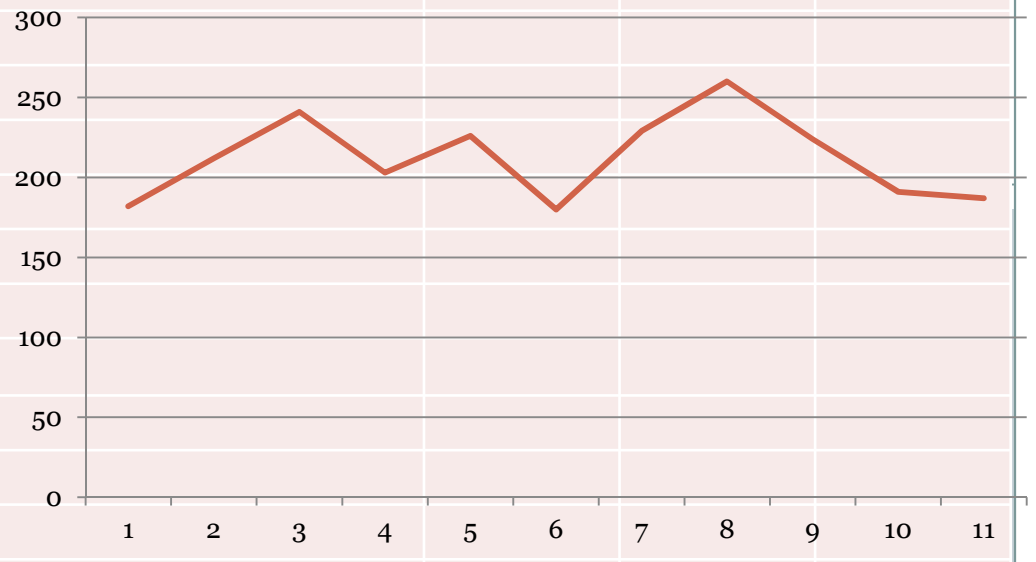
Università degli studi di Parma
Dipartimento di medicina clinica e sperimentale
Clinica Dermatologica
direttore Prof. Claudio Feliciani

Urgenze in dermatologia

CLAUDIO FELICIANI

ORTICARIA, TOSSIDERMIA E PRURITO		379
HERPES		112
PARASSITOSI		42
USTIONE		10
ERISIPELA		29
M. BOLLOSE		7
AUTOIMM		23
		602
PUSTOLOSI		123
ECZEMI		326
VERRUCHE		13
MICOSI		88
ANNESSI		21
VASCOLARI		26
PSORIASI		69
LICHEN		8
GRAN ANULARI		2
MTS		54
PUNTURE		140
NEOFORMAZIONI CUTE		117
		987
gennaio novembre 2016	1589	

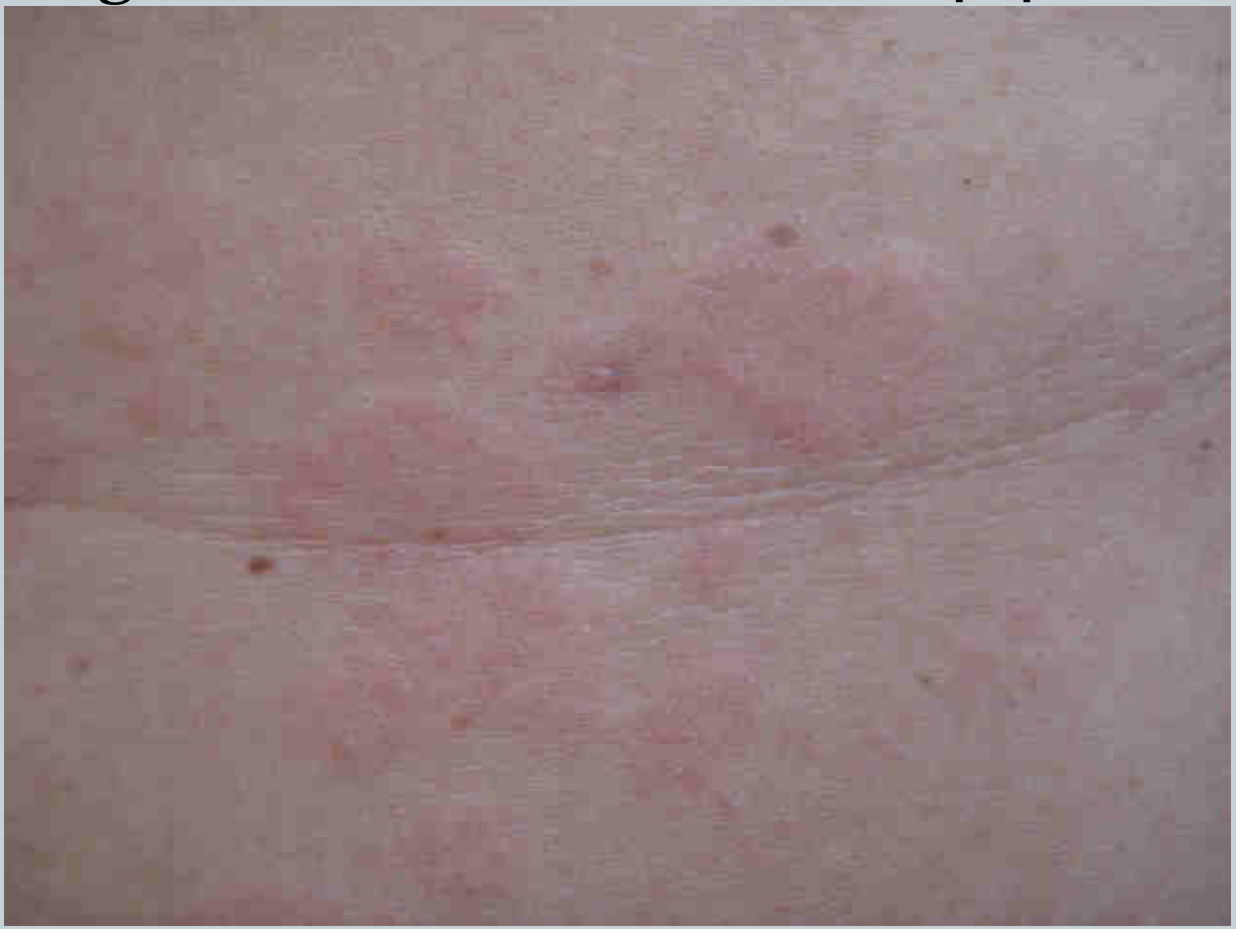


840 femmine

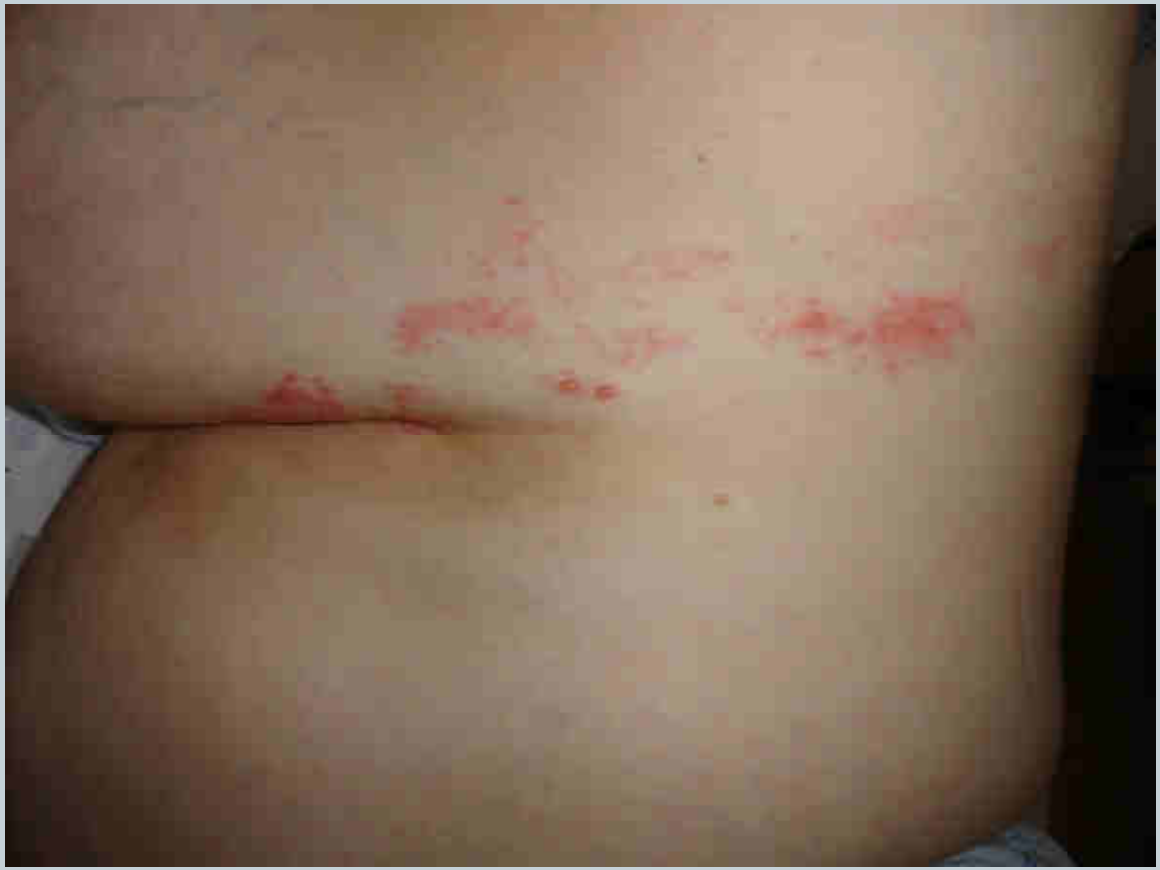
749 maschi

Orticaria

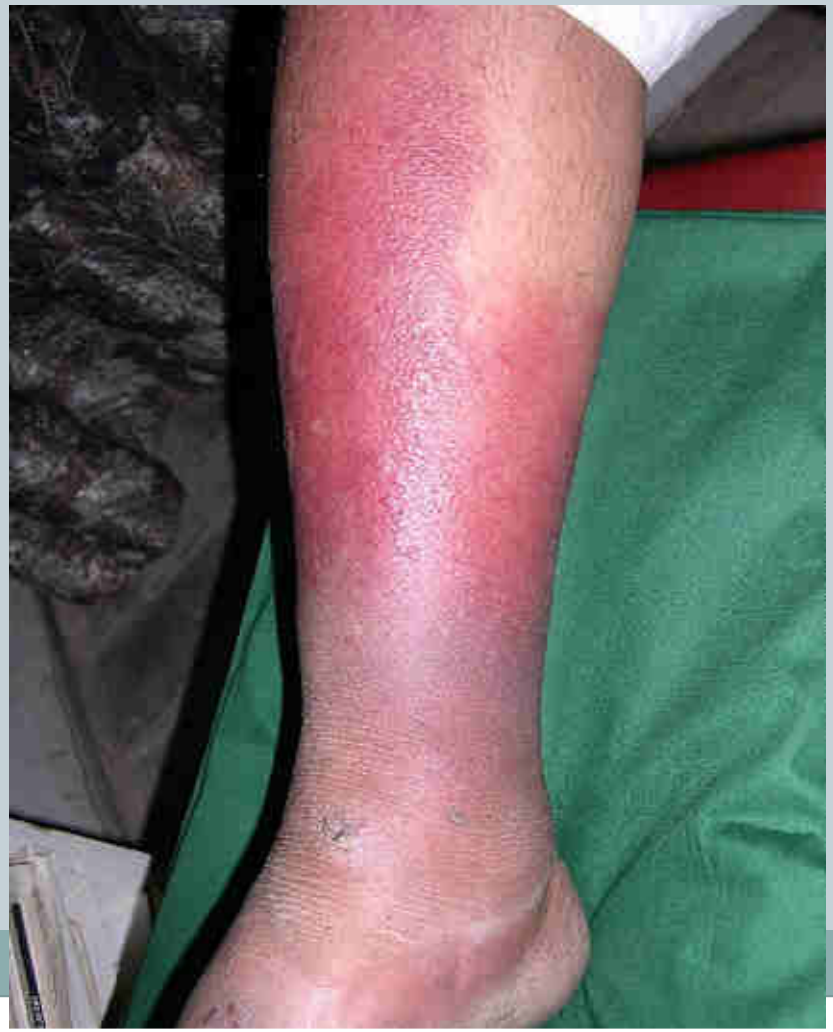
- Pomfi fugaci che durano meno di 24-48 ore



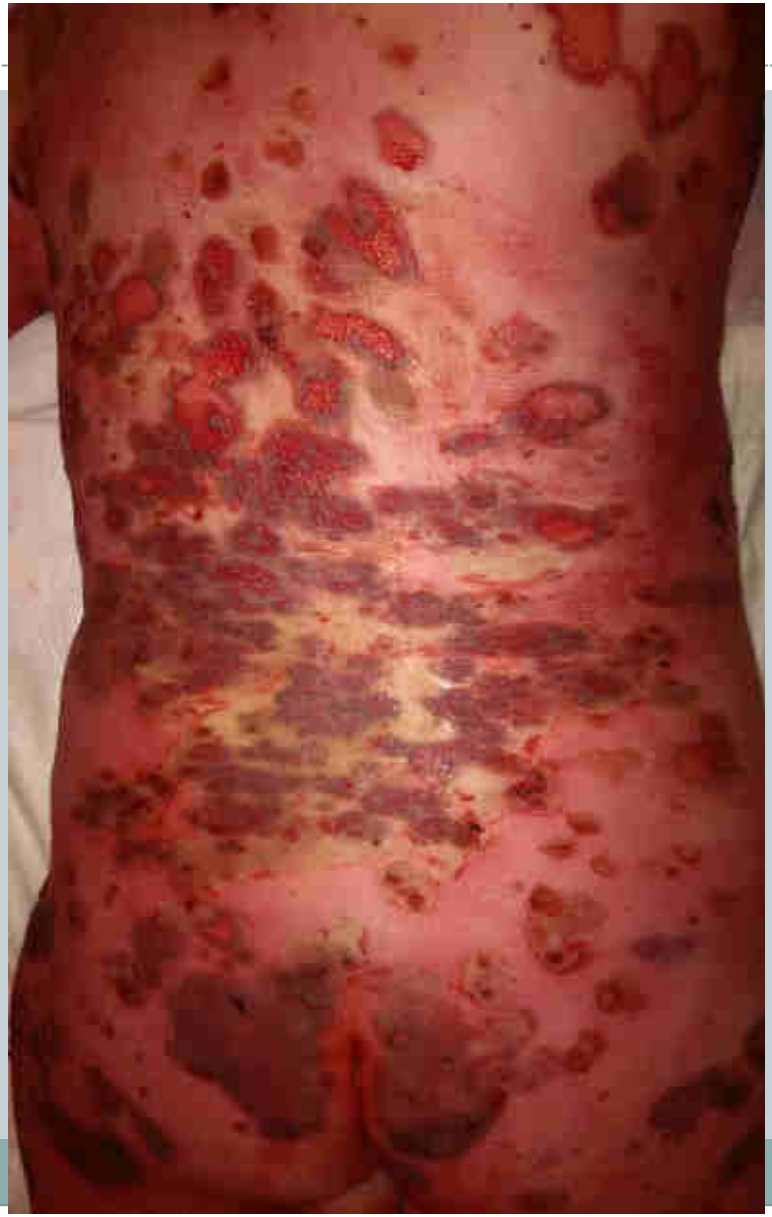
- Herpes sine Herpes

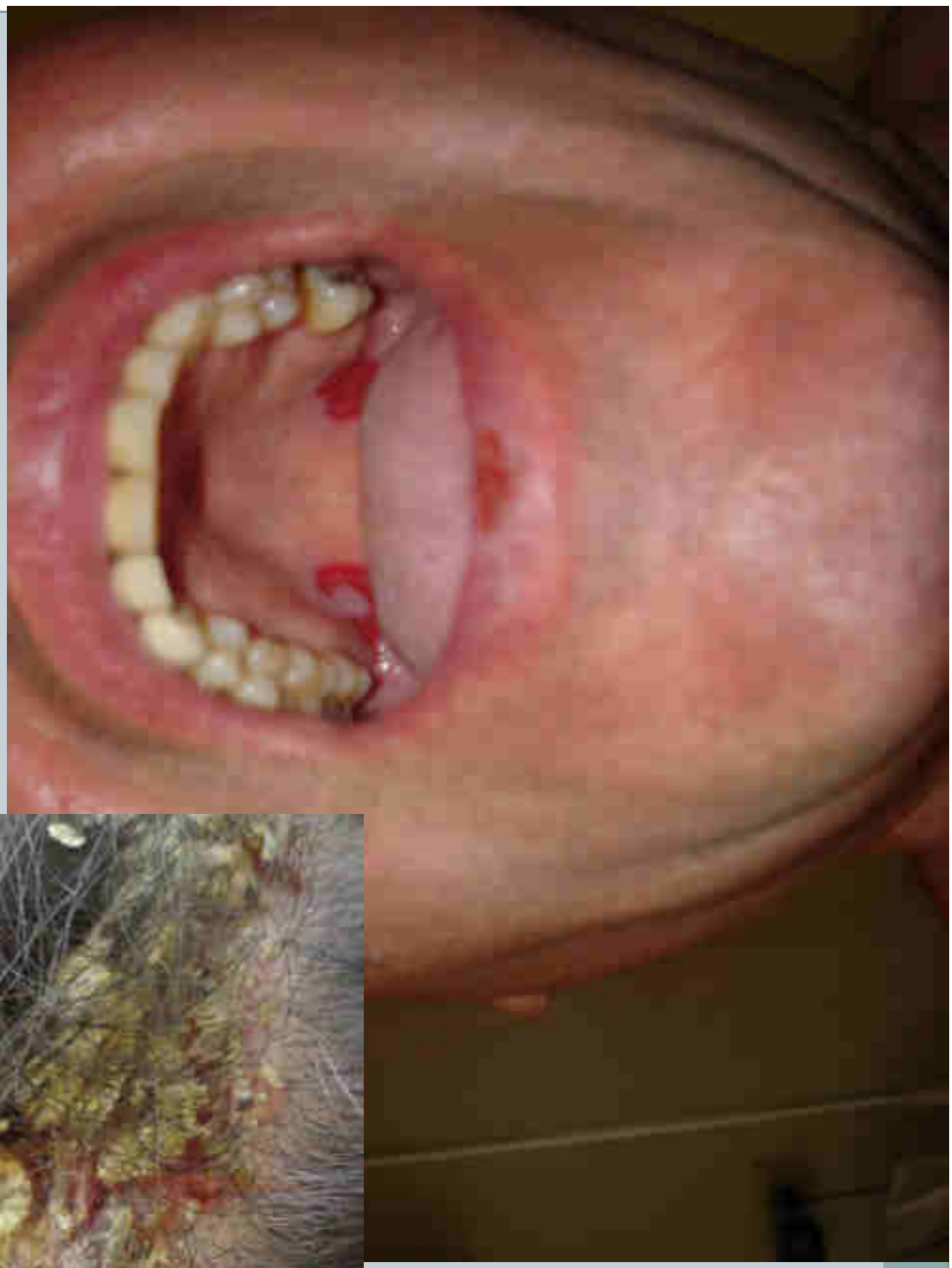


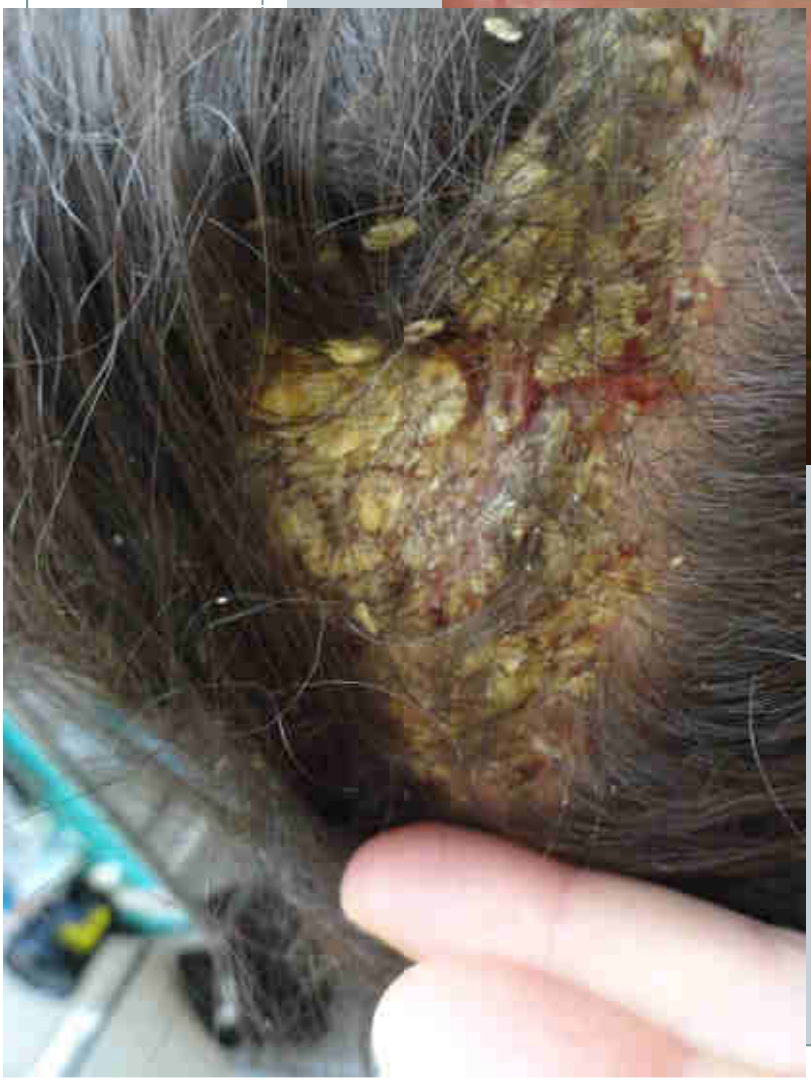
- Erisipela monolaterale e calda al tatto



Pemfigo / Pemfigoidi







condizioni cliniche identificate come "Appropriate" per la richiesta di Urgenza dermatologica H24:

- - rash o eruzione cutanea diffusa ad insorgenza improvvisa
- - herpes zooster
- - scabbia
- - dermatosi di ndd accompagnata da febbre
- - piodermiti
- - riacutizzazione di malattie autoimmuni (pemfigo, pemfigoide, eritrodermia, ecc)
- - orticaria ed angioedema
- - sovrainfezioni di dermatosi croniche
- - ulcera dell'area genitale

- Urgenze mediche
  - Urgenza dermatologica «vera (h-24)»
  - Urgenza dermatologica «differibile (7 gg)»

- Urgenze del paziente
  - Urgenze degli «spazientiti» per patologie croniche che non migliorano
  - Urgenze «opportunistiche (partenze per vacanze)»
  - Urgenze «opportunistiche 2 (passavo di qua)»

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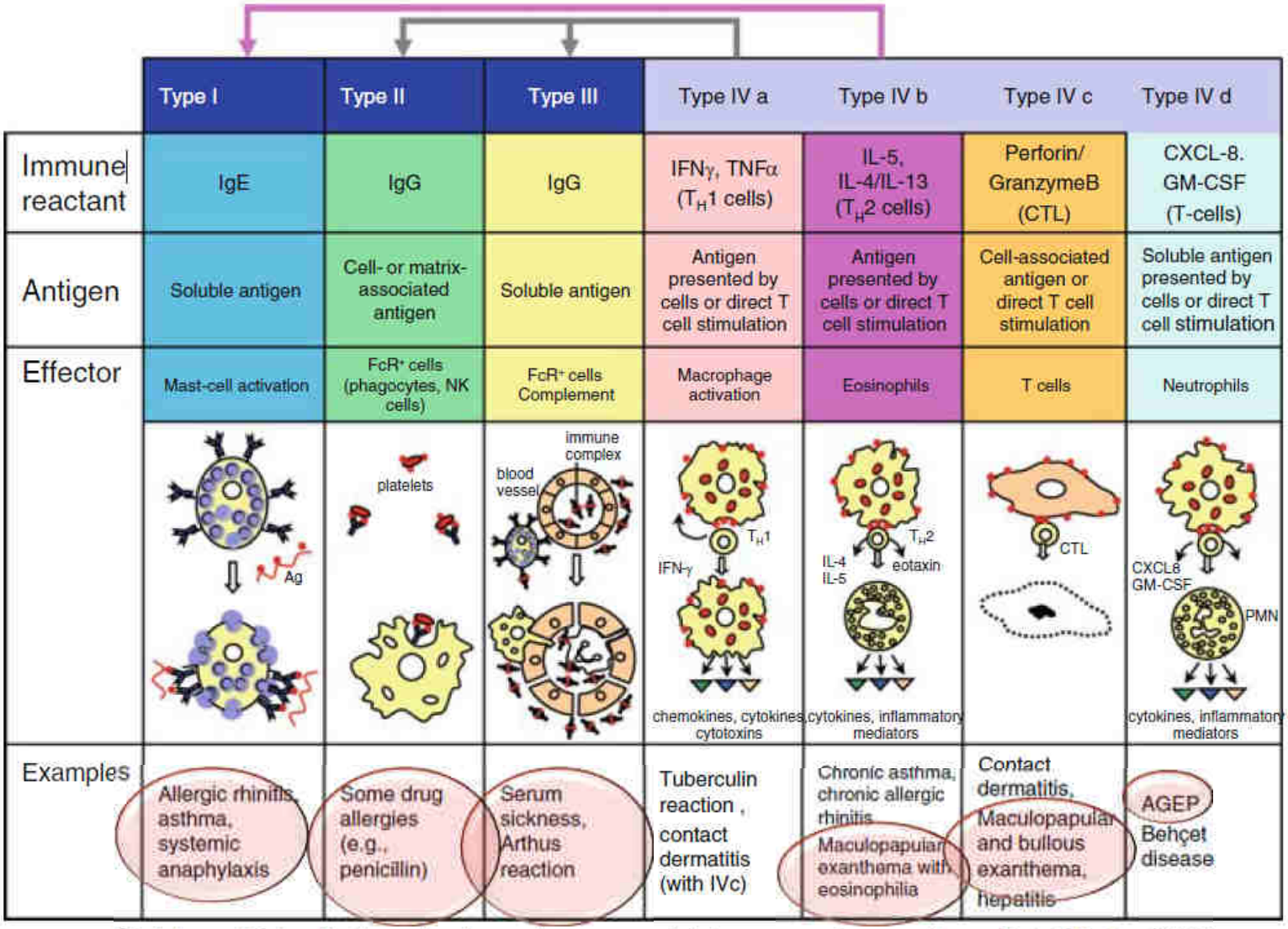
Reazioni a farmaco

- La reazione a farmaco [illegible] immediatamente dopo la assunzione di [illegible]rmaco già assunto in precedenza

Antibody mediated hypersensitivity reactions (I-III) and delayed type cell/cytokine mediated hypersensitivity reactions (IV a-d)



Pichler W.J. Delayed drug hypersensitivity reactions, ***Ann. Int. Med.*** *2003*

DRESS

- Rara (1:10.000 esposizioni)
- Colpisce tutte le età
- E' causata più frequentemente da sulfamidici ed antiepilettici.
- Latenza dall'assunzione: 7-28 giorni
- Durata: 1 mese o più
- Rash cutaneo, Enantema, Febbre, Interessamento di 1 o + organi (fegato, rene etc)
- Eosinofilia

Patogenesi

- Deficit di detossificazione del farmaco con formazione di metaboliti attivi in grado di agire da apteni che legandosi a macromolecole dei cheratinociti danno origine ad una reazione immunitaria

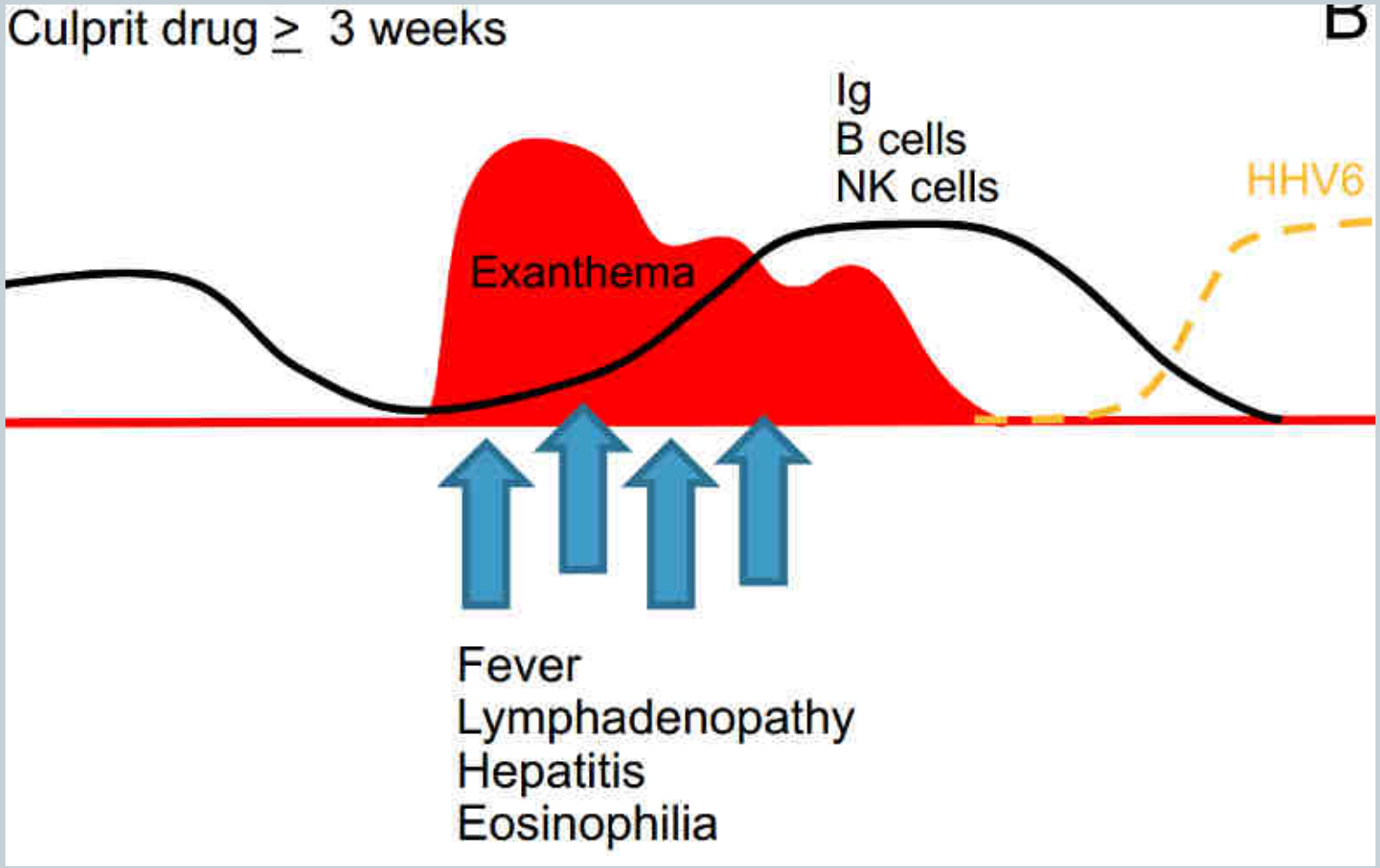

Culprit drug ≥ 3 weeks
B
Ig
B cells
NK cells
HHV6
Exanthema
Fever
Lymphadenopathy
Hepatitis
Eosinophilia

Table 2 Drugs eliciting severe cutaneous or systemic reactions[a]

Acute generalized exanthematous pustulosis (AGEP)	Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Drug induced hypersensitivity syndrome/Drug rash with eosinophilia and systemic symptoms (DiHS/DRESS)[b]
	Nevirapine	
Aminopenicillins	Allopurinol[c]	Carbamazepin[c]
Cephalosporins	Phenytoin	Phenytoin
Pristinamycin	Carbamazepin[c]	Lamotrigin[e]
Celecoxib	Lamotrigin[e]	Minocyclin[e]
Quinolone	Cotrimoxazole	Allopurinol[c]
Diltiazem	Barbiturate	Dapsone
Terbinafin[e]	NSAID (oxicams)	Sulfasalazin
Macrolides	Sertraline	Cotrimoxazole
	Pantoprazole	Abacavir[c]
	Tramadol	

Table II. Characteristic findings of severe cutaneous drug reactions

	SJS/TEN	DRESS	AGEP
Onset of eruption	1-3 wk	2-6 wk	24-48 h
Duration of eruption, wk	1-3	Several	<1
Fever	+++	+++	+++
Cutaneous features	Bullae, mucocutaneous erosions	Morbilliform characterized by a diffuse, pruritic, macular exanthema	Nonfollicular, sterile pustules on an erythematous base with minimal mucous membrane involvement
Histology	Epidermal necrosis	Perivascular lymphocytic infiltrate	Intracorneal, subcorneal, and/or intraepidermal pustules
Visceral involvement	Tubular nephritis and tracheobronchial necrosis	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	In up to 20% of cases
Neutrophils	↓	↑	↑↑↑
Eosinophils	—	↑↑↑	↑
Mortality, %	30-40	10	5

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and system symptoms; *SJS*, Stevens-Johnson

Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions

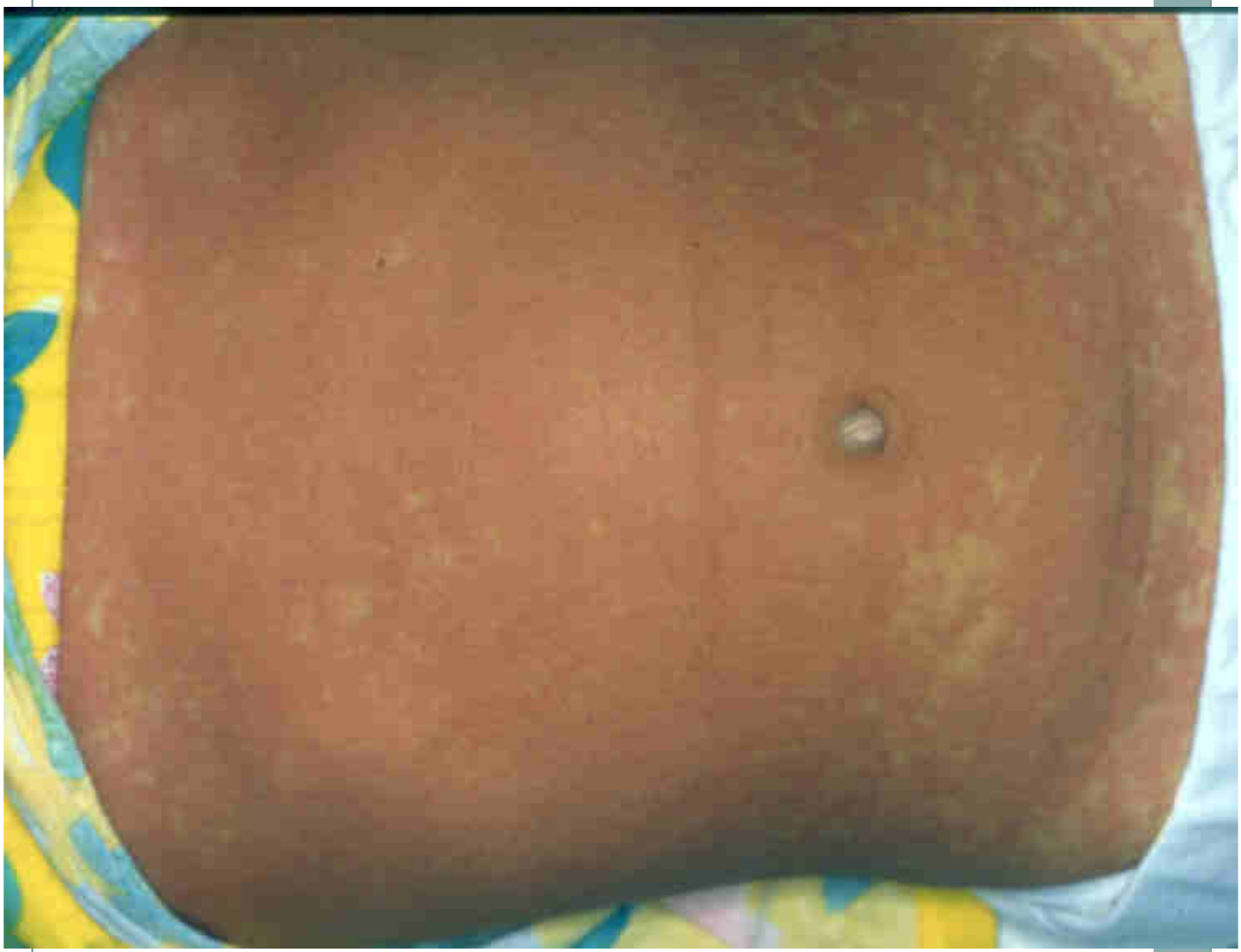
*†‡§Ursula Amstutz, ¶Neil H. Shear, #Michael J. Rieder, **Soomi Hwang, **†††‡‡‡Vincent Fung, §§Hidefumi Nakamura, ‡¶¶Mary B. Connolly, ##Shinya Ito, *†‡Bruce C. Carleton, and the CPNDS clinical recommendation group[1]

Epilepsia, 55(4):496–506, 2014
doi: 10.1111/epi.12564

Table 3. Proportions of patients expected to develop HSRs without test, with and without risk variants

Risk variant	HLA-A*31:01		HLA-A*31:01		HLA-B*15:02	
Associated hypersensitivity reactions (HSRs)	HSS		HSS, MPE, SJS/TEN, AGEP		SJS/TEN	
Population with approximate carrier frequencies	Caucasian	Japanese/Korean	Caucasian	Japanese	Thai, Indian, Malay	Chinese
Frequency of HSR in patients taking CBZ (f_{HSR}; risk of CBZ-HSR without genetic test), %	0.02–0.05[a]	0.02–0.05[a]	3–10[b]	3–10[b]	0.23[c]	0.23[c]
Risk variant frequency in patients with HSR (f_{cases}; Sensitivity), %[d]	**37**	**58–59**	**26**	**58**	**80–93**	**97**
Risk variant frequency in patients without HSR ($f_{tolerant}$; 1-Specificity), %[d]	4	13–14	4	13	10–19	4–15
Frequency of HSR in patients who are positive for the risk variant (PPV; risk of HSR with positive test), %	**0.2–0.4**	**0.1–0.2**	**17–42**	**12–33**	**1–2**	**1–5**
Proportion of patients carrying risk variant NOT developing HSR (1-PPV), %	99	99	58–83	67–88	98–99	95–99
Frequency of HSR in patients who are negative for the risk variant (risk of HSR with negative test), %[e]	0.01–0.03	0.01–0.02	2–8	1–5	0.02–0.05	0.007
Maximum fold risk increase (positive vs. negative)	14	10	7	8	117	735

[a]Incidence estimate from Caucasian population.[12]
[b]Incidence estimates for Caucasian patients: 10%[60]; incidence reported for Japanese: 3%.[43]
[c]Historical incidence in Taiwan Han Chinese patients.[41]
[d]Estimation based on results from case–control studies (Tables S1 and S3).
[e]Calculated using: $(f_{HSR}*(1-f_{cases}))/(f_{HSR}*(1-f_{cases})+(1-f_{HSR})*(1-f_{tolerant}))$.
Sensitivity and PPV are indicated in bold.

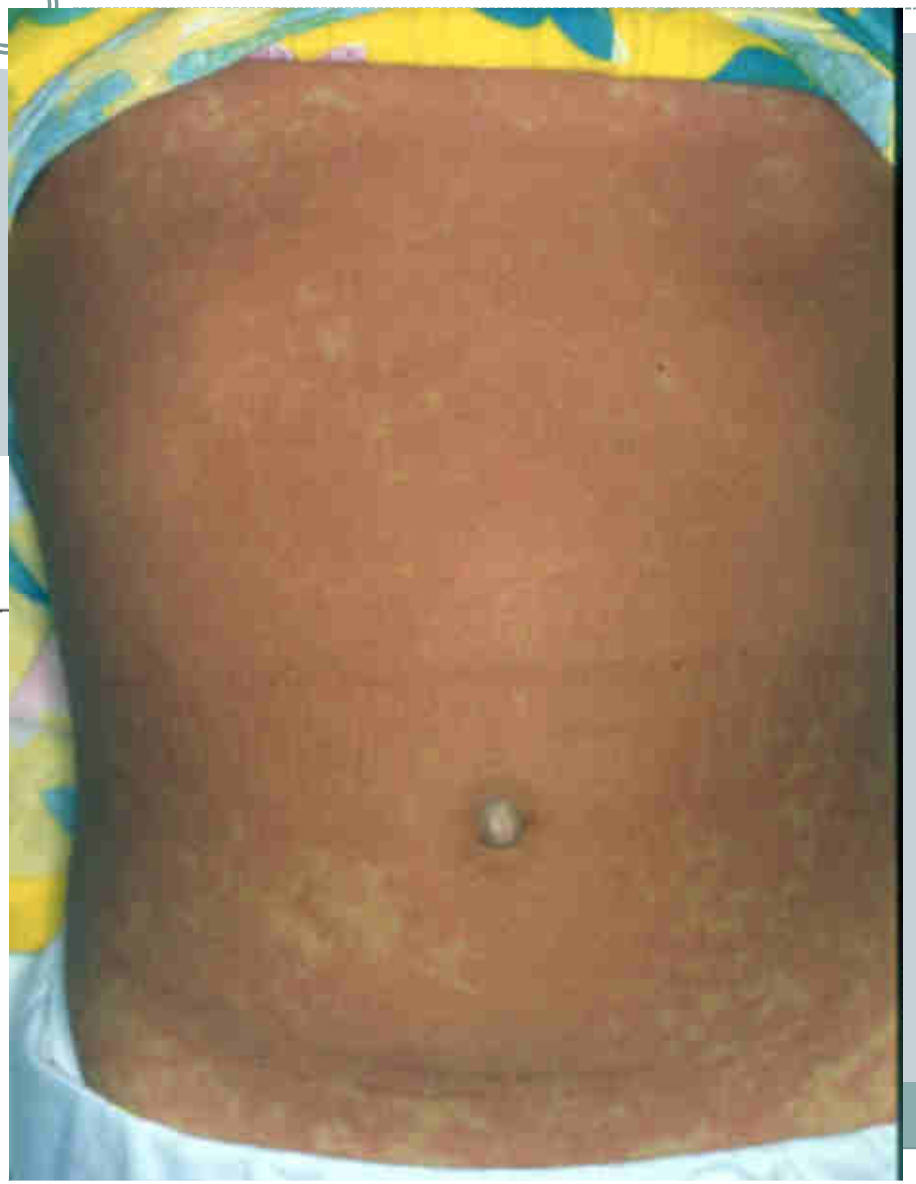


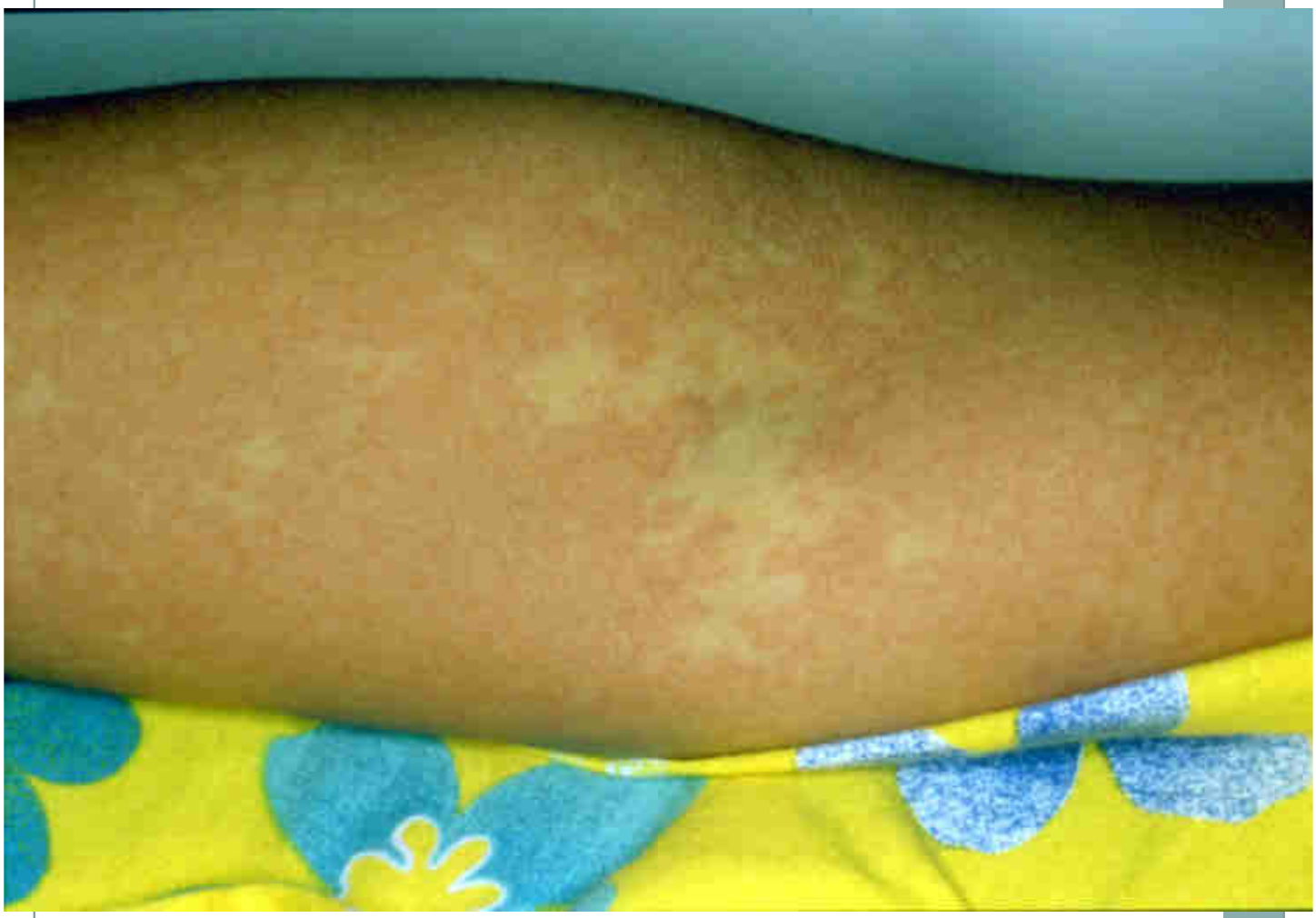
Eosinofilia
+ prurito
+ esteso

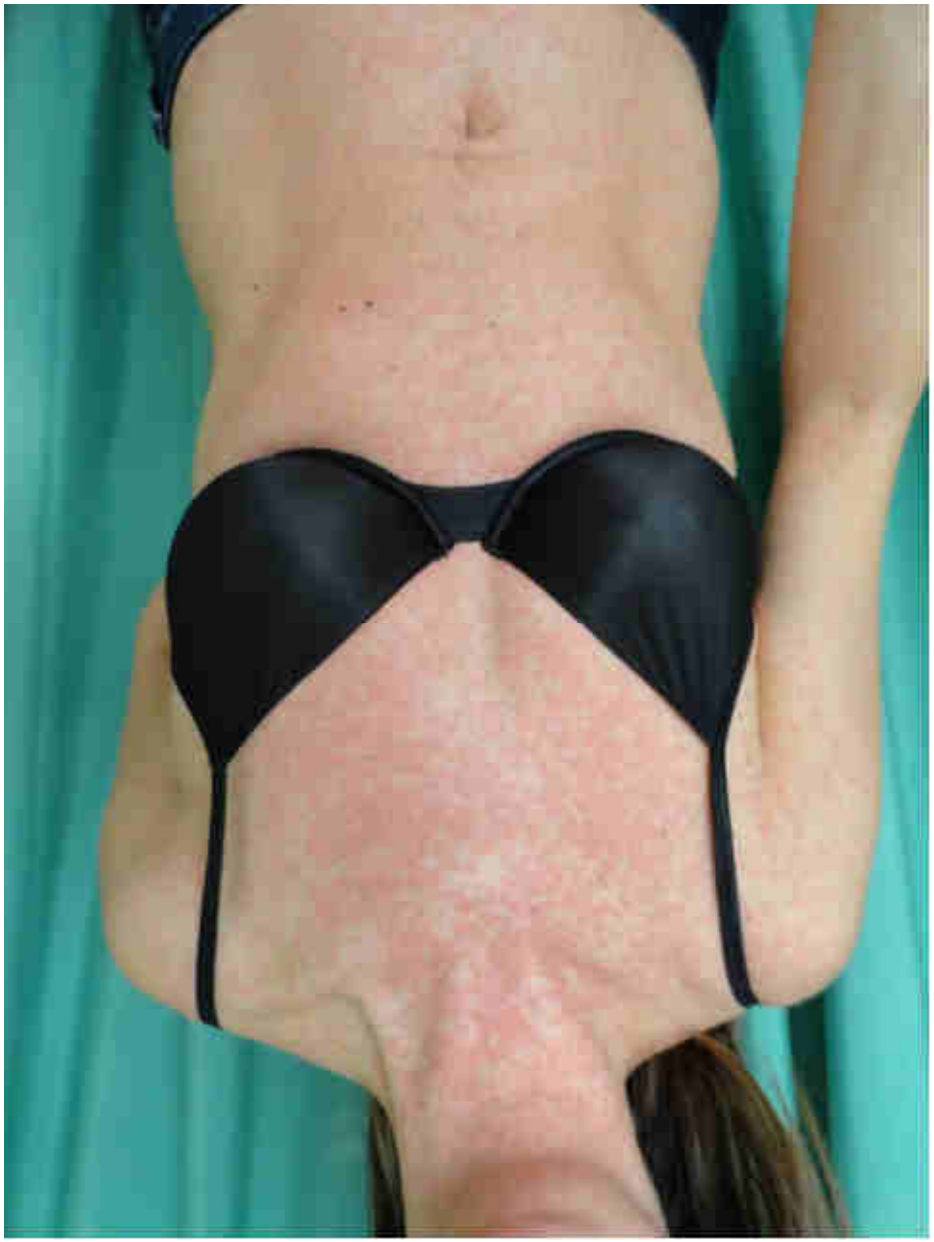
neutrofilia
enantema
Craniocaudale
adenopatia

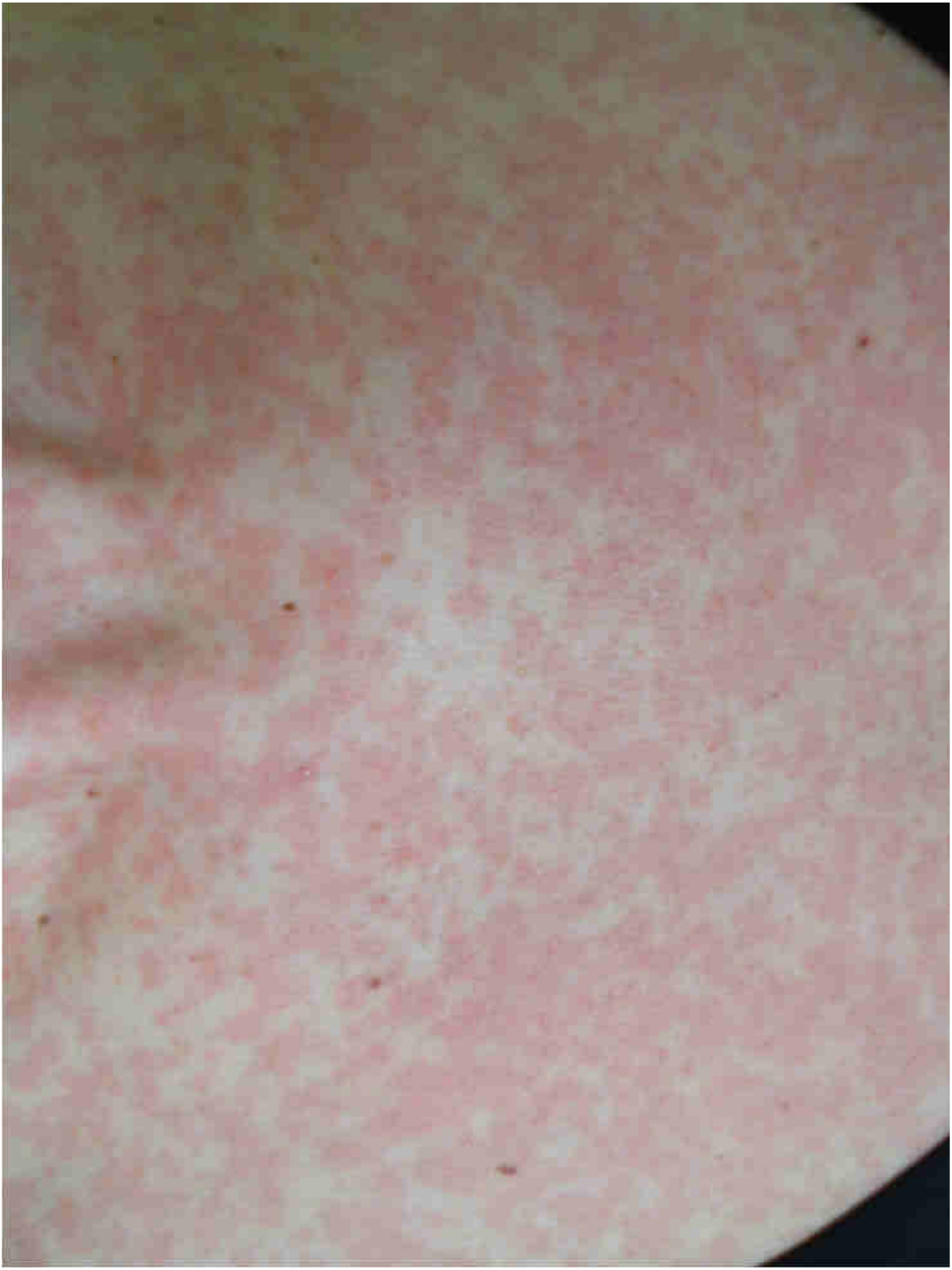
Diagnosi differenziale tra esantemi da farmaci ed esantemi (para)-infettivi

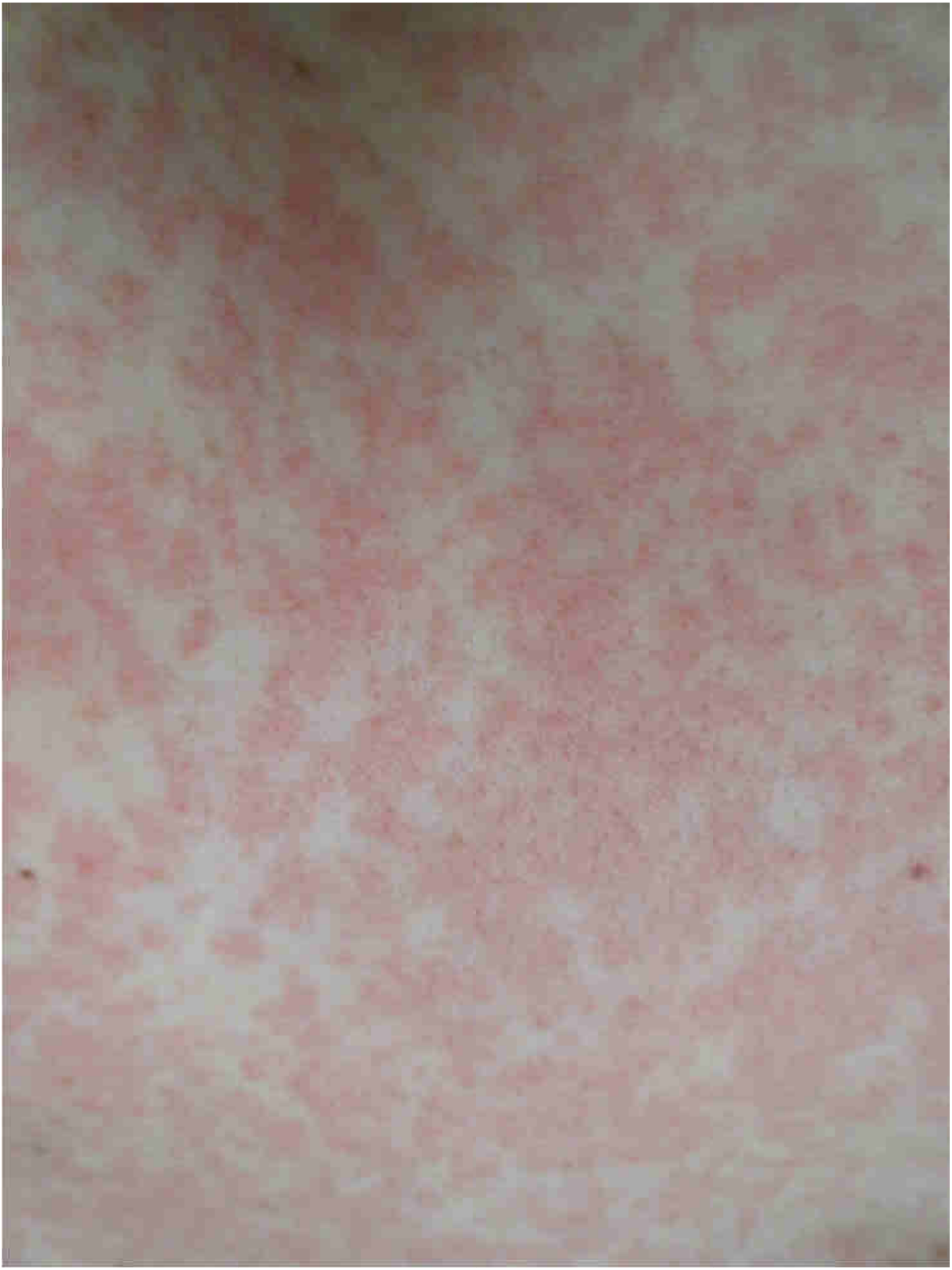
- Anamnesi (rapporto temporale, precedenti reazioni di intollerenza)
- Età del paziente
- Sintomi generali, decorso febbrile
- Aspetto delle lesioni
- Enantema
- Prurito
- Linfoadenopatia
- Ricerche di laboratorio











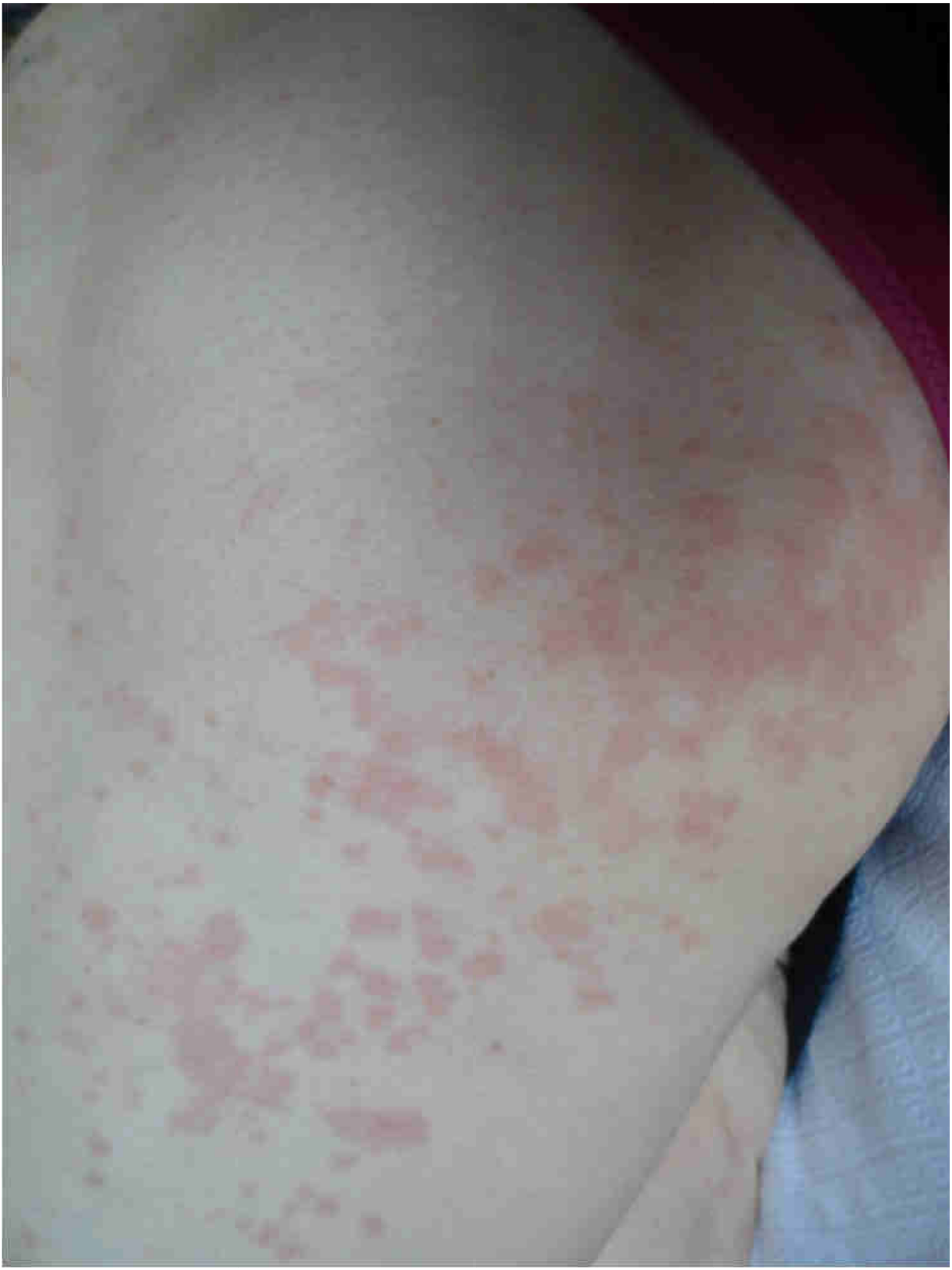


TABLE 4. Pharmacotherapeutic Options for Drug Rash With Eosinophilia and Systemic Symptoms

Agent	Example dosing	Comment
Corticosteroids	(1) Prednisone or equivalent (1-1.5 mg/kg/d) (2) Methylprednisolone, 30 mg/kg intravenously for 3 d, if no improvement with oral corticosteroids or in severe cases[98]	Oral corticosteroids are tapered over 3-6 mo
Intravenous immunoglobulin	(1) 0.5 g/kg/d for 2 consecutive days every month as a corticosteroid-sparing agent[77] (2) 2 g/kg divided over 5 d in severe, life-threatening cases[100]	Poor tolerability and minimal benefit reported in a small, open-label study (n=10)[101] Should be used in conjunction with corticosteroids, not as monotherapy
Cyclophosphamide	750 mg/m^2 intravenously once; approximately 2 wk later, begin 100 mg orally daily for 6 mo[5]	Limited to individual reports
Cyclosporine	100 mg twice daily for 5 d[102,103]	Used after corticosteroid failure and taper[102]
Topical corticosteroids, H_1 receptor antagonists, emollients	Various	Recommended for symptom control only if the patient has no systemic symptoms[98]
Antivirals	Various	For patients with evidence of viral reactivation Give in addition to corticosteroids, with or without intravenous immunoglobulin[98]
Mycophenolate mofetil	500-1500 mg twice daily[103-105]	Corticosteroid-sparing agent; use for up to 1 y[103]
Rituximab	A 1-mo course of weekly rituximab[105]	Dose not provided in report[105]

AGEP

- Rara (1:100.000 esposizioni)
- Cause farmacologiche o + raramente infettive
- Guarigione spontanea

PUSTOLE INTRAEPIDERMICHE NON FOLLICOLARI STERILI SU CUTE ERITEMATOSA - FEBBRE

- Esordio acuto con febbre > 38°C, eritema scarlattiniforme,rash pustoloso sterile con pustole non follicolari
- L'eruzione inizia al volto con successiva estensione al tronco e agli arti
- La durata media dell'eruzione pustolosa è di circa nove giorni
- Talora possono essere presenti lesioni a bersaglio centrate da una pustola, edema del volto e delle mani,lesioni di tipo purpurico alle gambe e ai piedi, tale polimorfismo è un aspetto caratteristico della malattia
- Esami di laboratorio:
  - Leucocitosi (> 10.000 per ml) Neutrofilia (7000 x ml)

Eosinofilia >700 x ml Ipocalcemia

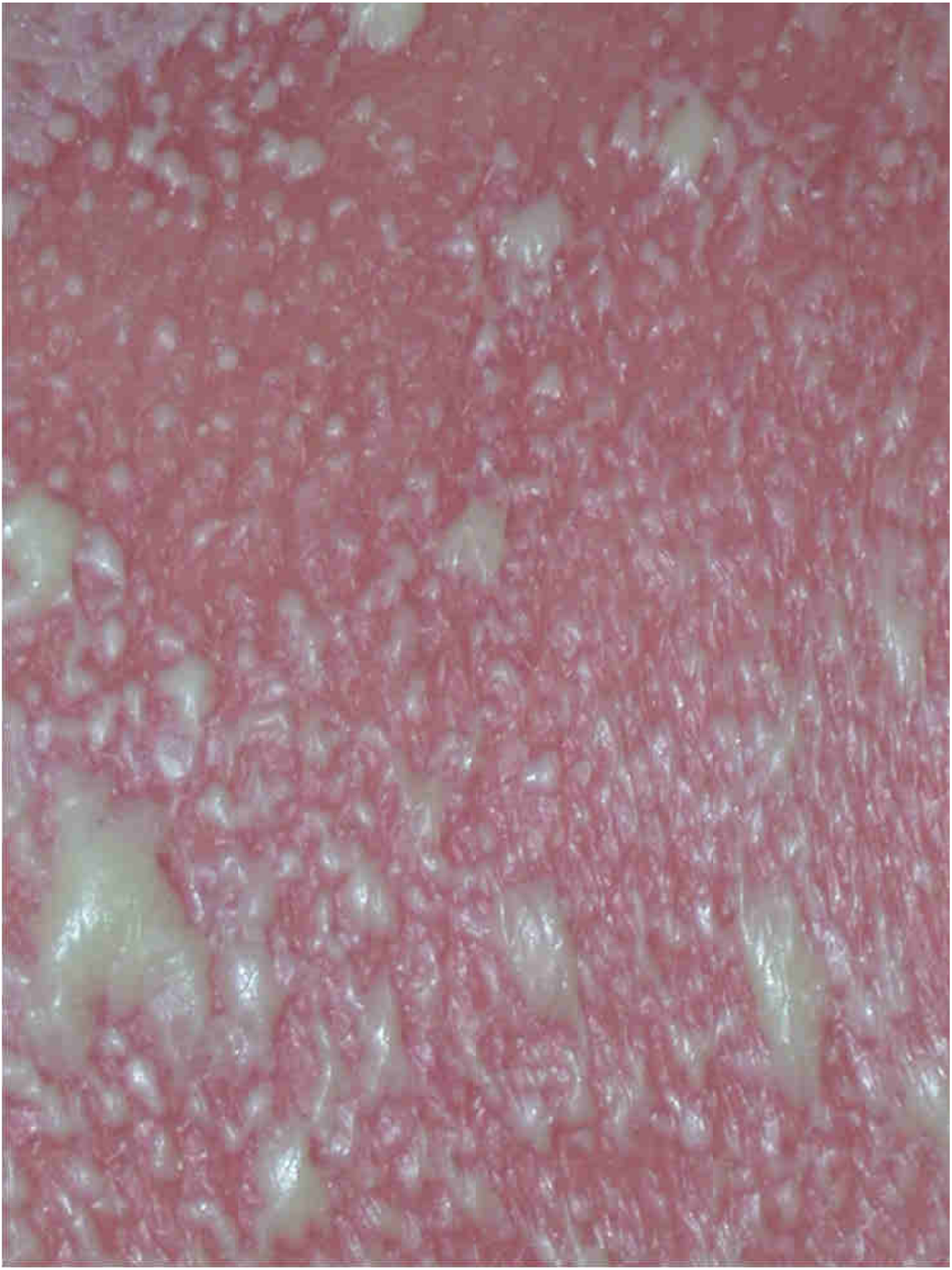


Table 1. Factors favoring the diagnosis of AGEP over pustular psoriasis.

	AGEP	Generalized Pustular Psoriasis
History of psoriasis (family/personal)	usually lacking	often present
Distribution pattern	initially predominance in the folds	more generalized
Onset of pustules	fast (hours or few days after use of medication)	slower
Duration of pustules	Shorter (rapid resolution in a few days, max. 15 days, after drug suspension)	longer
Size of pustules	tiny (pinhead)	larger
Duration of eruption/fever	shorter (resolution in a few days after drug suspension)	longer
History of drug reaction	usual	uncommon
Recent drug administration	very frequent	less frequent
Arthritis	rare	about 30%
Histology	single-cell necrosis of keratinocytes, edema of papillary dermis, vasculitis, exocytosis of eosinophils	papillomatosis, acanthosis, tortuous or dilated vessels

Table I. Diagnostic score for acute generalized exanthematous pustulosis from EuroSCAR study[40]

Variable	Score
Morphology	
Pustules	
Typical	+2
Compatible with disease	+1
Insufficient	0
Erythema	
Typical	+2
Compatible with disease	+1
Insufficient	0
Distribution	
Typical	+2
Compatible with disease	+1
Insufficient	0
Course	
Mucous membrane involvement	
Yes	−2
No	0
Acute onset	
Yes	0
No	−2
Resolution within 15 d	
Yes	0
No	−2
Fever ≥38°C	
Yes	+1
No	0
Polymorphonuclear cells ≥7000 cells/mm^3	
Yes	+1
No	0
Histology	
Other disease	−10
Not representative	0
Exocytosis of polymorphonuclear cells	+1
Subcorneal and/or intraepidermal nonspongiform or NOS pustules with papillary edema or subcorneal and/or intraepidermal spongiform or NOS pustules without papillary edema	+2
Spongiform subcorneal and/or intraepidermal pustules with papillary edema	+3

Score interpretation: ≤0 = no; 1-4 = possible; 5-7 = probable; 8-12 = definitive acute generalized exanthematous pustulosis.
NOS, Not otherwise specified.

1-4 = possibile
5-7= probabile
8-12= diagnostico

Table II. Characteristic findings of severe cutaneous drug reactions

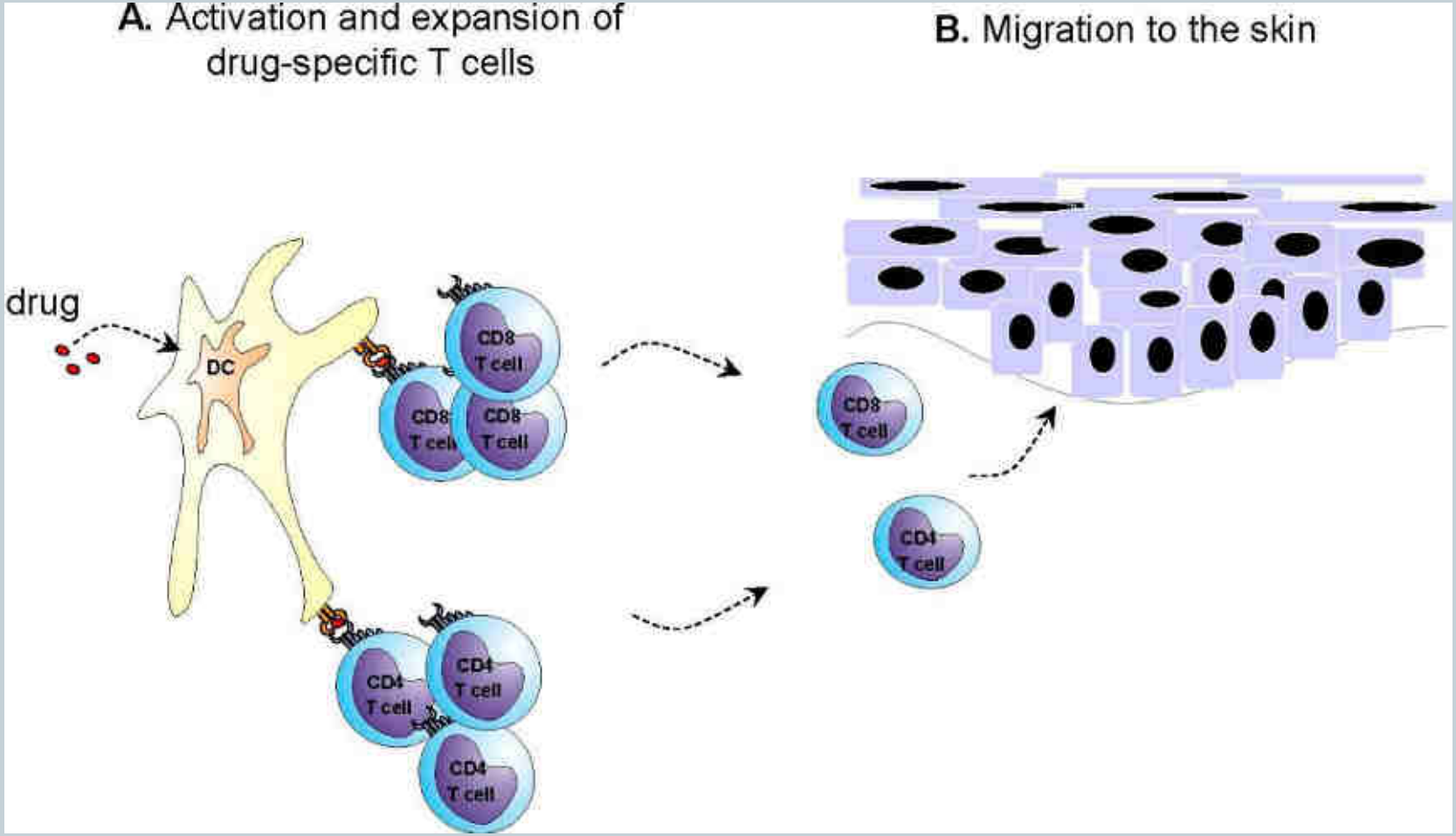
	SJS/TEN	DRESS	AGEP
Onset of eruption	1-3 wk	2-6 wk	24-48 h
Duration of eruption, wk	1-3	Several	<1
Fever	+++	+++	+++
Cutaneous features	Bullae, mucocutaneous erosions	Morbilliform characterized by a diffuse, pruritic, macular exanthema	Nonfollicular, sterile pustules on an erythematous base with minimal mucous membrane involvement
Histology	Epidermal necrosis	Perivascular lymphocytic infiltrate	Intracorneal, subcorneal, and/or intraepidermal pustules
Visceral involvement	Tubular nephritis and tracheobronchial necrosis	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	In up to 20% of cases
Neutrophils	↓	↑	↑↑↑
Eosinophils	—	↑↑↑	↑
Mortality, %	30-40	10	5

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and system symptoms; *SJS*, Stevens-Johnson

Table 2 Drugs eliciting severe cutaneous or systemic reactions[a]

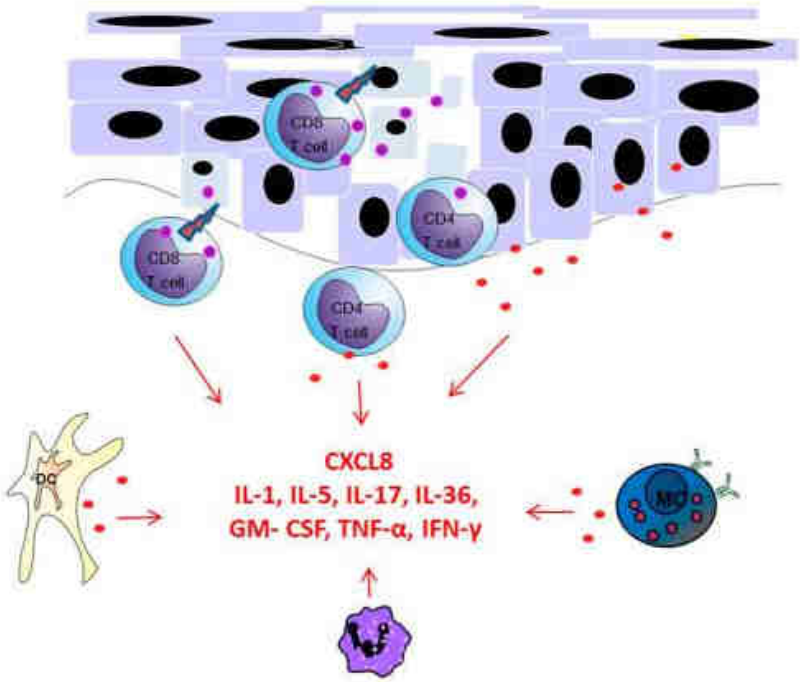
Acute generalized exanthematous pustulosis (AGEP)	Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Drug induced hypersensitivity syndrome/Drug rash with eosinophilia and systemic symptoms (DiHS/DRESS)[b]
	Nevirapine	
Aminopenicillins	Allopurinol[c]	Carbamazepin[c]
Cephalosporins	Phenytoin	Phenytoin
Pristinamycin	Carbamazepin[c]	Lamotrigin[e]
Celecoxib	Lamotrigin[e]	Minocyclin[e]
Quinolone	Cotrimoxazole	Allopurinol[c]
Diltiazem	Barbiturate	Dapsone
Terbinafin[e]	NSAID (oxicams)	Sulfasalazin
Macrolides	Sertraline	Cotrimoxazole
	Pantoprazole	Abacavir[c]
	Tramadol	

AGEP

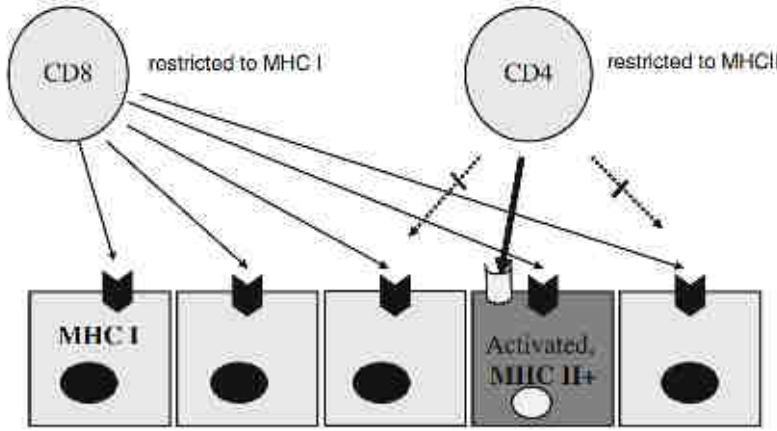

A. Activation and expansion of drug-specific T cells
B. Migration to the skin
drug
DC
CD8 T cell
CD8 T cell
CD8 T cell
CD4 T cell
CD4 T cell
CD4 T cell
CD8 T cell
CD4 T cell

C. Apoptosis of keratinocytes and formation of subcorneal vesicle

- Perforin
- Granzyme B
- Granulysin
- FAS-FASL



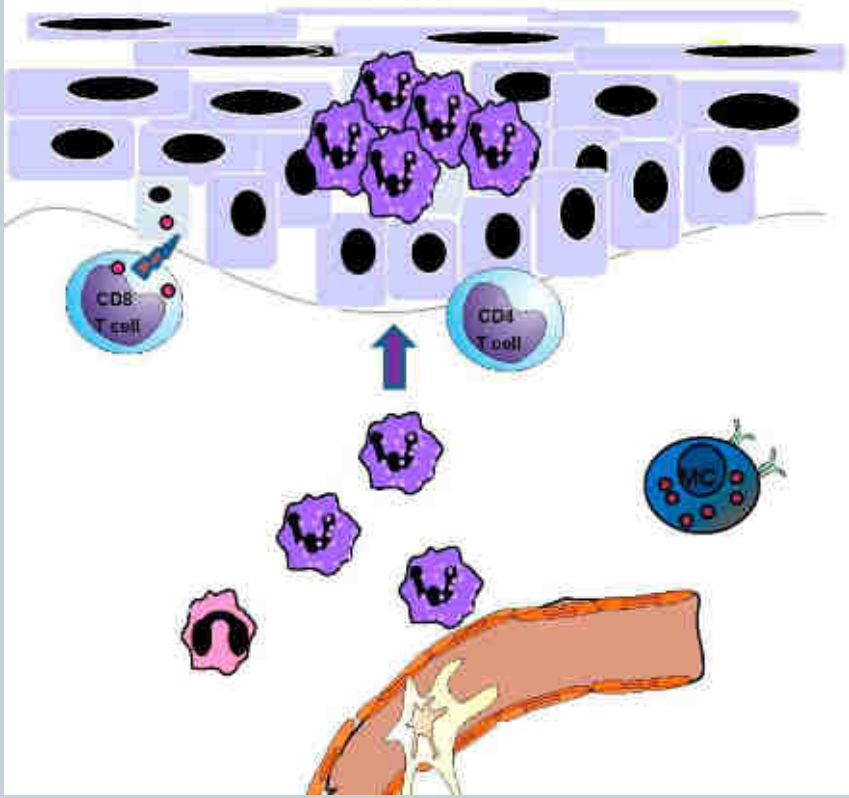
Why are cytotoxic CD8+ T cells more dangerous than CD4+ T cells ?

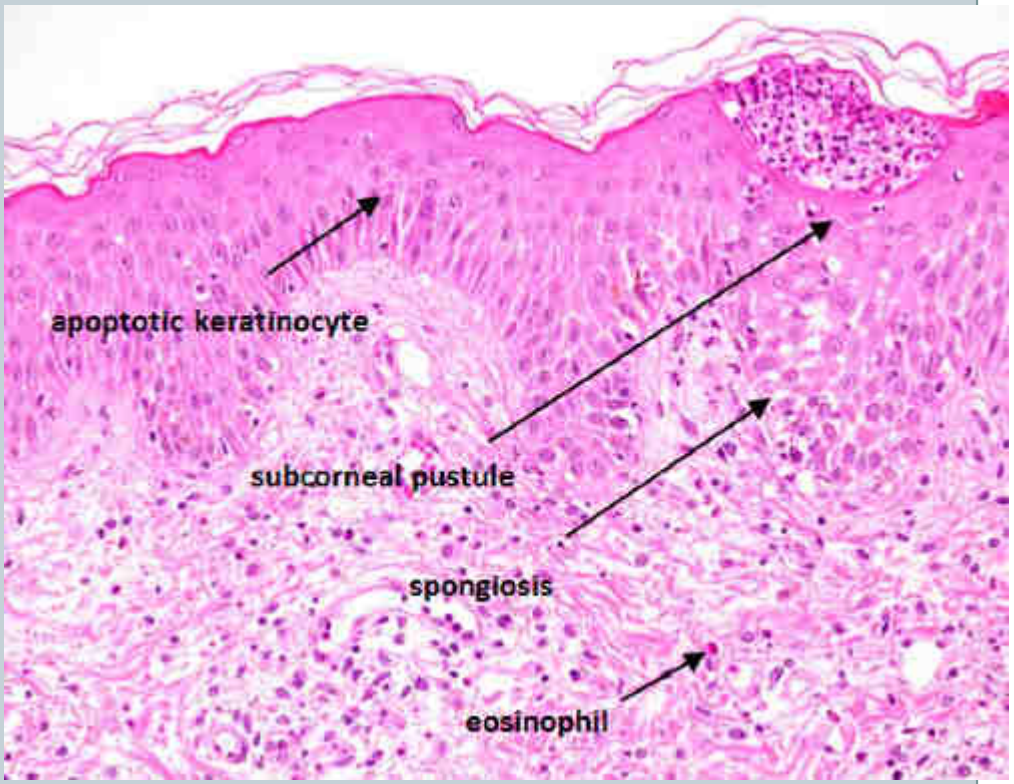


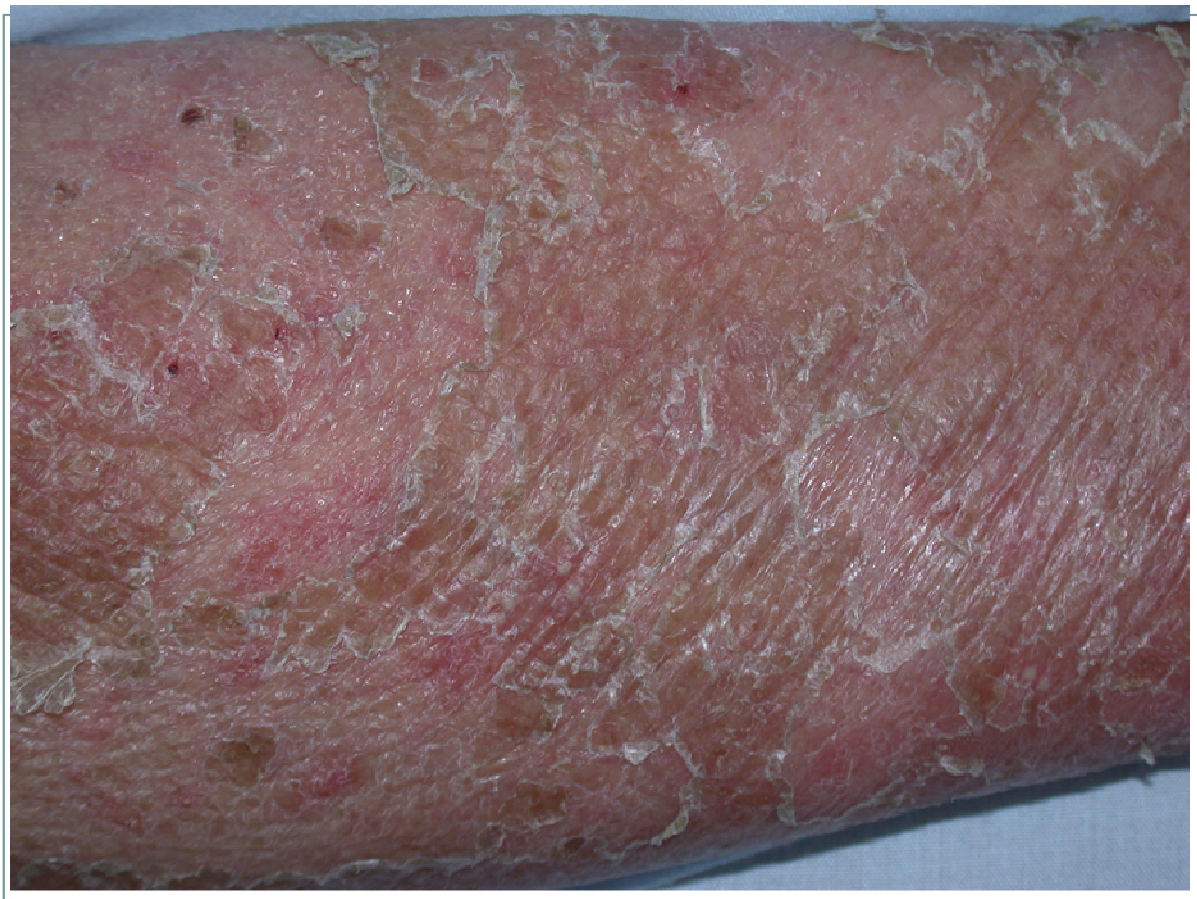
CD8 T cells can kill MHC-I expressing (=all) cells,
While CD4+ kill only activated cells, expressing MHC-II

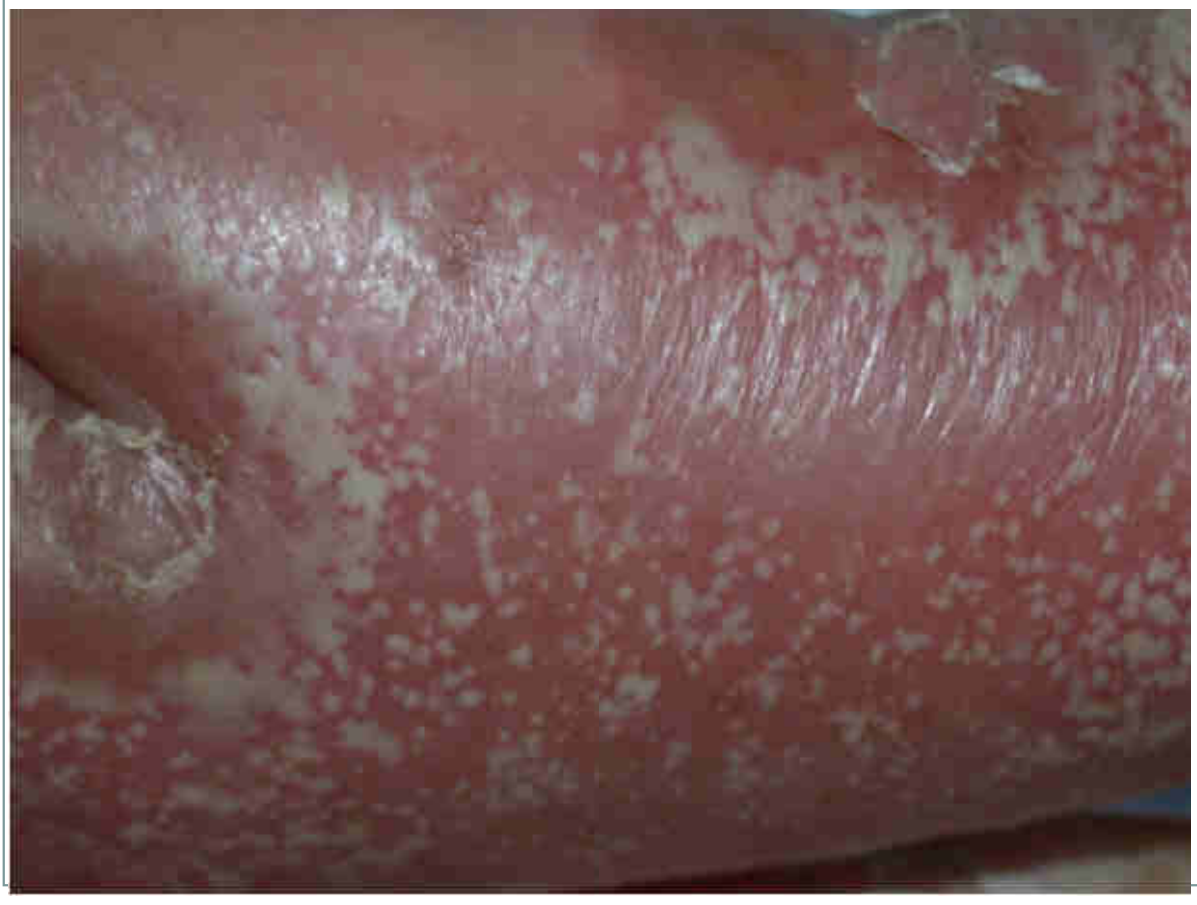
D. Release of various cytokines and chemokines (•) by innate and acquired immune cells and resident cells (i.e.keratinocytes)

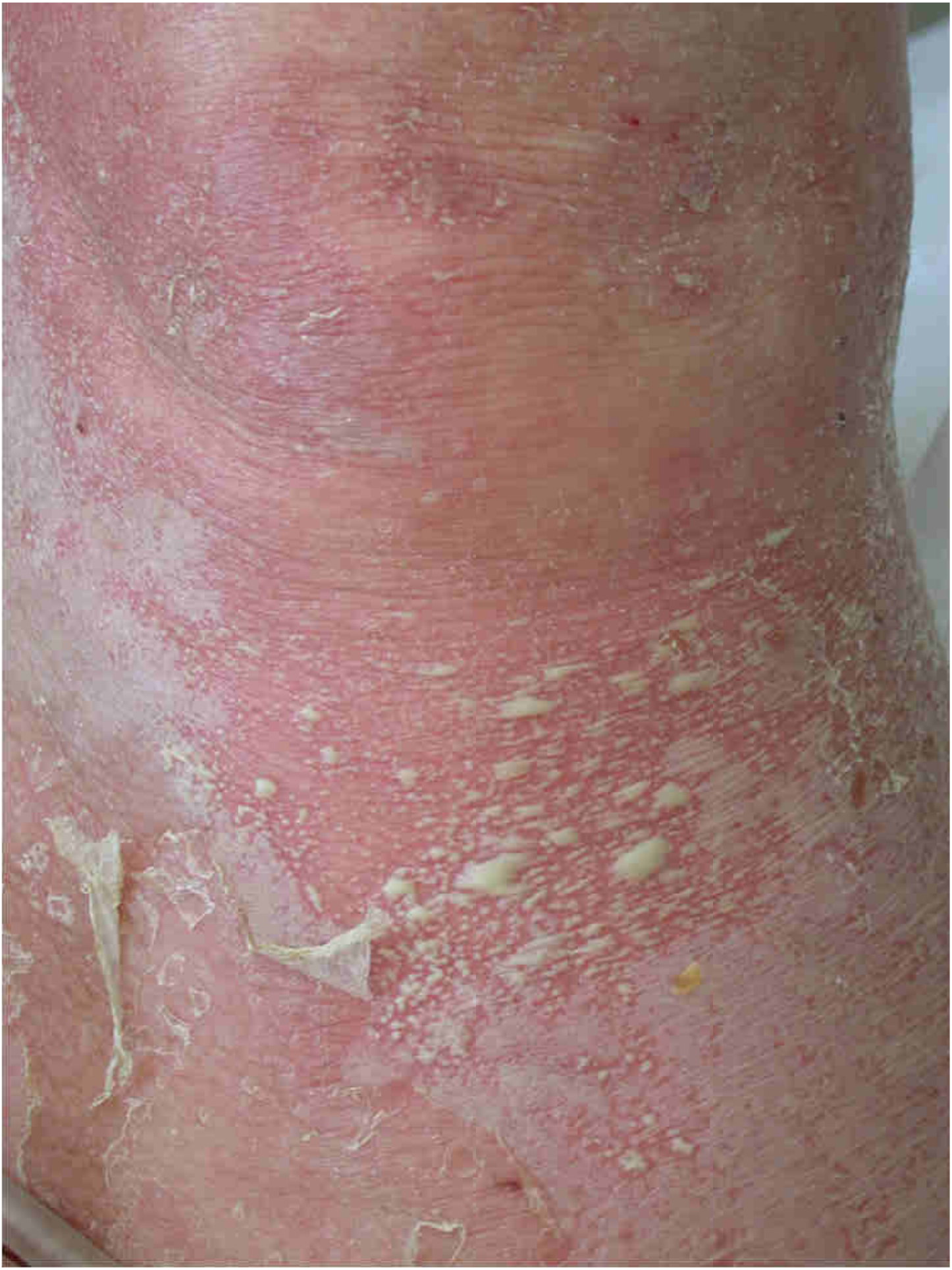
E. Recruitment of further leucocytes, i.e. neutrophils and formation of pustules

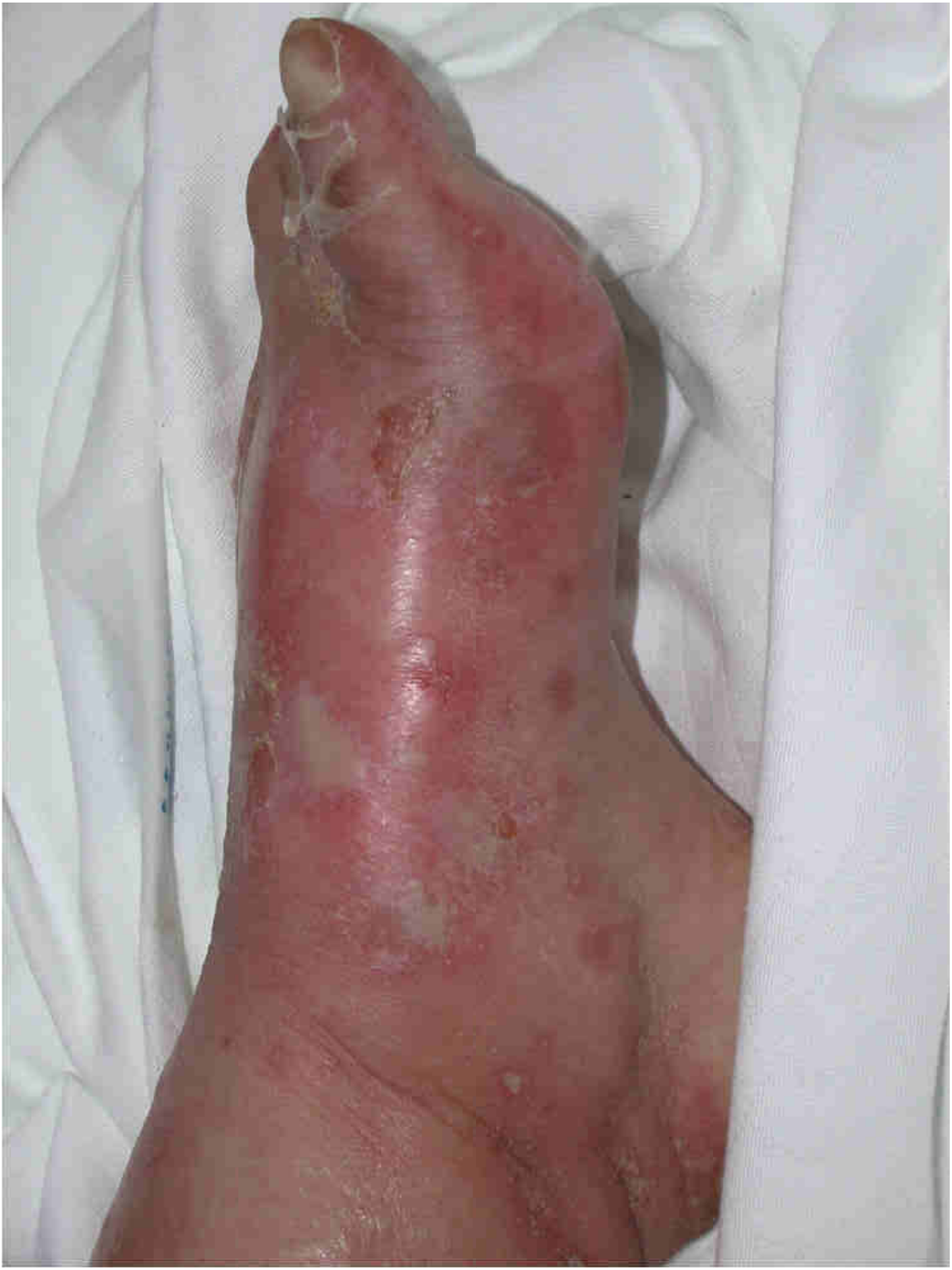


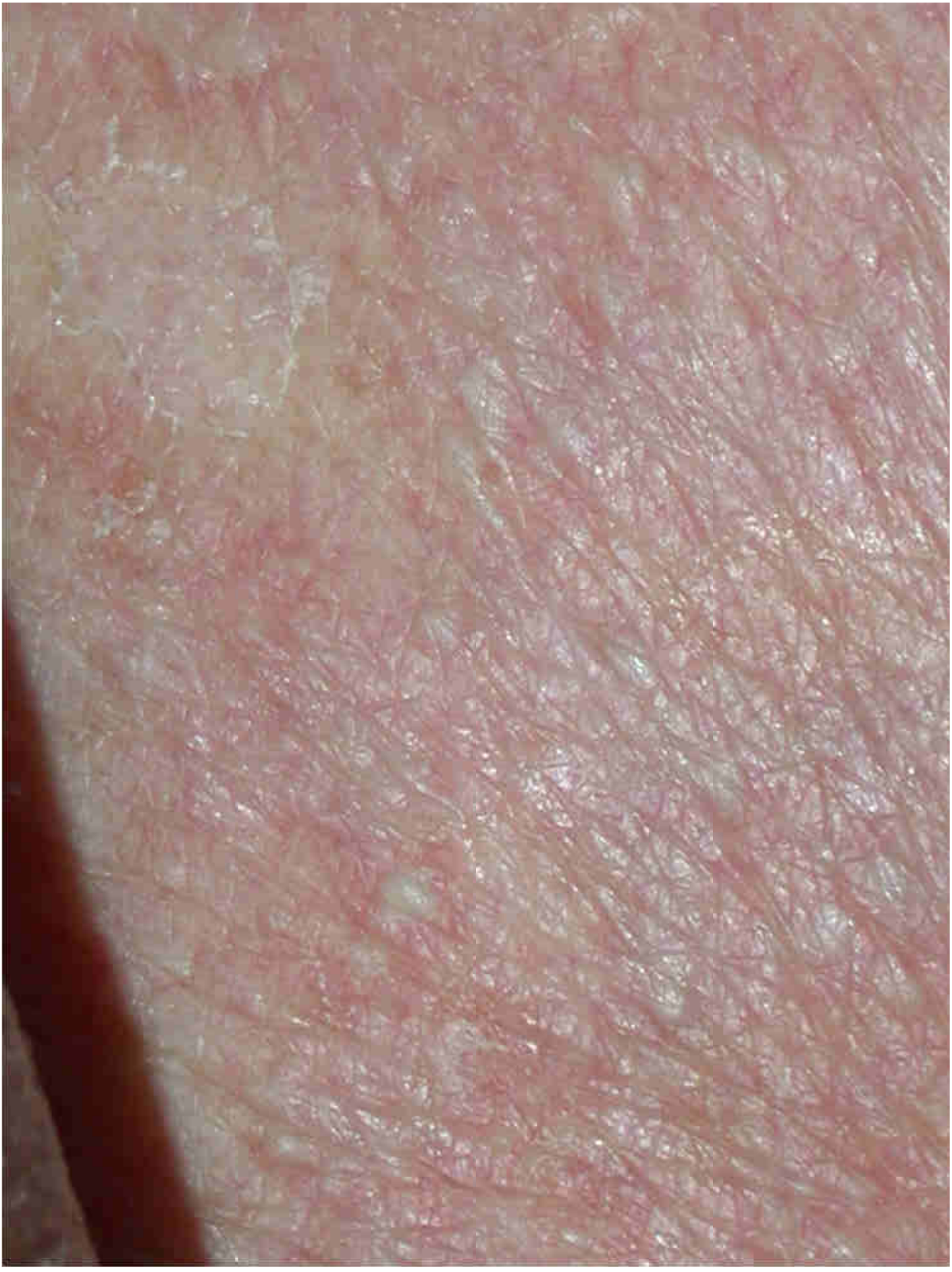


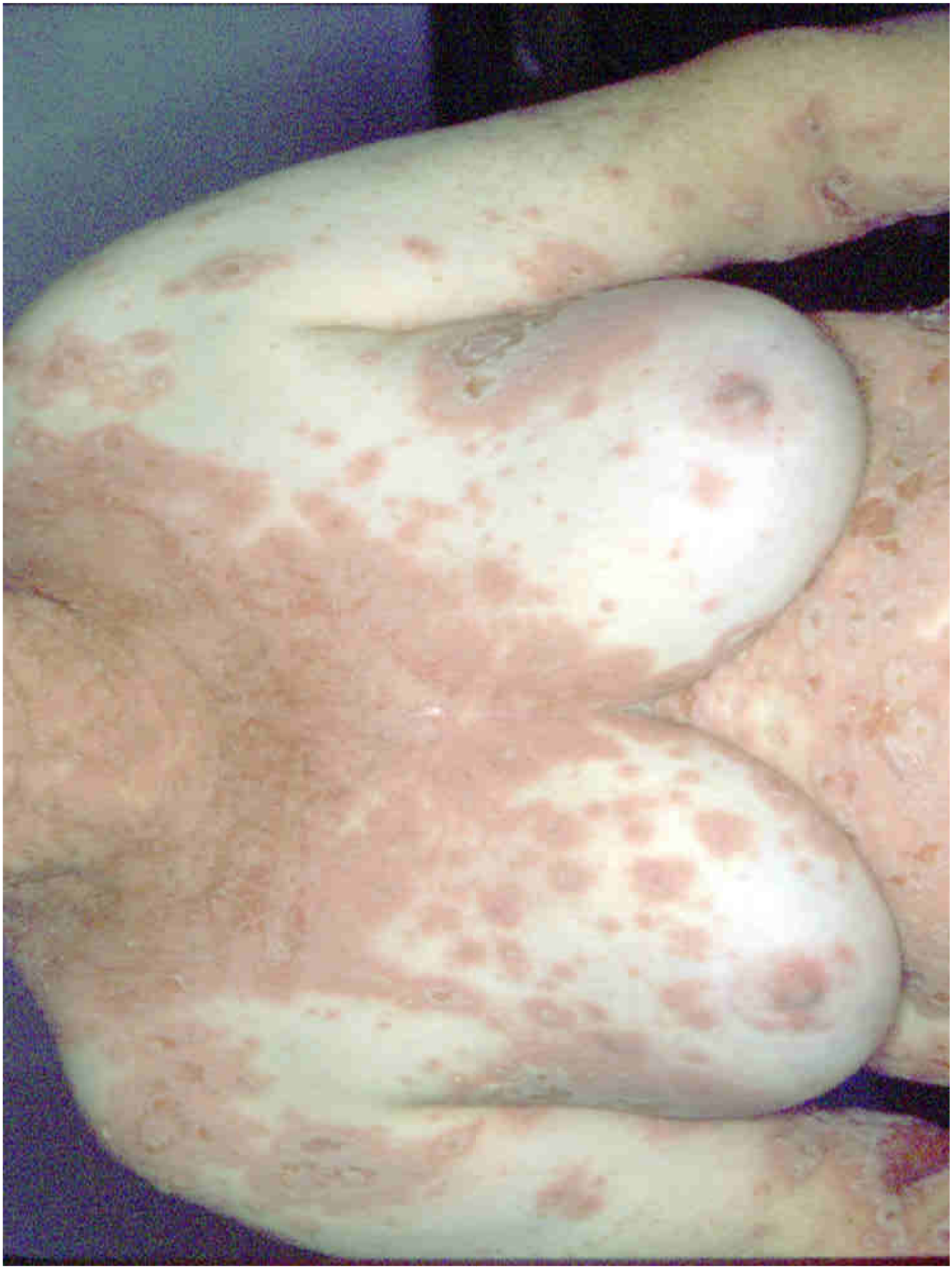


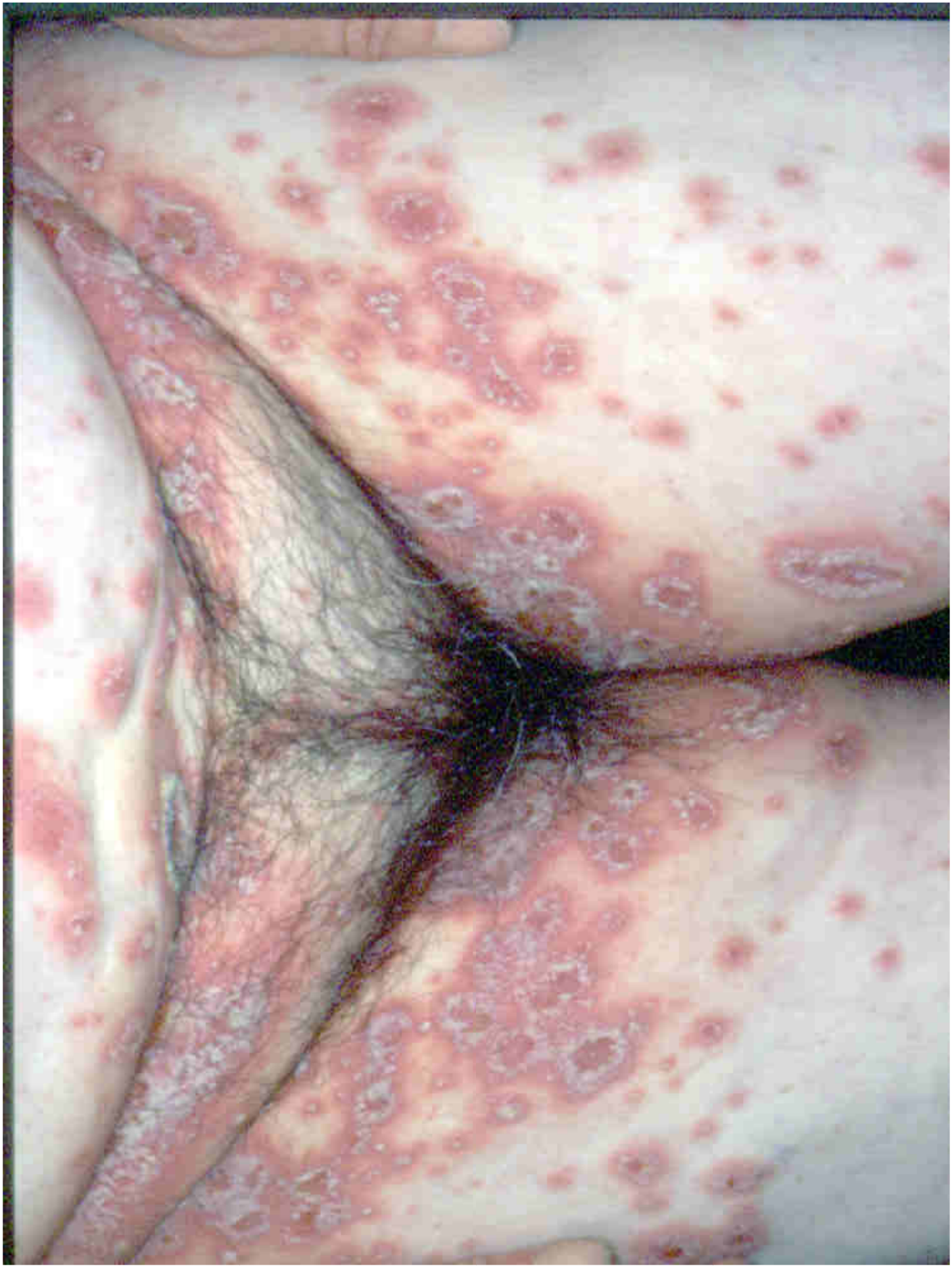


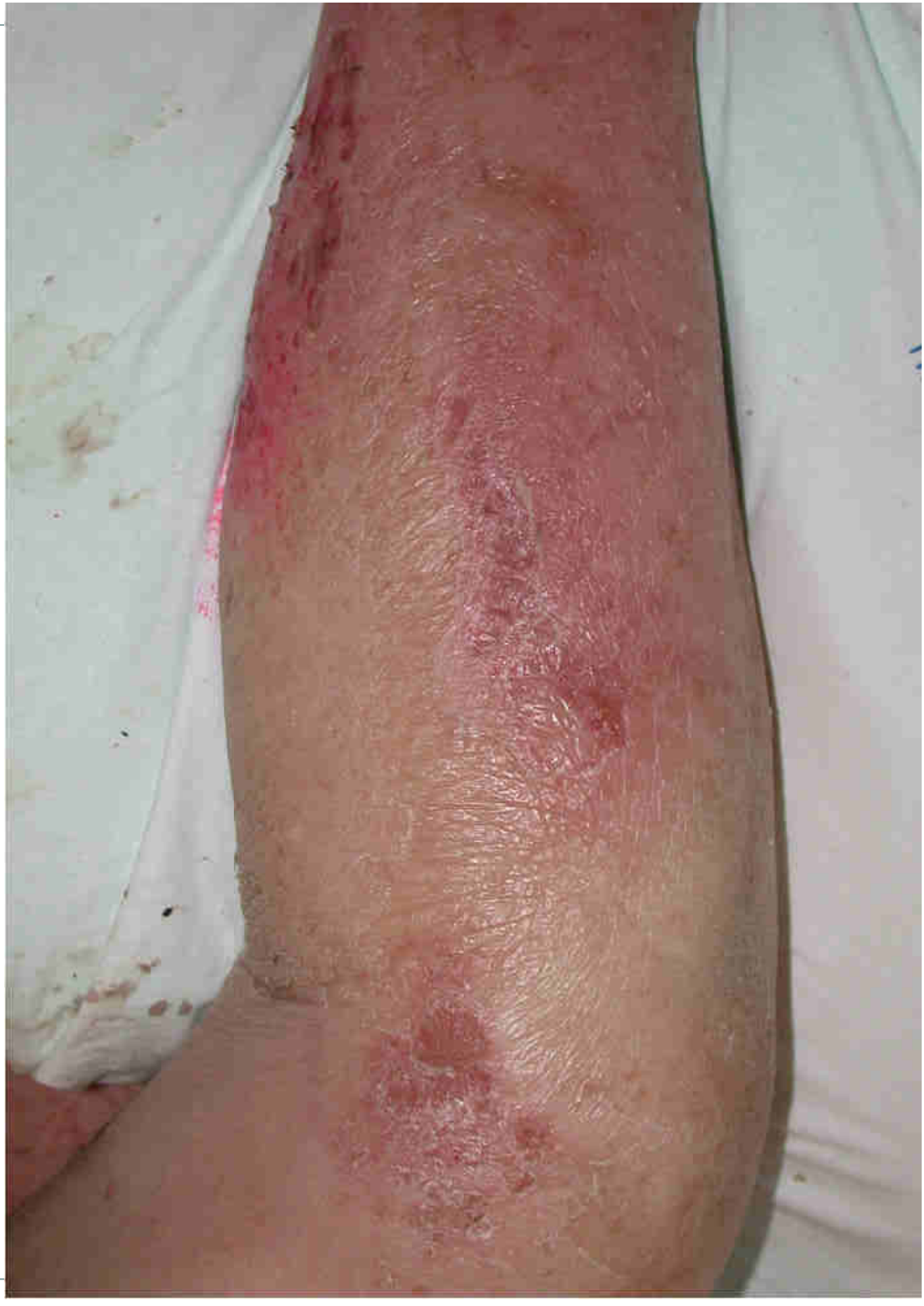


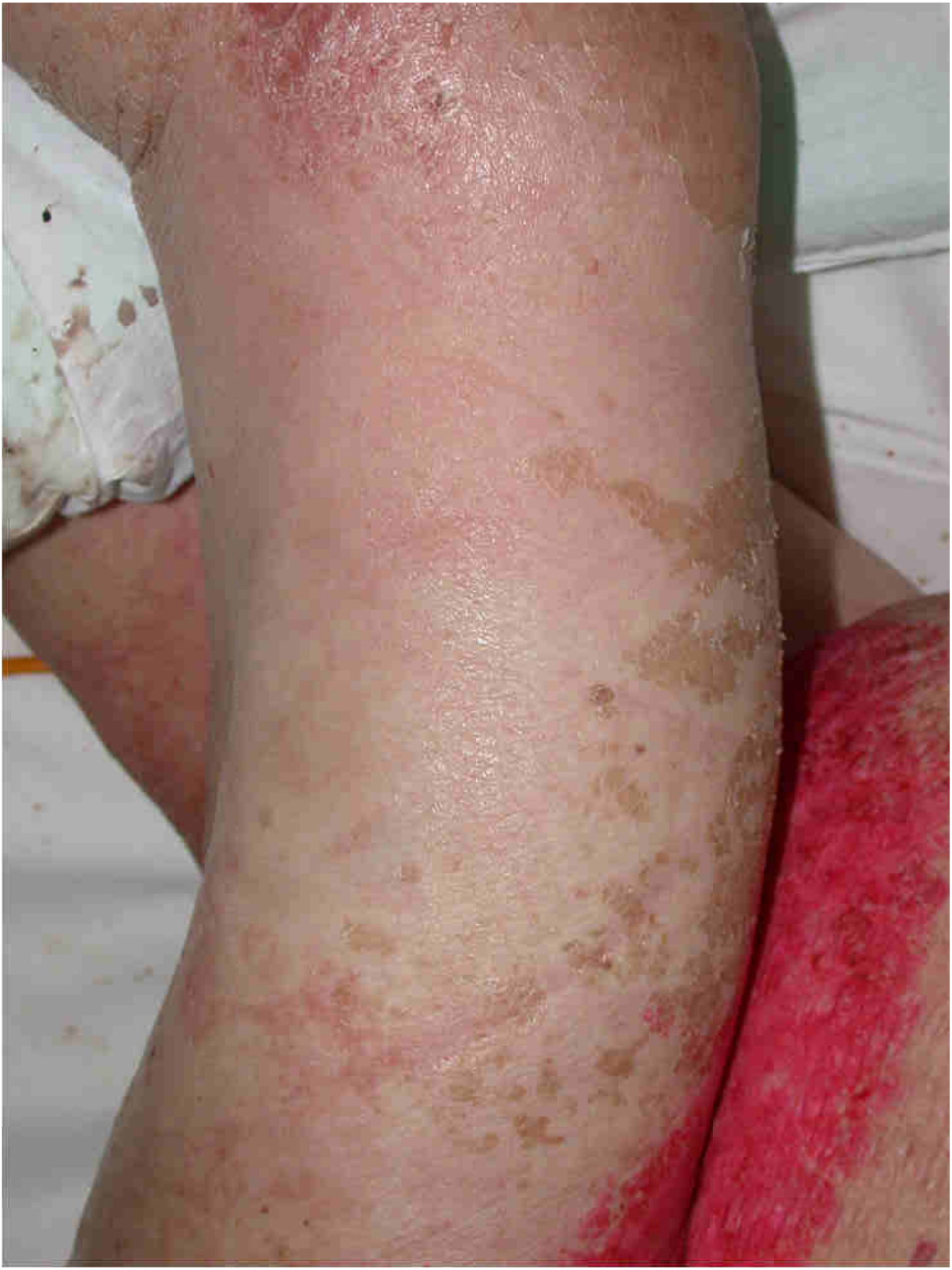


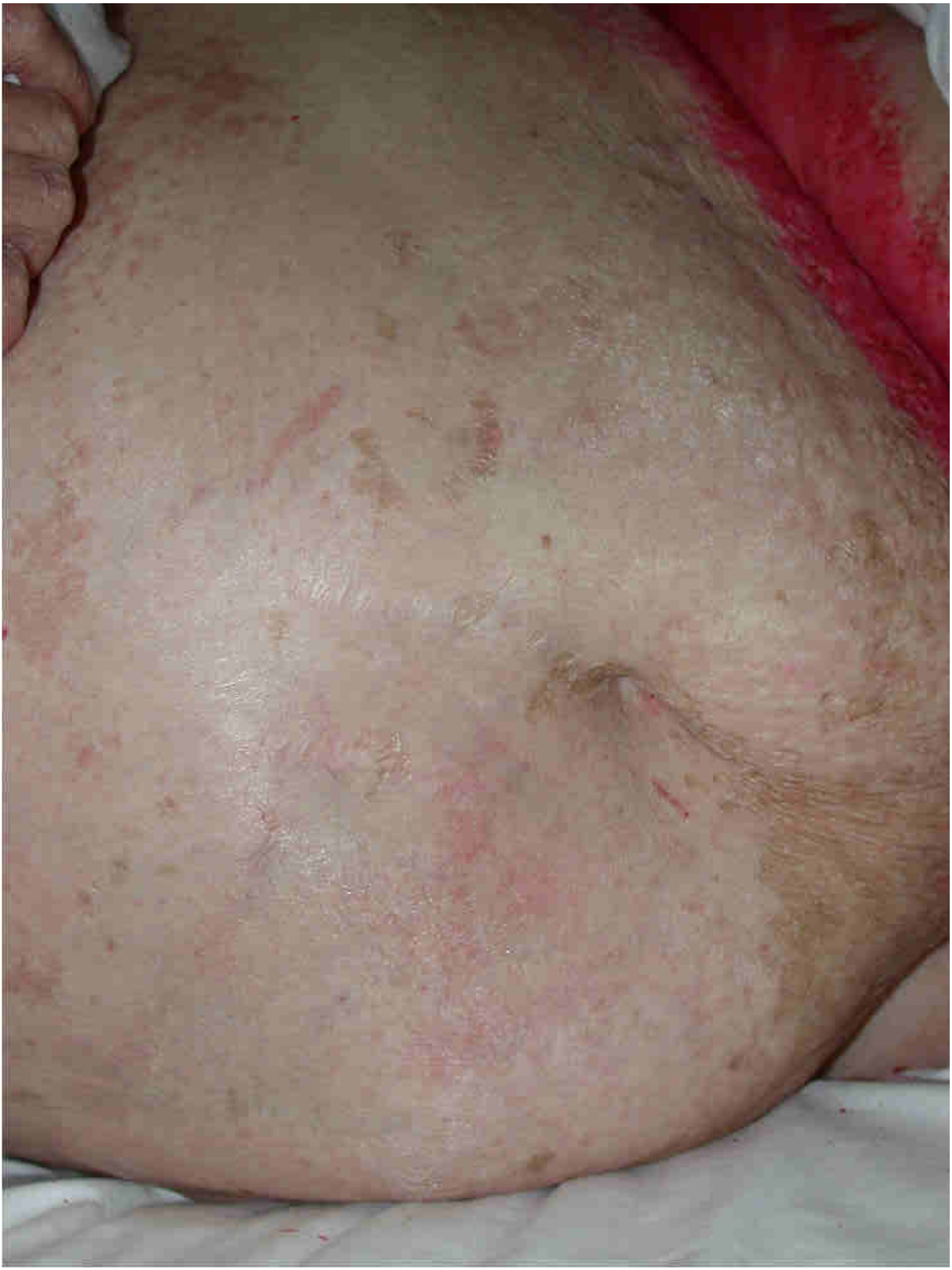


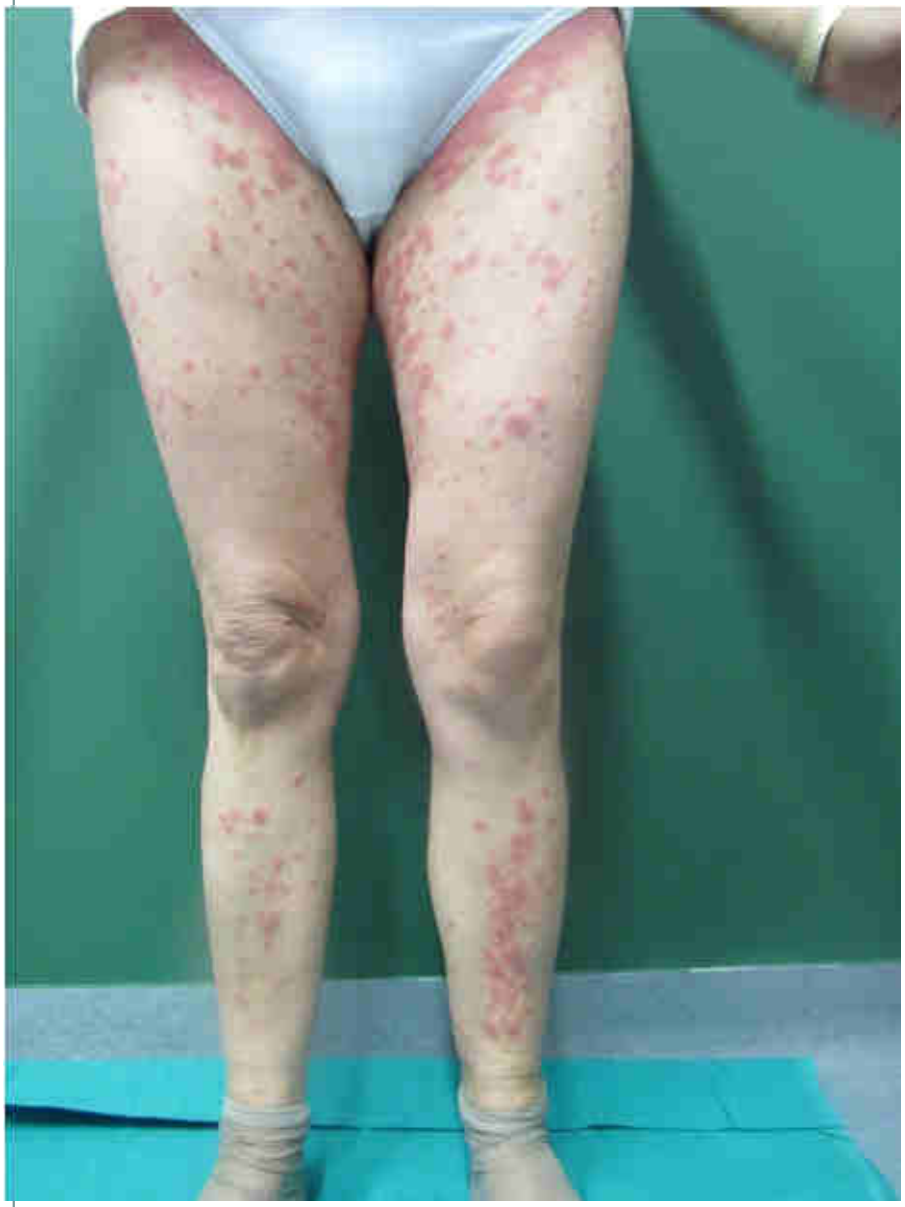


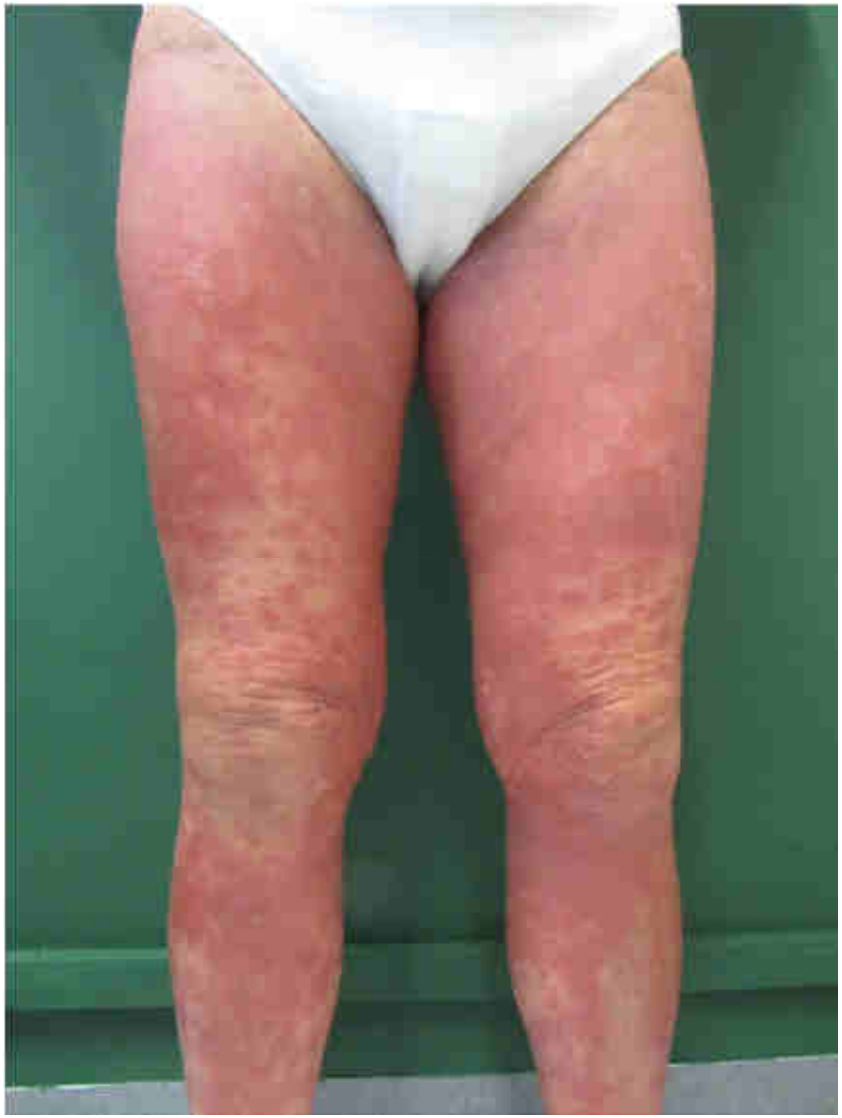


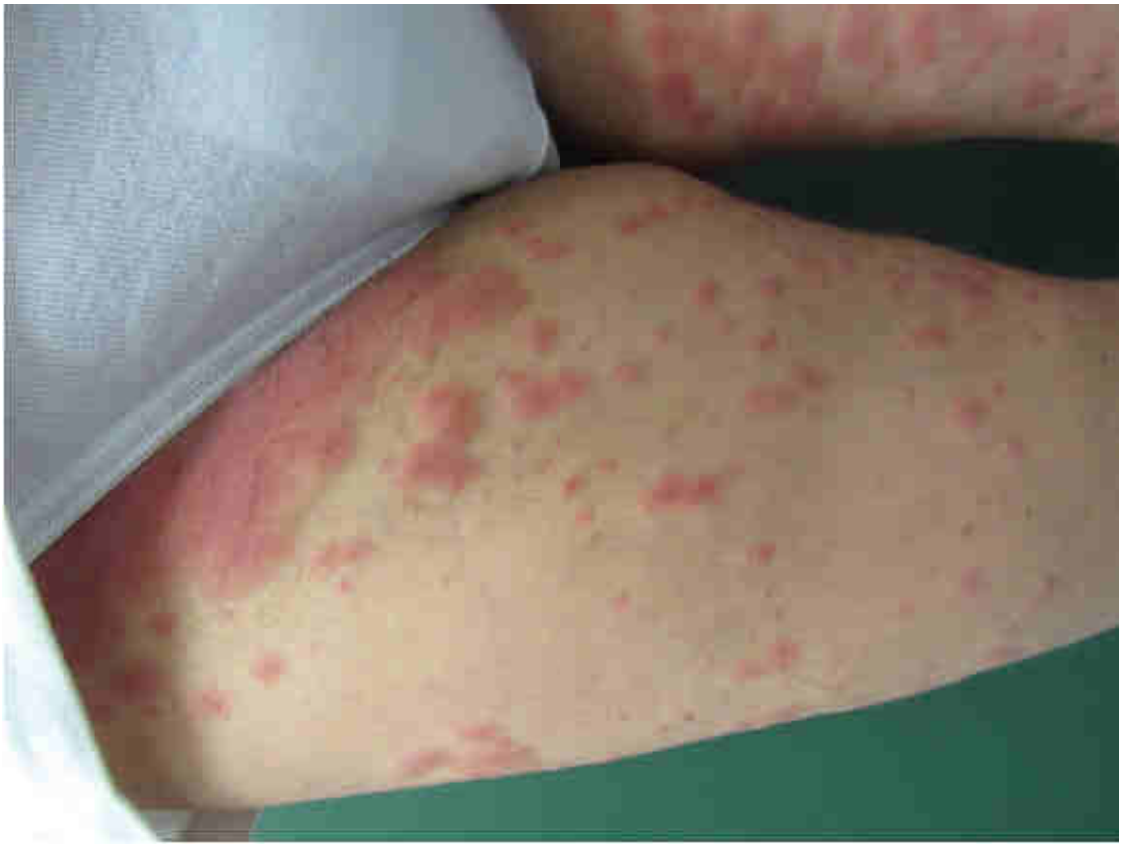


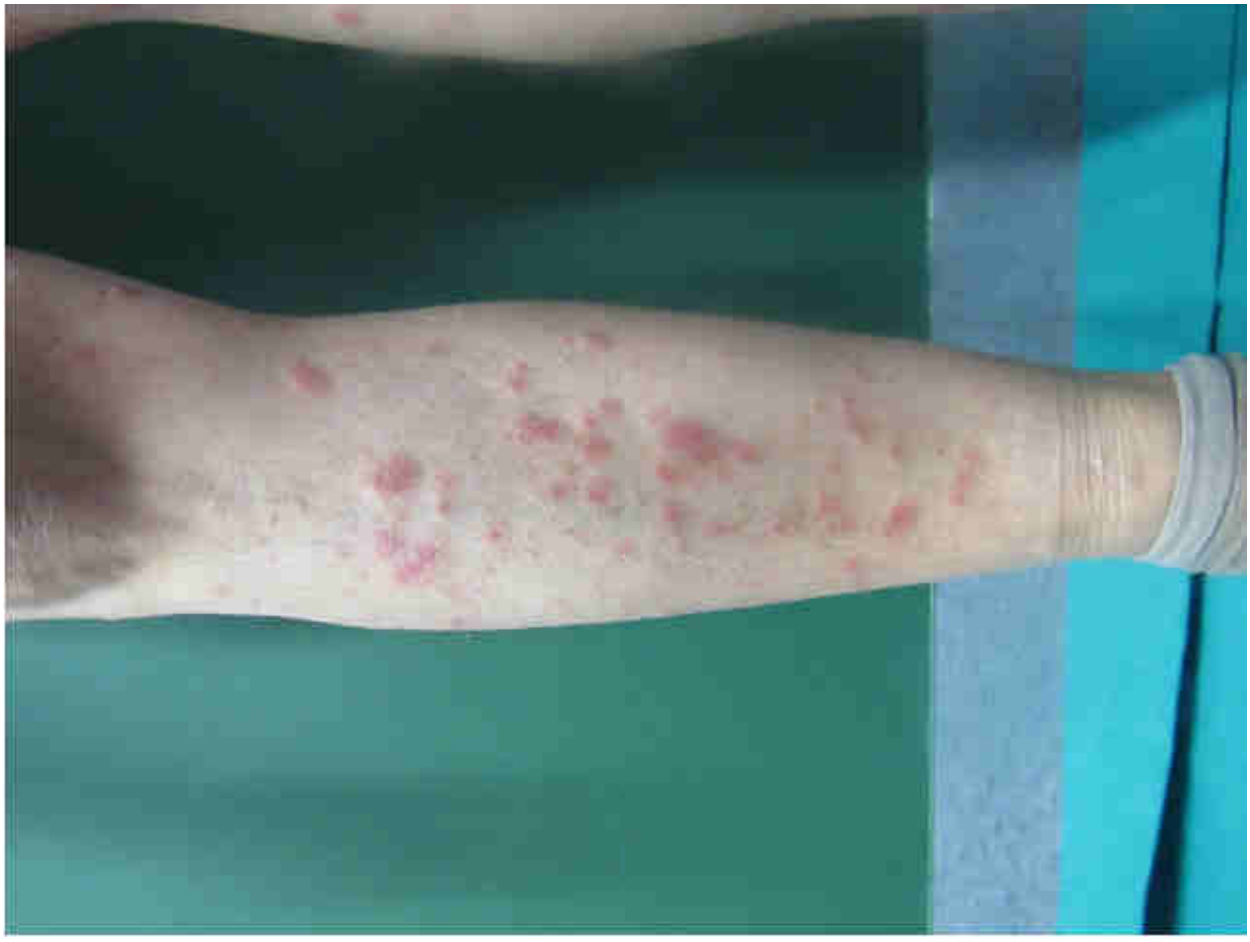


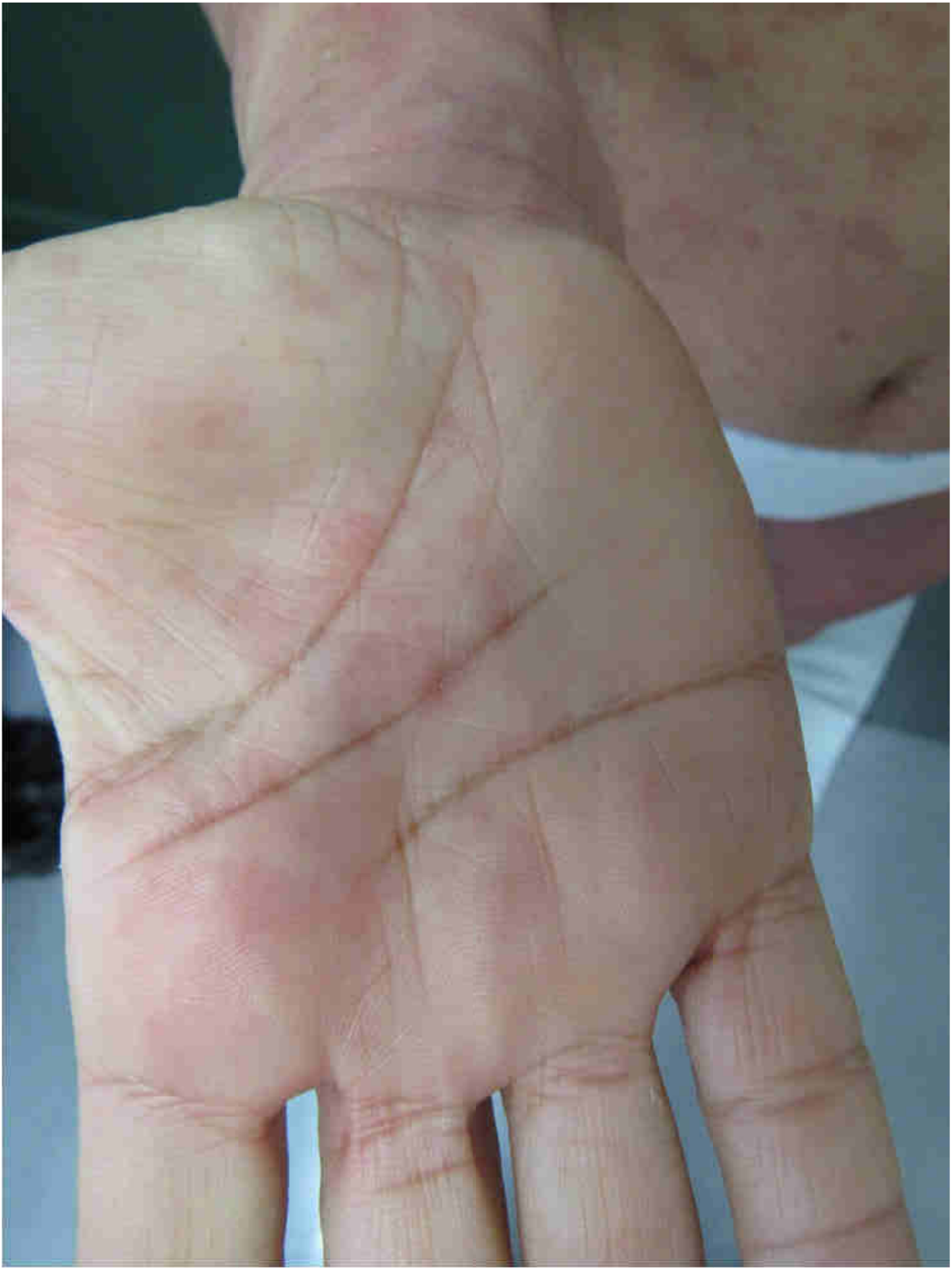


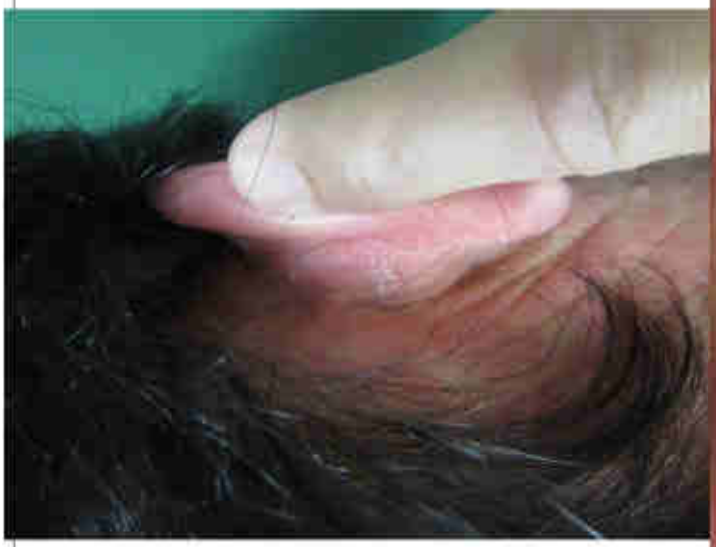


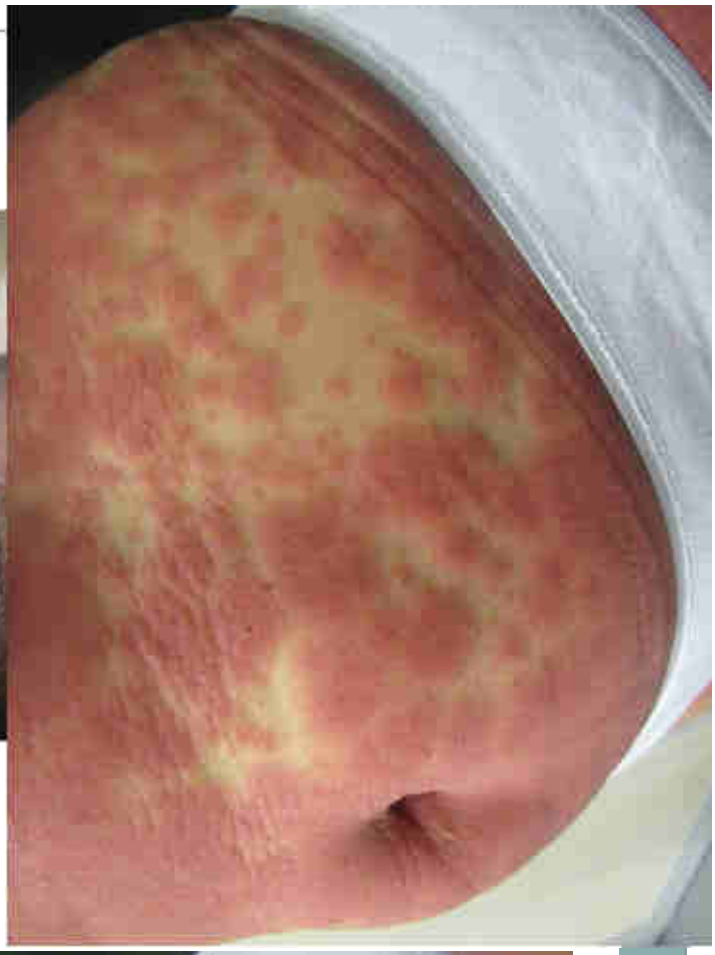


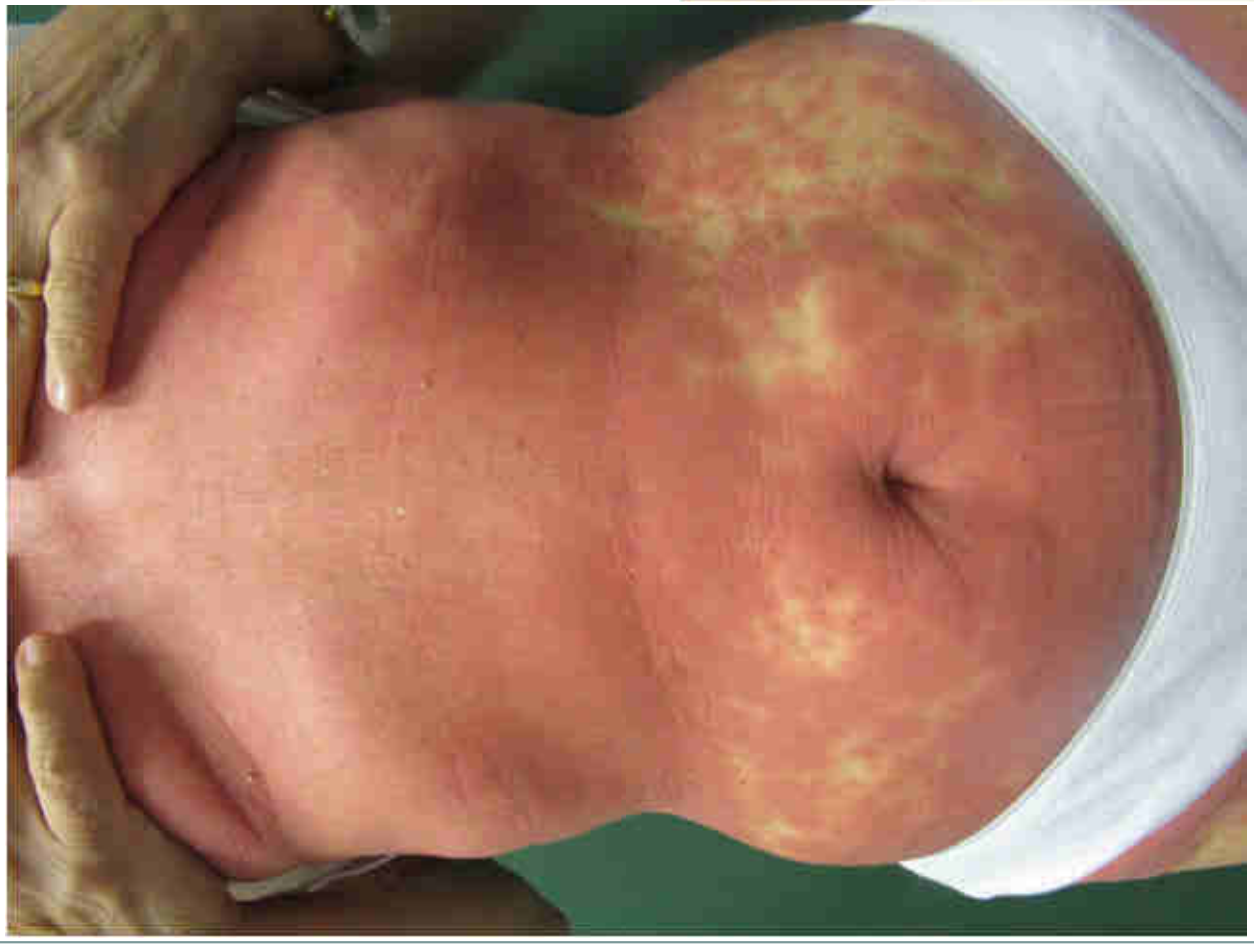


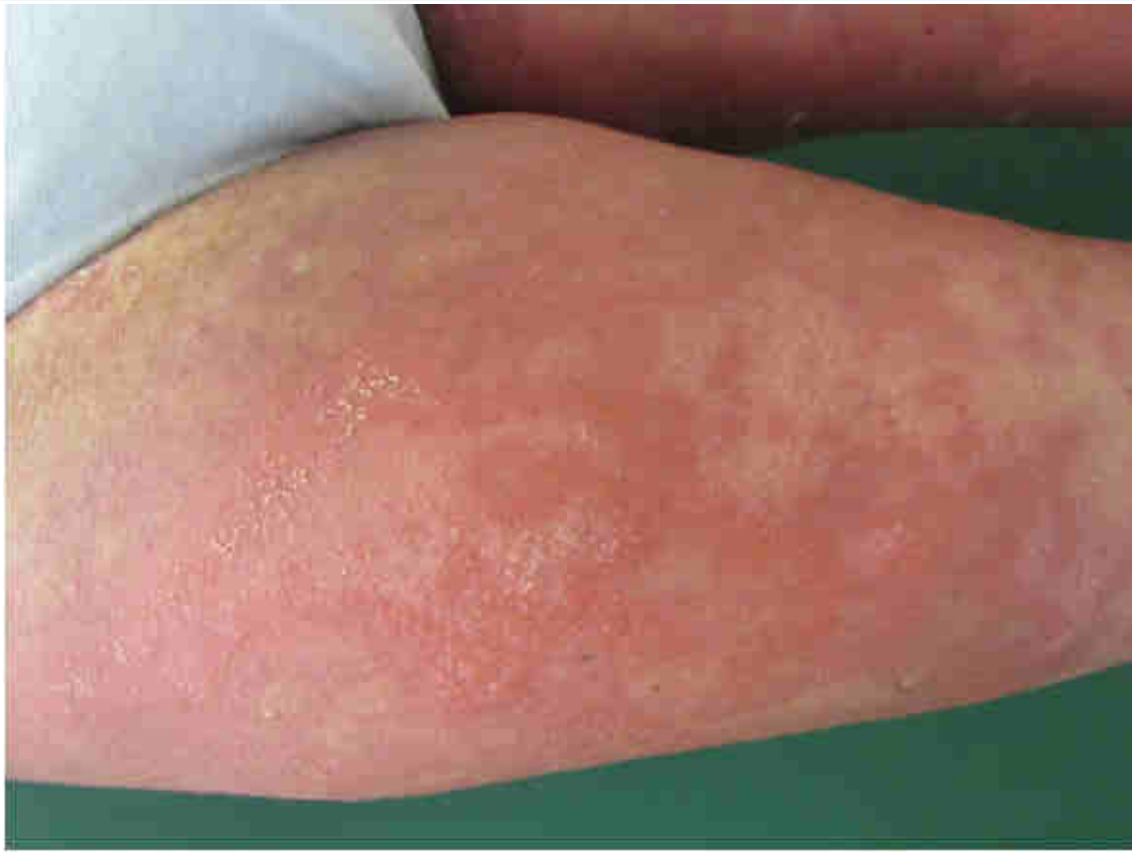


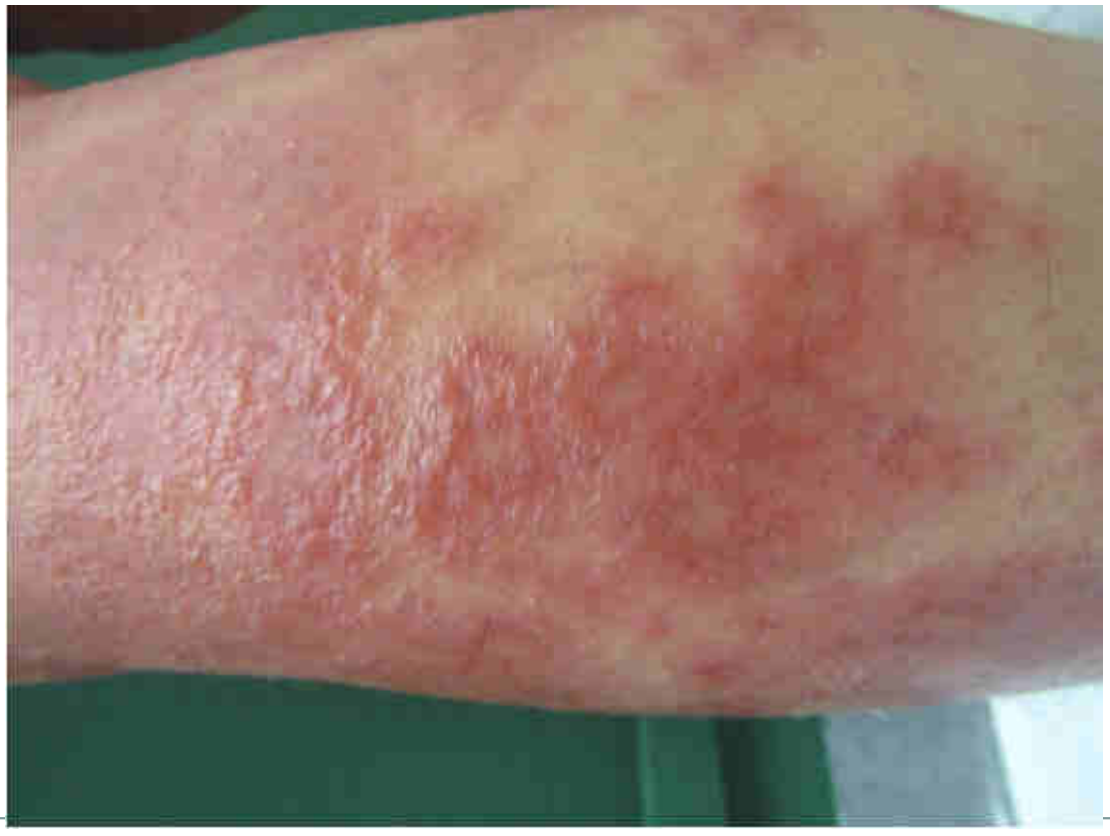


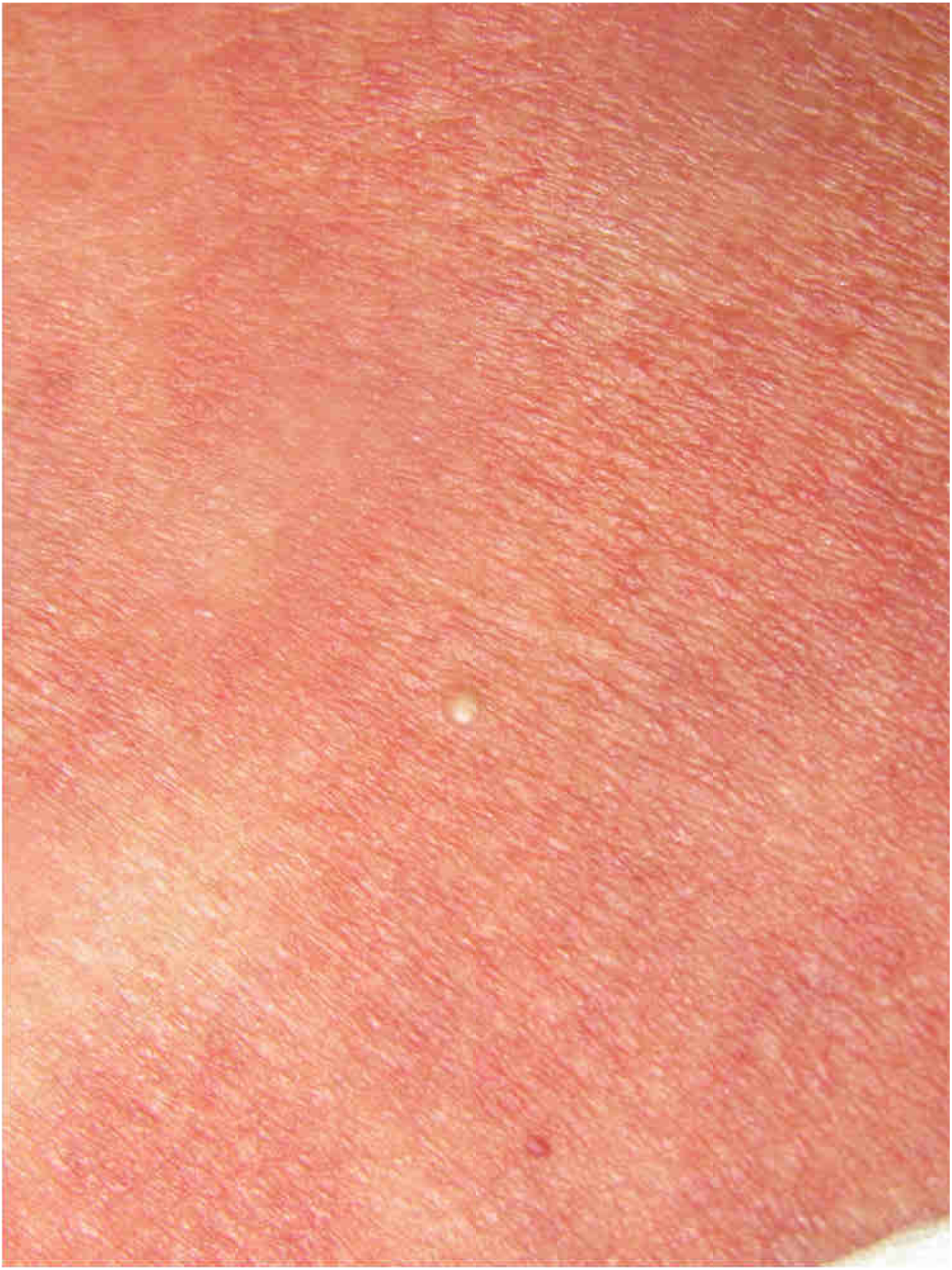


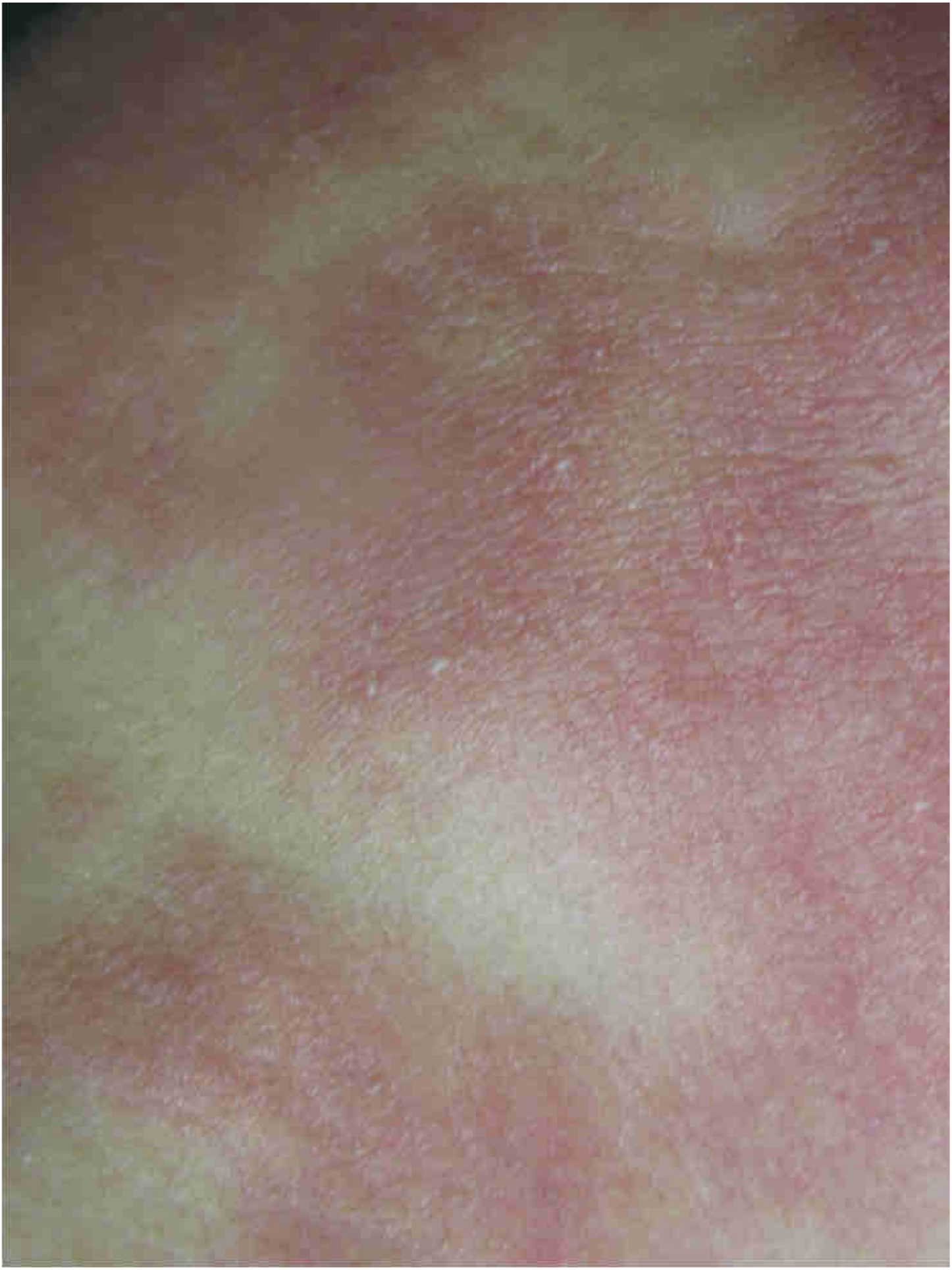


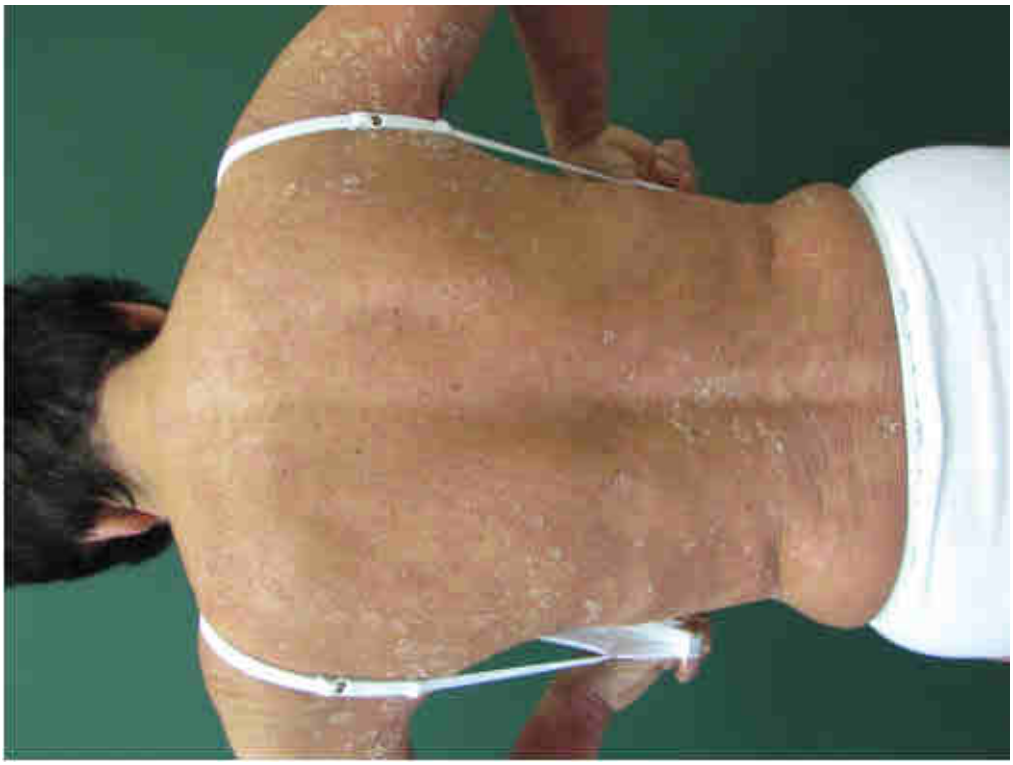


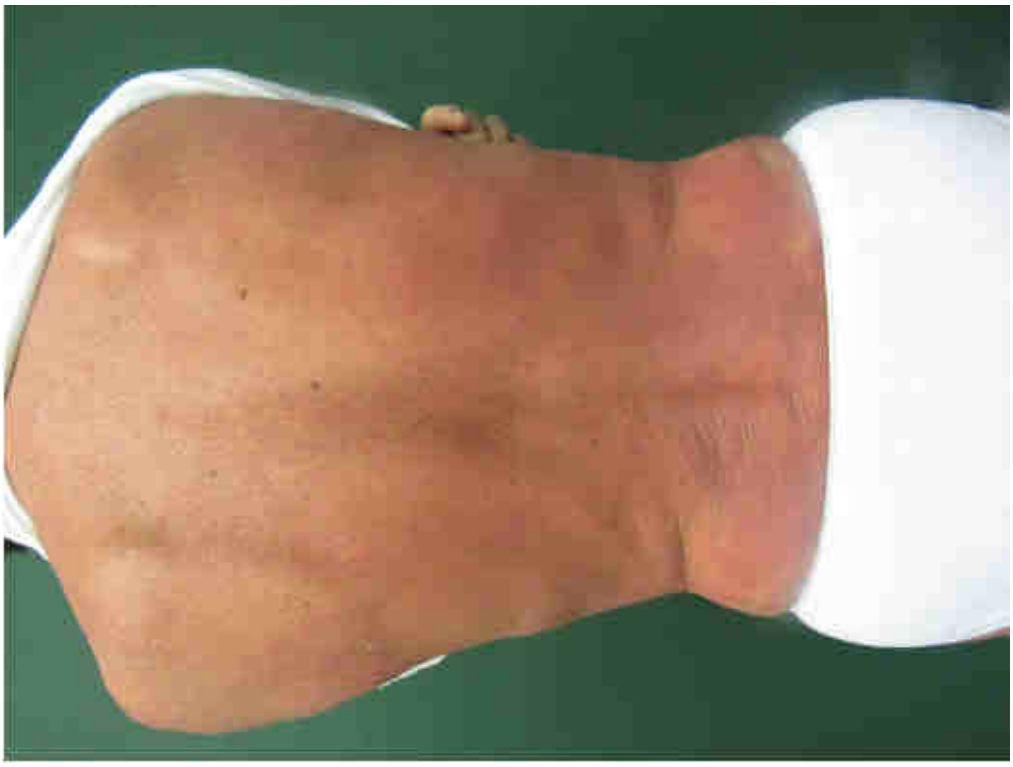


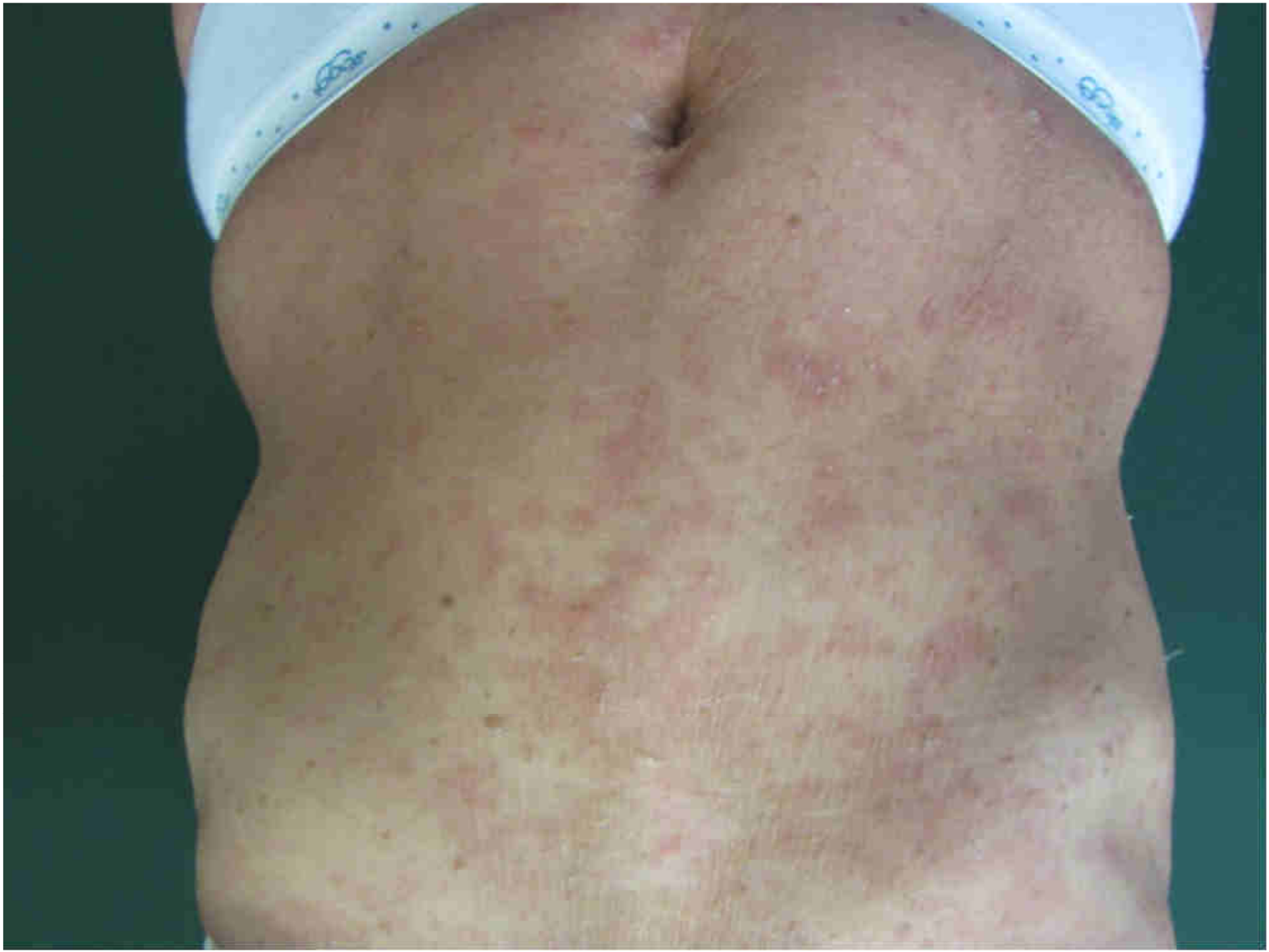


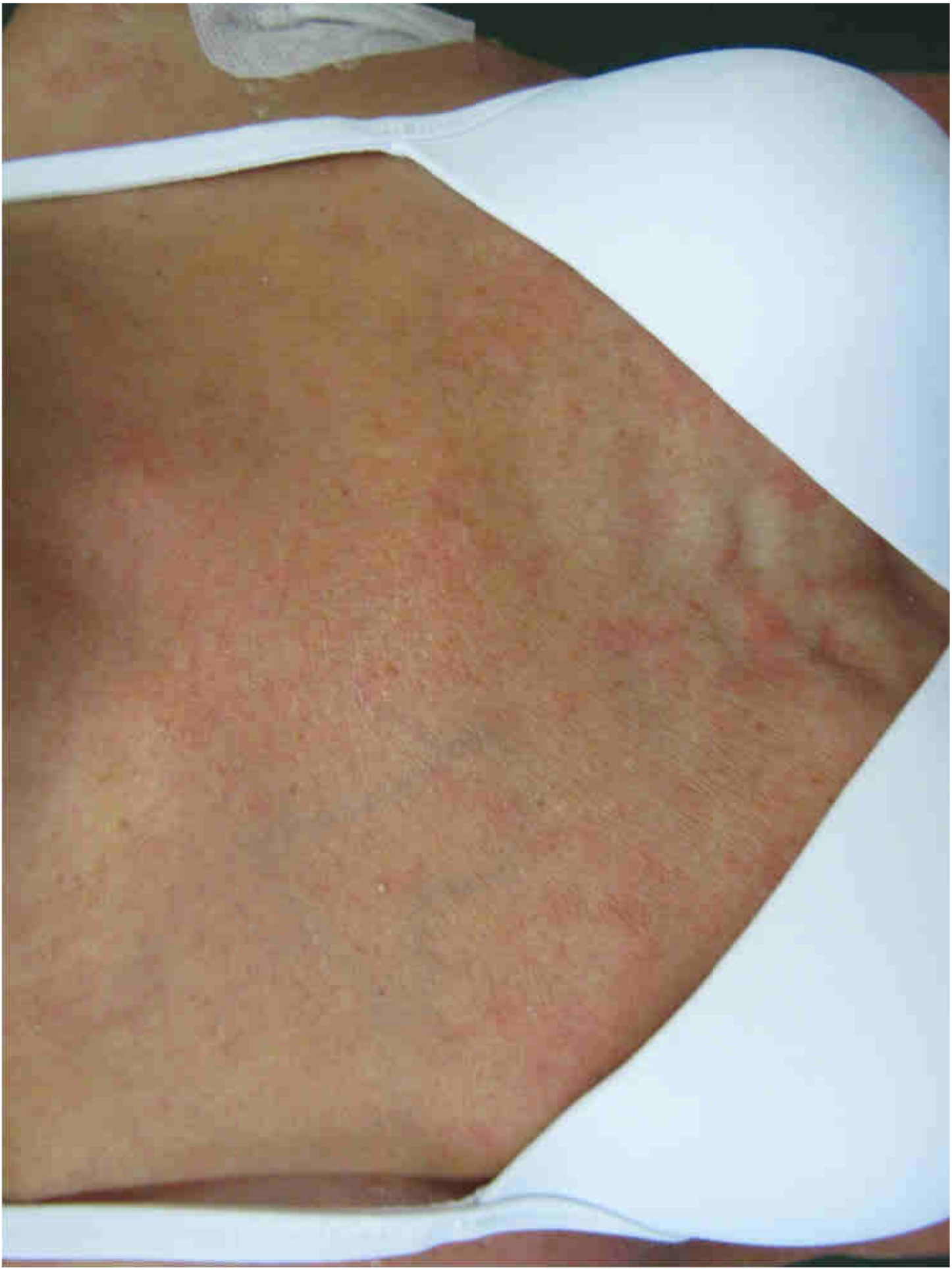


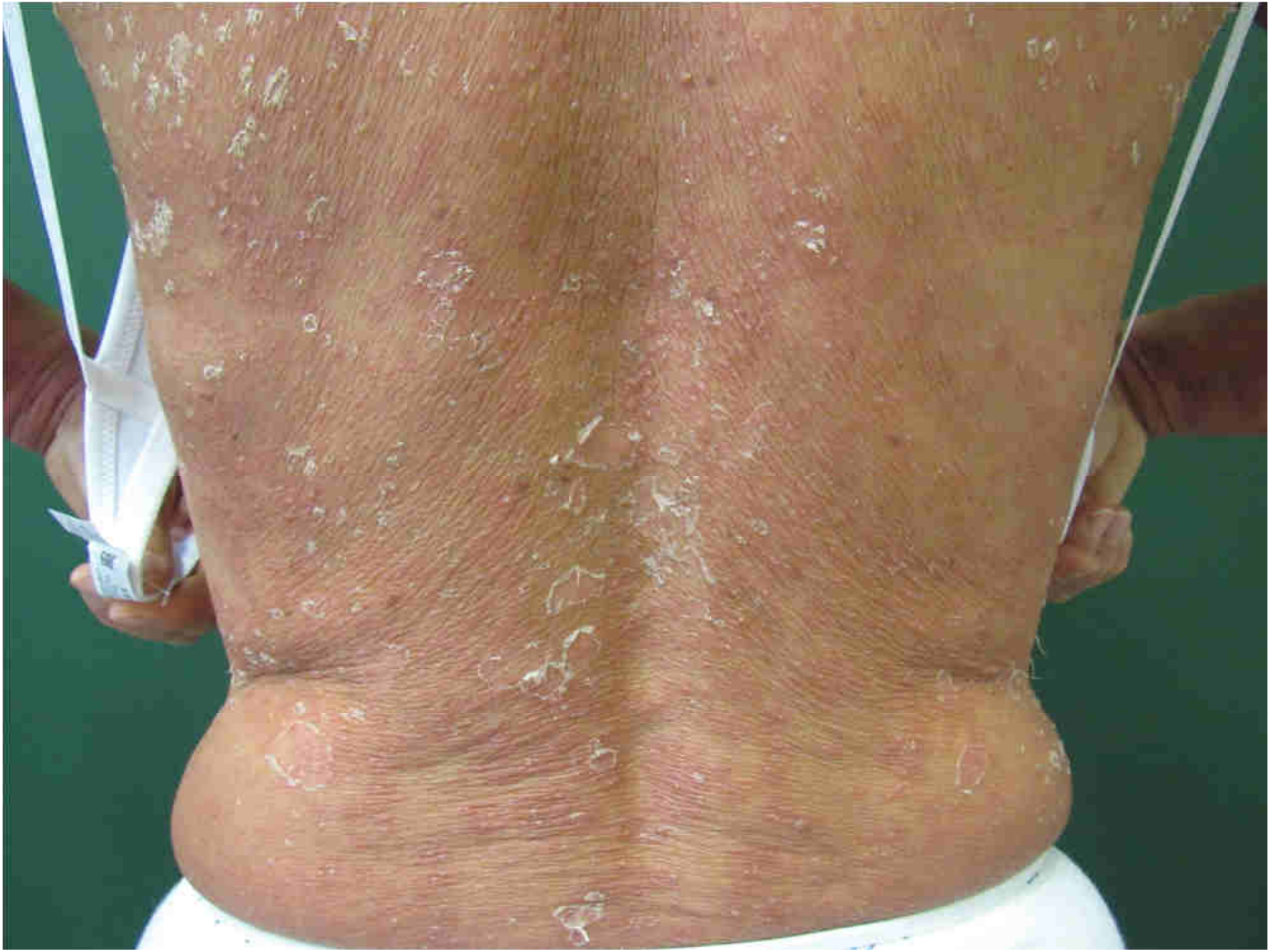












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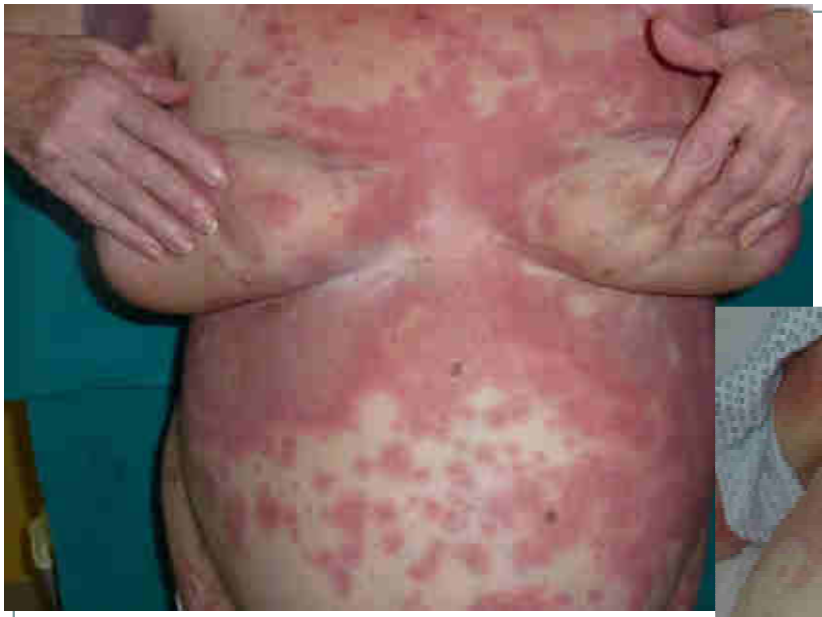

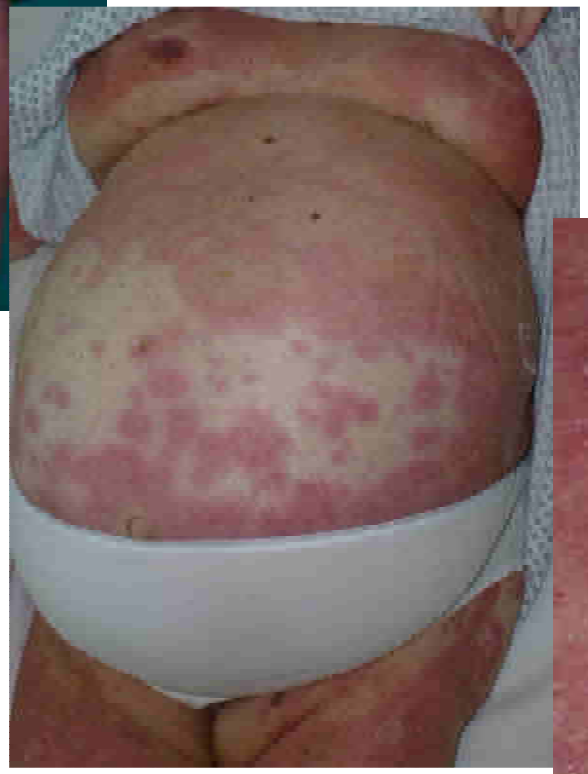

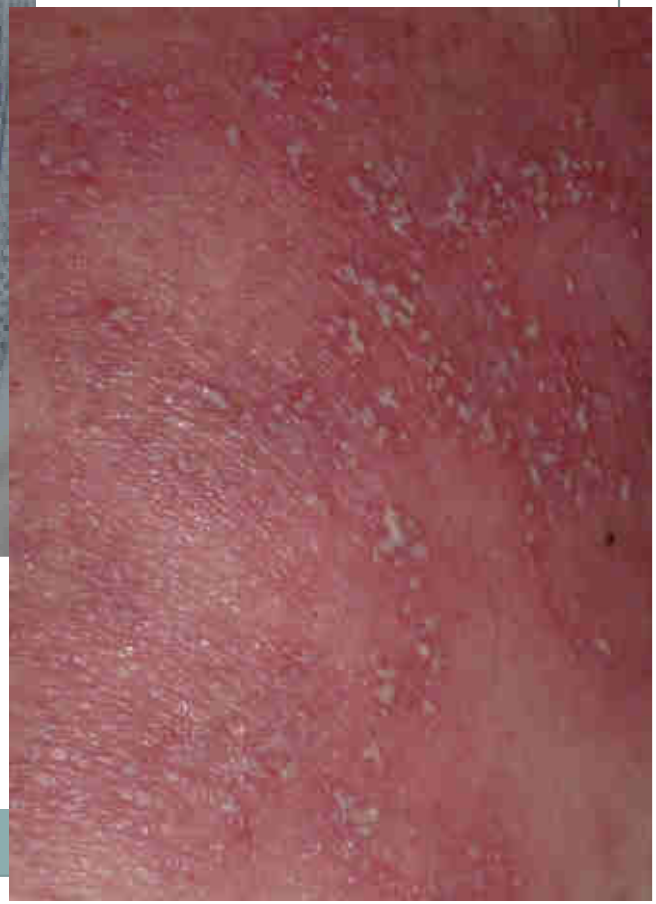

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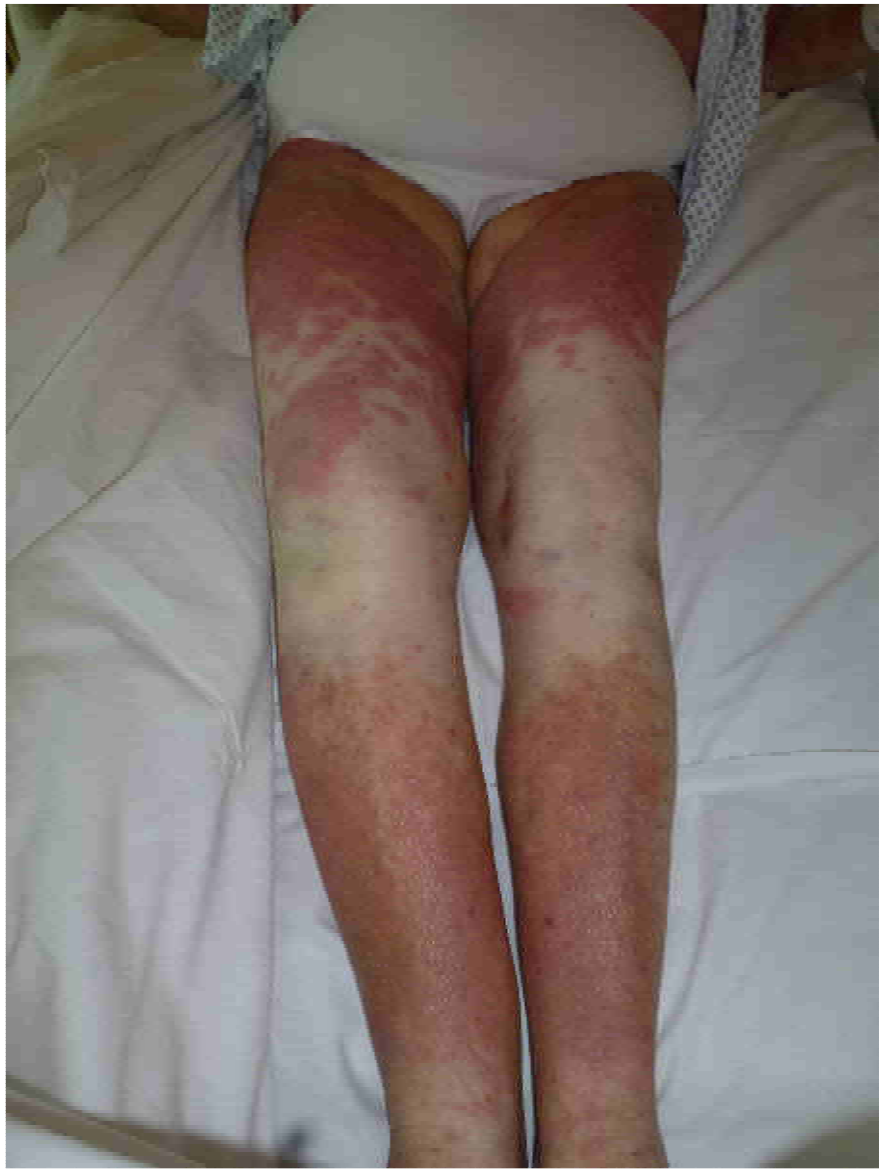

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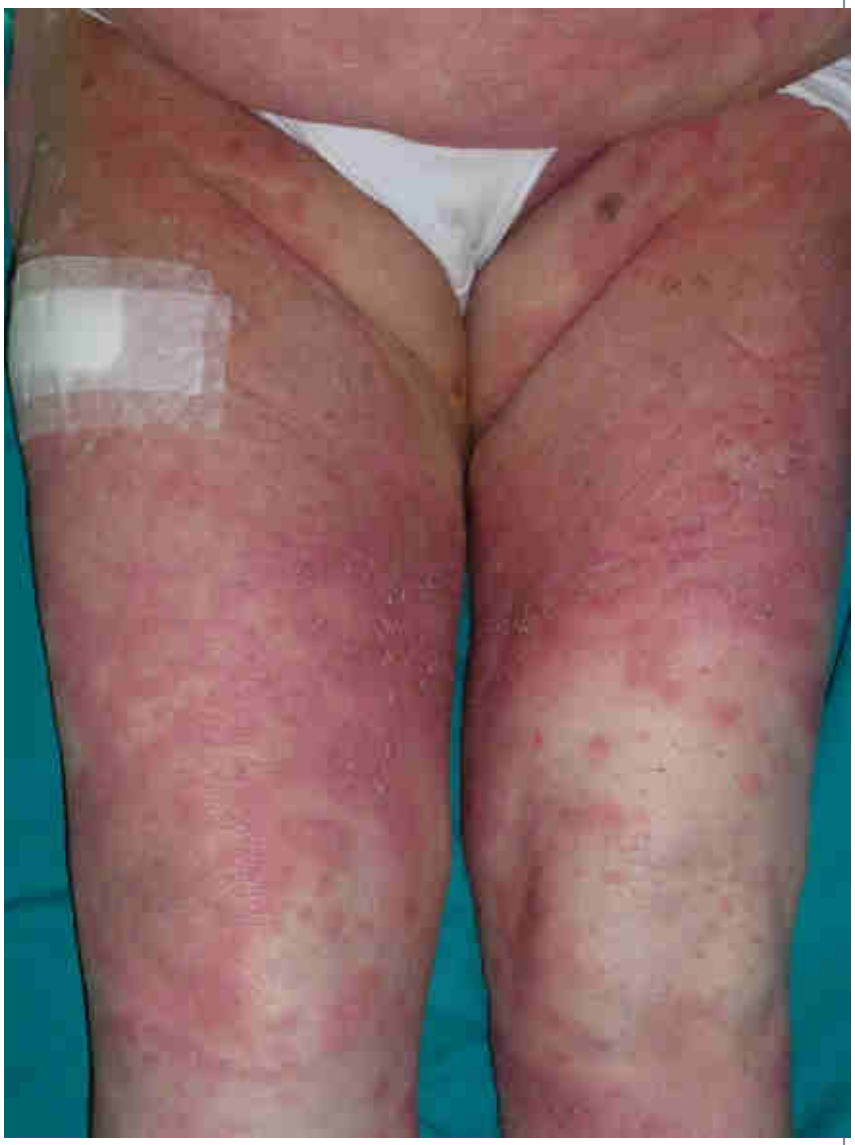
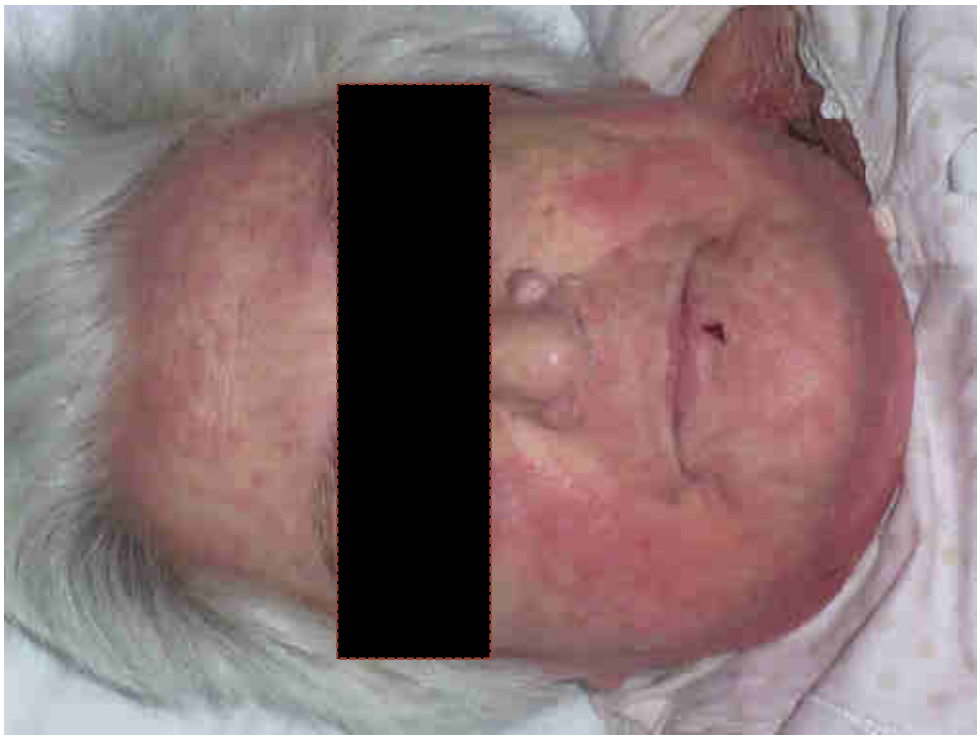
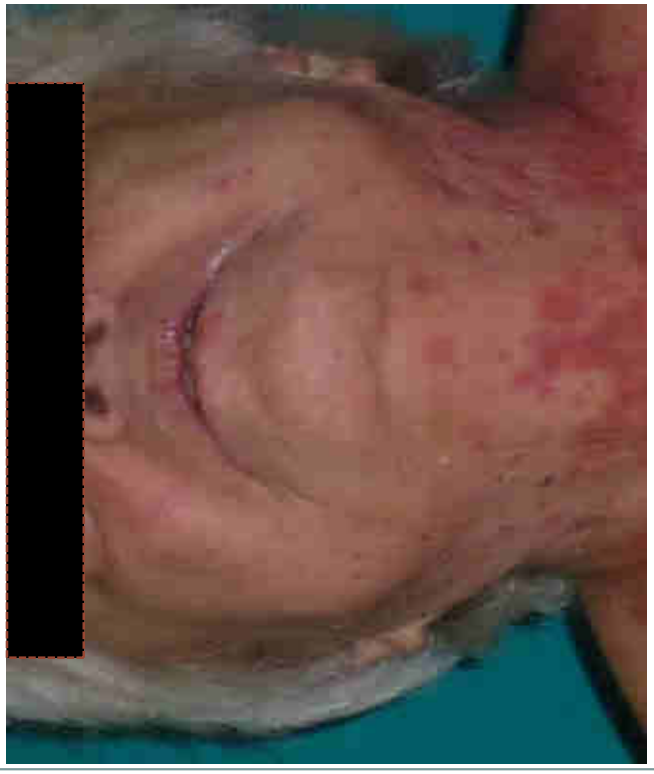
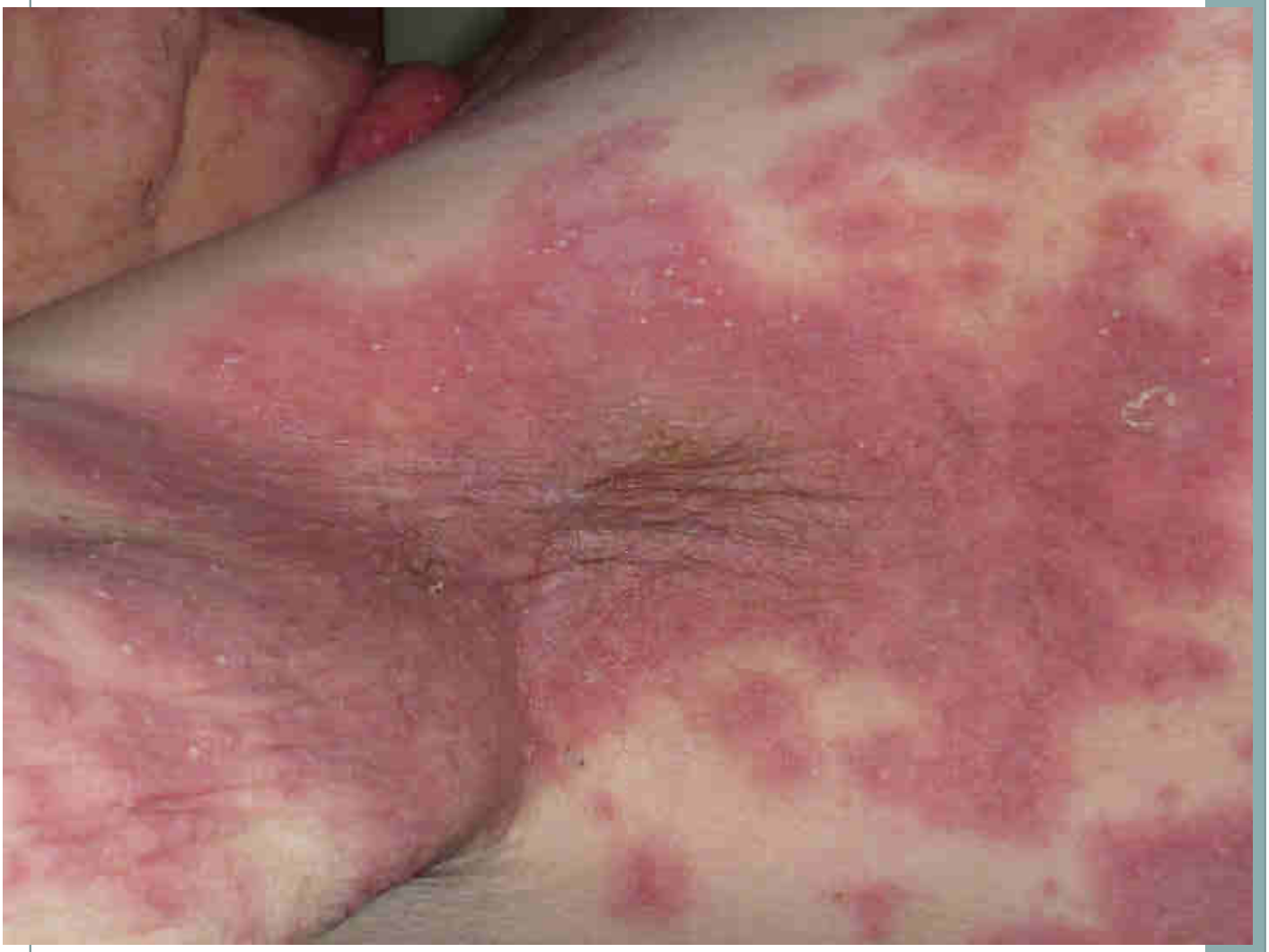
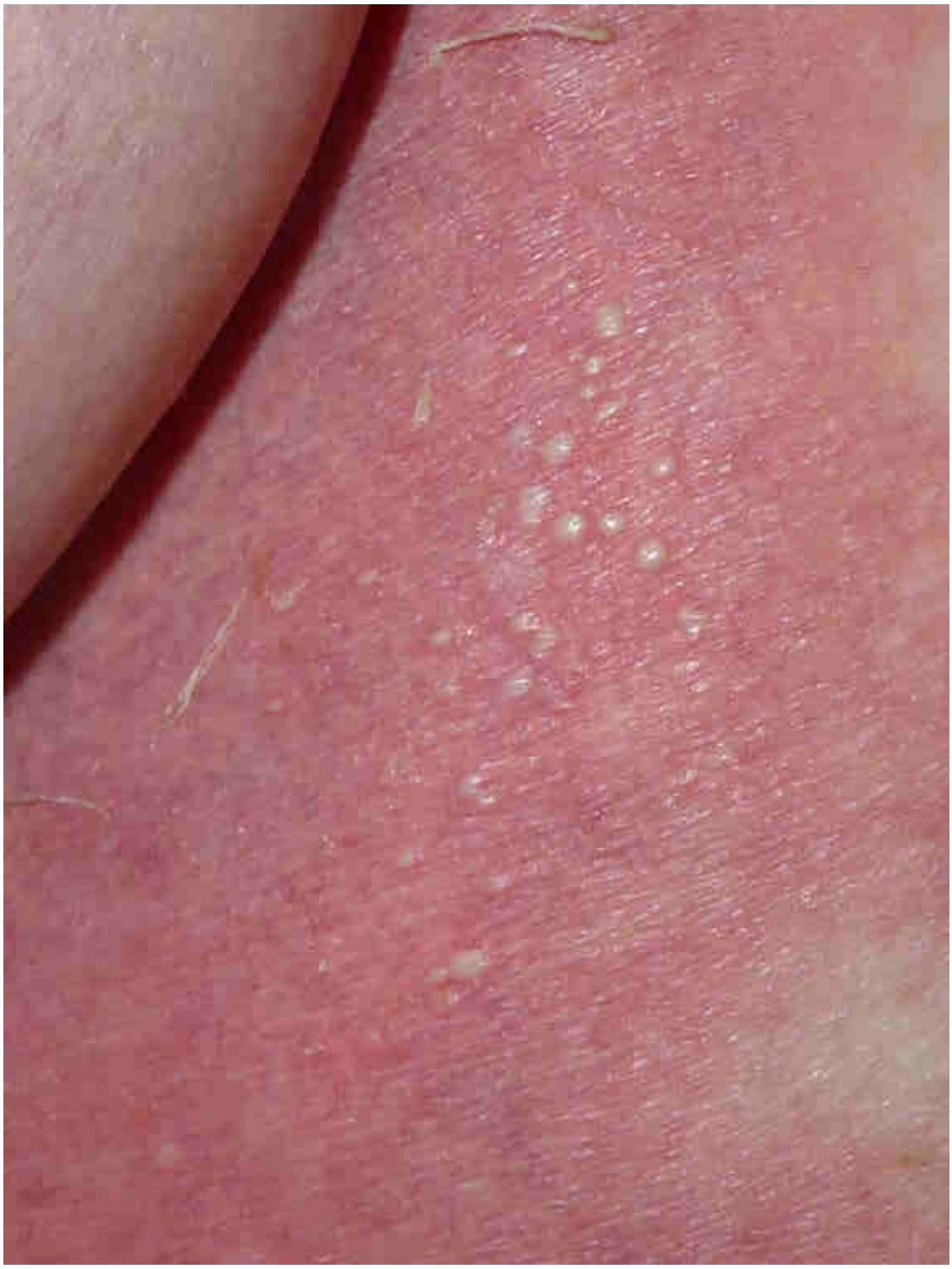
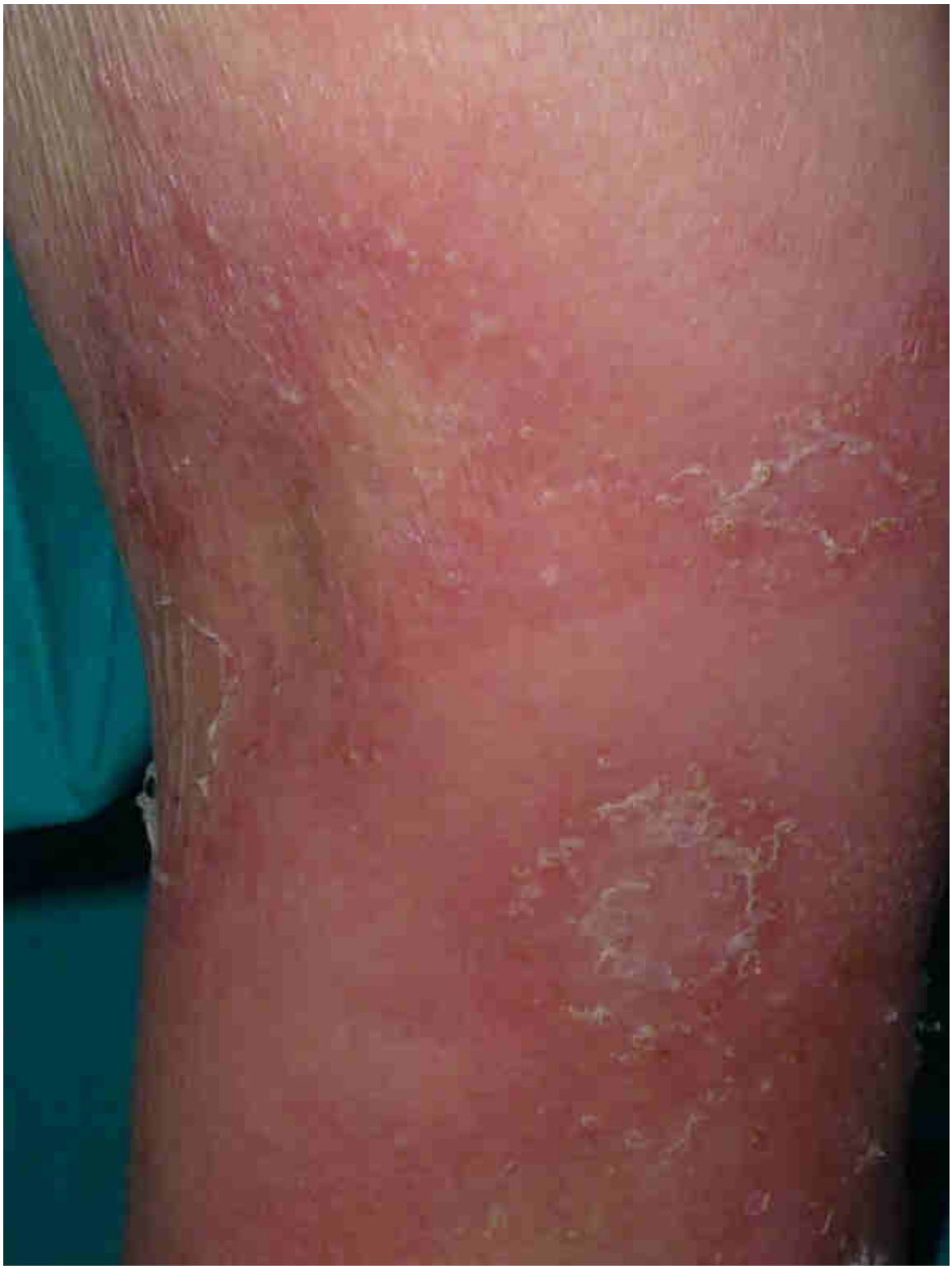












Eritema multiforme S. Steven-Johnson Lyell (TEN)

Entità clinica	TEN	SJS	SJS-TEN overlap
Disepitelizzazione	>30%	<10%	10-30%

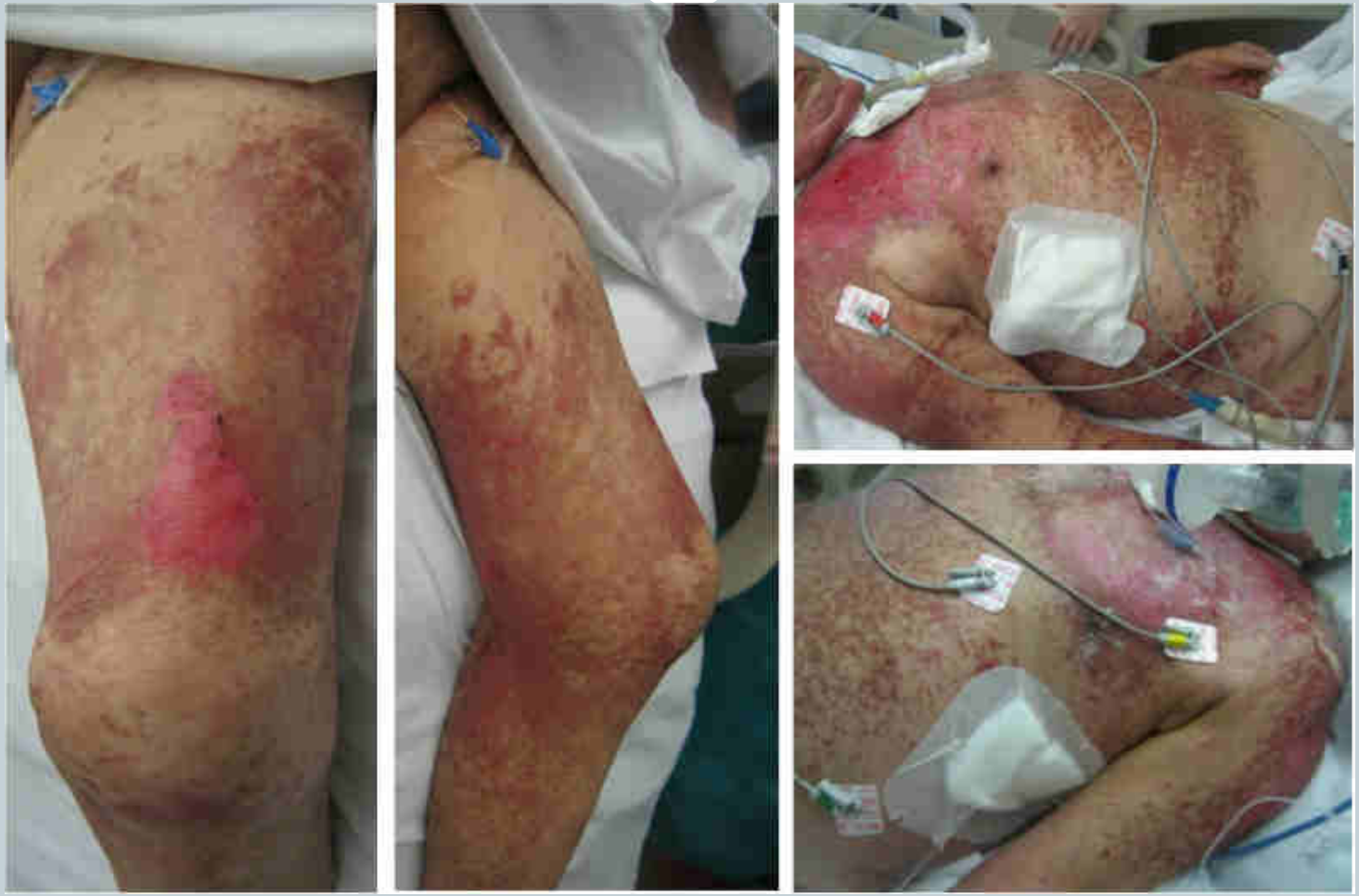
La diagnosi di SJS/TEN è essenzialmente clinica, il paziente frequentemente descrive sintomi prodromici, spesso esorditi 48-72 ore prima della comparsa delle manifestazioni cutanee: tosse, mialgia, inappetenza, senso di spossatezza.

L'eruzione cutanea esordisce sotto forma di rash maculare morbilliforme, caratterizzato da un colore variabile tra il roseo ed il purpurico, le lesioni tendono a confluire realizzando immagini figurate

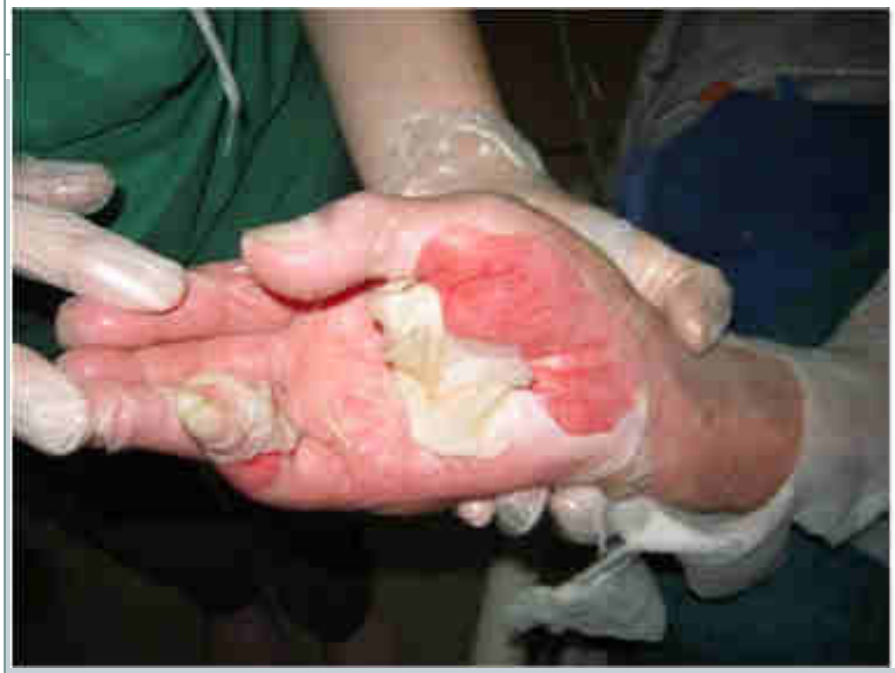
Il processo può evolvere rapidamente in poche ore o richiedere giorni. Altri elementi clinici che frequente si associano sono:

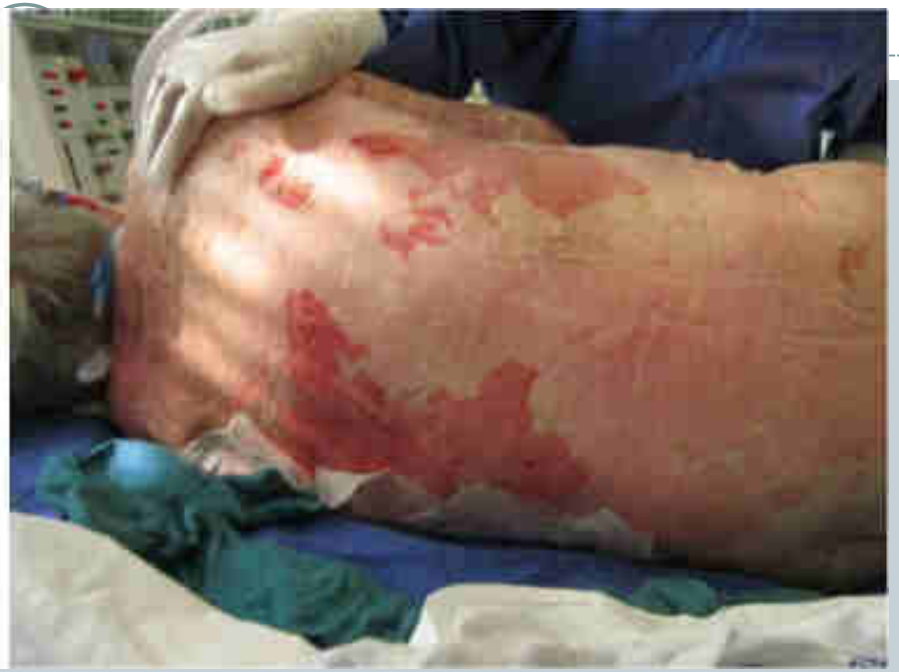
- erosioni emorragico-crostose delle labbra
- erosioni genitali
- congiuntivite
- febbre
- artralgie
- coinvolgimento esofageo e tracheale

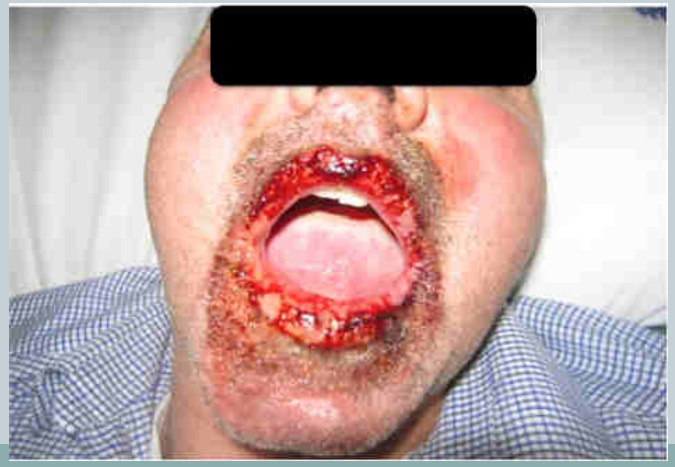
Steven-Johnson



Lyell







VARIABILI DELLO SCORTEN INDEX° ogni variabile indicata vale 1 punto
Distacco epidermico>10%
Età>40 anni
Anamnesi positiva per neoplasie in atto o pregresse
Frequenza cardiaca>120b/min
Azotemia >10 mmmol/L
Glicemia > 14 mmol/L
Bicarbonati < 20 mmol/L

SCORTEN index	Tasso di mortalità (%)
0-1	3.2
2	12.1
3	35.3
4	58.3
> 5	90

Table II. Characteristic findings of severe cutaneous drug reactions

	SJS/TEN	DRESS	AGEP
Onset of eruption	1-3 wk	2-6 wk	24-48 h
Duration of eruption, wk	1-3	Several	<1
Fever	+++	+++	+++
Cutaneous features	Bullae, mucocutaneous erosions	Morbilliform characterized by a diffuse, pruritic, macular exanthema	Nonfollicular, sterile pustules on an erythematous base with minimal mucous membrane involvement
Histology	Epidermal necrosis	Perivascular lymphocytic infiltrate	Intracorneal, subcorneal, and/or intraepidermal pustules
Visceral involvement	Tubular nephritis and tracheobronchial necrosis	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	In up to 20% of cases
Neutrophils	↓	↑	↑↑↑
Eosinophils	—	↑↑↑	↑
Mortality, %	30-40	10	5

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and system symptoms; *SJS*, Stevens-Johnson

Table 2 Drugs eliciting severe cutaneous or systemic reactions[a]

Acute generalized exanthematous pustulosis (AGEP)	Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Drug induced hypersensitivity syndrome/Drug rash with eosinophilia and systemic symptoms (DiHS/DRESS)[b]
	Nevirapine	
Aminopenicillins	Allopurinol[c]	Carbamazepin[c]
Cephalosporins	Phenytoin	Phenytoin
Pristinamycin	Carbamazepin[c]	Lamotrigin[e]
Celecoxib	Lamotrigin[e]	Minocyclin[e]
Quinolone	Cotrimoxazole	Allopurinol[c]
Diltiazem	Barbiturate	Dapsone
Terbinafin[e]	NSAID (oxicams)	Sulfasalazin
Macrolides	Sertraline	Cotrimoxazole
	Pantoprazole	Abacavir[c]
	Tramadol