Diagnosing DRESS: Is it Time to Reassess?

Lauren L. Levy MD
New York City
Arkansas Dermatological Society
April 2021

Disclosures and Conflicts of Interest

- None

Objectives

- Review clinical criteria for diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Review histopathology of DRESS and relevance to diagnoses
- Identify a histologically unique subset of patients with DRESS

Live it, Learn it , Love it

CHARACTERISTICS OF MAJOR DRUG-INDUCED ERUPTIONS

Clinical presentation	Percentage that are drug-induced (%)	Time interval	Mortality (%)	Selected responsible drugs
Exanthematous eruption	Child: 10–20 Adult: 50–70	4–14 days	0	Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants (aromatic) Allopurinol Abacavir Nevirapine
Urticaria	<10	Minutes to hours	0	Penicillins Cephalosporins NSAIDs Monoclonal antibodies Radiocontrast media†
Anaphylaxis	30	Minutes to hours	5	
Fixed drug eruption	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	TMP-SMX NSAIDs Tetracyclines Pseudoephedrine*
Acute generalized exanthematous pustulosis (AGEP)	70–90	< 4 days	1–2	β-Lactam antibiotics Macrolides Calcium channel blockers
Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS)	70–90	15–40 days	5–10	Anticonvulsants (aromatic) Lamotrigine (especially in combination with valproate) Sulfonamides Abacavir Allopurinol Dapsone Minocycline Nevirapine
Stevens–Johnson syndrome	70–90	7–21 days	5	Sulfonamides Anticonvulsants (aromatic) Lamotrigine Allopurinol NSAIDs NNRTIs, e.g. nevirapine
Toxic epidermal necrolysis			30	

†Often anaphylactoid reaction.
*Non-pigmenting.

Table 21.6 Characteristics of major drug-induced eruptions. See Chs 18 and 20 for additional details. NNRTIs, non-nucleoside reverse transcriptase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMX, trimethoprim–sulfamethoxazole (co-trimoxazole).

Bolognia et al, 2018

Table 2 Classification of Published DRESS Cases According to the RegiSCAR's Score[11]

Drugs	Classification of DRESS cases n = 172				
	No case n = 13 (8%)	Possible n = 35 (20%)	Probable n = 77 (45%)	Definite n = 47 (27%)	Nb of Cases n (%)
Abacavir[12-16]	4	1			5 (3)
Allopurinol[17-29]	1	6	8	4	19 (11)
Amoxicillin plus clavulanic acid[30]			1		1 (0.6)
Amitriptyline[31,32]			2		2 (1)
Atovarstatin[33]			1		1 (0.6)
Aspirin[34]				1	1 (0.6)
Captopril[6]			1		1 (0.6)
Carbamazepine[5,18,24,35-63]	3	10	20	14	47 (27)
Cefadroxil[64]			1		1 (0.6)
Celecoxib[65]			1		1 (0.6)
Chlorambucil[66]			1		1 (0.6)
Clomipramine[67]			1		1 (0.6)
Clopidogrel[68]	1				1 (0.6)
Codeine phosphate[69]			1		1 (0.6)
Cotrimoxazole/cefixime[70]			1		1 (0.6)
Cyanamide[71]			1		1 (0.6)
Dapsone[72-75]			4		4 (2)
Diaphenylsulfone[76]		1			1 (0.6)
Efalizumab[77]			1		1 (0.6)
Esomeprazole[78]			1		1 (0.6)
Hydroxychloroquine[79,80]				2	2 (1)
Ibruprofen[5,81]			2		2 (1)
Imatinib[82]			1		1 (0.6)
Lamotrigine[52,83-91]	3	3	2	2	10 (6)
Mexilletine[24,92-95]		2	3		5 (3)
Minocycline[96-98]			2	1	3 (2)
Nevirapine[99-104]		3	3	2	8 (5)
Olanzapine[105]				1	1 (0.6)
Oxcarbazepine[106-108]			1	2	3 (2)
Phenobarbital[18,37,47,109-115]		3	4	3	10 (6)
Phenylbutazone[116]				1	1 (0.6)
Phenytoin[24,47,58,117-120]	1	3	3		7 (4)
Quinine and thiamine[121]			1		1 (0.6)
Salazosulfapyridine[5,122]			1	1	2 (1)
Sodium meglumine ioxitalamate[123]			1		1 (0.6)
Sodium valproate/ethosuximide[124]				1	1 (0.6)
Spironolactone[125]				1	1 (0.6)
Streptomycin[126]				1	1 (0.6)
Strontium ranelate[127]			1	1	2 (1)
Sulfalazine[62,93,128-135]		3	2	5	10 (6)
Sulfamethoxazole[14,136]			2		2 (1)
Tribenoside[13]				1	1 (0.6)
Vancomycin[137-140]		1	2	1	4 (2)
Zonisamide[18]				1	1 (0.6)

DRESS — Drug Reaction with Eosinophilia and Systemic Symptom.

Cacoub P, Musette P, Descam

On any given Sunday, any team in the NFL can beat any other team

-BERT BELL

DRESS: a difficult diagnosis

- 10-60% of cases do NOT have eosinophilia
- Small percentage of patients have NO rash (2/176 in one study)
- Systemic involvement varies and may be related to the medication culprit
  - 10% of patients no systemic symptoms
- Other etiologies of clinical presentation must be investigated and ruled out before diagnosis of DRESS is made
  - Viral exanthem, connective tissue disease, hematologic malignancy , Hemophagocytic Lymphohistiocytosis

- Kardaun SH, et al . Br J Dermatol. 2007 Mar;156(3):609-11.

Table II. Drugs associated with specific internal organ risk in drug reaction with eosinophilia and systemic symptoms syndrome

Medication	Clinical abnormality
Allopurinol	Renal
Ampicillin	Cardiac
Carbamazepine	Renal
Dapsone	Hepatic and renal
Minocycline	Hepatic, pulmonary, and cardiac
Phenytoin	Hepatic

Husain Z, et al. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 2013 May;68(5):693.e1-14

How are we currently making the diagnosis?

- RegiSCAR criteria
- The Japanese criteria
- Bocquet’s criteria

RegiSCAR

RegiSCAR Diagnosis Score for DRESS			
Features	**No**	**Yes**	**Unknown**
Fever (≥ 38.5°C)	-1	0	-1
Enlarged lymph nodes (≥2 sites, ≥1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1499 or 10%-19.9%		1	
≥1500 or ≥20%		2	
Skin rash	0		0
Extent >50%	0	1	0
At least 2: edema, infiltration, purpura, scaling	-1	1	0
Biopsy suggesting DRESS	-1	0	0
Internal organ involvement	0		0
One		1	
Two or more		2	
Resolution in more than 15 days	-1	0	-1
At least 3 biological inv done and	0	1	0
negative to exclude alternative diagnosis			
Final score: <2 = no; 2-3 = possible; 4-5 = probable; >5 = definite			

Figure 2: Study of investigating severe cutaneous reactions.

Japanese Criteria

1 Maculopapular rash developing > 3 weeks after starting with a limited number of drugs
2 Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
3 Fever (> 38 °C)
4 Liver abnormalities (alanine aminotransferase > 100 U L^{-1})[a]
5 Leucocyte abnormalities (at least one present)
  a Leucocytosis (> 11×10^9 L^{-1})
  b Atypical lymphocytosis (> 5%)
  c Eosinophilia (> $1{\cdot}5 \times 10^9$ L^{-1})
6 Lymphademopathy
7 Human herpesvirus 6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical DIHS) or of the five (1~5) (atypical DIHS).
[a]This can be replaced by other organ involvement, such as renal involvement.

Shiohara T, et al The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007 May;156(5):1083-4.

Bocquet's Criteria:

- Skin eruption
- Blood eosinophilia (>$1.5\times10^3/\mu L$) or the presence of atypical lymphocytes
- Internal organ involvement, including lymphadenopathies (>2 cm in diameter), hepatitis (liver transaminases values > twice the upper normal limit), interstitial nephritis, and interstitial pneumonia or carditis

RegiSCAR study group[2]	Japanese consensus group[1,2]	Bocquet *et al.*[2]
1. Hospitalisation 2. Reaction suspected to be drug related 3. Acute rash* 4. Fever above 38°C* 5. Enlarged lymph nodes involving at least two sites* 6. Involvement of at least one internal organ* 7. Blood count abnormalities: a. Lymphocytes above or below laboratory limits* b. Eosinophils above laboratory limits (in percentage or absolute count)* c. Platelets below laboratory limits* *≥3 of the criteria marked '*' are required for the diagnosis of DRESS*	1. Maculopapular rash developing more than 3 weeks after starting therapy with a limited number of drugs 2. Prolonged clinical symptoms after discontinuation of the causative drug 3. Fever (>38°C) 4. Hepatitis (ALT >100 units/L) or renal involvement 5. Leukocyte abnormalities [leukocytosis >11,000/mm^3; atypical lymphocytosis >5%; eosinophilia (1500 cells/mm^3)] 6. Lymphadenopathy 7. HHV-6 reactivation *Presence of all 7 criteria -> typical DIHS* *Atypical DIHS -> except lymphadenopathy and HHV-6 reactivation*	1. Cutaneous drug eruption 2. Adenopathies ≥2cm in diameter or hepatitis (liver transaminases ≥2-times the upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis 3. Hematologic abnormalities eosinophilia ≥1.5 x 10^9/L or atypical lymphocytes *Presence of 1, 2 and 3 is required for the diagnosis of DRESS*

- Riyaz N,et al. Drug-induced hypersensitivity syndrome with human herpesvirus-6 reactivation. Indian J Dermatol Venereol Leprol 2012;78:175-7

Why does it matter?

- Diagnosis of DRESS may indicate a protracted treatment course with evolution of systemic involvement
- ~10% mortality in cases with systemic involvement
- Monitor for the development of late complications and autoimmune disease following an episode
  - Myocarditis
  - Thyroiditis
  - Pneumonitis
  - Pancreatitis
  - Nephritis
- Avoidance of culprit in the future

Chen YC, et al. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010 Dec;146(12):1373-9.

Case 1

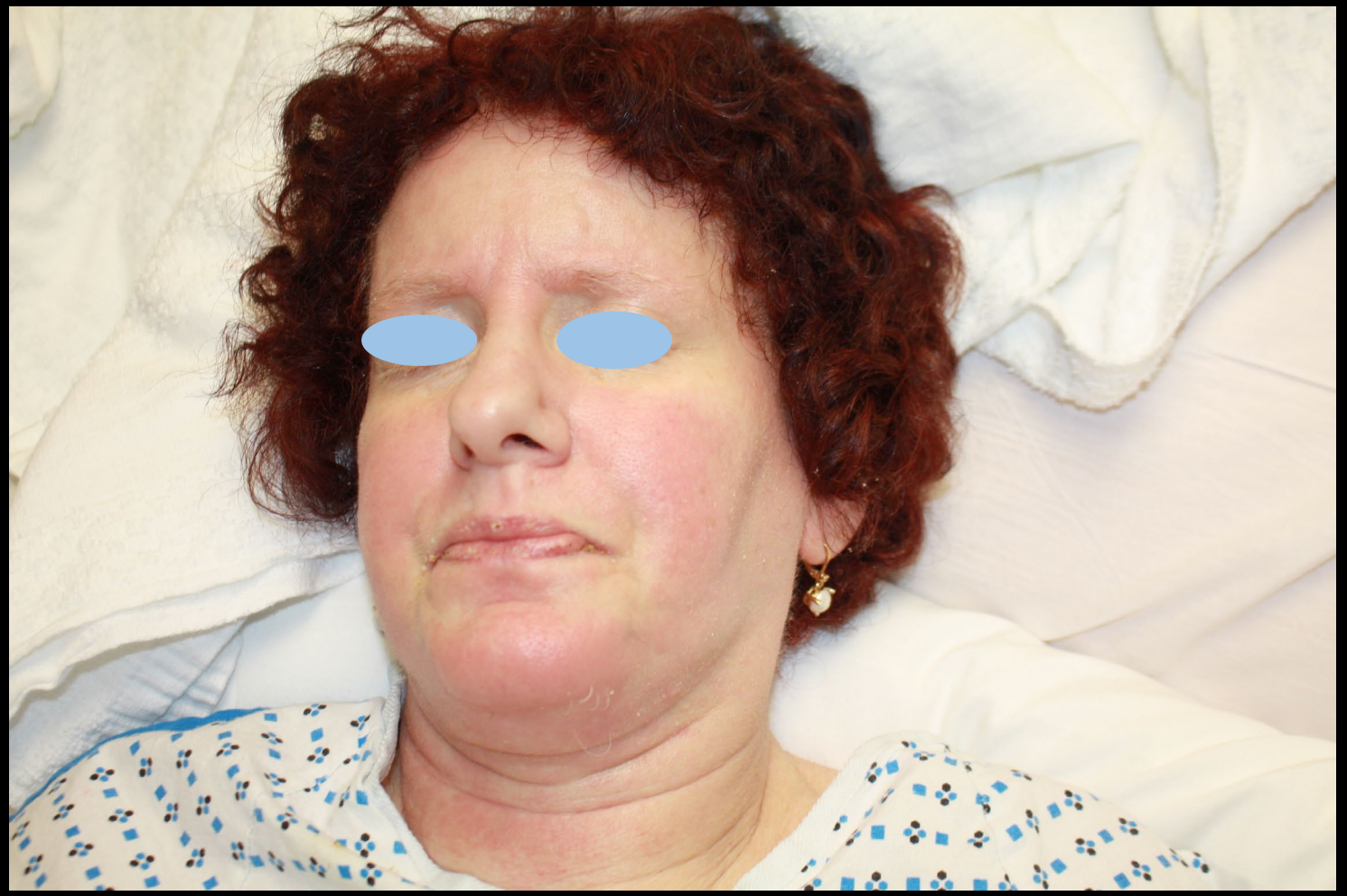
- 58 y/o Female with anxiety, mood disorder on chronic benzodiazepines and divalproex presented to an outside hospital with fevers to 103, weakness, and elevated LFTS.

- Treated for a urinary tract infection with ceftriaxone. She was noted to have on day 3 of her hospitalization with profound leukocytosis and increasing eosinophilia and was transferred to our institution for hematology evaluation and bone marrow biopsy.

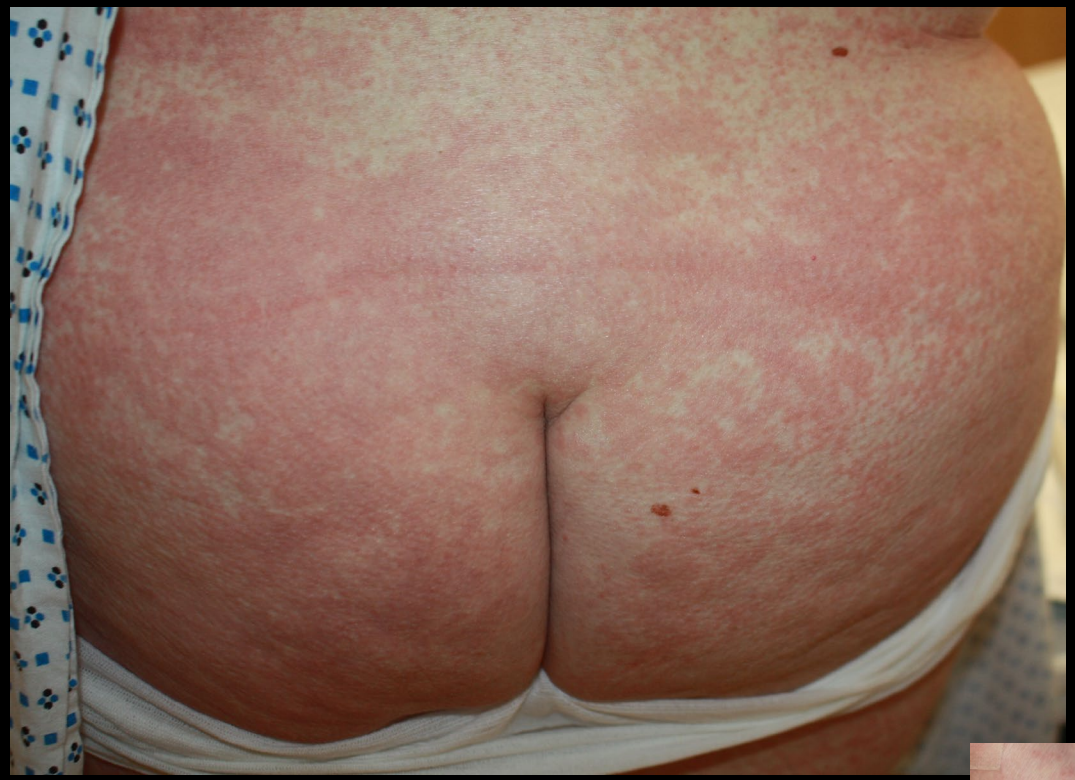
- Dermatology was consulted for evaluation at request of hematology

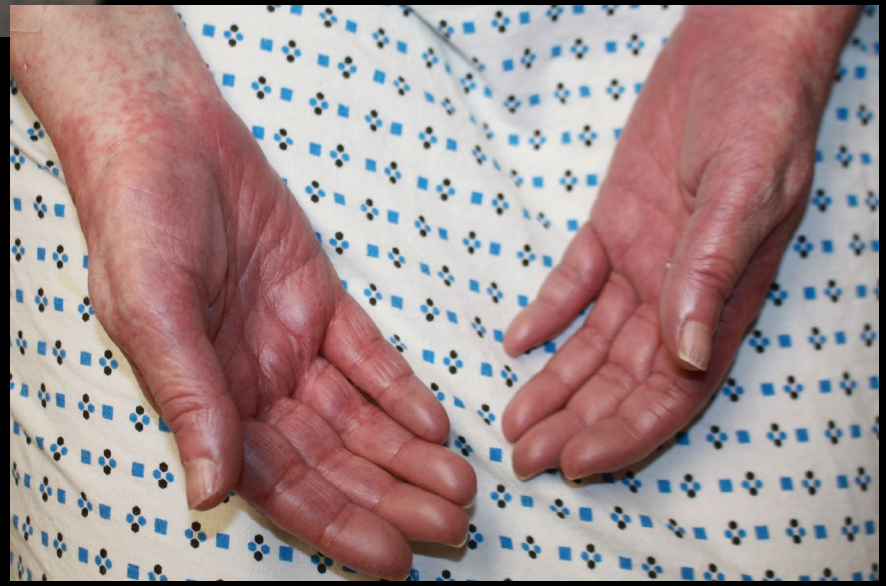
- Upon further review, noted she was started on lamotrigine 7 weeks prior to her initial presentation to the outside hospital.

Clinical Presentation



Courtesy of Nour Kibbi, MD





Courtesy of Nour Kibbi, MD

Labs

- CBC:
  - WBC: 31.2
  - Eos: 8.9% (absolute eos 2800)
    - Atypical lymphocytes: 14%
  - Hgb: 10.3/ PLT:WNL
- Creatinine: 0.96 (baseline)
- LFTS
  - ALT:437, 13 x ULN (0-34)
  - AST:574, 17 x ULN (0-34)
  - ALK Phos:454 (30-130)
  - INR:WNL
  - Bili:WNL

- ANA: negative
- HHV-6 PCR: negative
- EBV PCR and EBV IGM: negative
- CMV PCR and CMV IGM: negative
- Blood Cultures: negative
- no evidence of hepatitis B, or hepatitis C

Is this DRESS?

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS

Criteria	No	Yes	Unknown/ unclassifiable
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia 0.7–1.499 × 10^9/L - *or* - 10–19.9%* ≥ 1.5 × 10^9/L - *or* - ≥ 20%*	0	1 2	0
Skin involvement – Extent of cutaneous eruption > 50% BSA – Cutaneous eruption suggestive of DRESS** – Biopsy suggests DRESS	0 –1 –1	1 1 0	0 0 0
Internal organs involved† One Two or more	0	1 2	0
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

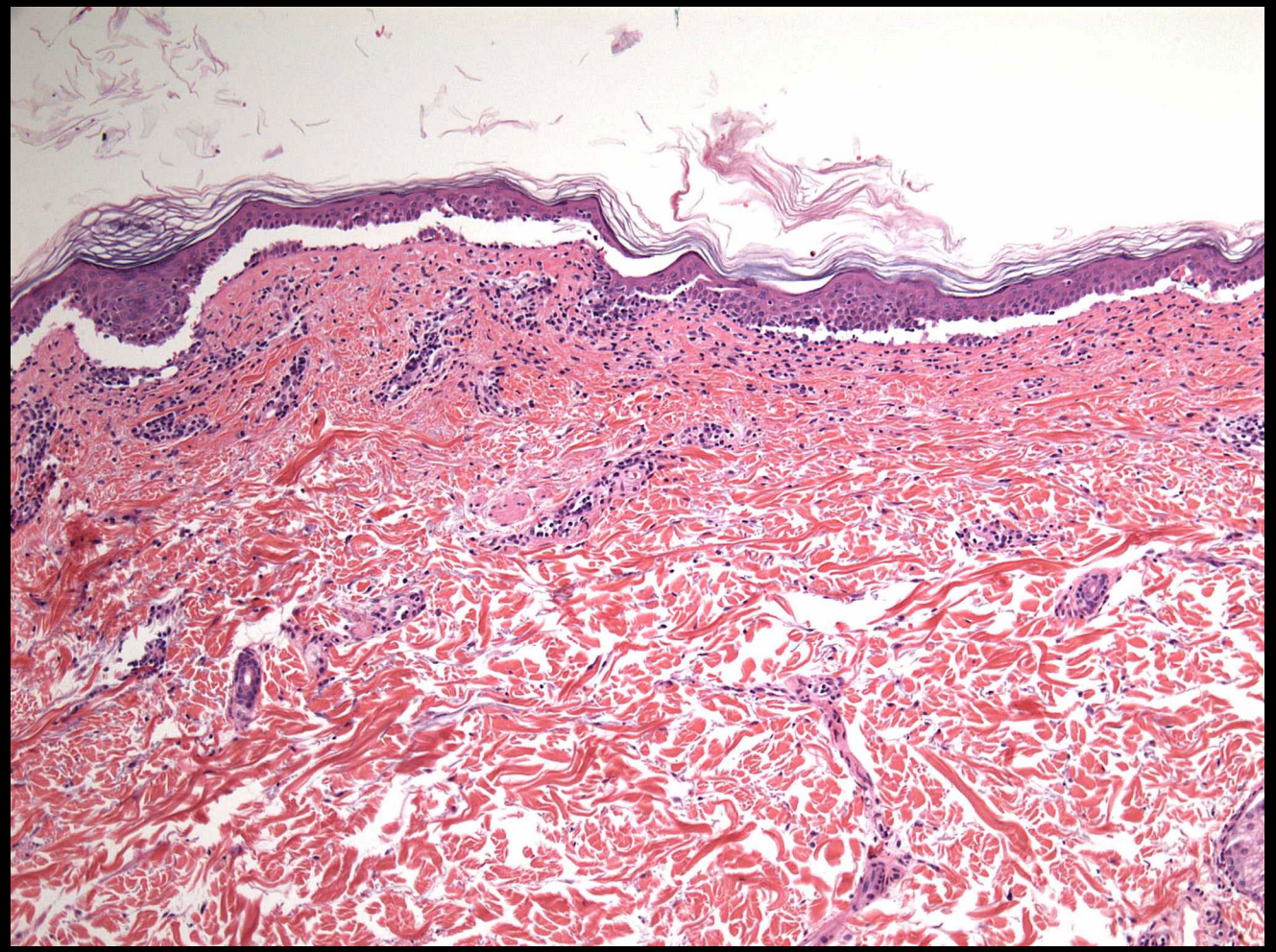
**At least two of the following: edema, infiltration, purpura and scaling.

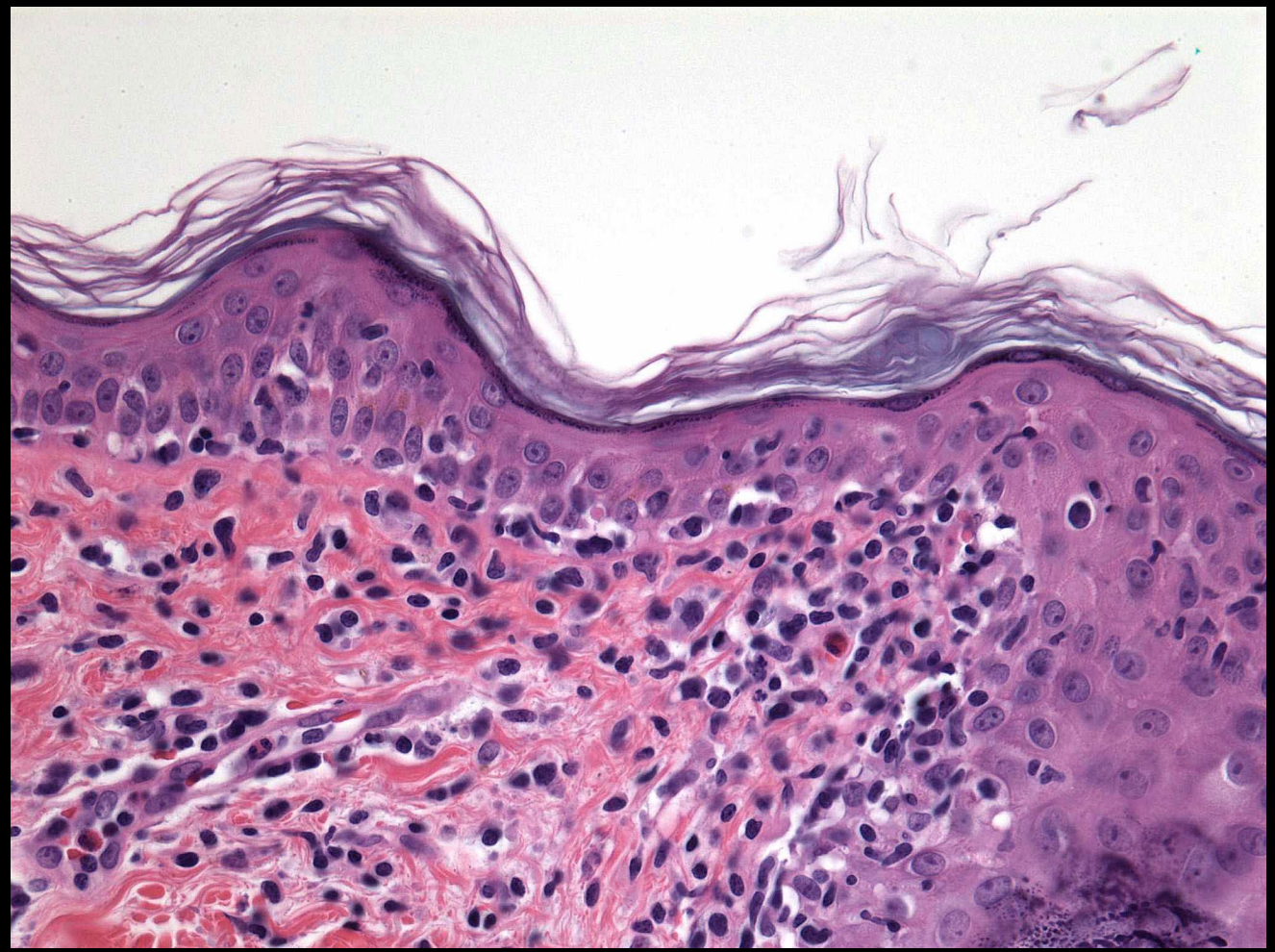
†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

Bolognia et al. , 2012

Would a biopsy be helpful in diagnosis?

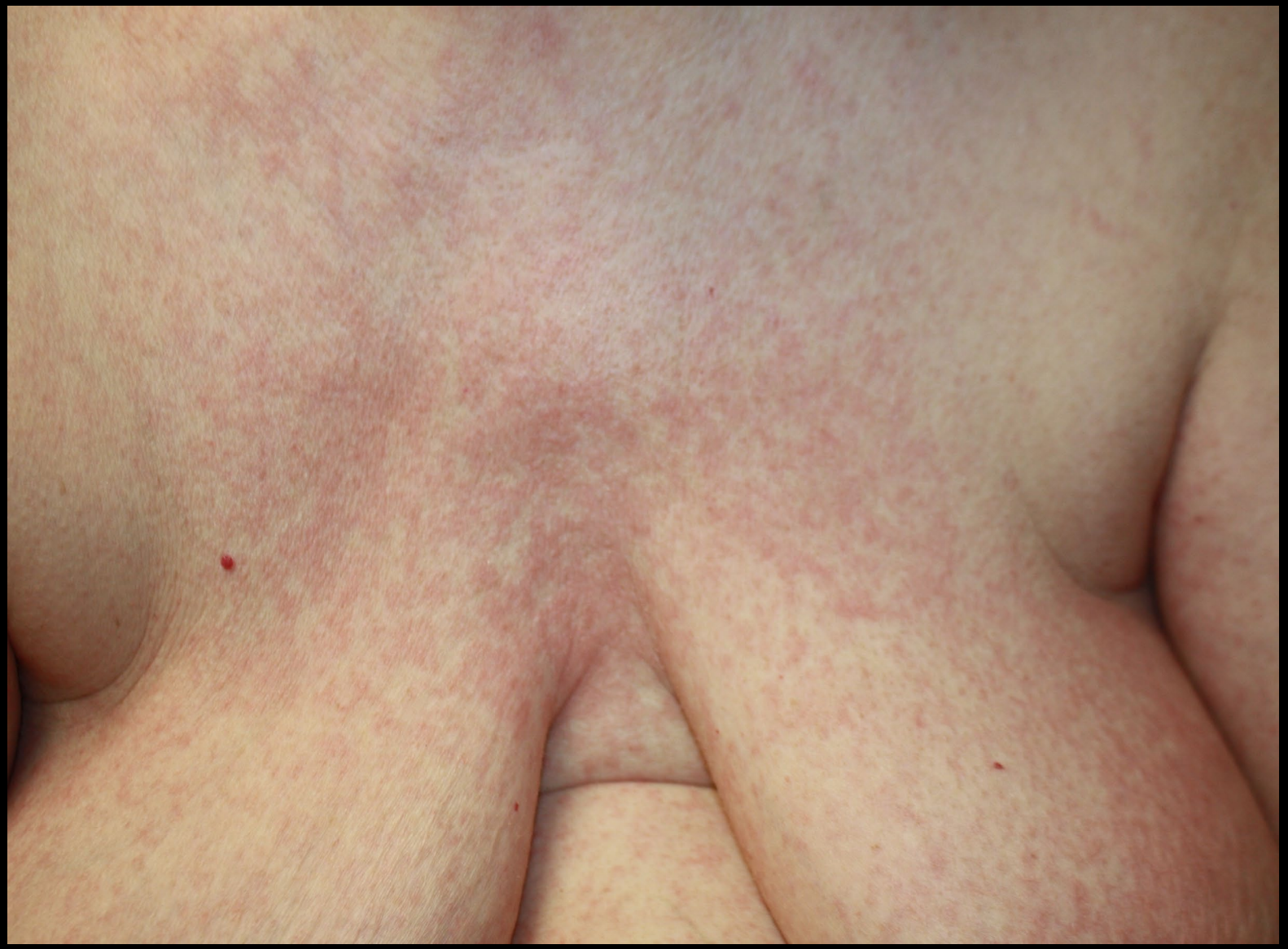
Skin Biopsy





DIAGNOSIS: RIGHT CHEST
  INTERFACE DERMATITIS WITH MIXED INFILTRATE

Note: The prominent epidermal change is consistent with a primary interface dermatitis reaction, such as can be seen in the spectrum of erythema multiforme tissue reactions, and in some drug hypersensitivity reactions. The presence of eosinophils would support the possibility of reaction to medication. The extensive epidermal changes are atypical for DRESS (drug rash with eosinophilia and systemic systems), but would still be consistent with other forms of drug hypersensitivity. Additional clinical correlation will be important.



Courtesy of Nour Kibbi, MD

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS

Criteria	No	Yes	Unknown/ unclassifiable
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia 0.7–1.499 × 10^9/L - *or* - 10–19.9%* ≥ 1.5 × 10^9/L - *or* - ≥ 20%*	0	1 2	0
Skin involvement – Extent of cutaneous eruption > 50% BSA – Cutaneous eruption suggestive of DRESS** – Biopsy suggests DRESS	0 –1 –1	1 1 0	0 0 0
Internal organs involved† One Two or more	0	1 2	0
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

**At least two of the following: edema, infiltration, purpura and scaling.

†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

Bolognia et al. , 2012

Case 2

- 26 y/o F with history of HSV encephalitis treated with levetiracetam and phenytoin one month prior admitted to OSH fevers to 102 F, fatigue, rash, and facial swelling and mouth pain found to have thrush.
- Transferred to our hospital with concern of SJS

Courtesy Claire Hamilton, MD/PHD

Labs

- CBC
  - WBC: 5.6
    - Eos:0%
    - Atypical lymphocytes: 0
  - HGB/PLT:WNL
- Creatinine: WNL
- LFTS:
  - AST:139, 4 x ULN(<34)
  - ALT:219, 6 x ULN(<34)
- CMV/EBV PCR: negative
- Blood Cultures: negative
- Hepatitis Panel: negative
- ANA: negative

Is this DRESS?

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS

Criteria	No	Yes	Unknown/ unclassifiable
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia 0.7–1.499 × 10^9/L - *or* - 10–19.9%* ≥ 1.5 × 10^9/L - *or* - ≥ 20%*	0	 1 2	0
Skin involvement			
– Extent of cutaneous eruption > 50% BSA	0	1	0
– Cutaneous eruption suggestive of DRESS**	–1	1	0
– Biopsy suggests DRESS	–1	0	0
Internal organs involved† One Two or more	0	 1 2	0
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

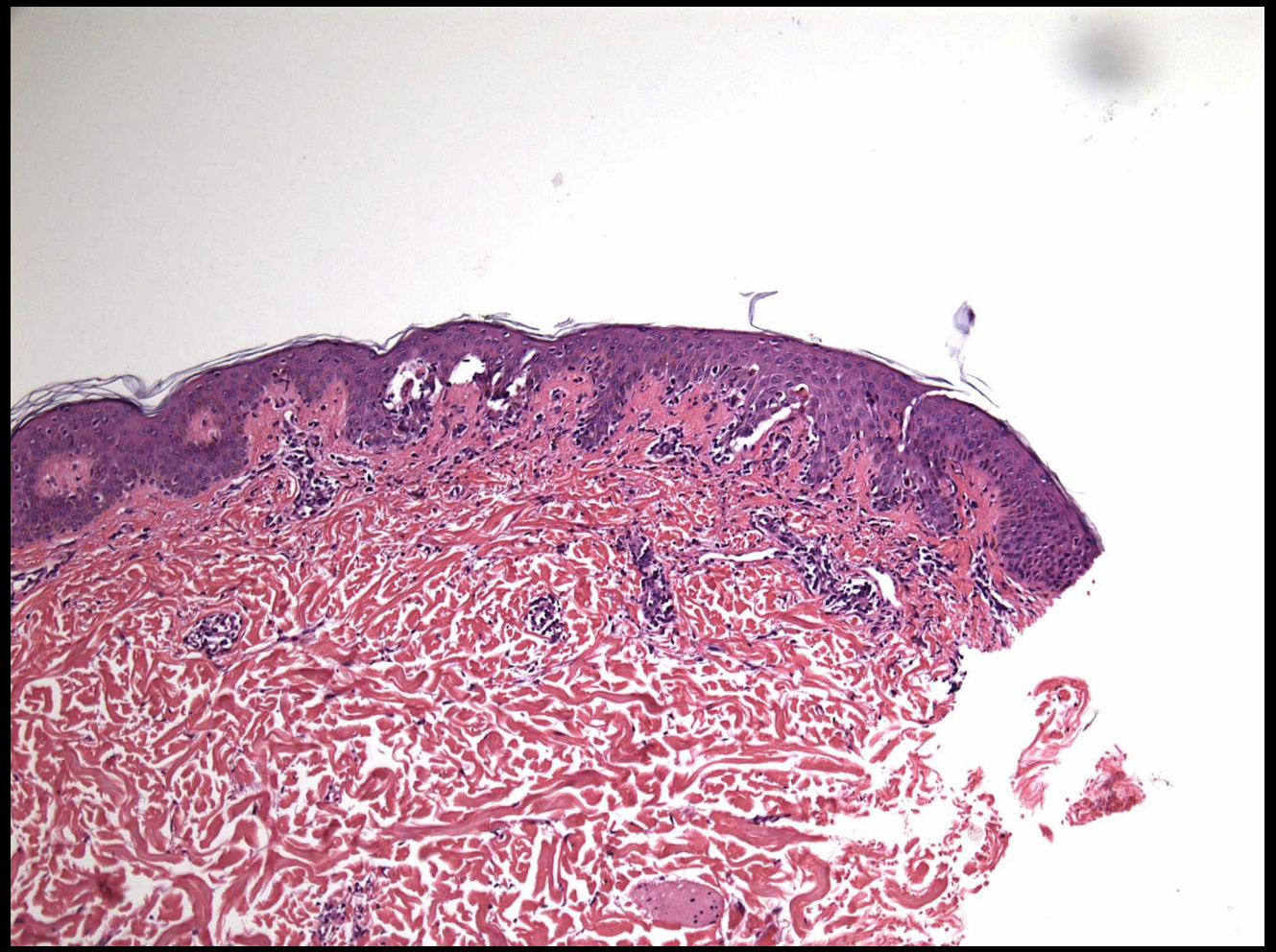
**At least two of the following: edema, infiltration, purpura and scaling.

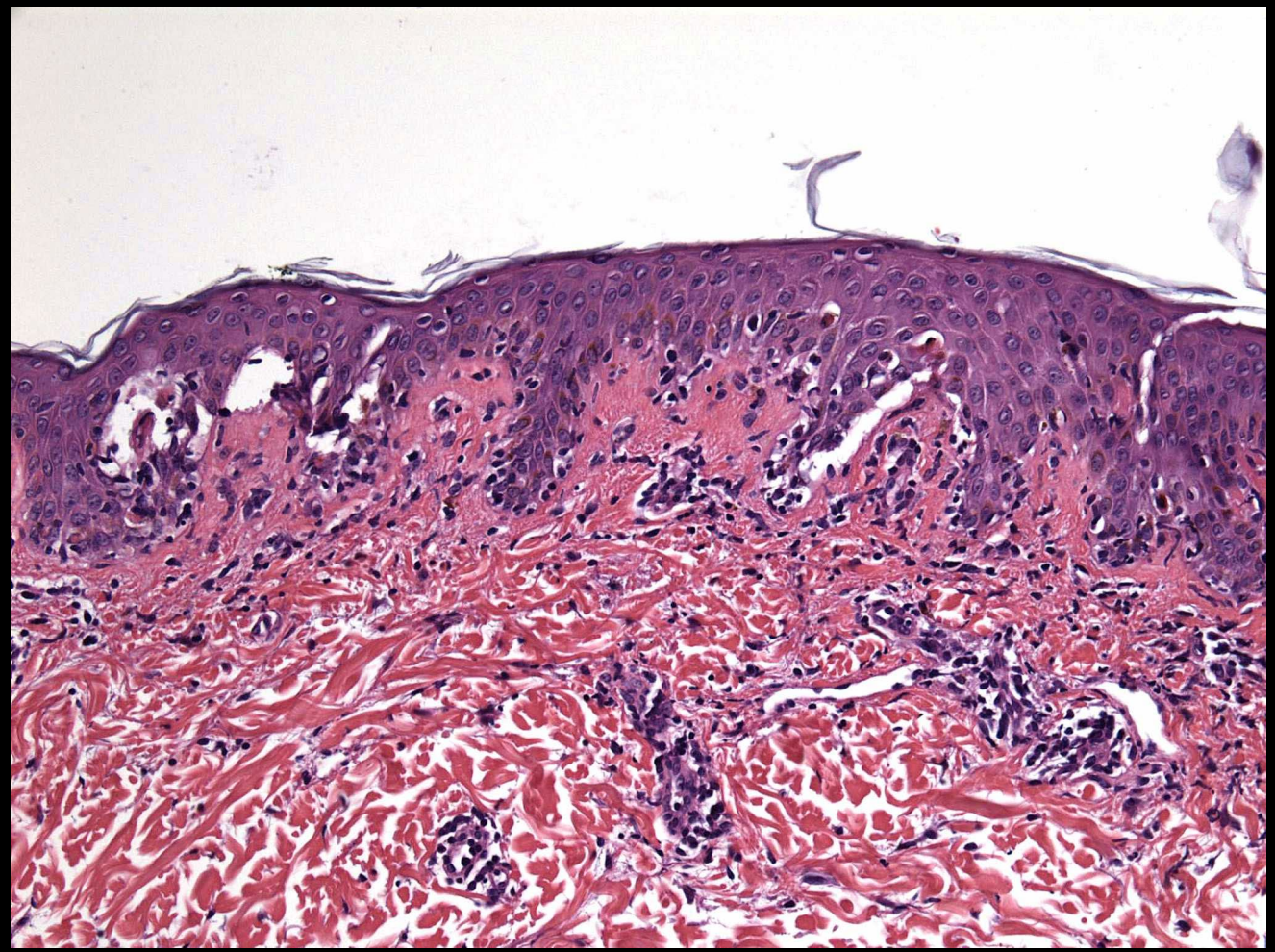
†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

Bolognia et al. , 2012

Would a biopsy be helpful in diagnosis?

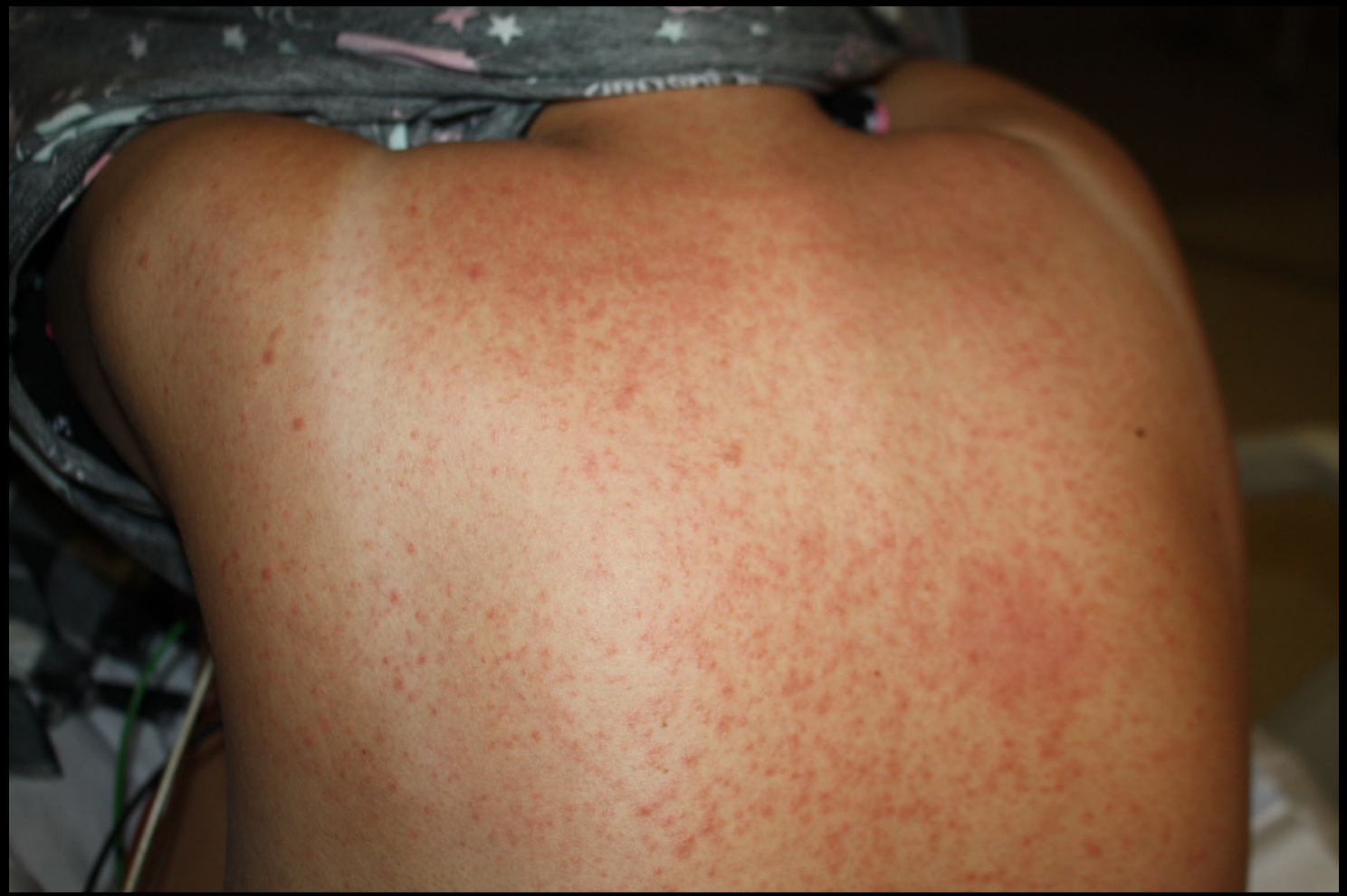
Biopsy





DIAGNOSIS: RIGHT UPPER BACK
  INTERFACE DERMATITIS (SEE NOTE)

Note: The changes are compatible with a drug reaction, including an erythema multiforme-like drug reaction. Clinical pathological correlation is recommended.



Courtesy Claire Hamilton, MD/PHD

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS

Criteria	No	Yes	Unknown/ unclassifiable
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia 0.7–1.499 × 10^9/L - *or* - 10–19.9%* ≥ 1.5 × 10^9/L - *or* - ≥ 20%*	0	 1 2	0
Skin involvement			
– Extent of cutaneous eruption > 50% BSA	0	1	0
– Cutaneous eruption suggestive of DRESS**	–1	1	0
– Biopsy suggests DRESS	–1	0	0
Internal organs involved† One Two or more	0	 1 2	0
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

**At least two of the following: edema, infiltration, purpura and scaling.

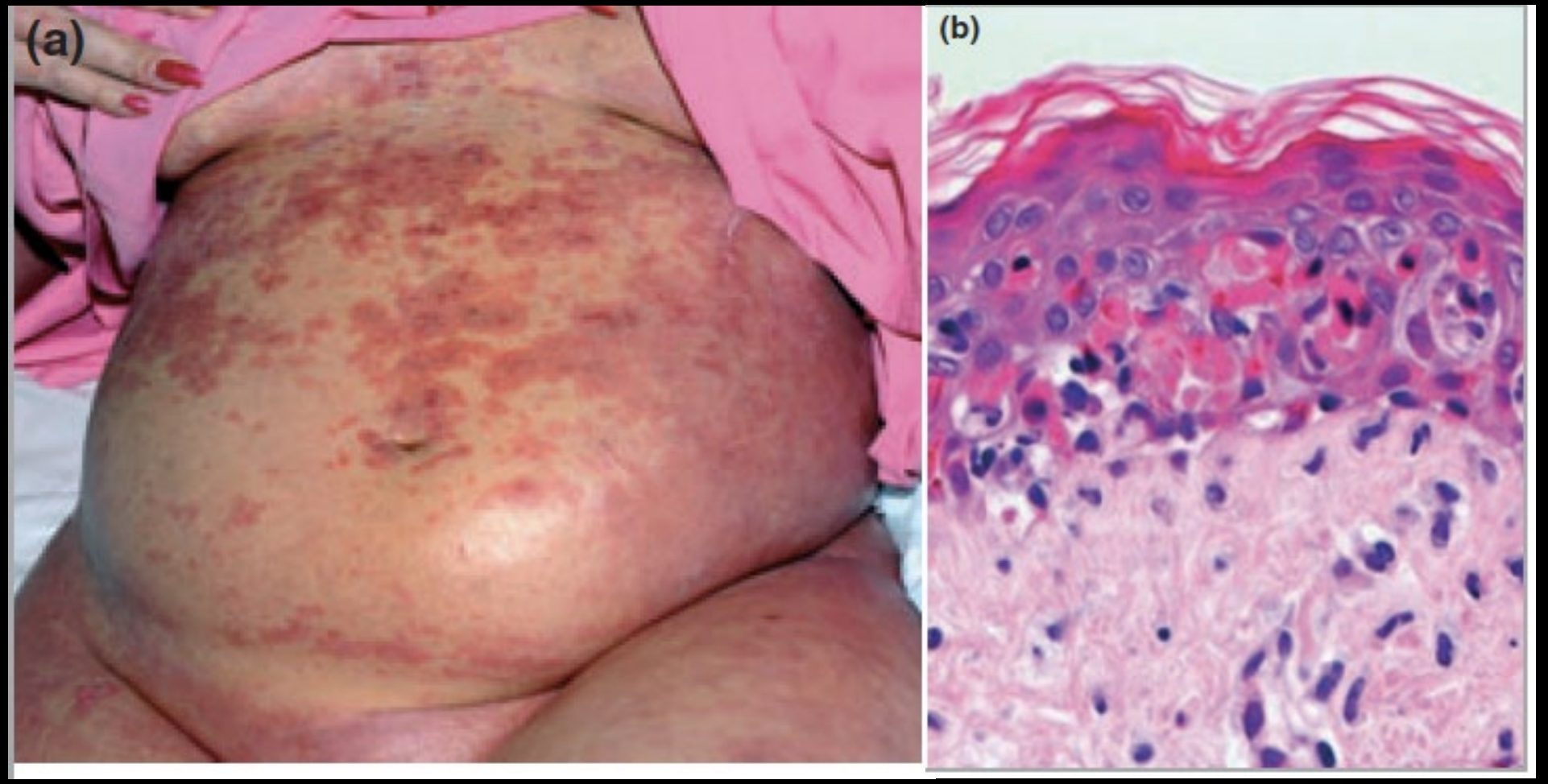
†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

Bolognia et al. , 2012

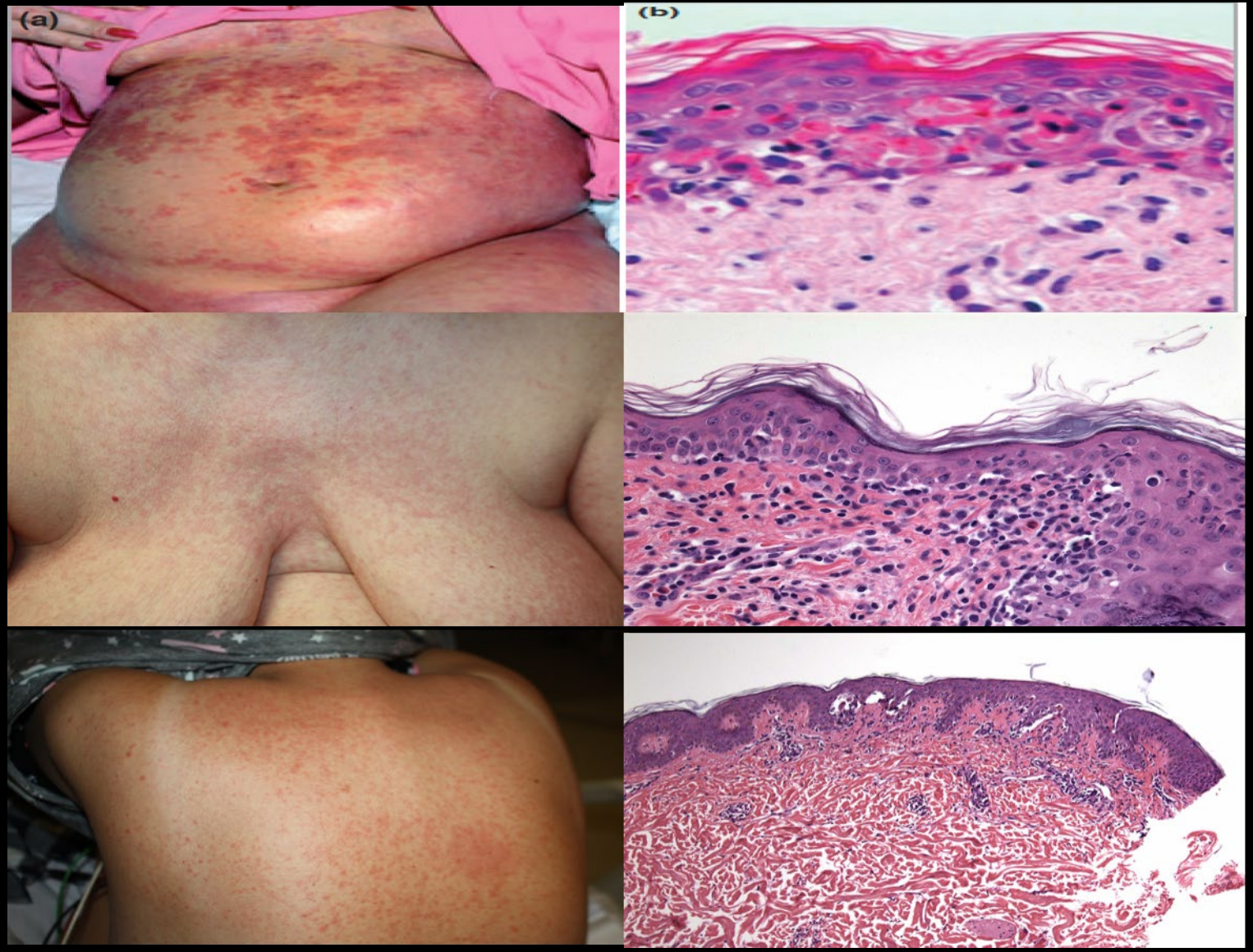
Histology of DRESS

- Various patterns described in the literature
- In one study of 36 patients with DRESS, histology findings included
  - Eczematous pattern (40%)
  - Interface dermatitis (usually focal) (74%)
  - Acute generalized exanthematous pustulosis-like (20%)
  - Erythema-multiforme-like pattern (24%)
- A retrospective review of 27 cases of DRESS, the histologic features were defined as
  - superficial spongiotic dermatitis (16/27)
  - Basal cell vacuolar degeneration with necrotic keratinocytes (9/27)
- Pseudolymphoma pattern also reported

- Ortonne N, et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. Br J Dermatol. 2015 Jul;173(1):50-8.
- Chiou CC, et alClinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol. 2008 Sep;22(9):1044-9.
- Walsh S, et al. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. Br J Dermatol. 2013 Feb;168(2):391-401.



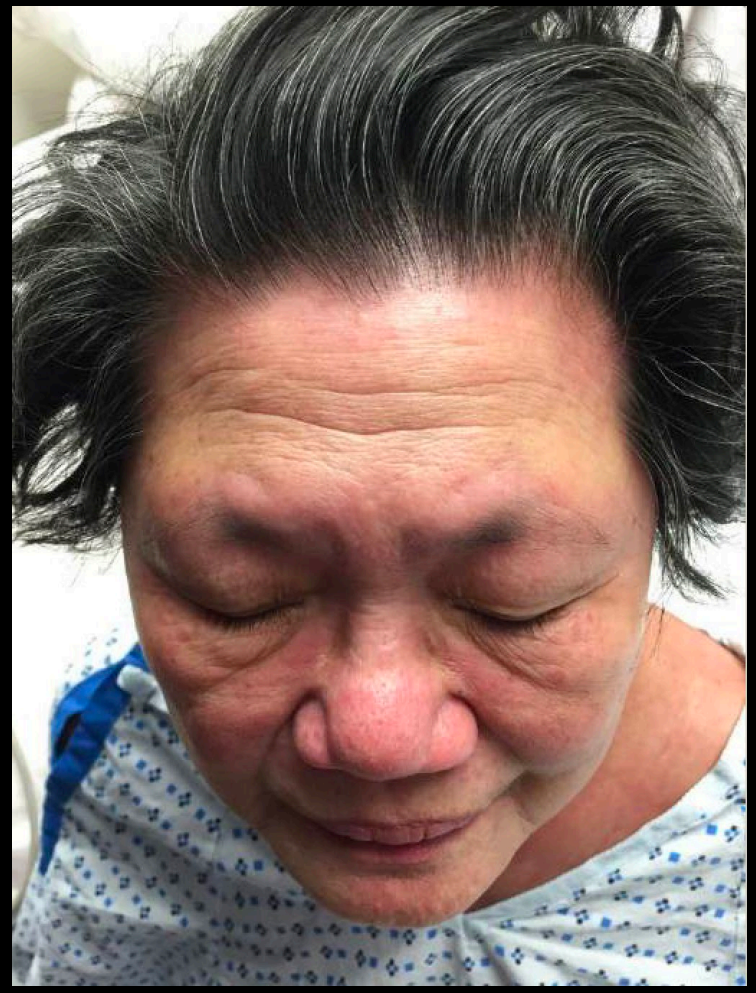
Walsh S, et al. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. Br J Dermatol. 2013 Feb;168(2):391-401.

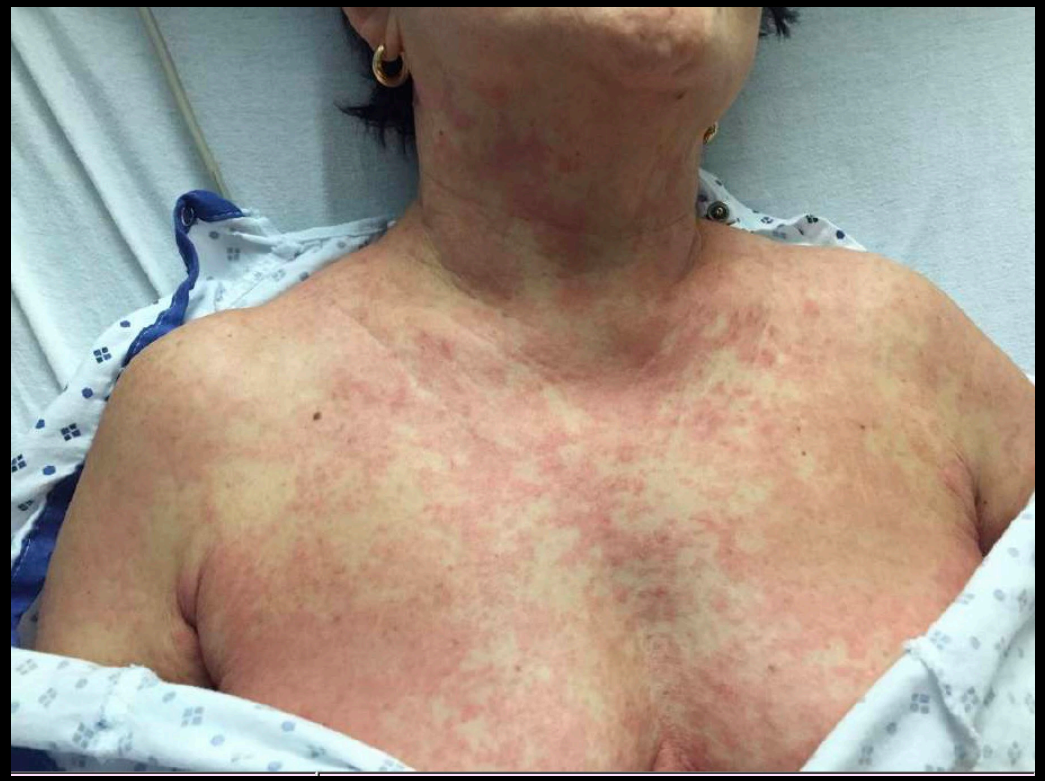

(a)
(b)

OK so maybe the prior two cases are outliers

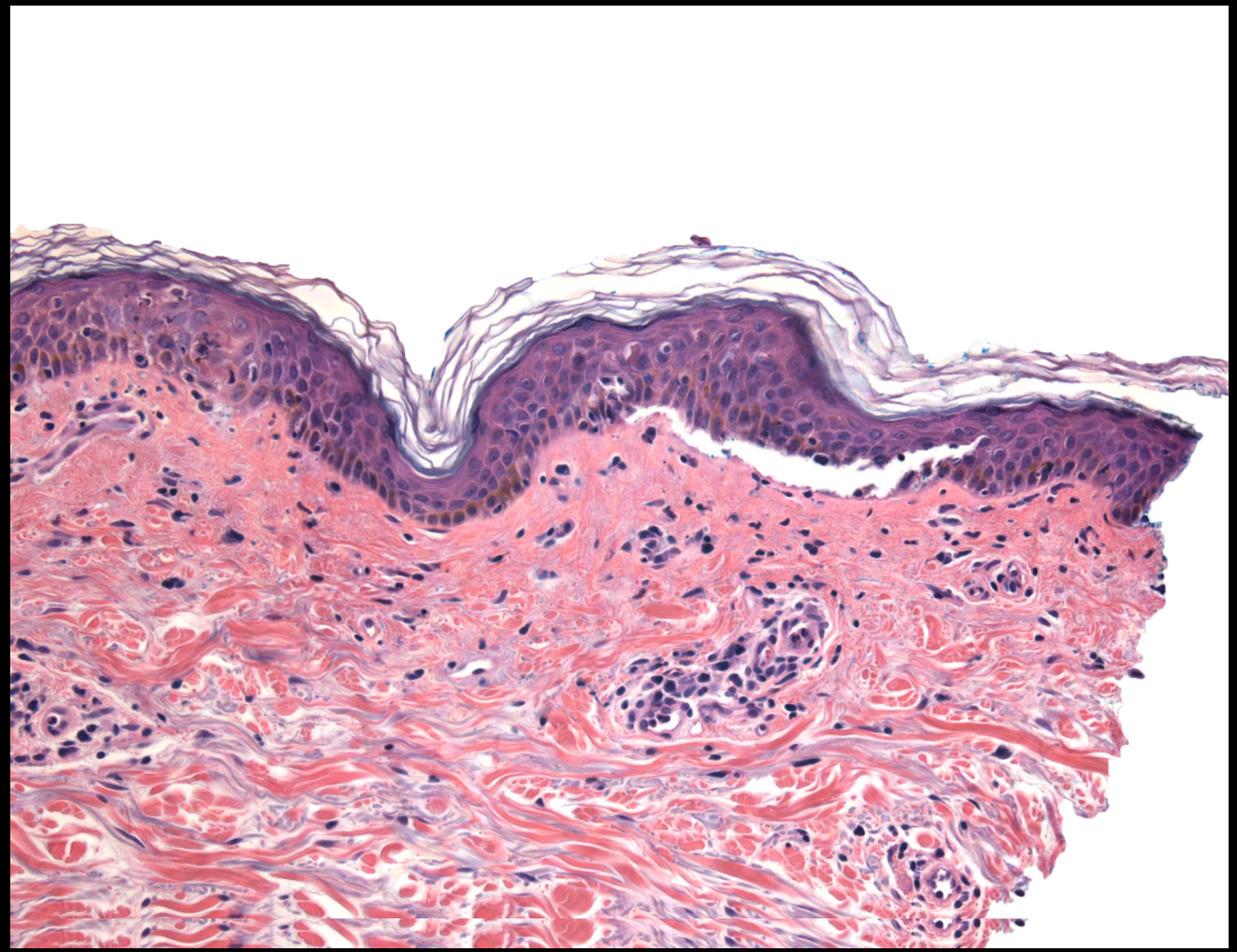
- Maybe this has to do with anticonvulsants as the previous two cases both had anticonvulsants as the culprit

74 y/o Female with rash, facial edema, fevers to 101, LFTS 8X ULN, atypical lymphocytes 14 days after allopurinol





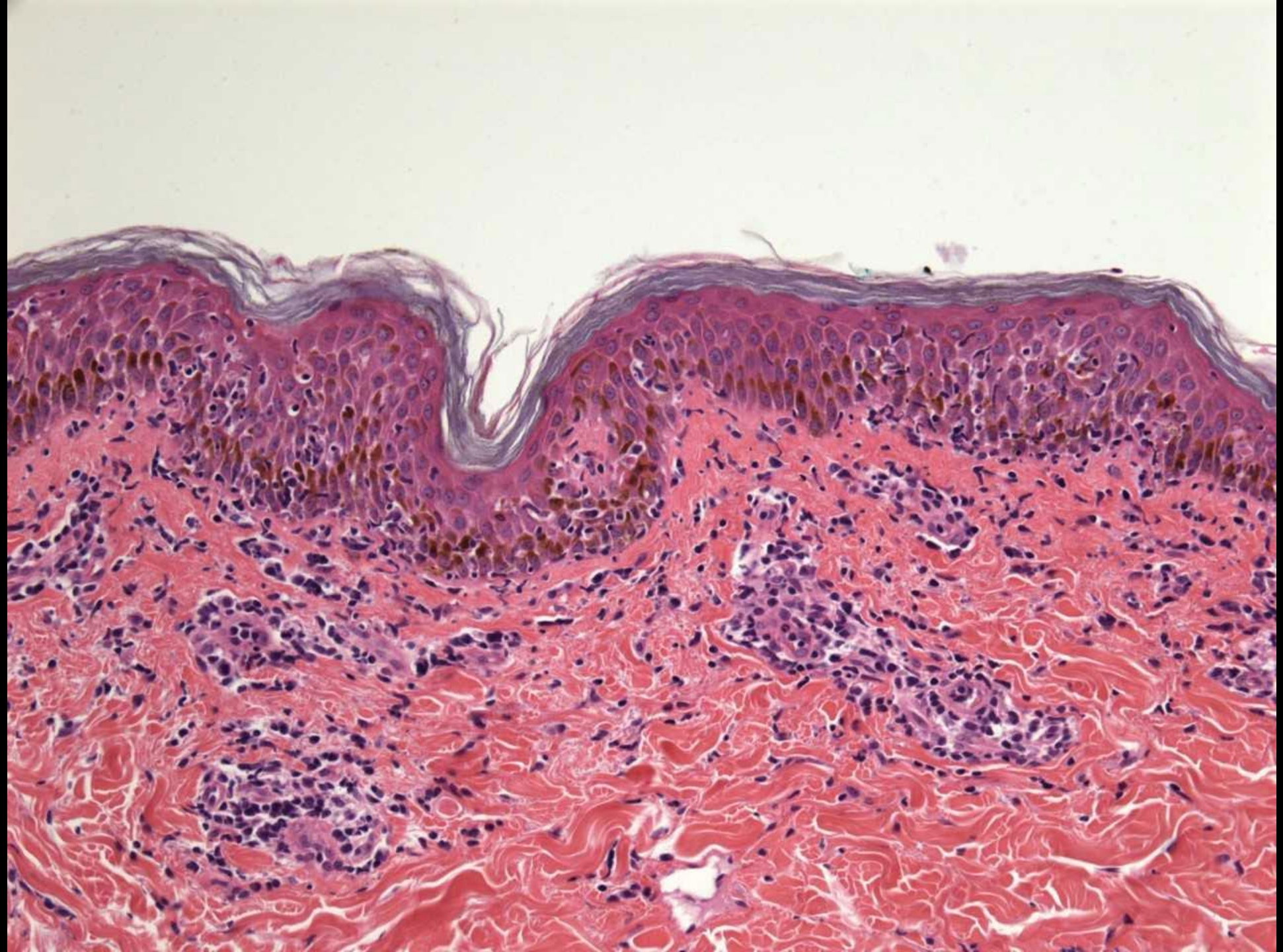
Courtesy Sara Perkins, MD



DIAGNOSIS: RIGHT ARM
  INTERFACE DERMATITIS WITH MIXED INFILTRATE

Note: The features would be consistent with a drug reaction, such as anticonvulsant hypersensitivity syndrome. Eosinophils are present but rare, making the diagnosis of drug reaction with eosinophilia and systemic symptoms less likely on histologic grounds alone. Clinical correlation will be helpful. The features are not typical of a viral reaction.

55 y/o F with generalized eruption, AKI, LFTS 21 x ULN, fevers, hypotension started on allopurinol 5 weeks prior



DIAGNOSIS: ABDOMEN
  INTERFACE DERMATITIS

Note: The histologic features are those of acute interface dermatitis, such as can be seen in the erythema multiforme spectrum of disorders and some drug induced hypersensitivity reactions. Typical changes of toxic shock syndrome are not identified. Clinical correlation will be necessary to further classify the acute vacuolar interface dermatitis seen in this biopsy.

DRESS: Does Histology help with diagnosis?

- Certainly not required to make the diagnosis
- Only RegiSCAR includes histology as a criterion
  - Histology may not be available at time of evaluation
- Cases above are examples how histology could be misleading so correlation and clinical picture always important

Histology and Prognosis

- Patients with apoptotic keratinocytes showed a tendency to have more liver (80% versus 64%) and renal involvement(60% versus 43%) so pathology may help to predict more clinically significant disease course

- Patients with Erythema Multiforme-like rash and necrotic keratinocytes histologically had worse hepatic involvement than groups with spongiosis and dermal infiltrates.

Take Home Points

- Findings of interface dermatitis with DRESS in patients with a morbilliform eruption clinically do not suggest that patients will progress to an EM/TEN like picture

- Histology is important but there can be a disconnect between histology, clinical picture and the clinical course

- EM/TEN has acute morbidity/mortality but important to differentiate from DRESS which may have long term sequelae

Acknowledgements

- Christine Ko MD
- Yale Dermatology Residents
- My family