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Skin in the Game: Dermatologic Conundrums for the Rheumatologist

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MGH 1811
MASSACHUSETTS GENERAL HOSPITAL
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Disclosures

- I have received honoraria from Pfizer for service on an advisory board for digital media.
- None of the therapies discussed in this presentation are FDA approved for the indications suggested.
- Not everything I present will be a rheumatologic disease, as I want to emphasize the situations where rheumatologic issues are on the differential diagnosis, and how we can help differentiate them!

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Objectives

- To demonstrate dermatologic challenges in rheumatologic disease using a case-based approach.
- To build a framework for approaching skin disease based in morphologic differences on examination.
- To review potential treatment algorithms depending on underlying pathophysiology, especially in cases of diagnostic uncertainty.

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Case 1

- 33 man presents to clinic with new rash on legs and bumps only within old tattoos (at least 5 years old). These problems started 2 weeks ago.
- Rash on legs is warm and tender to touch.
- Bumps in tattoos are asymptomatic.
- No shortness of breath. Does have new ankle pain. No eye problems.

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History Continued

- Past Medical History
  - Deviated nasal septum
- Medications
  - Albuterol
  - Trazadone
- Allergies:
  - NKDA
- Social History
  - Denies EtOH and TOB
- Family History
  - Negative for skin disease

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Exam

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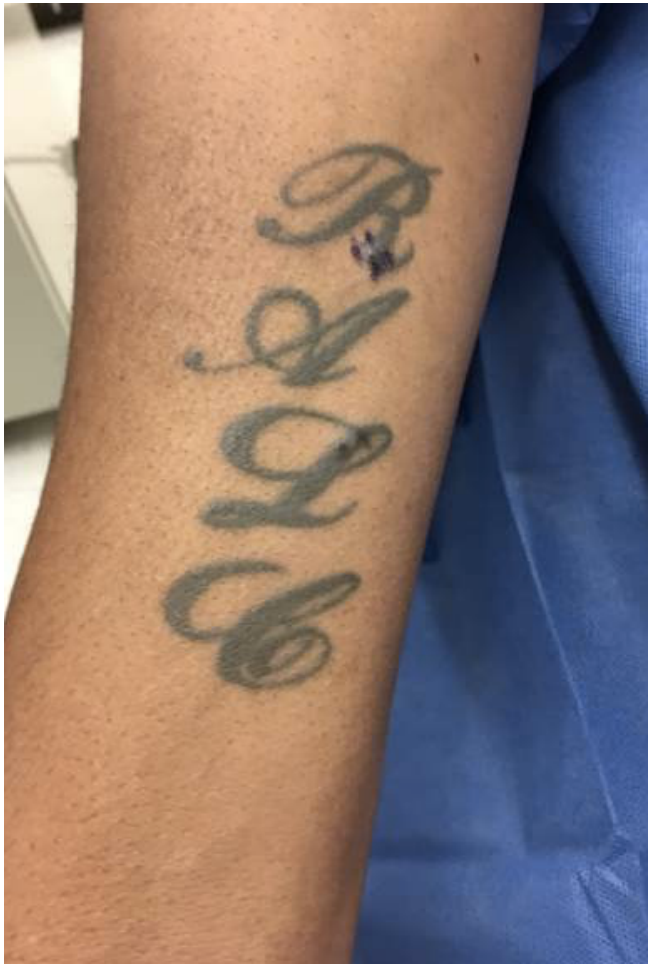

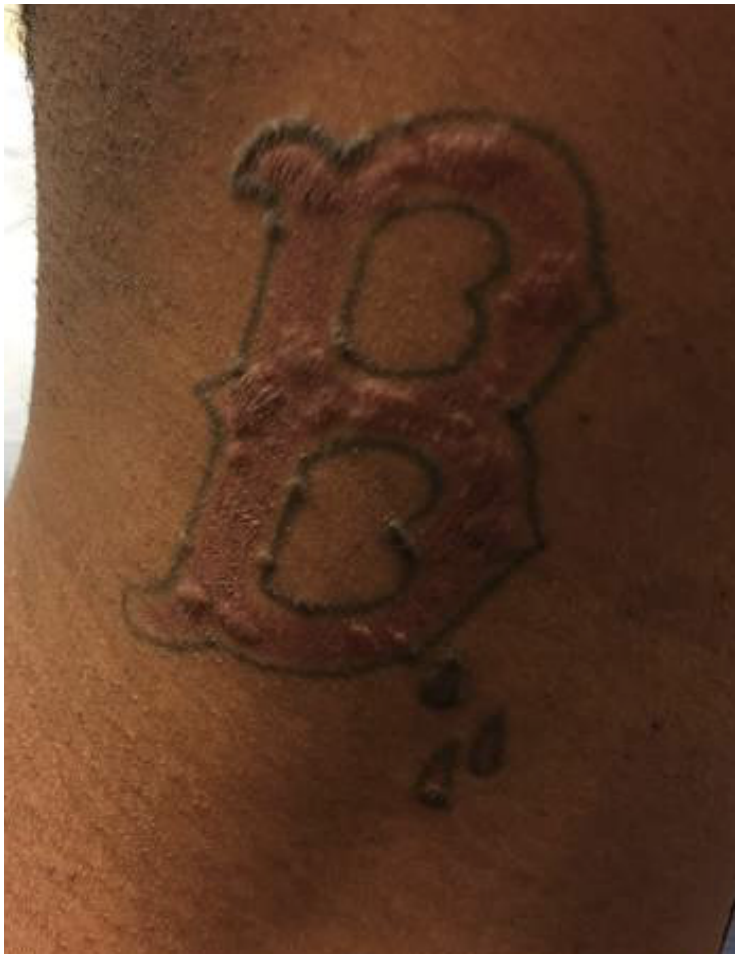

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King

Plan

- Given the constellation of findings (erythema nodosum, arthralgias), concern for sarcoidosis
  - Lofgren's Syndrome is triad of:
    - Hilar lymphadenopathy
    - Arthralgia
    - Erythema nodosum
- Chest X-ray ordered
- Biopsy of tattoo papule also performed
  - Concern for granulomatous process on exam, but unclear if from tattoo pigment versus sarcoid

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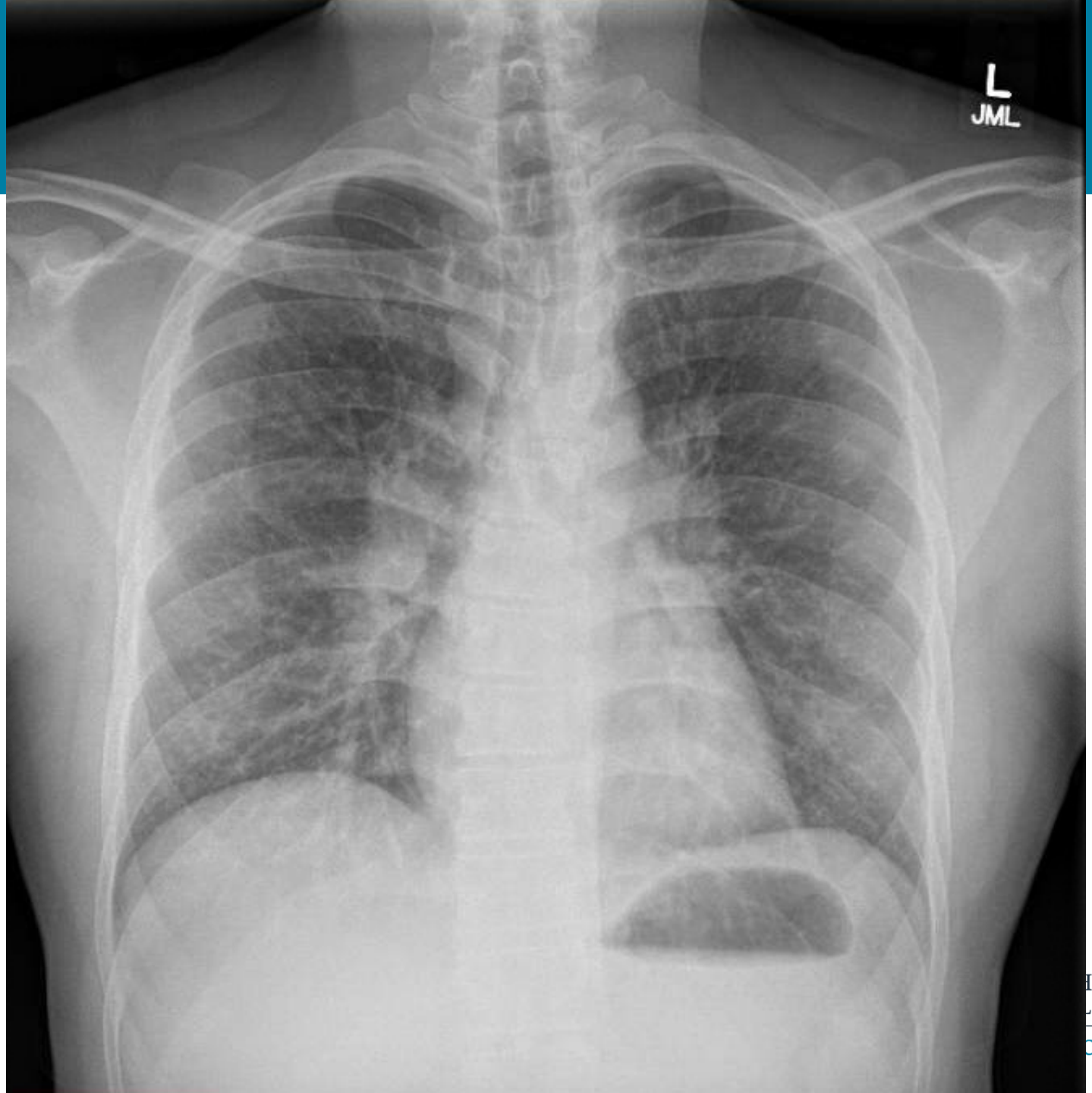

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Biopsy results

- A. SKIN, PUNCH BIOPSY, RIGHT FOREARM:
  Granulomatous dermatitis with scattered eosinophils and dermal tattoo ink (see note).

  Note: The sections show a dermal granulomatous dermatitis with peripheral lymphocytes and scattered eosinophils. Dermal tattoo is also present. The histologic findings are compatible with cutaneous sarcoidosis within a tattoo, although a granulomatous reaction to tattoo ink cannot be excluded. Clinicopathologic correlation is recommended.

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Laboratory Data

- CBC and CMP wnl
- ACE level: 97 U/L (0-53 U/L)
- 1, 25 (OH)2 Vitamin D - normal
- ANA negative

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Plan

- Given confirmation of Lofgren's syndrome, and biopsy that is consistent with sarcoid, referred to rheumatology.
- Initiated on prednisone 20 mg daily with plan for slow taper (over 8 weeks)
- Erythema nodosum has resolved, as has arthralgia.
- Skin changes are stubborn and don't change.
  - Started topical betamethasone to skin lesions.
  - If not working, can consider intralesional triamcinolone or methotrexate, as this is now the patient's main complaint.

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Take Home Points

- Lofgren's Syndrome can be a presentation of sarcoidosis
  - Good prognostic indicator
- Treatment of sarcoid in our experience: usually a trial of prednisone taper to see if the patient can remain treatment free.
- The skin disease can lag behind the response to therapy of the rest of the body.
- We can good therapies that target skin directly (topical or intralesional steroids), but can use steroid sparing agents as needed.

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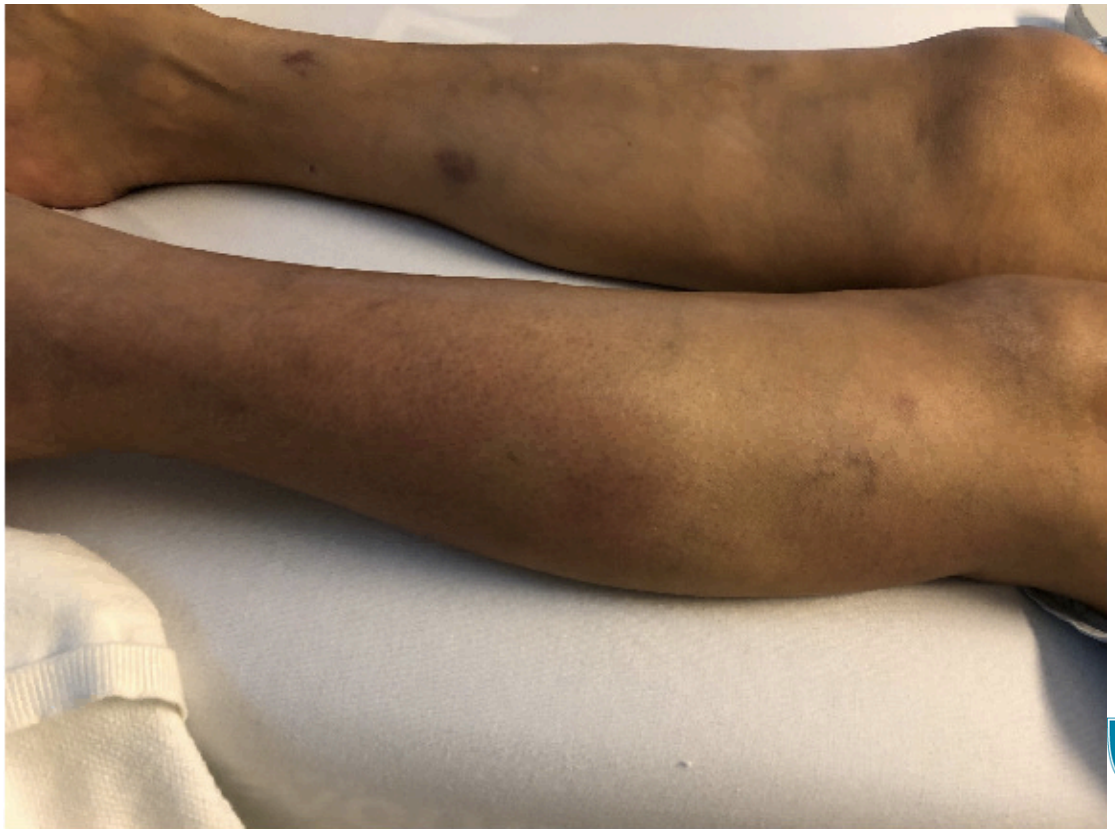
Case 2

- 52F from El Salvador s/p heart transplant for dilated cardiomyopathy. Now on immunosuppression with rash on legs.



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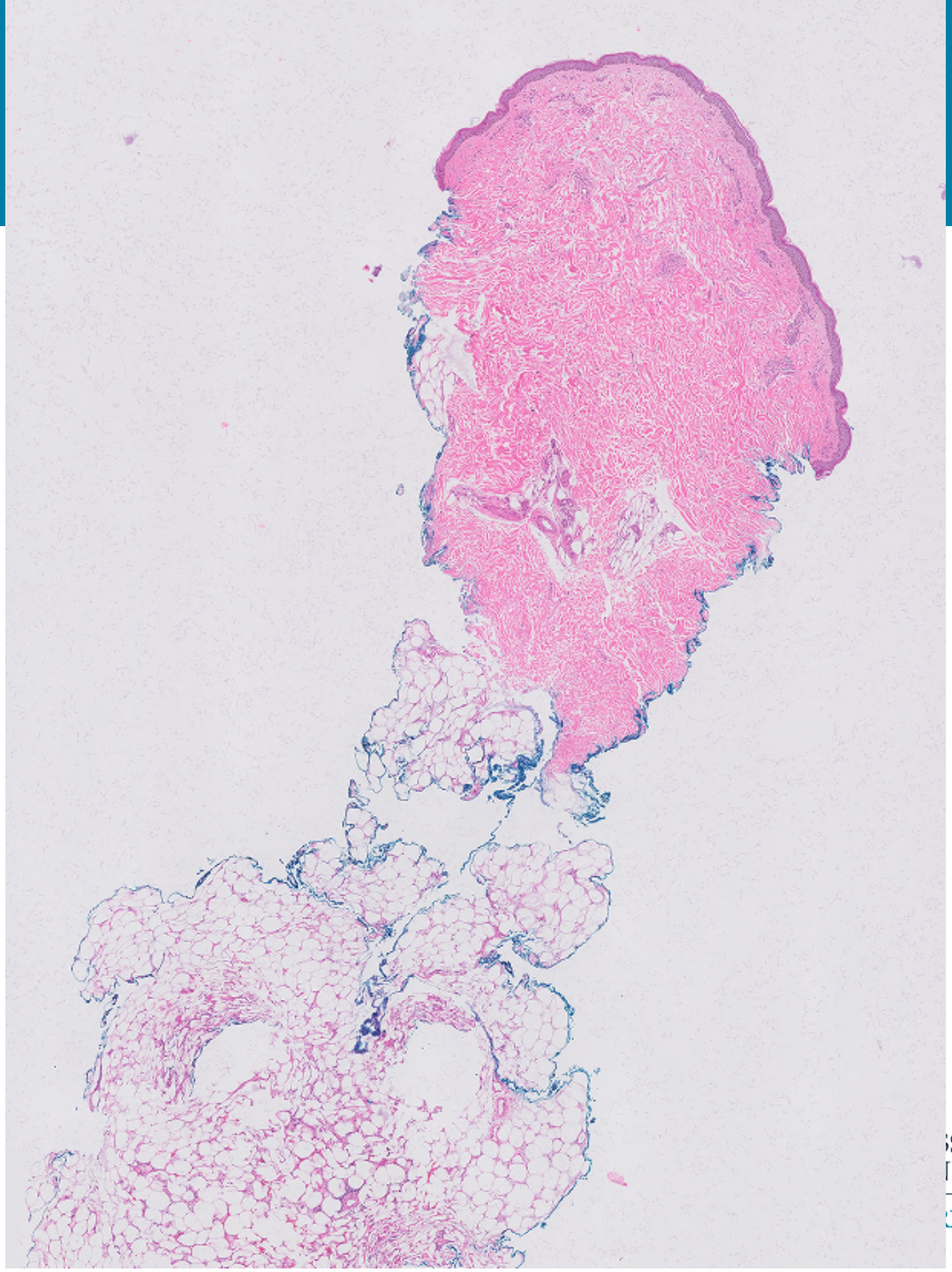
Clinical Course

- Exam consistent with erythema nodosum. Usually a clinically diagnosis.

- Given history, opted to biopsy.

Biopsy results:



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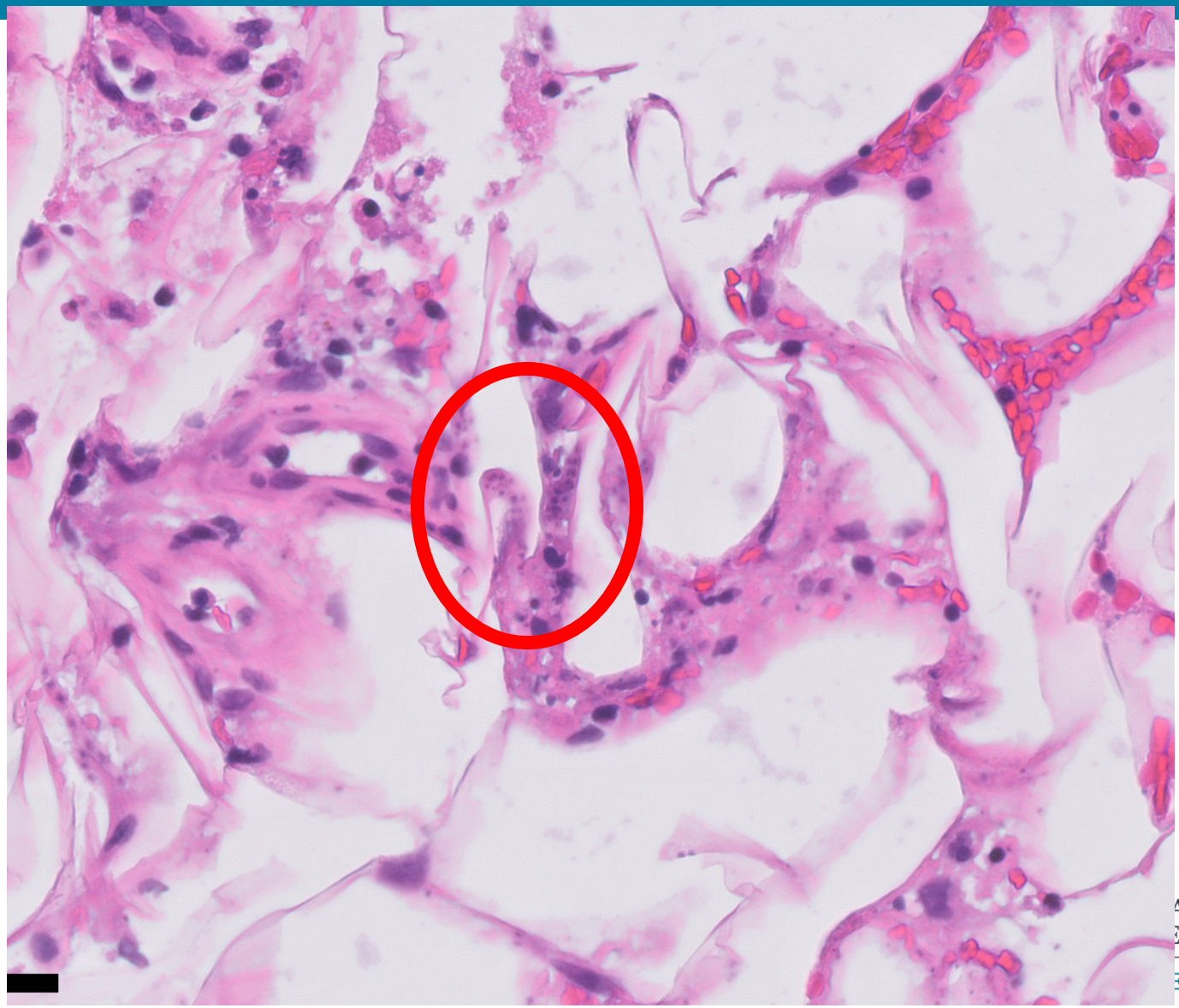
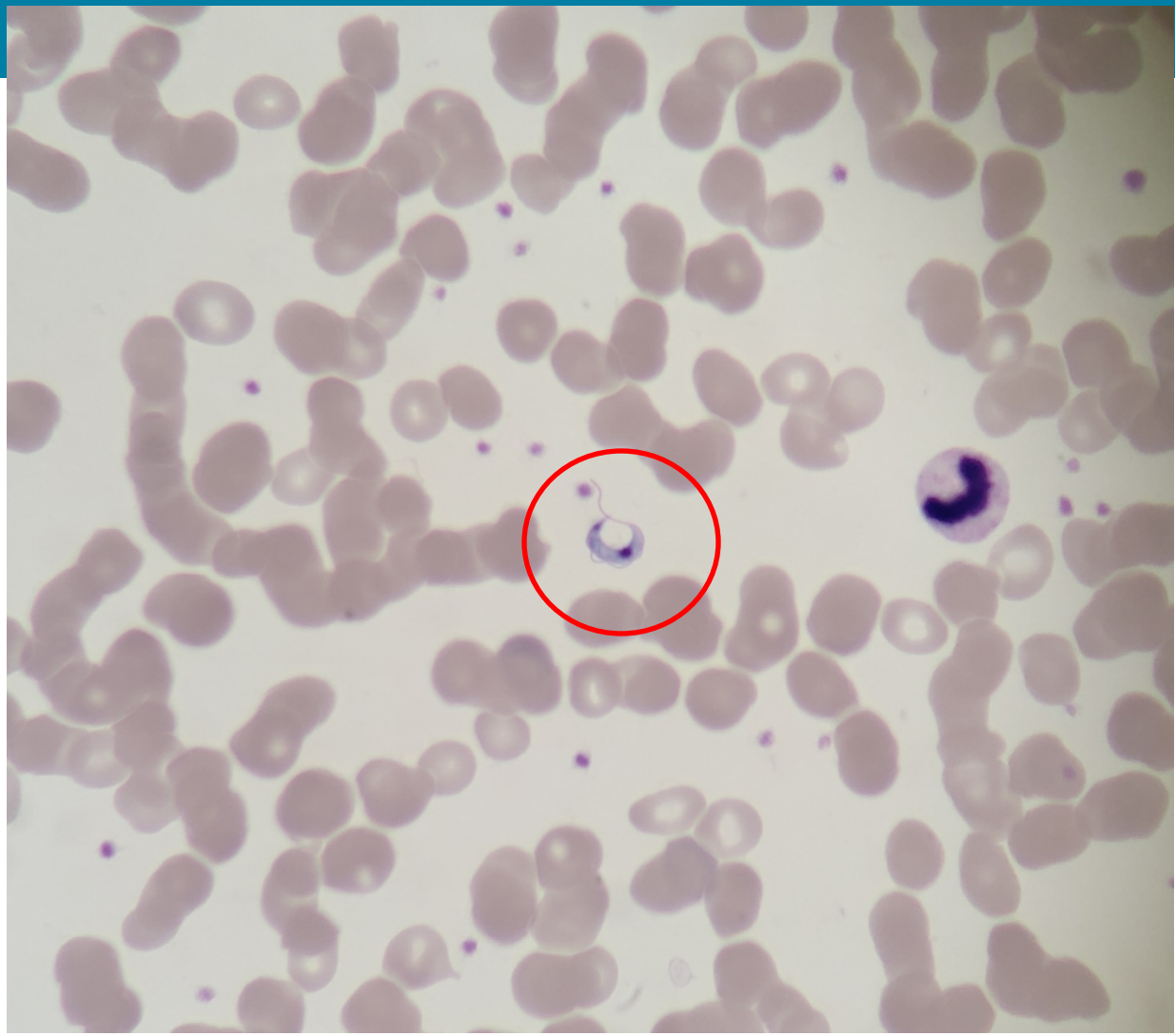
Zooming in:



Evaluation of blood smear



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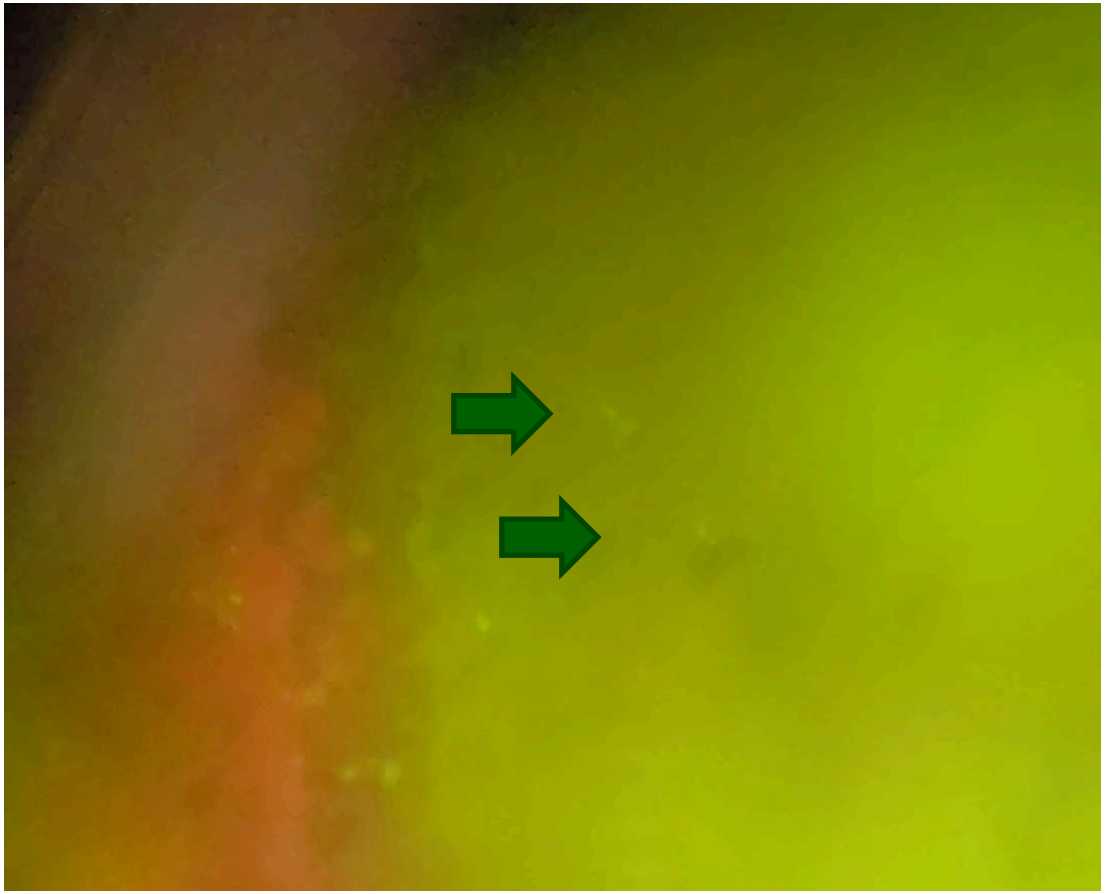
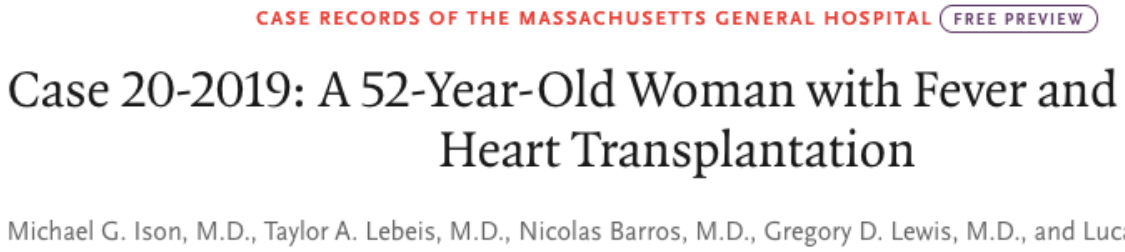
Evaluation of buffy coat



Take home points

- New erythema nodosum still requires a work up
- Sarcoid is a diagnosis of exclusion.
- A biopsy is still indicated even if the exam is “classic” for certain diseases.
  - Immunosuppressed patients
  - Atypical physical findings
  - Constellation of symptoms that are peculiar


CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL FREE PREVIEW

Case 20-2019: A 52-Year-Old Woman with Fever and Rash after Heart Transplantation

Michael G. Ison, M.D., Taylor A. Lebeis, M.D., Nicolas Barros, M.D., Gregory D. Lewis, M.D., and Lucas R. Massoth, M.D.

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Case 3

- 35 F with a history of “chronic lyme” treated by ID with multiple rounds of doxycycline and PICC placement for longer course of abx, currently on amoxicillin/clavulanate who was admitted to MGH with fever and rash x 5 days.

- Fever measured up to 103 at home. Rash started on neck and moved down, is painful, and came on at same time as fever.

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History continued

- Past Medical History
  - Chronic Lyme
  - Migraine
  - Abdominal Pain
  - Diplopia
- Allergies:
  - Ceftriaxone, Erythromycin, Macrolides, TMP-SMX
- Medications
  - Tizanidine, omeprazole, Amox/Clav, atenolol, cetirizine
  - Gabapentin and Topiramate are new in the last month
- Social History
  - No TOB. +EtOH
- Family History
  - +BPD, Breast cancer, Crohns

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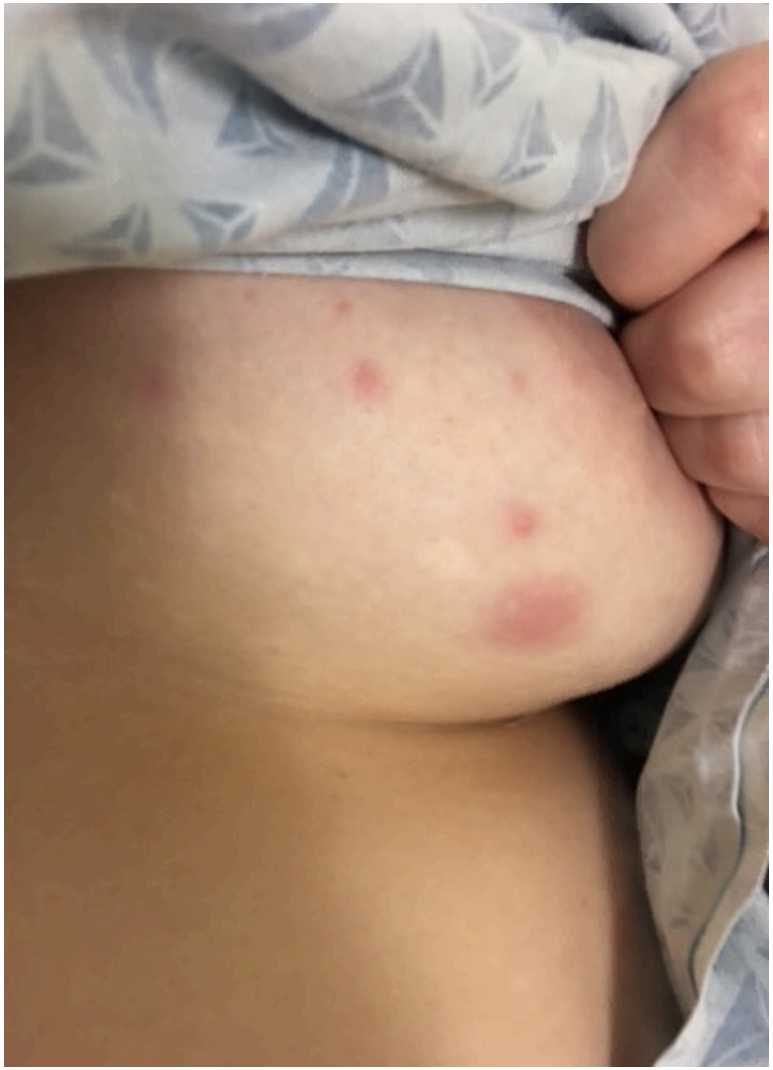
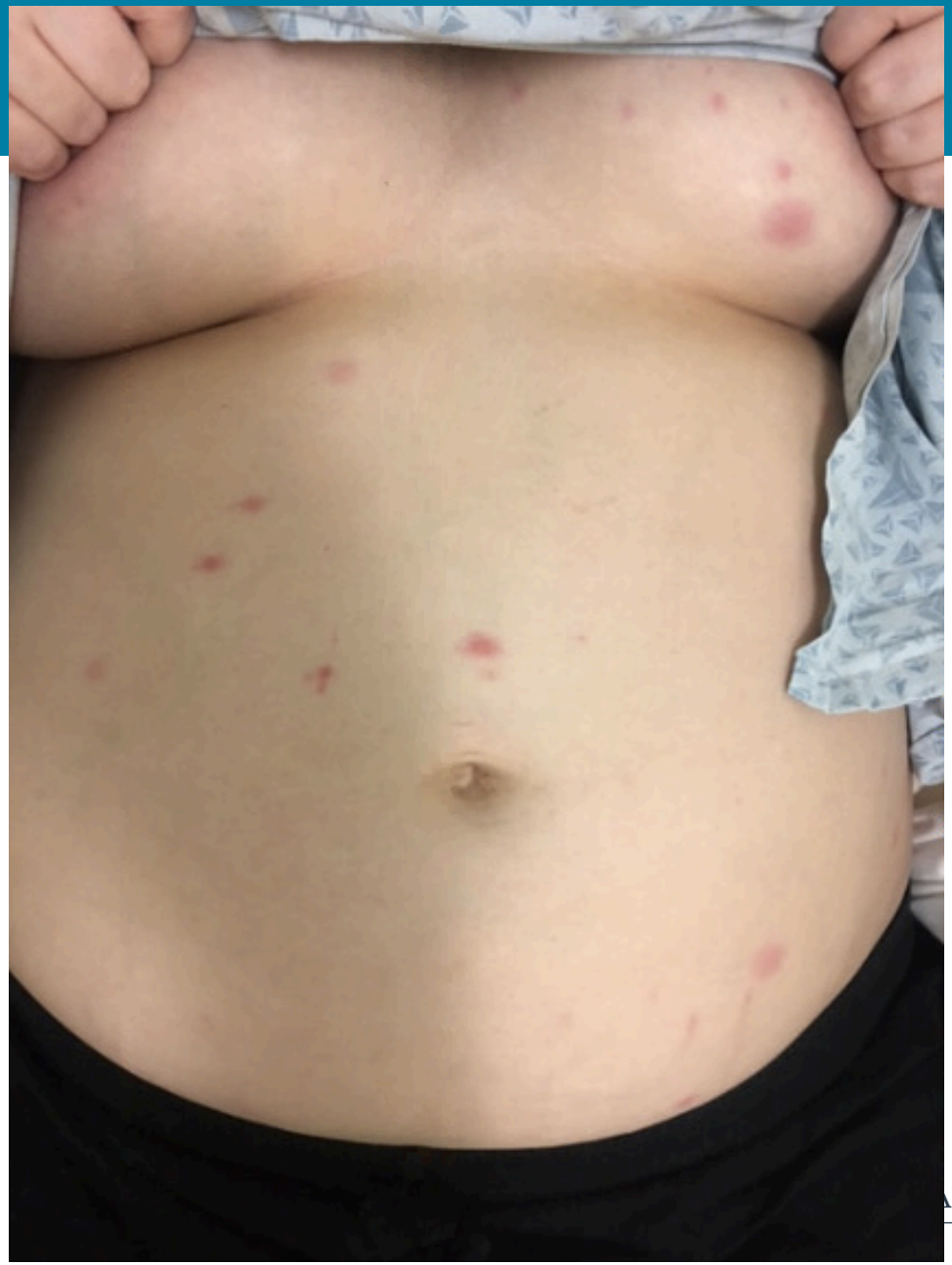
Exam:





Differential diagnosis

- Fever with rash –
  - Infection
  - Neutrophilic dermatoses
  - Rheumatologic diseases
  - Drug reactions (eg: DRESS)
  - Lyme

- Biopsy taken for H+E and Tissue Culture
- Blood cultures
- Antibody panel sent for rheumatologic disease

- No Abx were started, supportive care.
- New medications stopped.

- "Consult derm/our attending"

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Narrowing down the differential diagnosis

Regiscar Criteria for DRESS Syndrome

Items	Score			Comments
	−1	0	1	
Fever ≧ 38.5 °C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≧ 2 different areas
Eosinophilia ≧ 0.7 × 10^9/L or ≧ 10% if WBC < 4.0 × 10^9/L		N/U	Y	Score 2, when ≧ 1.5 × 10^9/L or ≧ 20% if WBC < 4.0 × 10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS: ≧ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Extent > 50% of BSA		N/U	Y	
Rash suggesting DRESS	N	U	Y	
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≧ 15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

ANA: anti-nuclear antibody; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; N: no; U: unknown; WBC: white blood cell; Y: yes.

Kardaun et al, Br J Dermatol. 2013 Nov;169(5):1071-80.

Narrowing down the differential diagnosis

Diagnostic criteria for sweets:

- Drug induced:
  - Abrupt onset of tender nodules/plaques
  - Biopsy consistent with sweets
  - Fever
  - Temporal relationship between drug and syndrome
  - Appropriate improvement with withdrawal of drug

Major criteria

1. Tender/painful erythematous plaques or nodules
2. Neutrophil infiltration of dermis without leukocytoclastic vasculitis

Minor criteria

1. Malaise and fever
2. Previous respiratory/GI infection or vaccination, associated inflammatory disease, or malignancy
3. ESR >20, positive CRP, bands >70% in peripherel smear, and leukocytes >8,000 (requires 3 of 4)
4. Response to corticosteroid or potassium iodide
5. Diagnosis requires 2 major and 2 minor criteria

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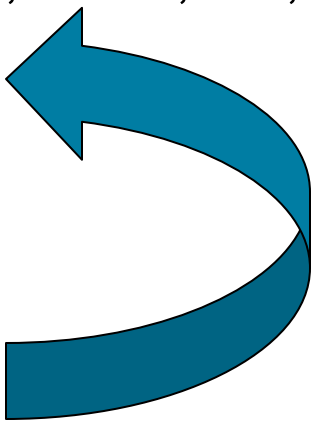
Walker DC, Cohen PR: J Am Acad Dermatol 1996;34:918-923.

Su and Liu. Cutis 1986 Mar;37(3):167-74.

Clinical Course

- Rheum panel:
  - Normal negative: ANA (+1:40), dsDNA, Ro/La, Sm, RNP
  - Complements: C3: 204, C4: 44 (high)
  - CRP: 149.7, ESR: 89



- Biopsy results: urticarial vasculitis!
  - *Neutrophilic dermatosis with LCV on biopsy*
- Tissue Culture: negative

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Clinical Course

- Initiated on prednisone with slow taper for acute management.
- Started dapsone, antihistamines, with plan for slow taper.
- Continued to hold gabapentin and topiramate.

- Continued to follow her over the next year with complete resolution of UV.
- At a follow up, had a new complaint: a “dent” in her forehead.

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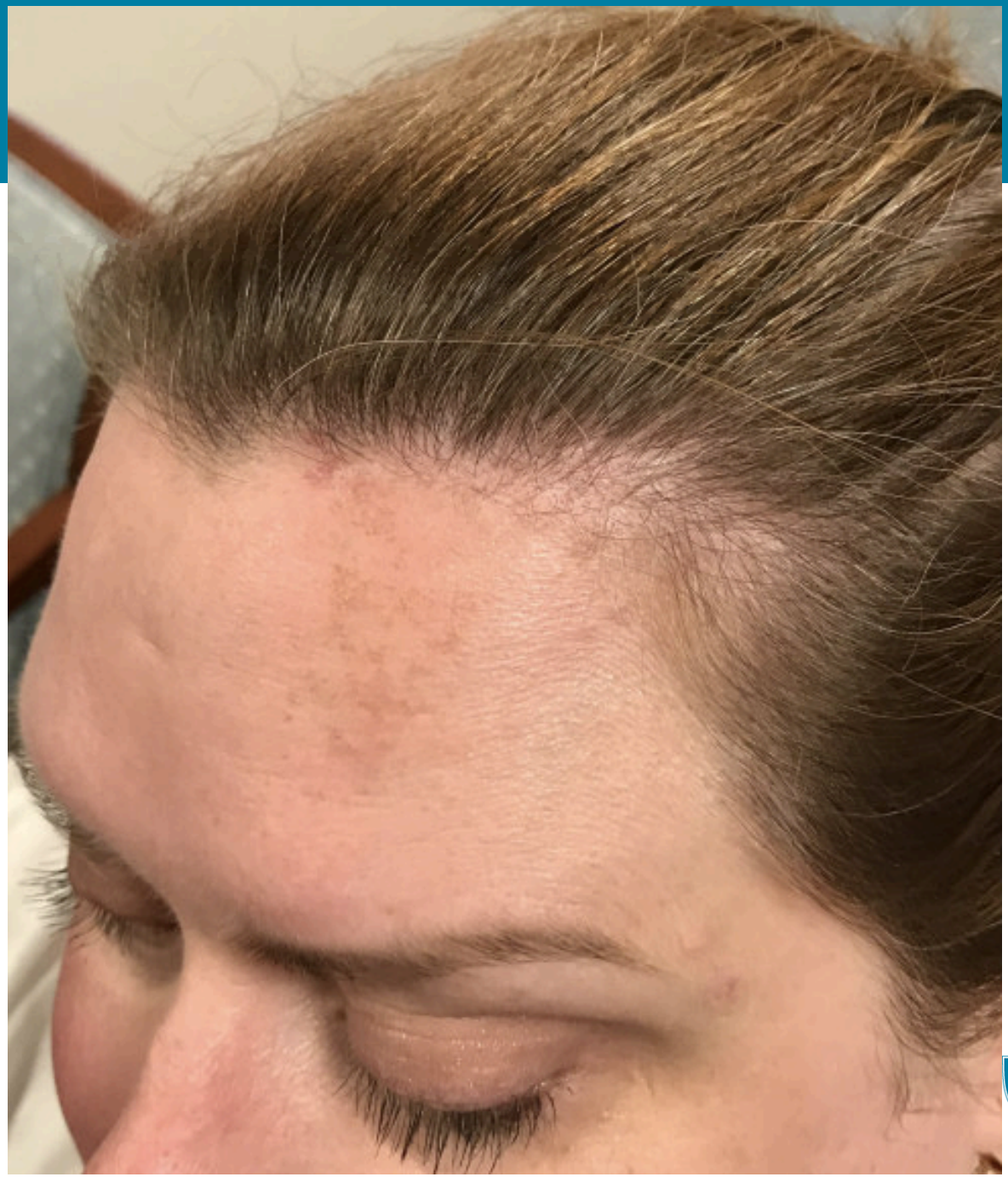
Exam



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Clinical Course

- I suggested to just watch given subtle exam findings.
- On follow up 3 months later, continued atrophy, more noticeable.
  - *Working diagnosis: Linear morphea (en coup de sabre)*
  - *Sent for Brain MRI*
  - *Referred to pediatric dermatology clinic!*

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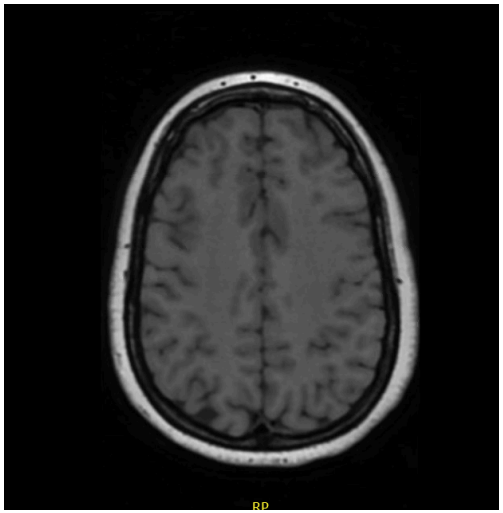
Clinical Course

- Brain MRI normal
- Biopsy taken showing fibrosis consistent with early morphea.



- Started on methotrexate at 25 mg PO weekly.

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Clinical Course

- Continuing atrophy despite MTX 25 (even SQ)
- Switched to mycophenolate.
- *What is her underlying disease process?*

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Take Home Points

- Many of the patient's unusual symptoms were ultimately attributable to her linear morphea.
  - Headaches, diplopia
  - Diseases may take time to reveal themselves
  - Some patients have this "auto-inflammatory" diathesis without clear connection

- Was told multiple times that this is all fibromyalgia. While she may fit that picture, I worry about diagnostic anchoring (even when we anchor on a "supratentorial" process).

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Case 4

- 53 year old woman, consult for “rule out Stevens Johnson Syndrome.”

- Recently started lisinopril for HTN 5 weeks ago. Lisinopril was stopped after she develop angioedema and cough 2 weeks ago. She noticed a new rash before stopping lisinopril. Saw her PCP today, who was concerned for SJS and sent her to ED.

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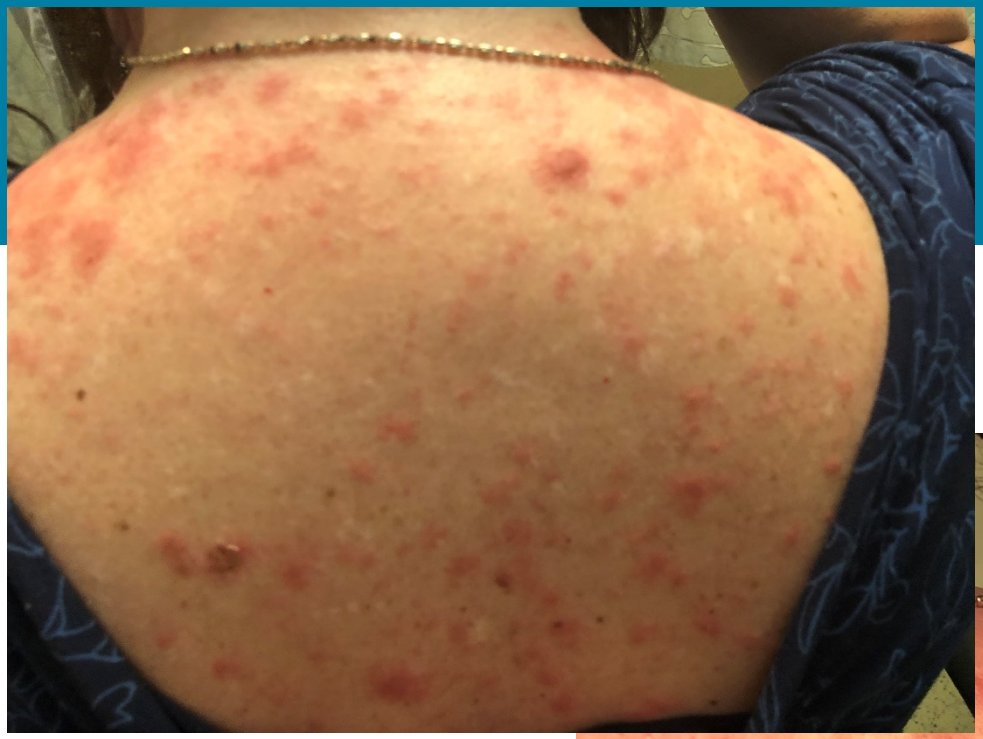

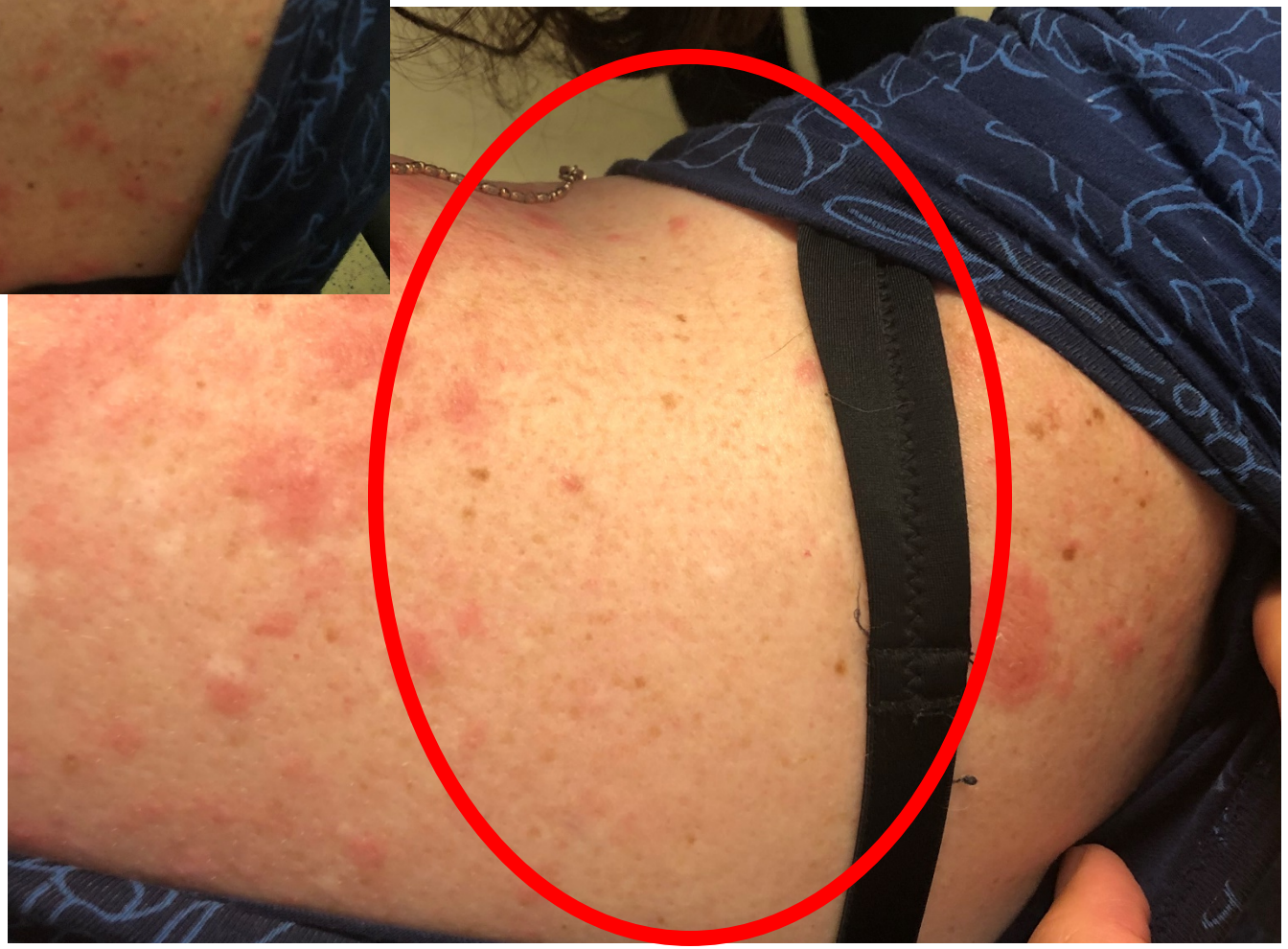

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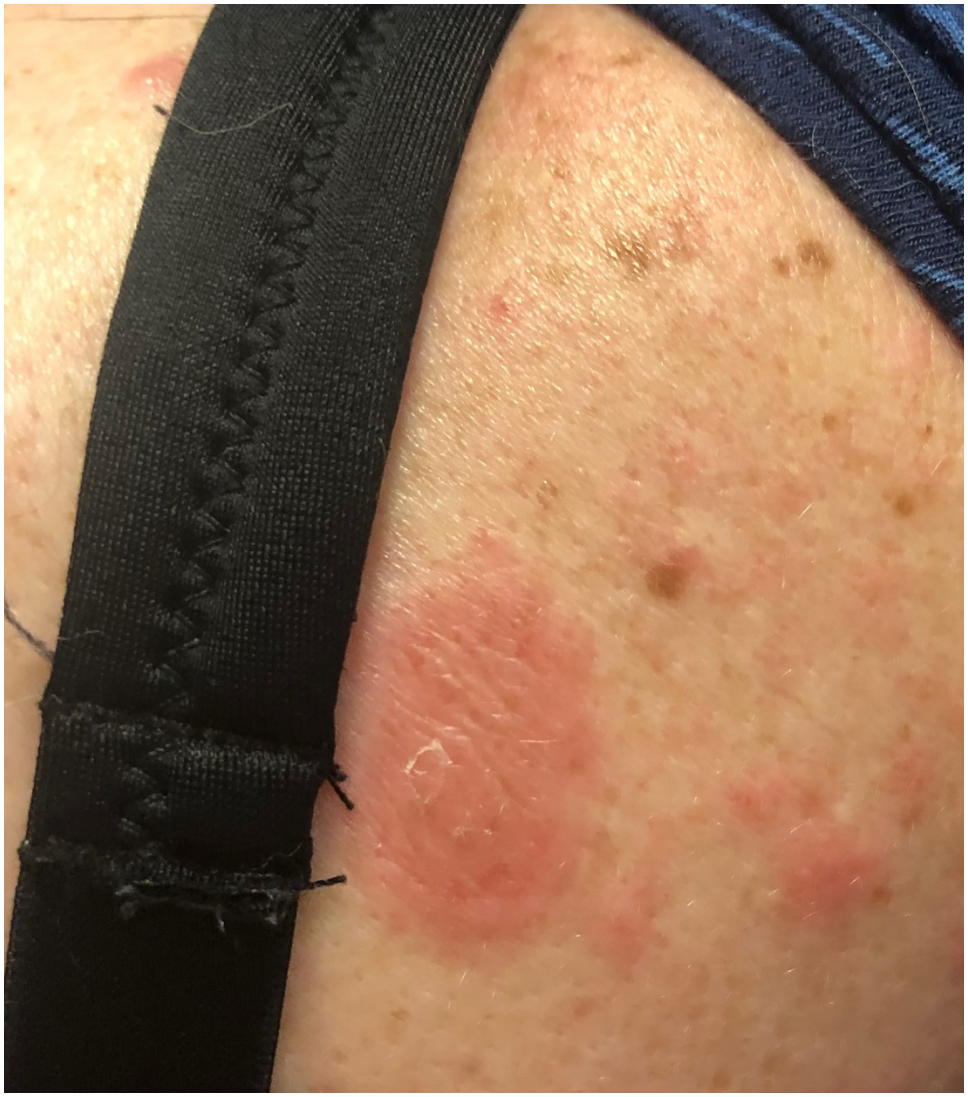

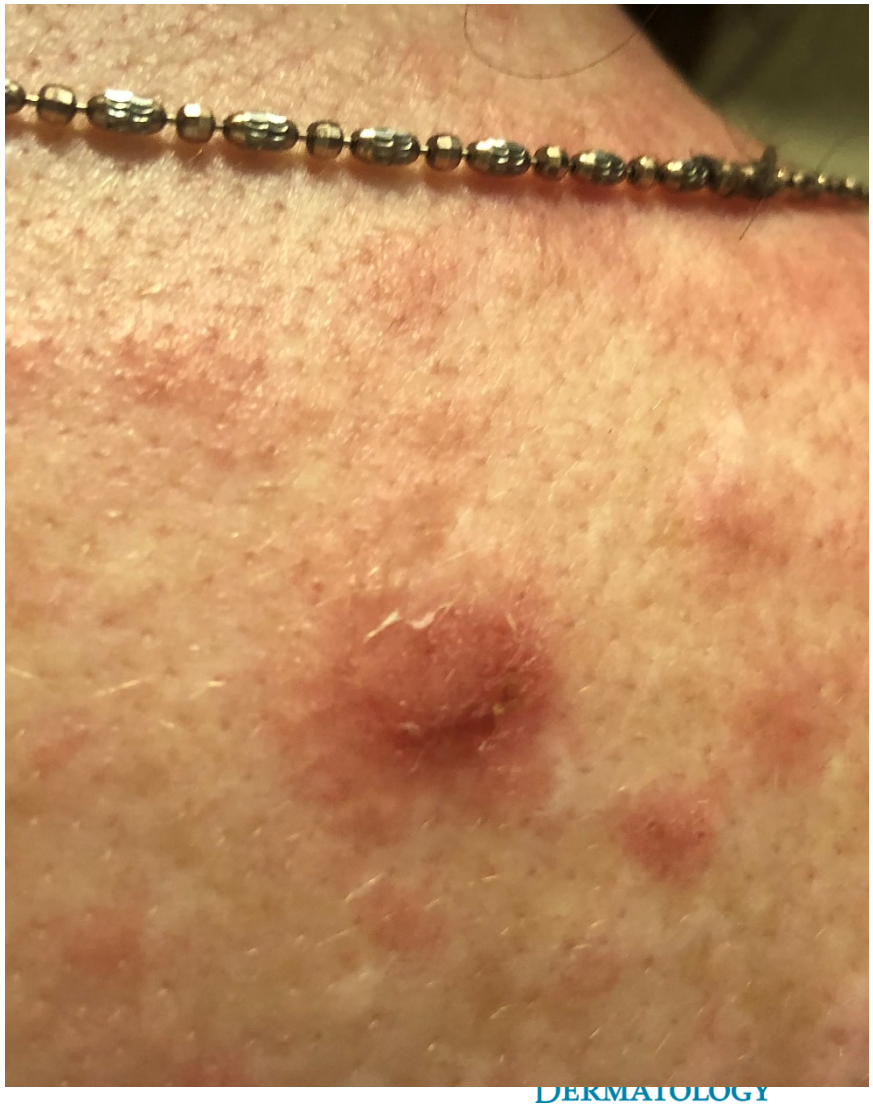

Differential diagnosis

- Photosensitive process
- NOT SJS
- Drug reaction?

Further questioning on drug exposure:

"Oh! I also started terbinafine at the same as lisinopril. I'm still on it since my doctor said it's not the cause of the problem!

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Drug induced SCLE

- As opposed to Drug induced SLE, usually not anti-histone, but rather anti-Ro.
- Drug discontinuation doesn't always lead to resolution of rash.
- Given the very classic presentation, we did not biopsy, but sent blood work for serologic testing.

	8/9/2019 1719	
ANA SCREEN		
ANA (qual)	NEGATIVE AT 1:... *	
dsDNA Ab	Negative at 1:10 *	
SS-A(Ro) Ab	111.56 *	▲
Interpretation (SS...	Positive *	!
SS-B(La) Ab	2.86 *	
Interpretation (SS...	Negative *	
IMMUNOLOGY MISCELL...		
dsDNA Ab	Negative at 1:10 *	
Histone Ab	<0.5	

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Take home points

- A biopsy is not always necessary for cutaneous lupus, even for types that aren't the typical malar rash!
- When it's a skin problem, do as the dermatologists do: Start with the exam and use it to direct questioning.
  - We saw photosensitive rash, considered SCLE, and asked about further drug exposure history.

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Case 5

- 78F with history of MGUS, HTN, HLD, DM, and recent diagnosis of HFpEF presented to the ED with increasing fatigue, respiratory distress, new lower extremity edema, and peripheral neuropathy (new). A rash was noted on the BL feet.

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History continued

- **Past Medical/Surgical History**:
  - MGUS
  - HTN
  - HLD
  - DM
  - HFpEF
- **Medications:**
  - Lisinopril
  - Metformin

Allergies: NKDA

Family History:
No history of skin diseases.

Social History:
Lives in a nursing home.
No TOB or EtOH.

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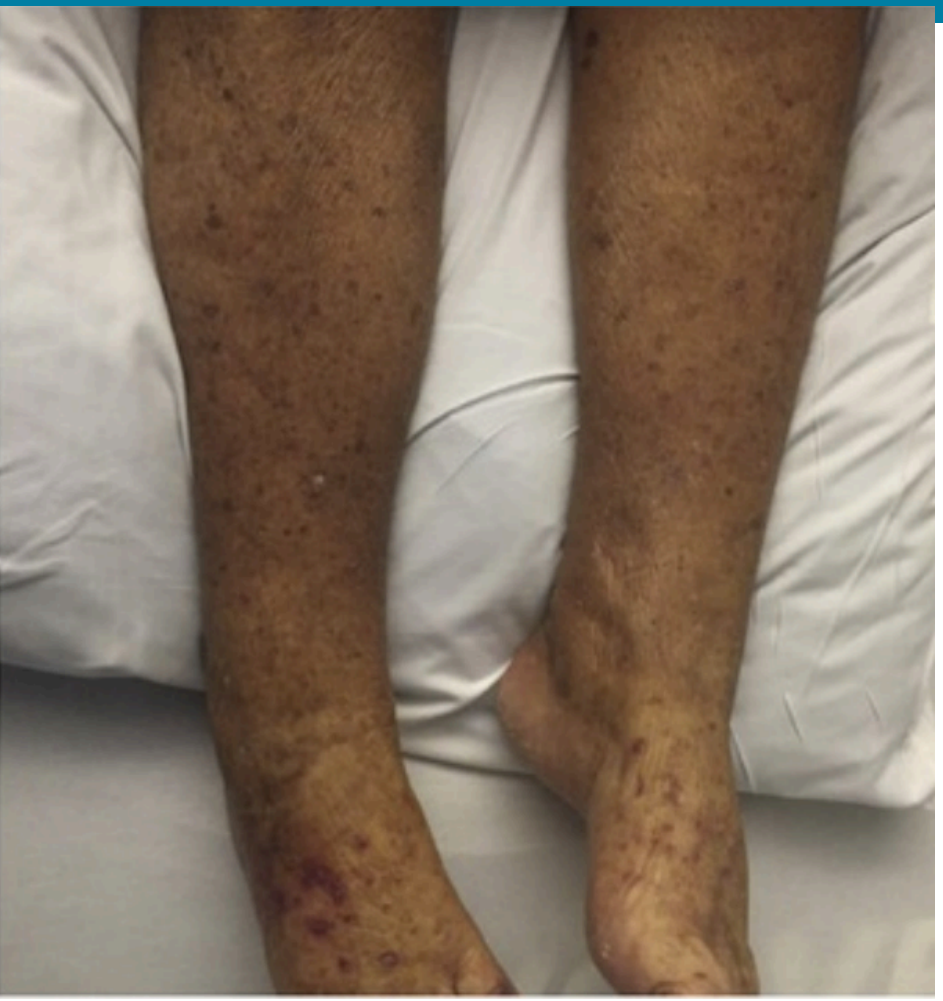
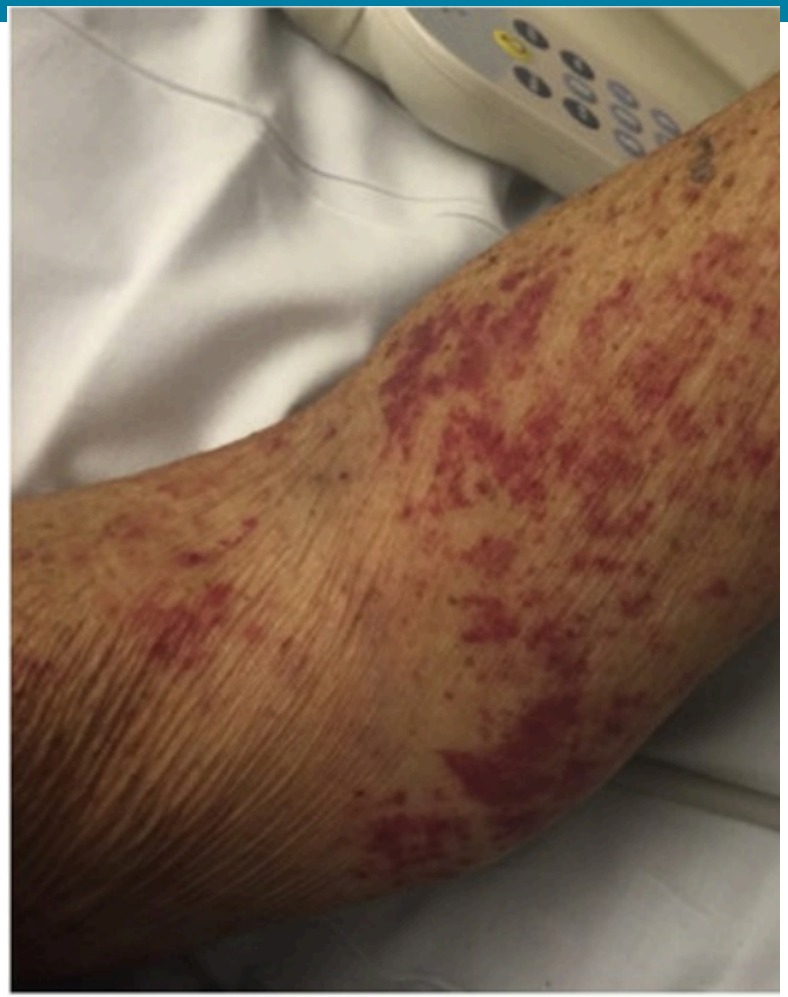
Exam





Hospital Day 1 → Hospital Day 2

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Clinical Course

- Biopsy taken for H+E and DIF given concern for vasculitis
- Work up suggested for small vessel vasculitis
  - What would you send?

Tests I routinely consider:
- ANA
- ANCAs
- Complements
- UA, CBC, CMP
- ESR/CRP
- Cryoglobulins (with Rheumatoid factor)
- Hepatitis serologies
- Blood cultures

Tests I routinely send:
- UA, CBC, CMP

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Clinical Course

- If the patient had a recent illness or a new medication, a small vessel vasculitis is most likely reactive.
- I treat to control symptoms (and to avoid ulceration), but I don't send everything.
- If not improved, then I work through my list.

- *In this case, no new drugs or recent infections. Given the history, we requested the following:*
- UA, CBC, CMP, ESR/CRP, Complements, ANA, hepatitis serologies, cryoglobulins with RF

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Clinical Course

- Creatinine on admission was 3 (from normal).
- Biopsy showed a leukocytoclastic vasculitis and granular C3 in the vessel walls.
- Cryocrit was 9% (normal: none)
- RF +
- Hepatitis serologies negative
- ESR/CRP elevated
- Remainder negative

- *Working diagnosis of Type II Cryoglobulinemia*

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Clinical Course

- Given the constellation of symptoms and acutely worsening renal function, initiated the following therapy:
  - Plasmapheresis
  - Rituximab
  - Solumedrol → prednisone
- Symptoms improved, Cr returned to normal, discharged for long prednisone taper.

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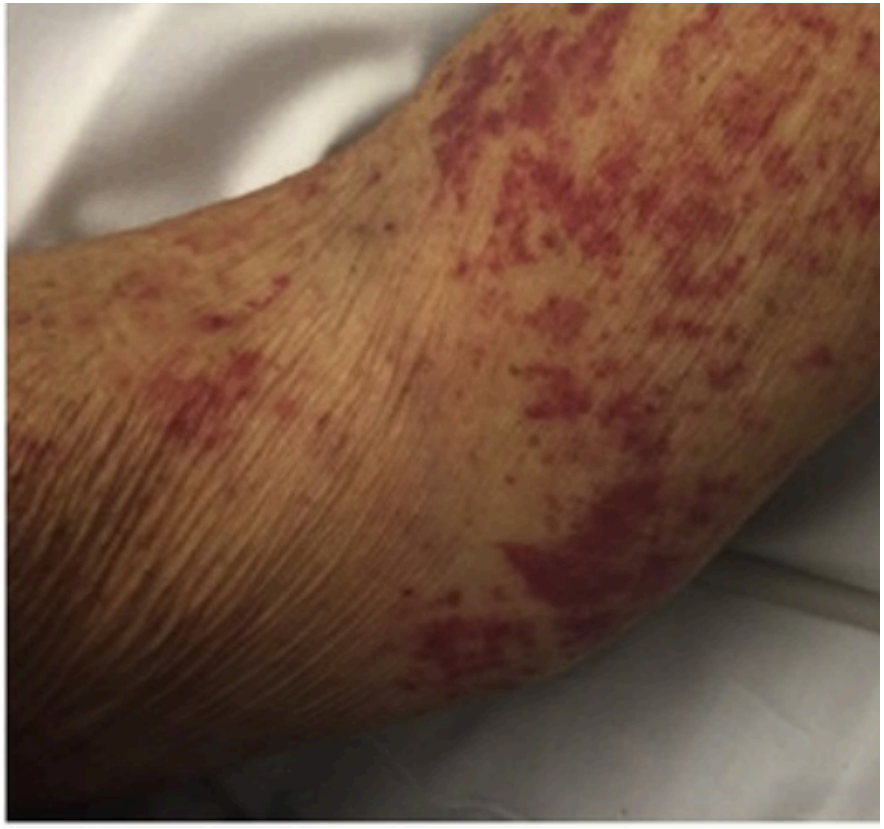
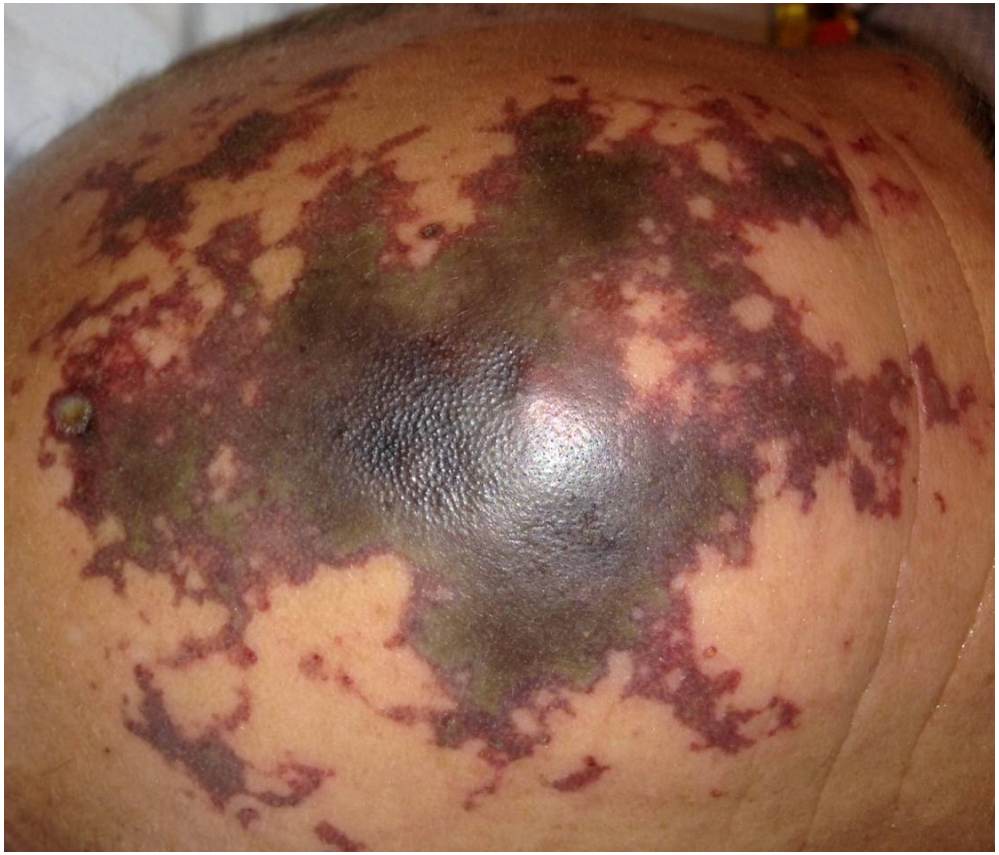
Reason for retiform purpura on skin exam





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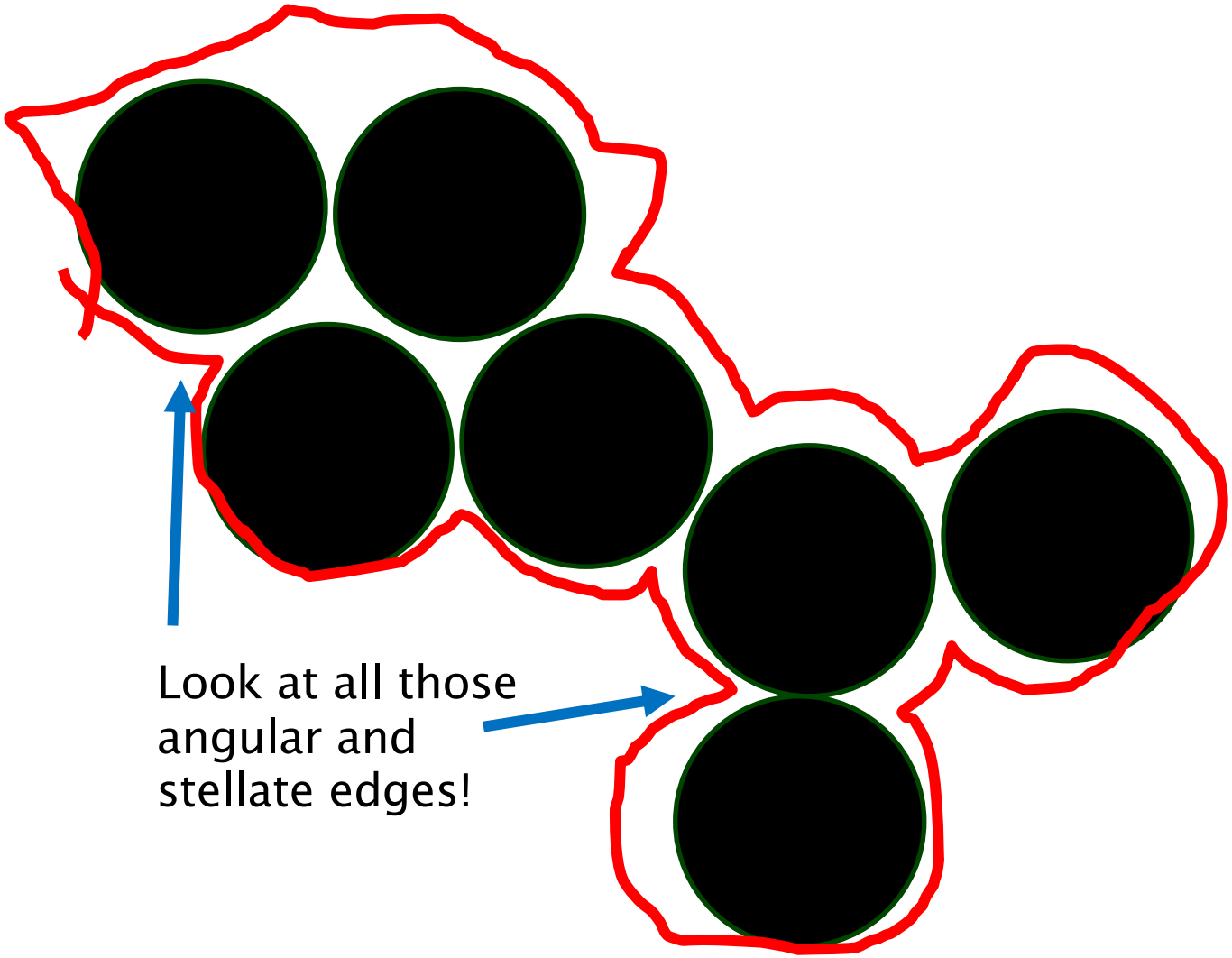
Skin perfusion



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Take home points

- Every case of vasculitis does not require a huge work up.
- Supportive care and close monitoring is reasonable.
- If you see “retiform purpura,” think about something blocking the vessels → either **vasculitis or vasculopathy**

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Case 5

- 83 woman presented to our blistering disorders clinic with fragile blisters on the feet. Rash is limited to dorsal feet.
- A dermatologist she was seeing out of state told her there was nothing that could be done, so she didn't seek another opinion.
- Recently, worsened, so prompted evaluation.

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History continued

- Past Medical History
  - HTN
  - Hyperlipidemia
  - Spinal Stenosis
  - GERD
- Medications
  - Valsartan
  - HCTZ
  - Atenolol
  - amolodipine
- Allergies: Sulfa
- Social History
  - Former Smoker
  - + EtOH
  - Denies illicits
  - Retired schoolteacher
- Family History
  - Melanoma

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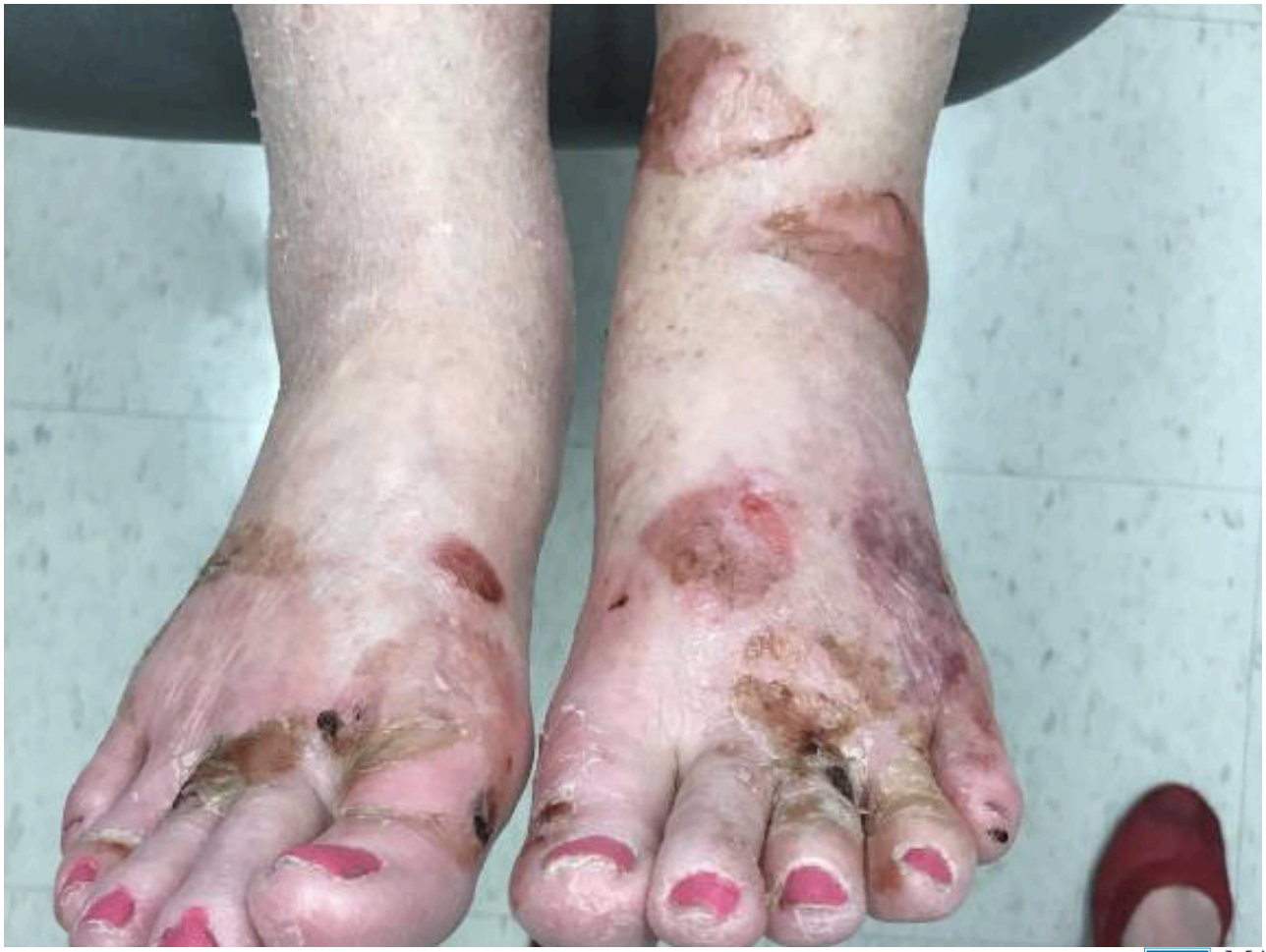
Exam



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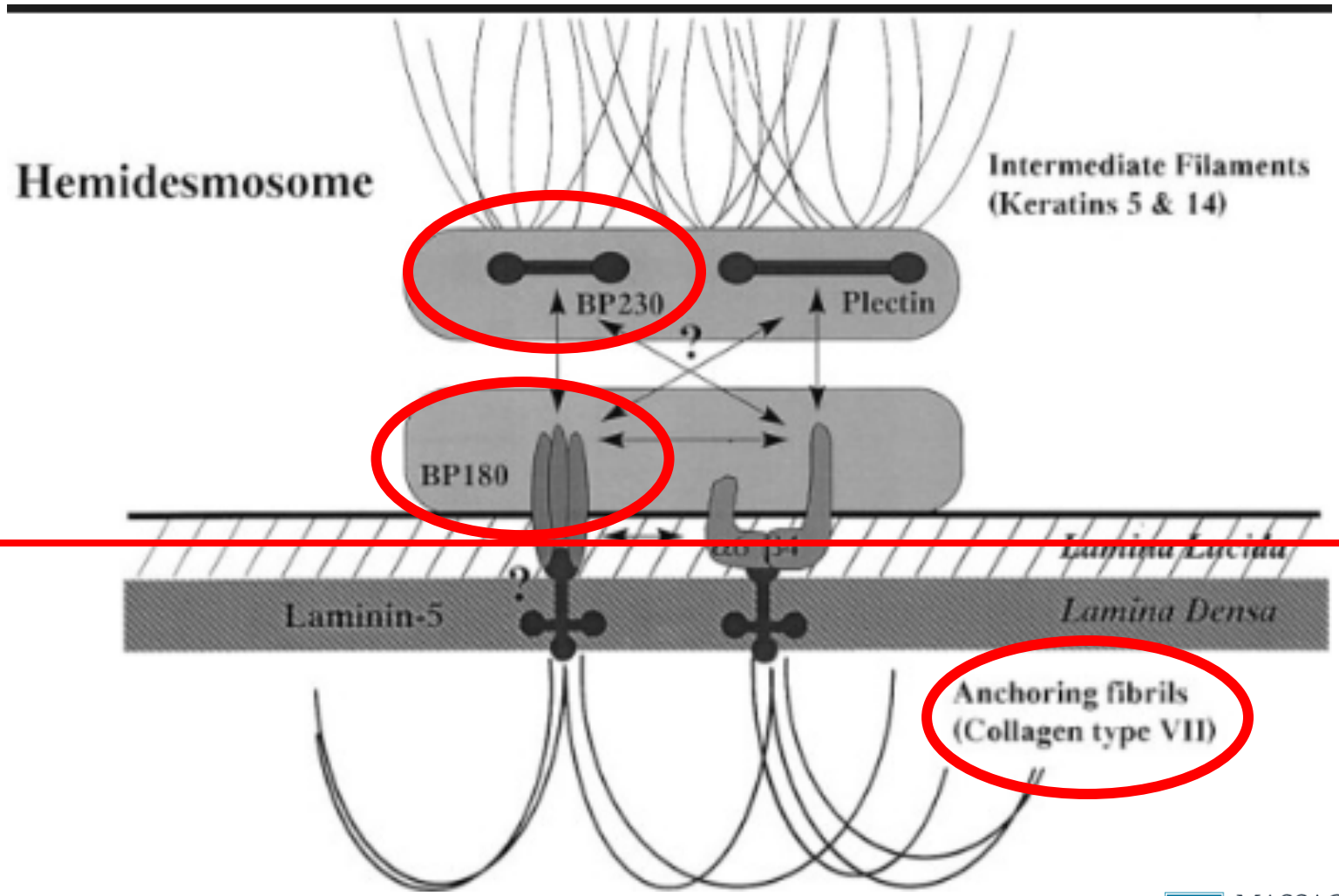
Differential Diagnosis

- *Blisters/bullae on the dorsal hands and feet.*
  - Bullous lupus
  - Epidermolysis bullosa acquisita
  - Bullous Pemphigoid

How to differentiate?



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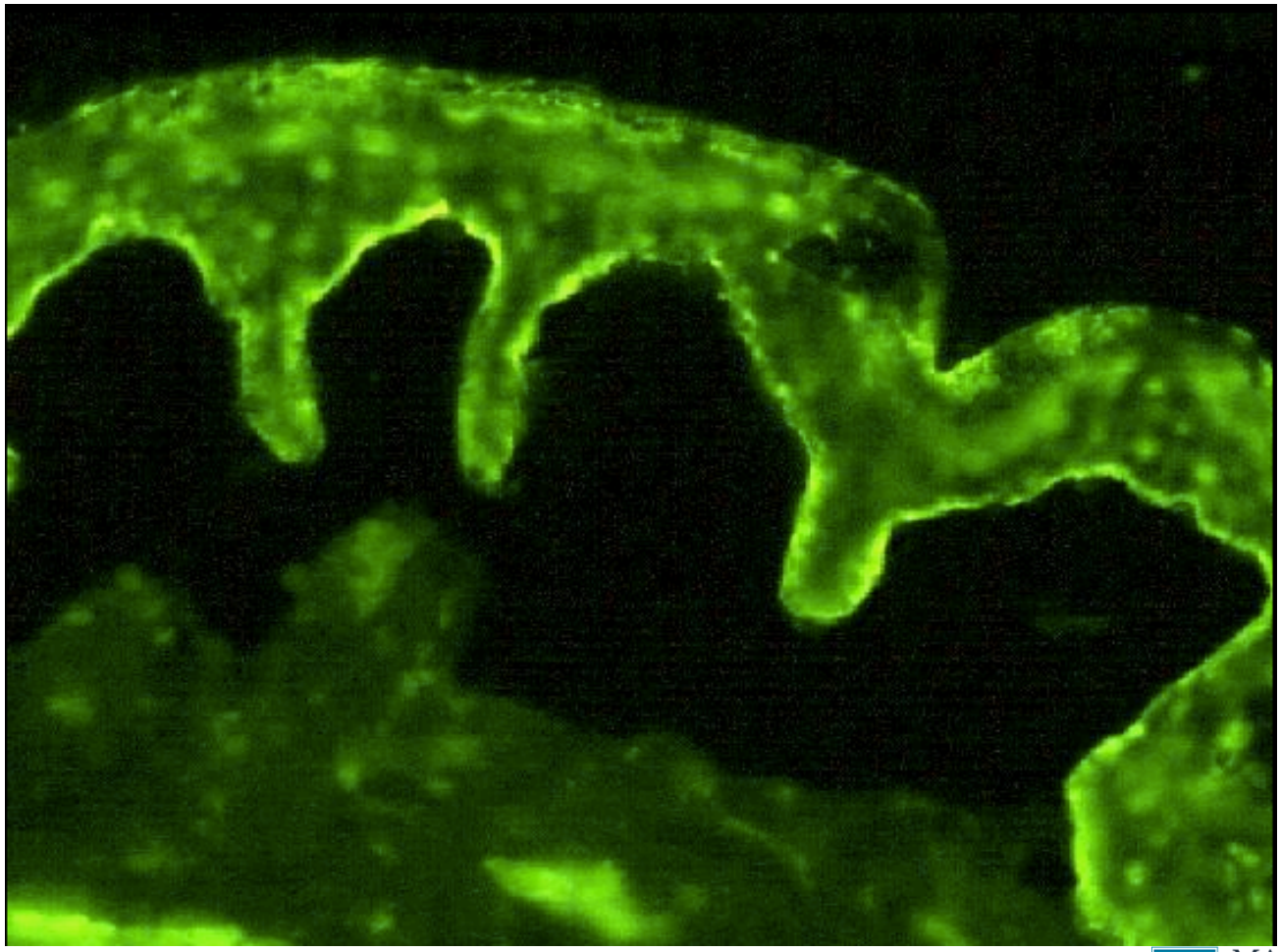
Borradori et al. JID, Volume 112, Issue 4, April 1999, Pages 411–418

Roof vs. floor



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Bullous lupus differentiation

- However, this still doesn't differentiate between EBA and Bullous lupus.
- Minimal trauma causing blisters is more consistent with EBA.
- Treatment is usually dapsone, with marked improvement with bullous lupus, and recalcitrant disease with EBA.
- Checked G6PD, ANA, Ro/La, CBC, CMP.
- Started dapsone (felt sulfa allergy may not have been real)

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Follow up

- At 1 month follow up, patient tolerating dapsone well.
- Complete resolution of blisters, despite continued minor trauma.
- ANA, Ro/La, G6PD were all negative/normal.

Take Home Points

- EBA and Bullous Lupus are similar on pathology.
- Response to dapsone is helpful in determining which entity you are dealing with.
- Sometimes, there still remains diagnostic uncertainty given history and lack of symptoms consistent with lupus.
- Continued management with dapsone and monitoring of skin disease is warranted when there is diagnostic uncertainty.

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Case 6

- 35 man with history of malignant melanoma, followed in dermatology, who presents with a new rash of 2 weeks duration.
- Burning pain at times, some pruritus. Leaves marks after it goes away, and lasts for over 24 hours.
- No new medications or foods.

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History continued

- Past Medical History
  - Melanoma
- Medications:
  - None
- Allergies: NKDA
- Social History
  - Denies illicits, EtOH, TOB
- Family History:
  - Negative for melanoma

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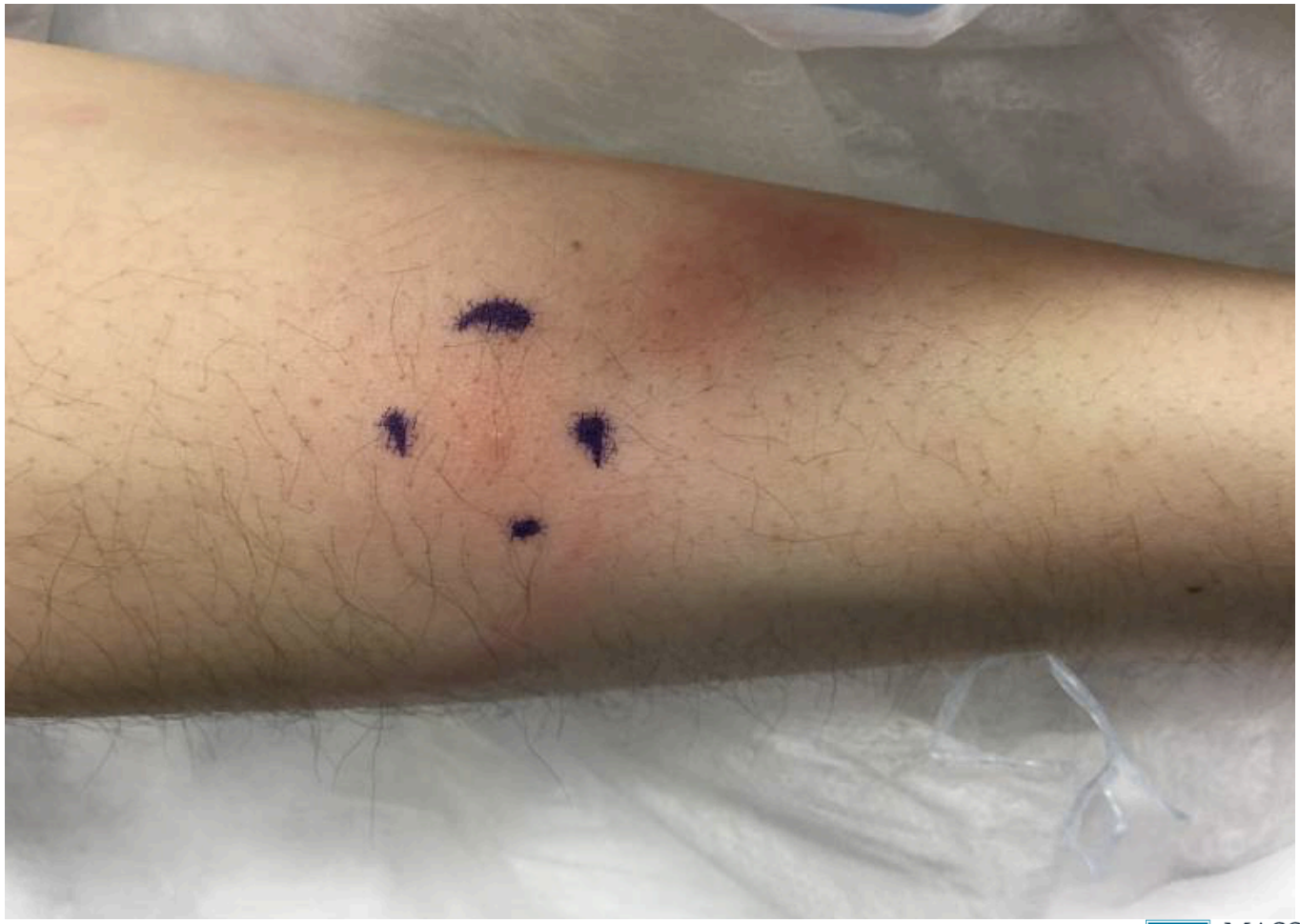
Exam



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Differential Diagnosis

- Urticarial Vasculitis
- Urticaria
- Hypersensitivity Reaction

Biopsy Results

- FINAL PATHOLOGIC DIAGNOSIS:
  A. SKIN, PUNCH BIOPSY, RIGHT FOREARM:

- Multifocal subepidermal blisters with superficial and deep dermal perivascular lymphohistiocytic and eosinophilic infiltrate with focal vascular necrosis consistent with urticarial vasculitis.

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Plan

- At follow up appointment, decided to initiate the following:
  - Dapsone 100 mg daily
  - Cetirizine 10 mg POBID
  - Fexofenadine 180 mg POBID
  - Diphenhydramine 25 mg POQ6H prn pruritus/rash
  - 2 week follow up

- Checked the following labs:
  - Complement, ANA, SPEP
  - G6PD
    - All labs were normal.

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2 week follow up

- Pt presented back for follow up and felt rash was improving. No other symptoms. Denied any new fatigue or dyspnea.
- On exam, generally seemed to be paler and greenish
- We checked vitals (normally not done in dermatology)
  - Afebrile, HR 90s, BP 120/72, RR 16, SaO2 88%

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New plan

- Given new dapsone therapy, concern for methemaglobinemia and hemolytic anemia.
- Referred to MGH ED where work up revealed:
  - Hct dropped 10 points
  - MCV now elevated to 106, RDW elevated
  - Total bilirubin – 3.6
  - Methemoglobin – 9.8% (0.0-1.5%)
- Was given methylene blue and admitted to medicine service.
- Discharged off of dapsone, and on colchicine instead.

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Take Home Points

- Dapsone, although usually well tolerated, can lead to life threatening side effects.
- Consider bringing patient back for follow up 2 weeks from initiation.
- Beware of hemolytic anemia, even with normal G6PD
- For dermatologists – vitals can be helpful.
- Remember your primary colors - when a patient is green, it could be from a combination of yellow (jaundice) and blue (cyanosis)….

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Case 7

- 72M with metastatic head and neck SCC on ipilimumab and nivolumab who developed a new skin condition ~ 12 months after last infusion if checkpoint inhibitor.

- Initially had stasis dermatitis, but developed skin tightening.

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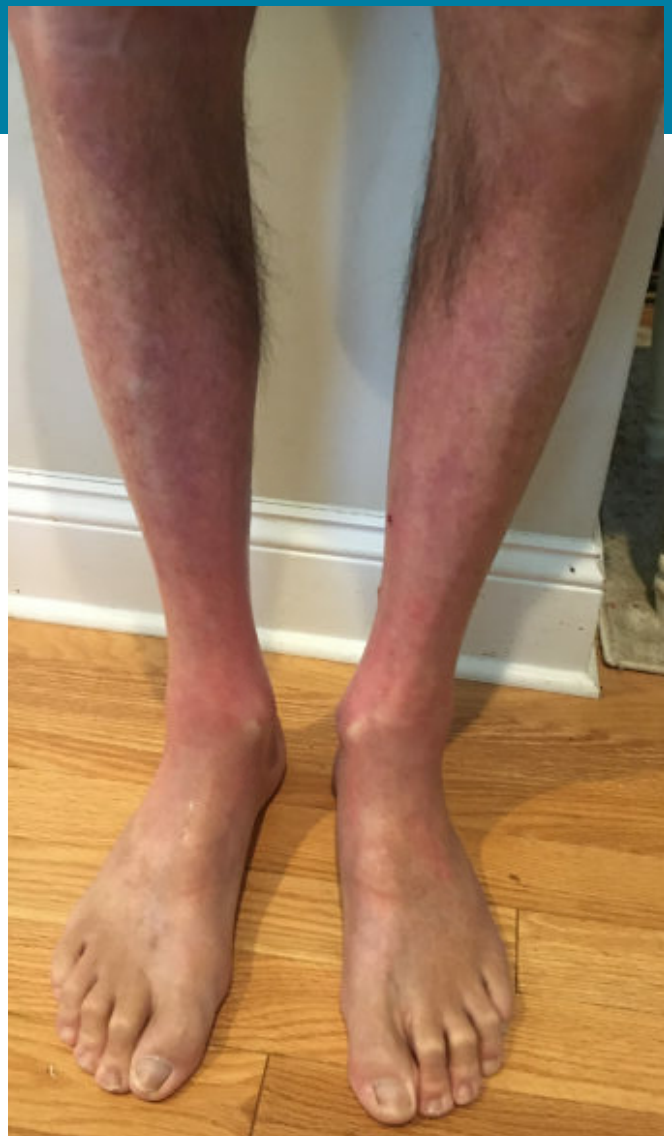
Patient photos

Shiny taught skin from knees down.

Possibly involved ankle and foot, but less convincing.

Rheum panel all negative (except ANA + 1:1280, homogenous).

Diagnosed with ICI-induced sclerodermoid reaction.



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Clinical course

- Patient was thought to have ICI-induced sclerodermoid reaction. Biopsy taken which found eosinophilic fasciitis.
- While I would usually use IVIG for a patient like this, theoretical risk of neutralizing ICI monoclonal antibodies.
- Instead, trialing dupilumab for treatment.

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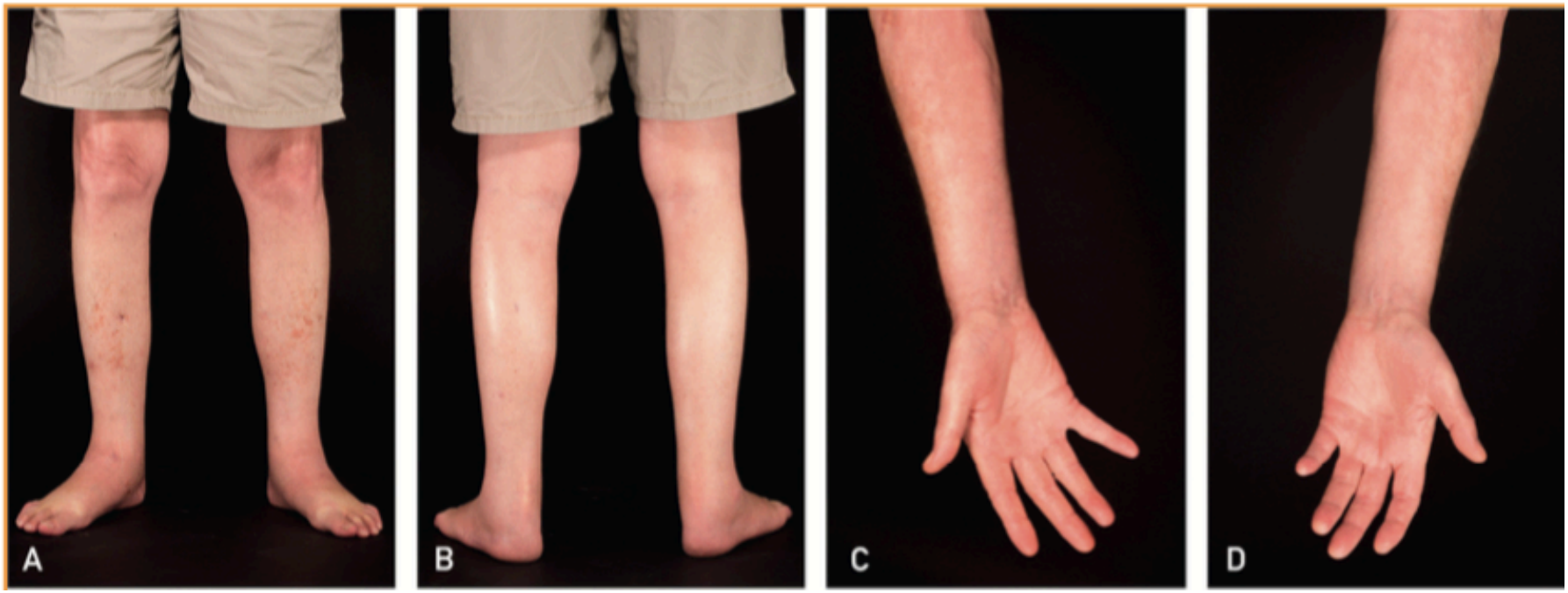
Skin tightening, reduced ROM



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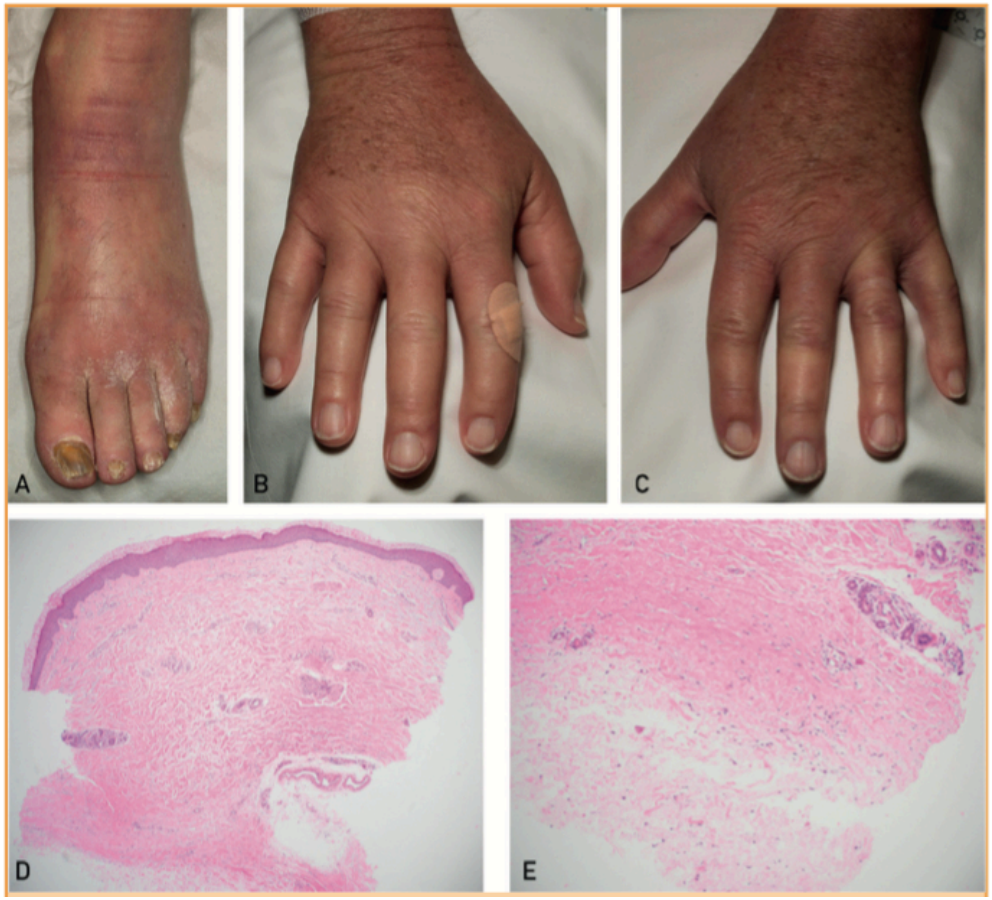
Barbosa et al, Mayo Clin Proc. July 2017;92(7):1158–1163.

Skin stiffness and tightening



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Barbosa et al, Mayo Clin Proc. July 2017;92(7):1158–1163.

Sclerodermoid reaction

- Skin tightening reported secondary to pembrolizumab
- No auto-antibodies reported
- Poor outcome potentially, but limited cases
  - One patient continued to worsen despite IVIG and discontinuation of ICI
  - One patient had concurrent pneumonitis, received hydroxychloroquine and prednisone, had to stop ICI, and did not get reinitiated

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Barbosa et al, Mayo Clin Proc. July 2017;92(7):1158-1163.

Take away points

- With checkpoint inhibitors, more dermatologic and rheumatologic diseases are occurring, many of which may be different than the “idiopathic” versions.

- Many occur much later than you would expect for being “drug induced.” Stopping/holding ICI is usually not enough.

- For now, need to consider the pathophysiology and mechanism of drugs before initiating “typical” treatment.

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Final Thoughts

- Dermatologists have easy access to an organ that can provide answers.
- Involve your local dermatologist for evaluation, and let him or her decide on whether a biopsy might be helpful.

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Thank you!

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