An update on Systemic Lupus Erythematosus (SLE)

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20 March, 2021
Talk outline

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

• Ms KB, 20 yo woman
• Presented several years ago with worsening fatigue and myalgias
• Some hair loss noted (clumps)
• No arthralgias, no Raynaud’s
• Non-specific rash (not in malar area, not photosensitive)
• Examination was largely unremarkable, with no rashes, arthritis, lymphadenopathy
Investigations:

- Pancytopaenia: Hb 89 g/L, WCC 3.2 x 10^9/L, platelet count 67 x 10^9/L
- High titre Speckled ANA (>1:2560 titre)
- Negative ENA
- DNA antibodies >2000 IU/ml (FIDIS assay)
- +++ proteinuria
- 24 hour urine – 4 grams of protein, with 50% dysmorphic red cells
Renal biopsy and treatment

• Renal biopsy revealed Class IV Lupus nephritis
• Pulsed with methylprednisolone and started on mycophenolate and oral steroids, along with hydroxychloroquine
• Proteinuria settled with steroids
• Eventually required pulse cyclophosphamide (6 months)
• Went on to have rituximab 1 gram x 2
  • Currently no proteinuria and symptomatically well
Issues

• Understanding what SLE is and the need for medications
• Compliance with regimen
• Concerns about weight gain with corticosteroids
• Need for adequate contraception
• Long-term control of disease
What is SLE?

• Systemic, multisystem autoimmune disease

• Strong female:male preponderance (~9:1)

• Considerable ethnic differences in frequency
  • More common in Africa, Asian population than Caucasian populations

• 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; particular interest focused on the role of EBV infection in SLE pathogenesis.
Pathogenesis of SLE

- Decreased removal of apoptotic cells
- Uptake of autoantigen by dendritic cells
- Activation of T cells and stimulation of B cells
- Deregulated apoptosis
- Induction of autoantigen modifications
- Formation of nucleosome/anti-nucleosome complexes
- Nucleosome-mediated binding to basement membrane
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 $\beta_2$-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
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

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<th>Immunological domains and criteria</th>
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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

• The steroid sparing agents most commonly used in SLE are azathioprine or mycophenolate, although methotrexate can also be used

• Belimumab has been licenced 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
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
Newer agents 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
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 dipstick 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
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
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, hydroxychloroquine and low dose steroids can be continued throughout pregnancy
Preserving fertility in SLE patients

• If co-existing antiphospholipid antibody syndrome is present, strong consideration of concurrent aspirin and low molecular weight heparin 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
Questions???