THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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APPENDIX

Score item	Points accorded			
	–1	**0**	**1**	**2**
Fever ≥38·5°C	No/U	Yes		
Enlarged lymph nodes*		No/U	Yes	
Eosinophilia		No/U		
Eosinophils			700–1499/mm^3	≥1500/mm^3
Eosinophils if <4 × 10^3 leukocytes/mm^3			10–19·9%	20%
Atypical lymphocytes		No/U	Yes	
Skin involvement			Yes	
Skin rash extent (% body surface area)		No/U	>50%	
Skin rash suggesting DRESS	No	U	Yes	
Biopsy suggesting DRESS	No	Yes/U		
Organ Involvement†				
Liver		No/U	Yes	
Kidney		No/U	Yes	
Lung		No/U	Yes	
Muscle/heart		No/U	Yes	
Pancreas		No/U	Yes	
Other organ		No/U	Yes	
Resolution ≥15 days	No/U	Yes		
Evaluation of other potential causes				
Positive antinuclear antibody				
Blood culture				
HAV/HBV/HCV serology				
Chlamydia/Mycoplasma pneumoniae				
If not positive and ≥3 of the above negative			Yes	

DRESS=drug reaction with eosinophilia and systemic symptoms. U=unknown/unclassifiable. HAV=hepatitis A virus; HBV=hepatitis B virus. HCV=hepatitis C virus.
The total score ranges from: –4 to 9, with final score: <2=no case; 2–3=possible case; 4–5=probable case; >5=definite case.
*Enlarged lymph nodes ≥1 cm in diameter at 2 different sites.
†After exclusion of other explanations or prior conditions (chronic liver and/or renal insufficiencies…): 1, one organ; 2, two or more organs; liver: transaminases >2 × upper normal limit (UNL), phosphatase >1·5 UNL, kidney: creatinine >1·5 × patient's usual value, abnormalities on at least 2 consecutive days.

Table S1: **RegiSCAR DRESS diagnosis-validation score[9]**

Morphology	Points
Pustules	
Typical	2
Compatible	1
Insufficient	0
Erythema	
Typical	2
Compatible	1
Insufficient	0
Distribution/pattern	
Typical	2
Compatible	1
Insufficient	0
Post-pustular desquamation	
Yes	1
No/insufficient	0
Evolution	
Mucosal involvement	
Yes	−2
No	0
Acute onset (≤10 days)	
Yes	0
No	−2
Resolution ≤15 days	
Yes	0
No	−4
Fever ≥38°C	
Yes	1
No	0
Neutrophils ≥7000/mm^3	
Yes	1
No	0
Histology	
Other disease	−10
Not representative/no histology	0
Exocytosis of neutrophils	1
Subcorneal and/or intraepidermal spongiform or not pustule(s) with or without papillary oedema	2
Spongiform subcorneal and/or intraepidermal pustules with papillary oedema	3

AGEP=acute generalized exanthematous pustulosis.
The total score ranges from: ≤0=no AGEP, 1–4=possible; 5–7=probable; 8–12=definite.

Table S2: **EuroSCAR retrospective AGEP-scoring system[12]**

Drugs	SCARs	HLA	Populations	
			Strongly associated	**Not associated**
Carbamazepine	SJS and TEN, DRESS	*B*15:02*	Han Chinese Asian ancestry Thai Indian	European Japanese
	SJS and TEN	*B*15:11*	Japanese, Korean	
	SJS and TEN	*B*59:01*	Japanese	
	SJS and TEN	*A*31:01*	Northern Europe	–
	SJS and TEN	*A*31:01*	Japanese	–
	DRESS	*A*31:01*	Northern Europe, Han Chinese Japanese	–
	SJS and TEN	*B*15:11*	Japanese	–
Oxcarbazepine	SJS and TEN	*B*15:02*	Han Chinese	–
Phenytoin	SJS and TEN	*B*15:02*	Han Chinese, Thai	–
	SJS and TEN	*B*13:01*	Han Chinese	–
	SJS and TEN	*Cw*08:01*	Han Chinese	–
	SJS and TEN	*DRB1*16:02*	Han Chinese	–
	SJS and TEN, DRESS	*B*15:02*	Thai	–
Lamotrigine	SJS and TEN	*B*15:02*	Han Chinese	–
	SJS and TEN	*B*38*	Han Chinese	–
	SJS and TEN	*B*58:01*	European	–
	SJS and TEN	*A*68:01*	European	–
	SJS and TEN	*Cw*07:18*	European	–
	SJS and TEN	*DQB1*06:09*	European	–
	SJS and TEN	*DRB1*13:01*	European	–
Allopurinol	SJS and TEN, DRESS	*B*58:01*	Han Chinese European Japanese Asian	–
Antibacterial sulfonamides	SJS and TEN, DRESS	*Cw*4*	Han Chinese	–
	SJS and TEN	*B*38*	European	
Nevirapine	SJS and TEN	*C*04:01*	Malawian	–
Dapsone	DRESS	*B*13:01*	Han Chinese	–
Methazolamide	SJS and TEN	*B*59:01*	Korean, Japanese	–
	SJS and TEN	*CW*01:02*	Korean, Japanese	–
Oxicam	SJS and TEN	*B*73*	European	–
	SJS and TEN	*A*2*	European	–
	SJS and TEN	*B*12*	European	–

SCARs=severe cutaneous adverse reaction. SJS and TEN=Stevens–Johnson syndrome and toxic epidermal necrolysis. DRESS=drug reaction with eosinophilia and systemic symptoms. HLA=human leukocyte antigen.

Table S3: **SCARs' Drug-HLA associations**[40–49]

SCORTEN	
Independent prognosis factors	**Points**
Age ≥40 years	1
Heart rate ≥120/min	1
Active cancer/hematological malignancy	1
Body surface area ≥10%	1
Serum urea (>10 mmol/L)	1
Serum bicarbonates (<20 mmol/L)	1
Serum glucose (>14 mmol/L)	1
Total score	**Predicted mortality (%)**
0–1	3·2
2	12·1
3	35·8
4	58·3
>5	90

Table S4: **Prognosis SCORE for Stevens Johnson Syndrome and Toxic epidermal necrolysis (TEN) at admission: SCORTEN[4]**

SCARs	High-risk drugs	Low-risk drugs	Unclassified-risk drugs	
			According to the literature review and case series	According to safety monitoring by regulatory agencies
SJS and TEN[15, 119-123,125]				
	Xanthine oxidase inhibitors Allopurinol*	**Antibiotics** ***β-lactams*** Aminopenicillins, Cephalosporins	Moxifloxacin Pantoprazole	Doxycycline (2007)[†] Strontium ranelate (2007)[†] Modafinil (2008)[†] Lenalidomide (2008)[‡]
	Antiepileptics **Amine aromatic agents** Carbamazepine*, Oxcarbazepine, Hydantoins*, Phenobarbital*	***Fluoroquinolones*** Ciprofloxacin, Grepafloxacin, Levofloxacin, Norfloxacin, Ofloxacin		Armodafinil (2008, 2010)[†] Bumetamide (2010)[‡] Febuxostat (2010)[‡] Levetiracetam (2010)[‡] Atazanavir (2011)[†] Telaprevir (2011)[‡] Ipilimumab (2011) [‡‡]
	Others Lamotrigine*	***Tetracyclines*** Doxycycline, Methacycline, Minocycline		Tetrazepam (2013)[†] Acetaminophen (2013)[‡] Paracetamol (2014)[†] Nivolumab (2015)[††] Pembrolizumab (2015) [††]
	Antibacterial sulfonamides & derivates Co-trimoxazole*, Sulfadiazine*, Sulfasalazine*, Sulfadoxine*	**Others** Ethambutol, Rifampicin, Imidazole anti fungal agents		Ambroxol-bromhexine (2015)[†] Iodinated Contrast Media (2015)[‡] Bortezomib (2016)[‡] Bendamustine hydrochloride (2016)[†]
	NSAIDs Oxicam*	**NSAIDs** Ketoprofen, Naproxen, Acetylsalicylic acid		
	Others Nevirapine*, Efavirenz, Etravirine Sertraline, Amifostine	**Others** Sulindac, Amithiozone, Chlormezanone, Phenylbutazone, Corticosteroids		
DRESS [2, 96, 97, 115-116,124]				
			Xanthine oxidase inhibitors Allopurinol	Strontium ranelate (2007)[†] Minocycline (2008)[‡] Modafinil (2008)[‡] Gabapentin (2009)[‡] Armodafinil (2010)[‡]
			Antiepileptics **Amine aromatic agents** Carbamazepine, Oxcarbazepine,	Prasugrel (2010)[‡] Febuxostat (2011)[‡] Telaprevir (2011)[‡] Leflunomide (2013)[†]

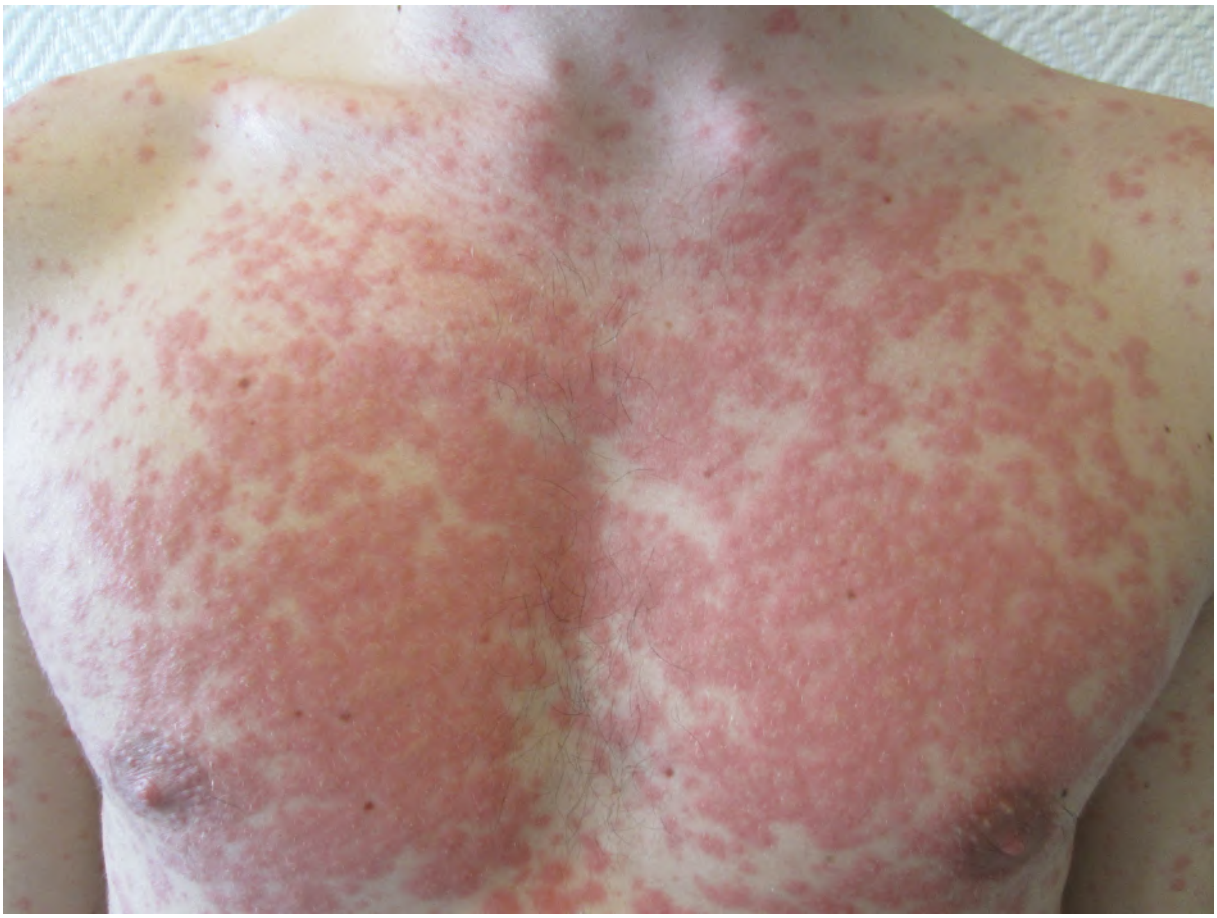
			Hydantoins, Phenobarbital	Cefepime (2014)†
				Regorafenib (2014)†
				Ziprasidone (2015)†
			Others Lamotrigine	Amikacin (2015)†
				Zonisamide (2015)‡
			Others Abacavir, Nevirapine, Salazosulfapyridine, Dapsone, Minocycline, Co-trimoxazole, Sulfasalazine, Salazosulfapyridine, Vancomycin, Amitriptyline, Streptomycin, (Hydroxy)chloroquine, Ibuprofen, Mexiletin, Omeprazole	Iodinated Contrast media (2015)‡ Bendamustine hydrochloride (2016)‡ Bonsentan (2016)‡ Olanzapine (2016)†
AGEP [28,29]	**Antibiotics** Pristinamycin*, Aminopenicillins*, Quinolones*, Antibacterial sulfonamides*, Macrolides	**Antiepileptics** Carbamazepine, Phenobarbital, Phenytoin, Lamotrigine	Allopurinol Fluindione	Acetaminophen (2013)‡ Paracetamol (2014)† Daptomycin (2015)† Iodinated Contrast media (2015)‡ Ambroxol-bromhexine (2015)† Hydroxyzine pamoate (2016)‡ Levocetirizine (2016)‡ Cetirizine (2016)‡ Flucloxacillin (2016)†
	Others Terbinafine*, (Hydroxy) chloroquine*, Diltiazem*	**Others** Oxicam, Corticosteroids		

SCARs=severe cutaneous adverse reactions. AGEP=acute generalized exanthematous pustulosis. DRESS=drug reaction with eosinophilia and systemic symptoms. SJS and TEN=Stevens–Johnson syndrome and toxic epidermal necrolysis. NSAIDs=nonsteroidal anti-inflammatory drugs.
*High- and low-risk drugs were identified using the results of case–control studies for SJS/TEN and AGEP; for DRESS they were identified using reported patient series. Unclassified drugs include those frequently reported to have a risk of SCARs or drugs under safety monitoring by regulatory agencies, ie, European Medicines Agency (EMA)† or Food and Drug Administration (FDA)‡. SCARs reported in FDA‡‡ or EMA†† approval drug notice.

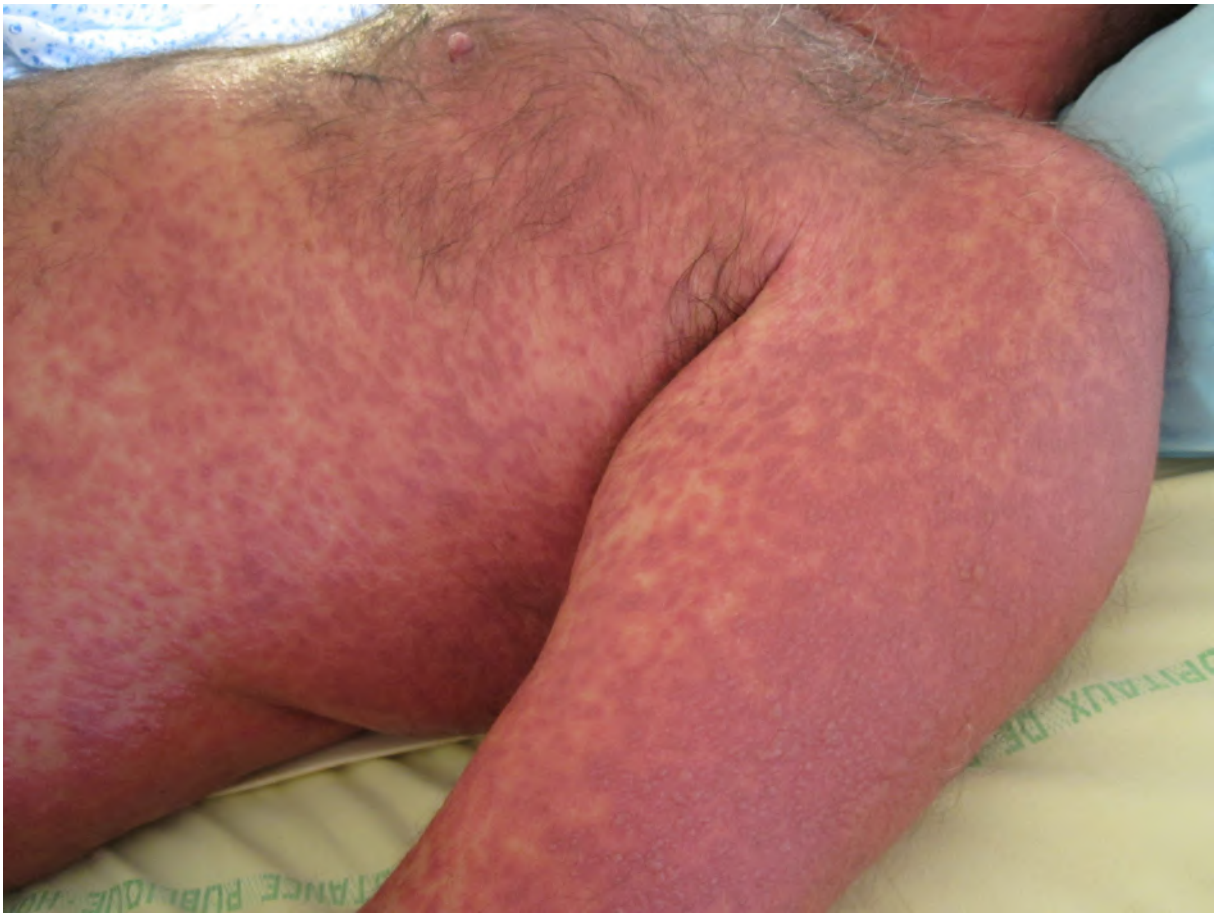
Table S5: **Main drugs associated with SCARs**

Supplemental Figure Legends

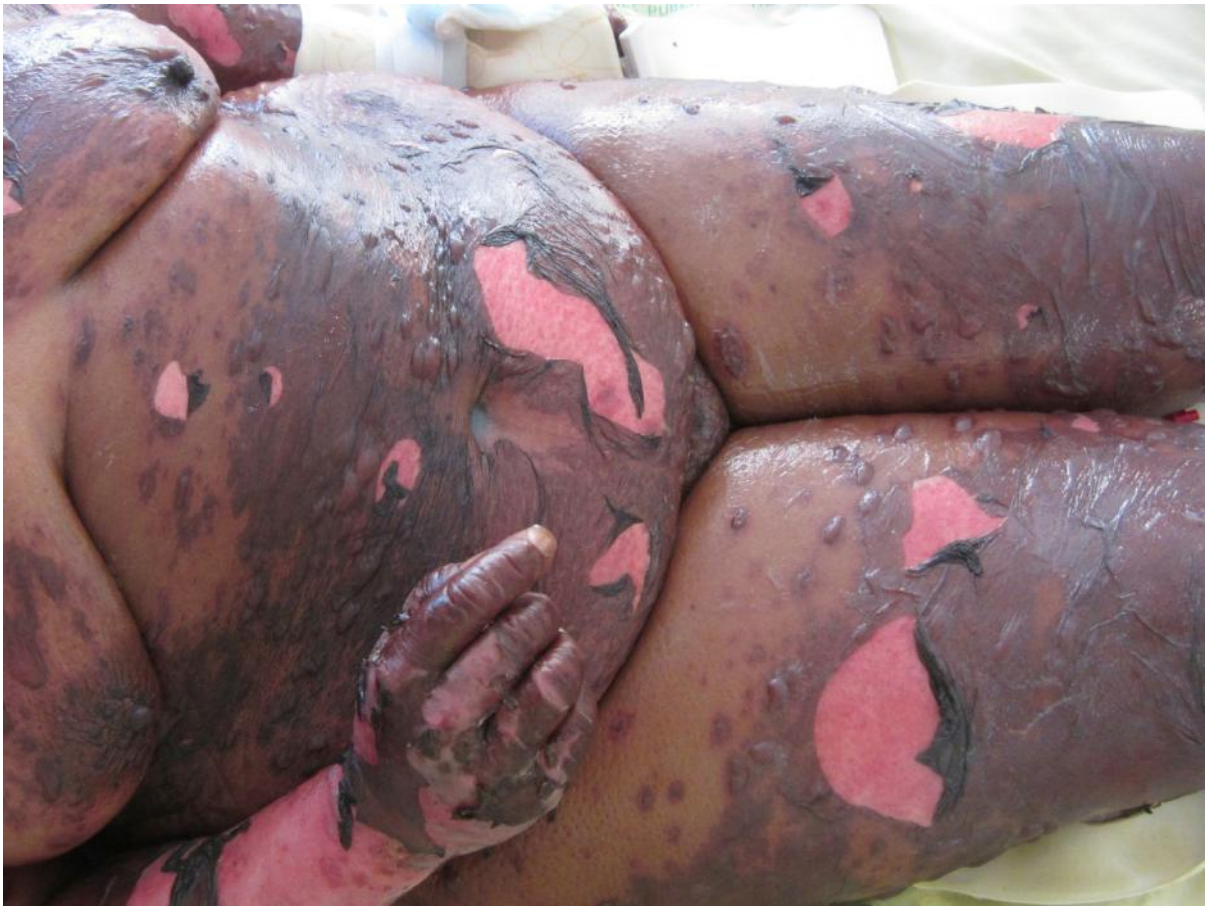
Figure S1: **Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).**
Early stage of SJS or TEN maculopapular rash (A).



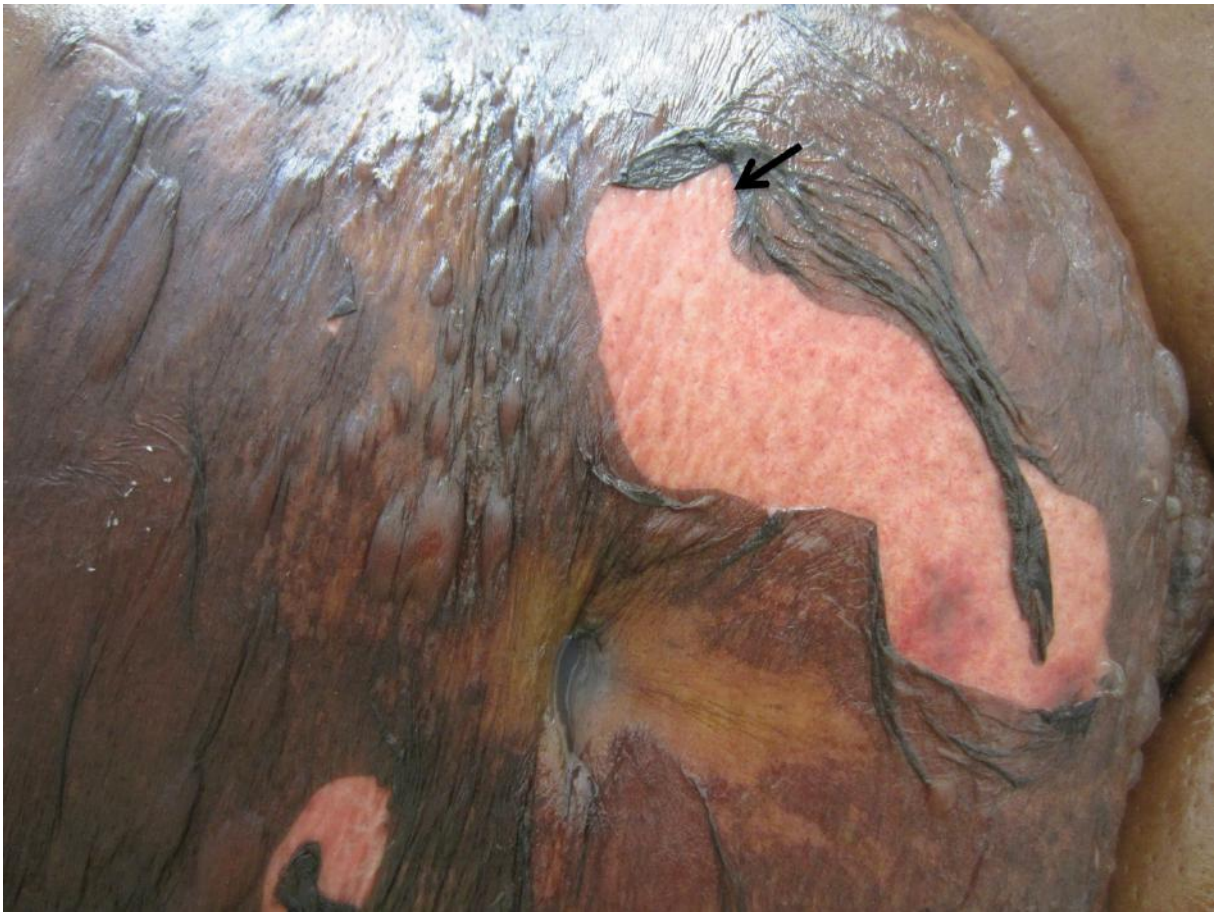
Atypical target lesions with dark centers, necrotic lesion confluence with extensive erythema (B).



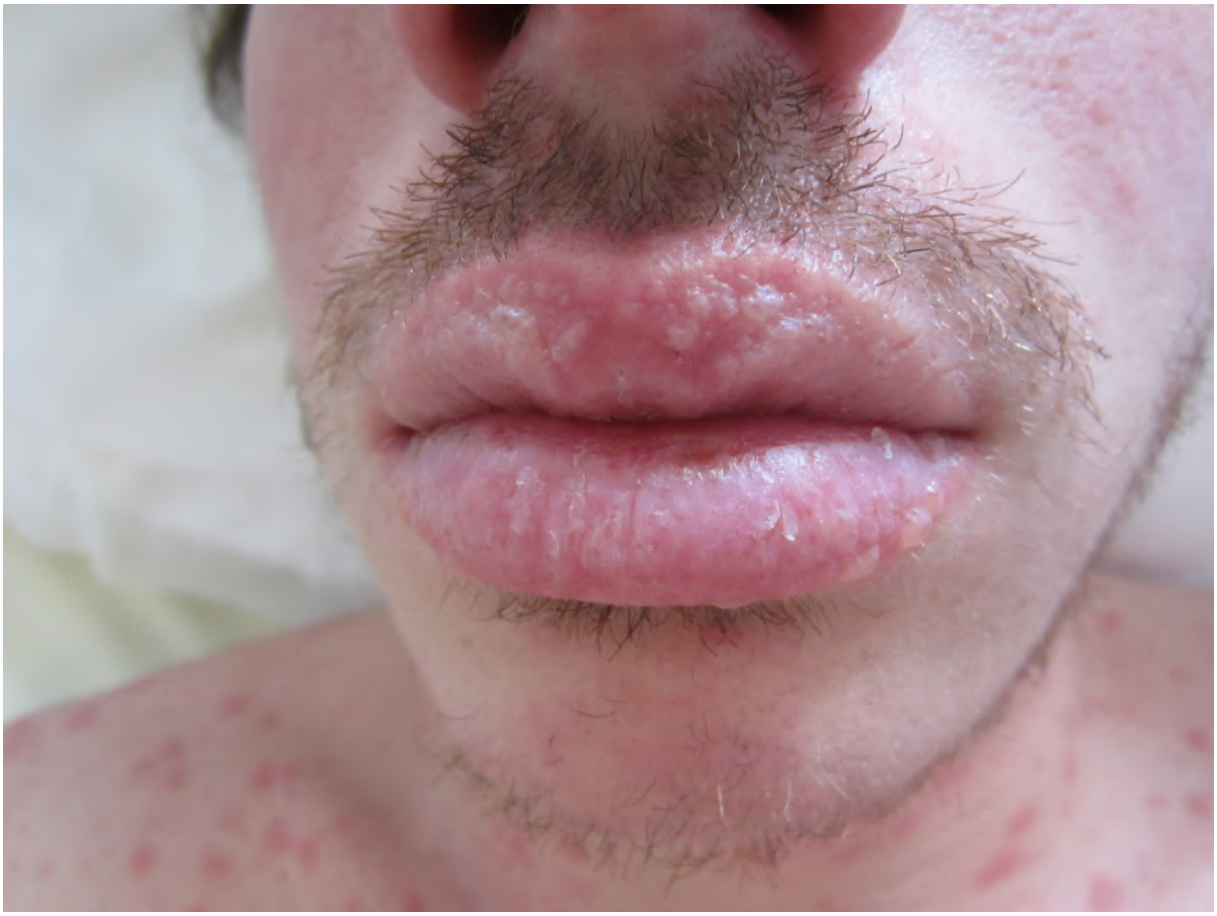
Flaccid blisters and large epidermal sheets easily detached at pressure points or minimal friction trauma, revealing large areas of exposed, red sometimes oozing dermis (C).



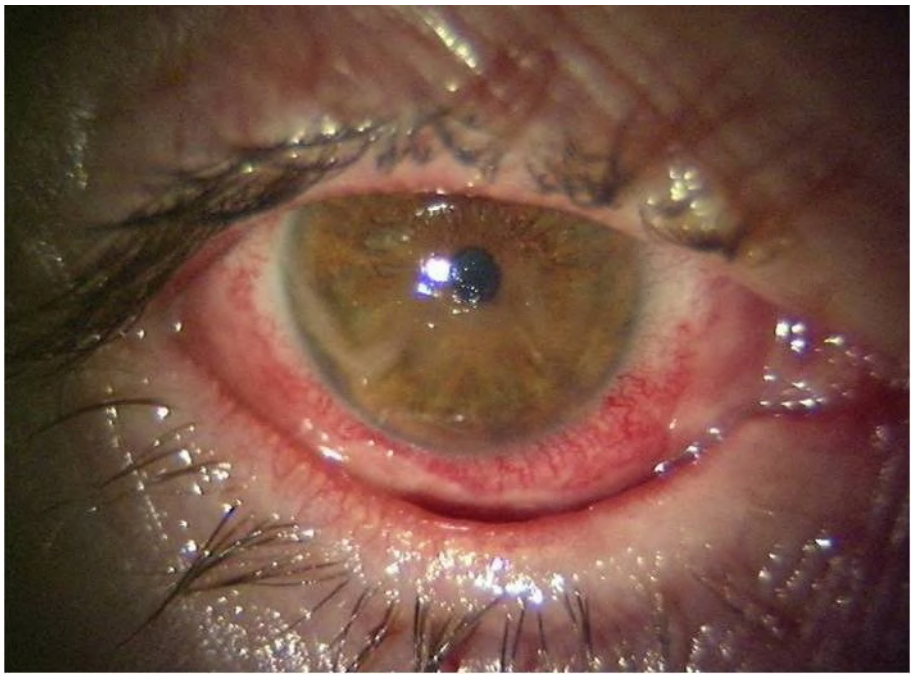
Nikolski’s sign (arrow) (D).



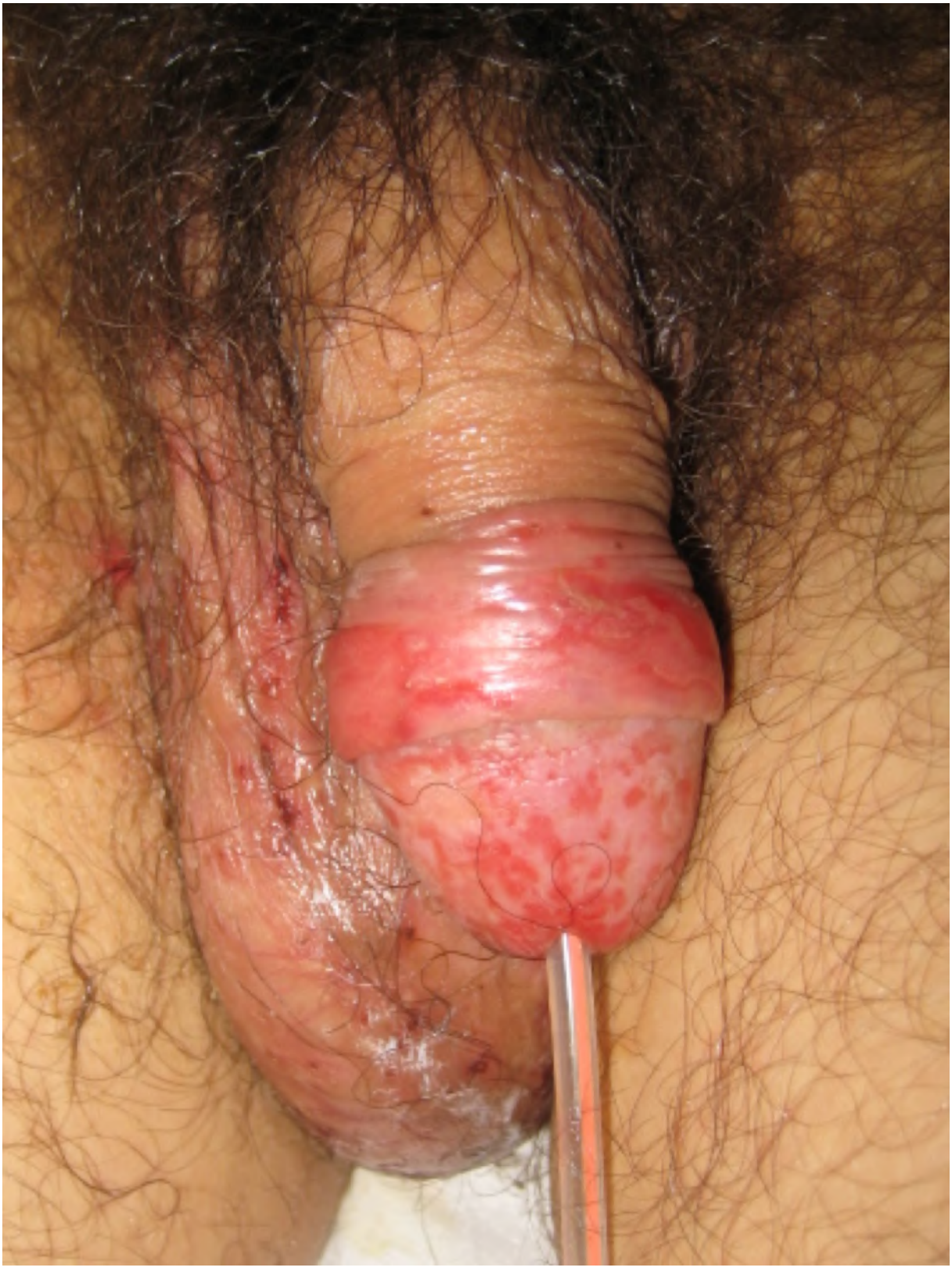
Labial vesicles at early stage (E).



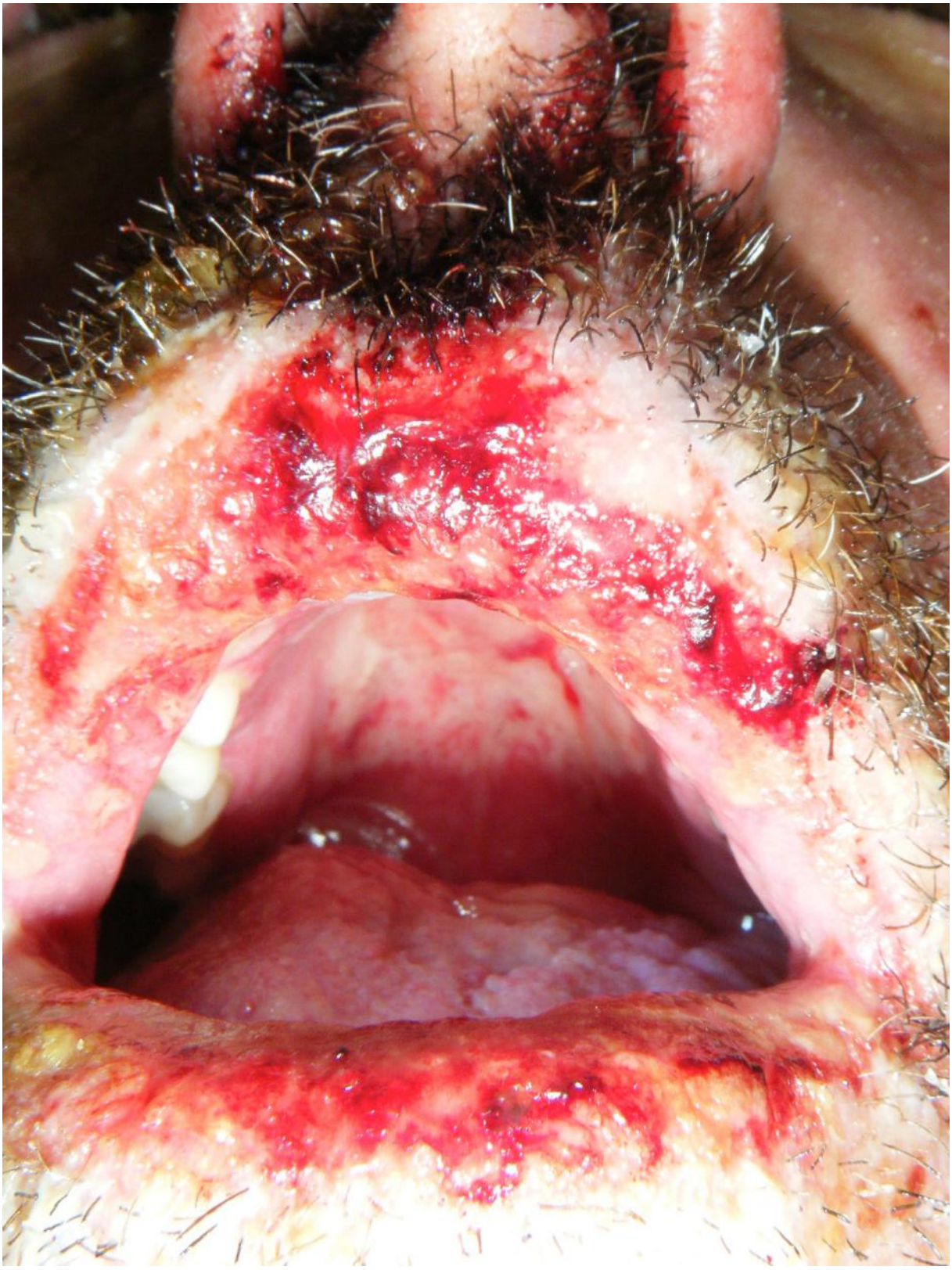
Membranous conjunctivitis associated with corneal ulcer during the acute stage (F).



Genital erosions (G).



Hemorrhagic erosions and crusts on the lips, nasal and oral cavity erosions (H).



Histology (I): the epidermis contains numerous apoptotic keratinocytes (arrow), often clustered and grouped focally with cleavage at the dermal–epidermal junction, while only a few inflammatory cells, mostly lymphocytes, are present in the superficial dermis (hematoxylin–eosin stain; original magnification: ×200). Full epidermal necrolysis can be observed in other acute syndrome of apoptotic panepidermolysis, where a fulminant epidermal cleavage is observed eg erythema multiform, lupus erythematous…)

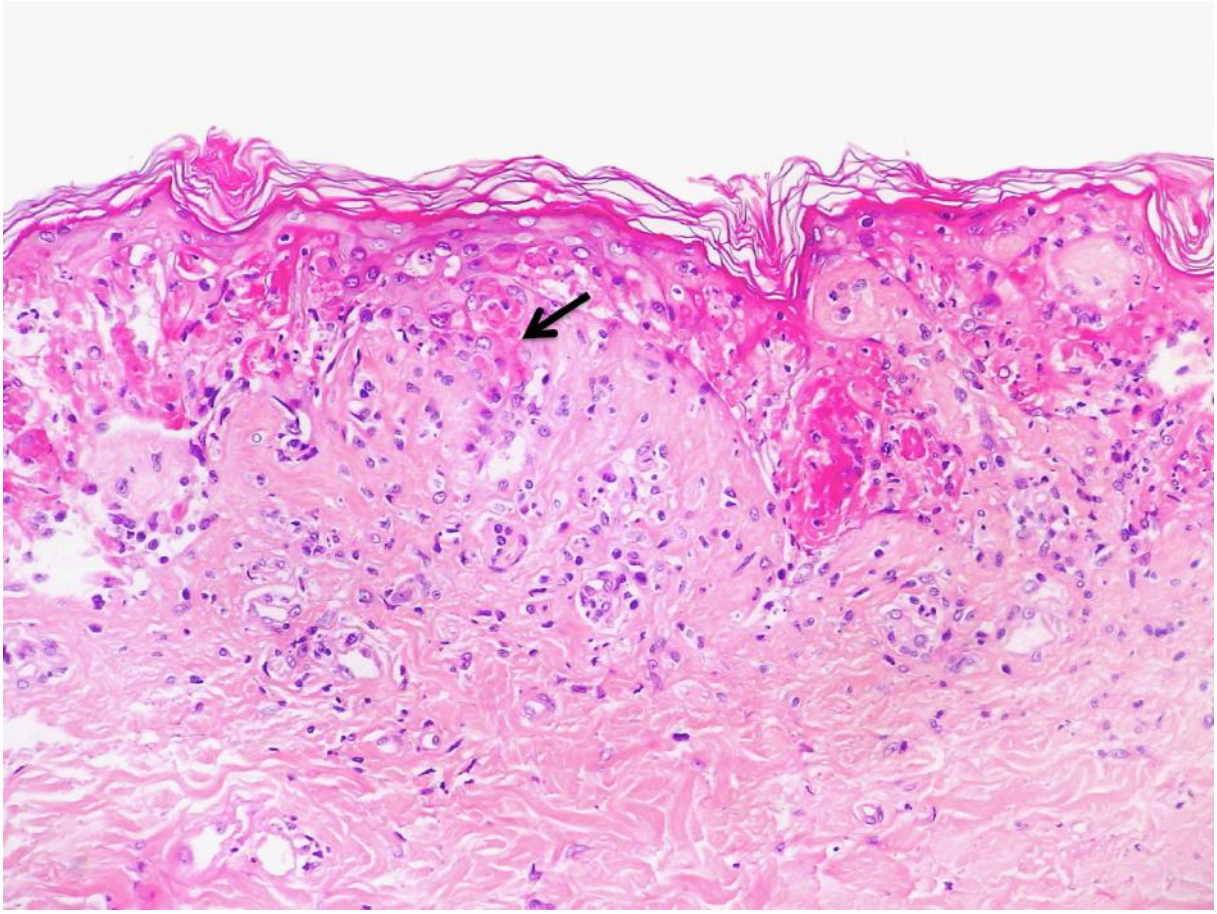


Figure S2: **Drug-induced IgA bullous dermatosis.**
Large blister with central erosions and string of pearl (arrow). Some cases of linear IgA bullous dermatosis may be drug-induced. It occurs within 24 hours to 15 days after culprit-drug intake. Clinical features include tense vesicles and blisters with annular distribution mainly on the trunk leading to a TEN-like presentation with extensive detachment. Mucous membranes are usually spared. Histology and direct immunofluorescence are mandatory and display subepidermal blisters with dermal neutrophil infiltrates and linear IgA in the basement membrane zone, respectively.[21] Resolution occurs within 3 weeks after drug withdrawal; topical corticosteroids may be useful. Main reported culprit-drugs include vancomycin, β-lactam antibiotics, captopril, NSAIDs…

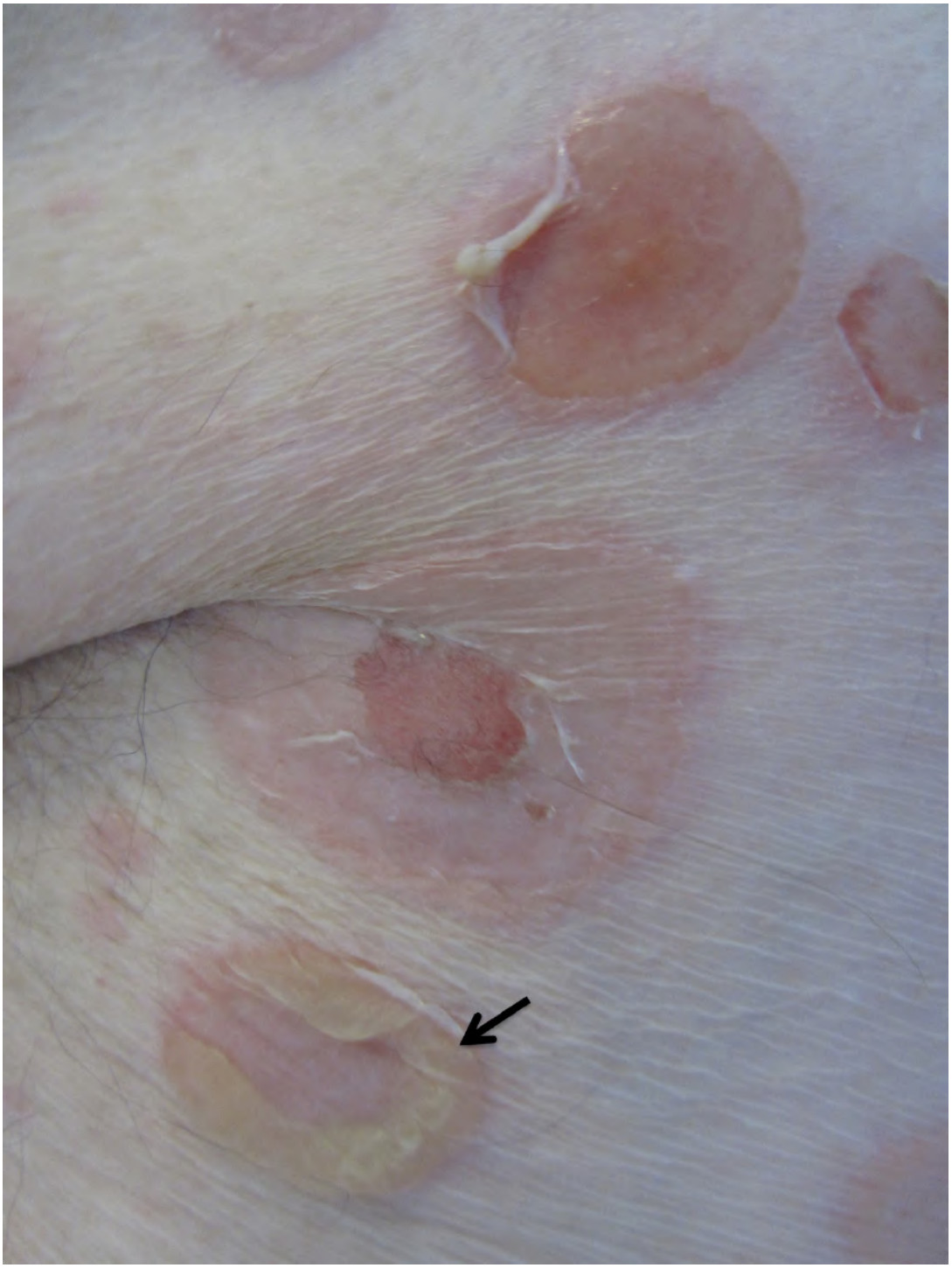


Figure S3: **Generalized bullous fixed-drug eruption of the trunk.**
Fixed-drug–eruption (FDE) lesions develop within 24 hours to 1 week after drug exposure. Lesions are numerous, round, sharply demarcated erythematous or violaceous plaques, sometimes with central blisters or detached epidermis. Confluent plaques may lead to large sheet of epidermal detachment in the so-called generalized bullous FDE. Focal or monopolar labial or genital involvement is observed. Topography is usually asymmetric, sparing a part of the body. Resolution occurs after drug withdrawal, often leaving a residual post-inflammatory brown pigmentation. Rechallenge of the causative drug leads to recurrence at the same sites, sometimes with extension. When detachment is extensive, specific management in a referral center is mandatory, because the prognosis reflects the extent of involved body surface area.[22] Histology reveals necrotic keratinocytes, dense interstitial and peri-vascular dermal mononuclear infiltrates. Focal neutrophils and eosinophils may be seen, and sometimes melanophages in non-inflammatory lesions. In comparison to SJS and TEN immunohistological pattern, FDE inflammatory infiltrate contains more CD4+ FoxP3+ T-cells and fewer CD56+ cells or intradermal granulysin.[22] Direct immunofluorescence is negative. Main culprit drugs include phenazone derivates and other NSAIDs, antibiotics (cyclines, antibacterial sulfonamides), paracetamol, carbocysteine, acetaminophen, carbamazepine and allopurinol.[22]

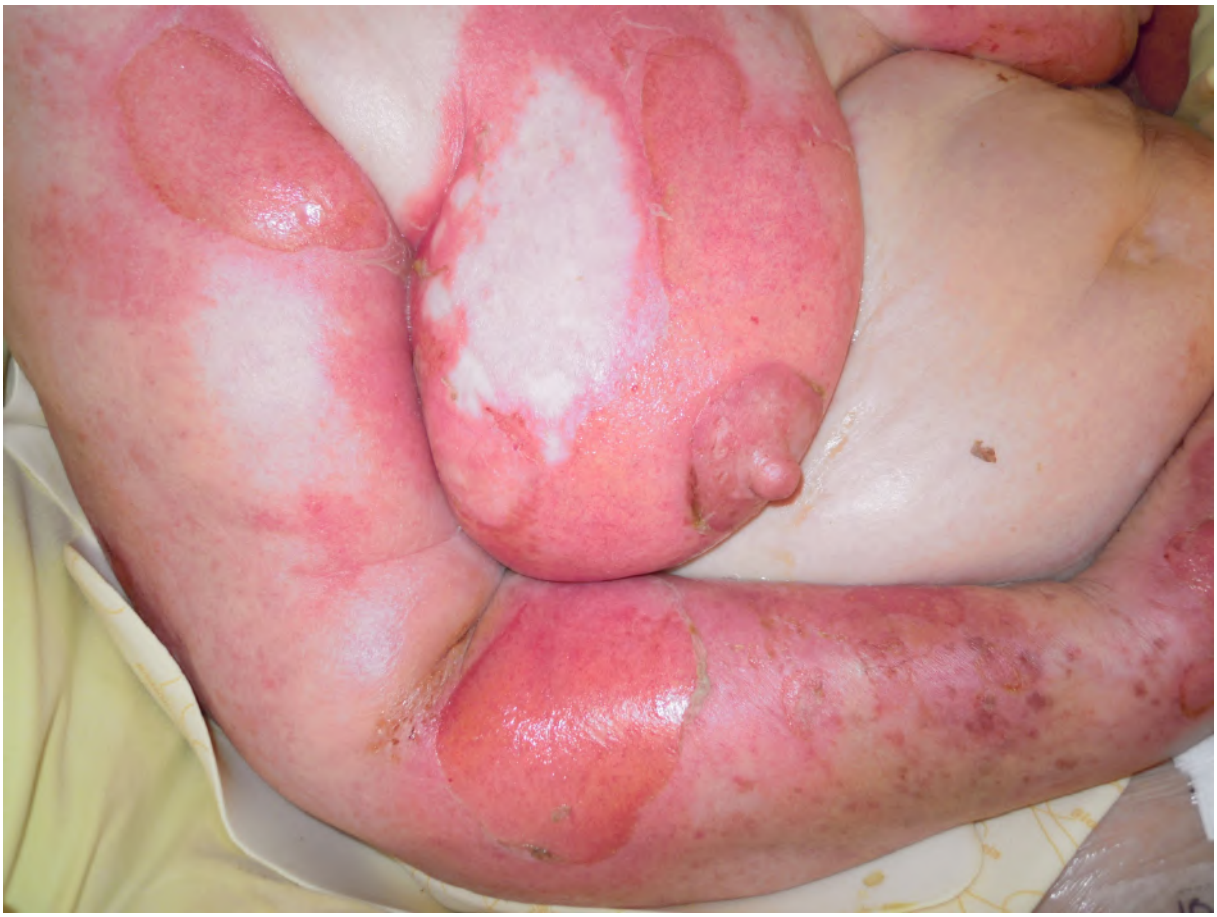
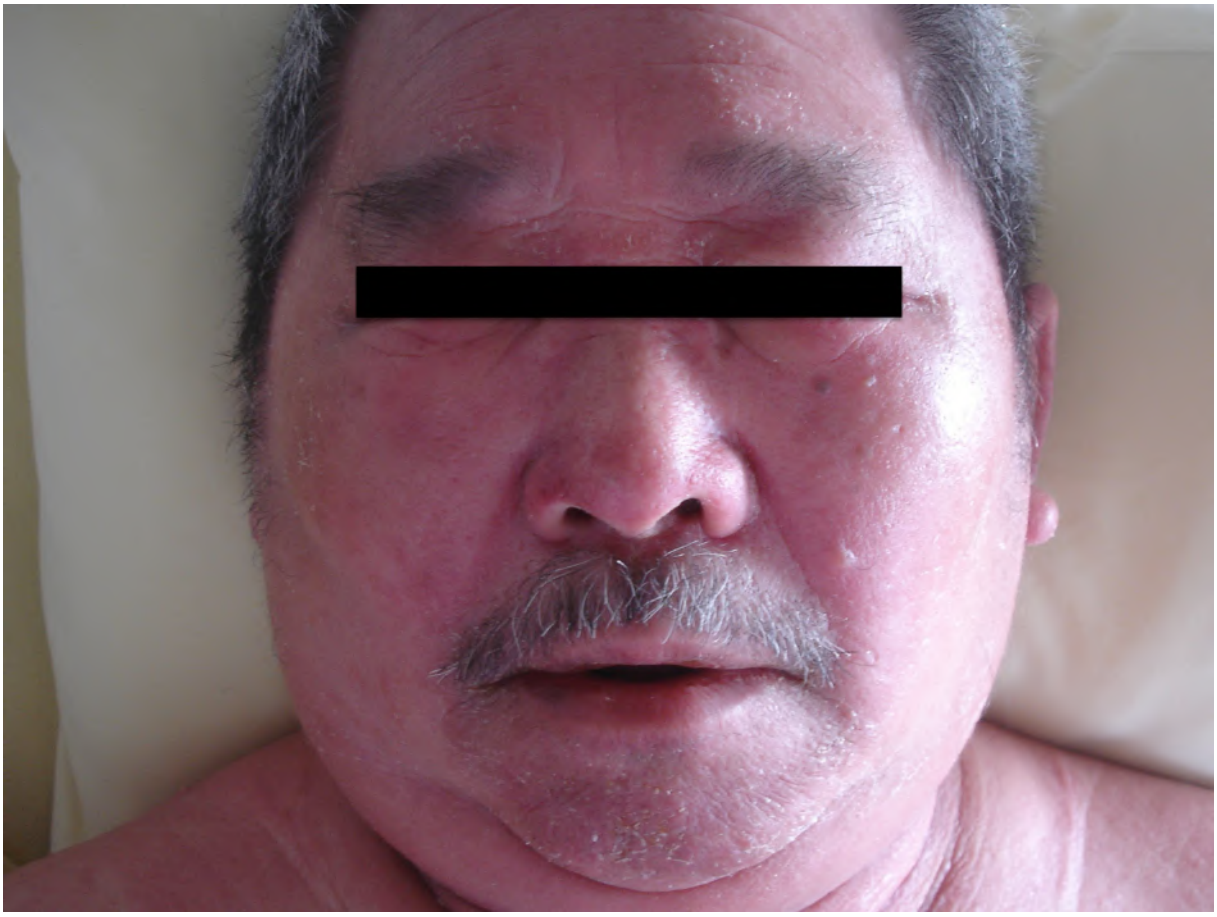
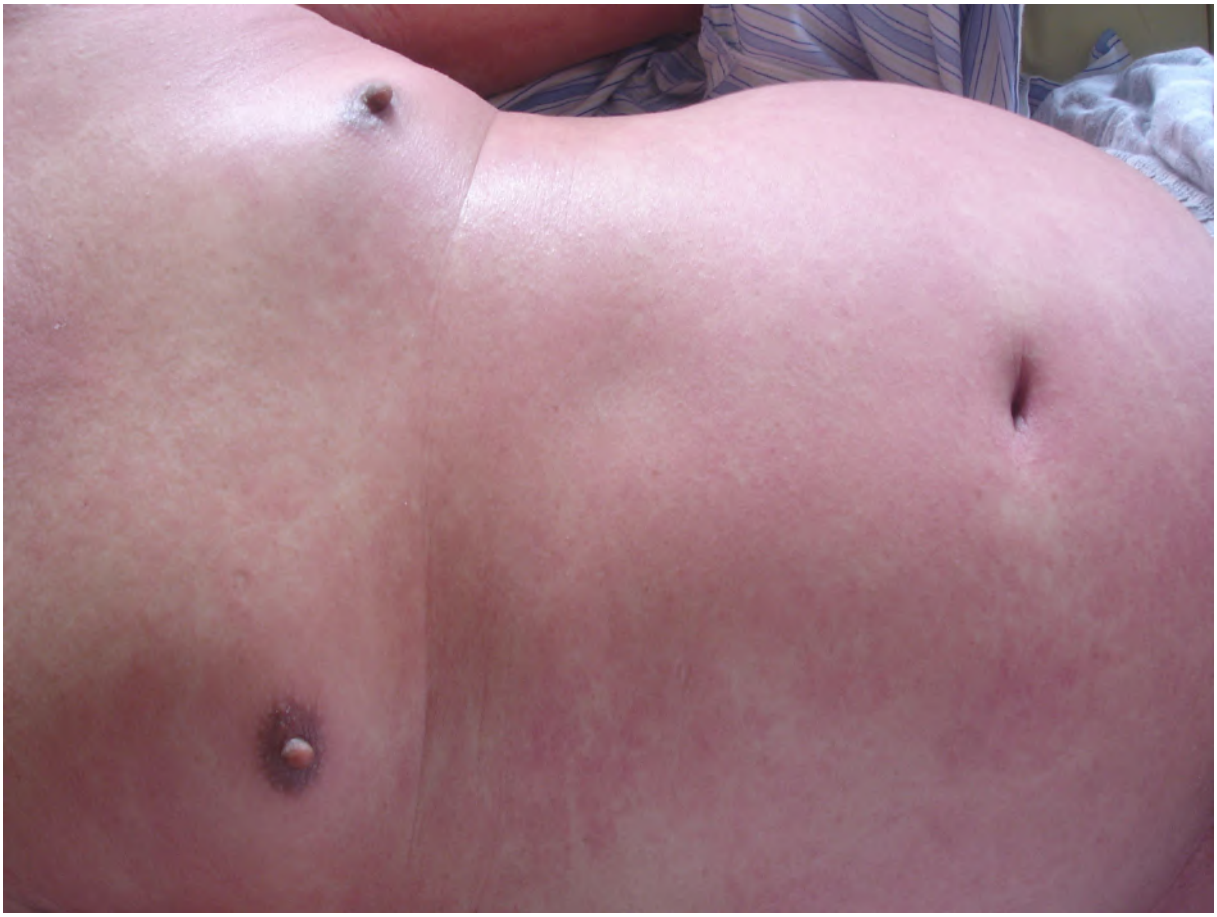


Figure S4: **Drug reaction with eosinophilia and systemic symptoms (DRESS).**
Facial oedema (A).



Erythroderma of the trunk (B).



Histology (C): the epidermis contains clusters of apoptotic keratinocytes, spongiosis with a vesicle and interface dermatitis with lymphocytes located within the vacuolised basal layer. A dense polymorphous infiltrate of lymphocytes, neutrophils and eosinophils (arrow) is seen in the superficial dermis (hematoxylin–eosin stain; original magnification: ×100).

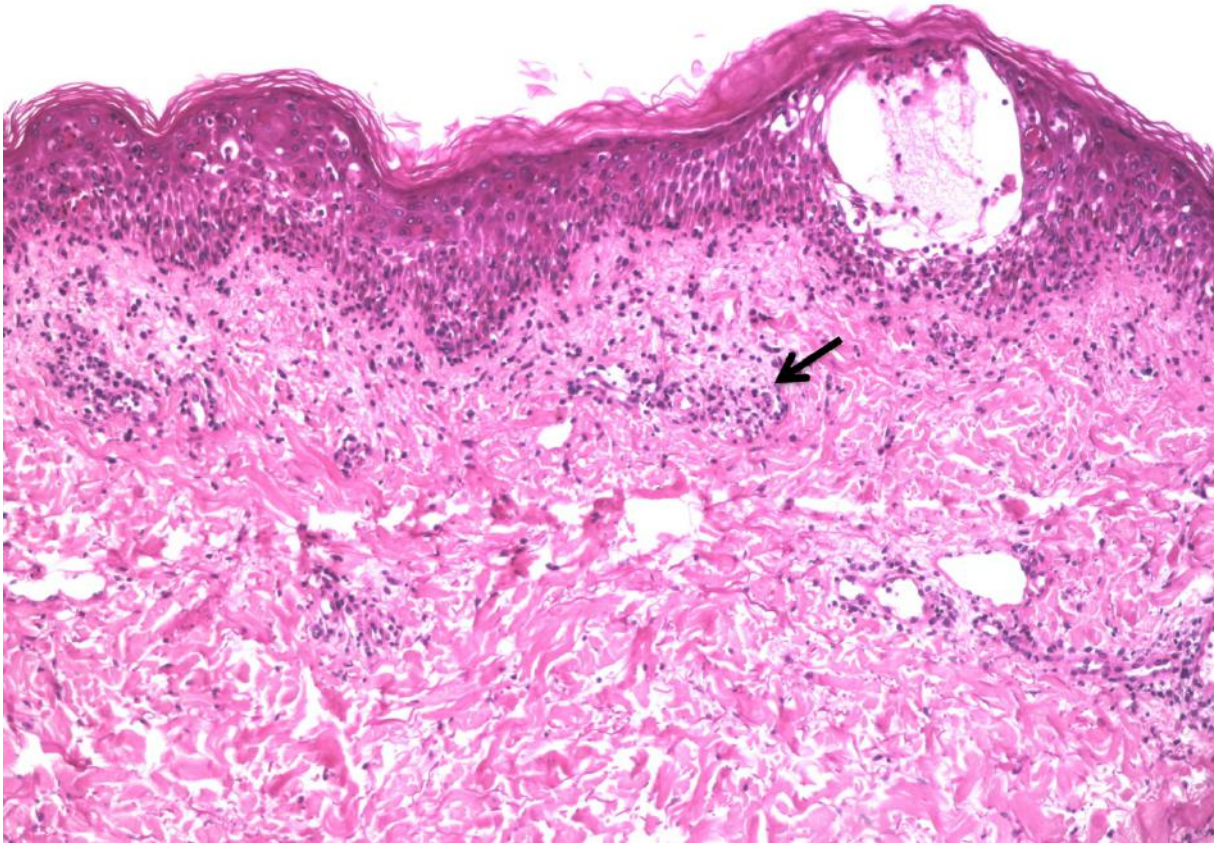
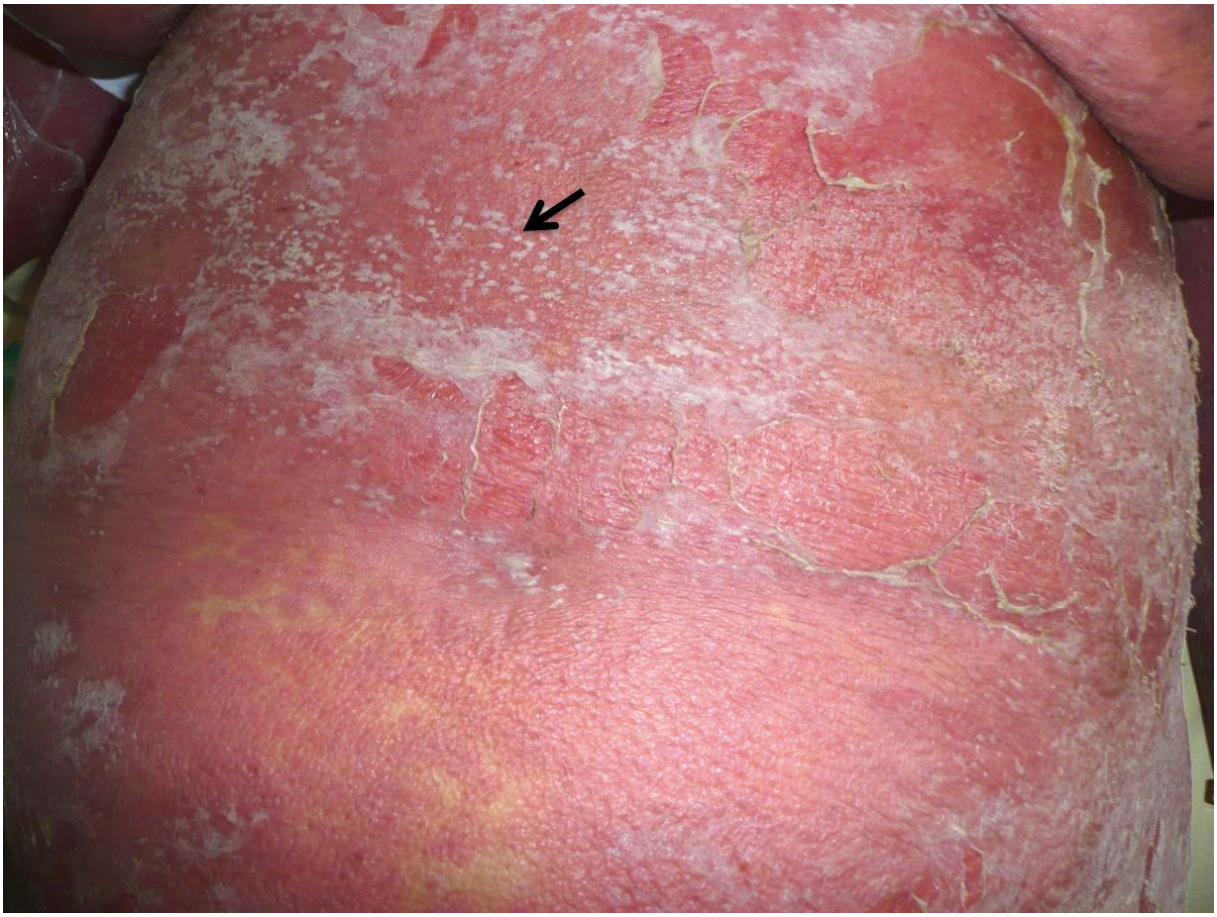
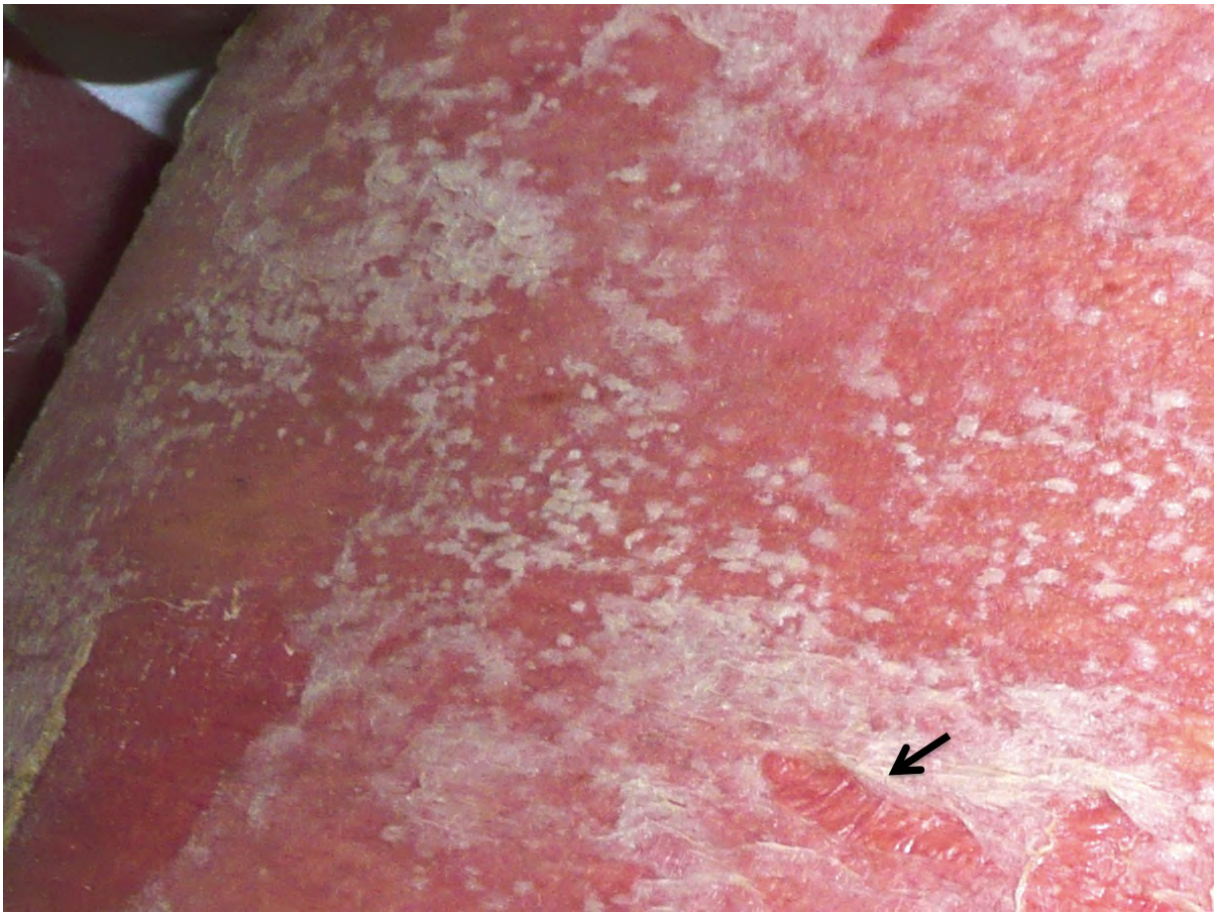


Figure S5: **Acute generalized exanthematous pustulosis (AGEP).**
Non-follicular pustules (arrow) arising on oedematous erythema of the trunk (A).



Pustule confluence mimicking Nikolski's sign (arrow) (B).



Histology (C): subcorneal multilocular pustule (arrow) with papillary oedema and a mild dermal inflammatory infiltrate composed of lymphocytes and neutrophils (hematoxylin–eosin stain; original magnification: ×100).

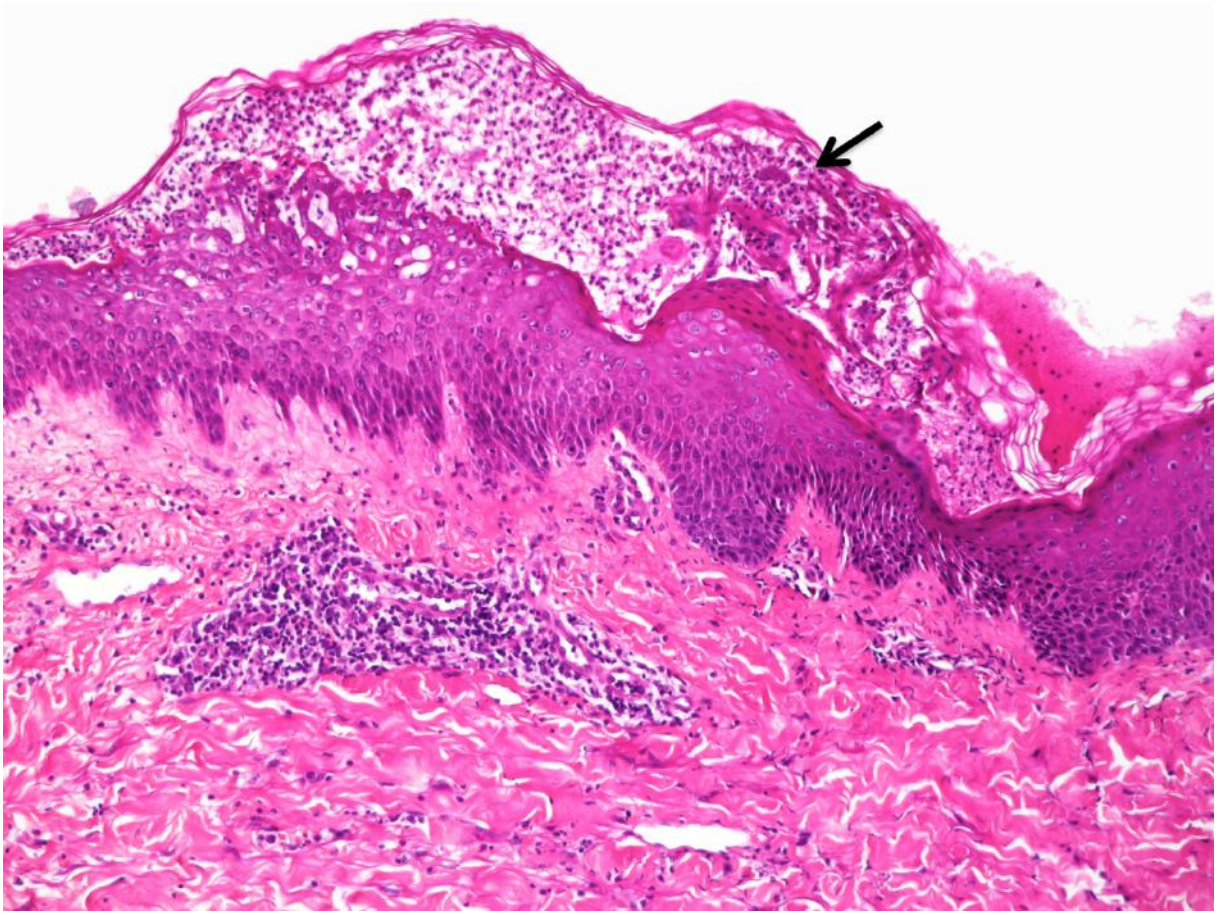
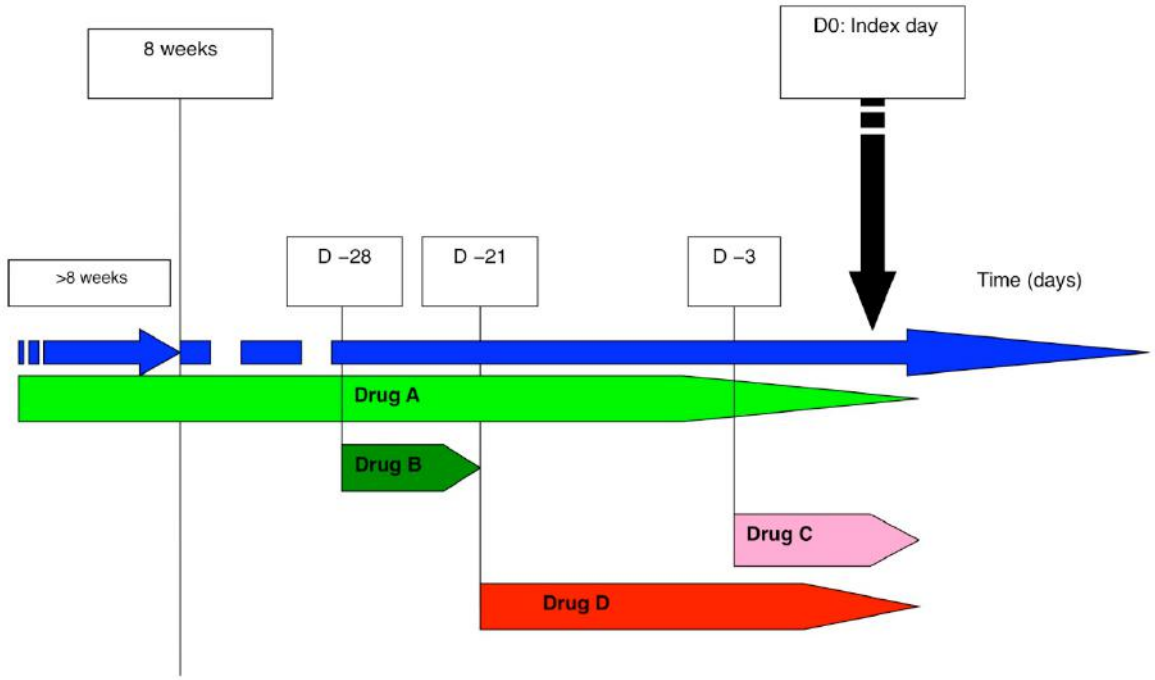


Figure S6: **Drug-causality assessment* in SCAR clinical practice†.**

*For each suspected drug, one should define: Index day D0: date of the onset of SCAR-related symptoms or signs that progressed within 3 days.[2,16,28,119] Time interval from initiation of drug intake to SCAR onset. Interpretation of the time interval includes: plasma and tissular half-lives, renal and hepatic functions, first introduction of the drug or not, and SCAR type.

Case report

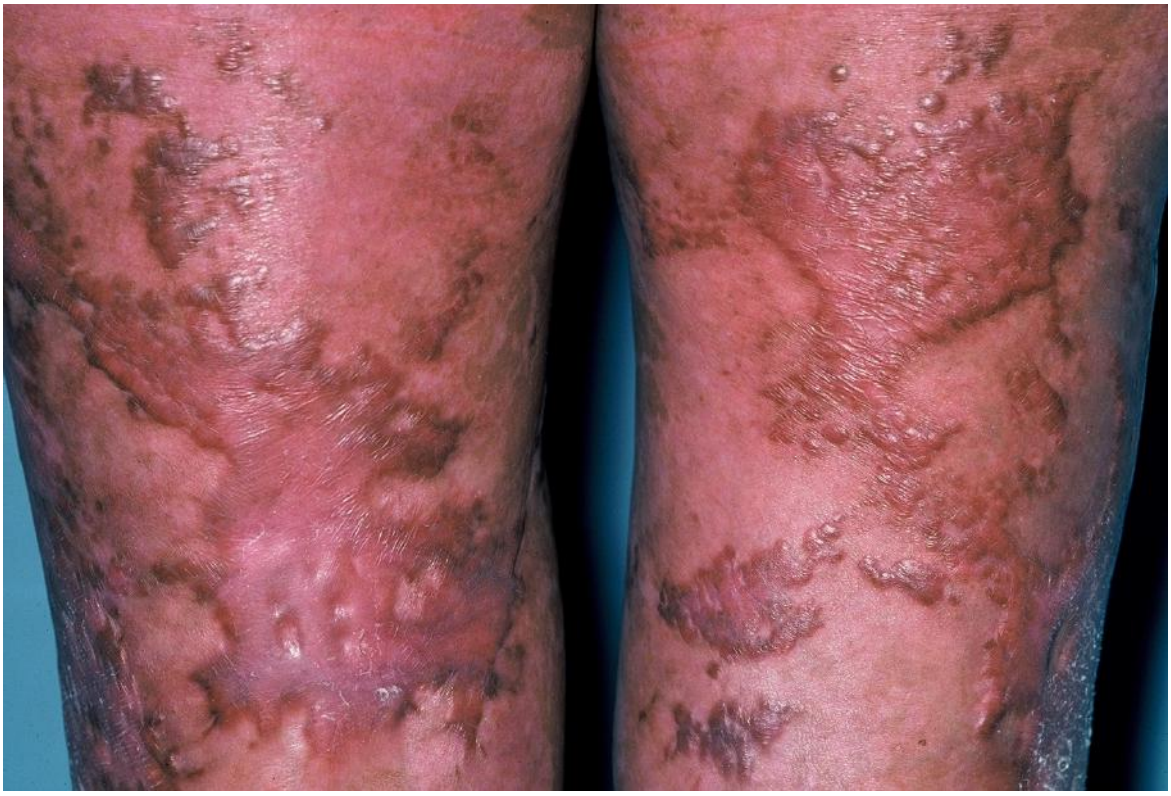
†This patient was admitted for SJS. During the preceding 2 months, 4 drugs had been taken A, B, C, and D and were never prescribed previously. He had no preexisting history of hepatic or renal dysfunction. Erosions and blisters occurred on D0, defining the index day. **What is the culprit drug ?**



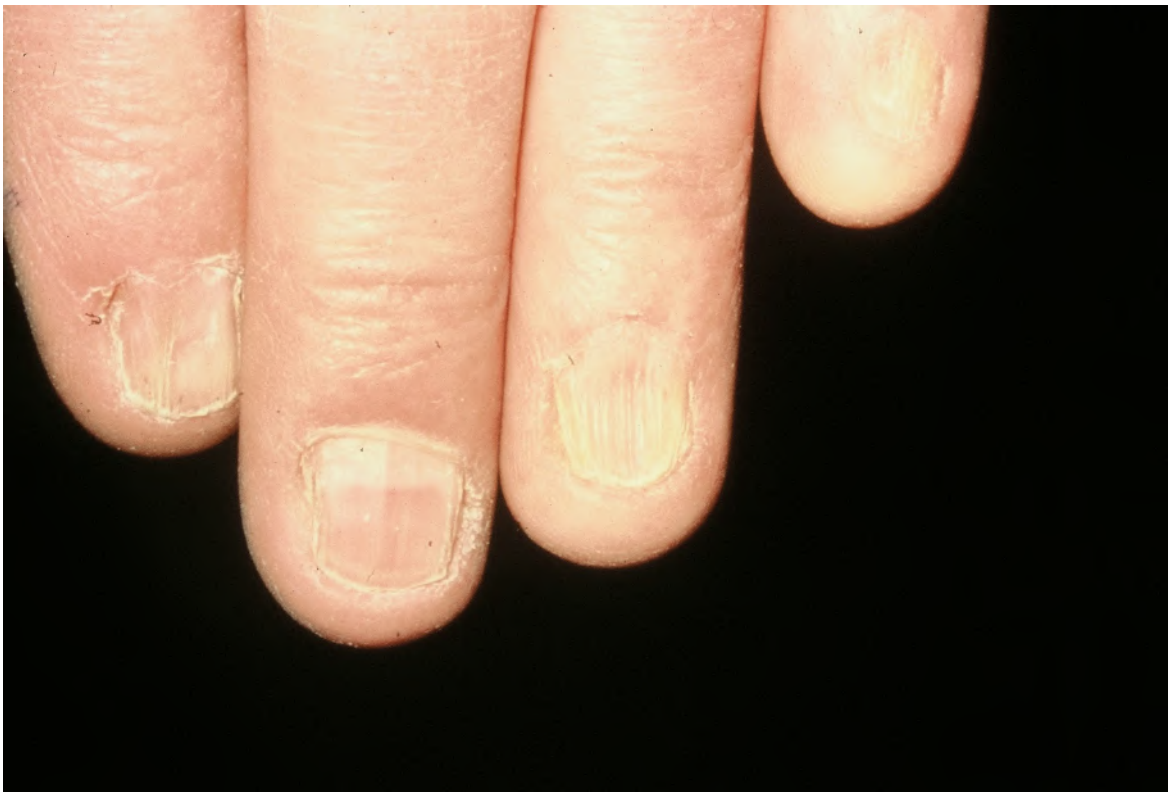
Answer

According to the specific SJS and TEN timeframe (4–28 days) (see Table 1): Drug A was taken for >8 weeks (6 months in this case report) with good tolerance. **Drug A is excluded**. Drug B was started within the 8 weeks preceding D0, **drug B is unlikely** because it was stopped 21 days before D0 and its plasma half-life is short. If drug B had had a long plasma half-life, eg, 7 days, the drug could still be present after five half-lives (35 days) and should be then suspected. Moreover, drug C was started 3 days before D0, once the patient's SJS or TEN prodromes started (ie, flu-like syndrome, skin pain, conjunctivitis). Drug C was self-prescribed and self-administered by the patient because of those "unspecific symptoms". **Drug C is unlikely**. Drug D was started 21 days before and taken until D0. Considering the type of SCARs (ie, SJS and TEN), **Drug D has to be considered the probable culprit drug**.

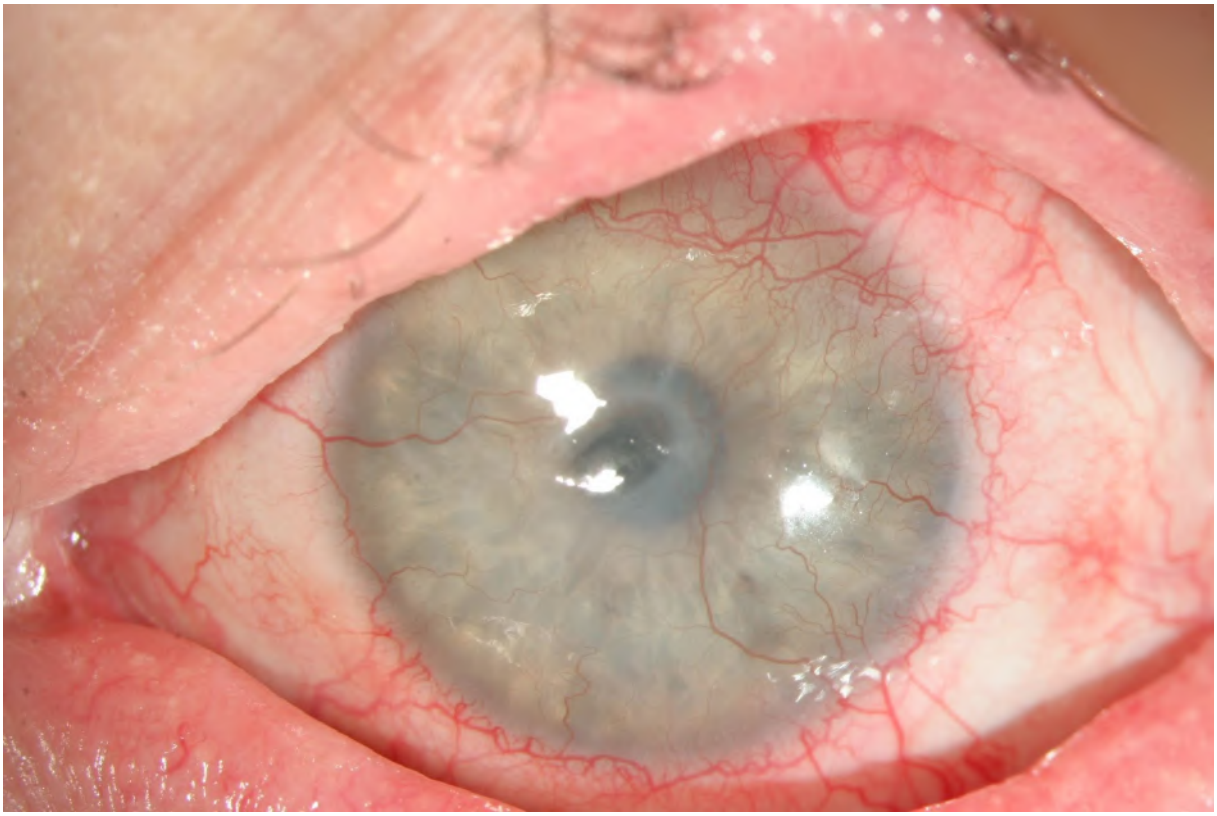
Figure S7: **SJS and TEN sequelae**
Hyperchromic, hypertrophic scars (A).



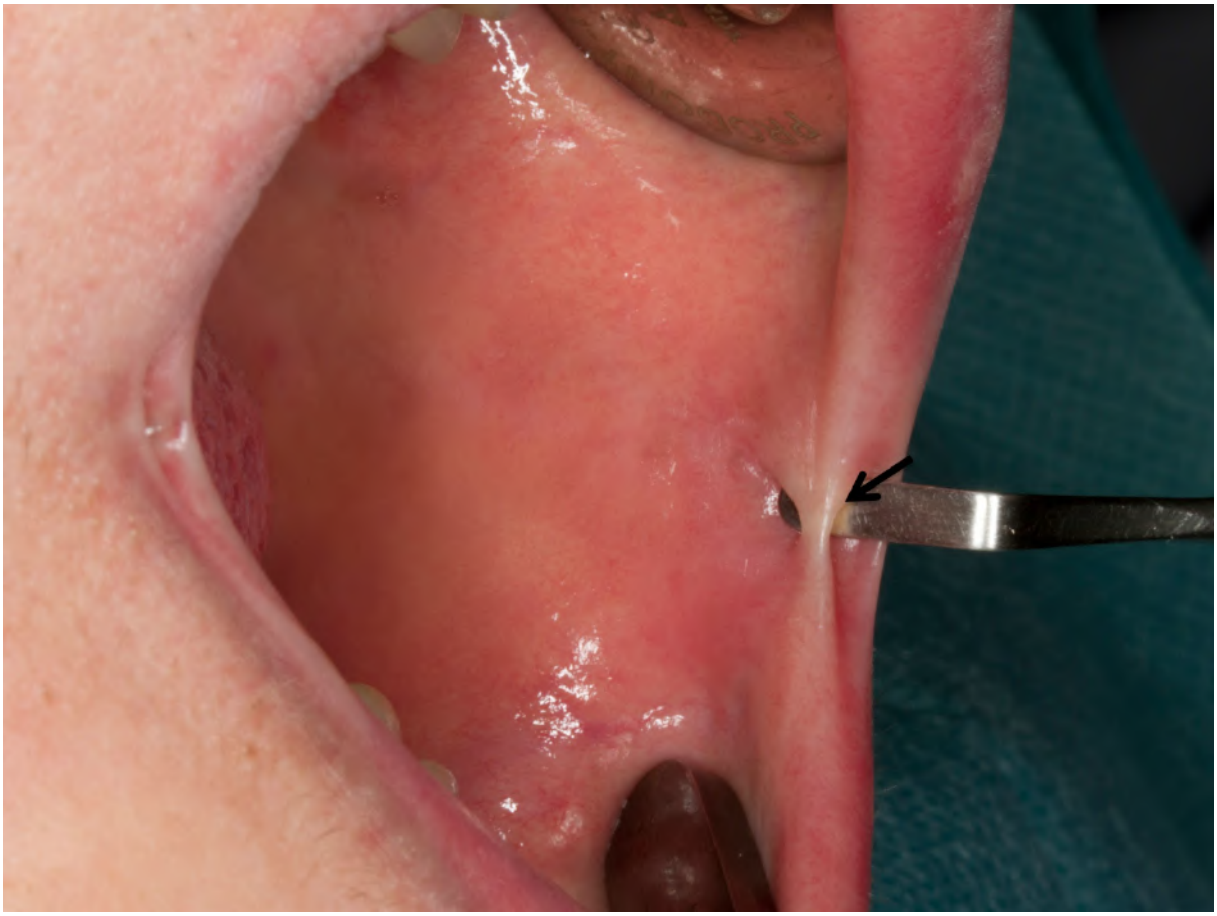
Onychodystrophy after nail loss (B).



Complete corneal neovascularization associated with central corneal ulceration as late ocular complications of TEN (C).



Oral synechiae (arrow) (D).



Chronic parodontopathy, gingival recession and synechiae (arrow) (E).