Systemic Lupus Erythematosus

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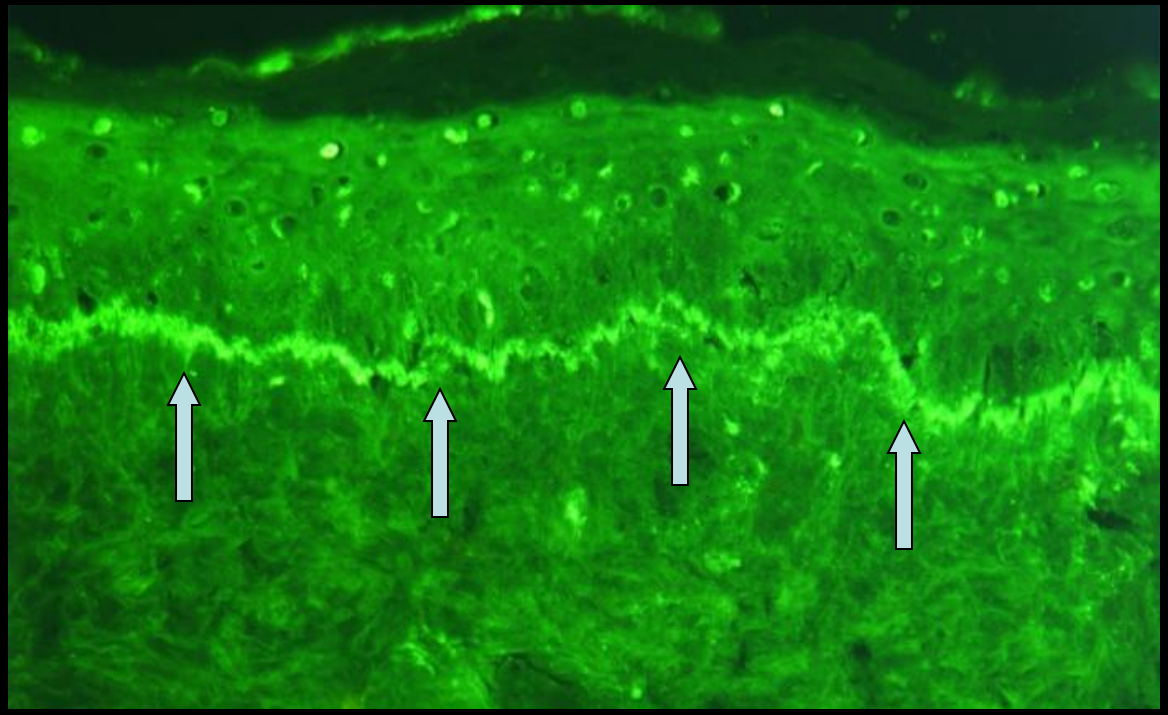
Disclosures

None.

Learning Objectives

1. Understand that SLE is a disease of immune complexes involving autoantibodies.
2. Consider how clinical and laboratory manifestations of SLE are used for classification and diagnosis, including analysis of a patient case.
3. Review the available medications used to manage SLE and their potential indications for use.
4. Identify primary care issues of unique importance to the management of SLE patients.

Lupus band test



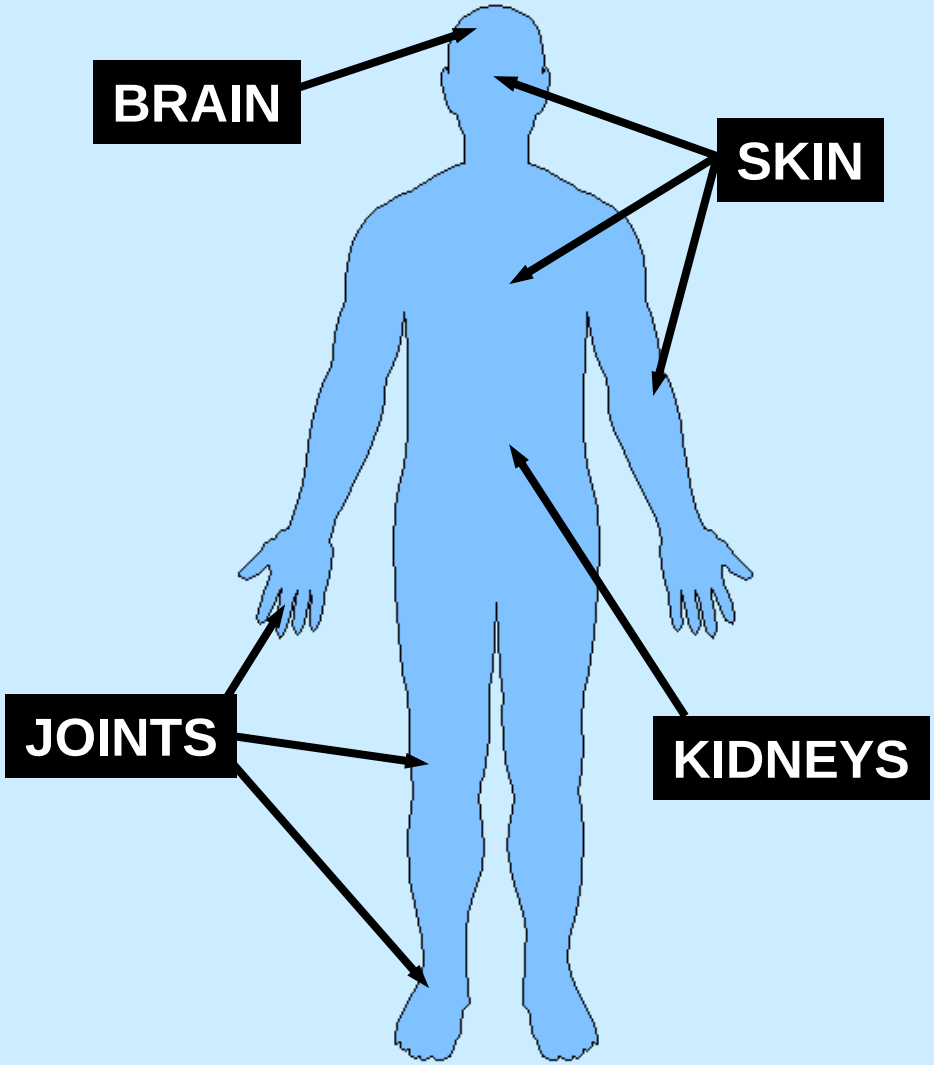
IgG deposition (immune complexes) along the basement membrane in affected skin → complement activation.

SLE: Thinking immunologically

SLE = Prototypical immune complex disease

- **Type III hypersensitivity reaction**
  - Immune complexes (ICs) deposit in skin, renal glomerulus, blood vessels.
  - Complement activation by ICs.
- Antigens in ICs are **nuclear antigens** derived from apoptotic/necrotic cells.
- **Interferon-α** + other cytokines and chemokines are produced.

Systemic Lupus Erythematosus (SLE)



Clinical Manifestations

- Rash / Sun sensitivity
- Arthralgia / Arthritis
- Serositis
- Nephritis
- Neuropsychiatric
- Blood clots
- Pregnancy loss
- Recurrent miscarriage
- Fatigue, fever, etc.

SLE: Classification criteria

1997: Original American College of Rheumatology Criteria

2012: SLICC Criteria

2019: EULAR/ACR Criteria

- Adds a “scoring” system, positive ANA is an entry criterion.

The 2012 and 2019 classification systems aimed to improve upon the sensitivity and specificity for SLE diagnosis from the system devised before it. We still generally use the 2012 criteria clinically.

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

http://www.rheumtutor.com/2012-slicc-sle-criteria/

Petri M, et al. Arthritis and Rheumatism. Aug 2012

EULAR/ACR Criteria – 2019

(point scoring system)

Classification Criteria (*Ann Rheum Dis* 2019;78:1151) for *research/classification* not dx

Required criteria: **ANA titer ≥1:80** AND **≥10** points (at least one clinical):

Clinical domains (points*) *only one entity per domain can be scored

Renal • proteinuria >0.5 g/d (4) • class II or V nephritis (8) • class III or IV nephritis (10)	**Hematologic** • leukopenia (3) • thrombocytopenia (4) • autoimm. hemolytic anemia (4)	**Neuropsychiatric** • delirium (2) • psychosis (3) • seizure (5)
Mucocutaneous • non-sclarring alopecia (2) • oral ulcers (2) • discoid lupus (4); subacute (4) or acute (6) cutan. lupus	**Serosal** • pleural/pericardial effusion (5) • acute pericarditis (6)	**Musculoskeletal** • joint involvement (6) **Constitutional** • fever (2)

Immunology domains (points*)

Antiphospholipid antibodies • anti-CL, anti-B2GP1, or a lupus anticoagulant (2)	**Complement proteins** • low C3 or C4 (3) • low C3 and C4 (4)	**SLE-specific Abs** • anti-dsDNA or anti-Smith (6)

Pocket Medicine (8th ed.), in press.

Building a Case for SLE

Mucocutaneous

Things that Hurt

Organs Gone Awry

Cytopenias

Autoantibodies

Immunology in Action

Building a Case for SLE

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia

Things that Hurt

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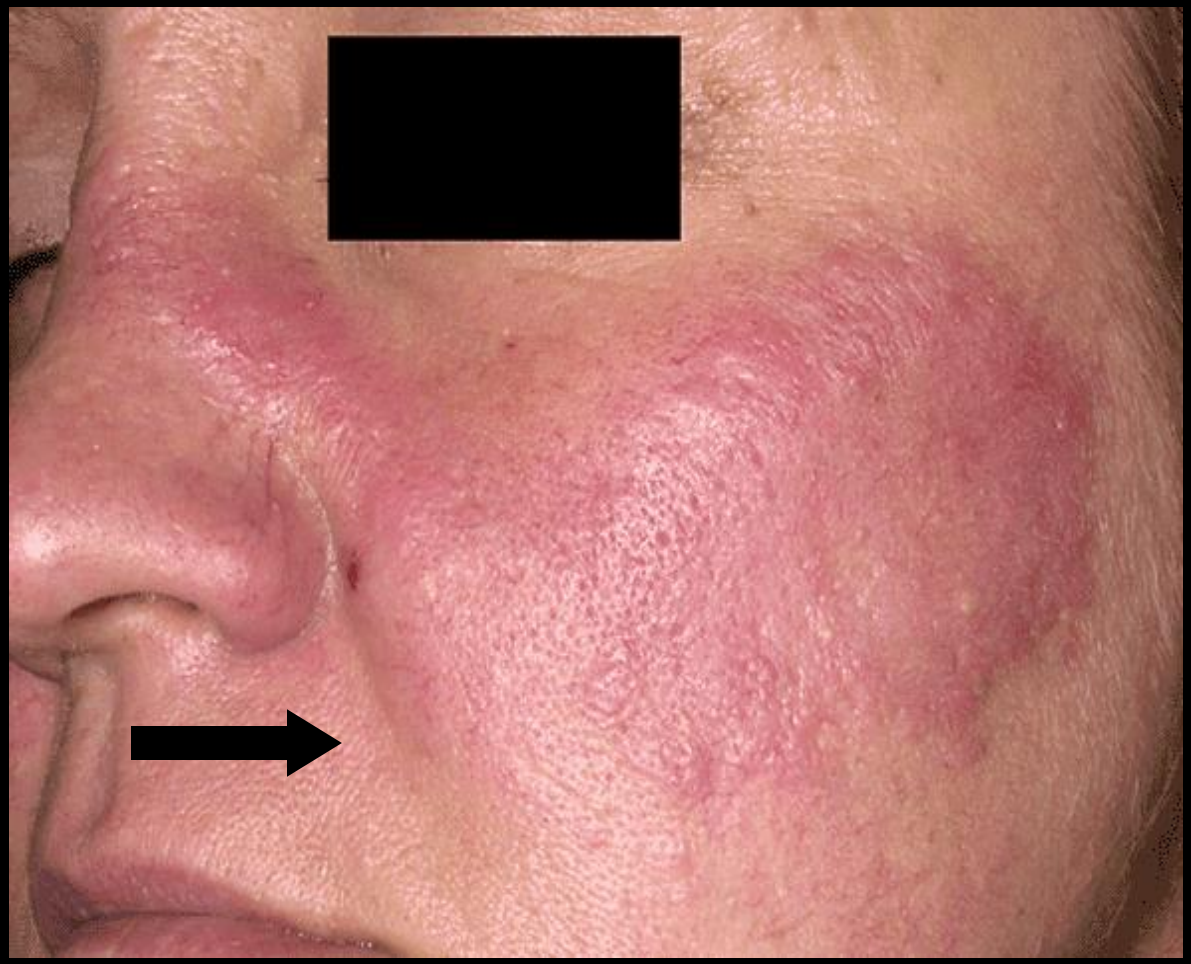
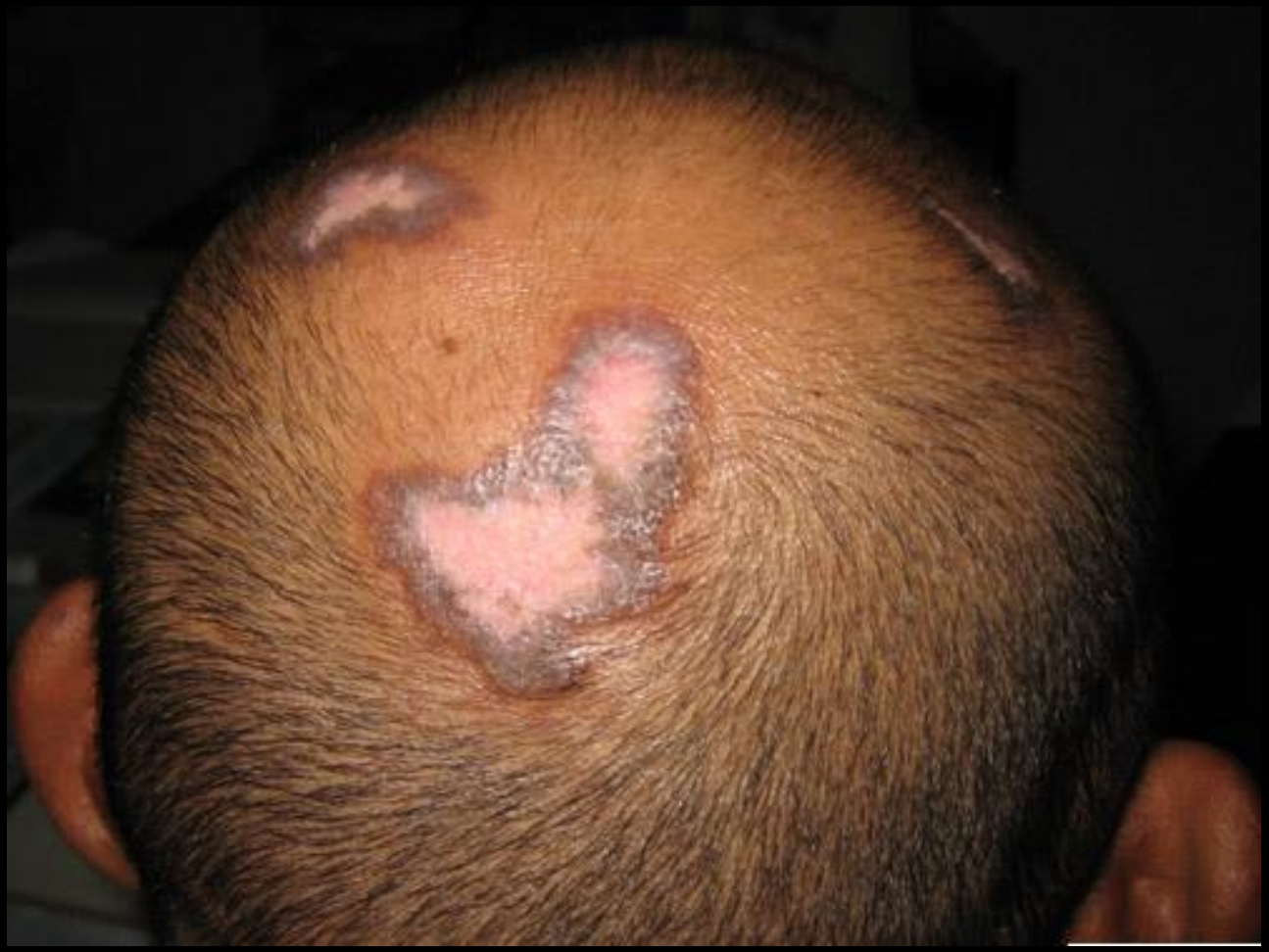
Immunology in Action

Malar Rash

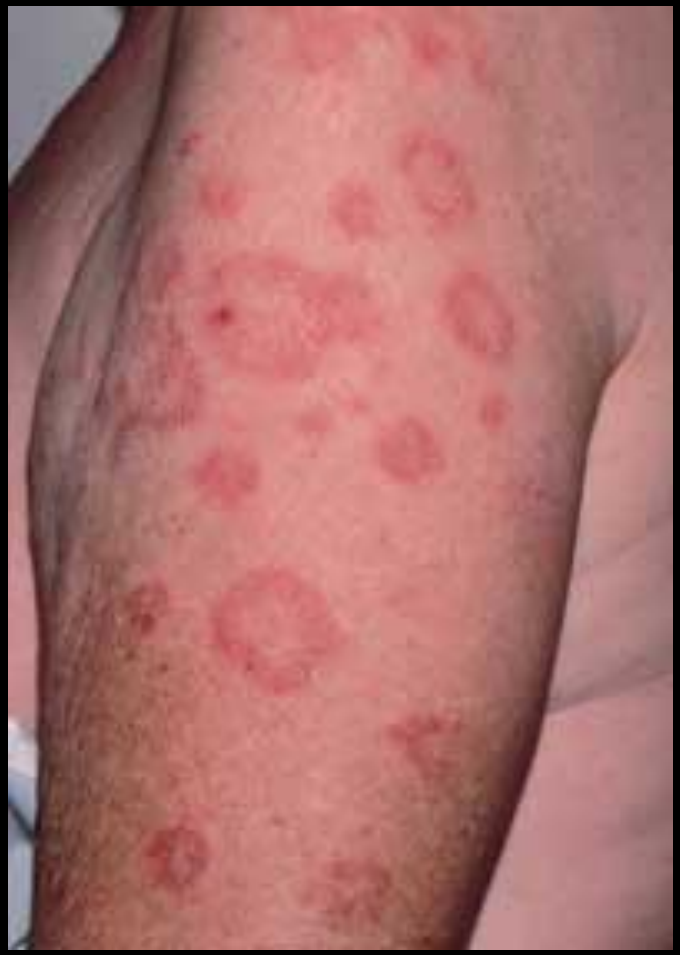


Spares the nasolabial fold

Discoid lupus

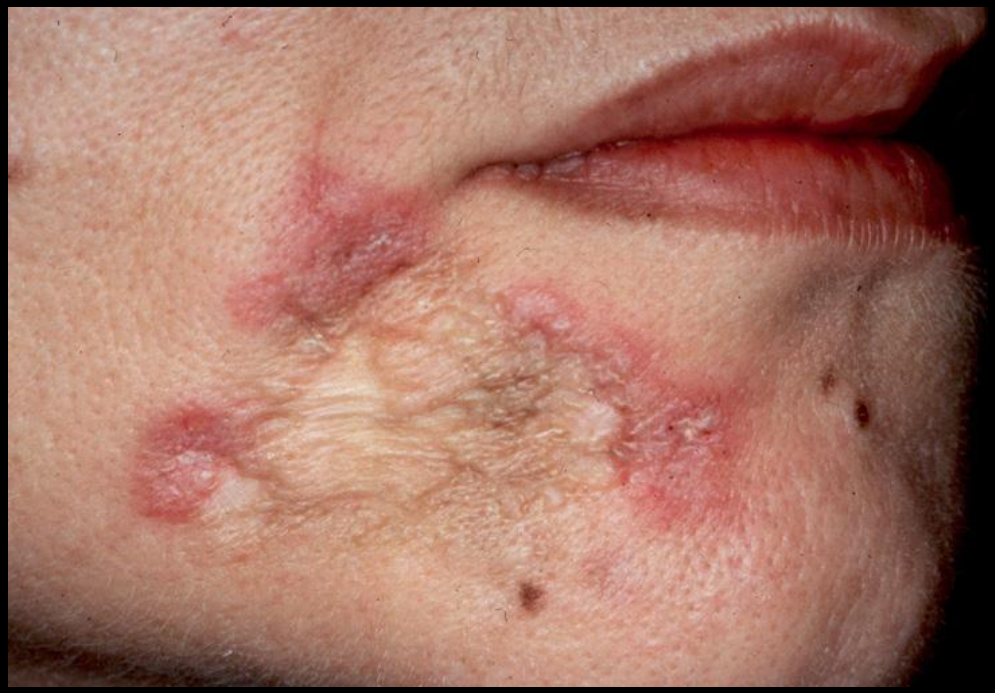


SCLE



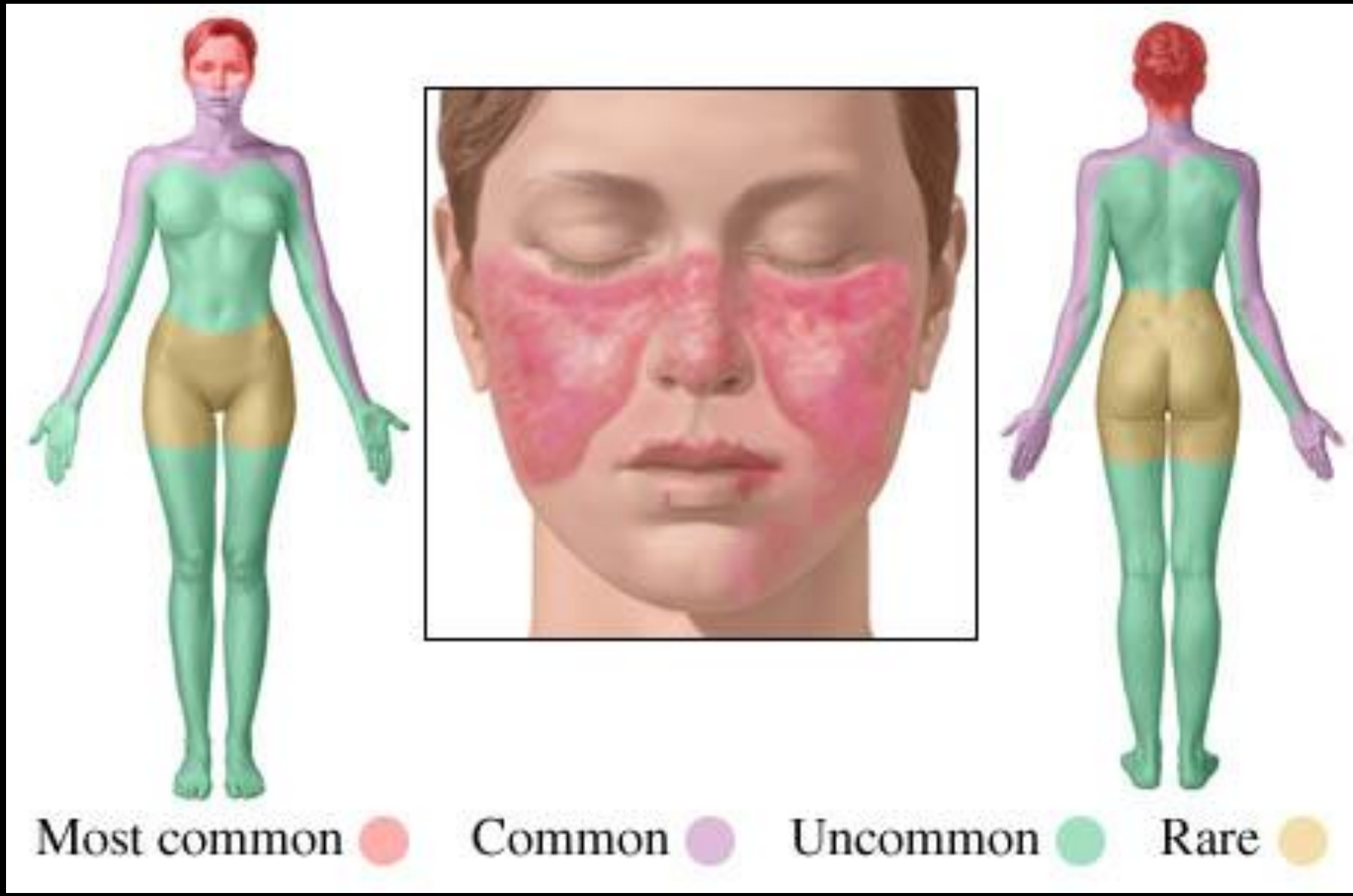
Non-scarring

Discoid lupus

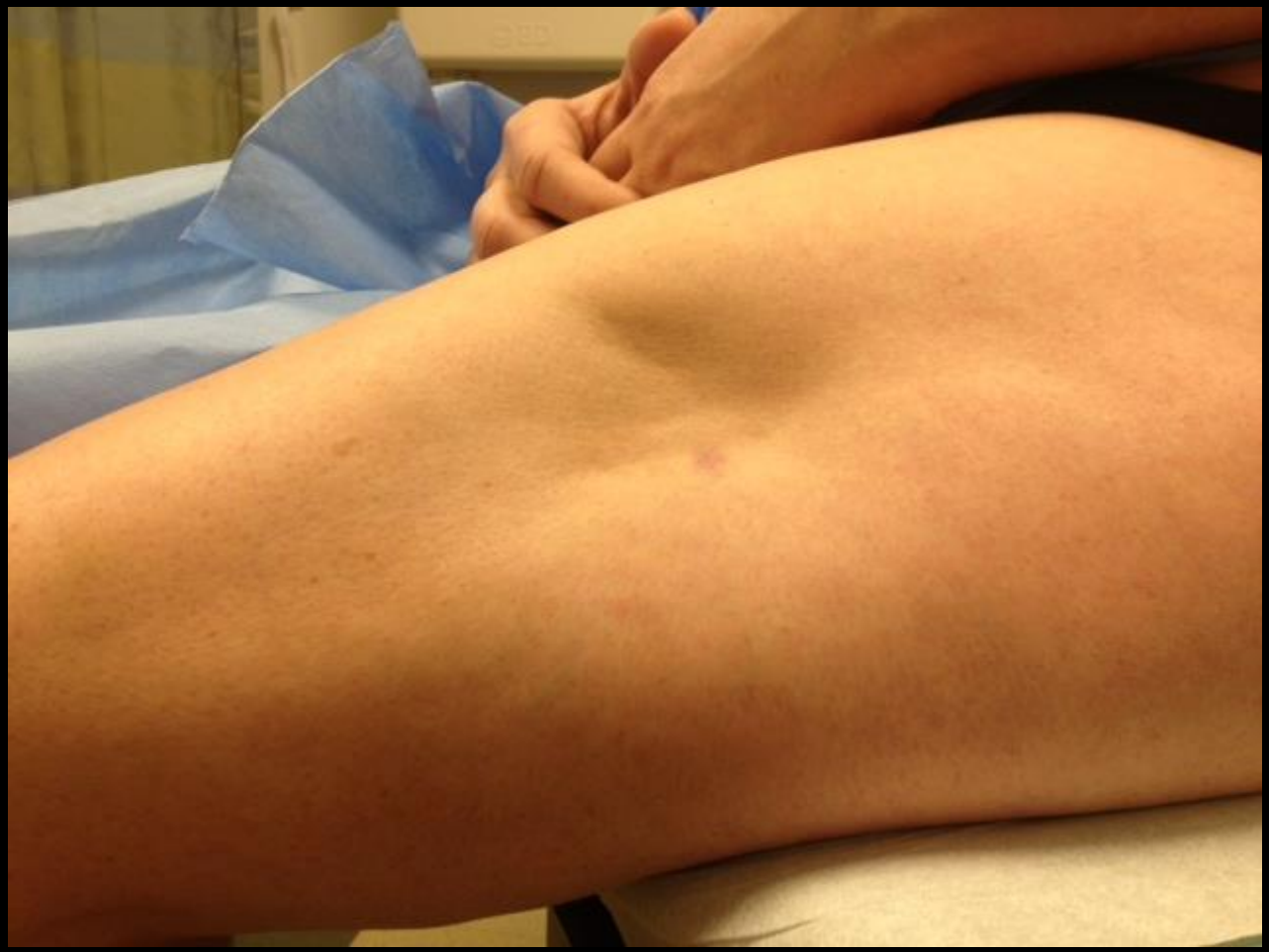


Scarring

Rashes of SLE are typically photodistributed



Lupus profundus (panniculitis)



Types of cutaneous lupus

Acute cutaneous lupus:

- Lupus malar rash
- Bullous lupus
- Toxic epidermal necrolysis variant
- Maculopapular lupus rash
- Photosensitive lupus rash

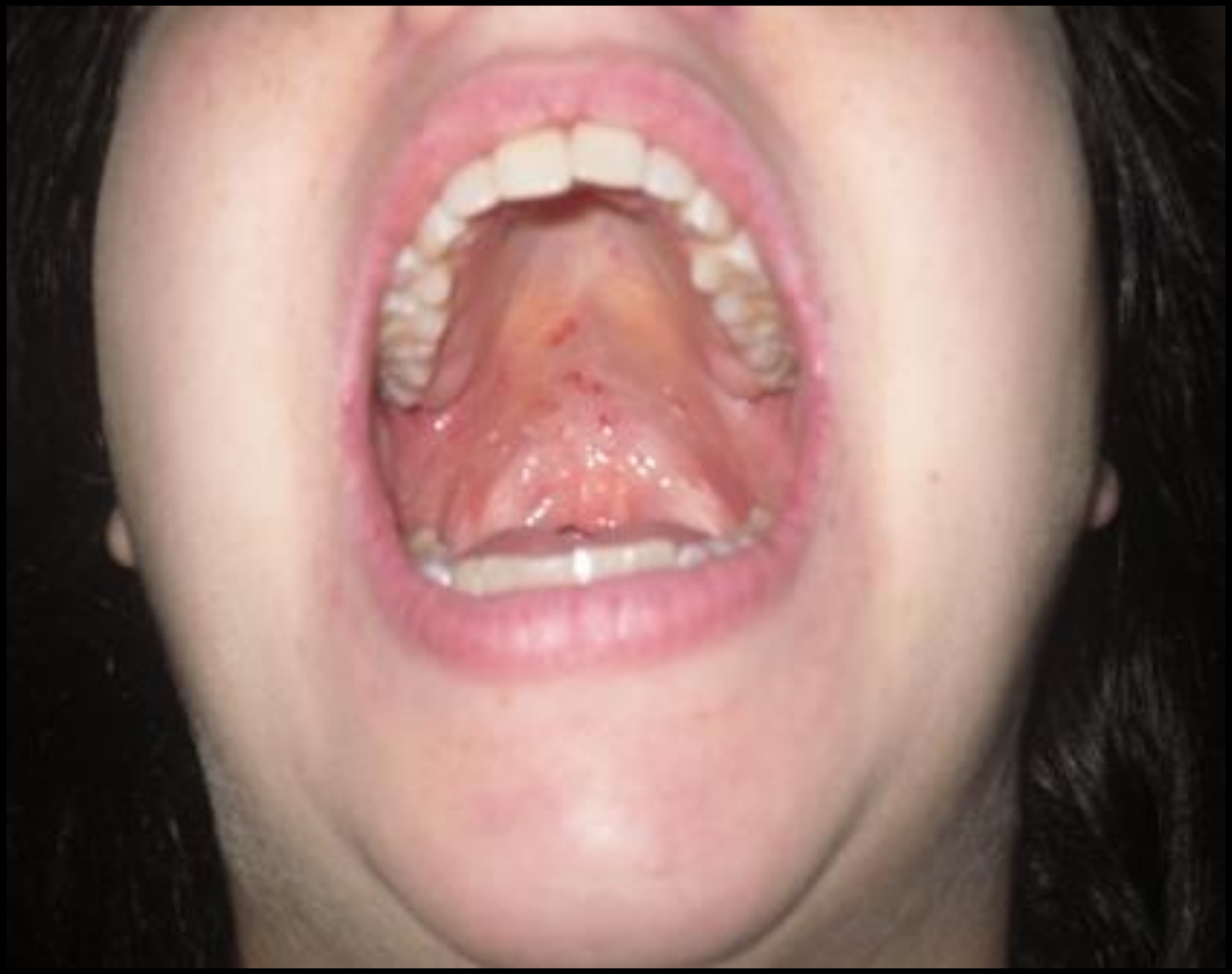
Subacute cutaneous lupus

- Nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring.

Chronic cutaneous lupus:

- Classic discoid rash
  - Localized (above the neck)
  - Generalized (above+below the neck)
- Hypertrophic (verrucous) lupus
- Lupus panniculitis (Profundis)
- Mucosal lupus
- Lupus erythematosus tumidus
- Chilblains lupus
- Discoid lupus/lichen planus overlap

Mucosal ulcers



Building a Case for SLE

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Arthritis
6. Serositis

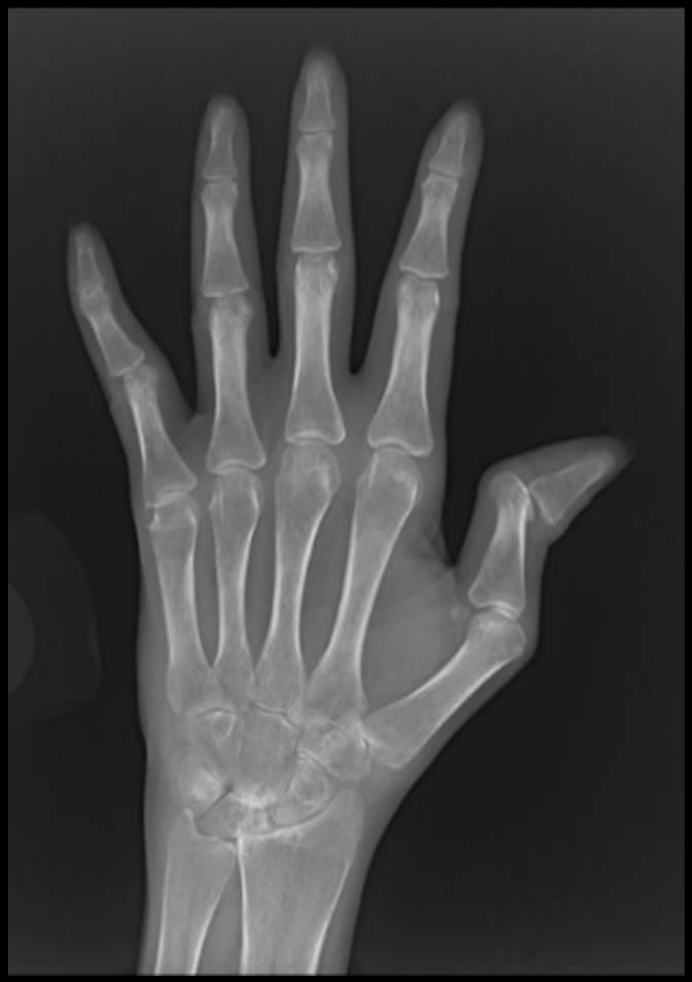
Organs Gone Awry

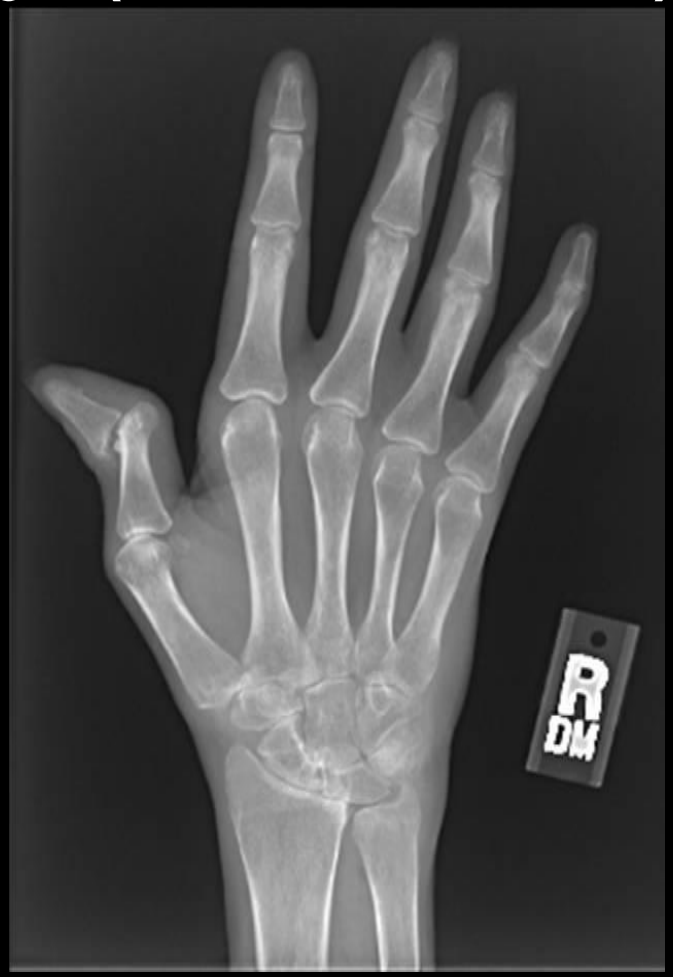
Cytopenias

Autoantibodies

Immunology in Action

Lupus arthropathy (Jaccoud's)





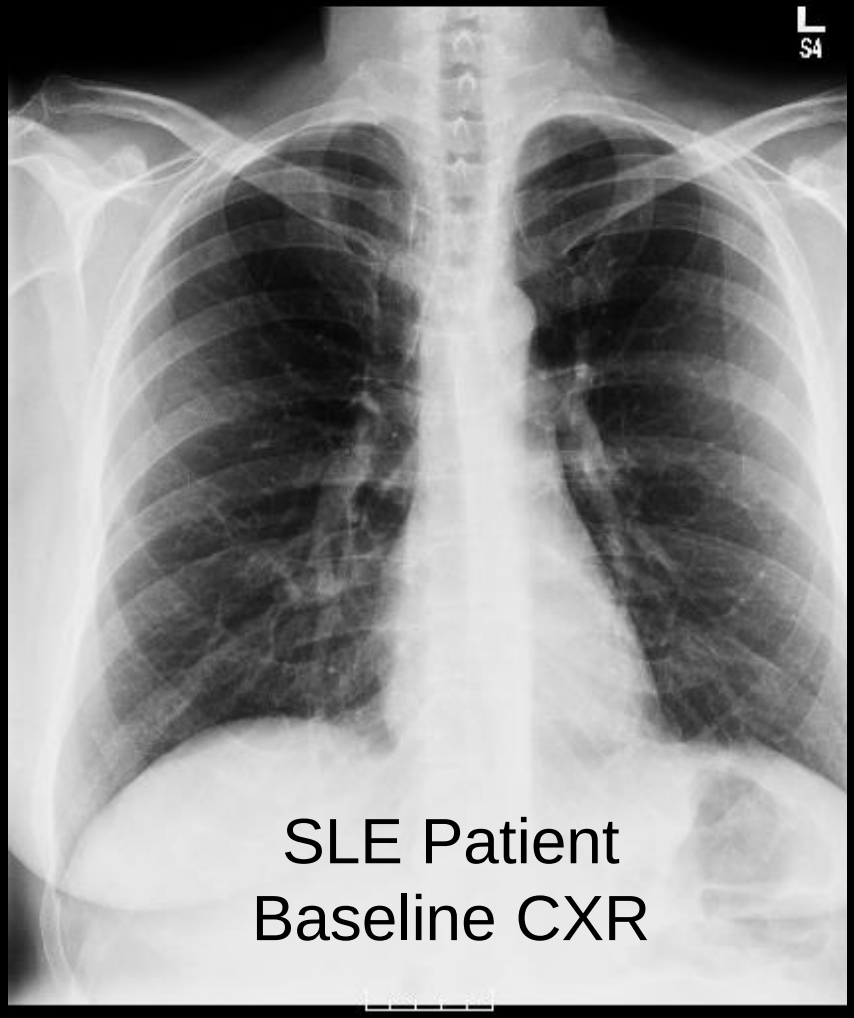
Diffuse osteopenia. Joint space loss in wrists. Ulnar deviation. Thumb IP joints subluxed. NO joint erosions.

SLE Arthropathy: Take Home Points

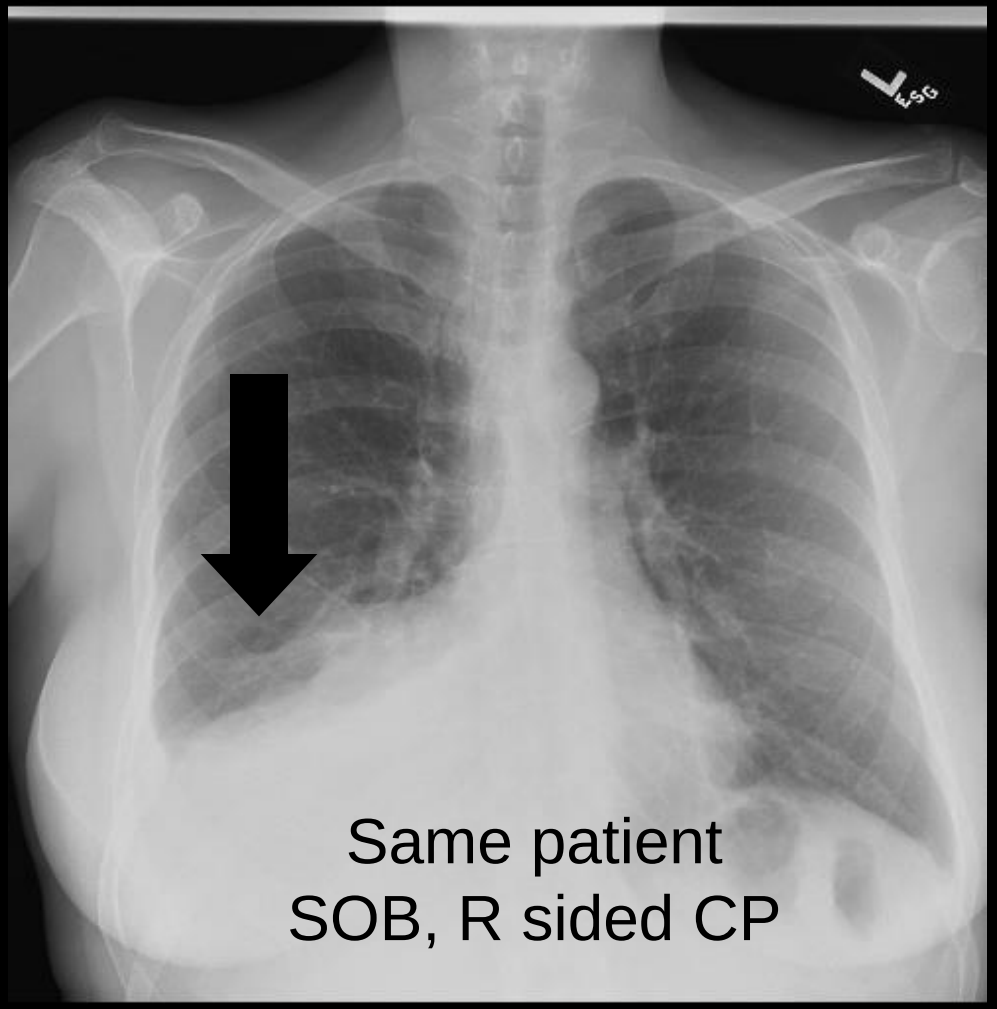
Arthropathy: up to 95% of SLE patients.

- Symmetrical, polyarticular usu. involves knees, wrists, PIPs.
- Non-erosive, migratory, may resolve in a given joint in <24h.
- Lax joint capsules, tendons, ligaments = reducible deformity.
- Often pain >> physical findings.

Pleuritis

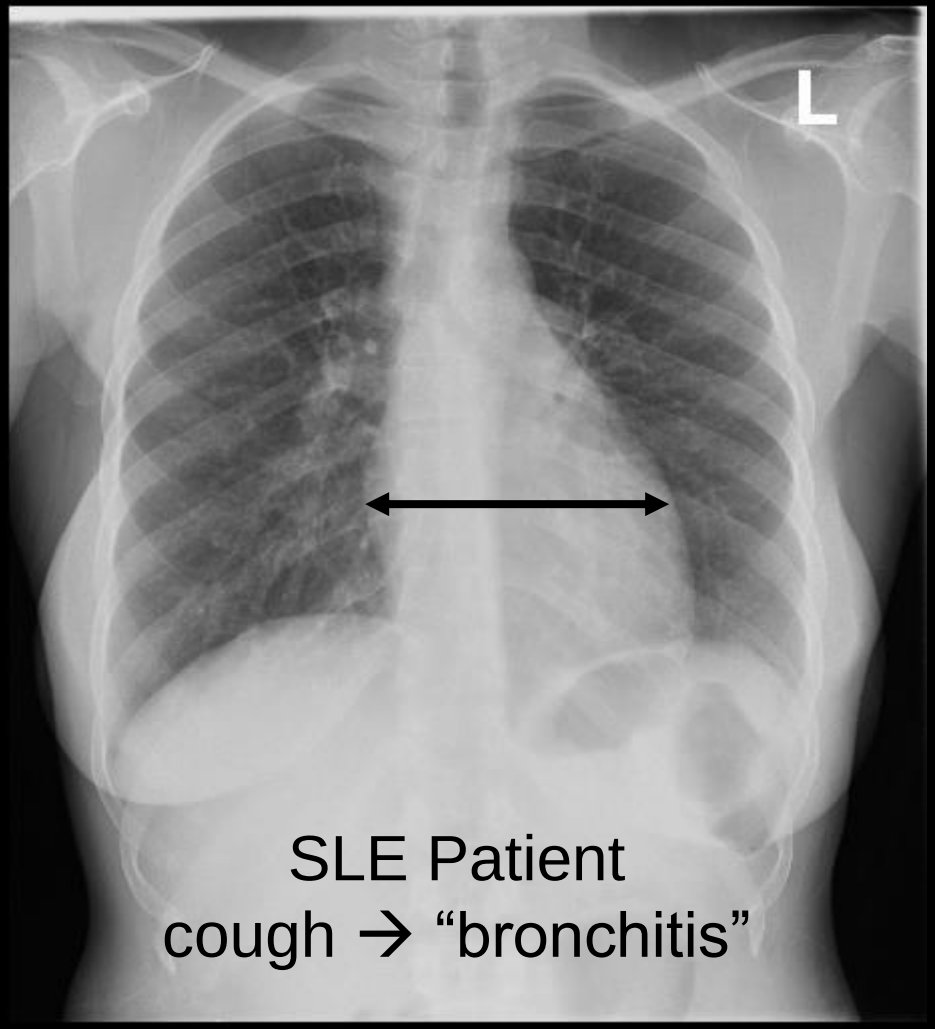


SLE Patient
Baseline CXR

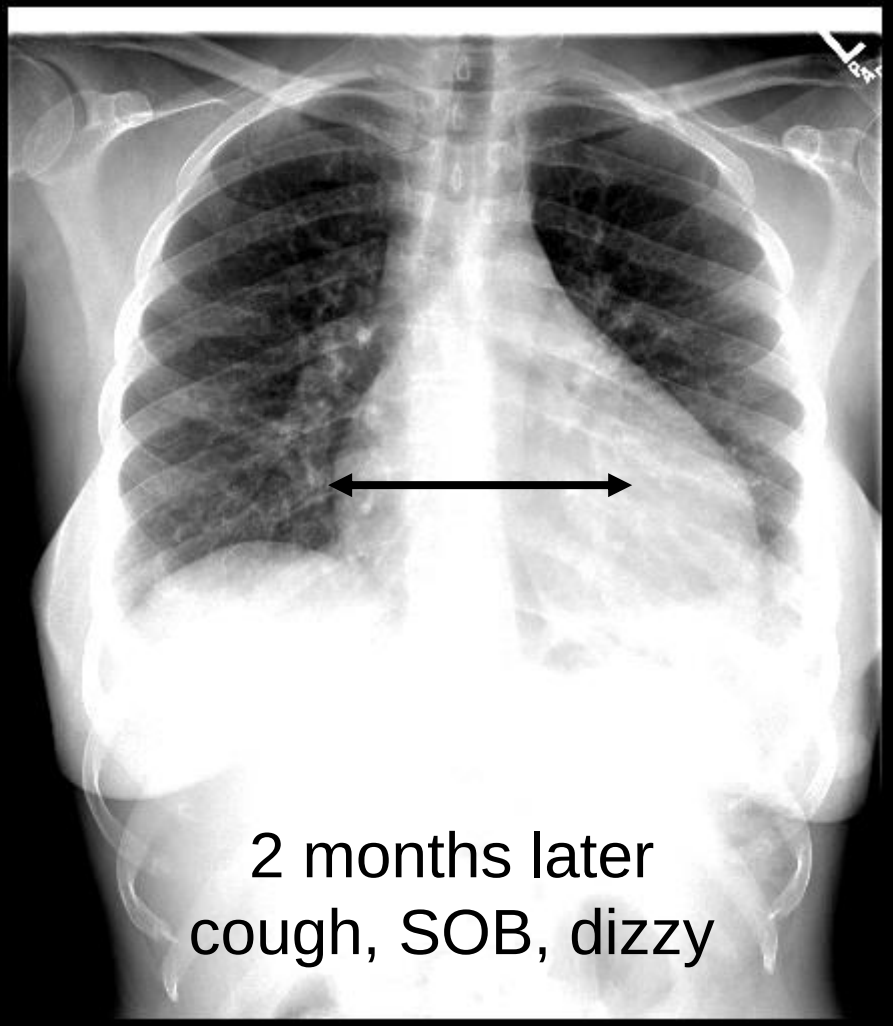


Same patient
SOB, R sided CP

Pericarditis/Myopericarditis



SLE Patient
cough → “bronchitis”



2 months later
cough, SOB, dizzy

Building a Case for SLE

1. Acute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral or nasal ulcers
4. Non-scarring alopecia
5. Arthritis
6. Serositis
7. Renal
8. Neurologic

Autoantibodies

Immunology in Action

Cytopenias

Lupus Nephritis

BIOPSY

BIOPSY

BIOPSY

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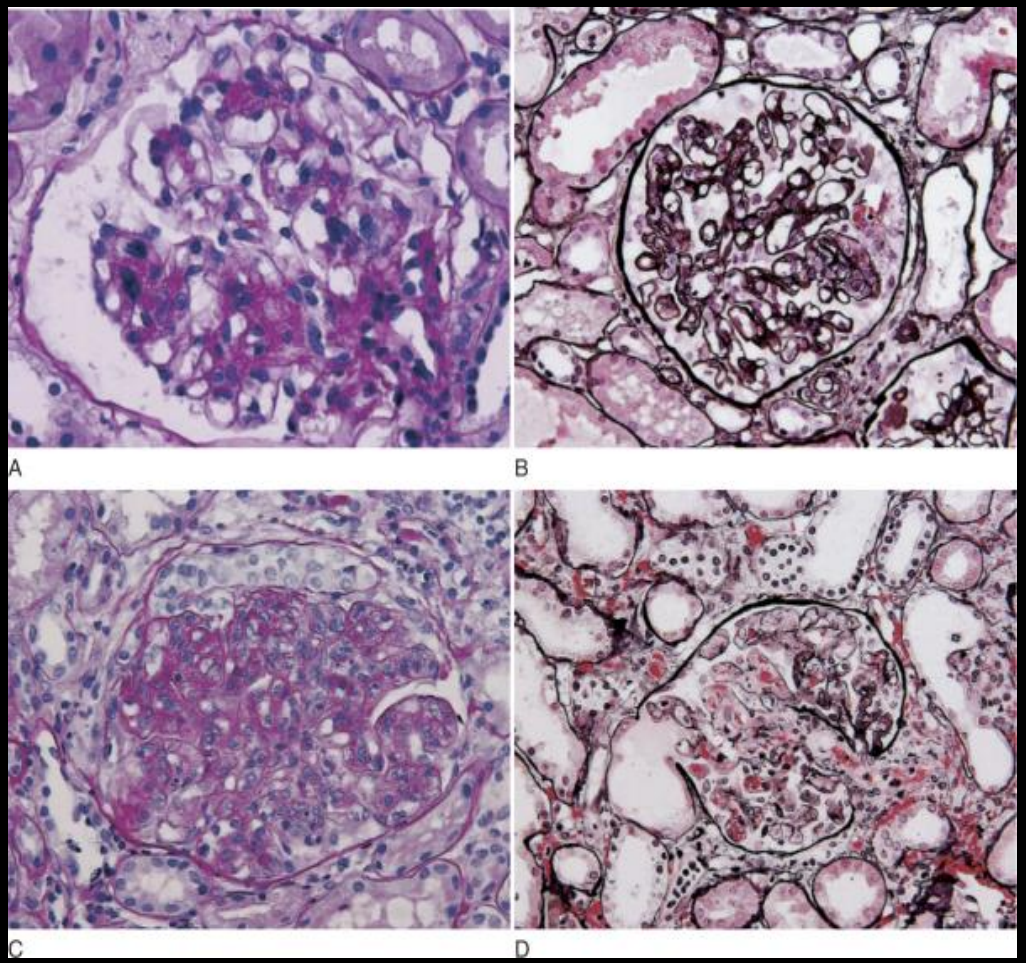

BIOPSY

BIOPSY

BIOPSY

BIOPSY

BIOPSY

BIOPSY

SLE Renal Disease: Take Home Points

Renal: consider all pts at risk -- at all times. (~75% in some form)

- Urinalysis:
  - TWICE yearly without h/o nephritis (asymptomatic)
  - QUARTERLY with h/o nephritis (in remission)

- Biopsy necessary to determine LN Class and, therefore, treatment.

- Class III & IV most aggressive forms, elevate creatinine and BP.

Neuropsychiatric SLE**

Central nervous system

1. Headache
2. Seizures
3. Cerebrovascular disease
4. Demyelinating syndrome
5. Myelopathy
6. Movement disorder
7. Aseptic meningitis
8. Cognitive dysfunction
9. Mood disorder
10. Anxiety disorder
11. Psychosis
12. Acute confusional state

Peripheral nervous system

1. Mononeuropathy
2. Polyneuropathy
3. Cranial neuropathy
4. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
5. Plexopathy
6. Autonomic disorder
7. Myasthenia gravis

****Based on 1999 American College of Rheumatology recommendations.**

Neuropsychiatric SLE

2,049 SLE patients, 56% had NPSLE manifestations.

- 90% purely CNS disease
  - Headache (28%)
  - Mood disorders (21%)
  - Cognitive dysfunction (20%)
  - Seizures (10%)
  - Cerebrovascular disease (8%)

Blood-brain barrier disruption is necessary for NPSLE to occur.

Rarely is NPSLE an isolated manifestation of SLE.

Possible Mechanisms

- Antibody-mediated neurotoxicity
  - Anti-ribosomal P
  - Anti-dsDNA
  - Anti-GABA
- Vasculopathy
  - Antiphospholipid antibodies
  - Other vascular injury
- Cytokine-induced neurotoxicity
- Loss of neuroplasticity

Kivity et al. BMC Medicine (2015) 13:43

Building a Case for SLE

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Immunology in Action

Cytopenias

Hemolytic anemia

Leukopenia (<4000/mm3) or Lymphopenia (<1000/mm3)

- Leukopenia at least once not due to other causes such as Felty's syndrome, drugs, and portal hypertension.
- Lymphopenia at least once not due to other causes such as corticosteroids, drugs, and infection.

Thrombocytopenia (<100,000/mm3)

- At least once not due to other causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura (TTP).

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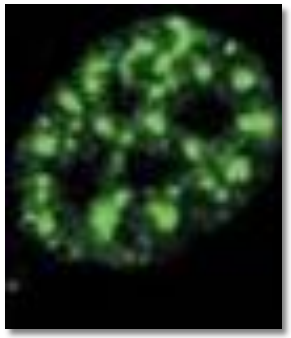
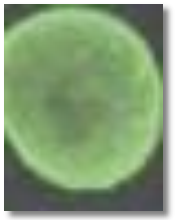
1. ANA
2. Anti-DNA
3. Anti-Sm
4. Anti-phospholipid antibody

Immunology in Action

Autoantibodies





ANA

- 1:40 = 25% of healthy individuals.

Anti-Sm (~25-30% of SLE patients)

Anti-dsDNA

- Must be 2-fold the reference range if tested by ELISA.
- Testing on *Crithidia lucilae* substrate is more specific.
- Titer often varies with SLE disease activity.

Antiphospholipid antibodies (APLA) – ~1/3 of SLE patients

- Positive test for lupus anticoagulant
- False-positive test result for rapid plasma reagin (RPR)
- Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
- Positive test result for anti-beta-2-glycoprotein I (IgA, IgG, or IgM)

Autoantibodies

Autoantibodies in SLE (*Nat Rev Rheumatol* 2020;16:565)			
Auto-Ab	**Frequency** (approx)	**Clinical Associations**	**Timeline**
ANA	95–99% if active disease 90% if in remission Homogeneous or speckled	Any or all of broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro **La**	15–35% ⊕ anti-Ro may be seen w/ ⊖ or low titer ANA	Sjögren's/SLE overlap Neonatal lupus; photosens.; subacute cutaneous lupus	
ds-DNA	70%; ~95% Sp; titers may parallel dis. activity, esp. renal	Lupus nephritis Vasculitis	Appears mos before or at dx, but may become ⊕ after dx
Sm	30%; very specific for SLE	Lupus nephritis	
U1-RNP	40%	MCTD; Raynaud's; Tend *not* to have nephritis	
Histone	90% in DLE; 60–80% in SLE	Mild arthritis and serositis	At diagnosis

Pocket Medicine (8th ed.), in press.

ANA Testing by Indirect immunofluorescence

HEp-2 Cell

Permeabilize Cells

Incubate with patient serum

Immunofluorescence detection of human antibodies

1 2 3

Positive ANA

$\neq$

Systemic lupus

ANA-associated *Systemic* Autoimmune Diseases

1. SLE (< 0.5% of highest risk population)
2. Sjögren's syndrome
3. Mixed connective tissue disease
4. Rheumatoid arthritis (1% of the population)
5. Systemic sclerosis (scleroderma disorders)
6. Idiopathic inflammatory myopathy (DM/PM)
7. Pauciarticular JIA
8. Drug-induced lupus

ANA-associated *Organ Specific* Autoimmune Diseases

1. Hashimoto's thyroiditis
2. Graves' disease
3. Autoimmune hepatitis
4. Primary biliary cirrhosis
5. Primary autoimmune cholangitis
6. Idiopathic pulmonary arterial HTN

Autoimmune thyroid disease ~10% of the population

Building a Case for SLE

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1. ANA
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4. Anti-phospholipid antibody
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (without frank hemolytic anemia)

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SLICC criteria: Caveats

- Meant to be more clinically relevant.
- Requirement for both clinical and serologic criteria.
- Better sensitivity, but lower specificity.
- More detailed to offer better diagnostic guidance.

CASE: 47yo Caucasian woman

- **1990 (at age 29): Membranous glomerulonephritis on renal biopsy, ANA negative, no other lupus features. GN attributed to infection vs. OCPs, resolved with prednisone.**
- **1999-2000: ANA 1:160-1:640 homogeneous or speckled, negative anti-dsDNA, and negative extractable nuclear antigens (anti-Ro, La, Sm, RNP).**
- **2002-present: Mild thrombocytopenia (100-150K), occ. dips to 60-80K, usually with infectious illnesses.**
- **2005: False positive RPR, negative anti-phospholipid antibodies at the time.**

CASE: 47yo Caucasian woman

Does this patient have SLE?

Criteria are cumulative.

Manifestations need not be concurrent.

At least 4 criteria must be met to establish the diagnosis of SLE.

CASE: 47yo Caucasian woman

Nov 2008:

- **Polyarthritis of wrists, hands, elbows and knees.**
- **Pancytopenia.**
- **ANA 1:640 homogeneous.**
- **Anti-dsDNA = 1:160**
- **aCL IgG and IgM both positive at 20-25 units (<15 nl).**

CASE: 47yo Caucasian woman

- **NOW she has lupus (or did she all along?)**
  - **Meets many clinical + laboratory criteria for SLE.**
- **Responded well to moderate/low dose prednisone taper + hydroxychloroquine.**
- **Disease quiet for 1½ years, asks to stop HCQ due to daily nausea from the drug.**
  - **HCQ discontinued in 2010.**

CASE: 47yo Caucasian woman

April 2012:

- **Notes ~10 lb weight gain over 1 month.**
- **Acute hard swelling of both legs one morning.**
- **Mild malar erythema also noted.**
- **No joint pain, otherwise feels well.**
- **Urine with 3+ blood and 3+ protein.**
  - **Spot urine TP/Cr ~ 4.5 (estimate of 24h urine protein)**
- **Cr 0.74 — C3 & C4 low — anti-dsDNA 1:80**
- **BP 137/84 (usually 105/70); 3 days later repeat assessment of BP = 165/105.**

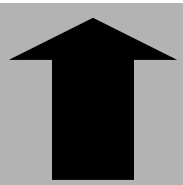
Classes of Lupus Nephritis

Table 1
Correlation between clinical and laboratory findings and histological classification of lupus nephritis

	Class II	Class III	Class IV	Class V
Arterial hypertension	None	Rare	Frequent	Rare
Proteinuria (grams/24hours)	< 1	< 2	1-20	3,5-20
Hematuria Erythrocytes/per field)	5-15	5-15	> 15	None
Leucocyturia/leucocytes per field)	5-15	5-15	> 15	None
Creatinine (mg/dl)	Normal	Normal or incremented	Frequently incremented	Normal
Glomerular filtration rate (ml/min)	Normal	60 - 80	< 60	Normal
CH50	↓	↓	↓↓	Normal
C3	↓	↓	↓↓	Normal
Anti-dsdna	↑	↑	↑↑	Normal

Esdaile, 1991 and 1992

Prednisone
Mycophenolate mofetil
Hydroxychloroquine



SLE: FDA Approved Therapies

1. **Corticosteroids**
   - Acute control of disease, occasionally needed long-term
   - Adverse effects! (osteoporosis, weight gain, HTN, diabetes)
2. **Hydroxychloroquine**
   - Cutaneous and joint involvement
   - Decrease flare risk / maintain remission
   - Small risk for retinal toxicity (dose and duration related)
3. **Belimumab (Benlysta®)**
   - Anti-BlyS mAb → prevents survival of B lymphocytes
   - Mucocutaneous and joint involvement
   - May worsen depression and anxiety, suicidality reported
4. **Anifrolumab (Saphnelo®)**
   - mAb against type 1 interferon receptors (IFNAR)
   - Cutaneous and joint involvement
5. **Aspirin** (No longer used therapeutically)
   - Low dose prophylaxis for +APLA

SLE: Other effective therapies

Mycophenolate mofetil
- Nephritis, cutaneous lupus, CNS disease
- Steroid sparing agent

NSAIDs (use with caution)
- Short-term symptomatic therapy for arthritis or serositis

Methotrexate and **Leflunomide**
- Long-term control of persistent arthritis
- Methotrexate for cutaneous lupus

Azathioprine
- Steroid sparing agent
- Serositis, arthritis, cutaneous lupus, systemic inflammatory symptoms
- Previously (and sometimes still) used for nephritis, CNS disease

Cyclophosphamide
- Nephritis, CNS disease

*****NOTE: Above treatments are not FDA approved for SLE*****

SLE: Infrequently used treatments

- Cyclosporine or Tacrolimus – if resistant to therapy
- Intravenous immunoglobulin
- Rituximab – not effective in trials for renal or non-renal disease, though many anecdotal reports of success. May be an option for refractory disease when all else fails.
- TNF antagonists – theoretical risk of worsening SLE, as these agents can induce ANA and anti-dsDNA.

*****NOTE: Above treatments are not FDA approved for SLE*****

SLE and COVID-19

- SLE, hydroxychloroquine (HCQ), and COVID-19:
  - ***Early pandemic shortage of HCQ*** due to increased use for COVID-19 patients >> Risk of SLE flare significantly increases if HCQ is discontinued.
  - Maintenance of SLE in remission is likely critical for avoiding more severe COVID-19, balanced against the risks of immunosuppression.
  - Baseline use of ***HCQ does NOT protect*** against SARS-CoV-2 infection and development of COVID-19.
- Risk factors for severe COVID-19 in SLE patients are generally the same as those identified in the population at large.
  - Exception: Connective tissue disease patients develop more severe COVID-19 related to certain immunosuppressive therapies such as mycophenolate, azathioprine, and rituximab.
- Immunosuppression may (1) prolong the clinical course of COVID-19 illness and (2) impact a patient's ability to generate protective immunity to vaccines and/or SARS-CoV-2 infection.
  - https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf

Practical management issues in SLE

1. **Day to day primary care issues**
   - Not every ache, pain, sniffle, etc. is due to SLE.
   - Depression and fibromyalgia syndrome are common.

2. **Contraception**
   - Non-estrogen hormonal contraception is considered safe (unless anti-phospholipid Ab positive).
   - IUD also OK, consider risk of infection if immune suppressed.

3. **Pregnancy**
   - Only if disease is stable on or off meds for 6 months.
   - Referral for high-risk pregnancy management.
   - Prior pregnancy complications → case by case basis.
   - Anti-Ro +/- Anti-La antibody = risk for neonatal lupus and congenital heart block

Practical management issues in SLE

4. **Manage cardiac risk factors.**
   - SLE introduces a significant risk for CAD in a usually low risk population.
   - Adverse effects of corticosteroid therapy on metabolic factors.

5. **Attention to bone health / osteoporosis.**
   - Limit corticosteroid exposure.
   - Calcium and vitamin D.
   - Pharmacotherapy when needed for prevention of GIOP or treatment of established osteoporosis.

Thank you!