Systemic Lupus Erythematosus

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Revise Nephrology

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Talk outline

- Case study
- SLE defined
- Pathophysiology
- Clinical findings
- Laboratory tests
- Classification criteria
- Management of SLE
- Lupus nephritis

Case Study

- Mr DW, 18 year old man first presented to Blacktown Hospital
  - Initial presentation with cough, weight loss, fevers and night sweats
  - Born in Sudan but had spent considerable time in Egypt
  - Initially thought to have TB and was in isolation until cultures cleared him
  - Developed a widespread rash (difficult to appreciate), small joint synovitis

Blood and urine tests

- 0.99 g/L proteinuria
- C3 0.42 g/L (0.74-1.57 g/L)
- C4 <0.07 g/L (0.13 – 0.41 g/L)
- ANA: 1:2560 speckled
- DNA antibodies were 2,313 IU/ml (normal <29)
- ENA: RNP positive

Renal biopsy and treatment

- Renal biopsy revealed Class III Lupus nephritis
- Pulsed with methylprednisolone and started on mycophenolate and oral steroids, along with hydroxychloroquine
- Proteinuria settled with steroids

Issues

- Understanding what SLE is and the need for medications
- Compliance with regimen – has been poor due to financial constraints, incarceration
- Long-term control of disease
  - What are the determinants that will determine his prognosis?

2023 Upate…..stop the press

- In 2022, DW developed Class IV NYHA Heart Failure
  - Admitted to Westmead ICU
  - Being considered for transfer to St Vincent's for heart transplant consideration
  - EF was in the low 20s

- We decided to pulse him with IV steroids and give him 2 x 1 grams of rituximab
- 6-9 months down the track, he is very well and active again
- The patient was asking about CAR-T cell therapy…..

What is SLE?

- Systemic, multisystem autoimmune disease
- Strong female:male preponderance (~8:1)
- Considerable ethnic differences in frequency
  - More common in Africa, Asian population than Caucasian populations
- Globally, estimates of SLE prevalence in adults range from 30 to 150 per 100 000, and incidence ranges from 2·2 to 23·1 per 100 000 per year
- Characterised by autoantibodies directed against nuclear components

Pathophysiology

- Defining feature is autoantibodies directed against chromatin or DNA
- Antibody-antigen complexes may lodge in small blood vessels, leading to disease manifestations
- Exposure to DNA may occur by aberrant apoptosis and release of DNA into the circulation
  - This may, in some individuals, lead to an auto-reactive immune response
- Also thought to be a defect in clearance of immune complexes and persistence of apoptotic cell debris

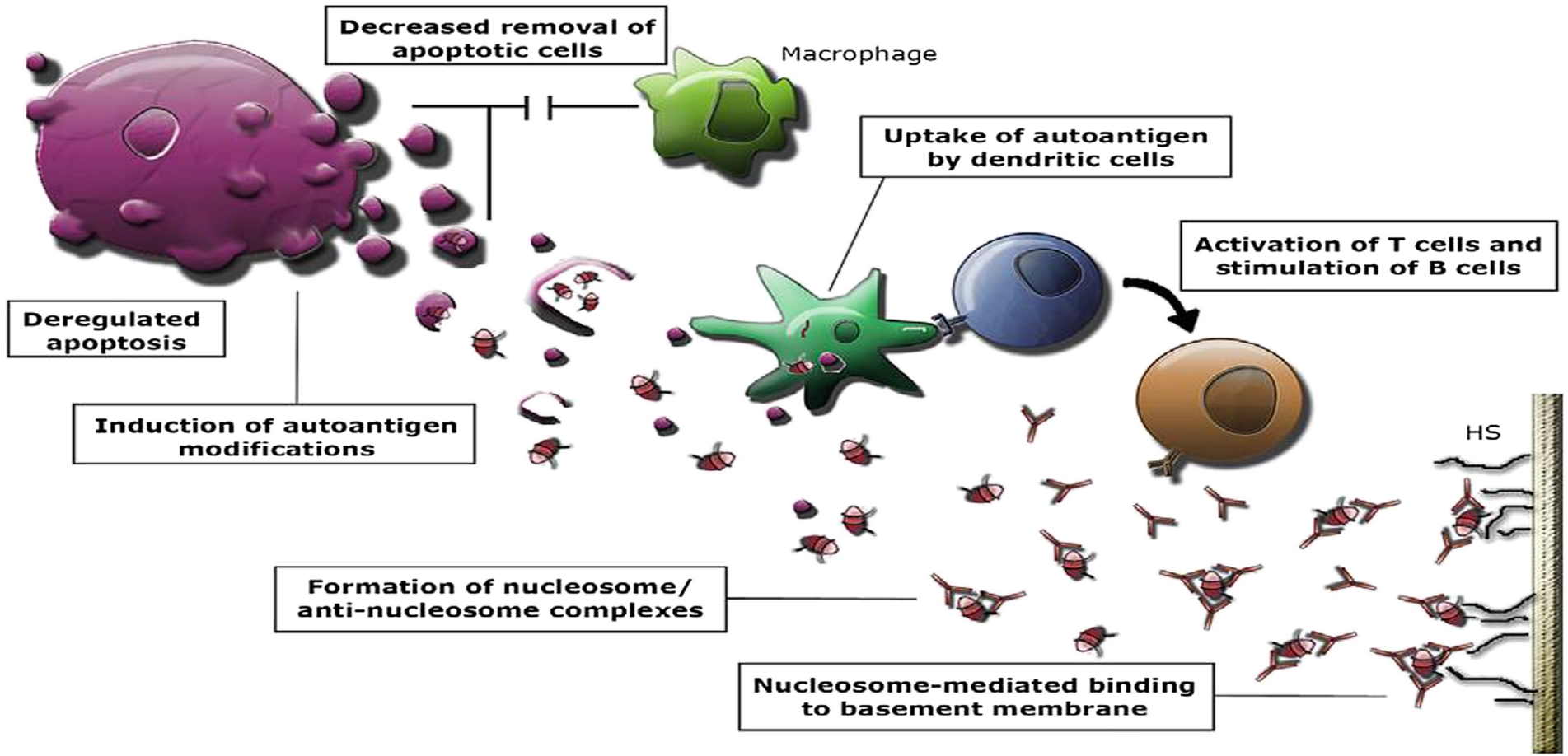
B cell responses in SLE

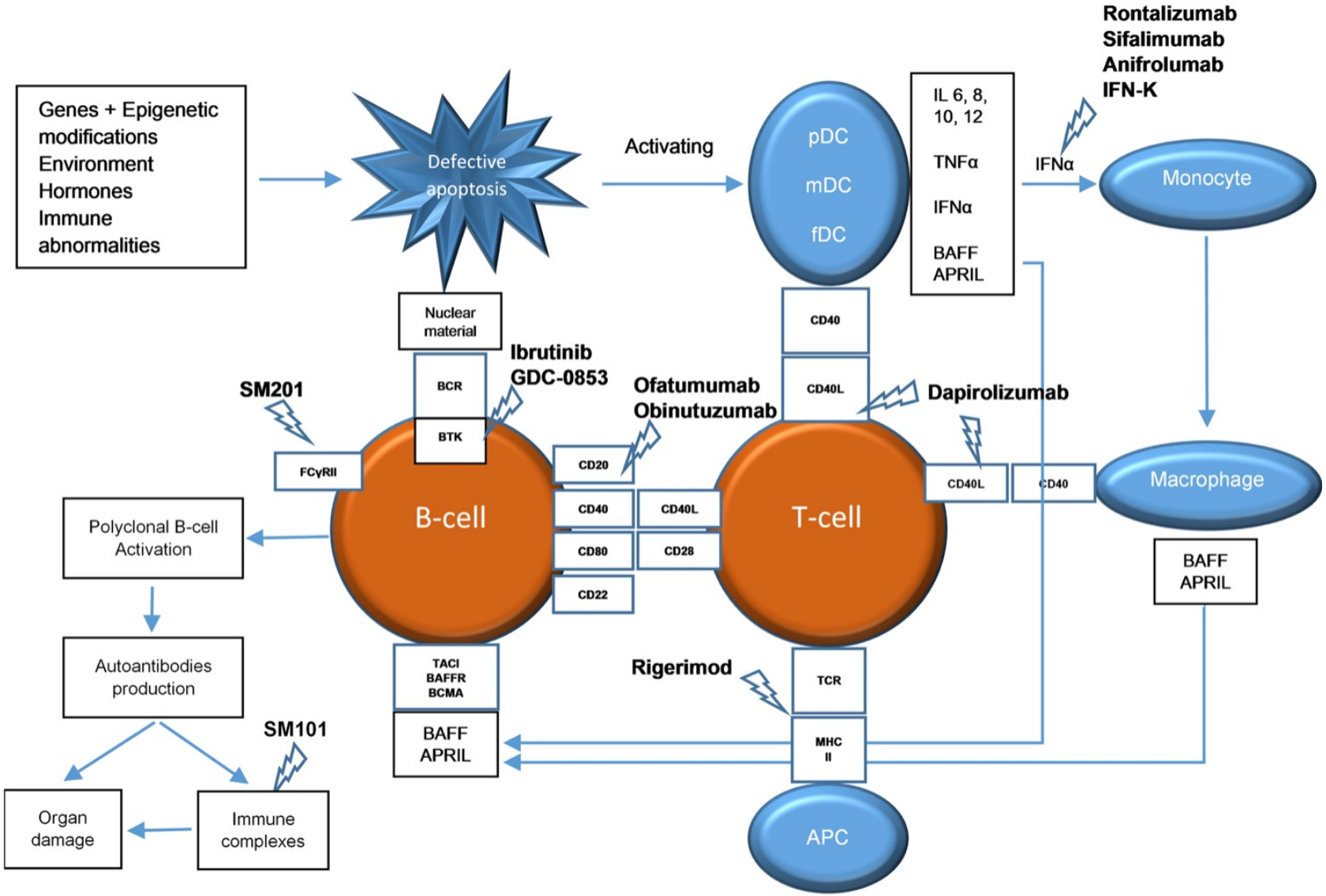
- Persistently active B cell responses may be partly driven by B cell activating factor, BAFF (targeted by new SLE drug, Belimumab).

- Innate immune responses may be also involved, with Toll like receptors (TLRs) binding to DNA or RNA ligands

- Pathogens, such as viruses or bacteria, may lead to innate immune activation and disease progression

Pathogenesis of SLE



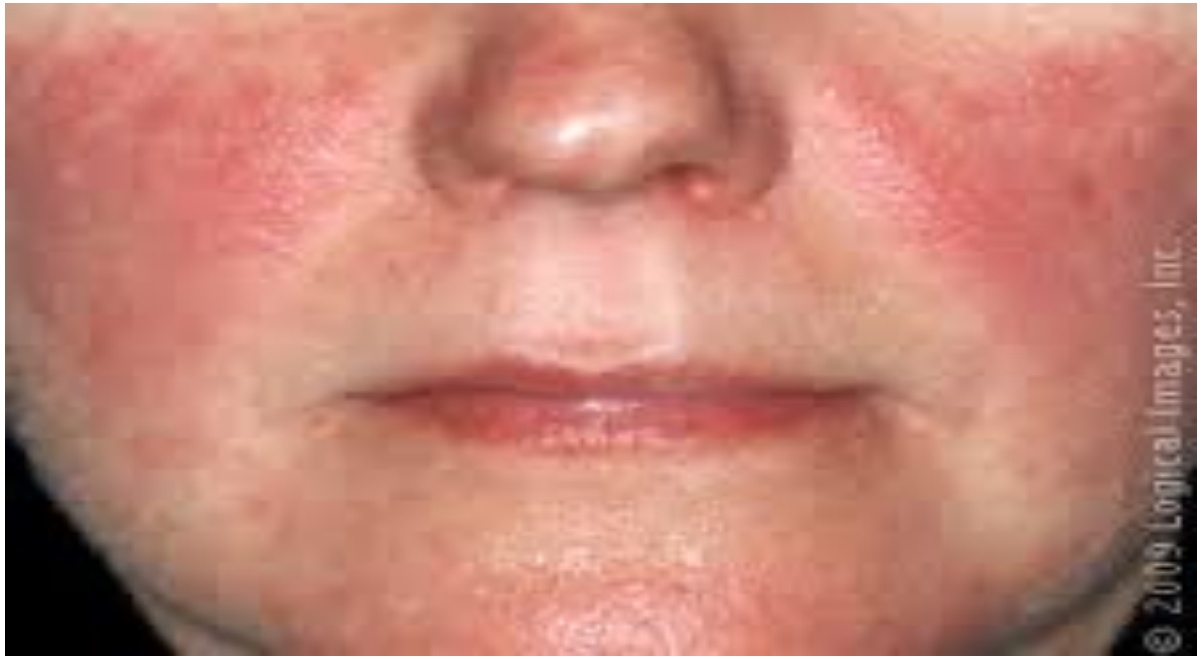


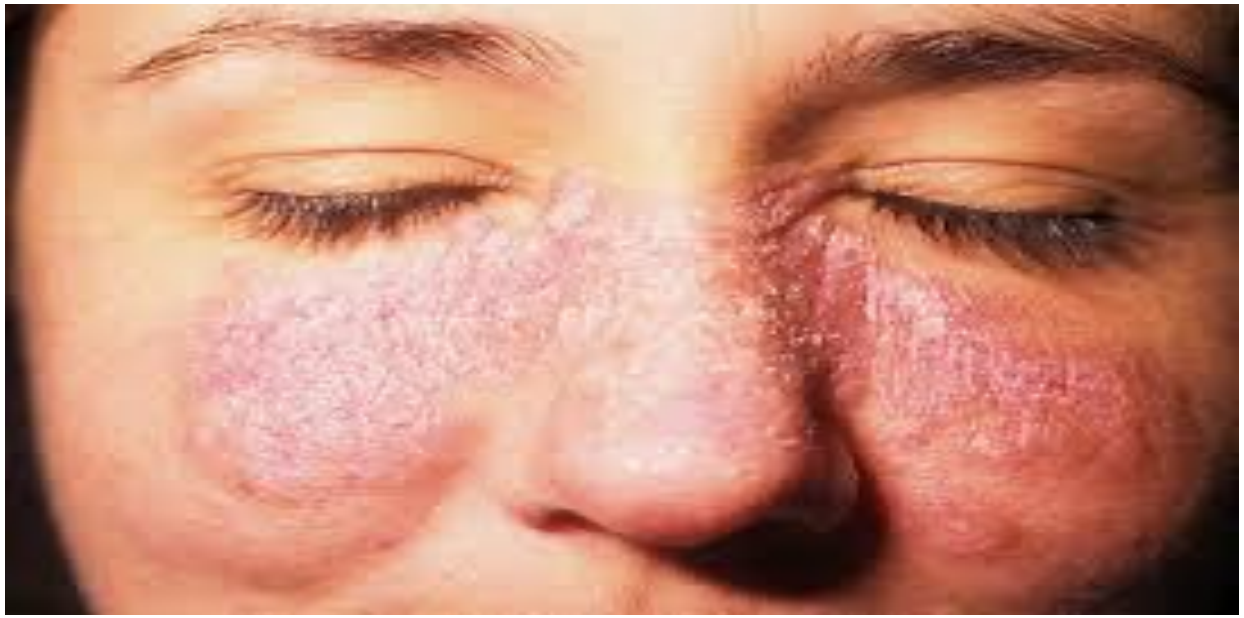
Rheumatology, Volume 58, Issue 3, March 2019, Pages 382–387

Clinical features

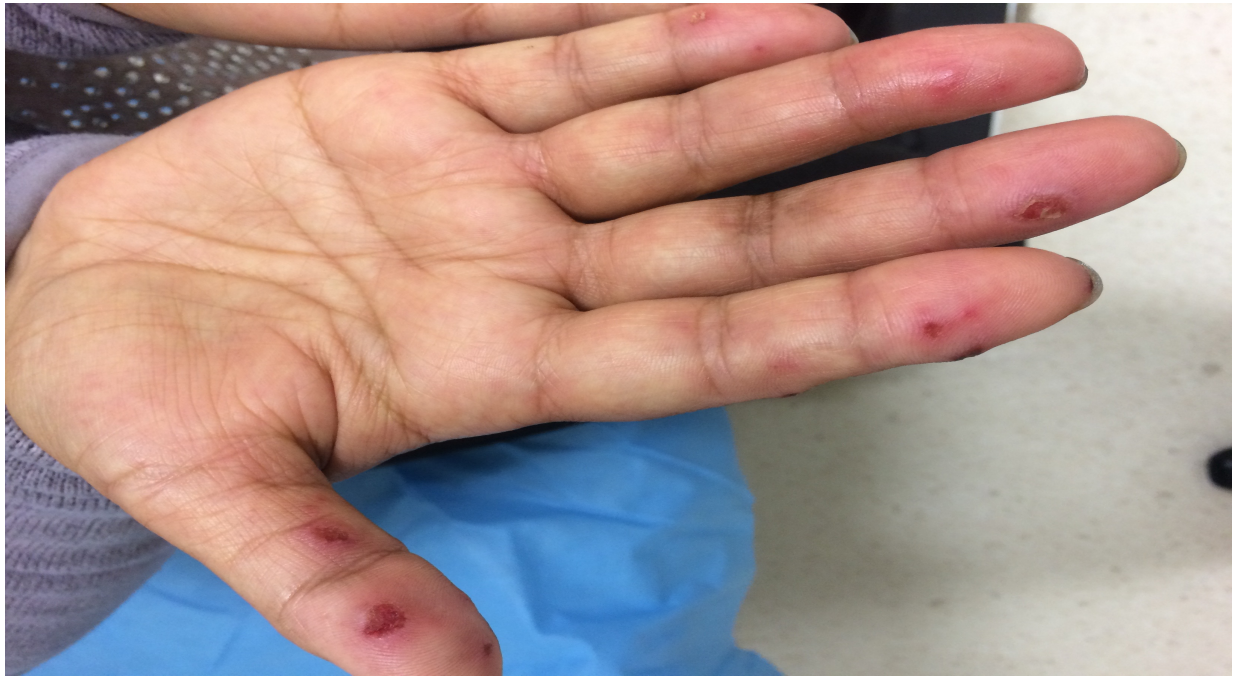
- Constitutional symptoms: fevers, weight loss (or gain), fatigue, myalgias
- Cutaneous and joints manifestations are the commonest:
  - Malar rash, discoid lupus, photosensitive rash
  - Arthralgias/arthritis of hands, wrist, feet, knees
- Raynaud's phenomenon
- Oral ulceration
- Alopecia
- Sicca symptoms
- Serositis
- Neurological complications
- Renal (nephrotic range proteinuria)
- Can affect any organ!

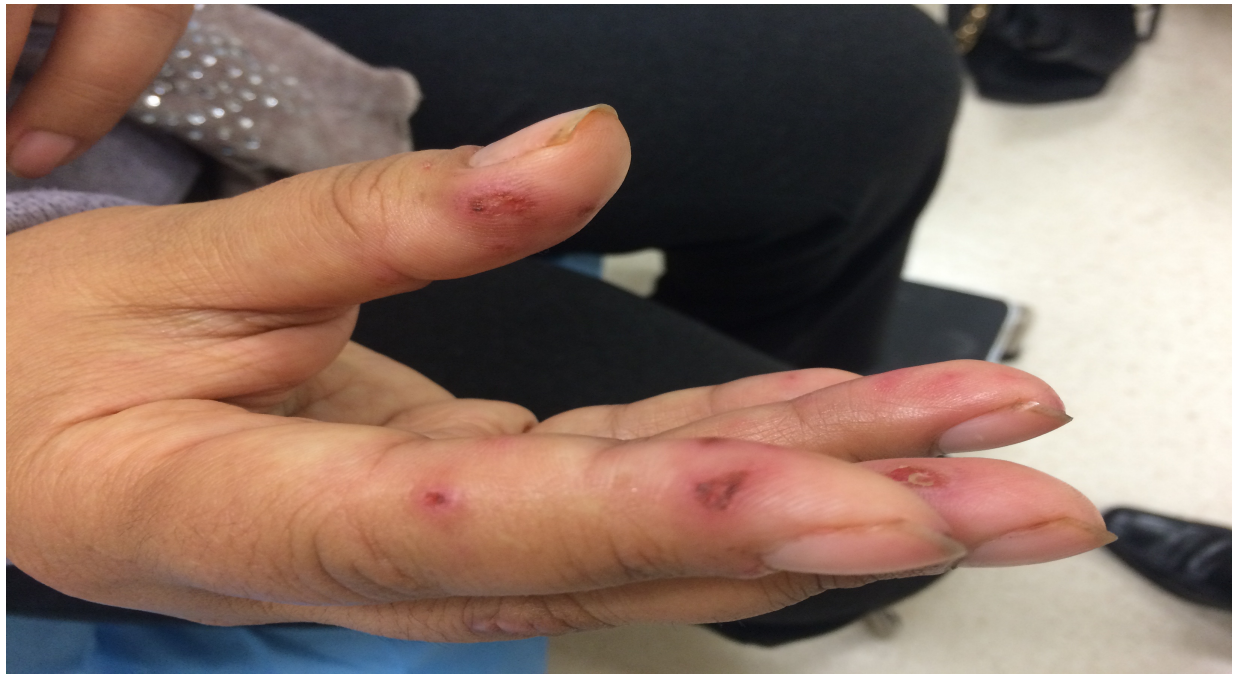
Malar rash



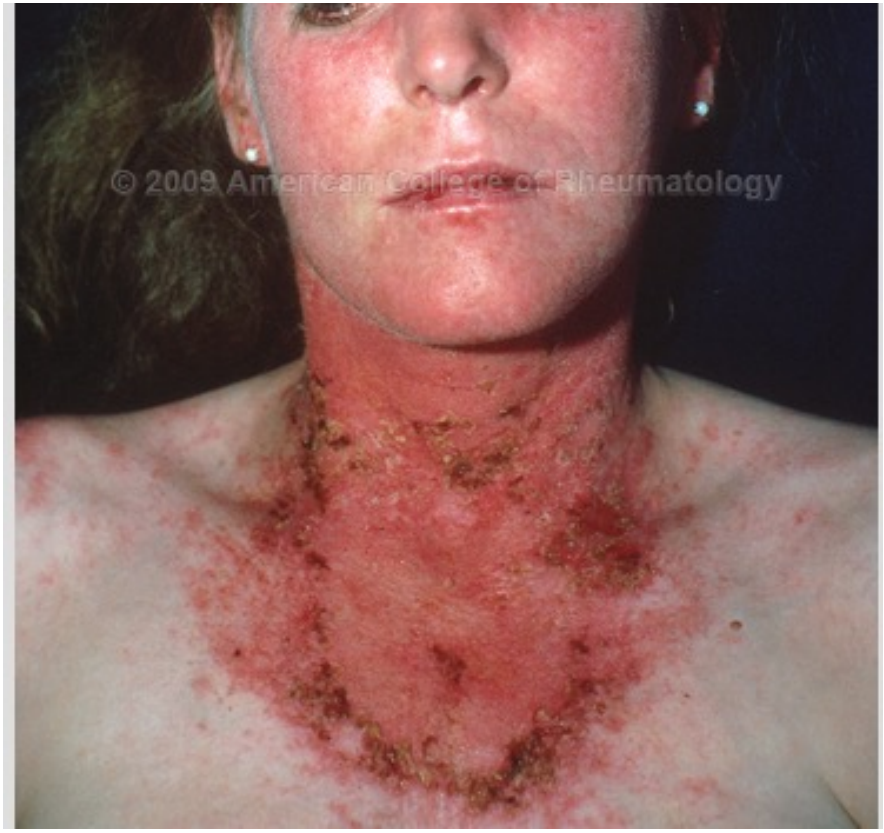


Discoid Lupus





Photosensitive rash



Laboratory tests

- Tests can be divided into those useful in diagnosis or in monitoring

- **Diagnostic tests:**
  - Anti-nuclear antibody (ANA)
  - Extractable nuclear antigens (ENA)
  - DNA antibodies (both diagnostic and monitoring)
  - Antiphospholipid antibodies: Lupus anticoagulant, Cardiolipin antibodies and β_2-glycoprotein 1 Ab

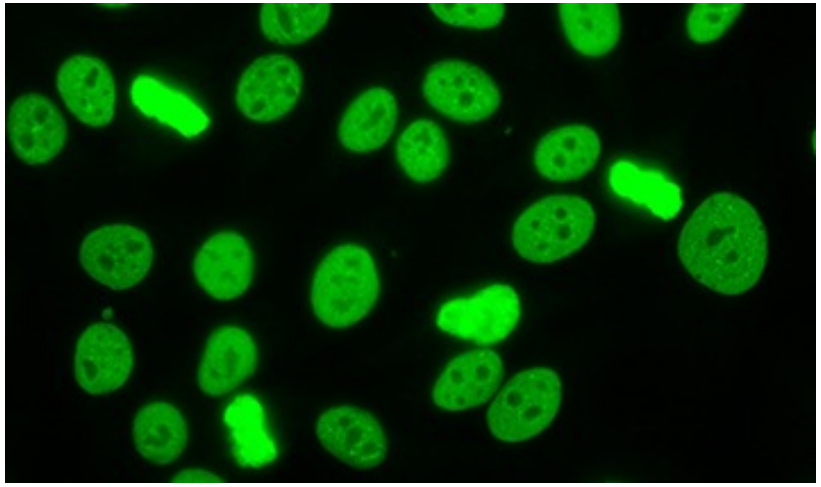
- **Monitoring tests:**
  - ESR, CRP
  - C3, C4 levels
  - Urine dipstick; microscopy for casts, testing for proteinuria

ANA testing

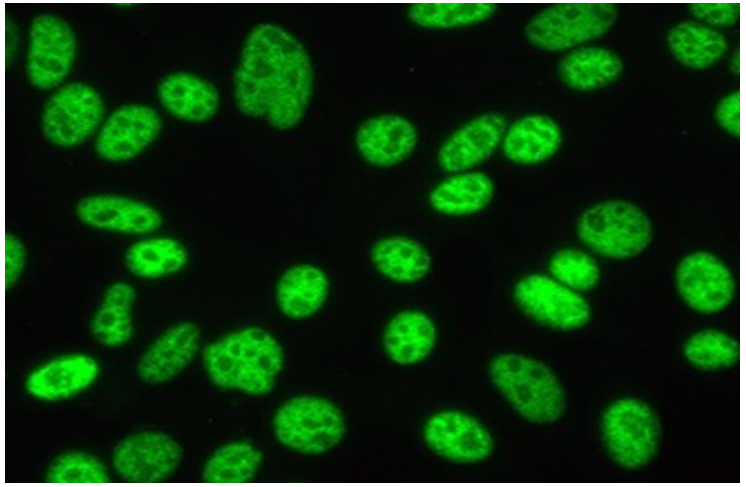
- ANA testing is performed by indirect immunofluorescence (IIF)
  - Patient's serum is added to slides fixed with human cells
  - If serum contain antibodies, they bind to various target proteins; following washing steps, an anti-immunoglobulin with a fluorescent tag is added and cells are visualised under a fluorescent microscope
  - A number of staining patterns can be observed including homogeneous, speckled and nucleolar patterns
  - Patient's serum are commonly diluted at 1:40;
    - if no fluorescence is seen, then this is called negative
    - A positive result means that the serum is diluted further 4 fold (1:40, 1:160, 1:640, 1:2560)
- An ANA titre is the dilution of serum that results in a positive result
  - Titres are commonly reported as positive if ≥1:40, although the higher the titre, the more significant the result; commonly our patients will have a titre of ≥1:640.

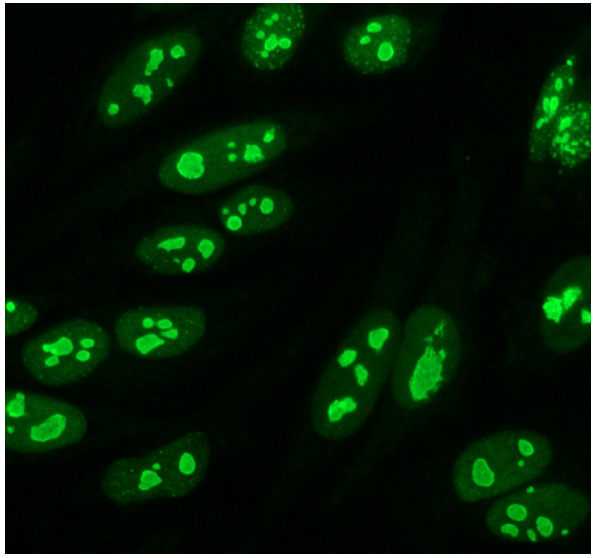
Anti-nuclear antibody staining patterns

Homogeneous pattern



Speckled pattern





Nucleolar pattern

Extractable nuclear antigens (ENA)

- Used as a supplementary test to ANA tests to try and ascertain the targets of a positive ANA result
- Most common ENAs tested include:
  - SS-A (Ro), SS-B (La) and Ro-52 (seen in SLE or Sjogren's syndrome)
  - **Sm (Smith) – highly specific for SLE**
  - RNP (positive in mixed connective tissue disease)
  - Scl-70 (seen in systemic sclerosis)
  - Jo-1 (dermatomyositis, anti-synthetase syndrome)

DNA antibodies

- Presence of DNA antibodies is a very specific marker of SLE
- Measured in several ways, including by a radioimmunassay (Farr), which is the most specific way of measuring this
- In many labs (including Westmead), assay has been switched to an ELISA type assay (non-radioactive) which is less specific
- ACR criteria states that a positive DNA antibody result is one criteria for SLE classification, but if ELISA is used, the DNA Ab result needs to be >2 x the upper range of normal

Other tests

- Low C3 and C4 indicate that complement is being consumed, presumably by antibody and antigen complexes being deposited in small blood vessels
  - Sign of active lupus
- Always check for antiphospholipid antibodies
- Inflammatory markers: ESR may be a better marker of disease activity than CRP, which can be normal even in active SLE; although low level rises in CRP are often seen
- Check for urinary sediment, proteinuria
- Renal biopsy – see later section

There are several SLE classification systems

- American College of Rheumatology (ACR) classification criteria often used as a diagnostic aid, first developed in 1982 (revised in 1997)
- Need to meet 4 of 11 criteria to be classified as SLE, with 95% sensitivity and 85% specificity
- Mostly used in trial settings to make sure patients are “standardised”
- Patients can still have SLE without necessarily having met 4 criteria
- Other classification schemes exist, such as SLICC (require 4/17 criteria but at least 1 clinical and 1 laboratory or biopsy proven lupus nephritis with positive ANA or DNA antibodies).
- New classification scheme introduced in 2019: EULAR/ACR criteria
    - Need to meet entry criteria and reach 10 points for a classification of SLE

ACR classification criteria

Criterion	Definition
Malar rash	"Butterfly rash" with nasolabial sparing
Photosensitivity	Skin rash on exposure to sun (either patient or physician observed)
Discoid Lupus	Erythematosus raised patches with adherent keratotic scaling
Oral ulceration	Oral or nasopharyngeal involvement
Renal involvement	>0.5 g proteinuria (or 3+ on dipstick) OR cellular casts (red cell, haemoglobin, granular, tubular or mixed)
Non erosive arthritis	2 or more joints need to be involved, with tenderness, swelling or effusion
Serositis	Pericarditis (ECG, rub or effusion) or Pleuritis (rub, effusion or good history)
Neurologic disorder	Seizures of psychosis
Haematological disorder	Haemolytic anaemia or leukopenia or lymphopenia or thrombocytopenia
Immunological disorder	Raised DNA antibodies or Sm antibody or presence of antiphospholipid antibodies
Positive ANA	Positive titre of ANA

Entry criterion
Anti-nuclear antibodies at a titre of ≥1:80* on HEp-2 cells or an equivalent positive test

Additive criteria
Do not count a criterion if an explanation other than systemic lupus erythematosus is more likely
Occurrence of a criterion on at least one occasion is sufficient
At least one clinical criterion is required
Criteria need not occur simultaneously
Within each domain, only the highest weighted criterion is counted toward the total score

Clinical domains and criteria	Weight	Immunological domains and criteria	Weight
Constitutional		**Anti-phospholipid antibodies**	
Fever	2	Anti-cardiolipin antibodies or anti-β2GP1 antibodies or lupus anticoagulant	2
Cutaneous		**Complement proteins**	
Non-scarring alopecia	2	Low C3 or low C4	3
Oral ulcers	2	Low C3 and low C4	4
Subacute cutaneous or discoid lupus	4		
Acute cutaneous lupus	6		
Arthritis		**Highly specific antibodies**	
Either synovitis characterised by swelling or effusion in ≥two joints or tenderness in ≥two joints plus ≥30 min of morning stiffness	6	Anti-dsDNA antibody†	6
		Anti-Smith antibody	6
Neurological			
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Haematological			
Leucopenia	3		
Thrombocytopenia	4		
Autoimmune haemolysis	4		
Renal			
Proteinuria >0·5 g/24 h	4		
Renal biopsy class II or V lupus nephritis	8		
Renal biopsy class III or IV lupus nephritis	10		

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled

My approach to diagnosis

- SLE diagnosis is not an exact science!
- Screen patients who have signs/symptoms compatible with SLE with appropriate lab tests (ANA, ENA, DNA Ab, C3,C4 etc)
- Patients with a high titre ANA, with suggestive ENA antibodies or raised DNA antibodies **and** an appropriate history are more likely to have SLE
- Although ANA negative lupus does exist, it is a rare entity; vast majority will be ANA +

Management of SLE

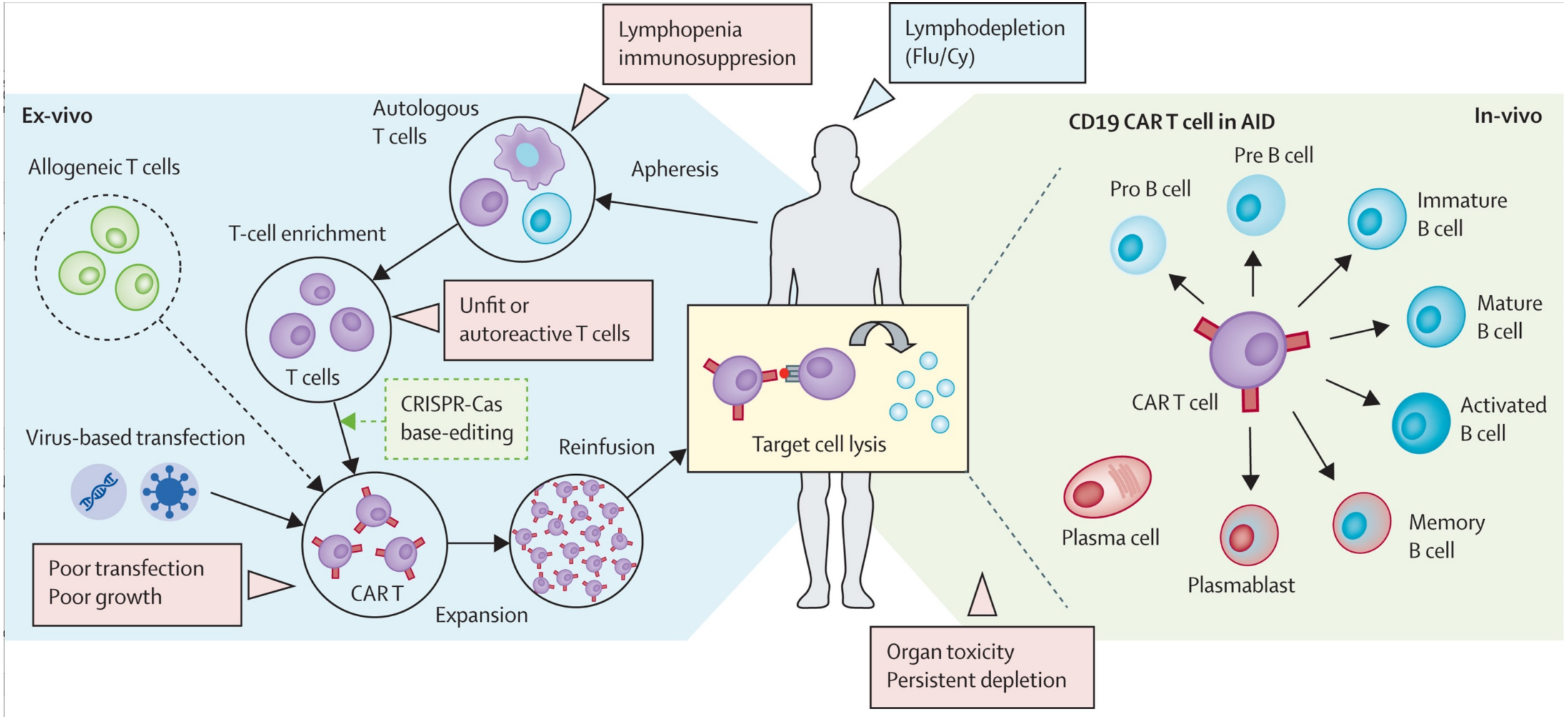
- Patient education
- Advice regarding sun exposure, sunscreen, wearing broad brimmed hats
- Exercise and stopping smoking
- Addressing CV risk factors
- Skin and joint manifestations often respond well to hydroxychloroquine (Plaquenil)
- Many lupus specialists put all their patients on Plaquenil:
  - Very safe drug, with no regular blood testing required
  - Can cause retinal toxicity but this is dose and time dependent

Management of SLE

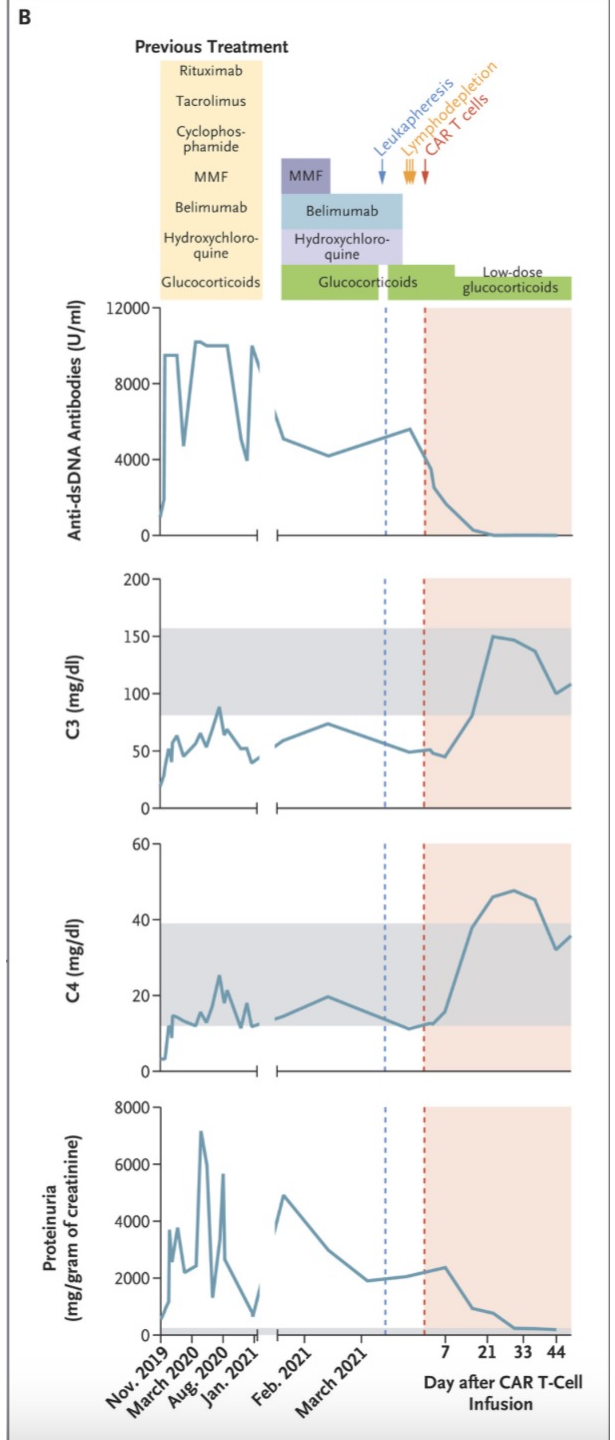
- Further management depends on the disease manifestation
- Low to medium dose corticosteroids are often used
- If doses can't be reduced to <7.5 mg/day of prednisolone, then a steroid sparing agent needs to be considered
- Target to treat approach with aim of achieving lupus low disease activity state (LLDAS) or remission is a new concept in last few years
- The steroid sparing agents most commonly used in SLE are azathioprine or mycophenolate, although methotrexate can also be used, particularly for synovitis
- Belimumab has been licensed but its exact role in treating patients with lupus has yet to be established; probably use will be those with active musculoskeletal or cutaneous disease

Newer agents/therapies being considered in SLE

- Multiple newer agents are in various phases of clinical trials
  - Voclisporin, a calcineurin inhibitor, has been shown to be effective in lupus nephritis
  - Targeting Type I interferons
  - B cell depletion with rituximab
  - JAK Inhibition with baricitinib
  - B cell intracellular signaling (Bruton's tyrosine kinase)
  - T cell co-stimulation blockade
  - Immune complex inhibition
- CAR-T cells – thus far 7 patients have been described so far



CAR T-cell therapy in autoimmune diseases, Georg Schett et al, Lancet, 2023



Mougiakakos et al, NEJM, 2021

Management of severe SLE

- For SLE with potentially life threatening organ involvement, pulse methylprednisolone (1 gram x 3-5 days) is often employed, followed by oral steroids
- This may be followed by pulse IV cyclophosphamide
- Alternatives would be to use Mycophenolate mofetil
- Rituximab (B cell depletion) has also been used, although exact role in SLE has not been established

Lupus Nephritis (LN)

- Renal involvement is very common in SLE, with clinically relevant disease present in up to 50% of patients
- Most commonly diagnosed following a urine disptick but requires a renal biopsy (LM, EM and DIF) for definitive diagnosis
- Regular checks for increased proteinuria (with an albumin:creatinine ratio), red cell casts and checking of serum creatinine (and eGFR) should be performed in all patients with SLE
- Patients with elevated DNA antibodies and low C3/C4 are at higher risk of developing Lupus nephritis

Indications for renal biopsy

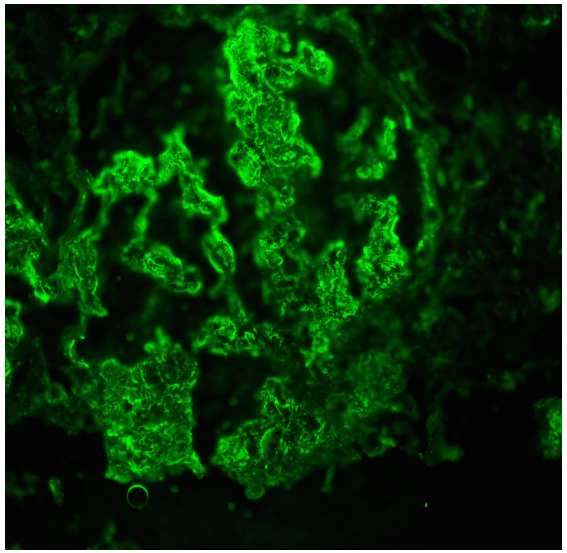
- Renal biopsy is only performed on selected patients:
  - Those with >0.5 grams of proteinuria/day
  - Patients with a rising serum creatinine (where other causes have been excluded)
  - Active urinary sediment with dysmorphic red blood cells

Classes of Lupus Nephritis

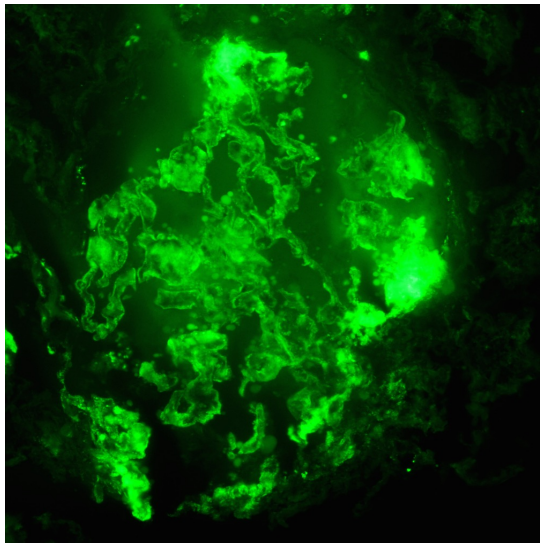
- Class I – minimal mesangial LN (not commonly diagnosed)
- Class II – mesangial proliferative LN
  - manifests as microscopic haematuria and/or proteinuria
- Class III – focal proliferative LN
  - <50% of glomeruli affected
  - presents with haematuria and/or proteinuria with some of the following: ↓GFR, ↑BP, nephrotic syndrome
- Class IV – diffuse proliferative LN
  - >50% glomeruli affected
  - Most patients have present with haematuria and proteinuria and ↓GFR, ↑BP, nephrotic syndrome frequently seen
- Class V – membranous LN
  - Present with nephrotic syndrome
- Class VI – advanced sclerosing LN
  - Slowly progressive renal dysfunction with bland urinary sediment

Immunoglobulin staining on DIF in Class IV lupus nephritis

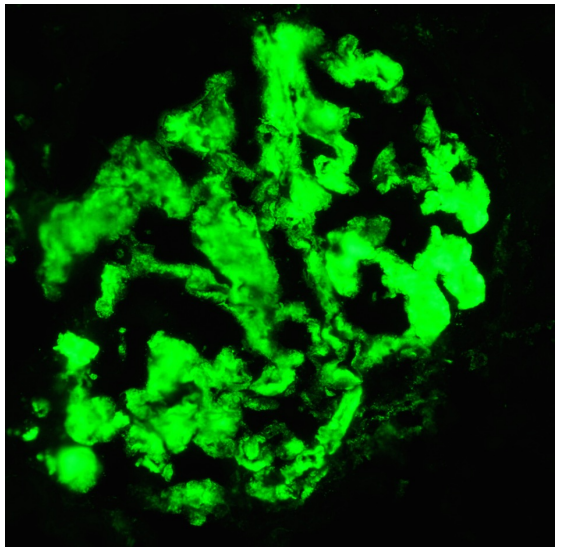
IgG



IgA

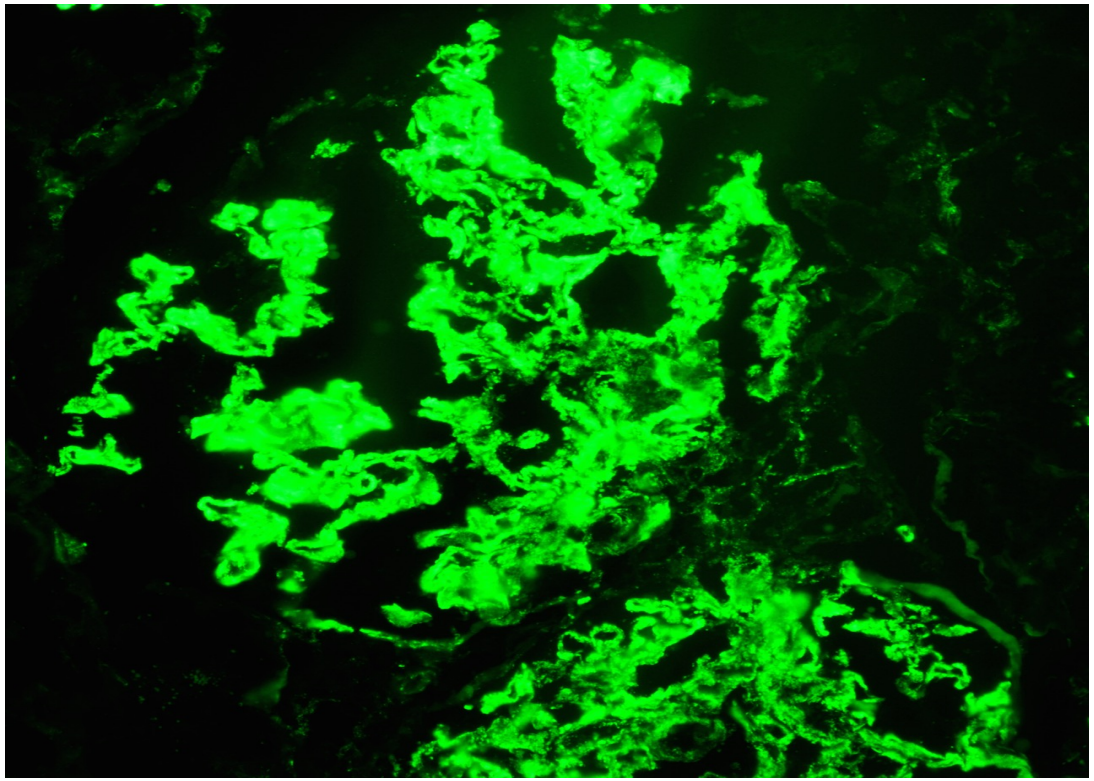


IgM

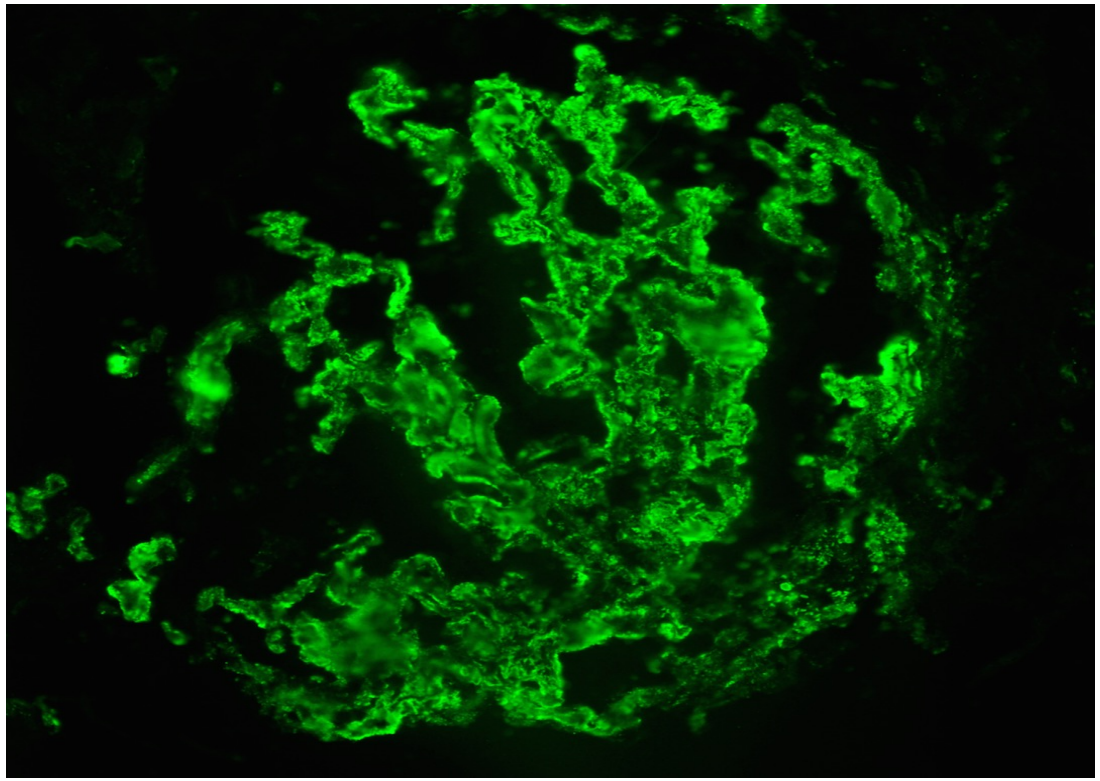


Complement staining in Class IV Lupus Nephritis

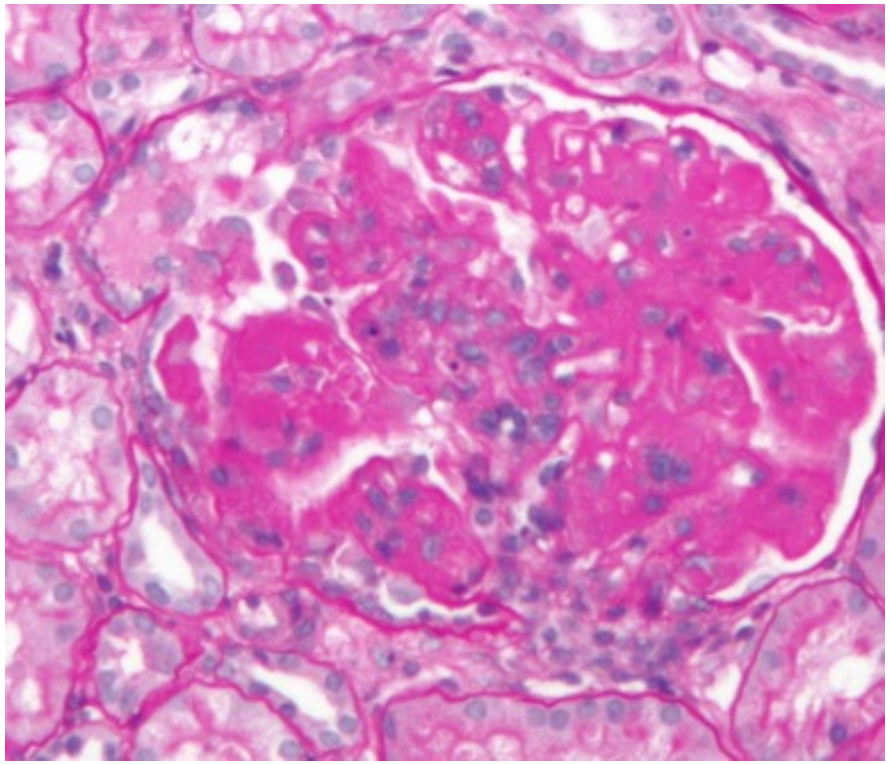
C3 staining



C1q staining



Light microscospy finding Diffuse LN



Renal biopsy findings in Class IV Lupus nephritis

- Typical light microscopy findings:
  - >50% of glomeruli are affected on LM
  - Diffuse wire loop changes and mesangial proliferation

- Typical direct immunofluorescence findings:
  - Usually the “full house” of immunoglobulins (IgG, IgA and IgM), with C3 and C1q. C1q staining is very specific for SLE and background staining for C1q is very weak in normal tissue

- Typical electron microscopy findings:
  - Sub-endothelial deposits

Management of Lupus Nephritis

- Data is mostly for Type IV LN
- Induction therapy
  - IV Cyclophosphamide for 3- 6 months (although exact duration is not known
  - Eurolupus protocol is 500 mg every 2 weeks
  - Most specialists would also pulse with methylprednisolone, followed by tapering oral steroids
- Alternative induction agent would be using mycophenolate, particularly in patients with less severe renal disease (near normal kidney function)
- Maintenance is usually with azathioprine or mycophenolate for 2 – 3 years
- Recent studies have suggested that belimumab may have a role

Management of Membranous LN

- Membranous nephropathy (Class V)
  - Not a consensus of how to approach this, however most experts in the field will treat if there is nephrotic syndrome, proteinuria >3.5 g/L despite non immunosuppressive therapy, a rise in creatinine or if there is a mixed membranous and proliferative picture seen on the kidney biopsy
  - First line: Mycophenolate mofetil (MMF) with Azathioprine and CNIs if patient is pregnant
- Other measures to consider: Dietary sodium and protein restriction, management of CV risk factors such as BP/hyperlipidaemia, minimization of proteinuria with antagonism of the renin-angiotensin system
- Need to consider infection prophylaxis whilst on these immune suppressants as well

Choice of immune suppression in consideration of pregnancy or preserving fertility in the future

- Choice of immune suppressants is very important in young SLE patients as they are often female and of child bearing age
  - Ideally SLE is well controlled for >6 months before pregnancy is attempted
  - Severe disease flares need to be factored in, as well as transitioning patients from one regimen to another

- Drugs such as mycophenolate, methotrexate and cyclophosphamide are contraindicated

- Azathioprine, hydroxycholoroquine and low dose steroids can be continued throughout pregnancy; suggested that patients be on hydroxycholoroquine

Preserving fertility in SLE patients

- If co-existing antiphospholipid antibody syndrome is present, recommended to use concurrent aspirin and low molecular weight heparin

- EULAR guidelines in 2019: In women with high risk aPL profile but without a history of thrombosis or pregnancy complications (with or without SLE), treatment with 100 mg/day of aspirin should be considered

- In preserving fertility, the Eurolupus protocol (500 mg cyclophosphamide 2 weekly) provides much better protection in preserving fertility than higher dose regimens
  - Consideration of sperm or egg freezing

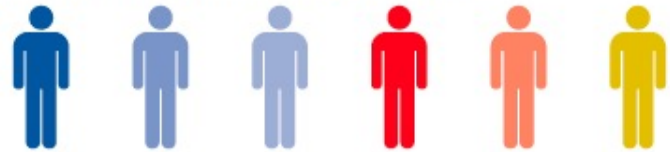
A

New ACR–EULAR classification criteria for systemic lupus erythematosus and definitions for lupus low disease activity state and remission

B

One (oligo)-target approach
Targeting key nodes of immune activation

Multiple faces of systemic lupus erythematosus



Multitarget therapy
- Simultaneous inhibition (ie, ustekinumab, baricitinib)
- Sequential (ie, rituximab followed by belimumab) or combination therapy

C

Individual patient(omics)-tailored therapy
Profile consisting of:
- Genome
- Epigenetics
- Transcriptome
- Proteome
- Immunome

Examples of personalised therapy

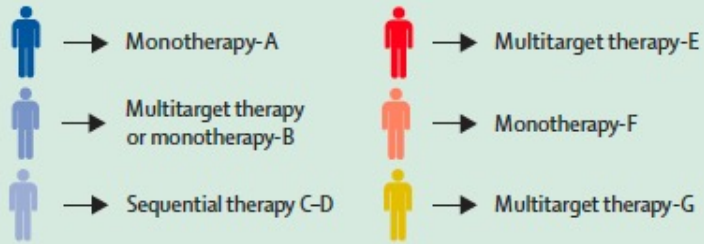


Figure 4: **Concepts to improve therapeutic outcomes in systemic lupus erythematosus**

References

- 1. Novel paradigms in systemic lupus erythematosus; Lancet 2019; 393: 2344–58
- 2. Management strategies and future directions for systemic lupus erythematosus in adults; Lancet 2019; 393: 2332–43
- 3. Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus; Rheumatology, Volume 58, Issue 3, March 2019, Pages 382–387

Questions???