Overview of common connective tissue diseases:
Rheumatology for primary care series

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PRESENTER DISCLOSURE

NONE

LEARNING OBJECTIVES

- **Definition of ANA testing and interpretation**
- **Recommendations for the use of serological testing in clinical practice**
- **Lupus in your primary practice**
- **Sjogren's syndrome in primary care**

Prestest Questions

- What percentage of the population has a positive ANA?

A. 10-20%

B. 50%

C. 1%

D. 80%

Pretest Questions

- Which ANA patterns are least worrisome?

A. Nucleolar

B. Homogenous

C. Speckled

D. Centromere

E. Dense fine speckled

F. B and E

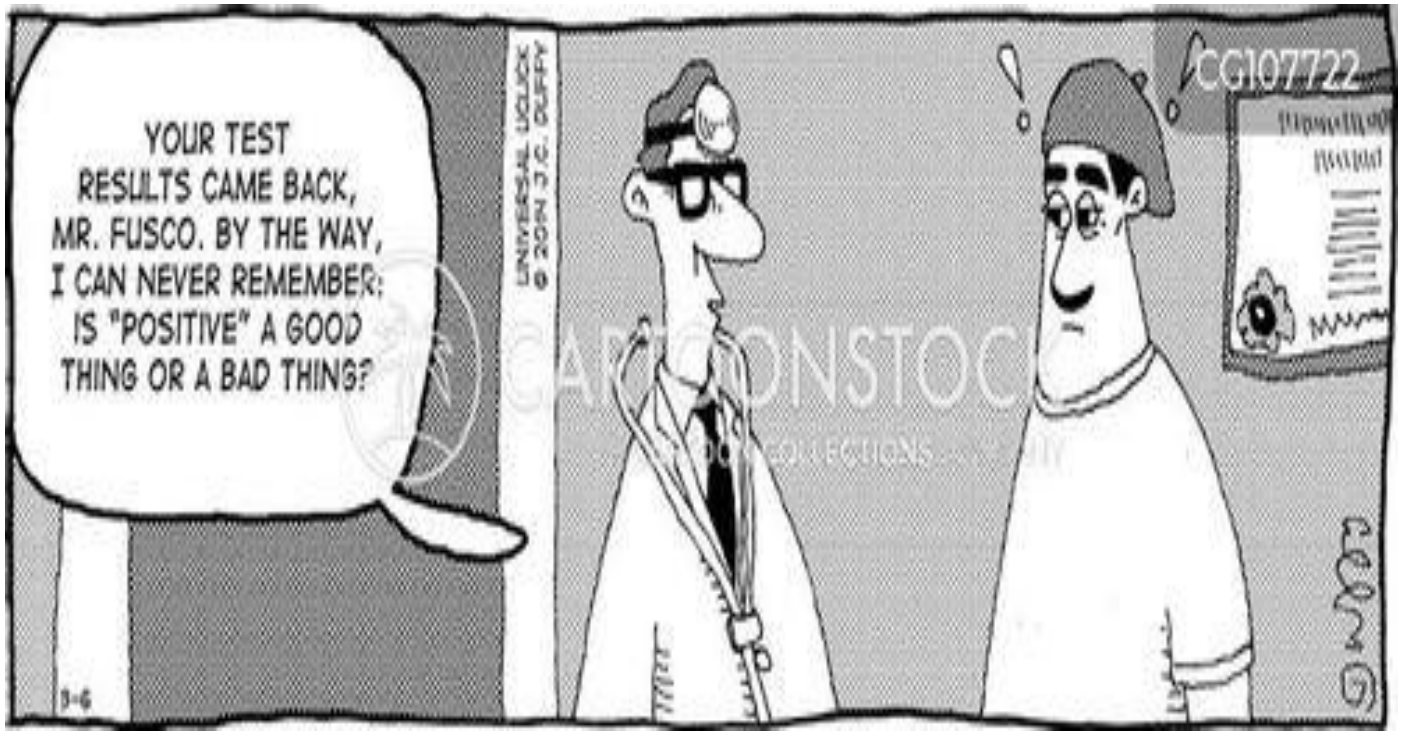
Pretest Questions

- The following can lead to a positive ANA:

A. Connective tissue disease
B. Infections
C. Medications
D. Healthy individuals
E. All of the above

INTERPETATION OF THE ANA (anti-nuclear antibody)

- ANA test is a detection of autoantibodies against contents inside cells (nucleus, cytoplasm, etc)
- Antibodies can be components outside the nucleas – ie ACA- anticellular antibody

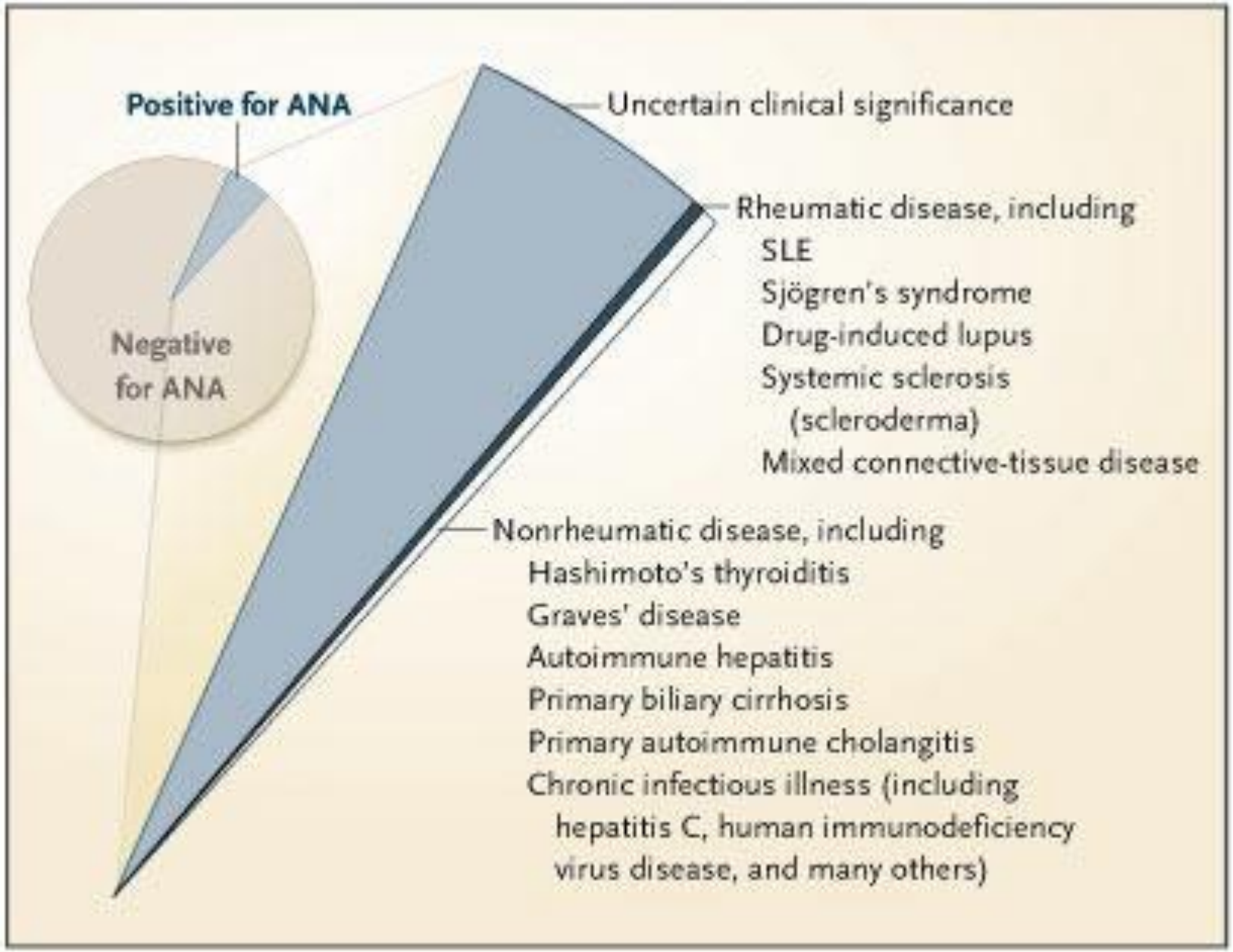


What is the ANA?

- Production of an ANA is a normal physiologic response to cell turnover
- Antinuclear antibody is an autoantibody that produced against normal proteins in cells.
- At a normal rate, the body “sees” the nucleus at a low rate however a high antibody response can occur producing a high number of antibodies
- These antibodies can also have “autoimmunity” resulting in destruction of healthy cells when it fails to recognize “self”

ANA testing

- Indirect immunofluorescence
- Immunodiffussion
- Counterimmunoelectrophoresis
- Western blotting
- Line immunoassays
- ELISA
- Laser bead immunoassay
- Multiplex

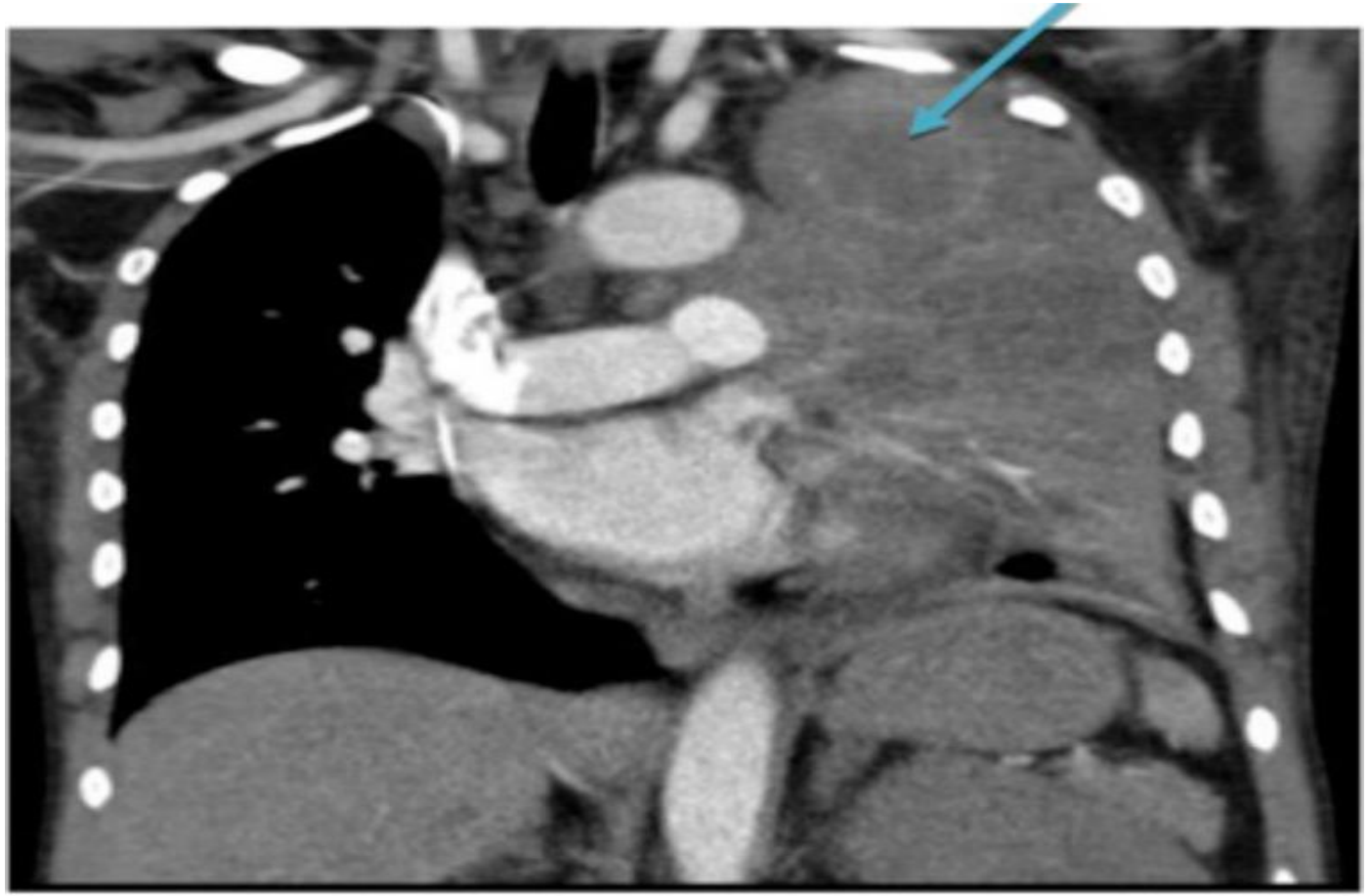


Shmerling 2003.NEJM **2003;349:1499-1500**

Case- A

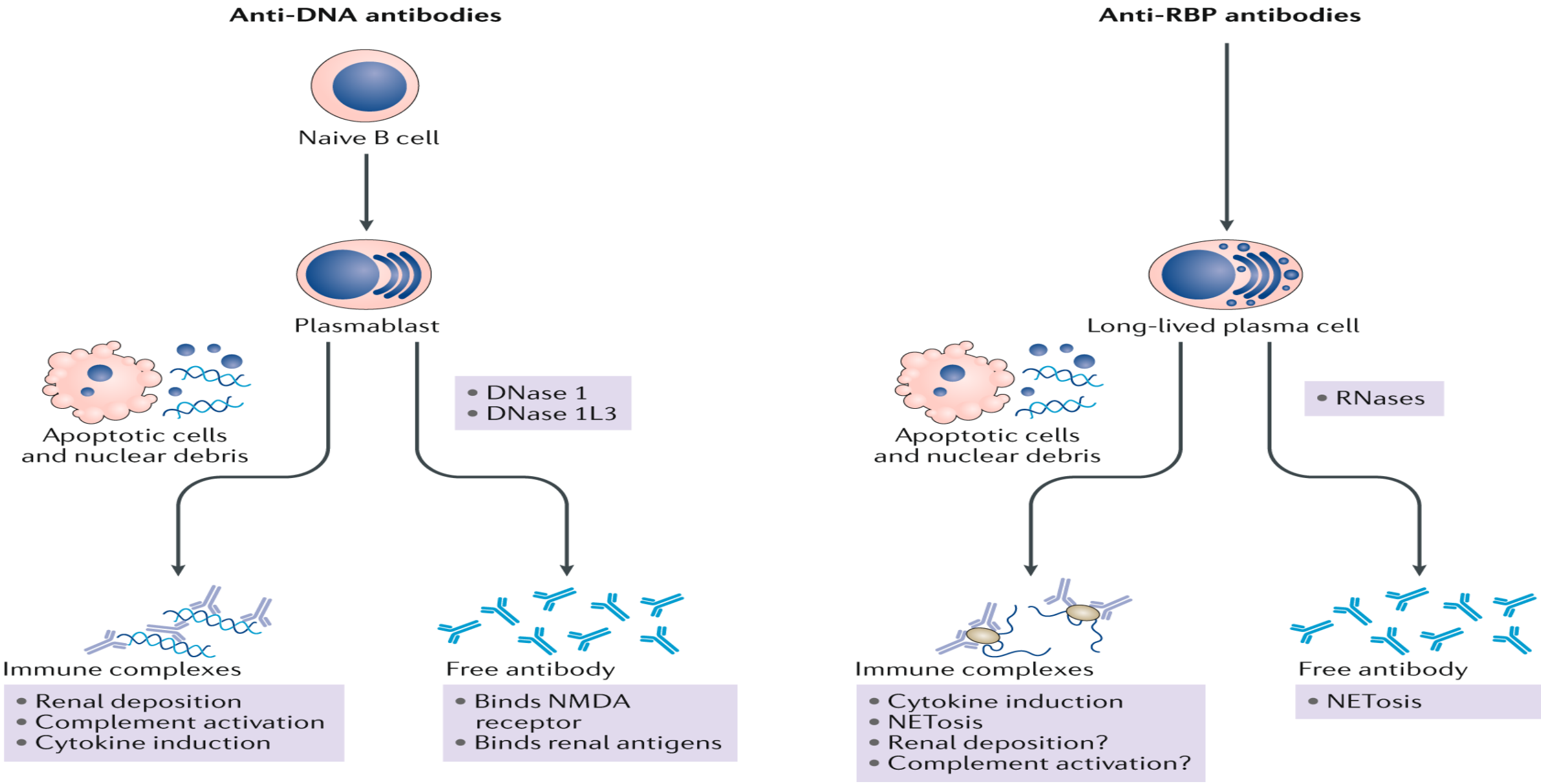
- 47 F smoker presents with arthritis and dry eyes
- PMHx: Hypertension
- Medcations: Telmisartan
- 3 month history of joint pain in hands and swelling. Shortness of breath and cough (not new)
- Exam: clubbing, tenderness and swelling in her MCP’s (3)
- Serology: ANA 1:160 homogenous, anti-dsDNA 170, normal complements, normal hgb with low WBC 3.5

Case - A



ANA Titre

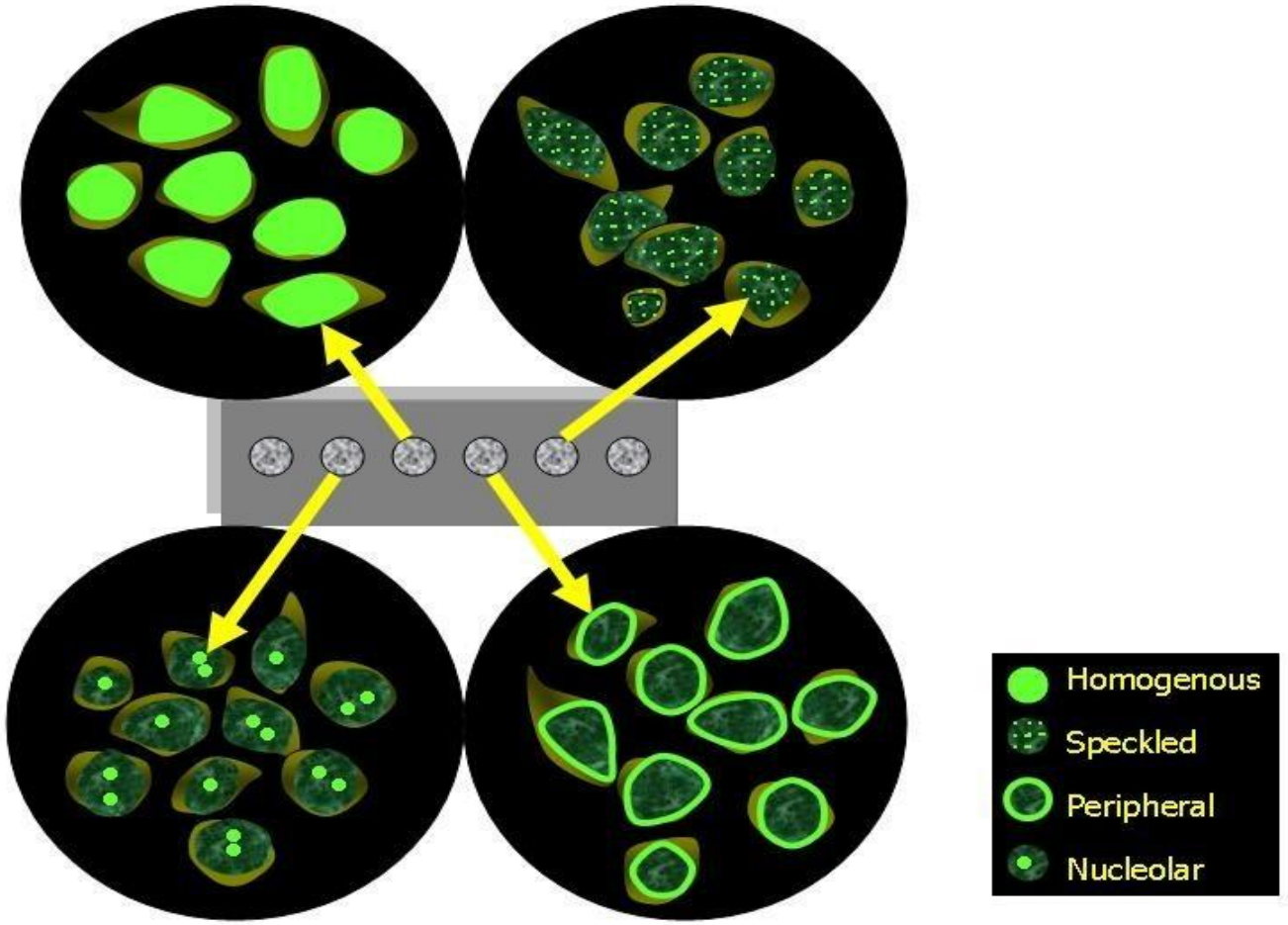
- Simply how many anti-nuclear antibodies are present after the serum is diluted
- At 1:80 to 1:160 about 10-20% of the healthy population can have ANA detected
- However as the serum is diluted, the ANA would be difficult to detect unless the concentration is high.



Pisetsky, D.S., Lipsky, P.E. New insights into the role of antinuclear antibodies in systemic lupus erythematosus. *Nat Rev Rheumatol* **16**, 565–579 (2020). https://doi.org/10.1038/s41584-020-0480-7

ANA patterns

- Often patient serum can have more than one



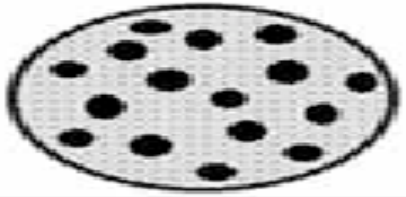
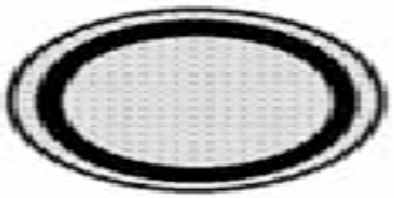
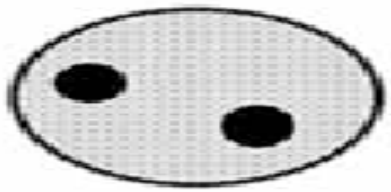
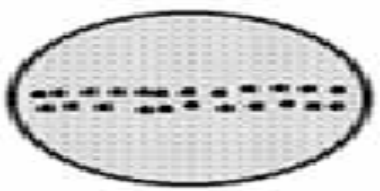
Kumar, Y., Bhatia, A. & Minz, R.W. Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited. *Diagn Pathol* **4**, 1 (2009). https://doi.org/10.1186/1746-1596-4-1

- How to follow up a positive ANA result?

ENA- extractable nuclear antigens

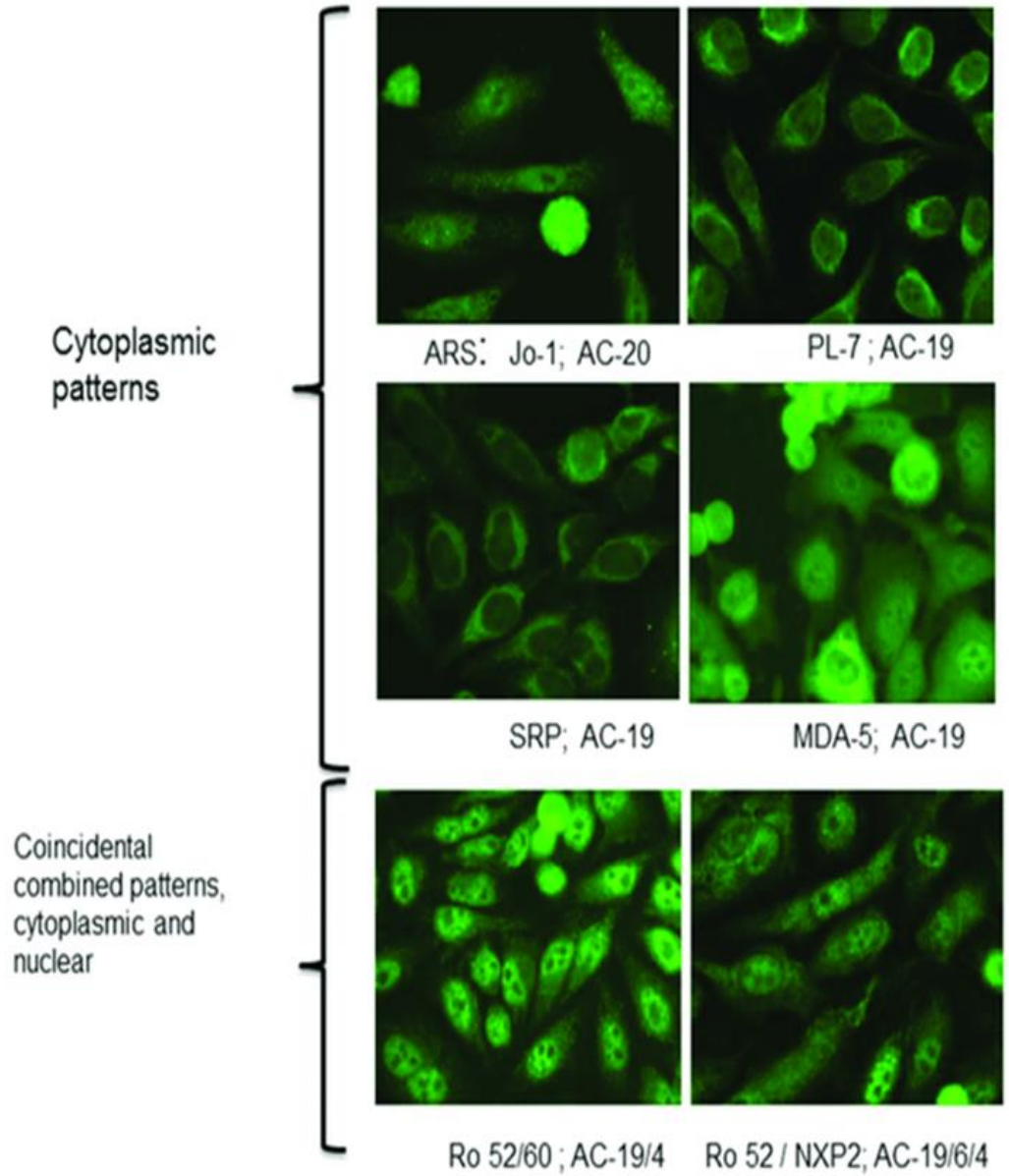
- Checks for antibodies in the serum
- Antigens that bind to the antibodies can be:
  - DNA
  - RNA
  - Nucleic acid proteins complexes
  - Proteins

- These antigen can leave the cell during death

ANA pattern	Antigen	Associated diseases
Speckled 	ENA, RNP, Sm, Ro/SSA, La/SSB, Scl-70, Jo-1, ribosomal-P	SLE, MCTD, Systemic sclerosis, Sjögren's syndrome, PM
Homogenous 	dsDNA, Histones	SLE, Drug-induced SLE
Peripheral (rim) 	RNP, Sm, Ro/SSA	SLE, Systemic sclerosis
Nucleolar 	Anti-PM-Scl, anti-RNA polymerase I-III, anti-U3-RNP, To RNP	Systemic sclerosis, PM
Centromere 	CENP A-E	Limited systemic sclerosis

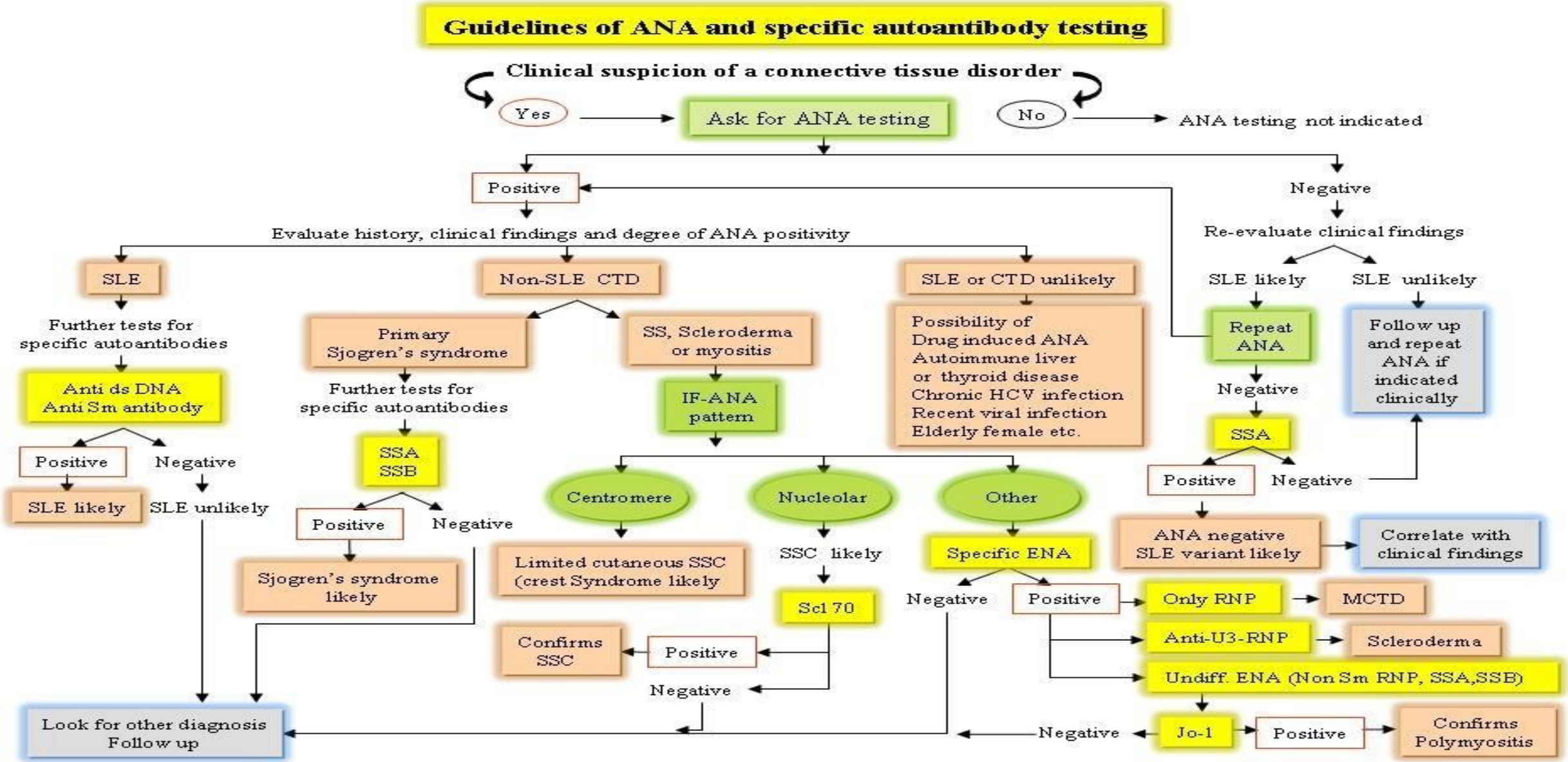
ENA: Extractable nuclear antigens; RNP: Ribonucleoproteins; SLE: Systemic lupus erythematosus; MCTD: Mixed connective tissue disease; PM: Polymyositis; dsDNA: Double-stranded deoxyribonucleic acid; CENP: Centromere protein.

Birtane, Murat. "Diagnostic Role of Anti-Nuclear Antibodies in Rheumatic Diseases." *Archives of Rheumatology* 27 (2012): 079-089.

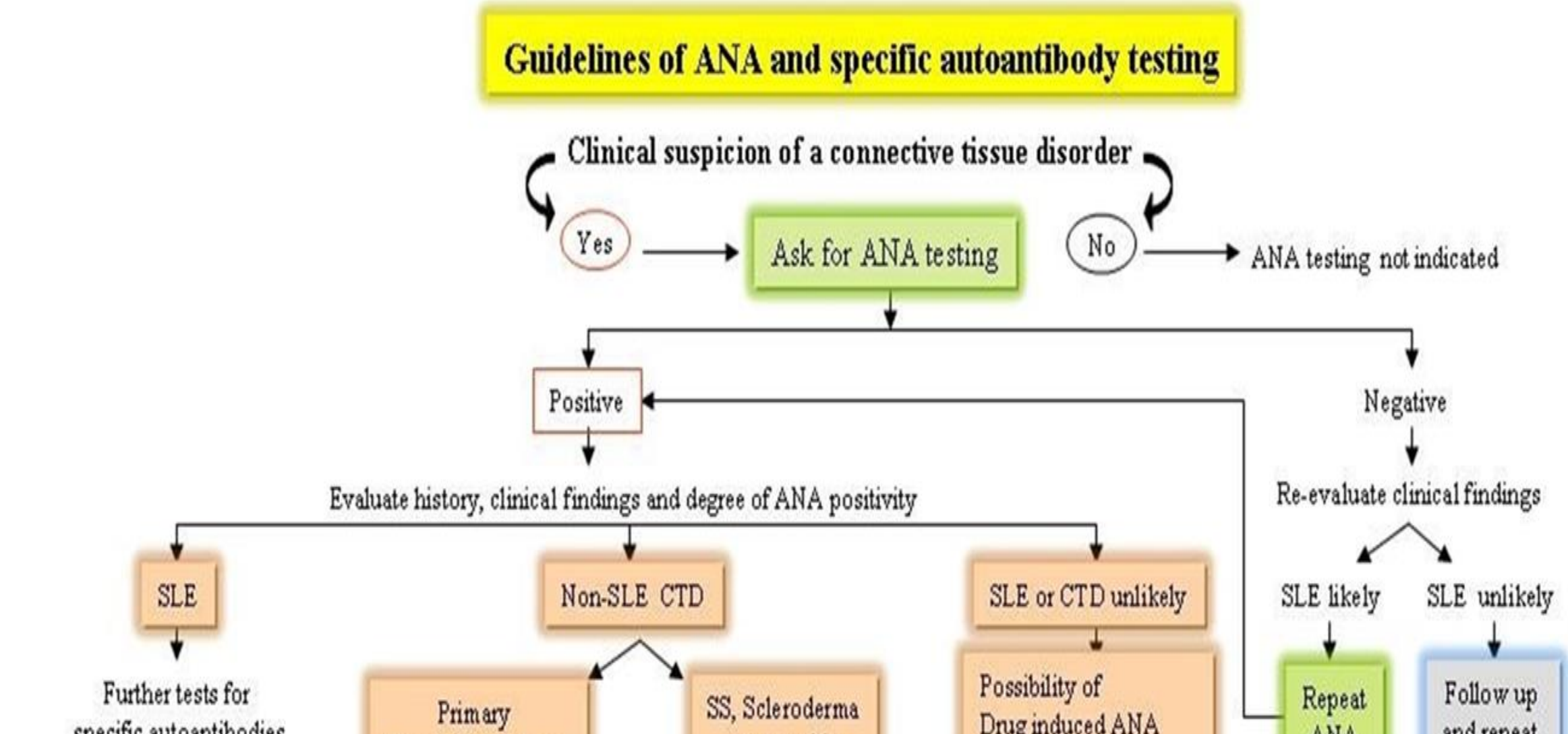


A negative ANA DOES NOT imply Antibody negativity in myositis

Feist et al 2019

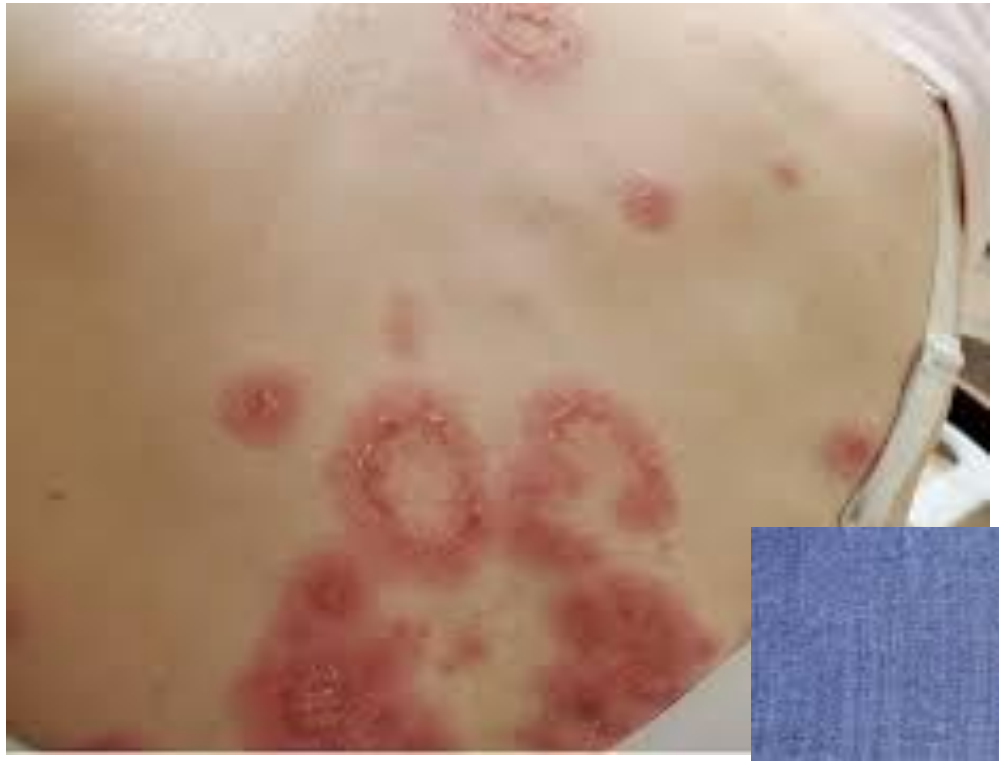


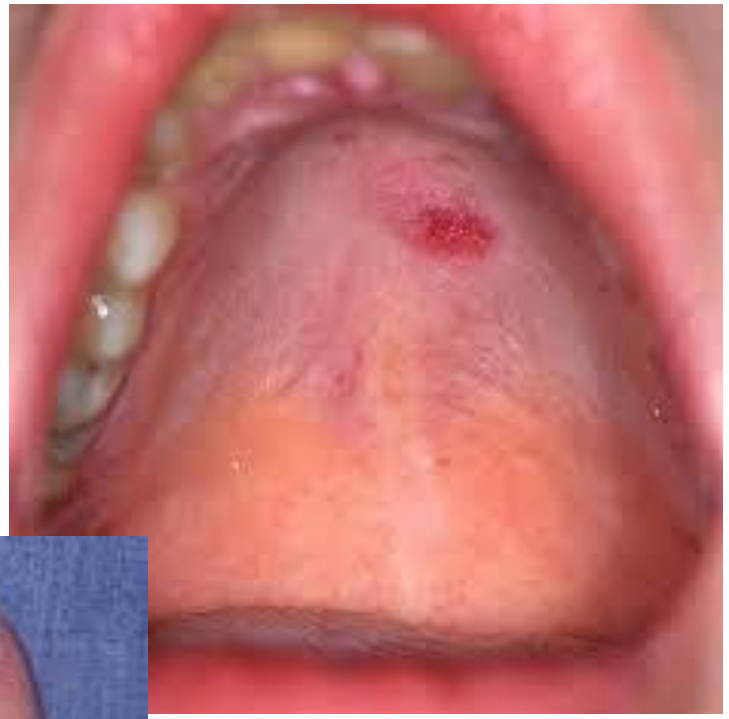
Kumar, Y., Bhatia, A. & Minz, R.W. Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited. *Diagn Pathol* **4**, 1 (2009). https://doi.org/10.1186/1746-1596-4-1

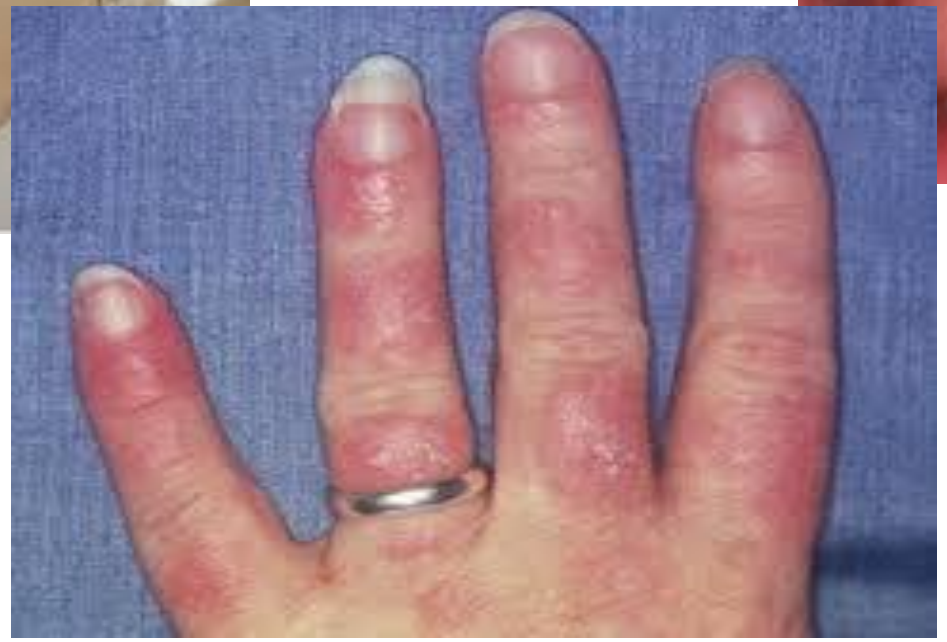

Guidelines of ANA and specific autoantibody testing
Clinical suspicion of a connective tissue disorder
Yes
Ask for ANA testing
No
ANA testing not indicated
Positive
Negative
Evaluate history, clinical findings and degree of ANA positivity
Re-evaluate clinical findings
SLE
Non-SLE CTD
SLE or CTD unlikely
SLE likely
SLE unlikely
Further tests for
Primary
SS, Scleroderma
Possibility of
Drug induced ANA
Repeat
Follow up

Case-B

- 40 F presents with arthralgia and rash on her arms and back
- She is otherwise healthy
- No home medications
- Family history: osteoarthritis
- HPI: she has been feeling a low grade fever, fatigue, stiffness in hands > 30 min







Case

- Tests to order:
  - CBC, liver enzymes, creatinine, ANA, ENA, RF, CRP, ESR, complements and antidsDNA, and chest x-rays prior to referral.
  - Baseline hands and wrists x-rays. CXR
  - Start NSAID’s.

ANA and SLE

- Can ANA be used to screen patient for SLE?

Systemic lupus erythematosus (SLE)

- 2019 EULAR/ACR Classification criteria For SLE
- Important take aways:
  - **Is there another cause for the Clinical finding**
  - **7 clinical criteria**
  - **3 immunological criteria**
  - Sensitivity 96.1% and specificity 93.4%

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

↓

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

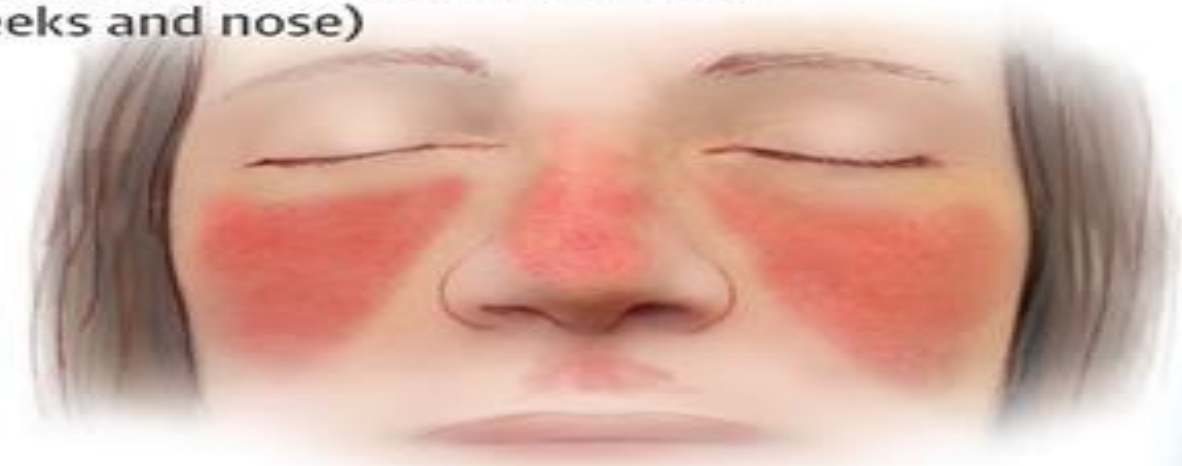
SLE

- Chronic autoimmune multisystem disease
- Challenging to diagnose due to clinical heterogeneity
- If suspicion is high with a positive ANA usually >1:80 Tests to help with referral include:
  - CBC
  - ENA
  - Anti-dsDNA
  - Creatinine and urinalysis
  - Complements
  - CRP/ESR

Types of cutaneous lupus erythematosus

Acute cutaneous lupus ("acute skin lupus")

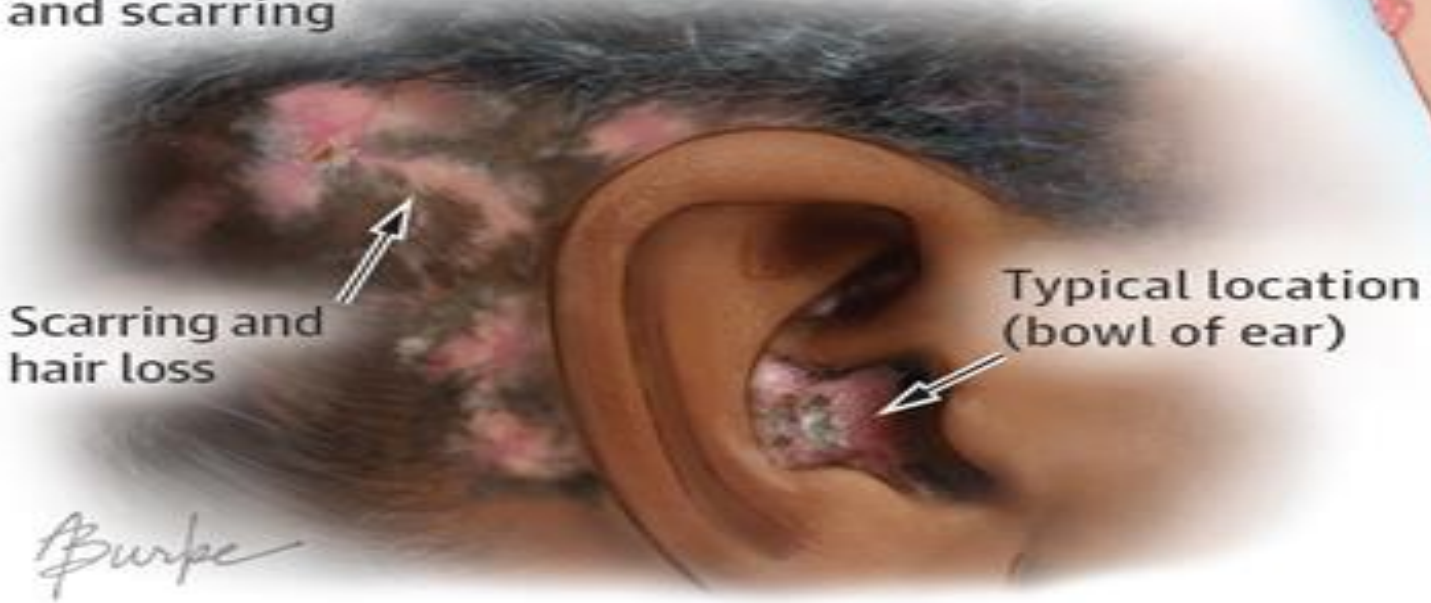
"Butterfly rash" (redness across cheeks and nose)



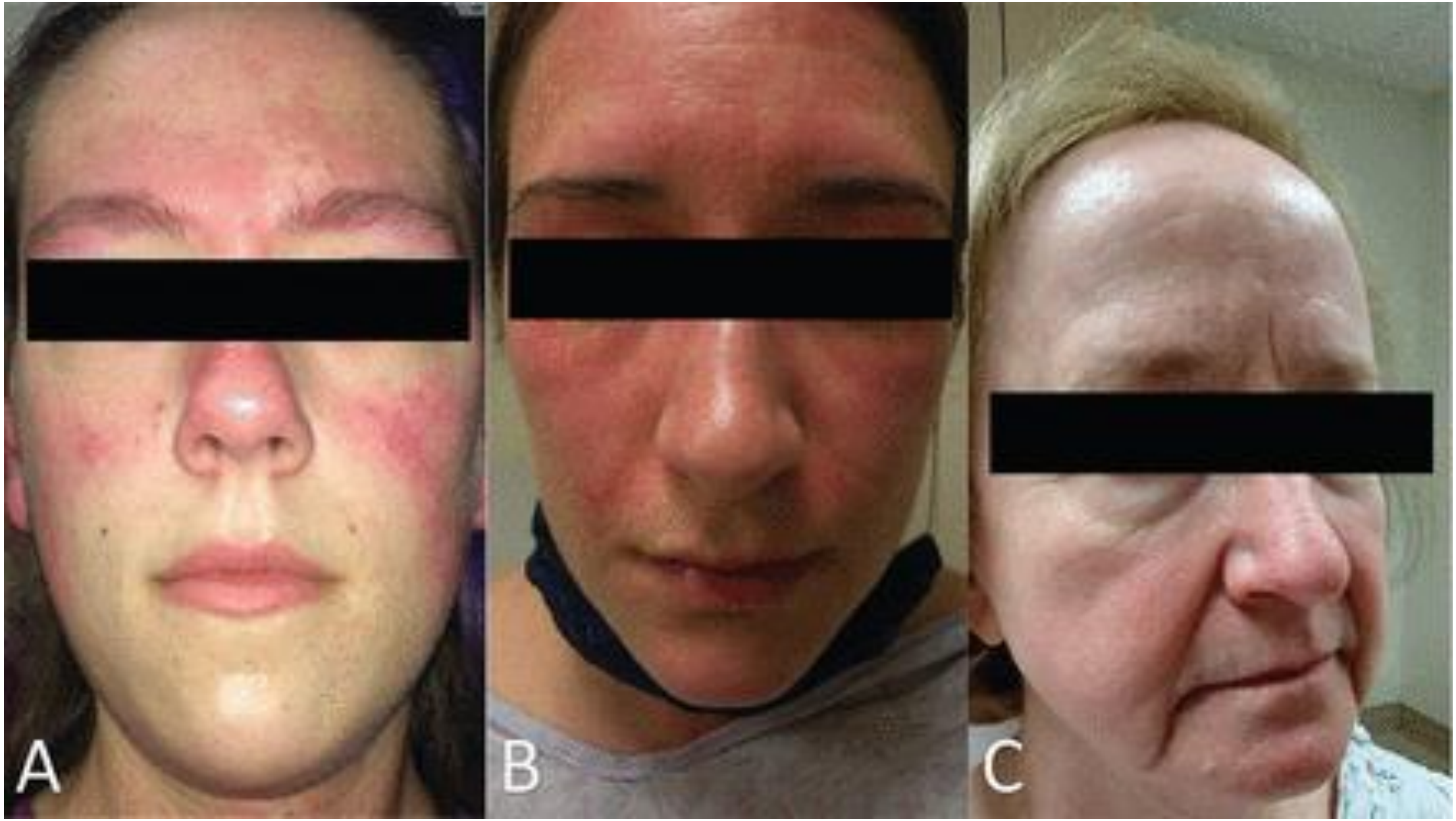
Subacute cutaneous lupus ("subacute lupus")

Chronic cutaneous lupus ("discoid lupus")

Red to purple rash with discoloration and scarring

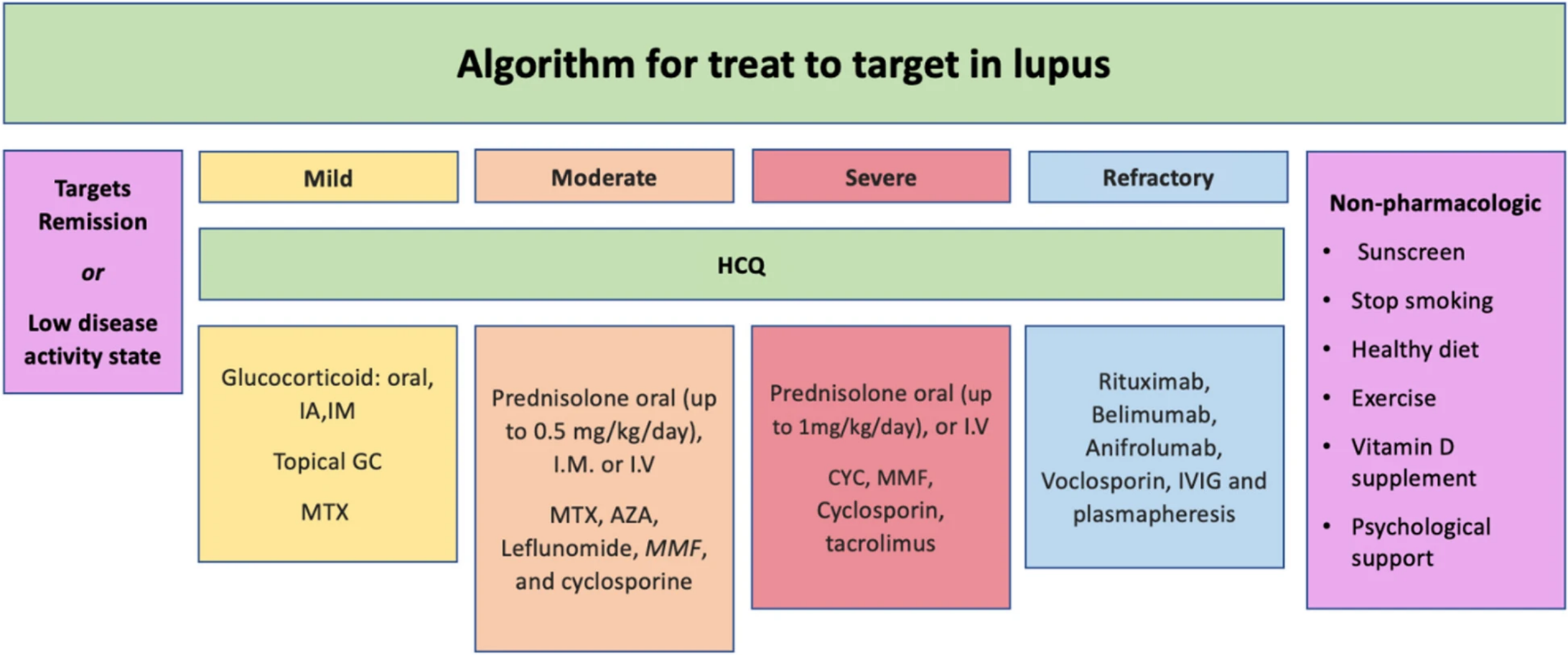


JAMA Dermatol. 2014;150(3):344. doi:10.1001/jamadermatol.2013.10393



Cutaneous Involvement in Systemic Lupus Erythematosus: A Review for the Rheumatologist. Courtney Stull, Grant Sprow, Victoria P. Werth.The Journal of Rheumatology Jan 2023, 50 (1) 27-35; DOI: 10.3899/jrheum.220089

Algorithm for treat to target in lupus

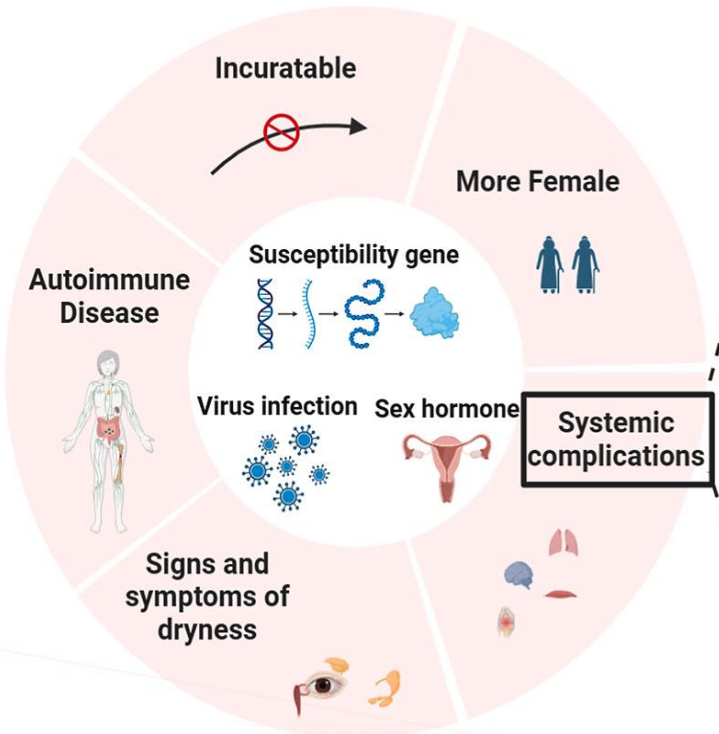


Age appropriate cancer screening due to increased risk of cervical cancer

El Miedany, Y., Elhadidi, K., Mahmoud, G.A. *et al.* Egyptian recommendations for the management of systemic lupus erythematosus: a consensus, evidence-based, clinical practice guidelines for treat-to-target management. *Egypt Rheumatol Rehabil* **50**, 23 (2023). https://doi.org/10.1186/s43166-023-00187-9

Sjogren’s syndrome- SS

- Chronic disease that is slow and progressive
- Lymphocytic infiltration of exocrine glands leading to xerostomia in eyes and mouth
- 30% have systemic manifestations
- F > M 9 to 1
- Risk of lymphoma



Central nervous system
- Cerebral vasculitis
- Transverse myelitis
- Demyelination injury

Lymph nodes
- Benign lymphadenophathy
- lymphoma

Heart
- Cardiovasular disease

Renal
- Interstitial nephritis
- cryoglobulinemia-associated glomeruloneghritis

Raynaud's phenomenon

Articular
- synovitis
- Arthralgias with morning stiffness

Skin
- Purpura
- Dryness
- Urticaria like skin damage
- erythematous nodule

Glandular body
- Palpable parotid
- submandibular
- lacrimal swelling

Thyroid
- Graves' disease
- Hashimoto's thyroiditis

Pulmonary
- Interstitial pneumonia
- Chronic bronchitis
- bronchiolitis

Digestive system
- Chronic gastritis
- Acute pancreatitis
- Liver function damage

Muscular
- Myositis with pain
- Weakness

Vessels
- Anaemia
- Cryoglobulin associated vasculitis
- Thrombocytopenia
- Anti-SSA/Ro antibodies

Peripheral Neuropathy
- Pure sensory axonal polyneuropathy
- Ataxic ganglionophathy
- Mononeuritis multiplex

Zhao et al. A comprehensive review of Sjögren's syndrome: Classification criteria, risk factors, and signaling pathways
Author links open overlay panel. Volume 10, Issue 17, 15 September 2024, e36220

Sjogren Syndrome

- ACR/EULAR Classification criteria for primary Sjogren's syndrome
- Review exclusion criteria first

    - History of head and neck radiation treatment
    - Active Hepatitis C infection (with positive PCR)
    - Acquired immunodeficiency syndrome
    - Sarcoidosis
    - Amyloidosis
    - Graft versus host disease
    - IgG4-related disease

Sjogren syndrome

- Screening patient for sicca symptoms- only need 1 positive response:
  - Have you had daily, persistent, troublesome dry eyes for more than 3 months?
  - Do you have a recurrent sensation of sand or gravel in the eyes?
  - Do you use tear substitutes more than 3 times per day?
  - Have you had a daily feeling of dry mouth daily feeling of dry mouth for more than 3 months?
  - Do you frequently drink liquids to aid in swallowing dry food?

ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)

The classification of SS applies to any individual who meets the inclusion criteria,[1] does not have any condition listed as exclusion criteria,[2] and who has a score ≥ 4 when summing the weights from the following items:

Item	Weight / Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1.[3]	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye[4]	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min[5]	1

2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient CohortsArthritis Rheumatol. 2017 January ; 69(1): 35–45. doi:10.1002/art.39859.

Secondary SS

- More common than primary SS
- It is common for SS to accompany other CTD diagnoses: Secondary Sjogren's syndrome
- Most commonly occur secondary to Rheumatoid arthritis, SLE and scleroderma
- Others: PBC, Chronic active hepatitis, MCTD

General approach to treatment

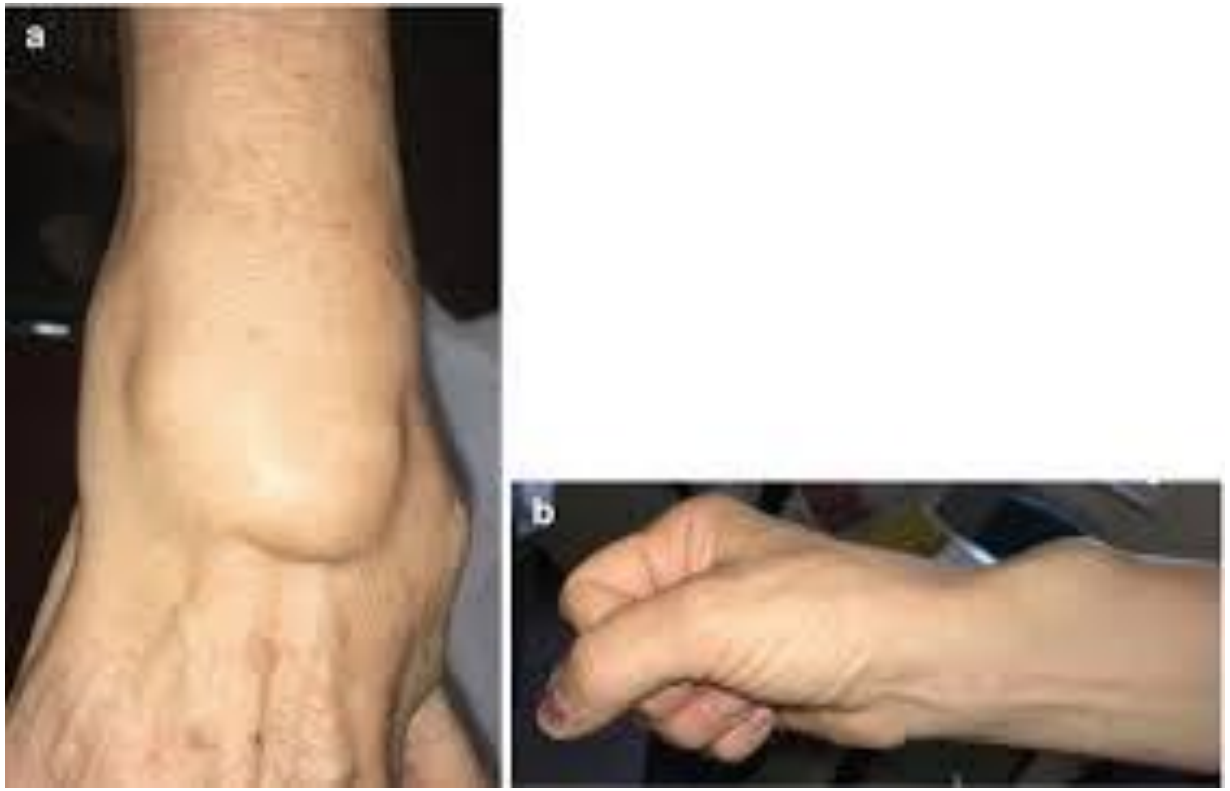
- Lubrication
  - Eyes: preservative free drops, topical gels, omega 3, cyclosporine drops
  - Mouth: lubrication with water, sugar free lozenges or gum, frequent oral hygiene for dental caries

- Immunosuppression can be indicated if there are systemic manifestations

Case

- 56 F with a 2 year history of dryness in mouth and eyes. She has keratoconjuctivitis as per Optometry
- PMHx: Hypothyroidism
- Medications: Synthroid
- She has been feeling swelling in her neck
- She has pain and swelling in wrists

Case – on exam



Pertinent results

CRP 15
RF 300
SPEP = no monoclonal band. Signs of inflammation
Anti-CCP 50

Likely Secondary SS in Seropositive RA

Pelechas, E., Kaltsonoudis, E., Voulgari, P.V., Drosos, A.A. (2019). Rheumatoid Arthritis. In: Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases. Springer, Cham. https://doi.org/10.1007/978-3-030-03664-5_3

Questions to keep in mind

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A. 10-20%

B. 50%

C. 1%

D. 80%

Questions to keep in mind

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B. Homogenous

C. Speckled

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E. Dense fine speckled

F. B and E

Questions to keep in mind

- The following can lead to a positive ANA:

A. Connective tissue disease
B. Infections
C. Medications
D. Healthy individuals
E. All of the above

Summary

- Antinuclear antibody is an autoantibody that produced against normal proteins in cells.
- At 1:80 to 1:160 about 10-20% of the healthy population can have ANA detected
- Pretest probability for connective tissue disease should be high when ordering an ANA
- Causes for a positive ANA include other than connective tissue disease.

Summary

- Diagnosis of SLE is complicated due to heterogeneity of disease
  - Criteria includes clinical and serological testing thus serology alone is not sufficient
  - Plaquenil/Hydroxychloroquine is strongly recommended for SLE patients leading to decreased mortality and less flares
  - Age appropriate malignancy screening is important due to high incidence of some cancers ie- cervical
- Secondary SS is more common than primary SS thus screening for other CTD diseases in patients with sicca symptoms is important.

REFERENCES

- Kumar, Y., Bhatia, A. & Minz, R.W. Antinuclear antibodies and their detection methods in diagnosis of connective tissue diseases: a journey revisited. *Diagn Pathol* **4**, 1 (2009). https://doi.org/10.1186/1746-1596-4-1
- Zhao et al. A comprehensive review of Sjögren's syndrome: Classification criteria, risk factors, and signaling pathways. Volume 10, Issue 17, 15 September 2024, e36220
- Shmerling 2003.NEJM **2003;349:1499-1500**
- Pelechas, E., Kaltsonoudis, E., Voulgari, P.V., Drosos, A.A. (2019). Rheumatoid Arthritis. In: Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases. Springer, Cham. https://doi.org/10.1007/978-3-030-03664-5_3
- 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient CohortsArthritis Rheumatol. 2017 January ; 69(1): 35–45. doi:10.1002/art.39859.
- El Miedany, Y., Elhadidi, K., Mahmoud, G.A. *et al.* Egyptian recommendations for the management of systemic lupus erythematosus: a consensus, evidence-based, clinical practice guidelines for treat-to-target management. *Egypt Rheumatol Rehabil* **50**, 23 (2023). https://doi.org/10.1186/s43166-023-00187-9