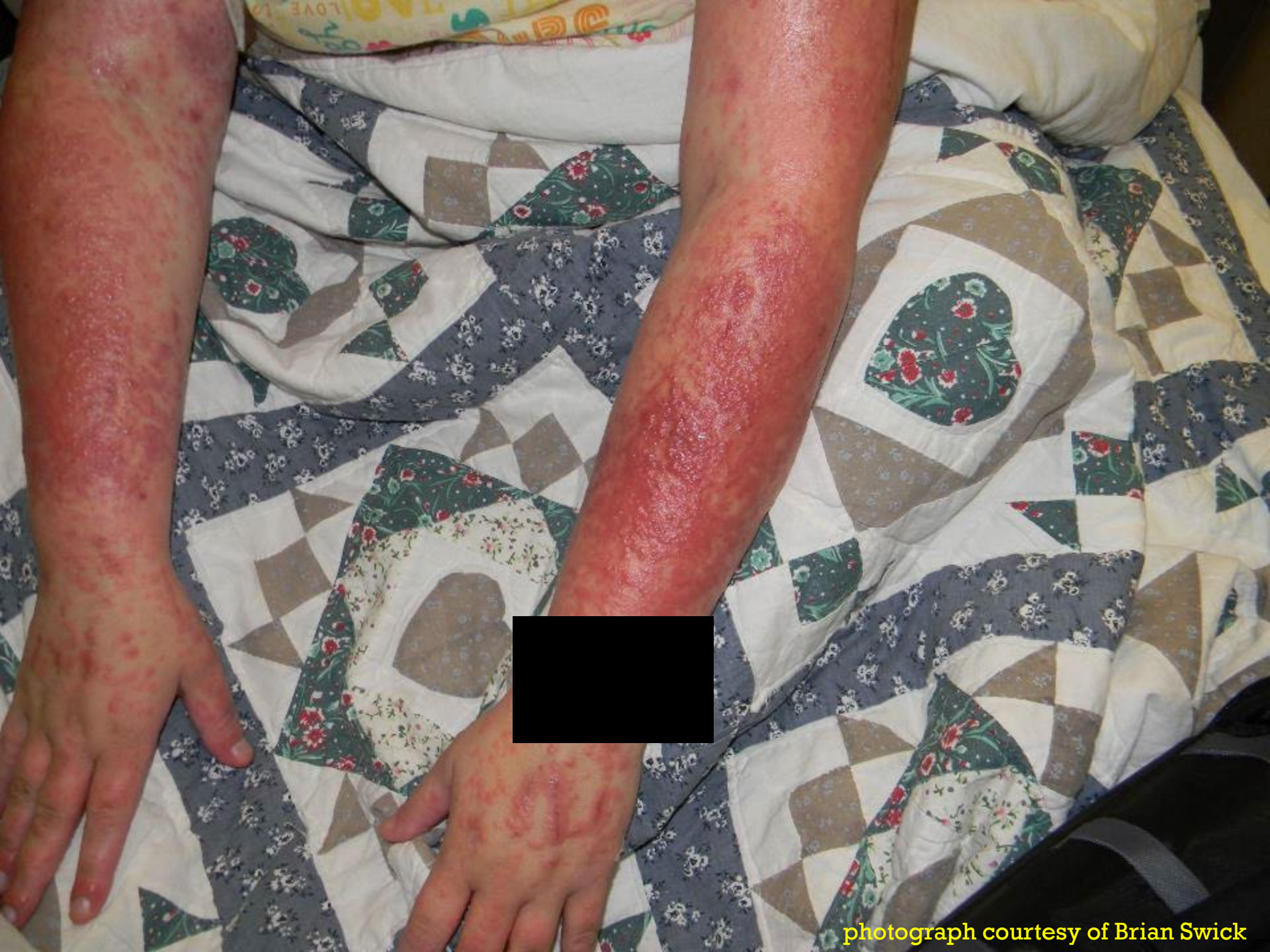
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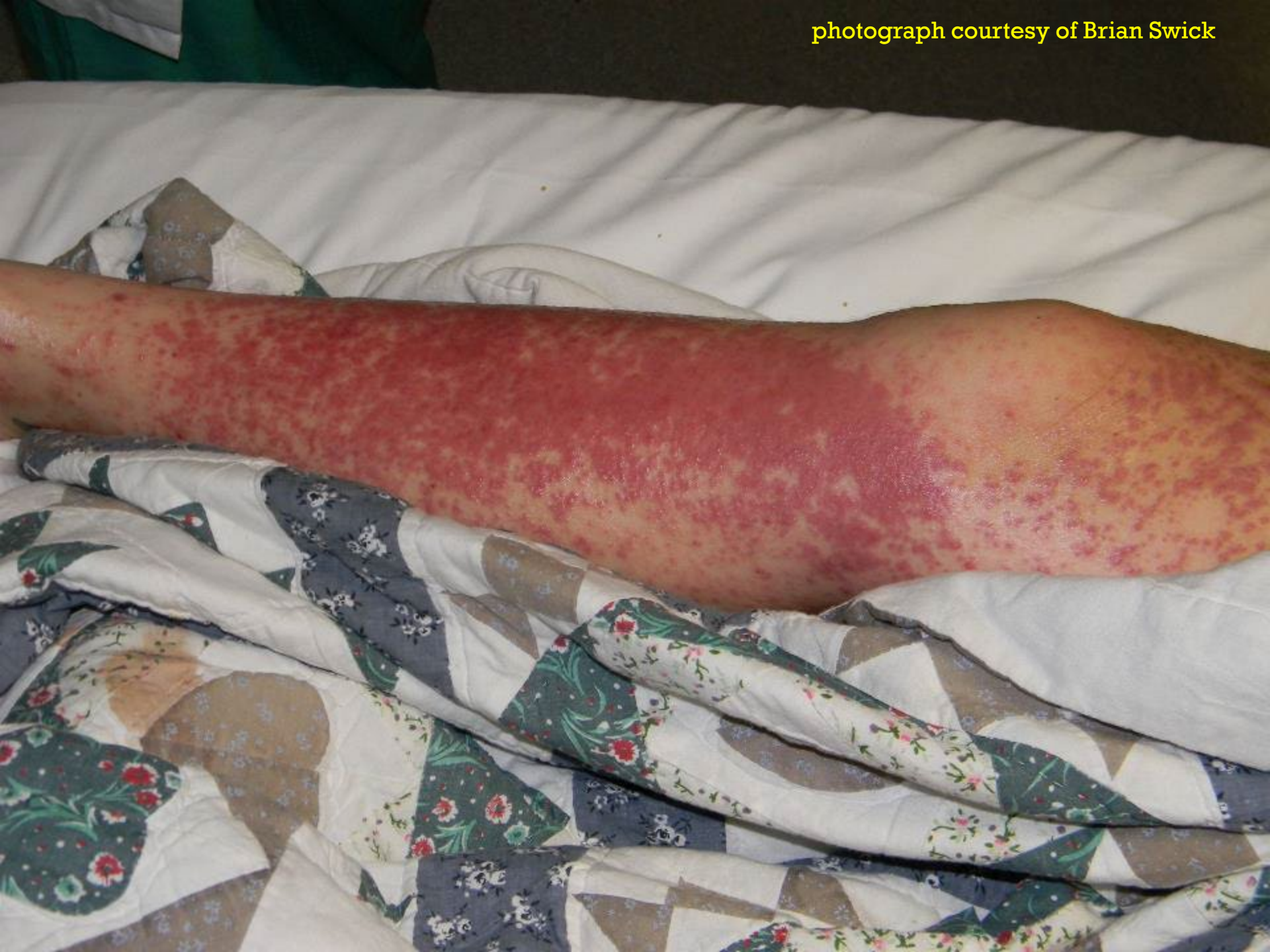
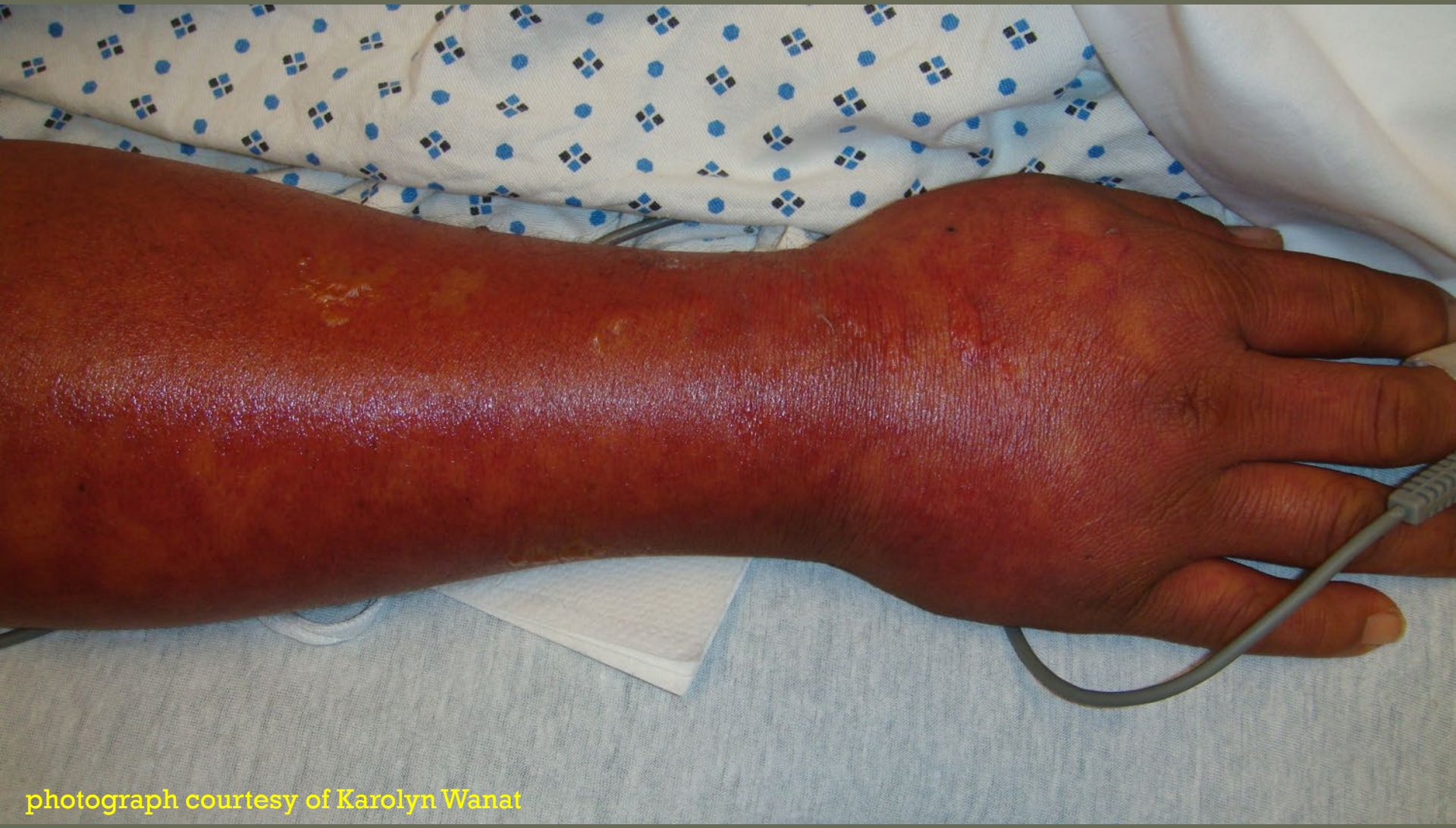

photograph courtesy of Brian Swick


Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
photograph courtesy of Brian Swick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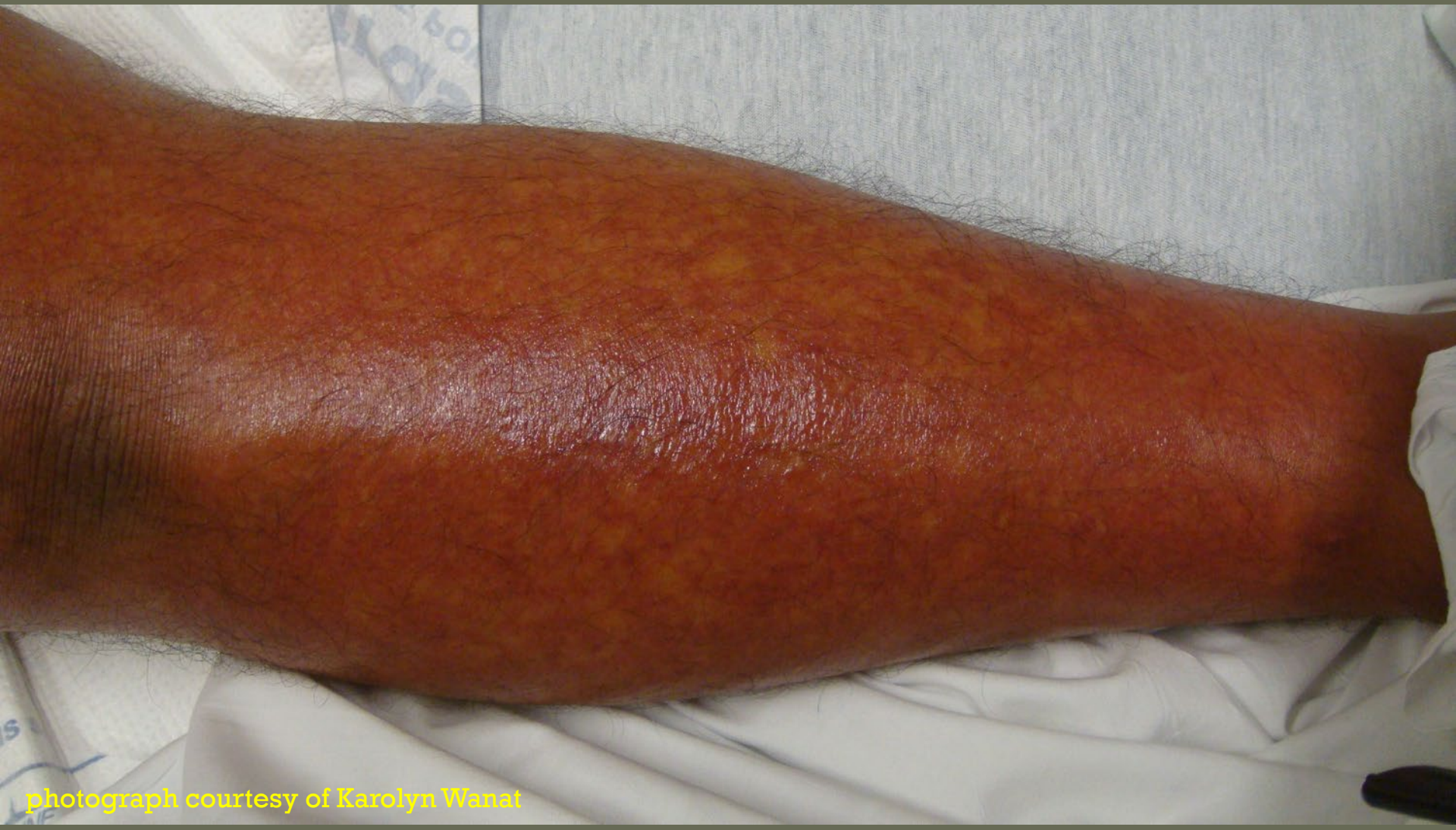

photograph courtesy of Karolyn Wanat

DRESS/DIHS

- *Acute* and potentially *life-threatening* cutaneous eruption triggered by drug exposure
  - T-cell mediated reaction with *multiple organ involvement*
  - Drug reaction with eosinophilia and systemic symptoms
  - Drug-induced hypersensitivity syndrome
    - *Eosinophilia is not always present*
  - Estimated mortality rate of 10%

DRESS/DIHS

- Drugs
  - *Anticonvulsants*
    carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid, zonisamide
  - *Antimicrobials*
    ampicillin, dapsone, cefotaxime, ethambutol, isoniazid, linezolid, metronidazole, minocycline, pyrazinamide, quinine, rifampin, sulfasalazine, streptomycin, sulfamethoxazole/trimethoprim, vancomycin
  - *Antivirals*
    abacavir, nevirapine, zalcitabine
  - *Others*
    buproprion, fluoxetine, amlodipine, captopril, efalizumab, imatinib, celecoxib, ibuprofen, allopurinol, epoetin alfa, mexiletine, ranitidine

DRESS/DIHS

- Associated clinical signs & symptoms
  - RASH HAS NO CHARACTERISTIC MORPHOLOGY
  - Rash begins 14-40 days following drug exposure (most >21 days)
  - Prodrome several days prior to onset of skin rash consisting primarily of *pruritus* and *fever*
  - Classic presentation is a maculopapular or morbilliform eruption involving the face, upper trunk, and upper extremities
  - Rash is often accompanied by *prominent facial edema* and *lymphadenopathy*
  - Rash can persist for weeks to months following discontinuation of the offending drug

DRESS/DIHS

- Associated clinical signs & symptoms (common)
  - Hematologic
    - leukocytosis up to 50,000 cells/mL
    - presence of atypical lymphocytes
    - eosinophilia >2000 cells/mL (~30% of cases)
    - leukopenia and/or lymphopenia may precede leukocytosis
    - thrombocytopenia and anemia
    - hemophagocytic lymphohistiocytosis (rare)
  - Hepatic (most frequent of all)
    - hepatosplenomegaly and hepatitis with elevated ALT & AST
    - hepatic necrosis is primary cause of mortality

DRESS/DIHS

- Associated clinical signs & symptoms (less common)
  - Renal
    - hematuria & proteinuria associated with acute kidney injury
    - acute interstitial nephritis
  - Pulmonary
    - interstitial pneumonitis
    - acute respiratory distress syndrome
  - Cardiac
    - myocarditis; can present months after withdrawal of the culprit drug

DRESS/DIHS

- Associated clinical signs & symptoms (least common)
  - Neurologic
    - encephalitis
    - meningitis
  - Gastrointestinal
    - enterocolitis
    - ulceration and hemorrhage
  - Endocrine
    - SIADH
    - thyroiditis

DRESS/DIHS

- Differential diagnosis
  - SJS/TEN, **morbilliform drug eruption**, AGEP, EM, other causes of erythroderma, systemic vasculitis, lupus erythematosus
- Work-up [no evidence-based guidelines]
  - DIAGNOSIS OF EXCLUSION
  - Detailed timeline of drug exposures to identify potential culprit drug(s)
  - No definitive laboratory tests for identifying the culprit drug
    - Lymphocyte transformation testing
    - Cutaneous patch testing

DRESS/DIHS

- Diagnosis: Bocquet et al. criteria

***Bocquet et al.* diagnostic criteria for DRESS/DIHS (37)**
1. Acute skin rash suspected to be drug-related
2. Hematologic abnormalities (any *one* of the following) eosinophils ≥1500 cells/μL presence of atypical lymphocytes on peripheral smear
3. Internal organ involvement (any *one* of the following) lymphadenopathy ≥2 cm diameter hepatitis with ALT/AST ≥2 times upper limit of normal interstitial nephritis interstitial pneumonitis carditis

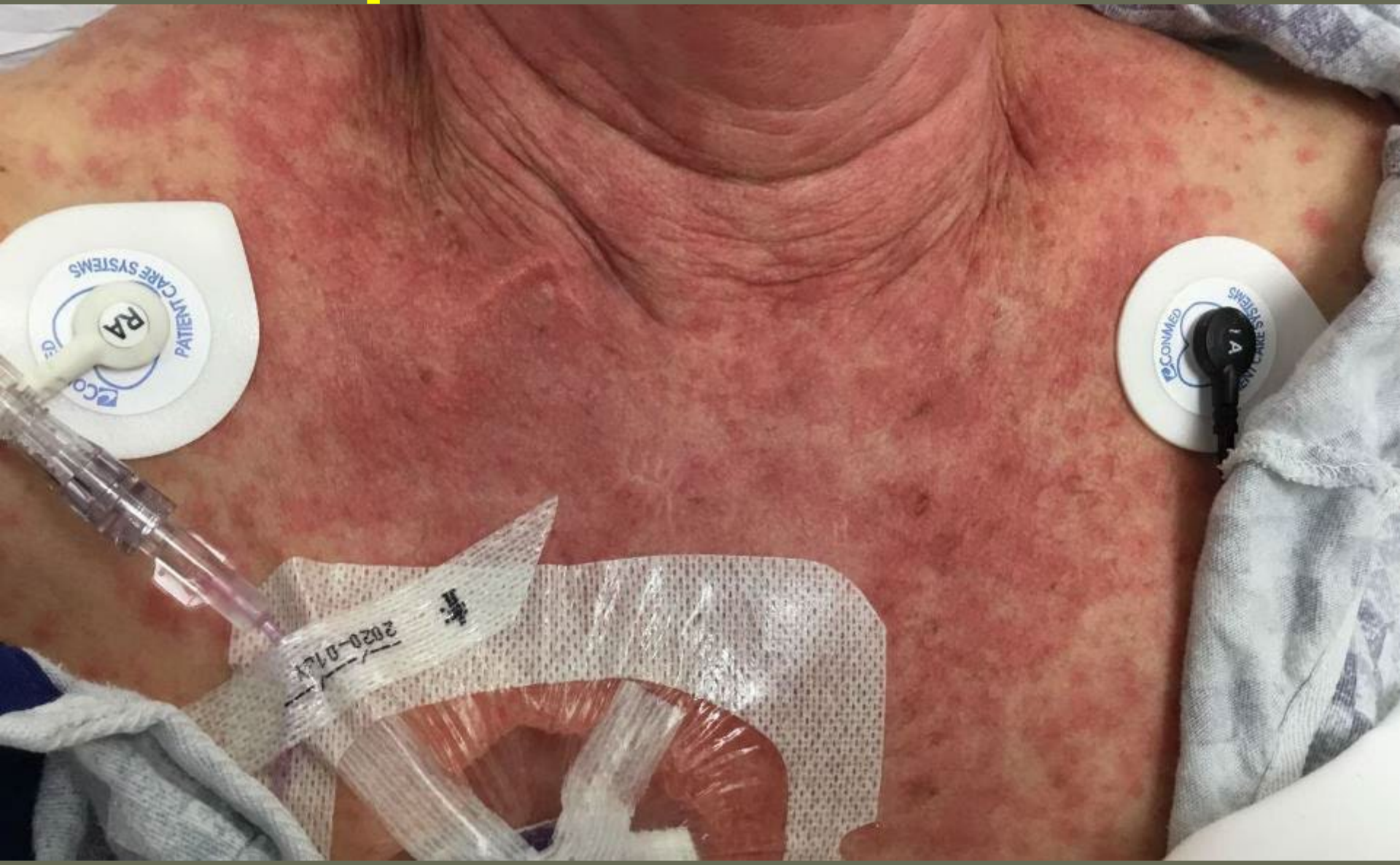
Each of the above *three* criteria must be met to establish a diagnosis of DRESS/DIHS.

DRESS/DIHS

- Work-up [no evidence-based guidelines]

Initial evaluation of patients suspected of having DRESS/DIHS
Evaluate other potential causes: Blood cultures, urine cultures, lumbar puncture with CSF culture chest X-ray, ANA titer Chest X-ray ANA titer, HIV screening
Studies to help support diagnosis of DRESS/DIHS: Skin biopsy- could be useful to rule-out other diagnoses in the differential Quantitative PCR testing for HHV-6, HHV-7, EBV, CMV
Assess internal organ involvement: CBC, LFTs, BMP, UA with microscopic, CPK, LDH (hematologic, hepatic, renal, cardiac) ferritin, triglycerides, CRP (inflammatory markers; hemophagocytic lymphohistiocytosis) calcium, PTH, TSH (endocrine)

- Morbilliform eruption with T=43°C, elevated AST/ALT, and neutropenia…



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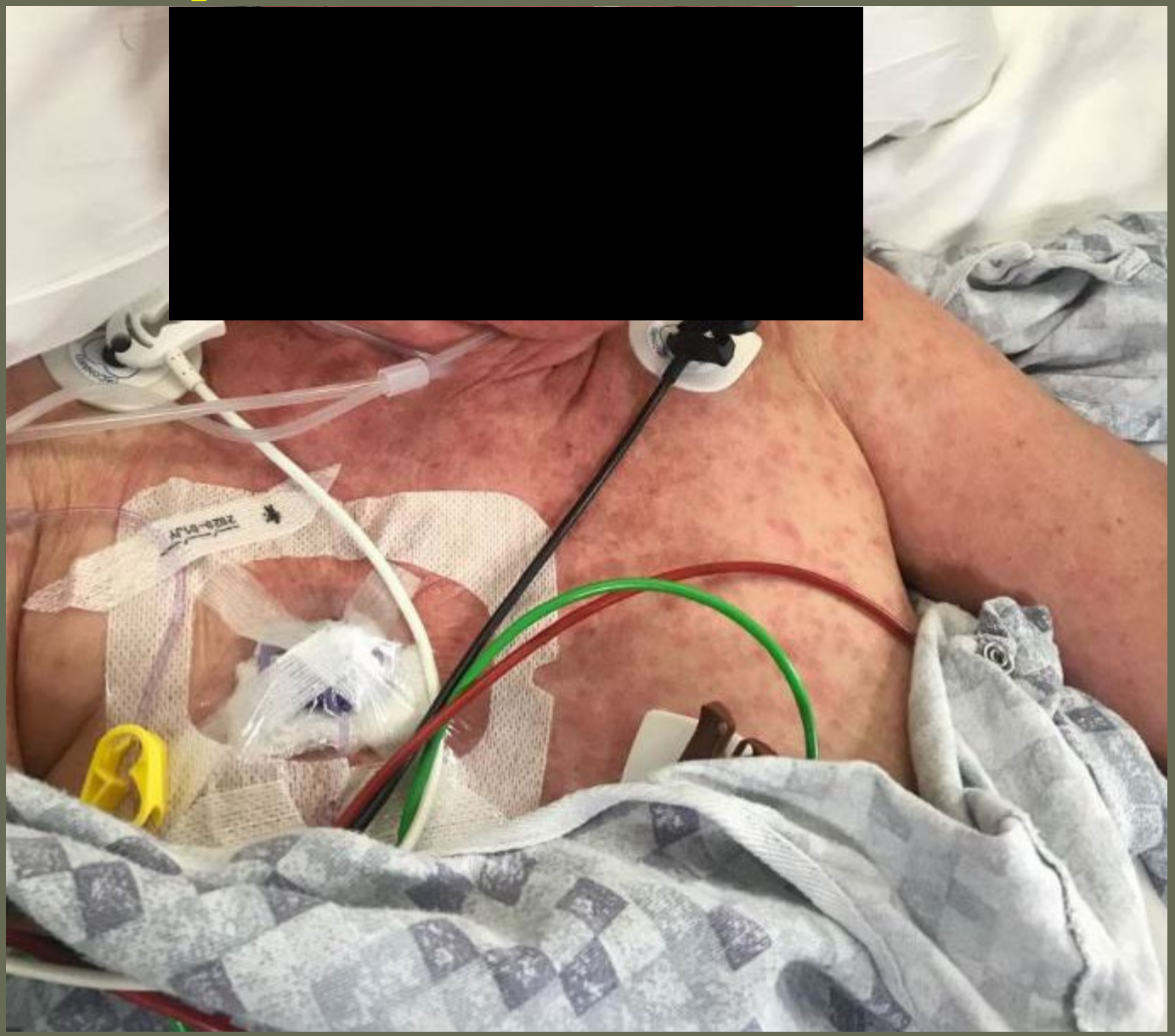

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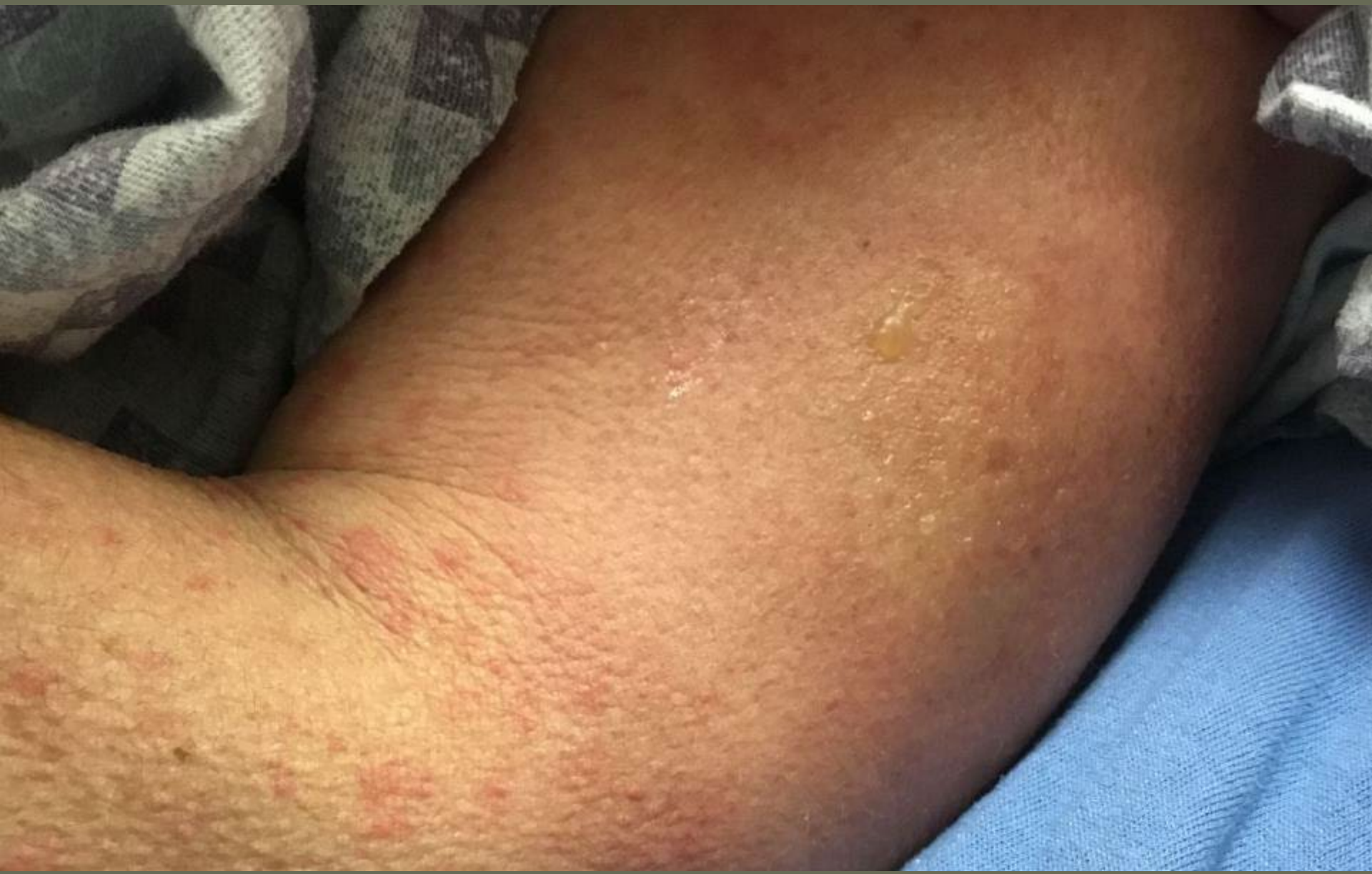
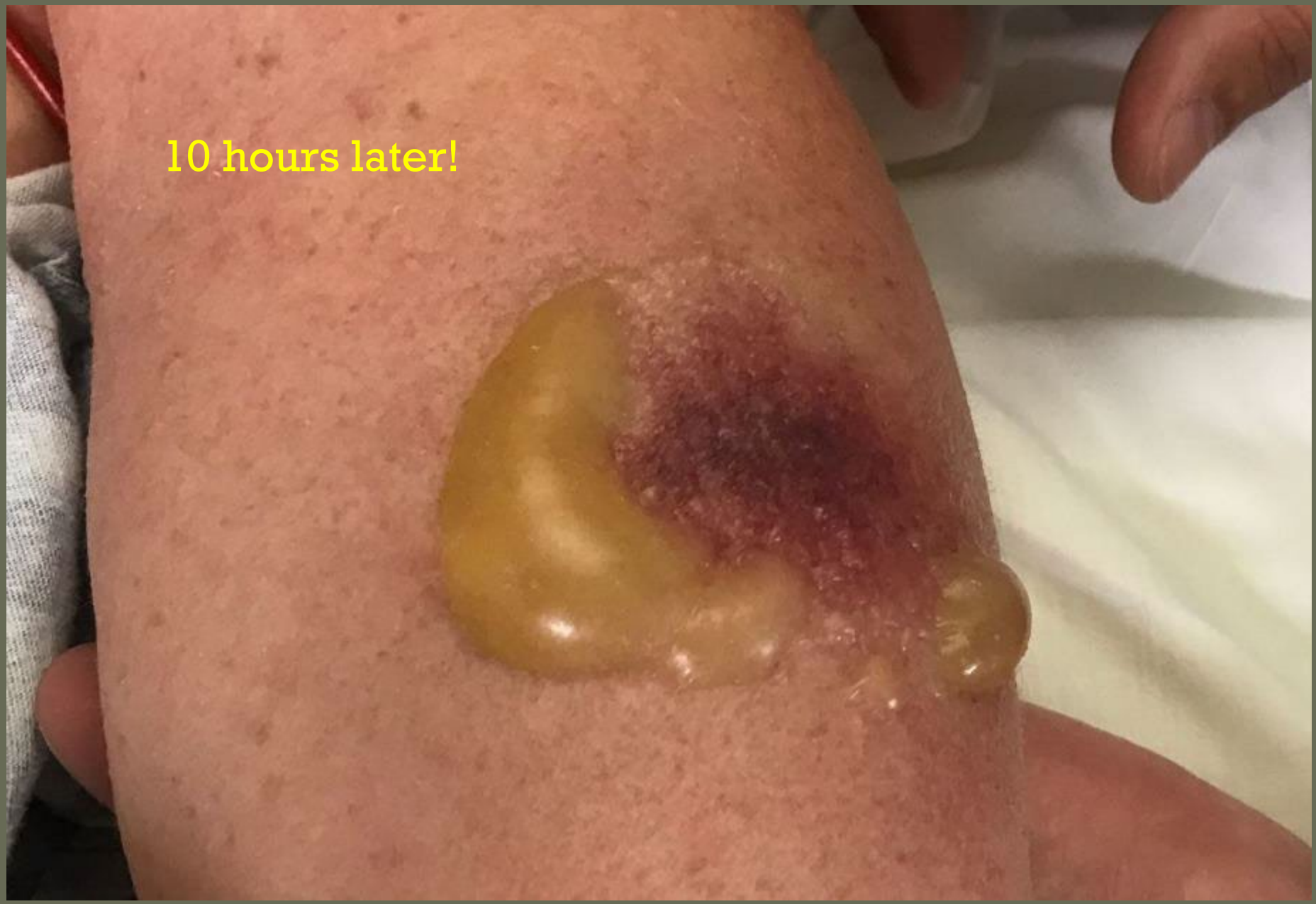


- Pseudomonas sepsis with ecthyma gangrenosum



DRESS/DIHS

- Management [no evidence-based guidelines]
  - *Immediate withdrawal of the culprit drug*
  - Hospital admission to provide supportive care and surveillance for secondary infection
  - Systemic steroids dosed 1 mg/kg/day; gradual taper over 3-6 months
  - Symptomatic treatment:
    - Antihistamines
    - Mid-potency topical steroid (triamcinolone 0.1% ointment/cream)
    - Emollients

DRESS/DIHS

- Management [no evidence-based guidelines]
  - Other therapies reported in the literature
    - IVIg, plasmapheresis
    - cyclophosphamide, cyclosporine, mycophenolate mofetil
    - interferon, muromonab-CD3, rituximab
    - antiherpesvirus medications (valgancyclovir)
    - free-radical scavengers (N-acetylcysteine)

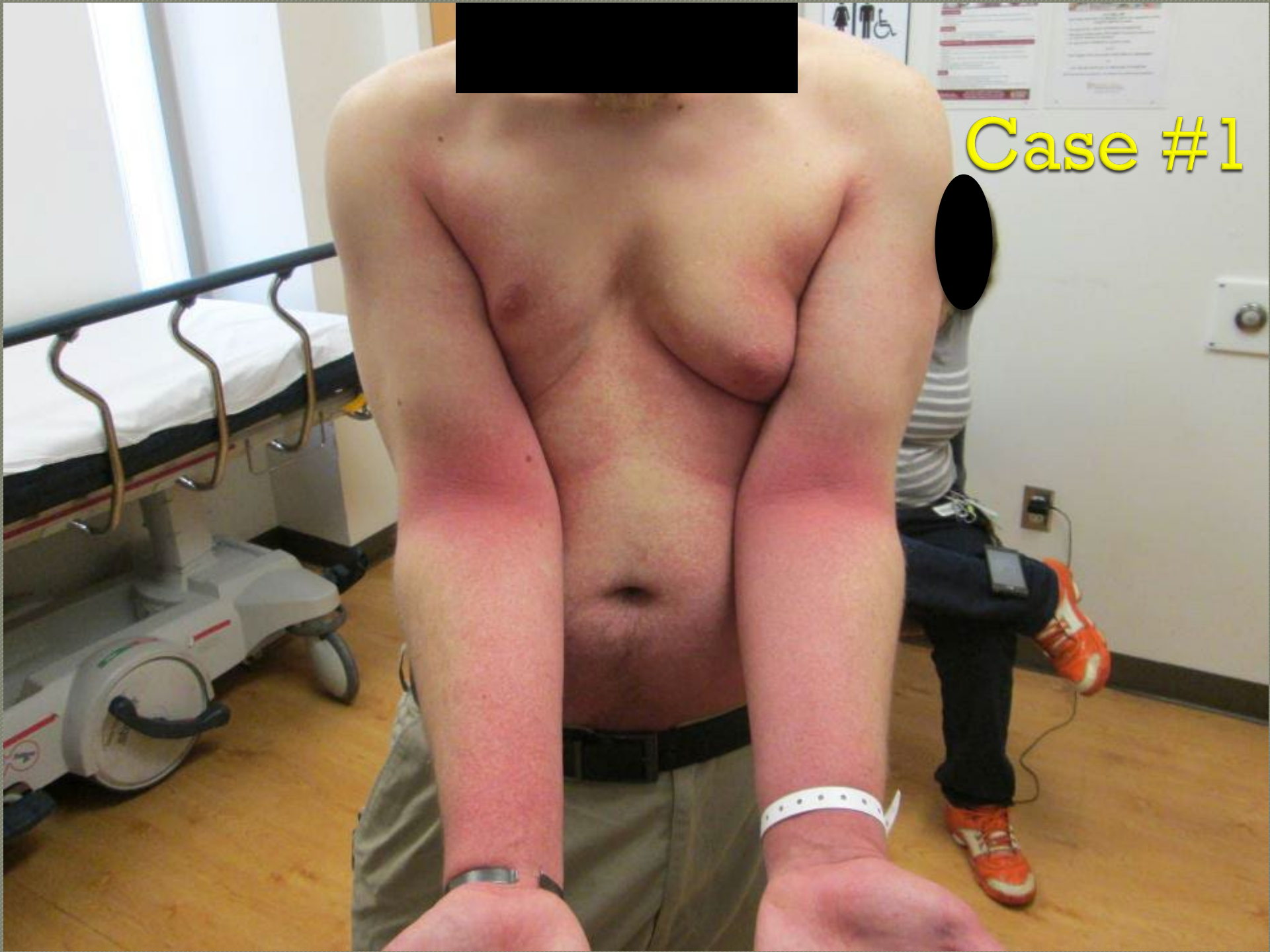
DRESS/DIHS Clinical Pearls

- Skin rash in DRESS/DIHS is non-specific, but multiple organs are involved by the immunologic reaction
- SJS/TEN:
  - Primary reaction is in the skin
  - Any other organ dysfunction is secondary to loss of barrier function
- AGEP typically lacks signs of other organ involvement
- Consider monitoring patients with morbilliform drug eruptions for the development of systemic internal organ involvement that could be suggestive of evolving DRESS/DIHS

Quiz Time!

Case #1

This 46 year-old male patient was admitted to the hospital with an asymptomatic skin rash, fever (38°C), mild leukocytosis with neutrophilia, and an otherwise normal complete blood count and comprehensive metabolic panel.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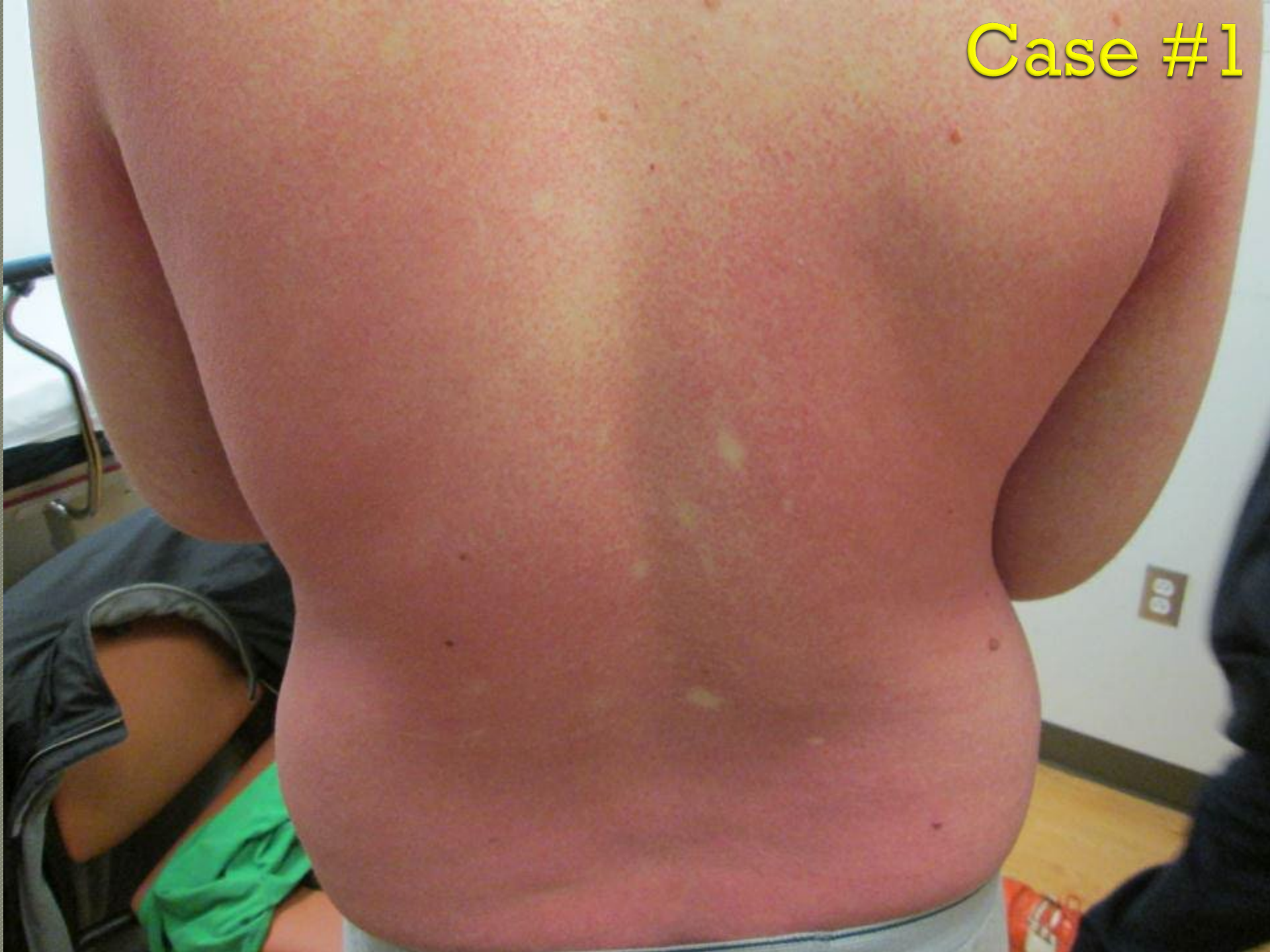
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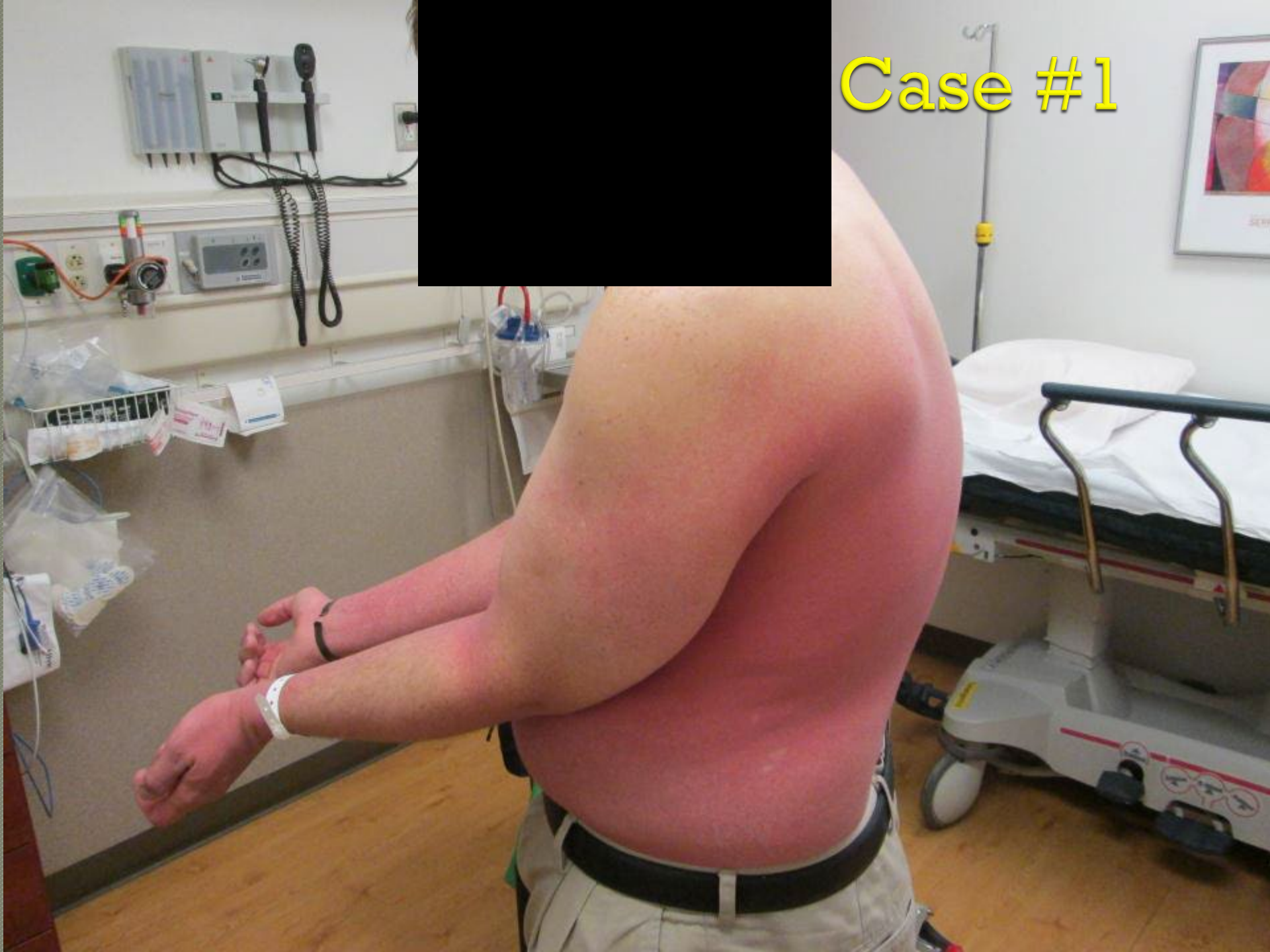
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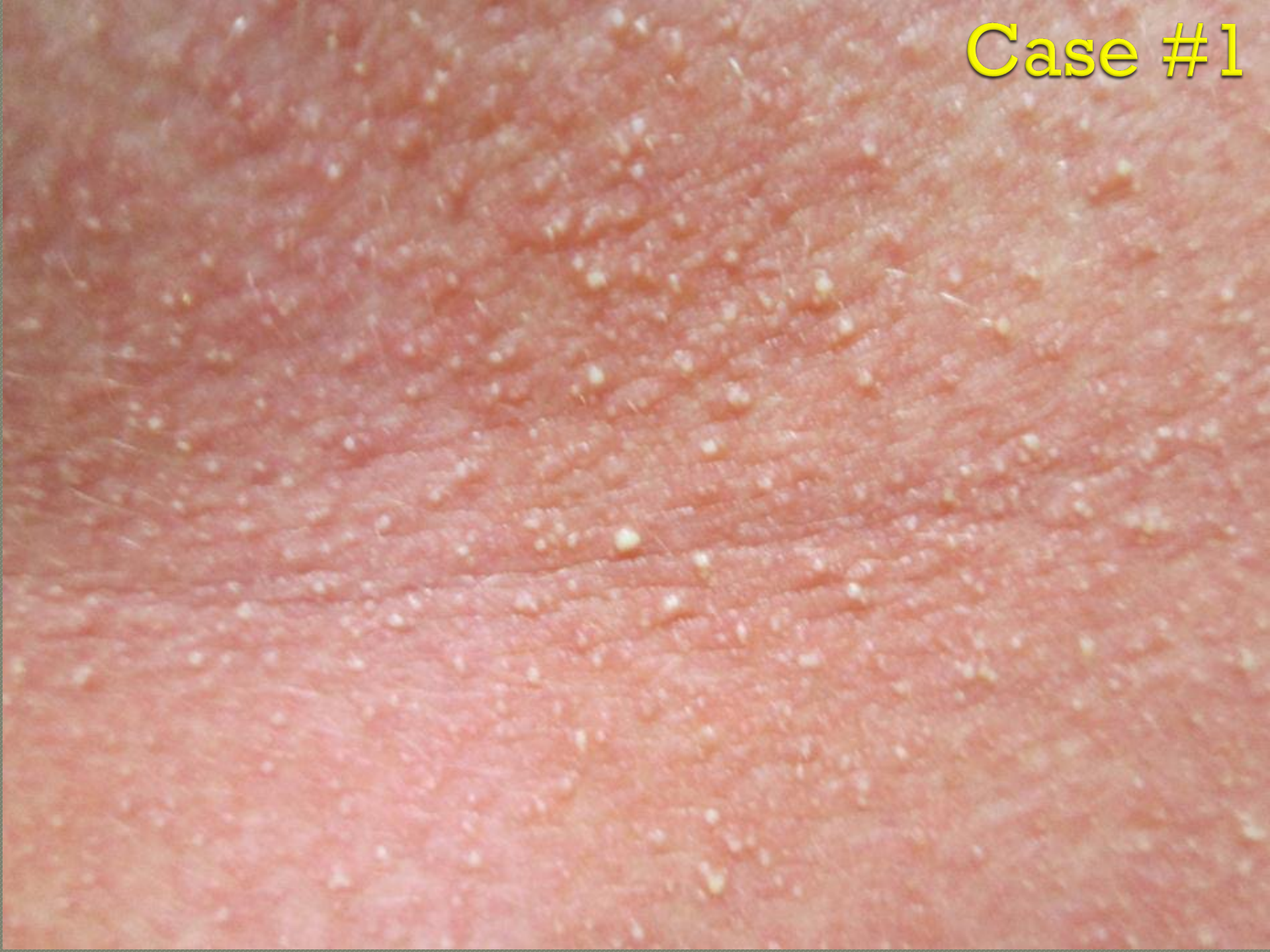
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Which of the following clinical scenarios most likely led to the development of his skin rash?

A. 48 hours after starting *terbinafine* for toenail onychomycosis
B. 7 days after starting *allopurinol* for gout
C. 14 days after starting *ciprofloxacin* & *metronidazole* for diverticulitis
D. 21 days after starting *cefazolin* for MSSA infective endocarditis
E. 4 days after developing an outbreak of orolabial HSV

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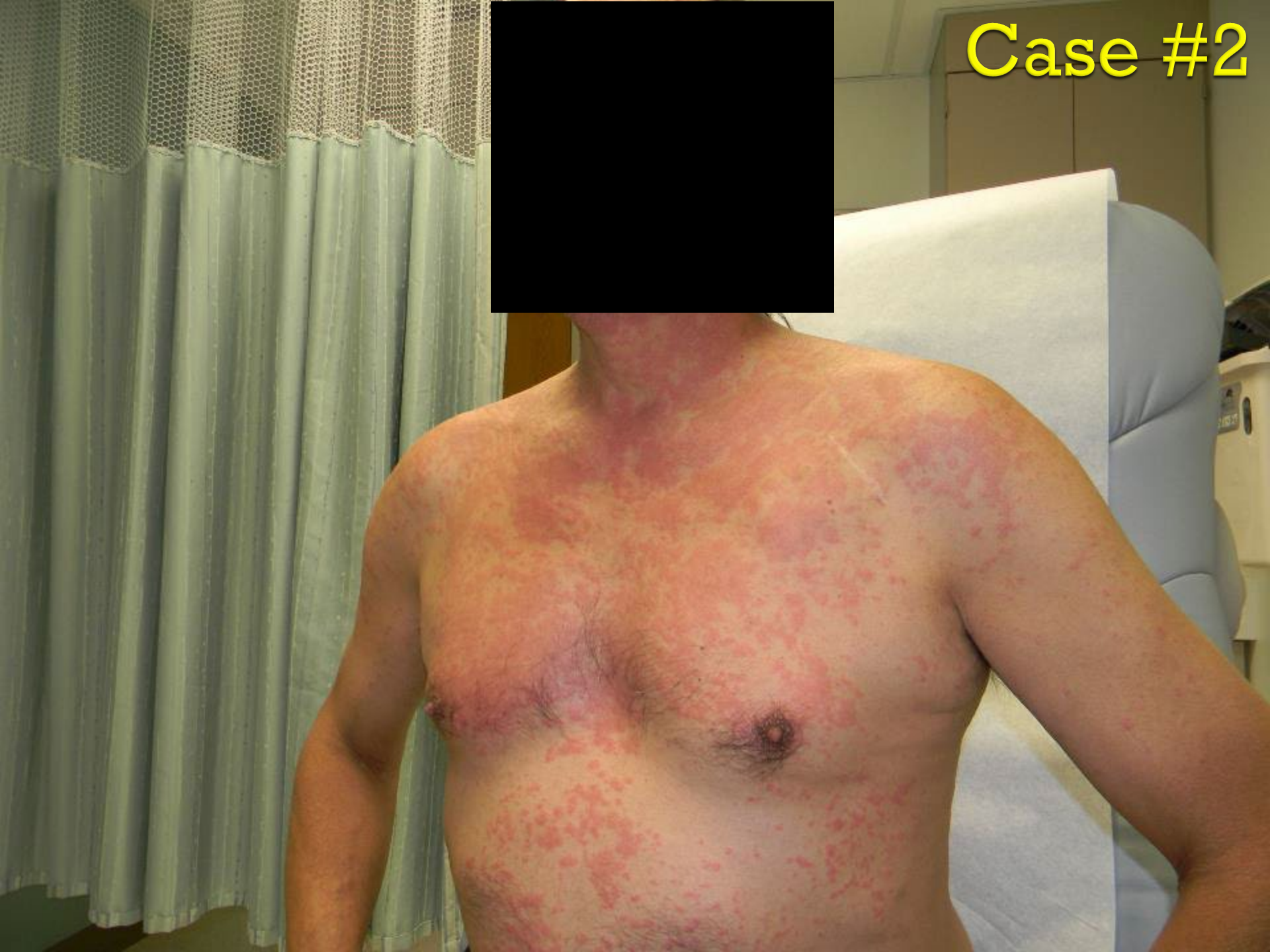
E. 4 days after developing an outbreak of orolabial HSV

Case #2

This 57 year-old male patient with no significant past medical history developed this skin rash about 3 weeks after starting carbamazepine. He is now admitted to the hospital with a low-grade fever (38.5°C), lymphocytosis with atypical lymphocytes on peripheral smear, facial edema, and cervical lymphadenopathy.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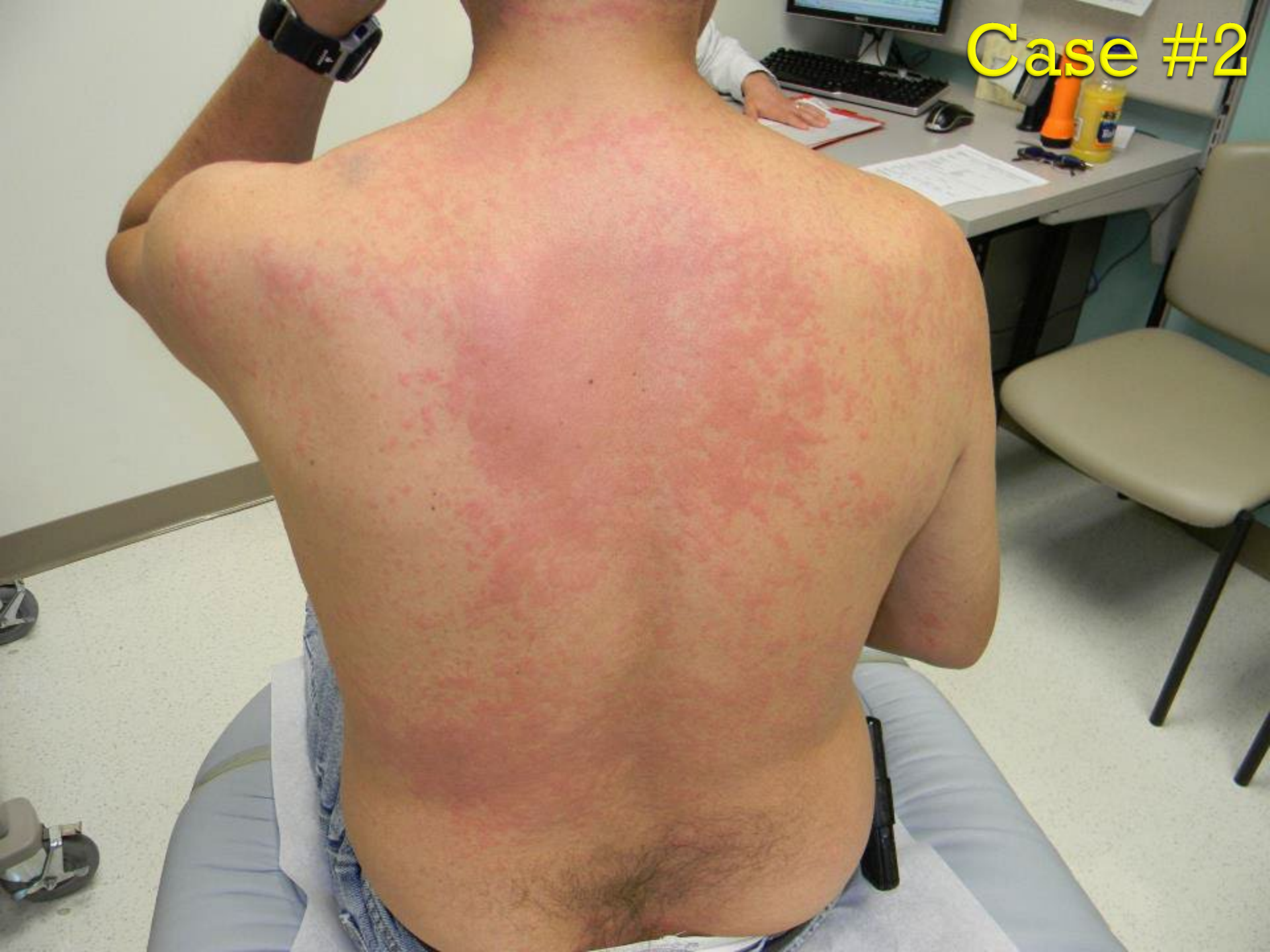
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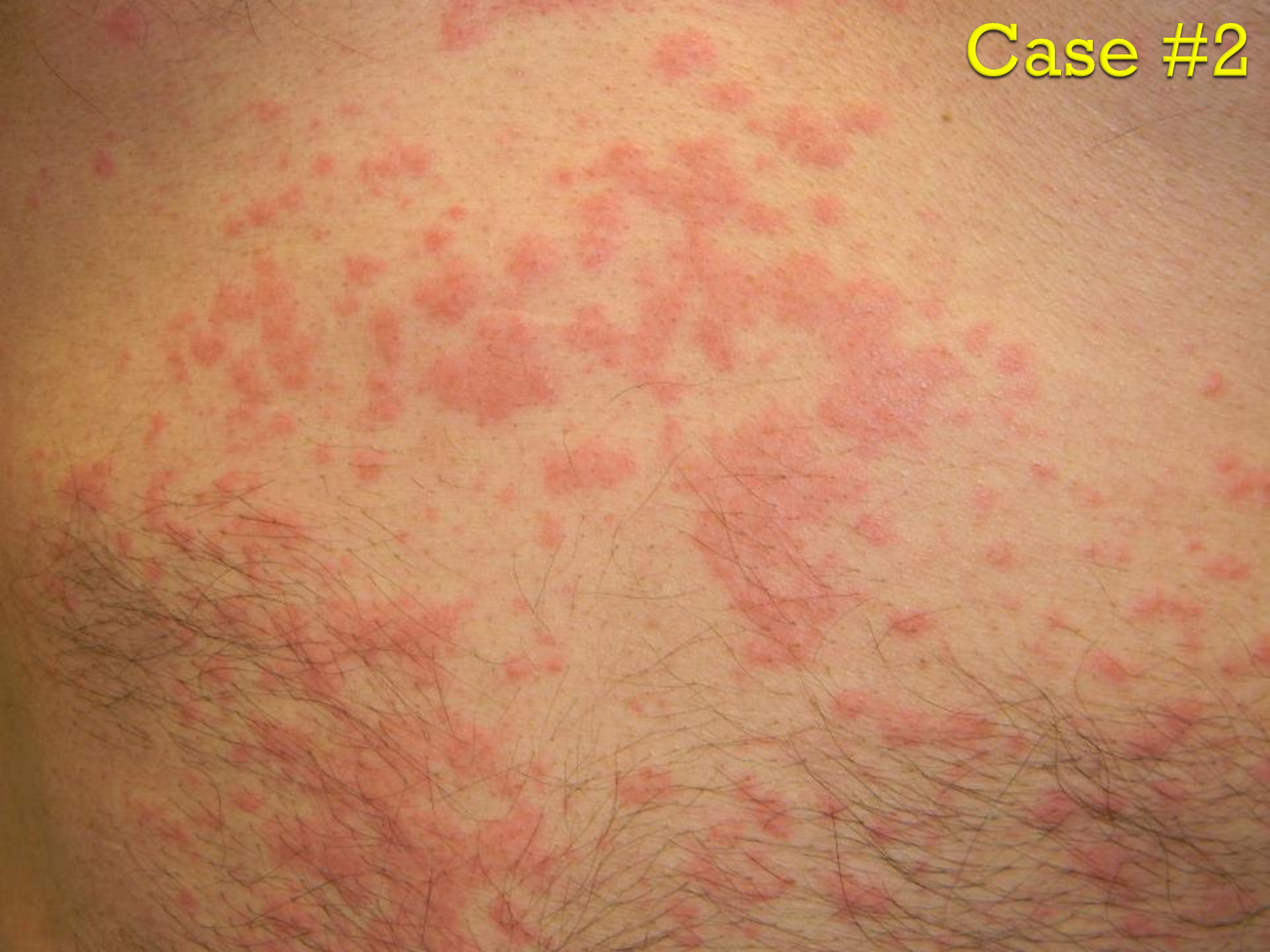
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Which of the following laboratory findings is most likely to be abnormal?

A. Fecal occult blood testing
B. Troponins I & T
C. BUN & Cr (blood urea nitrogen and creatinine)
D. ALT & AST (aspartate aminotransferase & alanine aminotransferase)
E. Urinalysis with microscopic examination

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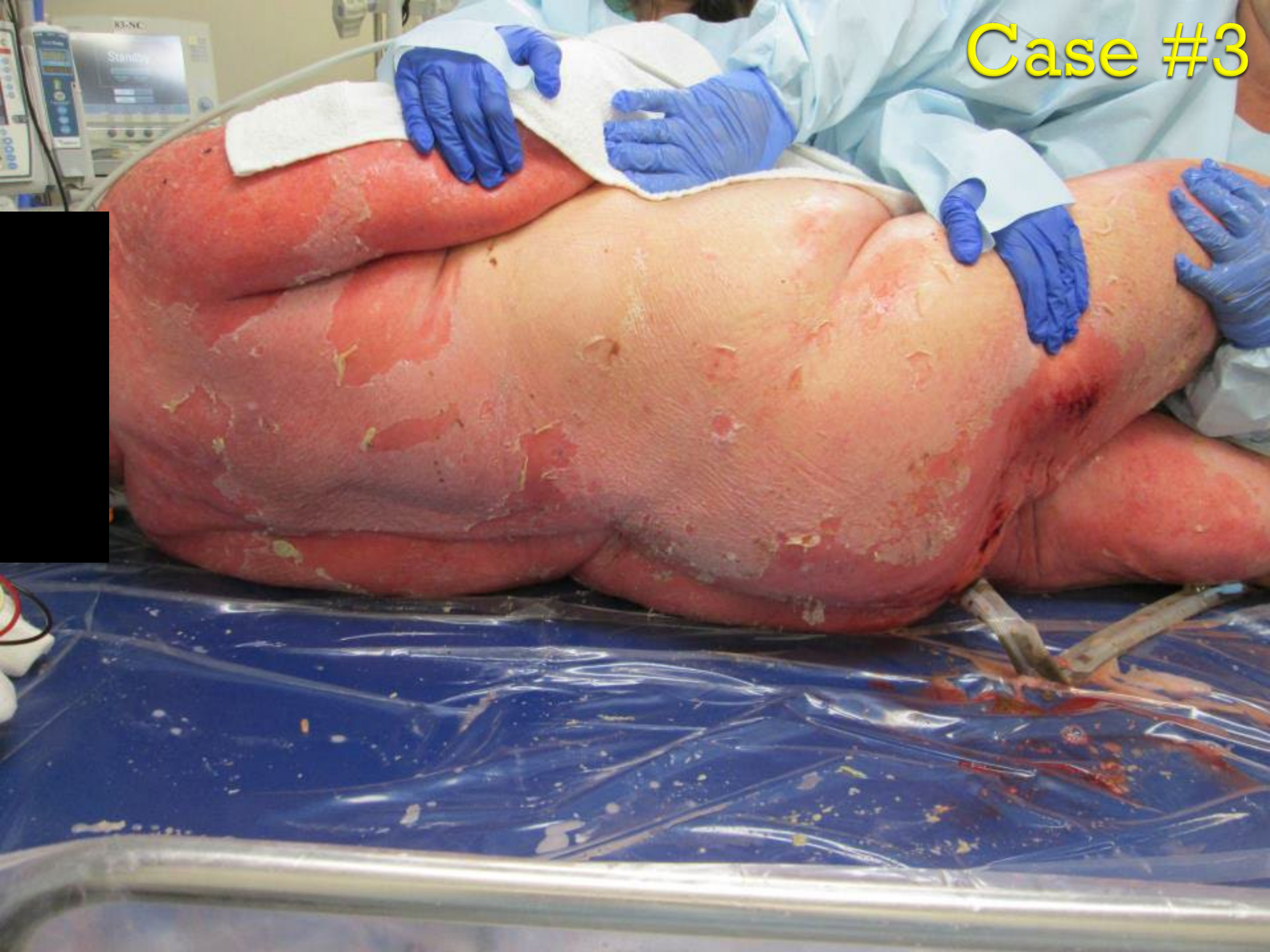
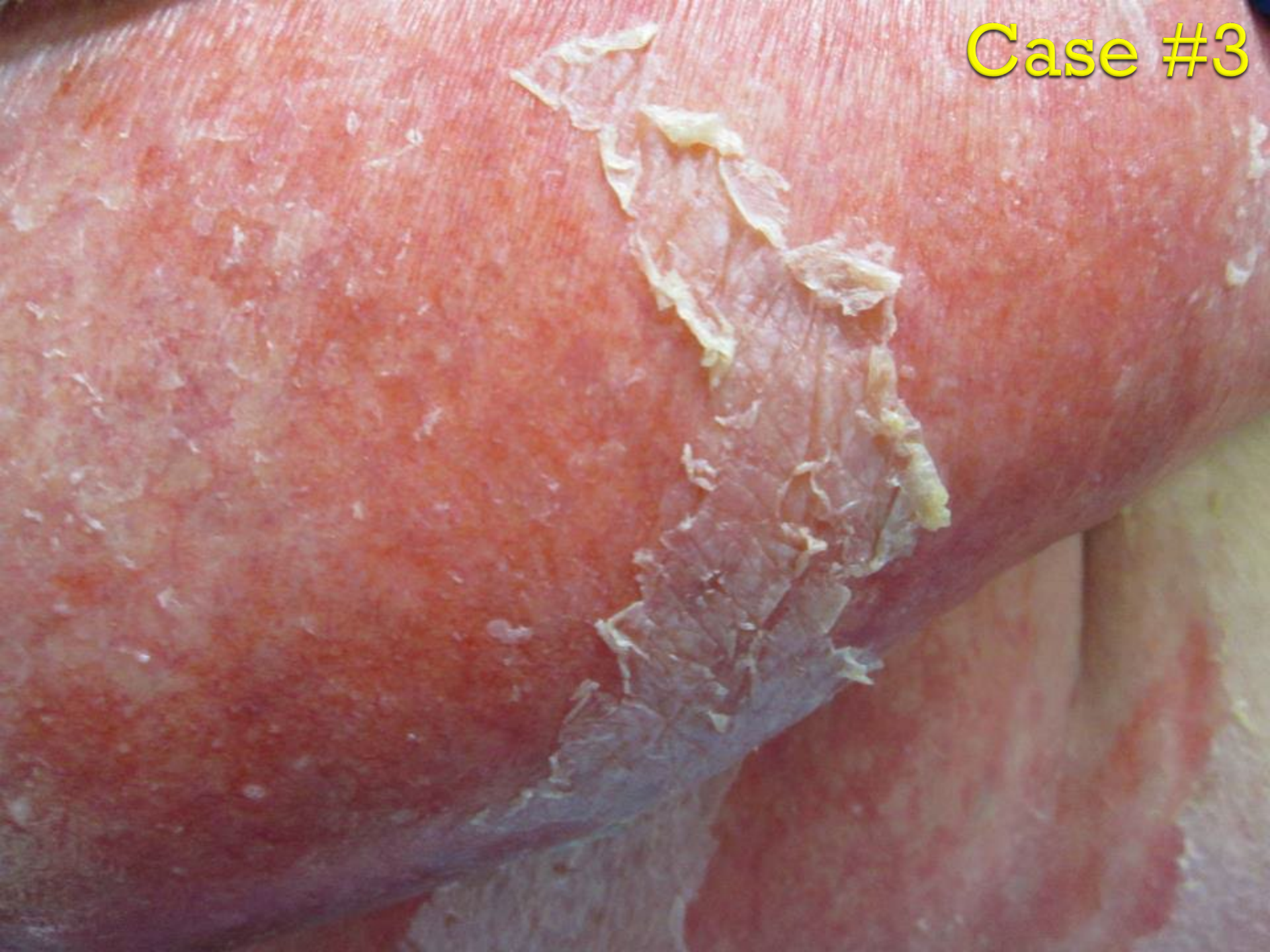
Case #3

This 86 year-old female patient with a history of recurrent orolabial HSV infection was admitted to the hospital for this skin rash that developed one day following completion of a 7-day course of combination sulfamethoxazole/trimethoprim for treatment of an uncomplicated acute cystitis.


Case #3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Which of the following studies could be done to confirm the diagnosis?

A. Serologic testing for *Mycoplasma pneumoniae* (IgM & IgG)
B. PCR testing for HSV 1 & HSV 2
C. Skin biopsy with direct immunofluorescence testing
D. Complete blood count with differential
E. None of the above

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References

1. Chung WH, Wang CW, Dao RL. Severe cutaneous adverse drug reactions. J Dermatol. 2016;43(7):758-66.

2. Roujeau JC. Immune mechanisms in drug allergy. Allergol Int. 2006;55(1):27-33.

3. Warrington R, Silviu-Dan F. Drug allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1:S10.

4. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S126-37.

5. Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. J Allergy Clin Immunol Pract. 2014;2(1):21-33.

6. Botelho LF, Porro AM, Enokihara MM, Tomimori J. Adverse cutaneous drug reactions in a single quaternary referral hospital. Int J Dermatol. 2016;55(4):e198-203.

7. Su P, Aw CW. Severe cutaneous adverse reactions in a local hospital setting: a 5-year retrospective study. Int J Dermatol. 2014;53(11):1339-45.

8. Revus J, Valeyrie-Allanore L. Drug reactions. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. Deramtology, Third Edition: Elsevier Saunders; 2012:335-56.

References

9. French LE, Prins C. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. Deramtology, Third Edition: Elsevier Saunders; 2012:319-34.

10. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129(1):92-6.

11. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)-a clinical reaction pattern. J Cutan Pathol. 2001;28(3):113-9.

12. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 2013;68(5):693.e1-14; quiz 706-8.

13. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. J Am Acad Dermatol. 2013;68(5):709.e1-9; quiz 18-20.

14. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69(2):173.e1-13; quiz 85-6.

15. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): A review and update. J Am Acad Dermatol. 2015;73(5):843-8.

References

16. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol. 2013;69(2):187.e1-16; quiz 203-4.

17. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-53.

18. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, Roujeau JC, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol. 2006;126(2):272-6.

19. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens-Johnson syndrome during an 8-year period at Mayo Clinic. Mayo Clin Proc. 2010;85(2):131-8.

20. Watanabe R, Watanabe H, Sotozono C, Kokaze A, Iijima M. Critical factors differentiating erythema multiforme majus from Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Eur J Dermatol. 2011;21(6):889-94.

21. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol. 1995;131(5):539-43.

References

22. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schroder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol. 2002;138(8):1019-24.

23. Hershfield MS, Callaghan JT, Tassaneeyakul W, Mushiroda T, Thorn CF, Klein TE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013;93(2):153-8.

24. Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496-506.

25. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51(8):889-902.

26. Wetter DA, Davis MD. Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. J Am Acad Dermatol. 2010;62(1):45-53.

References

27. Ting W, Stone MS, Racila D, Scofield RH, Sontheimer RD. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic pan-epidermolysis (ASAP): a case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. Lupus. 2004;13(12):941-50.

28. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010;146(12):1373-9.

29. Ang CC, Wang YS, Yoosuff EL, Tay YK. Retrospective analysis of drug-induced hypersensitivity syndrome: a study of 27 patients. J Am Acad Dermatol. 2010;63(2):219-27.

30. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609-11.

References

31. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-80.

32. Kim DH, Koh YI. Comparison of diagnostic criteria and determination of prognostic factors for drug reaction with eosinophilia and systemic symptoms syndrome. Allergy Asthma Immunol Res. 2014;6(3):216-21.

33. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156(5):1083-4.

34. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin North Am. 2010;94(4):743-59, xi.

35. Joly P, Janela B, Tetart F, Rogez S, Picard D, D'Incan M, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol. 2012;148(4):543-4.

36. Moling O, Tappeiner L, Piccin A, Pagani E, Rossi P, Rimenti G, et al. Treatment of DIHS/DRESS syndrome with combined N-acetylcysteine, prednisone and valganciclovir--a hypothesis. Med Sci Monit. 2012;18(7):Cs57-62.

References

37. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250-7.

38. Alniemi DT, Wetter DA, Bridges AG, El-Azhary RA, Davis MD, Camilleri MJ, et al. Acute generalized exanthematous pustulosis: clinical characteristics, etiologic associations, treatments, and outcomes in a series of 28 patients at Mayo Clinic, 1996-2013. Int J Dermatol. 2017.

39. Hotz C, Valeyrie-Allanore L, Haddad C, Bouvresse S, Ortonne N, Duong TA, et al. Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. Br J Dermatol. 2013;169(6):1223-32.

40. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157(5):989-96.

41. Mistry N, Gupta A, Alavi A, Sibbald RG. A review of the diagnosis and management of erythroderma (generalized red skin). Adv Skin Wound Care. 2015;28(5):228-36; quiz 37-8.

42. Sehgal VN, Srivastava G, Sardana K. Erythroderma/exfoliative dermatitis: a synopsis. Int J Dermatol. 2004;43(1):39-47.

References

43. Bruno TF, Grewal P. Erythroderma: a dermatologic emergency. Cjem. 2009;11(3):244-6.

44. Sterry W, Steinhoff M. Erythroderma. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. Deramtology, Third Edition: Elsevier Saunders; 2012:171-81.

45. Pal S, Haroon TS. Erythroderma: a clinico-etiologic study of 90 cases. Int J Dermatol. 1998;37(2):104-7.

46. Sigurdsson V, Toonstra J, Hezemans-Boer M, van Vloten WA. Erythroderma. A clinical and follow-up study of 102 patients, with special emphasis on survival. J Am Acad Dermatol. 1996;35(1):53-7.

47. Rothe MJ, Bernstein ML, Grant-Kels JM. Life-threatening erythroderma: diagnosing and treating the "red man". Clin Dermatol. 2005;23(2):206-17.