Lupus for the Allergist

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Objectives

- Review clinical manifestations and serologies seen in lupus
- Review when to appropriately order an ANA and interpret ANA results in the context of the patient's clinical presentation
- Recognize allergy clinic presentations that should prompt evaluation for lupus and autoimmune disease

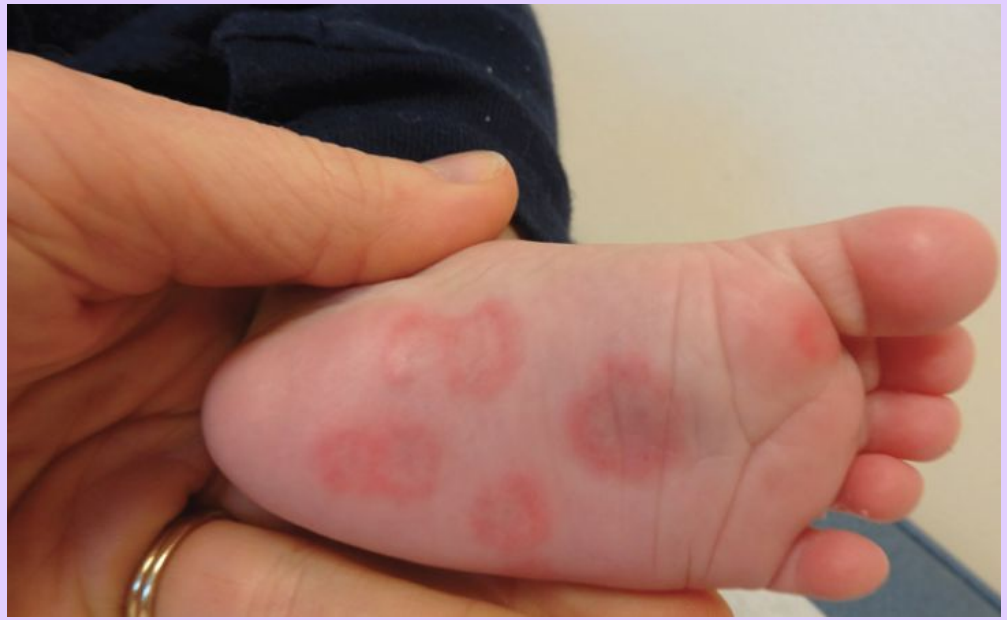
Systemic Lupus

- Chronic autoimmune disease characterized by immune dysregulation, autoantibody production and inflammation affecting multiple organ systems.
- 9:1 female predominance
  - Most commonly affects women of childbearing age (15-44)
  - Minority ethnic groups at higher risk and more severe disease

Seigel CH et al, JAMA 2024

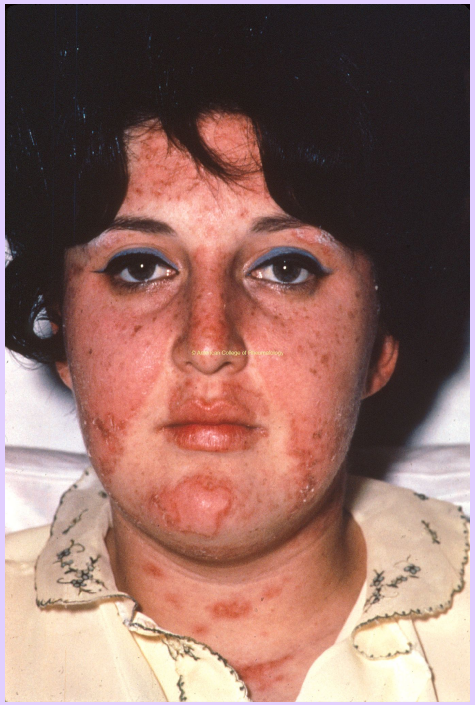
Types of Lupus

1. Systemic lupus
2. Cutaneous lupus
3. Drug-induced lupus
4. Neonatal lupus

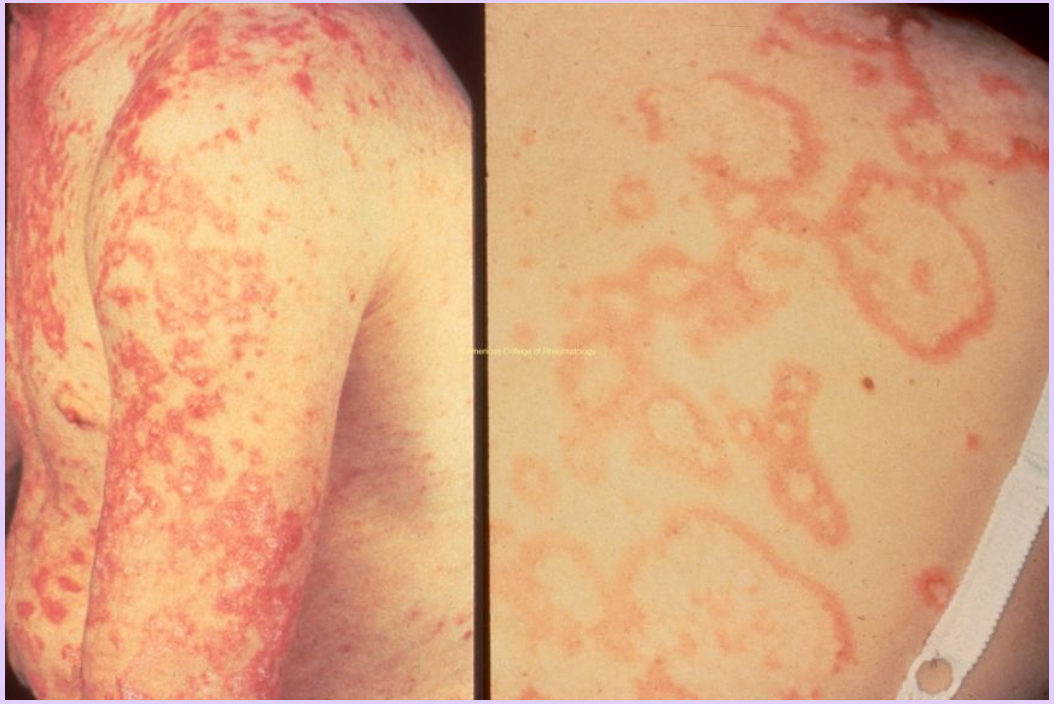


Pedi Derm 2023

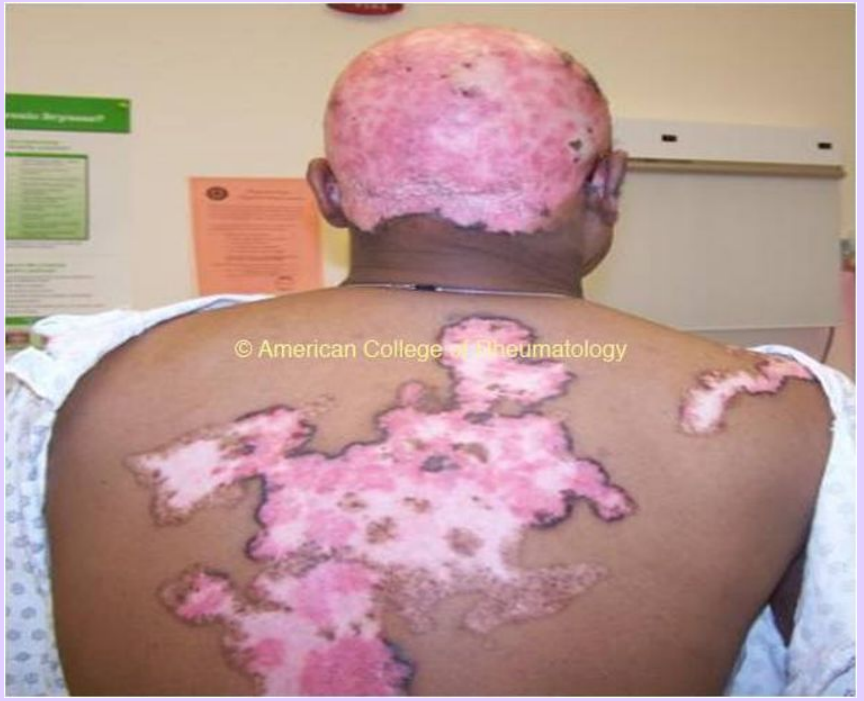
Cutaneous Lupus



Acute
- Malar rash
- Non-scarring



Subacute
- SSA associated
- Affects 10-15% of SLE pts



Chronic
- Discoid
- Scarring

How do you diagnose Lupus?

- There is no formal diagnostic criteria
- Clinical symptoms **PLUS** positive serologic lab tests
- This can be tricky!
  - Lab tests are non-specific
  - Symptoms are vague
  - May take time for disease to fully evolve
- Symptom onset diagnosis reportedly can take as long as 6 years!

2019 ACR/EULAR CLASSIFICATION Criteria

- Score of >= 10 classifies a patient as SLE with **96.1% sensitivity and 93.4% specificity**

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.

Occurrence of a criterion on at least one occasion is sufficient.

SLE classification requires at least one clinical criterion and ≥10 points.

Criteria need not occur simultaneously.

Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

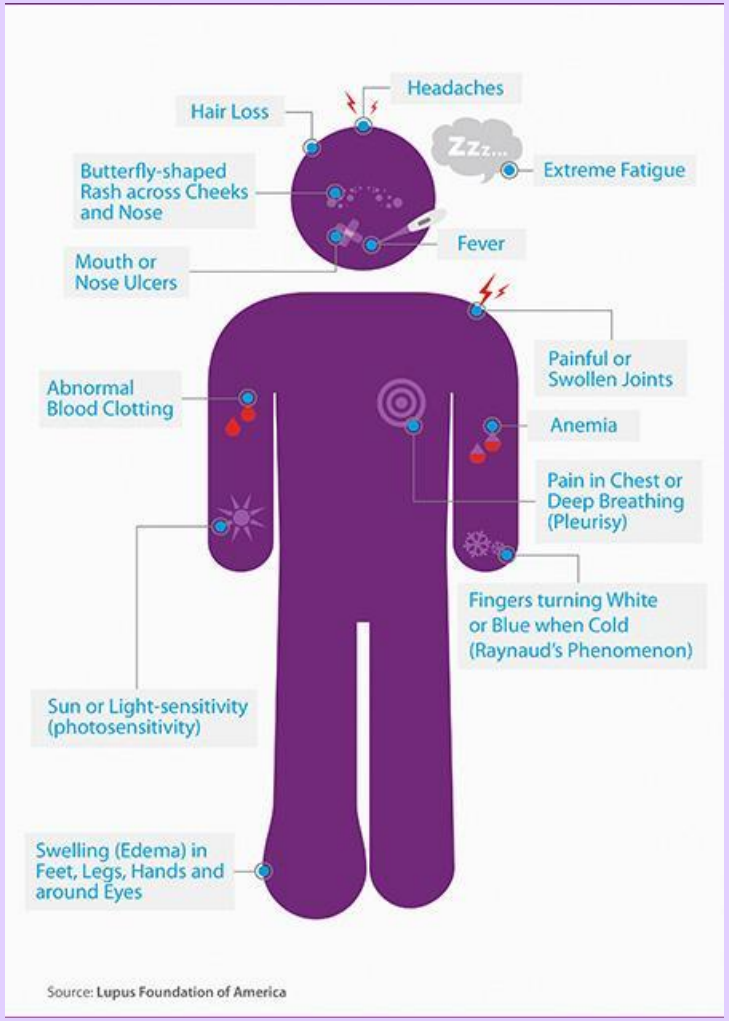
Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

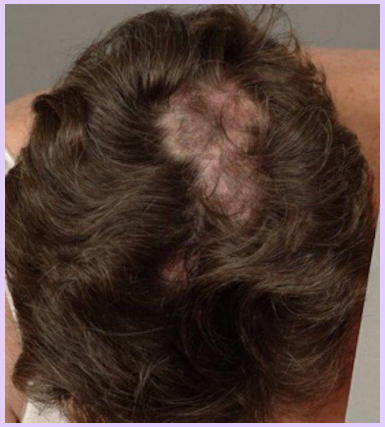
Aringer et al. DOI

What clinical symptoms should make you think of lupus?

Clinical Manifestations of SLE

- SLE can affect **every** organ system
- Individual symptoms are non-specific
- Think about the **constellation of symptoms**!
- Lupus nephritis occurs in ~40% of lupus patients
  - ~10% progress to ESRD at 10 years





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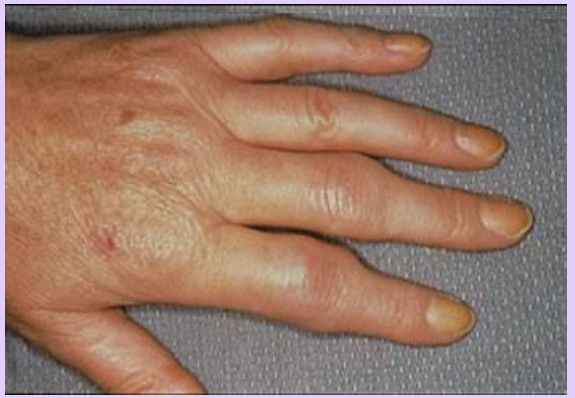
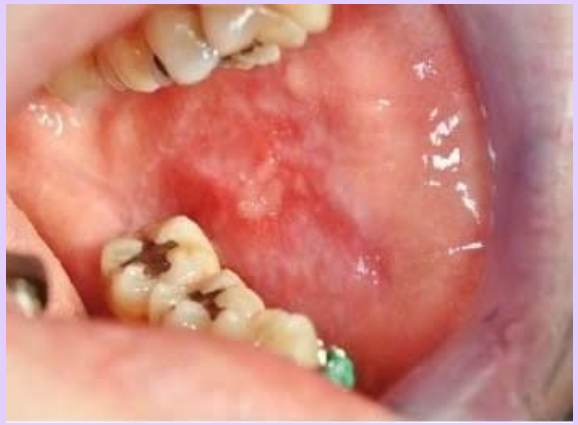
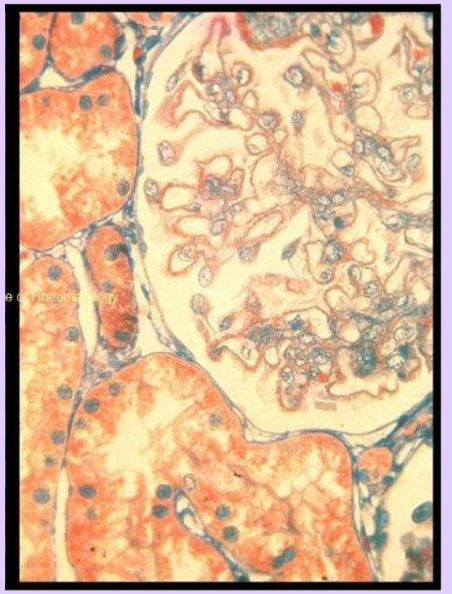
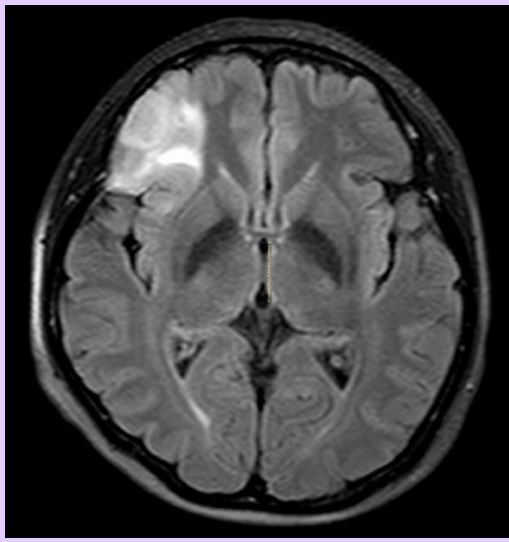








What labs should I order if I am suspicious for lupus?

2019 ACR/EULAR CLASSIFICATION Criteria

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

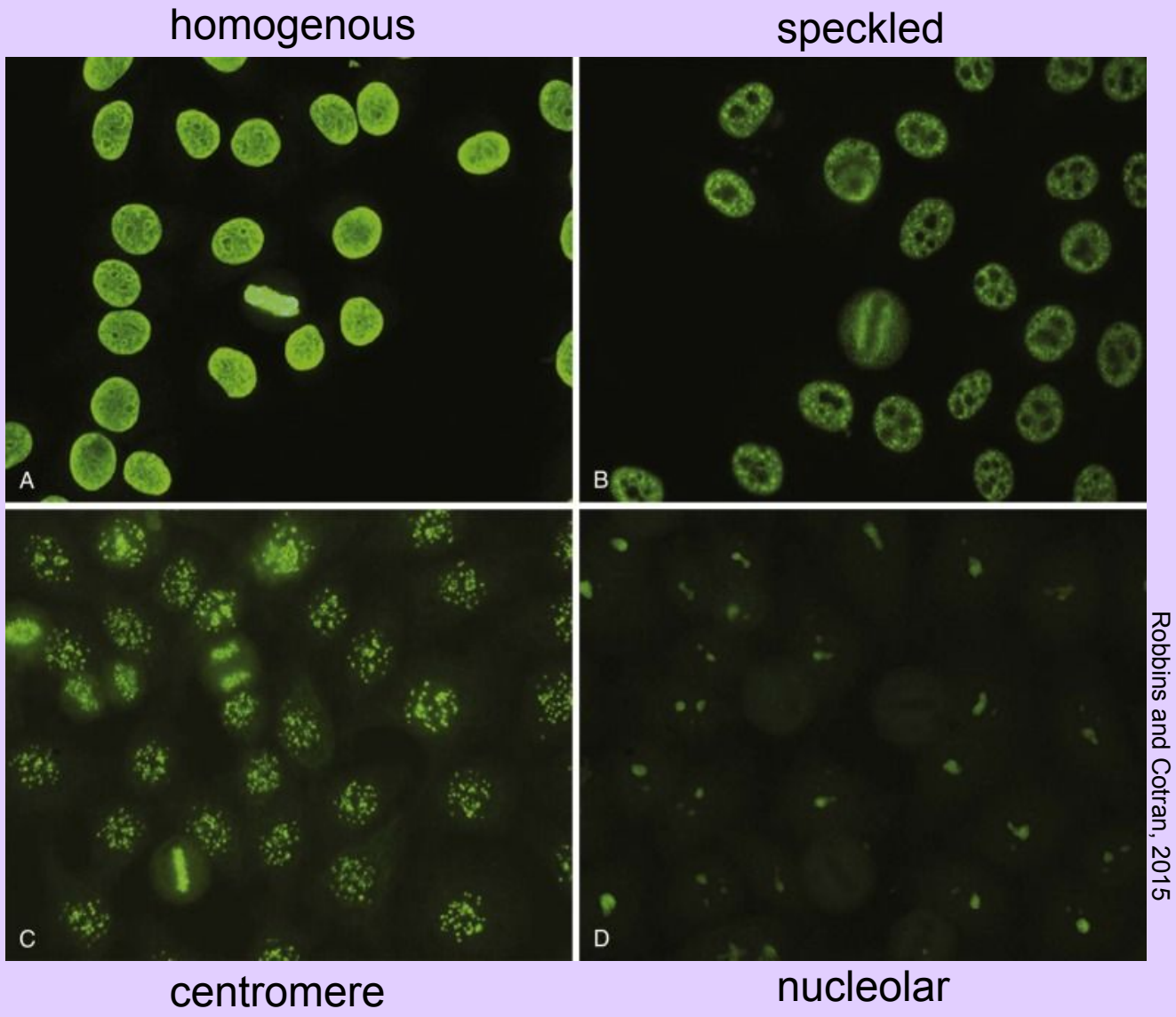
If absent, do not classify as SLE

If present, apply additive criteria

- You must have a +ANA to have lupus!
- At 1:80, ANA sensitivity is 97.8%, but specificity only 74.7%

Antinuclear Antibody

- An auto-antibody to something in the nucleus of your cells
  - There are a lot of things in the nucleus
- How is it reported:
  - Titer: serial dilutions
  - Pattern: how it looks under IFA
    - Nuclear dense fine speckled (DFS70) = normal variant



The ANA: helpful sometimes but not always

- It is very non-specific!
- Lab marks 1:40 as positive result, but this is clinically negative
- Can be positive:
  - Elderly
  - 1st degree relatives with lupus
  - Infections
  - Malignancy
  - Liver disease
- Overall prevalence has increased in the past 20 years

ANA titer in the healthy general population

Clinically significant ANA titer are > or ≥1:80*, often more

Percentage of the general population with ANA+

Titer	1:10 – 1:40	1:80 – 1:160	≥1:320
% positivity	32 %	13 %	3 %

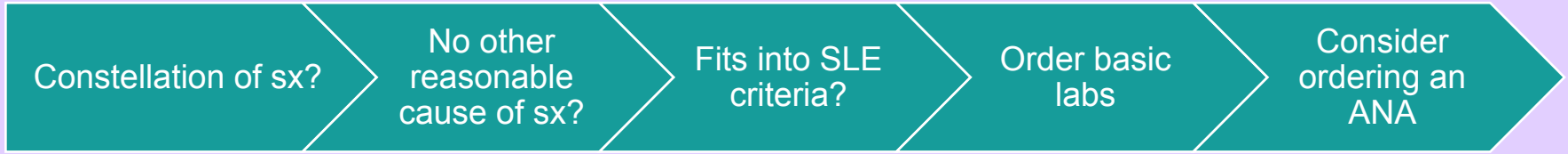
Age	<59yo	60-69y	70-79y	80-89y	>90y
% pos	3%	10%	12%	12%	20%

*There is a bit of debate about what is a clinically meaningful threshold. For me, it's typically ≥1/160

Tan et al., « ANA in healthy individuals » Arthritis Rheum. 1997

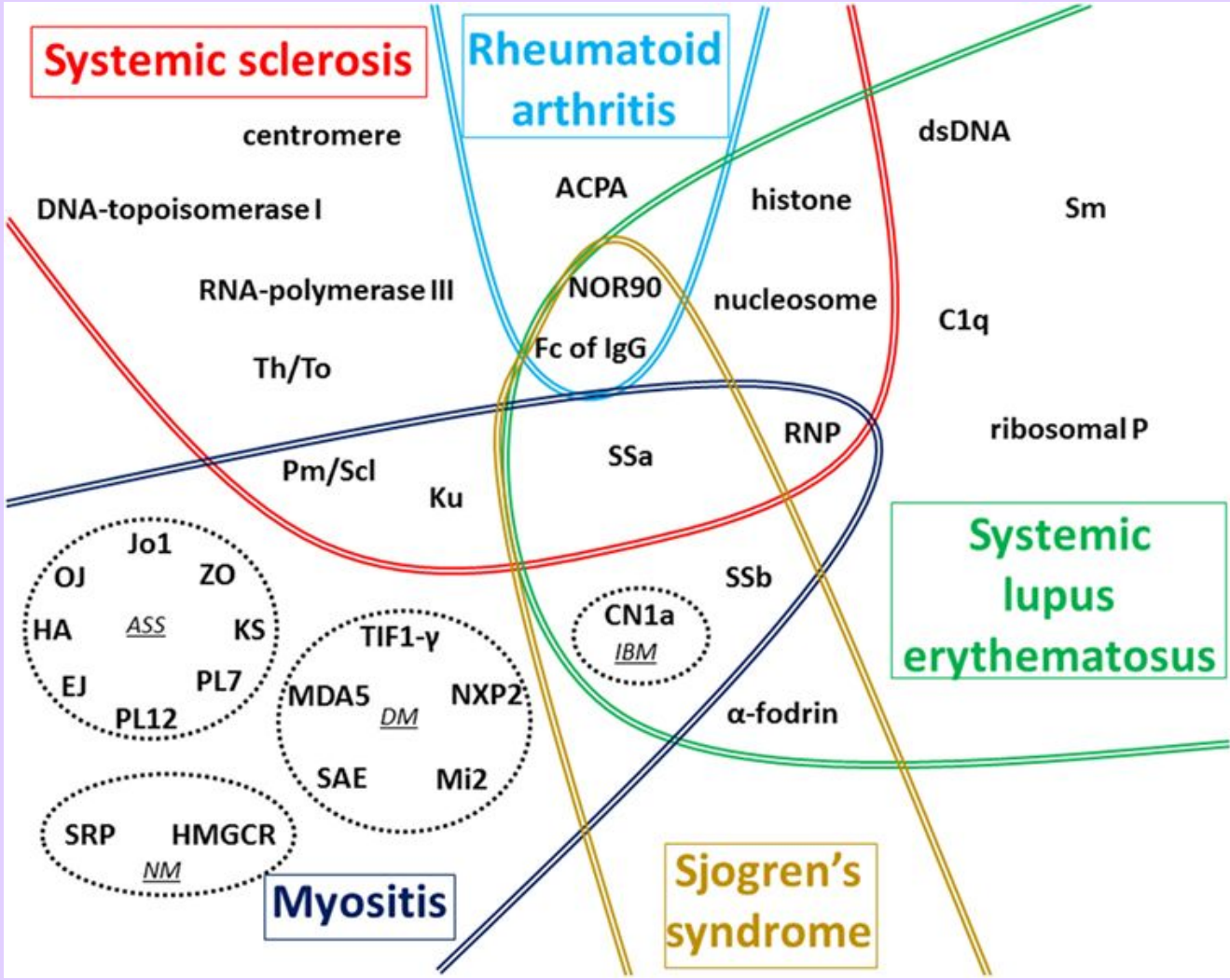
Don't rely on the ANA

- Often ordered without the right clinical context
- Do NOT need to trend it (just need a + value once)
- A lot of discordance between solid phase assays and Hep-2 IIF assays
- If ordered in populations with LOW pretest probability, the positive predictive value of a positive ANA for diagnosing SLE is as low as **2%**!!!



Extractable nuclear antigens (ENAs)

- More specific antibodies associated with different systemic autoimmune diseases
- Identifies SPECIFIC antigen in the nucleus you are making the antibody to:
  - anti dsDNA
  - anti Smith, anti-RNP
  - anti SS-A = Ro, anti SS-B = La
  - anti Scl-70 = anti-topoisomerase-I



Lupus specific labs

- C3/C4 **decrease** in active SLE
- DsDNA **increases** in active SLE
- No need to repeat Smith, ANA etc.
  - Do not fluctuate with disease activity
- 1/3 SLE patients have secondary antiphospholipid antibodies
- **Only** order lupus specific labs if your ANA is positive **AND** you have clinical suspicion

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

ANA assays and panels

- **Three platforms, one test name**
- **HEp-2 indirect immunofluorescence (IIF)** — historical reference method; reports titer + pattern; whole-cell substrate detects a broad antigen range [8]
- **Solid-phase assays (SPA)** — ELISA/FEIA/CLIA; a defined mix of ~10–17 recombinant antigens; reports a numeric unit, no pattern [8-9]
- **Multiplex bead (MBA)** — e.g., BioPlex ANA Screen; simultaneously reports individual specificities (dsDNA, Sm, RNP, SSA/SSB, Scl-70, centromere) [10]
- IIF = better rule-out. SPA/multiplex = better rule-in.
- IIF performs best when pretest probability is **high**; solid-phase assays are more useful when pretest probability is **low**
- Across three IIF kits in established SLE, ANA-negative rates ranged **4.9%–22.3%**; ELISA 11.7%, multiplex 13.6% [9]
- In one retrospective series, **47% of BioPlex-negative samples were IIF-positive**, and **55% of BioPlex-positive samples were IIF-negative**
-

A 29-year-old woman presents to your clinic for recurrent rash she thinks is an allergy. Rash develops when she is outside on sun-exposed areas.

She also mentions intermittent hives that don't improve much with antihistamines.

She often feels like she has the flu. She also reports joint stiffness in the mornings lasting an hour, painless mouth ulcers, and increased hair shedding over the past several months.

Should you order an ANA?

YES

A 45-year-old woman is referred to your allergy clinic for chronic rhinitis. She also complains of headaches, non-photosensitive rashes, and feels cold all the time.

She complains of "pain all over" for the past 3 years, she feels her body is puffy but no joint swelling. She reports fatigue and poor sleep.

Her maternal grandma has lupus.

Should you order an ANA?

NO

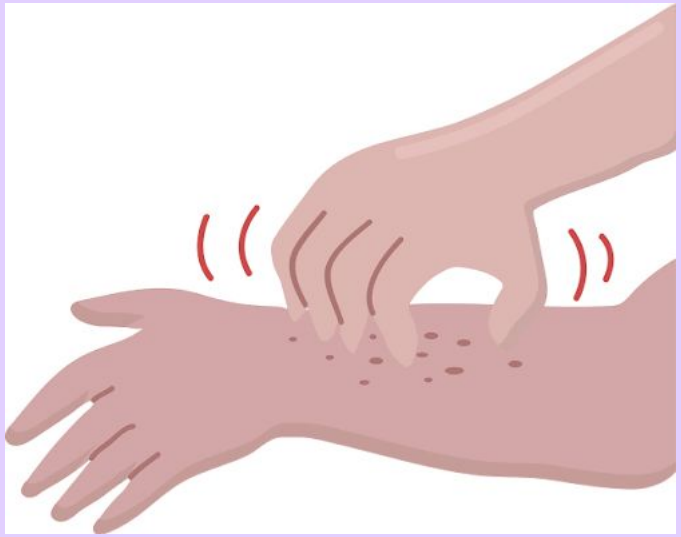
Drug-Induced Lupus (DILE)

- Usually mild presentation with malaise, fever, arthritis and rash
- Positive ANA and anti-histone Abs
- Symptoms usually resolve after discontinuing med
- Kidney and CNS disease are uncommon
- At no higher risk of SLE
- No absolute contraindication in SLE patients to use these meds
- Drug induced SCLE (HCTZ, terbinafine, PPIs, CCBs)

- Procainamide
- Hydralazine
- Minocycline
- Antithyroid Drugs
- Statins
- Calcium Channel blockers
- Thiazides
- ACE inhibitors
- TNF-alpha inhibitors

Allergy symptoms in Lupus patients

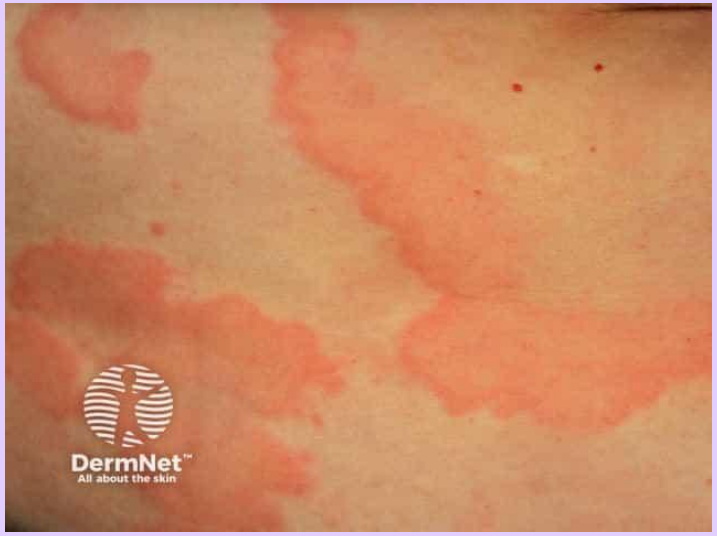
- **Pruritus**
  - Affecting 77% of patients with CLE
  - Persistent or refractory
  - Scarring



- **Angioedema**
  - Lupus associated is often bradykinin-mediated due to complement dysregulation
  - SLE patients are younger, female and African-American and get more severe disease
  - Estimated to occur in 15-30% of SLE patients
  - Don't respond to antihistamines

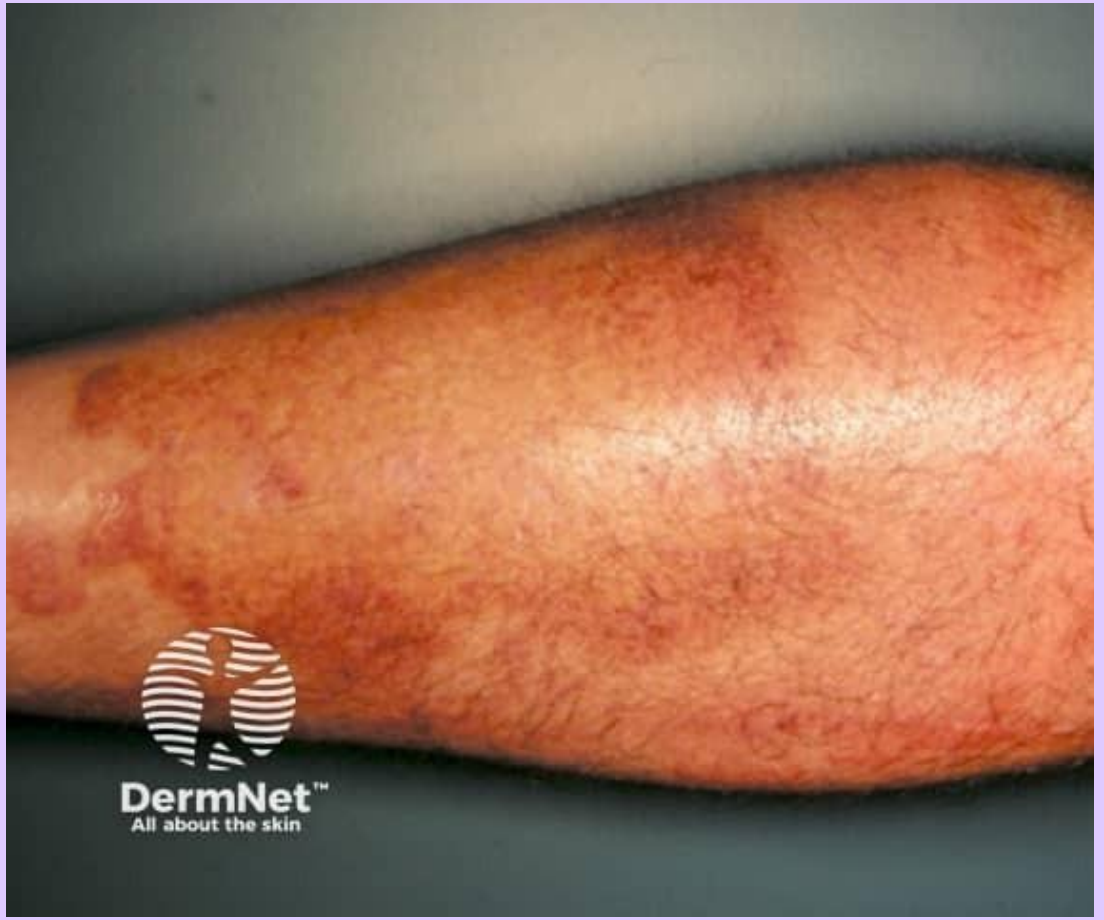
Allergy symptoms in Lupus patients

- **Chronic spontaneous urticaria (CSU)**
  - Can be autoimmune in a subset of patients
  - 10-28% of patients with CSU have an additional autoimmune disease
    - Hashimoto’s thyroiditis, RA, Sjogren's, celiac, T1 DM, SLE
  - Increased risk of developing autoimmune disease commonly in 1st 10 years after diagnosis.
  - Patients with chronic urticaria have approximately twice the risk of developing SLE
  - Urticaria is not a classic lupus manifestation itself, but both conditions may arise from shared immune dysregulation

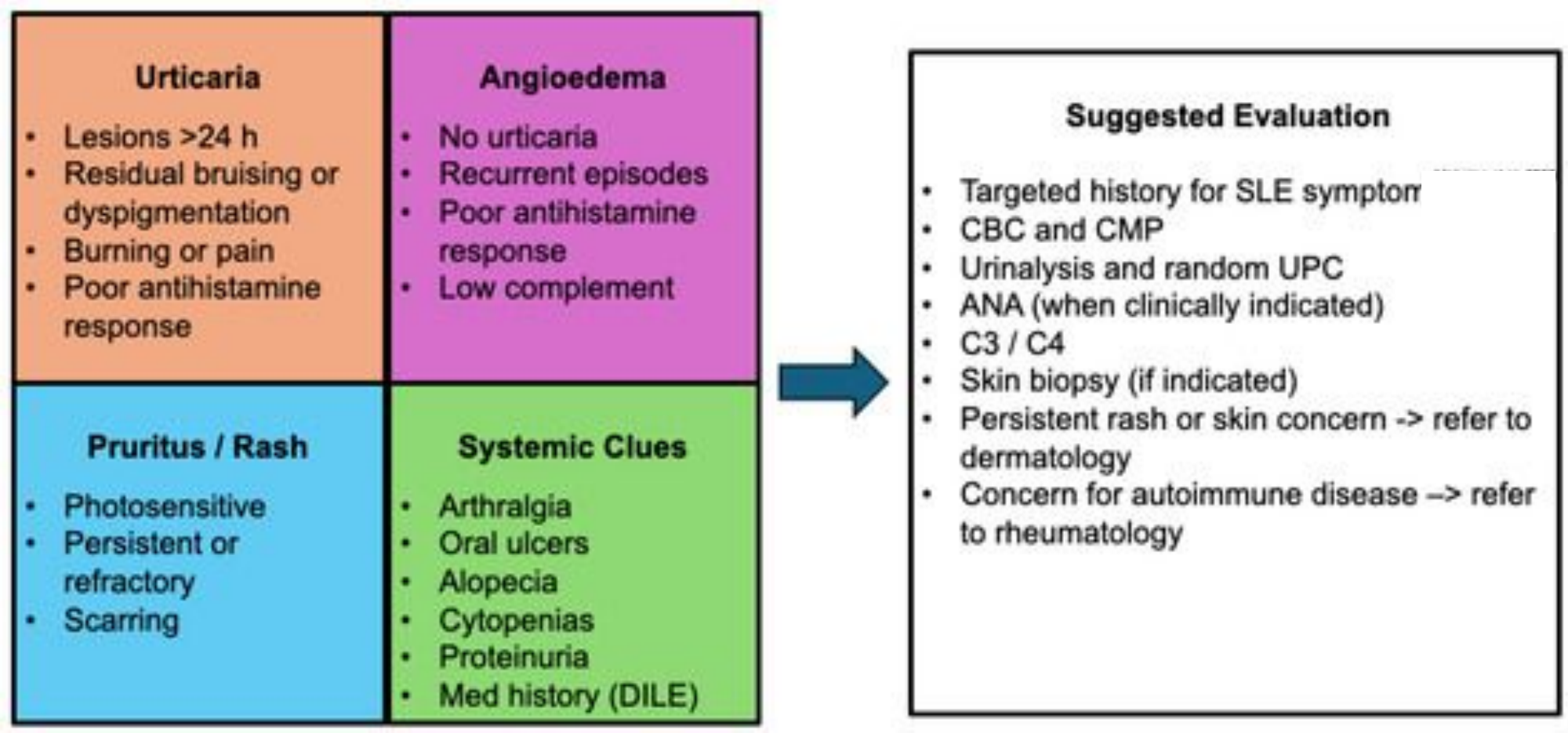


Allergy symptoms in Lupus patients

- **Urticarial Vasculitis**
  - Urticarial Lesions that last >24h with residual bruising or dyspigmentation,
  - Often have burning/pain and poor antihistamine response
  - Normocomplementemic UV – skin limited
  - Hypocomplementemic UV is more severe with arthralgias, uveitis, glomerulonephritis, abdominal pain and obstructive lung disease
    - Strongly associated with SLE
    - +anti-C1q antibodies
  - Need skin biopsy for diagnosis within 24-48h of lesion onset.



Practical workup



Patel V, Allergy 2026

Take aways

- Clinical symptoms should drive your suspicion for lupus.
- The ANA is a tool to support your clinical suspicion, not create it.
- Think beyond allergy when symptoms don't fit the expected pattern.
- When in doubt, basic labs can help guide the next step.

Thank you!

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