Using ANA and “Choosing Wisely”

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Learning Objective

"Choose Wisely" when investigating and treating rheumatological conditions.

Outline

- Choosing Wisely and EVOLVE
- ANA in Australia
- How is ANA done?
- ANA titre
- ANA patterns and significance
- When to consider ordering ANA
- What to do when ANA positive

Choosing Wisely®

An initiative of the ABIM Foundation

Choosing Wisely Australia

An initiative of NPS MedicineWise

- “Choosing Wisely” began in USA in 2012

- Australian initiative lead by NPS Medicine wise in liaison on specialty colleges.

evolve

evaluating evidence. enhancing efficiencies.

EVOLVE is a physician-led initiative to ensure the highest quality patient care through the identification and reduction of low-value practices and interventions.

https://evolve.edu.au/published-lists

“EVOLVE” initiative

- EVOLVE was established in March 2015
- Clinician-led with RACP and its specialty societies that aims to drive safer, higher-quality patient care.
- Over 20 medical specialities have completed or are developing their ‘top five’ lists of low-value clinical practices in its field.
- Aim is to ultimately reduce low-value medical care:
  - tests, treatments or procedures that are
  - overused, inappropriate or of limited effectiveness and/or potentially harmful.
  - by initially developing their lists of top 5 low value items to impact on practice
- Rheumatology list is not yet published but following are recommendations from the draft.

“EVOLVE” initiative- Rheumatology

1. Do not perform arthroscopy with lavage and/or debridement for symptomatic osteoarthritis of the knee nor partial meniscectomy for a degenerate meniscal tear

2. Do not order ANA testing without symptoms and/or signs suggestive of a systemic rheumatic disease

3. Do not undertake imaging for low back pain for patients without indications of an underlying serious condition

4. Do not use ultrasound guidance to perform injections into the subacromial space as it provides no additional benefit in comparison to non-image guided injection

5. Do not order anti dsDNA antibodies in ANA negative patients unless the clinical suspicion of SLE remains high

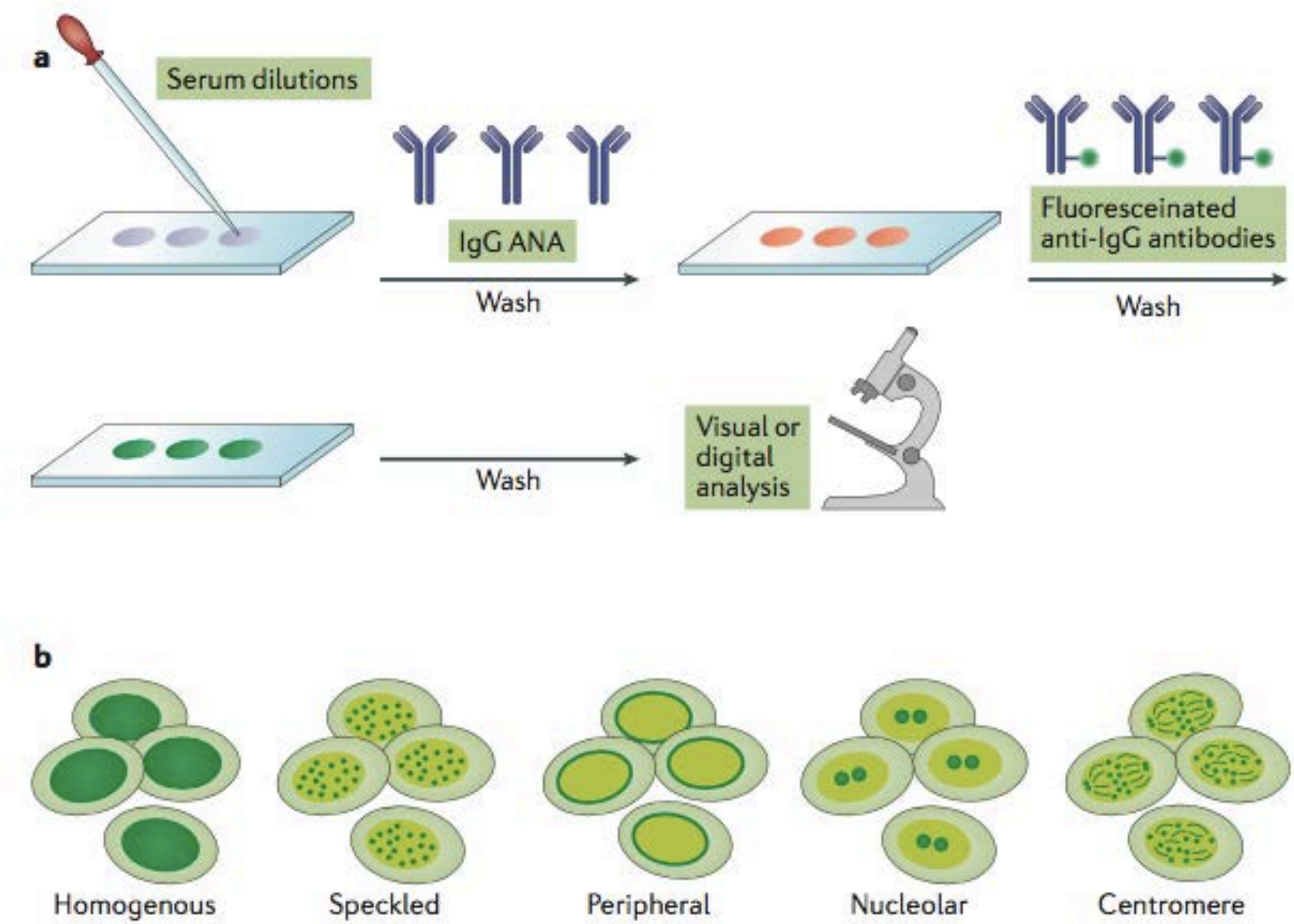
ANA - the cost

- Antinuclear Antibody.
- The test is over-used and can lead to unnecessary referrals and healthcare costs.
- Medicare rebate for ANA is $25.33 (ENA $22.84)
- There has been a steady increase over the last decade in the number of MBS-funded ANA tests ordered.
  - From $7.76 million in the 2004 financial year to
  - $10.96 million (for ANA alone) in the 2015 financial year

ANA - the pitfalls

- There are no gold standard tests for most autoimmune diseases.
- All ANA related diseases are clinical diagnoses with *supportive* investigations.
- It is important to remember:
  - Sensitivity up to100% but
  - Specificity of the ANA is 86% (Arch Intern Med. 1996 Jul 8;156(13):1421-5.)
  - The positive predictive value of the ANA test for SLE in the general population is poor at 7-11% (Solomon et al, 2002, Slater et al.,1996).
- Also ANA is:
  - User dependent
  - Non-specific
  - Lab dependent

ANA - How is it done?



Nature Reviews Rheumatology **13**, 495–502 (2017)

ANA - Importance of the Titre

- Reported as the highest titre that the immunofluorescent pattern is still visible.

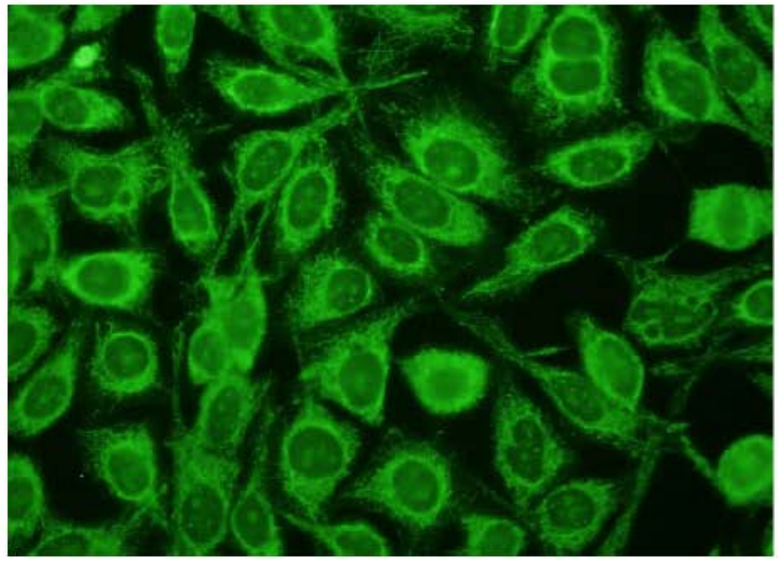
- 1:40 /80 /160 /320 /640 /2560

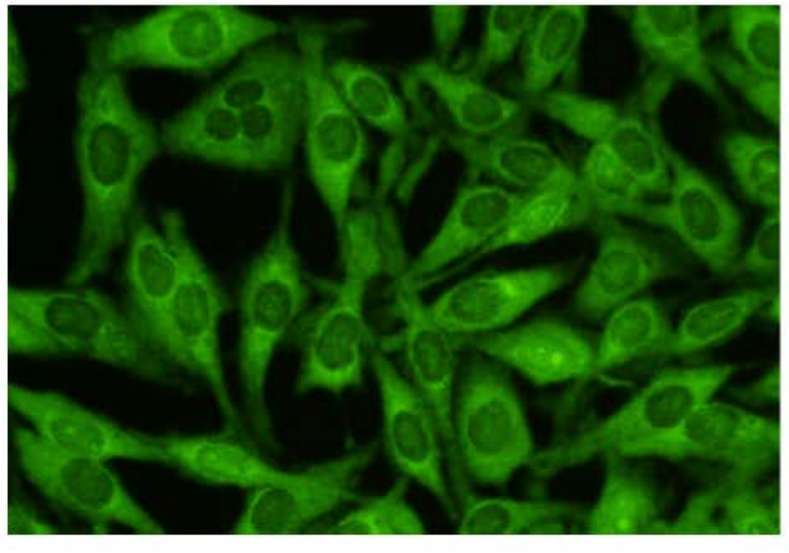
- Change in titre is rarely clinically useful.
- Repeating ANA is rarely clinically useful.

ANA - unexpected result

- Due to screening nature of the test, will also detect cytoplasmic antibodies:
  - AMA (anti-mitochondrial)
  - Ribosomal
  - Jo-1 (and other myositis specific antibodies)
  - Lysosomal

- *Only certain labs will report this*

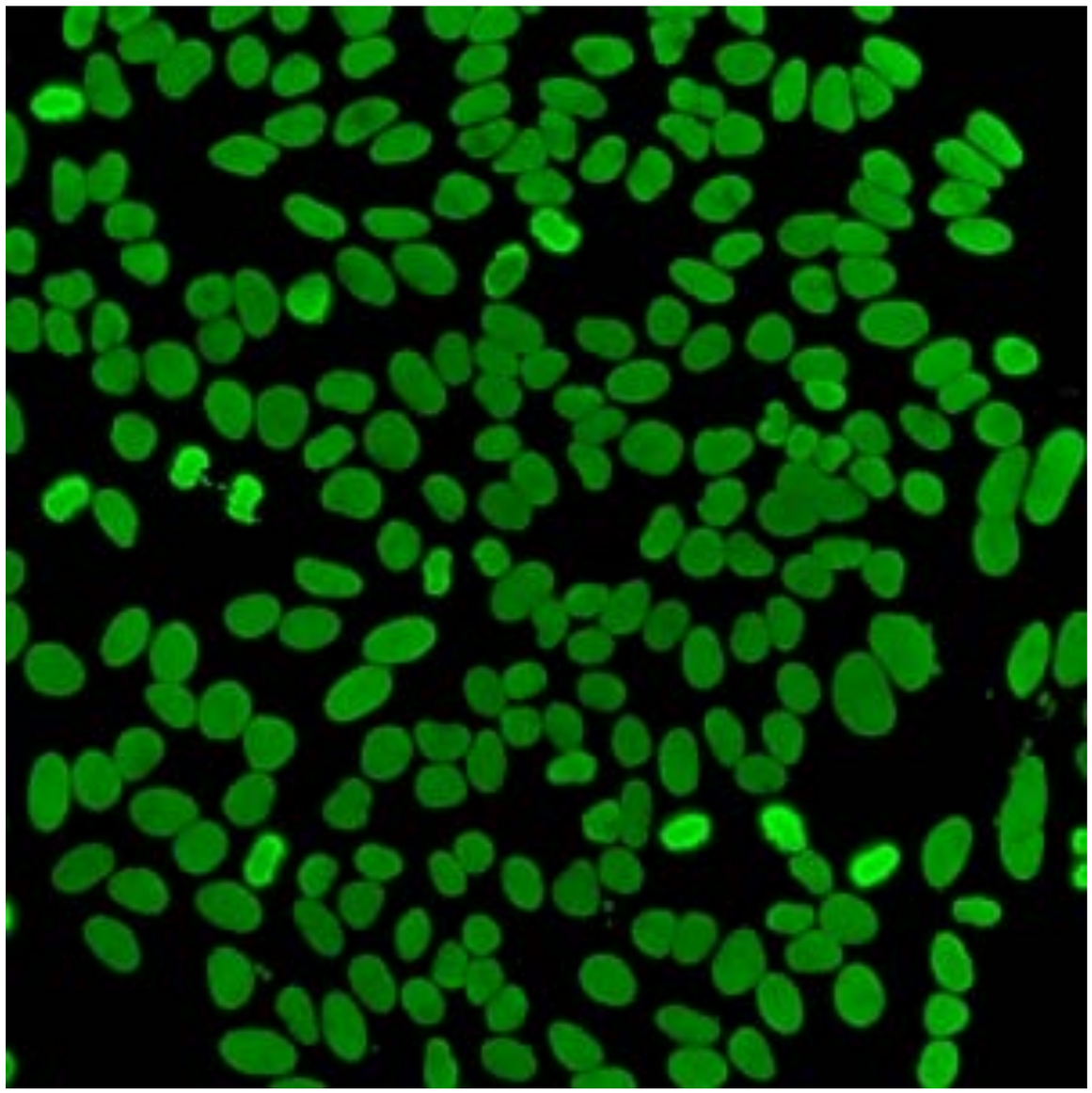


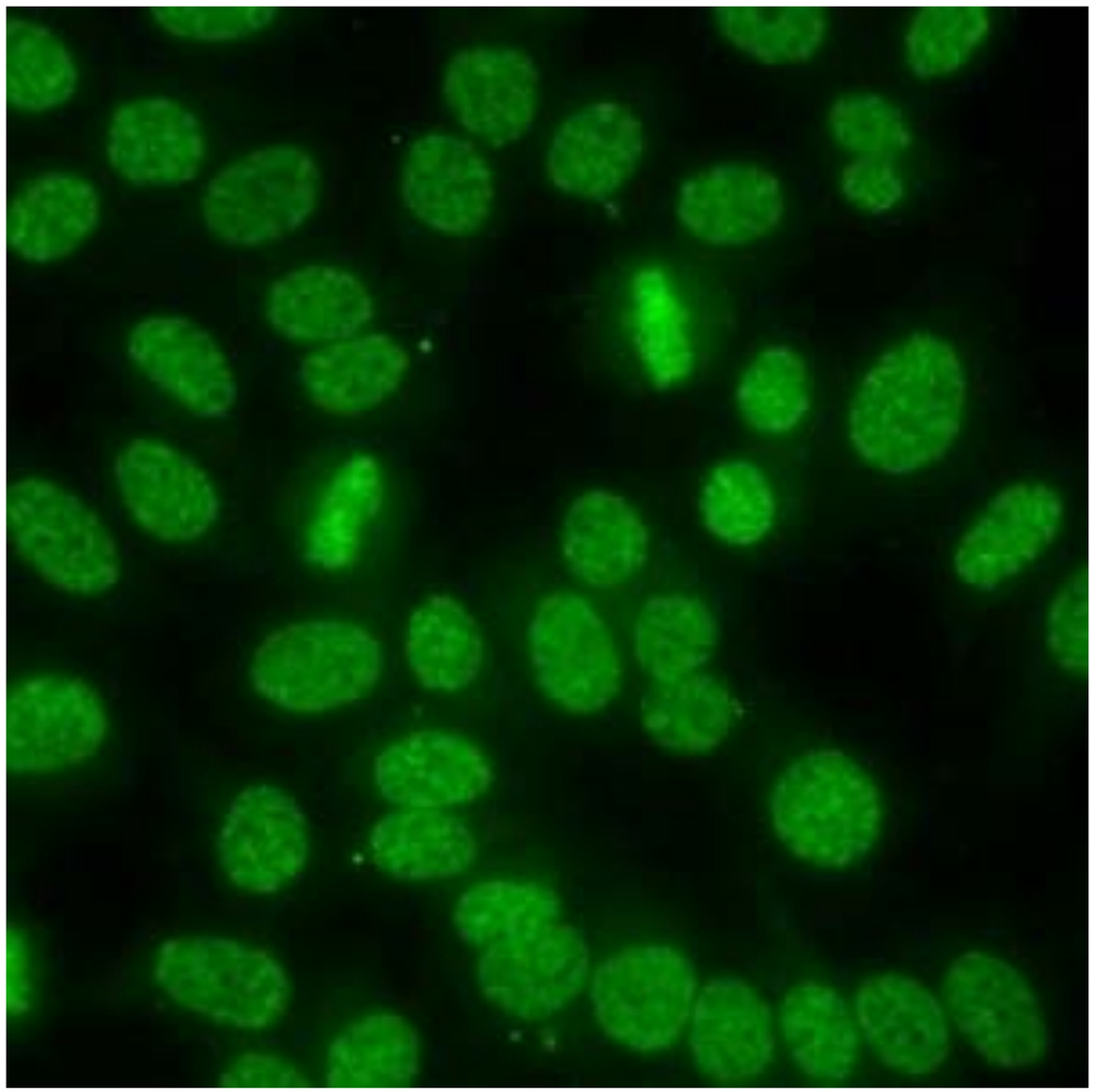


ANA - Importance of the Pattern

- Most patients with SLE will have homogenous or speckled
- Centromere pattern (with CENP-B ENA) high association with limited Scleroderma
- Most are non-specific
- Of interest - Dense Fine Speckled

Dense Fine Speckled





Dense Fine Speckled

- Can be very similar/confused with homogenous
- Curiously more prevalent in apparently healthy individuals than in autoimmune rheumatic disease (AIRD) patients.
- Discovered in 2011 initially patients with interstitial cystitis then autoimmune thyroid disease and dermatitis.
- Confirmed in multiple cohorts. With rates of AIRD of approximately 0.7%- 3.8%.
- Associated with ENA - DFS-70.
    - Because of their rare prevalence in AIRD patients, isolated anti-DFS70 antibodies are being increasingly considered as important biomarker to exclude the diagnosis of AIRD.
    - **The likelihood ratio (LR+) for the absence of AIRD 10.9 (if only this ENA positive)**
    - **ie/ very reassuring.**

Clin Lab. 2016;62(4):499-517.

ANA - when to order

Only when there is moderate to strong suspicion of having an autoimmune rheumatic disease (AIRD).

ie/ the art of medicine.

What diseases?

Table 2. Conditions other than SLE associated with positive ANA[23,24]

Systemic autoimmune diseases	Organ-specific autoimmune diseases	Non-autoimmune associations
Scleroderma	Autoimmune hepatitis	Viral infections (Infectious mononucleosis, parvovirus, hepatitis C, HIV)
Sjögren's syndrome	Primary biliary cirrhosis	Bacterial infections (infective endocarditis, TB)
Polymyositis or dermatomyositis	Grave's disease	Parasitic infections
Rheumatoid arthritis	Hashimoto's thyroiditis	Malignancy
Mixed connective tissue disease	Idiopathic pulmonary fibrosis	Normal population 1:40 (25–30%) 1:80 (10–15%) 1:160 (5%)

Table 10. Conditions associated with a positive antinuclear antibody (ANA)

ANA very useful for diagnosis
Systemic lupus erythematosus
Systemic sclerosis
ANA somewhat useful for diagnosis
Sjögren's syndrome
Polymyositis-dermatomyositis
ANA very useful for monitoring or prognosis
Juvenile chronic arthritis
Raynaud's phenomenon
ANA is a critical part of the diagnostic criteria
Drug-associated lupus
Mixed connective tissue disease
Autoimmune hepatitis
ANA not useful or has no proven value for diagnosis, monitoring or prognosis
Rheumatoid arthritis
Multiple sclerosis
Thyroid disease
Infectious disease
Idiopathic thrombocytopenic purpura
Fibromyalgia

so… when to order?

Signs and Symptoms

- Inflammatory arthritis of generally small joints
- Photosensitive or discoid rash
- Dry eyes or mouth
- Serositis (pericarditis or pleuritis)
- Sclerodactyly
- Raynaud's phenomenon
- Muscle weakness
- Alopecia
- Seizures
- Dilated nail fold capillary loops

Pathology Results

- Haemolytic anaemia
- Thrombocytopaenia
- Leucopaenia –lymphopaenia +/- neutropaenia
- Hypergammaglobulinaemia
- Haematuria
- Proteinuria

Adapted from “EVOLVE” Draft

SLE

2012 SLICC Classification Criteria for SYSTEMIC LUPUS ERYTHEMATOSUS

Biopsy proven LUPUS NEPHRITIS and ANA or anti-DNA

CLINICAL

- Acute cutaneous LE
- Chronic cutaneous LE
- Oral ulcer
- Alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leucopenia/ lymphopenia
- Thrombocytopenia

IMMUNOLOGIC

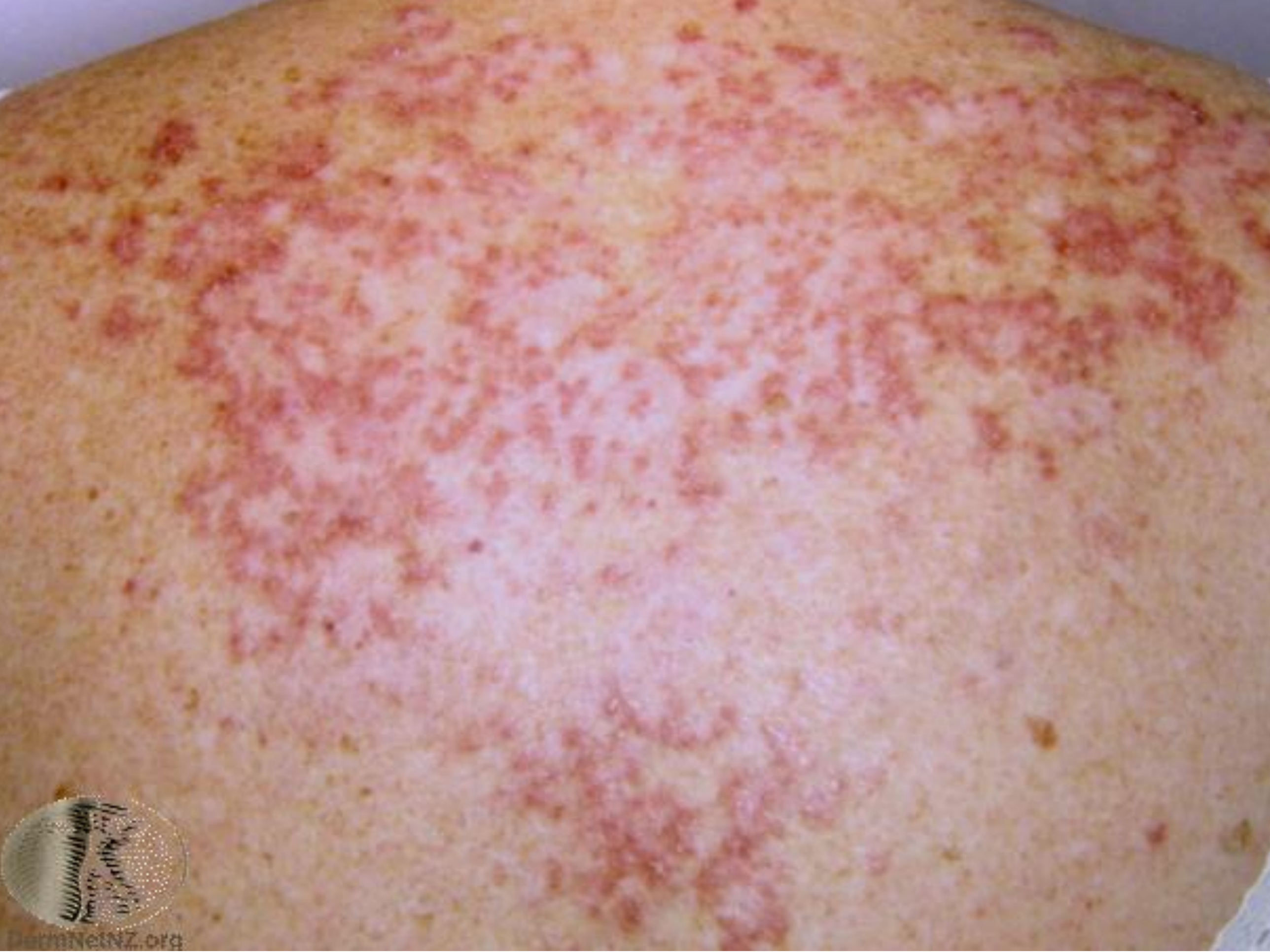
- ANA
- Anti-dsDNA
- Anti-Sm
- aPL antibodies
- Low complement
- Direct Coomb's test

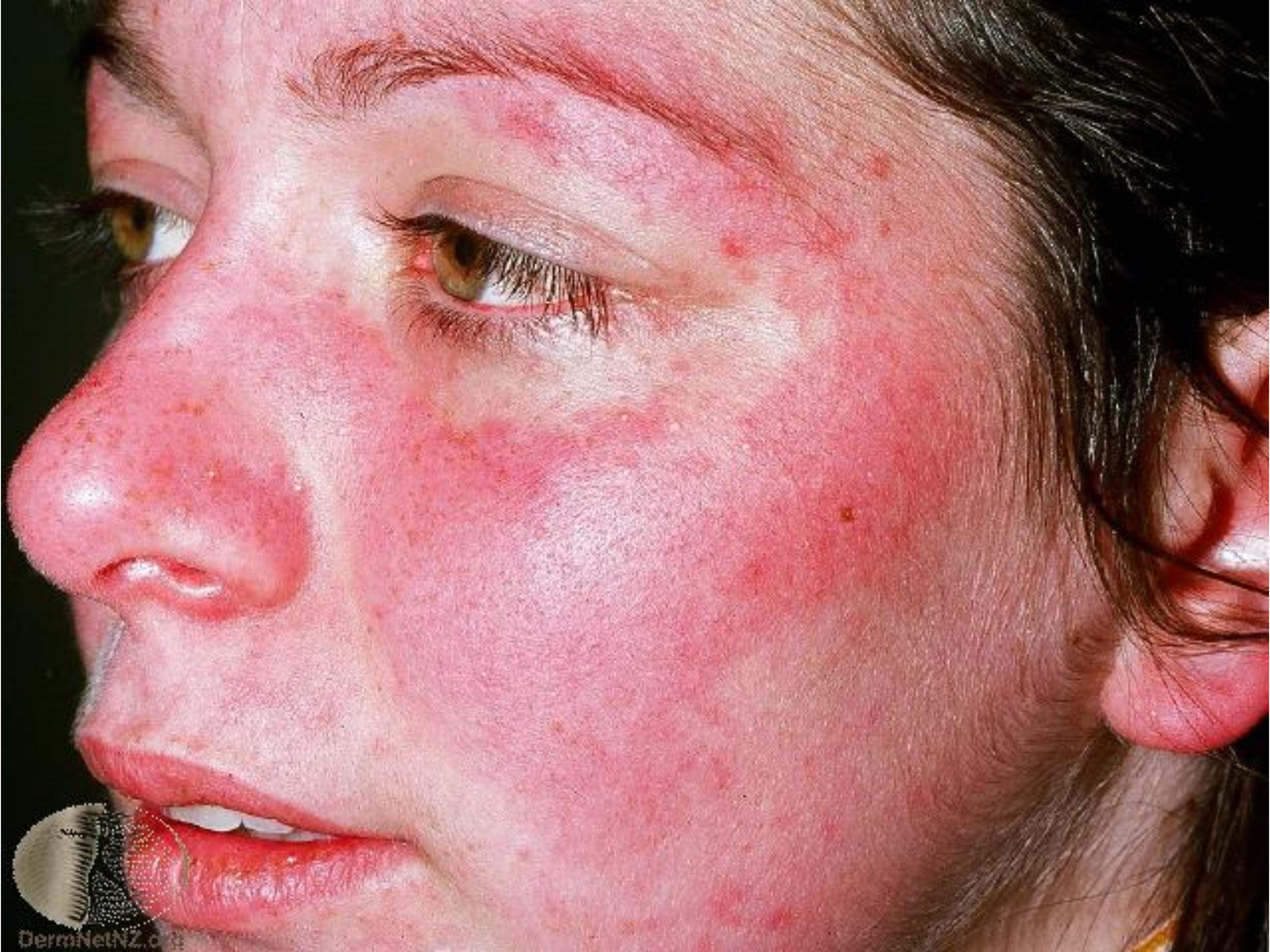
AT LEAST 4 CRITERIA
(1 Needs to be IMMUNOLOGIC)

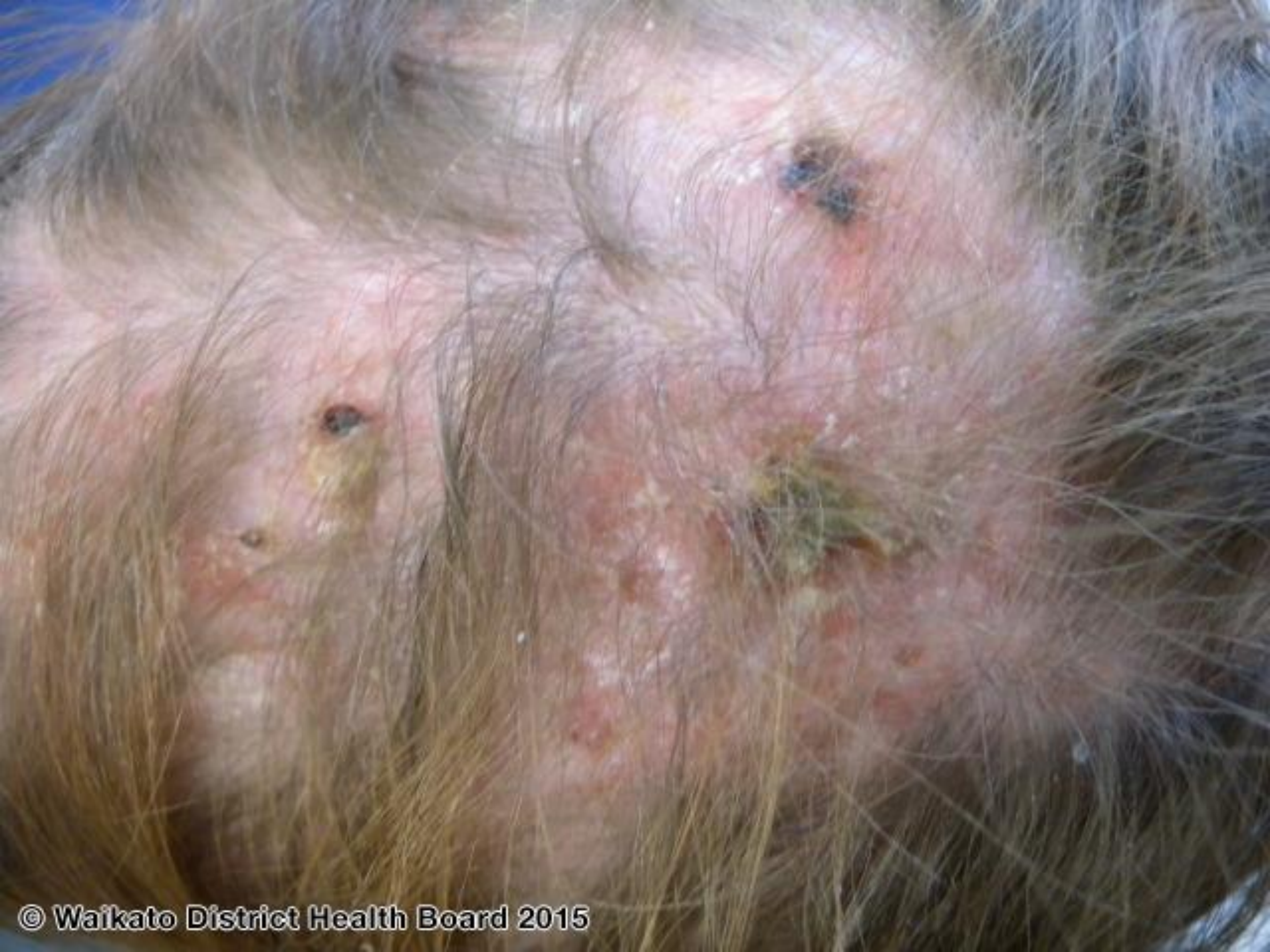
Petri M, Orbai AM, Alarcon GS, et al. Arth & Rheum 2012; 64 (8): 2677-86.

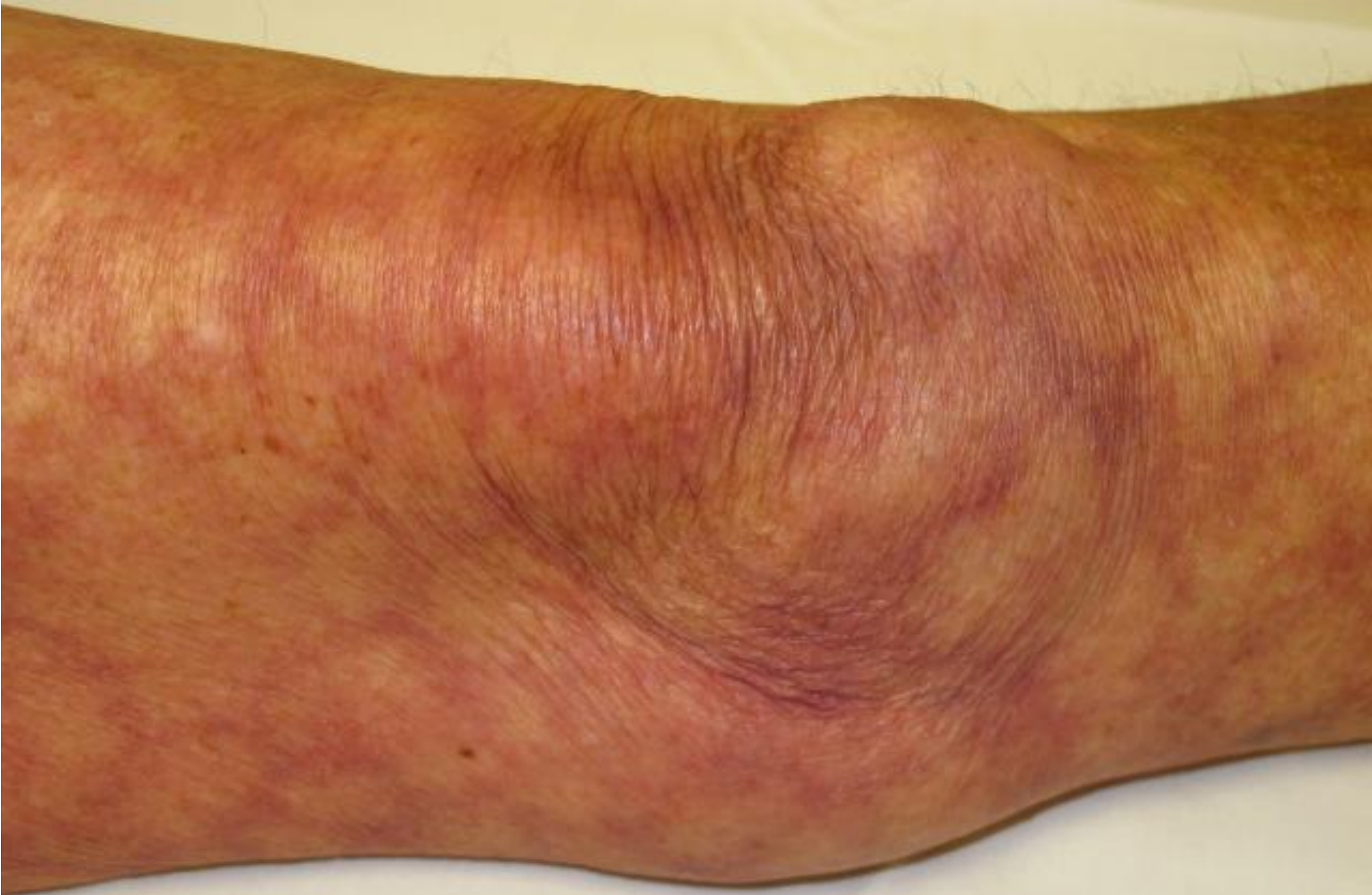
SLE

- Inflammatory arthritis of generally small joints (EMP/S)
- Dry eyes or mouth
- Serositis (pericarditis or pleuritis)
- Seizures
- Photosensitive or discoid rash
- Alopecia



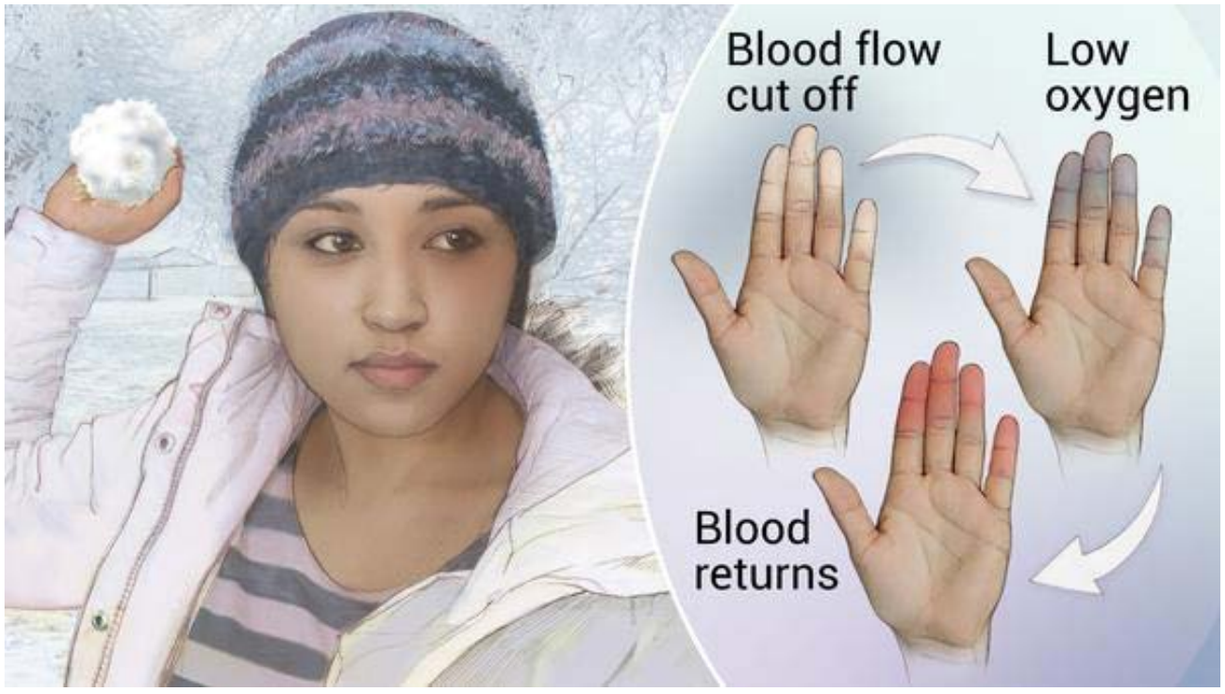

DermNetNZ.org

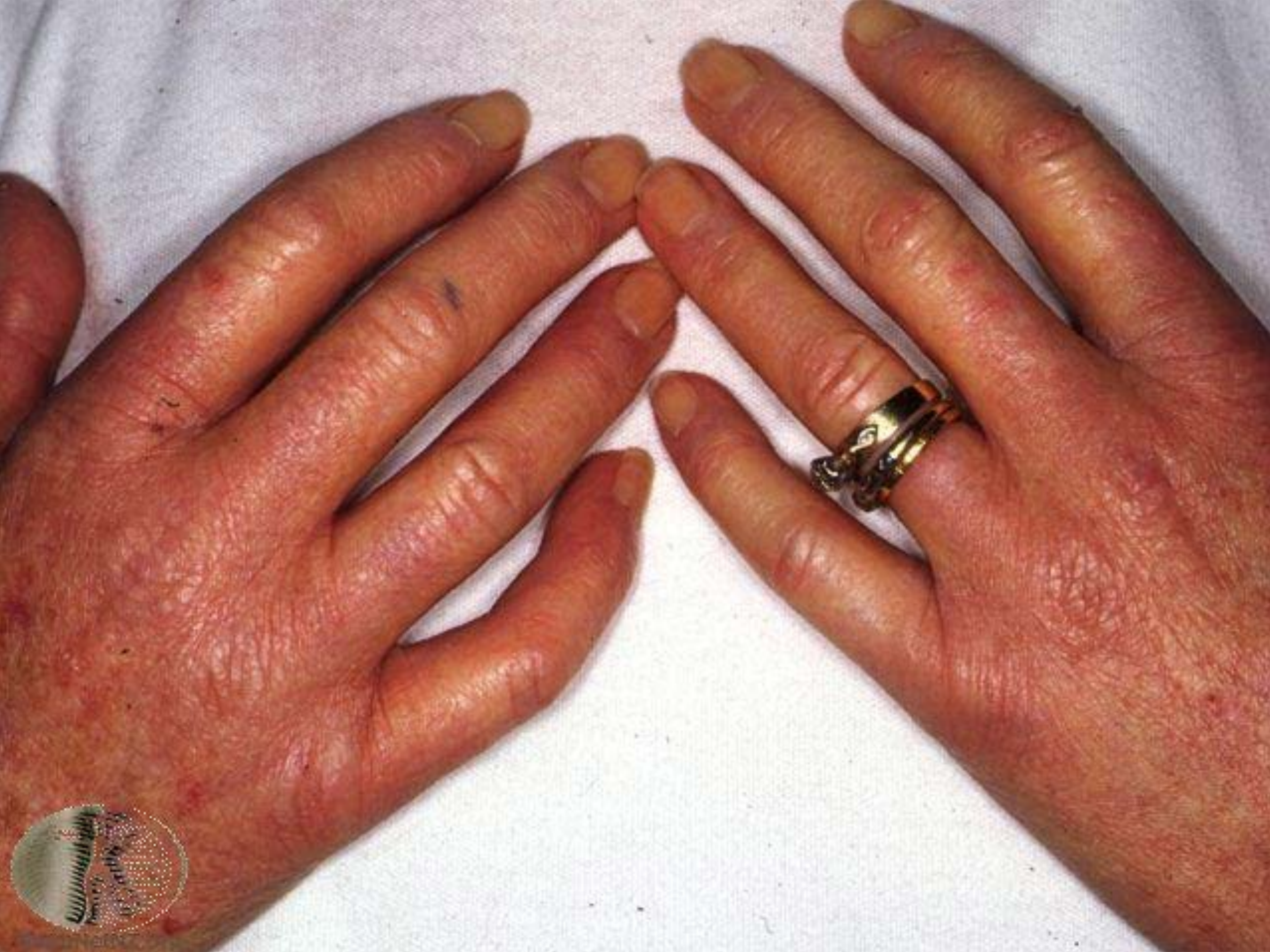


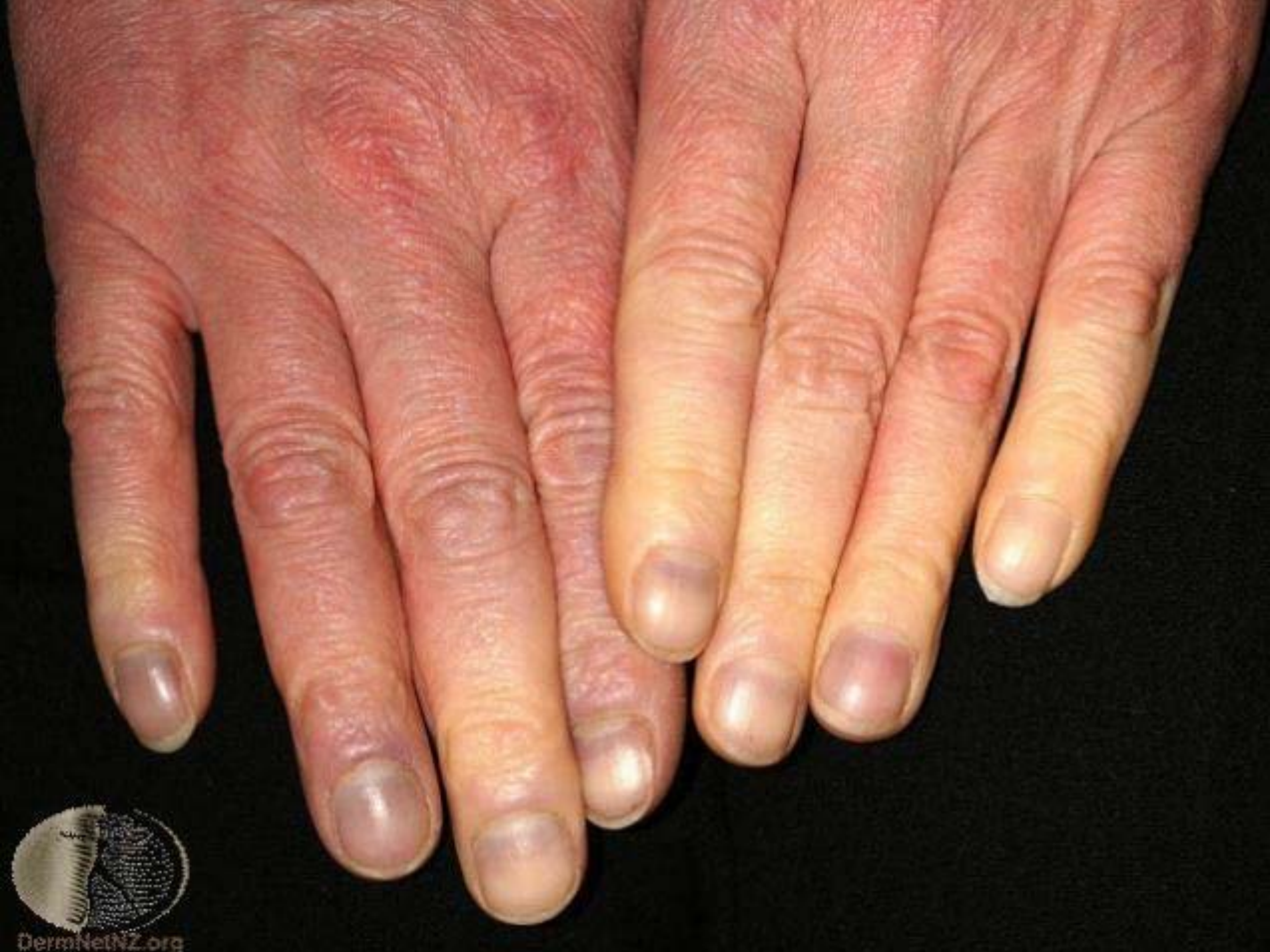


Systemic Sclerosis

- Raynaud's phenomenon
- Sclerodactyly
- Seizures
- Dilated nail fold capillary loops



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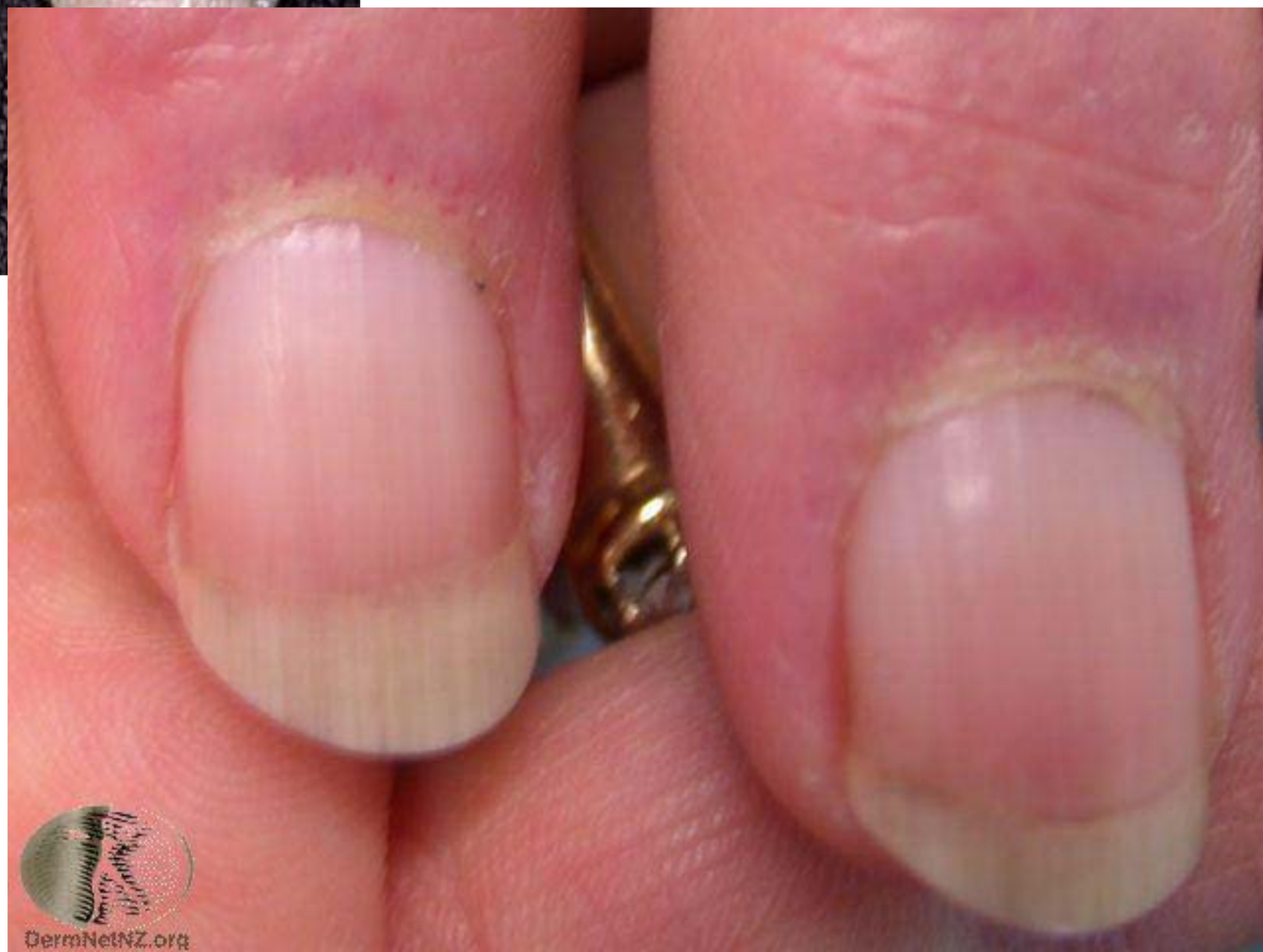
Dermatomyositis/ Polymyositis

- (proximal) Muscle weakness
- Pathognomonic rash
  - Gottrons papules
  - Shawl sign
  - Heliotropic rash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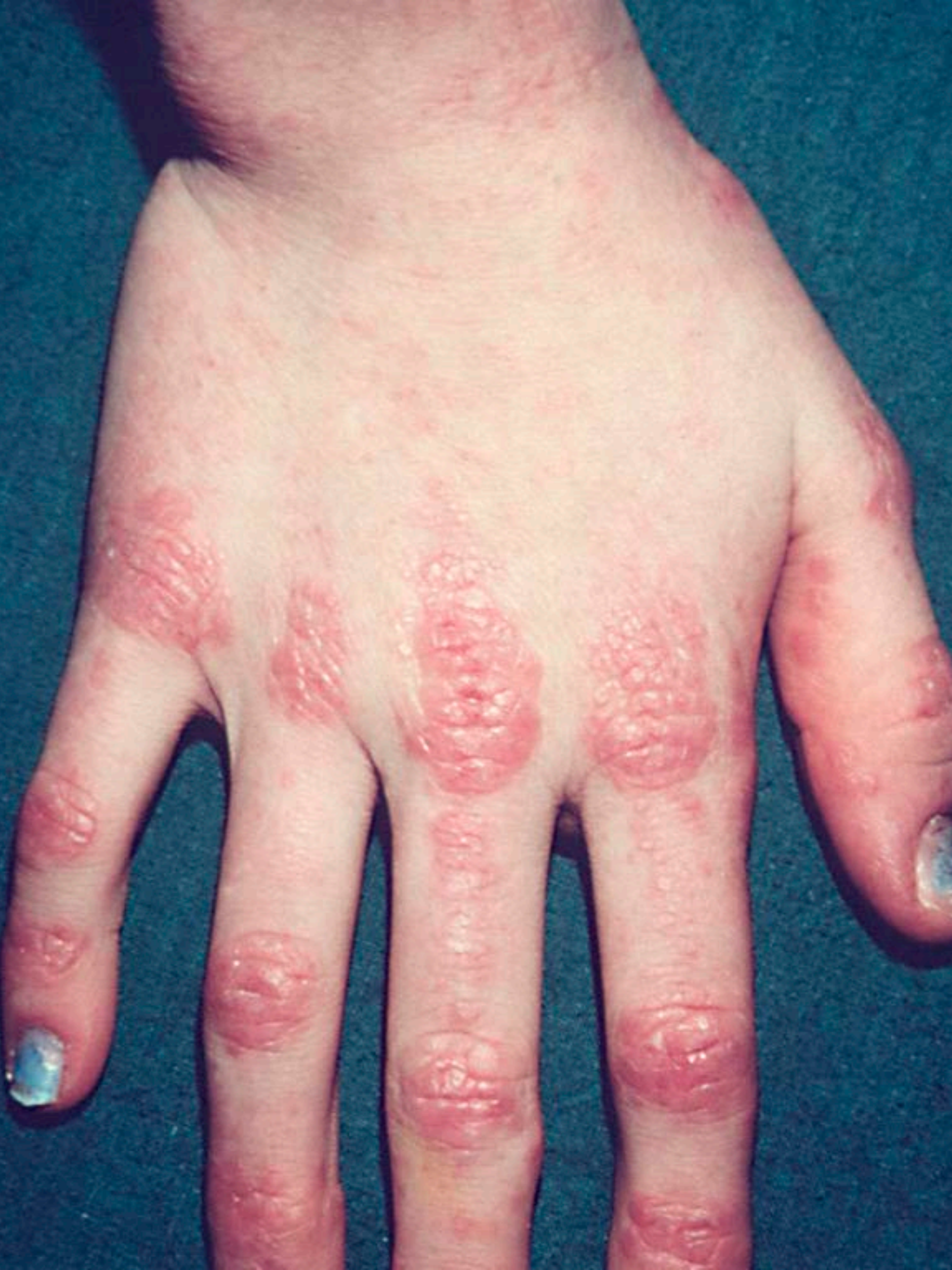
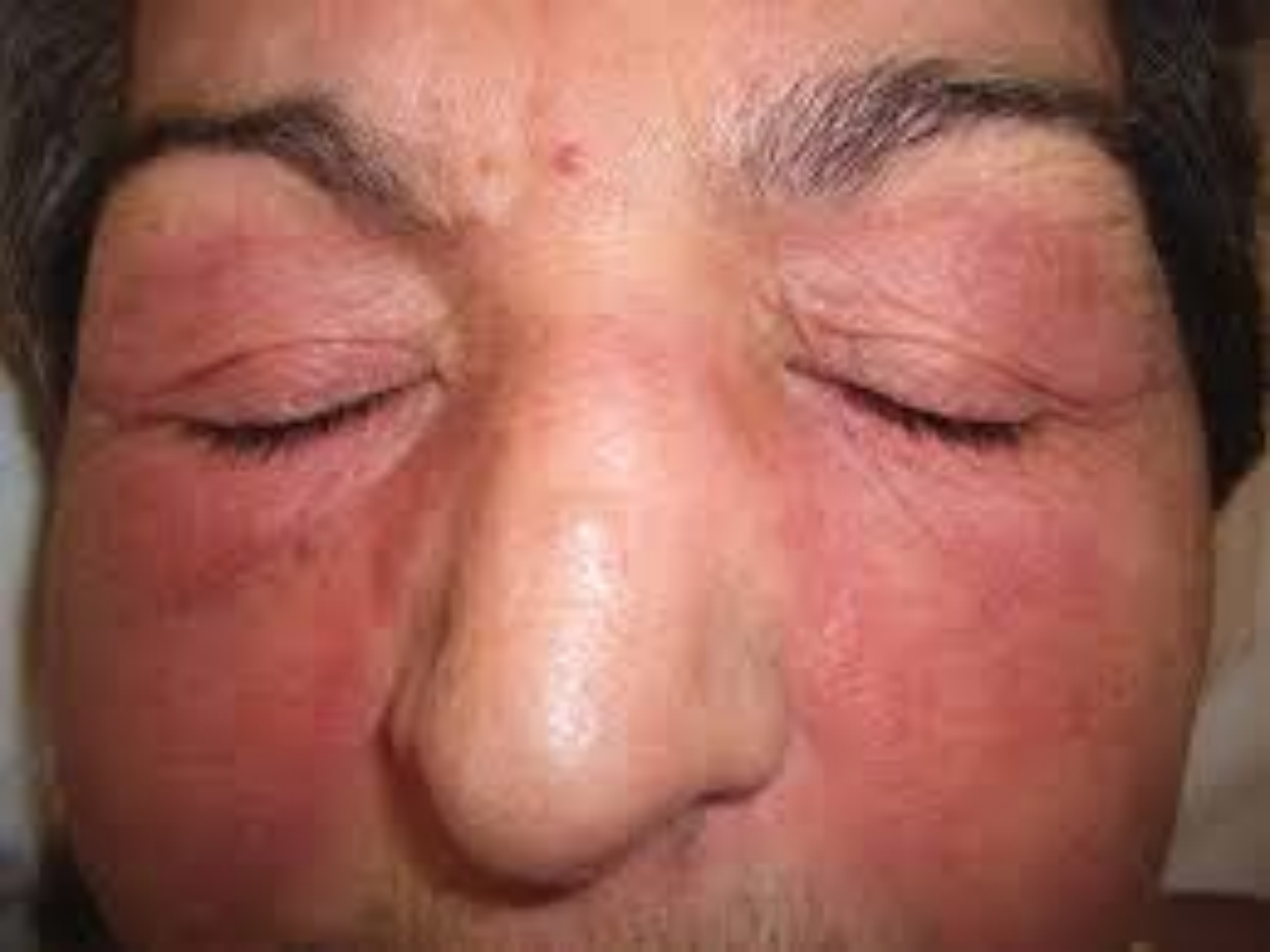
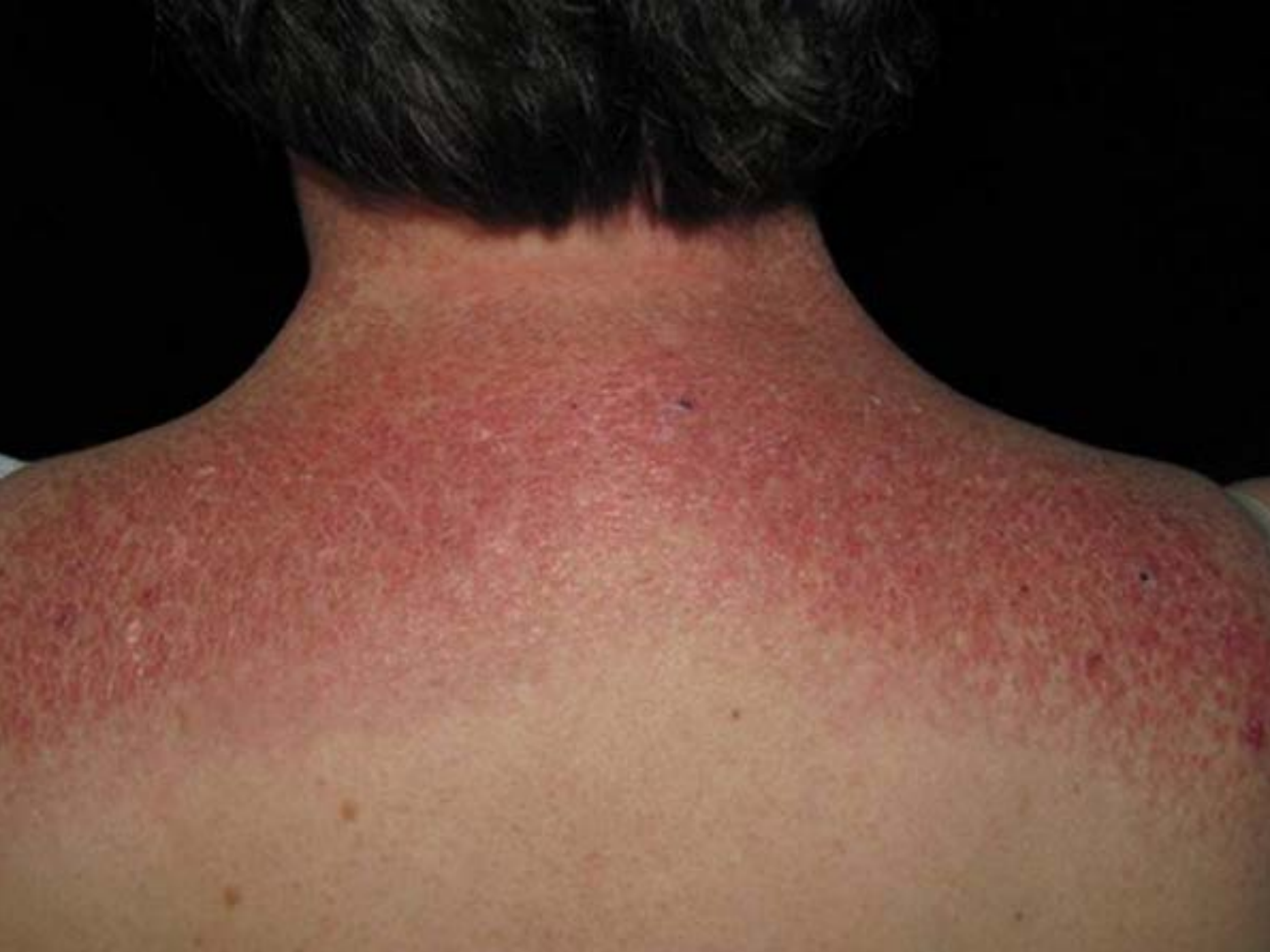






Juvenile Arthritis

so… when to order?

Pathology Results

- Haemolytic anaemia
- Thrombocytopaenia
- Leucopaenia –lymphopaenia +/- neutropaenia
- Hypergammaglobulinaemia
- Haematuria
- Proteinuria
- Renal failure

Adapted from “EVOLVE” Draft

Clinical Recommendations For ANA Testing

Recommendation 1

ANA testing should not be performed unless there is a significant clinical likelihood of autoimmune disease.

ANA should not be a first line test for the investigation of fatigue or musculoskeletal pain, unless accompanied by other clinical features to suggest autoimmune disease.

Recommendation 2

ANA testing may be indicated if patients present with one of the following:

- Arthritis/demonstrable synovitis
- Pleurisy, or pericarditis
- Photosensitive rash
- Clinical and laboratory evidence of myositis
- Skin changes to suggest scleroderma or vasculitis
- Raynauds phenomenon
- Haemolytic anaemia, thrombocytopenia or neutropenia
- Laboratory evidence of a renal disorder (eg active urinary sediment)
- Laboratory evidence of a hepatic disorder
- Evidence of a central nervous system disorder
- Recurrent thrombosis or late miscarriage

Some of the above symptoms may also occur in the setting of an intercurrent viral infection, such as CMV or EBV. These situations will lead to a false positive result.

Recommendation 3

ANA and ENA tests rarely need to be repeated. These are diagnostic, not monitoring, tests.

If an unexpected result is given, it is reasonable to repeat the test to confirm the finding. It is also useful to repeat if a person's illness has significantly changed.

ANA positive, now what?

Invariably useful to have **ENA and dsDNA**

Extractable Nuclear Antigens

Standard panel:

- Ro/SSA
- La/SSB
- Sm
- RNP
- SCL70
- PM/SCL
- JO-1
- PCNA

Note:

Anti-histone

&

Anti RNA polymerase III

Ordered separately.

Scleroderma panel:

- SCL-70
- CENP A
- CENP B
- RP11
- RP155
- Fibrillarin
- NOR90
- Th/To
- PMSCL100
- PMSCL75
- Ku
- PDGFR
- Ro-52

Myositis Panel:
HMG-Co (requested separately)

- Mi-2a
- Mi-2b
- TIF1 gamma
- MDA5
- NXP2
- SAE1
- Ku
- PMSCL100
- PMSCL75
- Jo-1
- SRP
- PL-7
- PL-12
- EJ
- OJ

ANA positive, now what?

- To help confirm diagnosis:
  - **ENA**, **dsDNA, C3,** Coombs, APLS Abs
    - if all of the above normal very unlikely to have AIRD
- To assess for extent of disease:
  - ELFT's, FBC, Urine dipstick,
  - (optional) CK, CXR etc

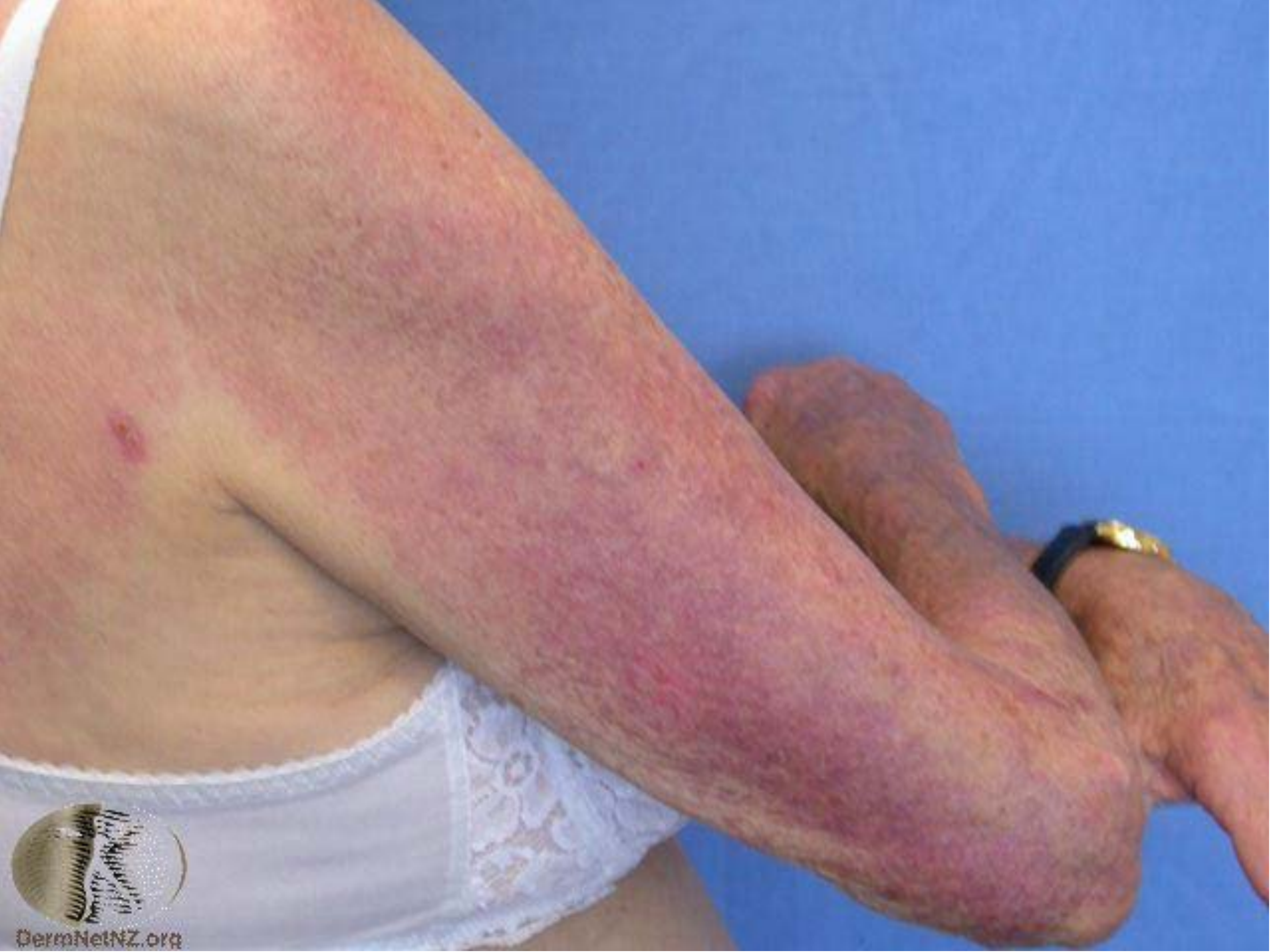
- Management of all AIRD is based on extent of organ involvement and severity of symptoms.

When to repeat the test?

- Generally don’t.
- Remember ANA is NOT a marker of disease activity.
- Could consider if there is a change/new in symptoms. eg/ development of sicca symptoms in a patient with RA.
- New drug and new symptoms- esp: minocycline, TNF inhibitor, Chlorpromazine, Hydralazine, Isoniazid, Methyldopa, Procainamide, Quinidine.
- Can be misleading - e.g.:
  - A phase II clinical trial in SLE for belimumab (monoclonal antibody against BAFF) during the trial measured all patients ANA - with 20-30% negative despite 99% having historical ANA positivity and active disease as entry requirement of study.

Exceptions that prove the rule…

- CASE:
  - 58yo F presented with classic dermatomyositis skin rash and muscle pain
  - No objective weakness on examination
  - Normal CK, negative ANA


DermNetNZ.org

Exceptions that prove the rule…

- Due to pain EMG arranged - borderline myopathic changes.
- ENA panel negative.

Exceptions that prove the rule…

- Sent for specific myositis panel and was anti-MDA5 positive.
- Muscle biopsy subsequently confirmed inflammatory myositis.
- Diagnosis: Anti-MDA5 Dermatomyositis
- Responded well to steroids and Methotrexate.

If high clinical suspicion or concern - refer even if ANA negative.

Summary

- Choosing Wisely and EVOLVE - *useful resource for other specialties*
- ANA in Australia - *significant cost, perhaps area reduce healthcare spending?*
- How is ANA done? ANA titre. ANA patterns and significance. *DFS - can reassure patients.*
- When to consider ordering ANA - when symptoms or signs of AIRD. Few reasons to repeat test in individual patient.
- What to do when ANA positive - supporting investigations and refer
- If strong clinical features still consider referral if ANA negative.

Take home message

“Choose wisely”

Do not order ANA testing without symptoms and/or signs suggestive of a systemic rheumatic disease.

Watch this space for EVOLVE publication soon.

Search

- Home
- Brisbane North Localised Pathways
- Acute Services
- Allied Health
- Child and Youth Health
- End of Life
- Investigations
  - Access Criteria
  - Cardiology Investigations
  - Gastrointestinal Investigations
  - Laboratory Tests
    - **Antinuclear Antibody (ANA) Testing**
    - Calprotectin
    - Children's Blood Tests
    - Fine Needle Aspiration (FNA)
    - Legionnaires' Disease
    - Laboratory Tests
    - Skin Prick Testing
  - Radiology
  - Spirometry Testing Requests
  - Thyroid Scans
- Lifestyle and Preventive Care
- Medical
- Mental Health
- Older Adults' Health
- Pharmacology
- Public Health
- Surgical
- Women's Health
- Our Health System

Red Flags

- Significant proteinuria
- Unwell patient e.g., fever, unexplained weight loss, severe rash or vasculitis

Assessment

1. Consider indications for ANA testing:
   - Request ANA testing in patients only when there is moderate to strong suspicion of having an autoimmune rheumatic disease (AIRD):
     - Signs and symptoms
     - Pathology results
   - ANA test results can be misleading – it is not indicated for:
     - investigating fatigue.
     - musculoskeletal pain without features of systemic rheumatic disease.
     - multiple unexplained physical symptoms.
2. Interpret test results:
   - General principles:
     - The higher the titre the greater the likelihood of significance.
     - titres ≤ 160 are generally not clinically relevant.
     - titres ≥ 320 are more likely to be clinically relevant.
   - A low-titre ANA almost always rules out:
     - drug-induced lupus.
     - systemic lupus erythematosus (SLE).
     - mixed connective tissue disease (MCTD).

   If clinical features suggest these conditions, request non-acute rheumatology assessment even if ANA negative.

Management

Positive ANA results prompt a clinical review and further testing based on the patient's condition.

1. If red flags, request rheumatology advice.

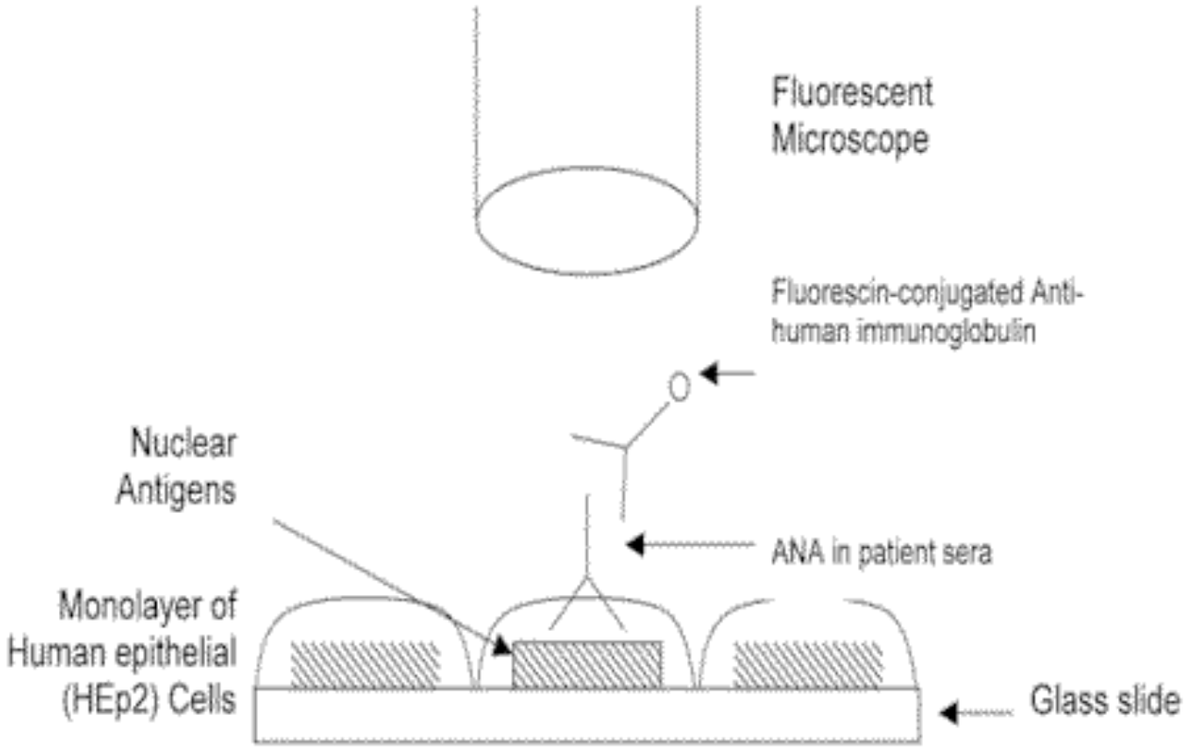
- Examples of ANAs recognizing RBPs include anti-Sm, anti-RNP, anti-Ro and anti-La antibodies1.

- Anti-Sm and anti-RNP antibodies, which are commonly expressed in the same patient, bind to protein components of snRNPs or complexes of snRNP with RNA. Anti-Ro and anti-La antibodies are also commonly expressed together, although antibodies recognizing two different anti-Ro antigens exist. Antibodies against Ro60 bind to the protein component of a complex comprising small cytoplasmic RNA molecules; by contrast, the anti-Ro52 antibody recognizes a member of the tripartite motif (TRIM) family, which is a ubiquitin ligase that does not form RNA
or protein complexes10,11. Other antigens recognized by ANAs, such as ribosomal P proteins and the Ku protein, which can bind DNA strand breaks as a dimer12,13, do not fit in this categorization, which has been most informative for SLE.

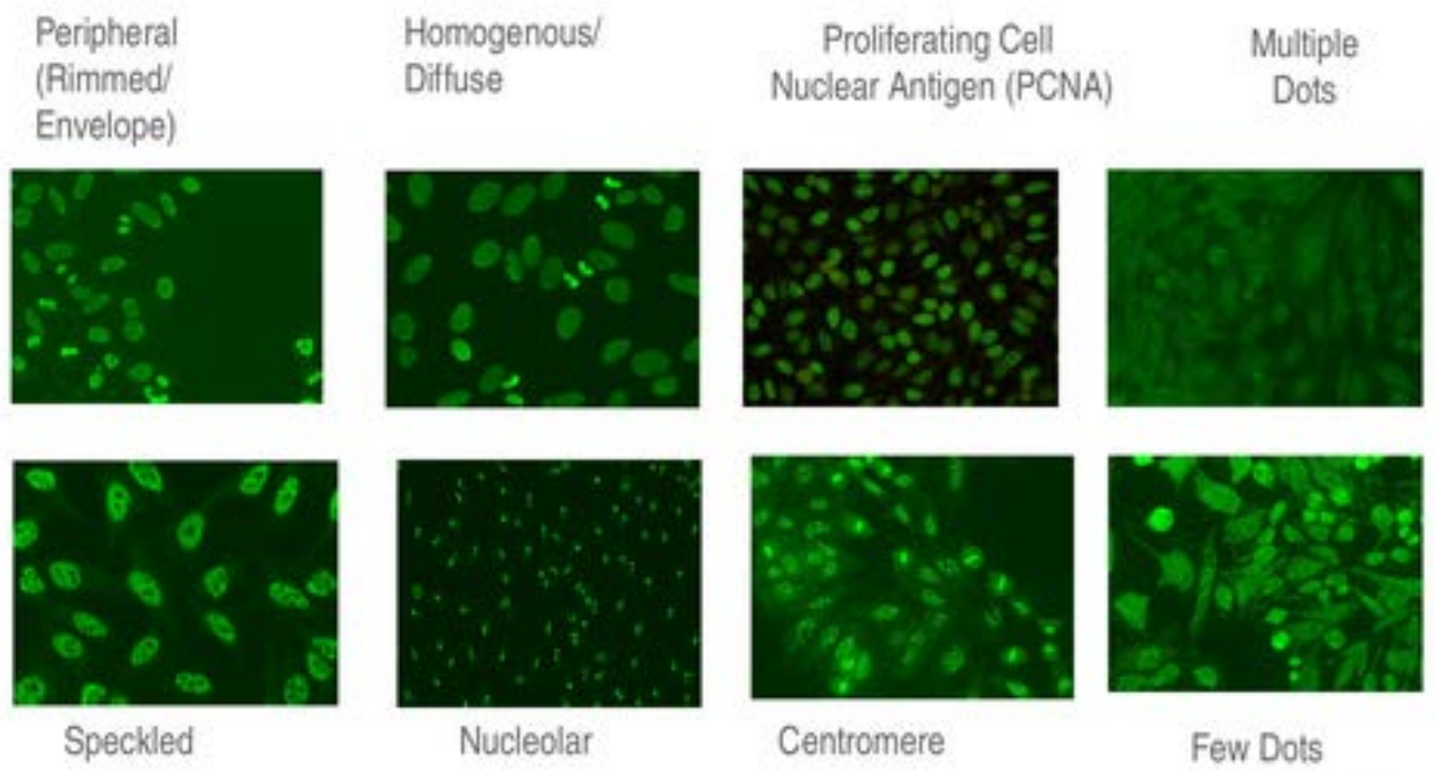
- Case studies
- three cases
- 1 - Positive ANA 1:160, (Ro and La positive) PO ulcers and arthralgia on HCQ and NSAIDs, became ANA negative. 16 years into diagnosis rising dsDNA and low complement - acute crescentic GN, (Class IV).
    - mild SLE - watch as can develop late severe disease
- 2 - ANA negative, deranged LFT’s, mild CK, classic skin disease
    - MDA5 positive myositis
- 3 - Fatigue, myalgia, wt gain
    - ana positive DFS, ENA DFS-70

- 181,819 patients had ANA tests performed and 51,905 were ANA positive. The DFS pattern was found in 5.7% of ANA positive patients. Within this group of patients, only 1.8% were positive for antibodies to ENA and only 0.7% had anti-dsDNA antibodies level greater than 9 IU/mL. RF and anti-CCP antibodies were positive in 6.3% and 4.1% of DFS positive samples, respectively. There were only two samples positive for anti-phospholipid antibodies when the DFS pattern was present. The presence of the DFS pattern as detected by IIF is infrequently associated with autoimmune markers of SARD which is consistent with international studies.

Dense fine speckled indirect immunofluorescence pattern in an Australian population
Broadfoot, Andrew et al.
Pathology , Volume 48 , Issue 3 , 247 - 250



Patterns



Quest Diagnostics