HARRISON'S BASED GENERAL MEDICINE

PART - 4

CONTENT

RHEUMATOLOGY & IMMUNOLOGY

SLE : ETIOPATHOGENESIS

Connective tissue disorders 00:01:10

Chronic multisystemic autoimmune inflammatory connective tissue disorders.

- Rheumatoid arthritis (mc).
- Sjogren syndrome (2nd mc).
- Systemic Lupus Erythematosus.
- Antiphospholipid antibody syndrome (APS).
- IgG4 related disorders.
- Scleroderma.
- Inflammatory muscle diseases :
  - Polymyositis.
  - Dermatomyositis.
- Overlap syndrome.

Systemic Lupus Erythematosus (SLE) 00:05:48

World lupus day : May 10.
Female : male = 9 : 1.
Disease of females in the reproductive age group.
Male SLE : Poor prognosis.
Childhood SLE : 100% renal involvement (lupus nephritis).
Very strong family history present.
Positive concordance of >40 % among identical twins.

List of diseases with female male ratio of 9 : 1 includes :

- Systemic lupus erythematosus.
- Sjogren's syndrome.
- Takayasu's arteritis.
- Primary biliary cirrhosis.
- Chronic fatigue syndrome.

Risk factors of SLE

00:16:18

1. Genetic risk factors :

Complement deficiency :

- Strongest genetic risk factor of SLE : Early component deficiency : C_{1q}, C_{2}, C_{4}.
- Single most important genetic risk factor : C_{1q} deficiency.
- Early component deficiency predispose to SLE.
- Late complement deficiency predispose to Neisseria and Toxoplasma infection.

TREX gene mutation (present on chromosome 3).

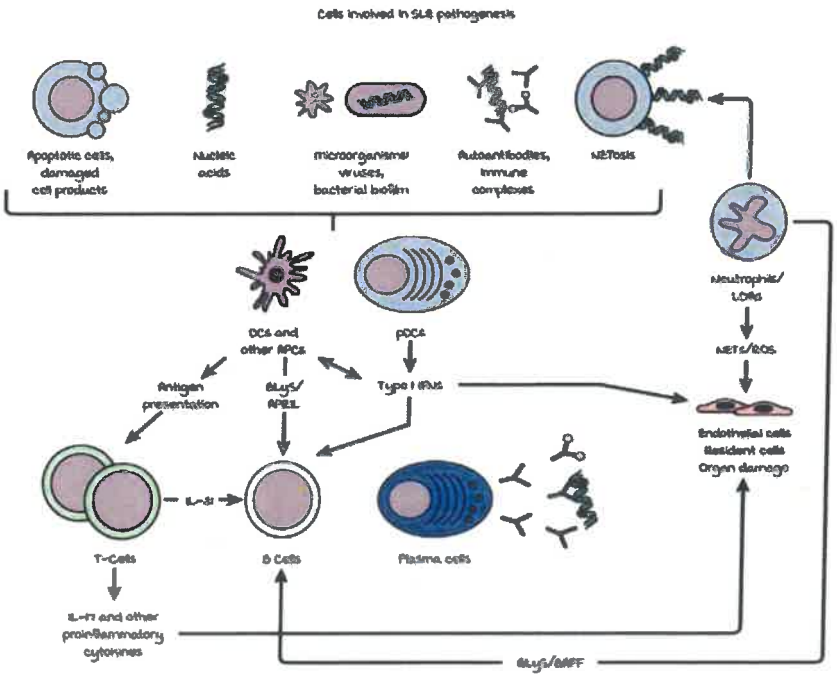
HLA DR B_1 03 , DR B_1 02.

HLA DR3 : Subacute cutaneous lupus.

2. Enironmental risk factor :

Important only in people affected without any genetic risk factors.

- OCP & HRT.
- UV B rays.
- Epstein Barr virus.
- Smoking.
- Deficiency of vitamin D.
- Silicosis.



Pathogenesis of SLE

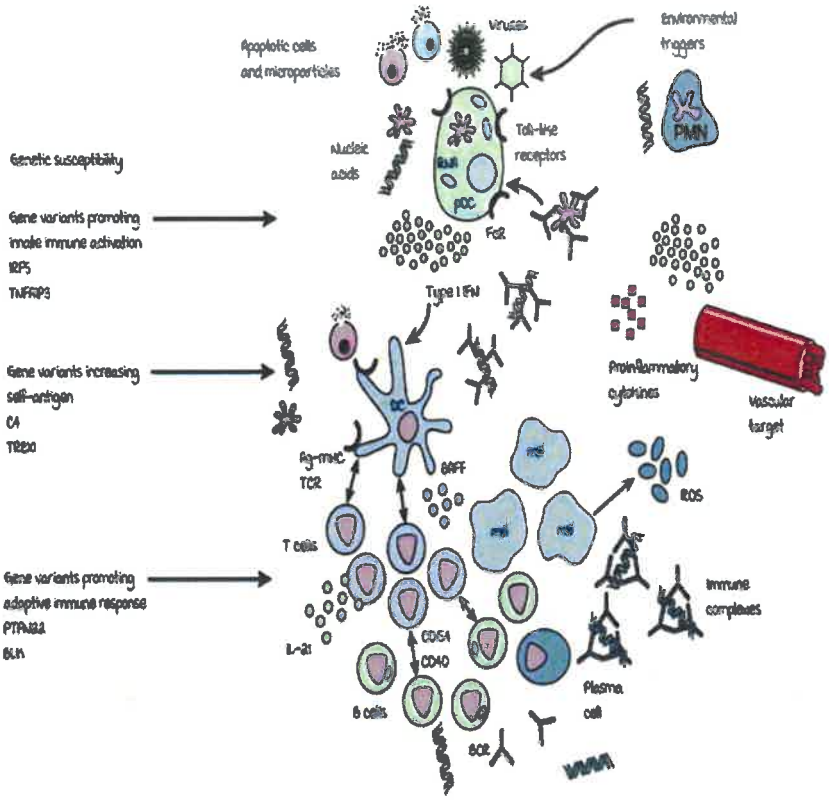
00:21:31

1. Immune dysregulation :
   Type 3 hypersensitivity reaction.
   Immune complex mediated disease.
2. Defective clearance of apoptotic debris or defective lymphocytic phagocytosis.
3. Inefficient degradation of DNA containing neutrophil extracellular traps (NET) : Defective NETosis.
4. Innate immune system activation :

Central key pathogenic cytokine : IFN-alpha or Type I IFN.
Produced by lymphoid dendritic cell (plasmacytoid dendritic cell).
Genetic signature of SLE : Upregulation of genes due to IFN alpha.

IFN alpha.
↓
Upregulates myeloid dendritic cells & activates them to present antigen to T cells.
↓
Activation of T cells.
↓
TH_1 TH_2 TH_{17}
↓
Predominant lineage : TH_2
$TH_2 > TH_1 > TH_{17}$
↓
IL-4, IL-5, IL-10, IL-13.
↓
Secondarily activates B cells.
↓
Produce antibodies.
↓
Immune complexes get deposited in various organs.
Vessel wall : Vasculitis.
Joints : Arthritis.
Glomeruli : Glomerulonephritis.

Contributors to systemic lupus erythematosus (SLE) pathogenesis



Activation of B cell

00:33:32

T cell activates B cell by multiple pathways :

1. IL 4 pathway.
2. IL 12/21 pathway.
3. CD 40 L - CD 40 interaction.

SLE - IMMUNOLOGICAL BASIS

Autoantibodies in SLE

00:00:08

Antibodies start to appear 3 years before the onset of the clinical features.

Antibody and prevalence	Antigen recognised	Clinical utility
Antinuclear antibodies (98%)	Multiple nuclear	Best screening tests for all autoimmune diseases, repeated negative tests make SLE unlikely.
Anti-dsDNA (70%)	DNA (double-stranded)	High titres are SLE specific and in some patients correlate with nephritis, vasculitis
Anti-Sm (25%)	Protein complexed to 6 species of nuclear U RNA	Specific : No definitie clinical correlations, most patients also have anti-RNP, MC in blacks and Asians than whites
Anti-RNP (40%)	Protien complexed to U RNA	Non-specific : High titres associated with syndromes that have overlap features of several rheumatic syndromes including SLE, MC in blacks than whites
Anti-Ro (SS-A) (30%)	Protein complexed to hY RNA, primarily 60 KDa and 52 KDa	Non-specific : Associated with sicca syndrome, predisposes to cutaneous lupus, and to neonatal lupus with congenital heart block, associated with decreased risk for nephritis
Anti-La (SS-B) (10%)	47-KDa protein complexed to hY DNA	Usually associated with anti-Ro, associated with decreased risk for nephritis
Antihistone (70%)	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE
Antiphospholipid (50%)	Phospholipids, B2 glycoprotein I cofactor, prothrombin	Three tests available : ELISAs for cardiolipin and B2 GI, sensitive prothrombin time (DRVVT), predisposes to clotting, fetal loss, thrombocytopenia
Antierythrocyte (60%)	Erythrocyte membrane	Measured as direct Coomb's test, a small portion develops overt hemolysis
Antiplatelet (30%)	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia, but sensitivity and specificity are not good, this is not a useful clinical test
Antineuronal (includes antiglutamate receptor) (60%)	Neuronal and lymphocyte surface antigens	In some series, a positive test in CSF correlates with active CNS lupus
Antiribosomal P (20%)	Protein in ribosome	In some series, a positive test in serum correlates with depression or psychosis due to CNS lupus

Screening test for Connective Tissue Disorders (CTD).
Antibodies against the nucleus, nucleoplasm, mitotic spindle, small nuclear riboproteins, cytoplasmic organelles.
97 % of the patients with SLE are ANA positive.

- methodology :
  Indirect immunofluorescence (gold standard),
  human epithelial-2/Hep-2 (derived from the laryngeal epithelial cells of laryngeal CA patients) cell line is used.
- Titre : Standard dilution ≥ 1:80, 1:160, 1:320, 1:640, 1:1280.
- Intensity : (1+) (2+) (3+) (4+).
- Pattern.

Antibodies checked under ENA profile (Extractable Nuclear Antigen profile) :

Antibody	Specific disease	% in lupus
Anti Sm	Specific for Lupus	10-44%
Anti- U1 RNP	MCTD	10%
Anti SSA (anti Ro)	Sjogrens	30%
Anti SS B (anti La)	Sjogrens	15%
Anti Scl 70	Scleroderma	10%
Anti Jo 1	myositis	10%

Antibodies checked under ANA profile (done by immunoblot) :

Anti Sm	Specific
Anti URNP	
Anti SSA	
Anti SSB	
Anti Histone	Drug induced lupus
Anti ds DNA	Specific
Anti Nucleosome	Specific
Anti Ribosomal P Protein	Neuro psychiatric lupus
Anti Centromere	
Anti Jo 1	
Anti Mi 2	
Anti Ku	Lupus association
Anti PCNA	Lupus association
Anti Pm Scl	

Diagnosis of lupus : Following ANA positivity, ANA profile by immunoblot is preferred rather than ENA.

Two important tests to be done after ANA (specific tests) :

- Anti ds DNA.
- Anti smith.

Specificity : Anti smith > Anti ds.

But clinically, anti-ds DNA is more important because :

- Anti-ds DNA : 75% of the patients with SLE have anti- ds DNA positive whereas only 25% of the patients with SLE have anti-smith DNA positivity.
- Anti-ds DNA titres correlates to disease activity in SLE.
- Anti-ds DNA ∝ increased risk for nephritis & vasculitis.

ANA pattern :

It may suggest the antibody which can appear in the antibody profile.

- Homogenous pattern : Suggestive of anti-ds DNA.
- Coarse speckled pattern : Suggestive of anti-Smith.
- Dense fine speckled pattern (DFS pattern): Rules out CTD.
- Fine speckled pattern : Sjogren's syndrome.

Anti-Ro and anti-La antibodies 00:13:45

Anti-Ro (SS-A) and anti-La (SS-B) positivity indicates secondary Sjogren's syndrome (associated with CTD).

MC CTD association of Sjogren's : Rheumatoid arthritis.

2nd m/c association of Sjogrens : SLE.

ANti-Ro (SS-A) and anti-La (SS-B) positivity :

- ANA negative lupus (3% cases) definitely has anti-Ro positivity (so, look for Anti-Ro-52 antibody in ANA negative lupus to completely rule out SLE).
- Indicates good prognosis (associated with decreased risk for nephritis and vasculitis).
- In pregnancy, it indicates the risk for neonatal lupus with congenital heart block.
- Associated with subacute cutaneous lupus erythematosus / SCLE (photosensitive).

- Associated with shrinking lung syndrome.
- Normally, Ro-52 antigen is protective in the skin and myocardium (so, anti-Ro 52 is linked to SCLE and myocarditis).

Anti U1 RNP(ribonucleoprotein) antibody 00:19:28

Associated with syndromes that have overlap features of several rheumatic syndromes including SLE.
It indicates Mixed Connective Tissue Disease (MCTD).
ANA antibody will be positive with coarse speckled pattern.
Conditions with 100% ANA positivity :

- MCTD.
- Autoimmune hepatitis type I (AIH type I).
- Drug Induced Lupus Erythematosus (DILE).

Anti-histone antibody 00:22:18

Seen in drug induced lupus.
Homogenous ANA pattern indicates either :

- Antihistone positivity : DILE.
- Anti-ds DNA positivity : SLE.

Antiphospholipid antibody :
Associated with antiphospholipid syndrome/APS (earlier known as antiphospholipid antibody syndrome/APLA).
1/3rd of the patients with SLE have APS (thrombosis).

Anti-RBC/erythrocyte antibody 00:24:25

Clinical scenario : A 32-year-old female, diagnosed with decomponsated cirrhosis & hepatic encephalopathy grade 2, was admitted in the ICU. Patient was managed with bowel washes with lactulose and routine symptomatic treatment. She continued to have Hb of 5-6 g/dL and even 3-4 g/dL on certain days. Peripheral smear : Abundant fragmented and nucleated RBC's, suggestive of hemolysis and with urine Hb negative, LDH levels high and S. haptoglobin levels low.

Diagnosis : Extravascular hemolysis (autoimmune unless proven otherwise).
Direct coomb's test came positive (4+).
Splenomegaly (due to increased breakdown of RBCs in the reticuloendothelial cells of the spleen).
S. bilirubin (indirect) : Hemolysis.
Urine urobilinogen : Positive.
Diagnosis : Autoimmune hemolytic anemia.
ANA, anti-ds DNA, anti-smith positvity : SLE.
Liver biopsy : Autoimmune hepatitis.

Anti-RBC/erythrocyte antibodies can be present in SLE causing autoimmune hemolytic anemia/AIHA (Ig G mediated warm antibody).

Antiplatelet antibody 00:31:14

Case scenario : A 17 year old girl, with severe menorrhagia and Hb 9.1 g/dL, total count 6,700 cells/mm^3, platelet count 18000 cells/mm^3, normal peripheral smear, and no other cutaneous manifestations of thrombocytopenia are present.
Diagnosis : Idiopathic thrombocytopenic purpura/ITP :

- Primary ITP.
- Secondary ITP, main causes :
  1. SLE.
  2. HIV.
  3. HCV.

Blood related presentations of SLE are common :

- AIHA (due to antierythrocyte antibody).
- ITP (due to antiplatelet antibody).

Neuronal antibodies in SLE 00:35:12

- Antineuronal antibody/anti-glutamate antibody : MC antibody seen in neuro SLE.
- Antiribosomal-P antibody : Correlates with depression/psychosis in CNS lupus.

Helps to differentiate between depression due to neuro lupus and functional depression in SLE.

MC neurological manifestation in SLE : Cognitive dysfunction.

Other ANA patterns 00:39:11

Cytoplasmic pattern :

- Suggests anti Jo-1 antibody.
- Antisynthetase syndrome, seen in inflammatory muscle diseases.

Centromere pattern :

- Anticentromere antibody.
- CREST syndrome.

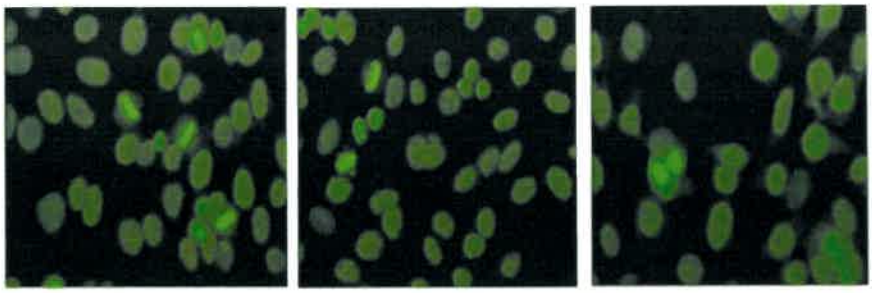
Nucleolar pattern :

- Overlap syndrome (PM/SLE-70 overlap : Polymyositis scleroderma overlap).

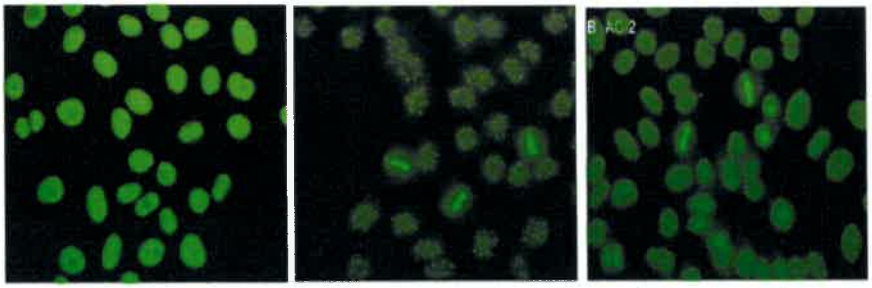
ANA and ANA profile in a lupus patient should not be repeated periodically because they just help in classifying the disease as SLE and not useful as prognostic markers.

Biomarkers in SLE 00:41:55

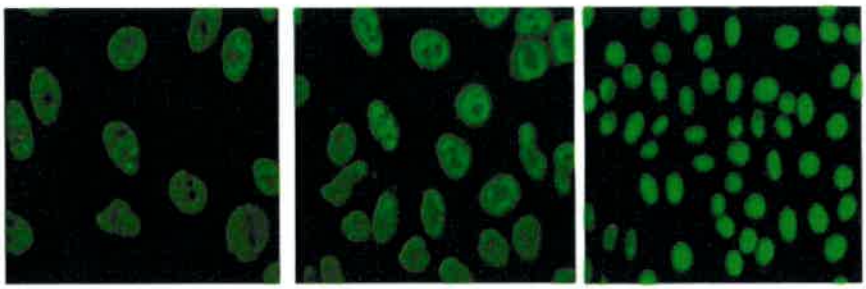
- ESR :
  Non-specific elevation.
  Almost 90% of lupus have an increased ESR.
  Can monitor disease activity.
- CRP : Low in active lupus (due to the presence of anti-CRP antibody and suppression of CRP by TNF α).
- Anti-ds DNA antibody : To assess the disease activity/ flare.
- Anti C1 Q antibodies : To assess nephritis.
- Complement C3 and C4 : SLE is characterised by low C3 and C4.
- ANA profile : To diagnose SLE.
- ENA profile : To diagnose SLE.



Dense speckled pattern



Homogenous pattern | Centromere pattern | Fine speckled pattern



Coarse speckled pattern | Nucleolar pattern

Anti-ds DNA :

3 major methodology :

- Crithidiae Luciliae : Immunofluorescence (qualitative).
- Immunoblot : ANA profile (semiquantitative).
- ELISA : For repeat measurement (quantitative).

MC pattern in SLE : Homogenous pattern.

MC specific pattern in SLE : Homogenous/Coarse speckled pattern.

Most common pattern in CTD : Fine speckled pattern.

SLE-LUPUS NEPHRITIS

Lupus nephritis 00:01:15

Rheumatoid arthritis : mainly on lungs.
SLE : Kidney involvement.
50 to 60% have clinically significant Lupus Nephritis.

Involvement in Lupus Nephritis :

- Vascular component :
  Not common.
  Develop Thrombotic microangiopathy :
    Small vessel disease of Kidney.
    Associated with Anti Phospholipid Syndrome.
- Glomerular component :
  Mainly involved.
  Commonly Seen.
- Tubulo Interstitial component :
  Rare .

Glomerular involvement in lupus nephritis .
Indication for biopsy :
Urine > 1g/day protein or 500 mg/dl with microscopic hematuria (more than or equal to 3 RBC per HPF after urine centrifugation).
On suspicion of nephritis :
The patient have to be assessed on URE.
URE to be done in all follow ups.

Based on biopsy Classification of lupus nephritis :
Class 1 : Minimal Mesangial lupus.
Normal in light microscope.
Asymptomatic .
No treatment required and good prognosis.
Class 2 : Mesangial Proliferative lupus.
Mesangial Proliferation seen in light microscope.
Asymptomatic.

No treatment needed & good prognosis.

Immunofluorescence in both Class 1 and Class 2 :
mesangial Immune Complex deposition seen and hence cannot be differentiated.

Class 5 : membraneous Lupus.
Difficult to treat.
Steroid refractory.

Better prognosis than class 4 as lesser chance for CKD.

Presententation : Adult Onset Nephrotic Syndrome.

manifestations :
Progressive facial puffiness, pedal edema.
Insidious onset.
RFT normal.
URE : Presence of albumin.
Increased total cholesterol.

Adult Onset Nephrotic Syndrome.
↓
Indication for biopsy.
↓
Shows membraneous nephropathy.
↓
Rule out secondary cause :
malignancy (colorectal).
HBV.
SLE.

Class 3 and 4 : Proliferative Lupus Nephritis.
Class 3 : Focal Proliferative Lupus Nephritis
< 50 %.
Class 4 : Diffuse Proliferative Lupus Nephritis :
> 50 %.
Worst prognosis as develops CKD.

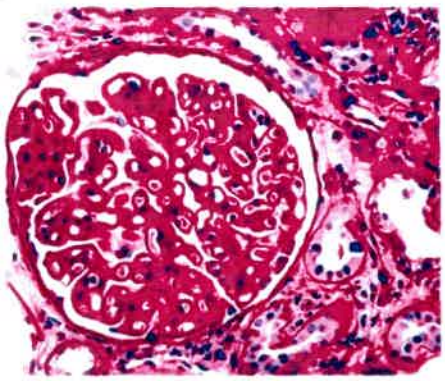
Global : Entire complete involvement
Segmental : In part involvement.

Presents with Type 2 RPGN.
Within days to weeks develops renal failure.
high coloured urine +.
within week :

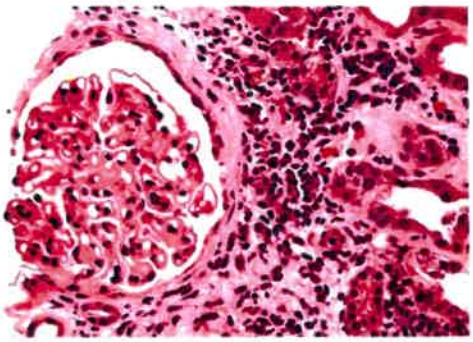
Facial puffiness ,Pedal edema develops & progresses,
reduced urine output .

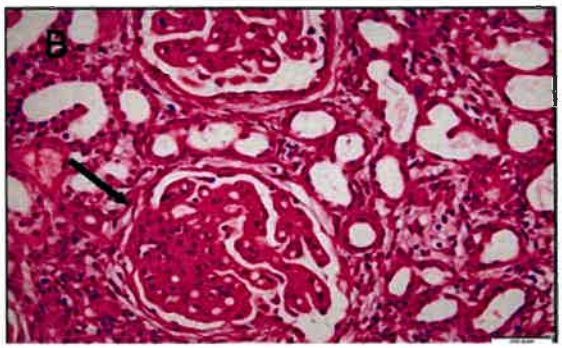
WHO Type	
Class I	Minimal Mesangial Lupus Nephritis : Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
Class II	Mesangial Proliferative Nephritis : Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. Few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
Class III	Focal Lupus Nephritis : Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving < 50 % of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class IV	Diffuse Lupus Nephritis : Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is subdivided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits, but with little or no glomerular proliferation.
Class V	Membranous Lupus Nephritis : Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V nephritis may occur in combination with class III or class IV, in which case both are diagnosed Class V nephritis may show advanced sclerotic lesions
Class VI	Advanced Sclerotic Lupus Nephritis ≥ 90 % of glomeruli globally sclerosed without residual activity.

Images :

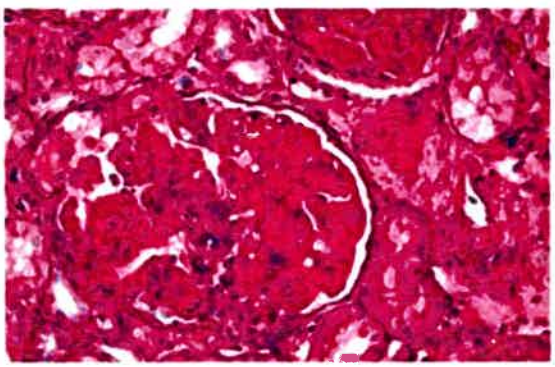


membranous nephropathy with thickened glomerular basement membranes (thick capillary loops).



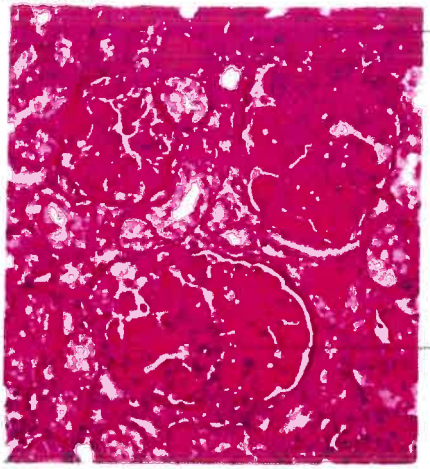


H&E high-power view of glomerulus showing thickened capillary loops and membranes (black arrow)

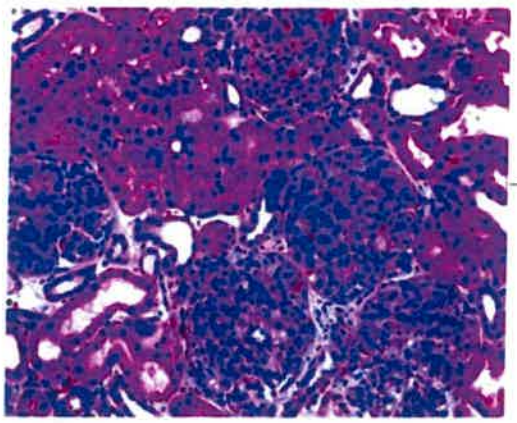


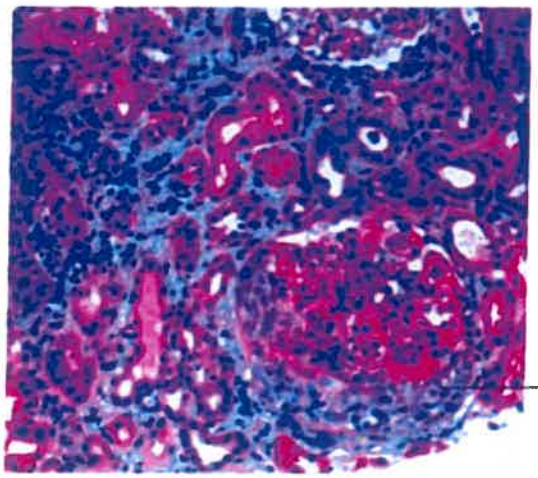
Very high magnification micrograph of diffuse proliferative lupus nephritis, class IV. PAS stain.

Case HP

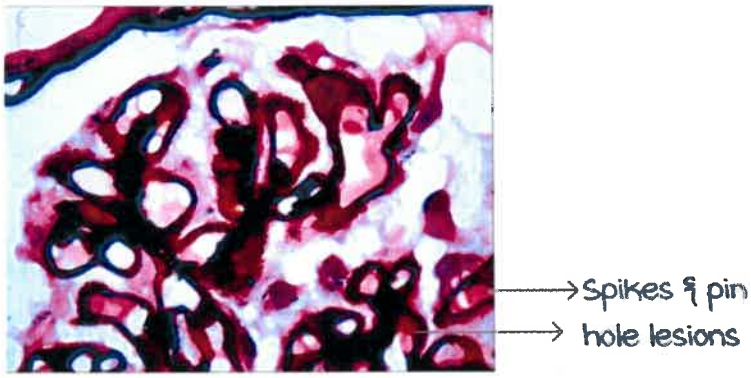


Complete proliferation :

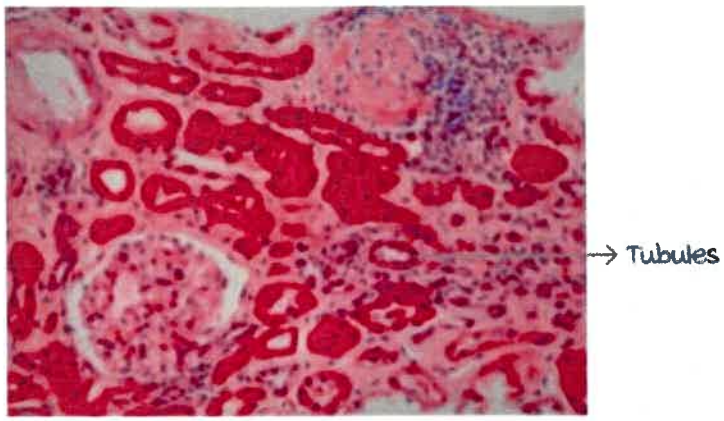


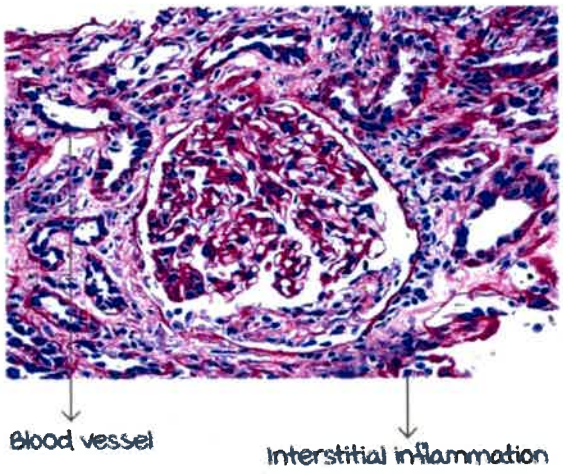


Spikes :



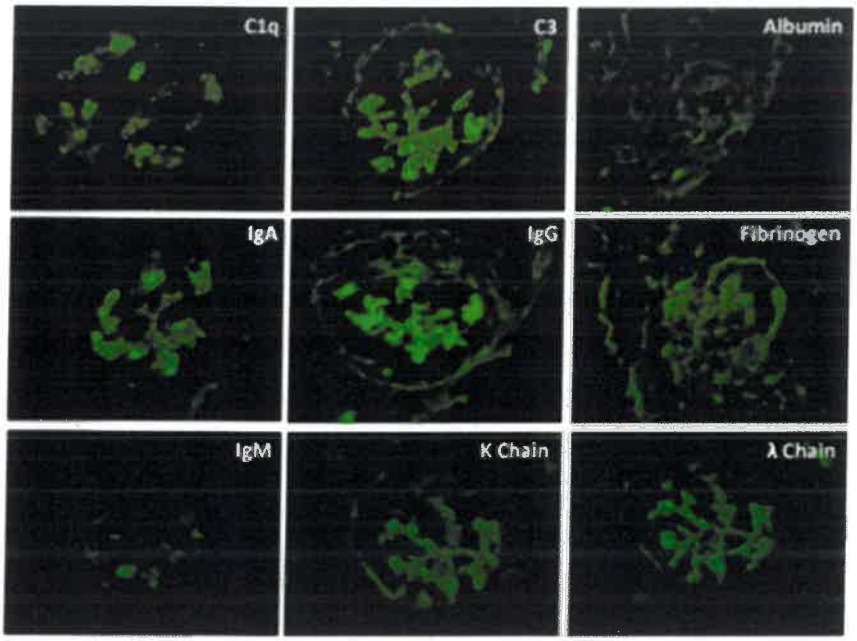
Normal glomeruli :





In class 3 & 4 SLE :

Immunoflurescence shows Full house effect : IgG IgA Kappa Lambda C_1q C_3



In Class 4 : wire loop due to subendothelial deposition.

most specific finding :

In electron microscopy hematoxylin bodies of gross.

Rule out in :

PUO & female of reproductive age group

Fever+ fatigue + weightloss,hairloss.

Female +fever + arthritis.

Female + DAH presentation.

Female + mesentric/ CNS vasculitis.

Female + adult onset nephrotic syndrome.

Female + RPRF.

Female + stroke.

Female + rapid progressive anemia.

Female + bleeding & thrombocytopenia.

SLE : CLINICAL PRESENTATION

Manifestations in SLE

00:00:34

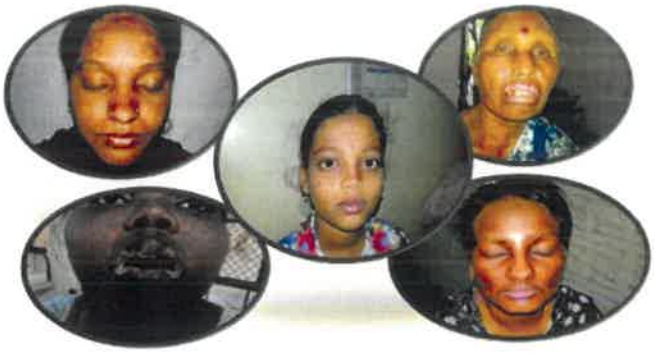
Frequencies of various manifestations of systemic lupus erythematosus :

Manifestation	Frequency (%)
Constitutional symptoms (fatigue, fever, weight loss)	90 - 95
Mucocutaneous involvement (malar rash, alopecia, mucosal ulcers, discoid lesions, etc.,)	80 - 90
Musculoskeletal involvement (arthritis/arthralgia, avascular necrosis, myositis etc.,)	80 - 90
Serositis (pleuritis, pericarditis, peritonitis)	50 - 70
Glomerulonephritis	40 - 60
Neuropsychiatric involvement (cognitive impairment, depression, psychosis, seizures, stroke, demyelinating syndromes, peripheral neuropathy etc.,)	40 - 60
Autoimmune cytopenia (anaemia, thrombocytopenia)	20 - 30

Most important system involved in SLE : Skin and joint.

Risk group :
Female of reproductive age group having pyrexia of unknown origin.
PUO and leukopenia (lymphopenia).
Any young female with fatigue and weight loss.

Faces of SLE :



Classification of cutaneous LE (Gilliam and Sontheimer) :

LE specific skin lesions — LE Non specific skin lesions

Lupus erythematosus specific skin lesions :

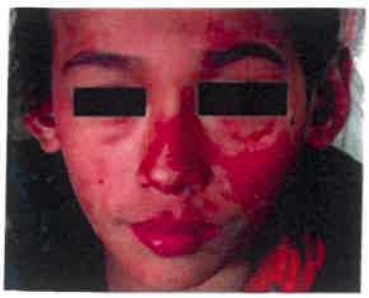
1. ACLE/ acute cutaneous lupus erythematosus :

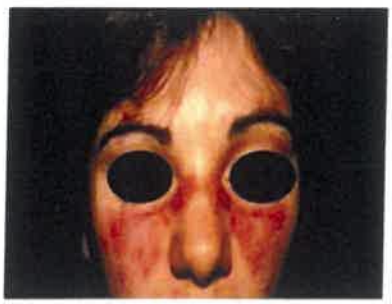
Is most often localised, sometimes generalised.

Very rarely has toxic epidermal necrolysis/TEN like picture.

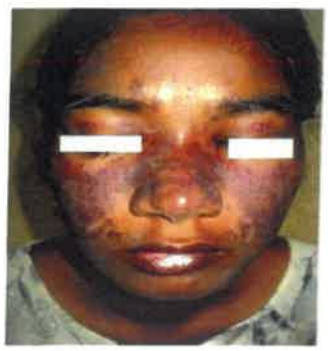
Localised ACLE : malar rash/butterfly rash.

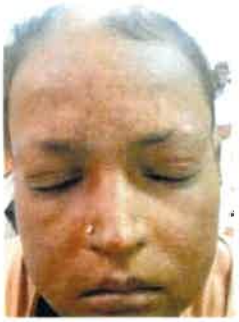
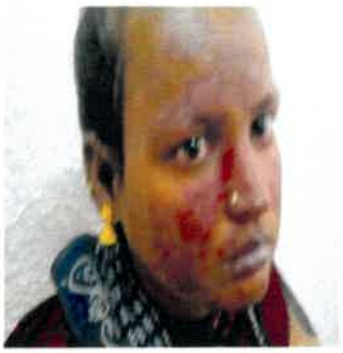
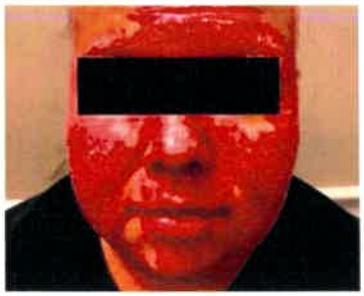
Most common rash in SLE patient (50%).





Erythematous malar rash sparing nasolabial fold



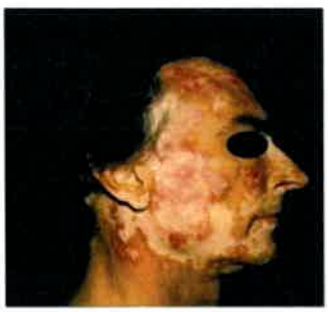
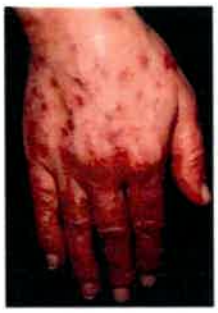





Malar rash :

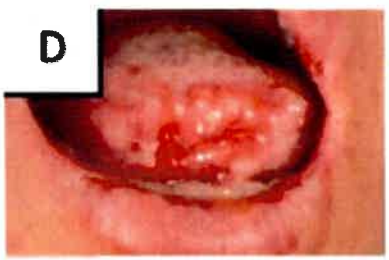
- Photosensitive rash.
- Bilaterally symmetrical, erythematous & edematous rash Scaling, non scaring rash.
- Spares the nasolabial fold.
- Younger age of disease onset.

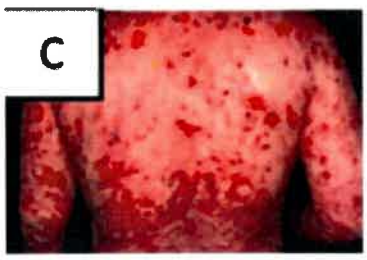
Dermatomyocytis rash, acne rosacea involves nasolabial fold.

Generalised ACLE :

Toxic epidermal necrolysis/TEN like picture (very rarely) :



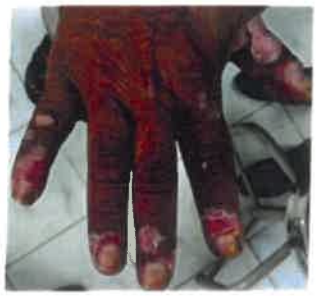


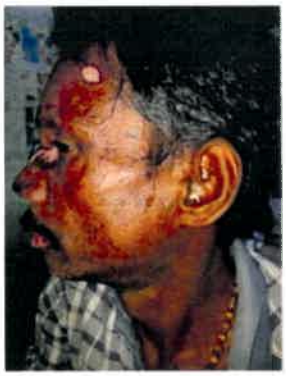
SLE specific skin lesions :

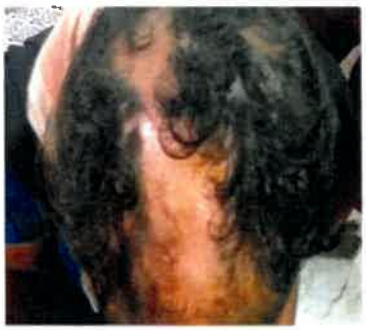
Acute cutaneous LE (15%)	• Localised ACLE (malar rash/butterfly rash) : 90–95%. • Generalised ACE (morbilliform) : 5–10%. • Toxic epidermal necrolysis like ACLE : very rare.
Subacute CLE (8%)	• Annular SCLE : 42% • Psoriasiform SCLE : 39%
CCLE/DLE	• Discoid LE 80–85%, Localised DLE : 70%, Generalised DLE : 30%. • Hypertrophic/verrucous LE • LE tumidus • Chilblain LE • LE profundus/panniculitis • Mucosal LE • Lichenoid DLE–LE/LP overlap

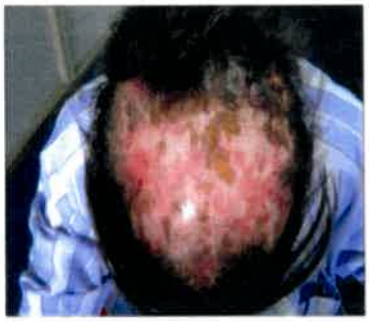
a. Chronic cutaneous lupus erythematosus/Discoid lupus erythematosus/DLE :

- Is a chronic erythematous rash.
  Disfiguring rash (scaring rash).
  Characterised by keratotic scaling, follicular plugging, dermal atrophy.
  Associated with scaring/cicatricial alopecia.
- Site : Face, neck, back (carpet track appearance : Back).
- 5 % of patients with DLE have SLE also.
  20% of patients with SLE have discoid rash.
- Circular raised erythematous patches.
- Is a premalignant rash (risk factor for squamous cell carcinoma).
- Investigation : Biopsy from skin lesions.



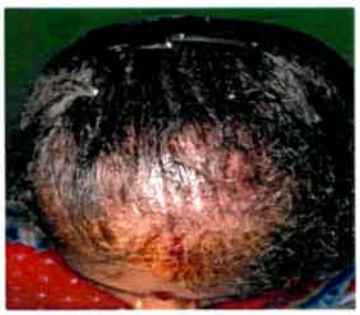


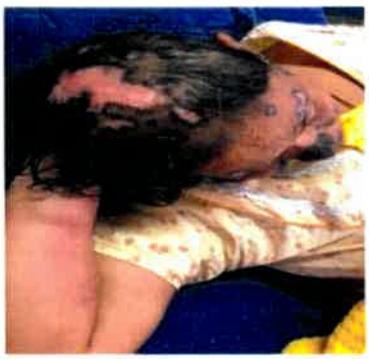




Scaring alopecia : DLE

Non scarring alopecia : SLE





DLE rash

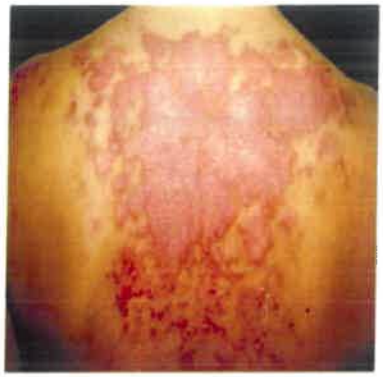
Carpet tract sign : DLE

3. Subacute cutaneous lupus erythematosus /SCLE :

Are of 2 types/pattern :

Annular SCLE.

Psoriasiform SCLE.



Bilaterally symmetrical superficial lesions.

Non scaring lesions.

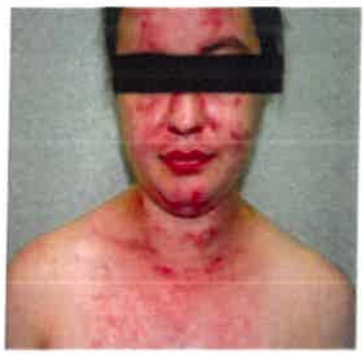
50% of SCLE patients develop SLE.

Photosensitive rash.

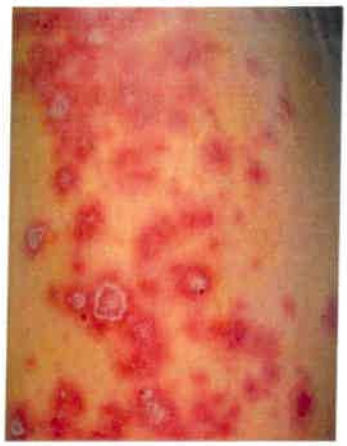
Site : Sun exposed parts.

Associated with Anti Ro/anti La : Hence decreased risk of nephritis and vasculitis : Good prognosis in SLE.

Associated with HLA DR 3.

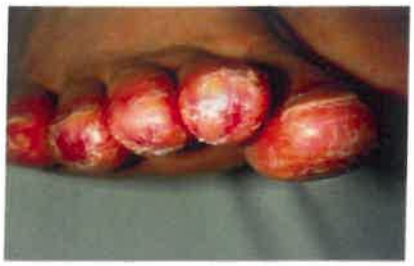


Widespread SCLE involving face and V-neck area

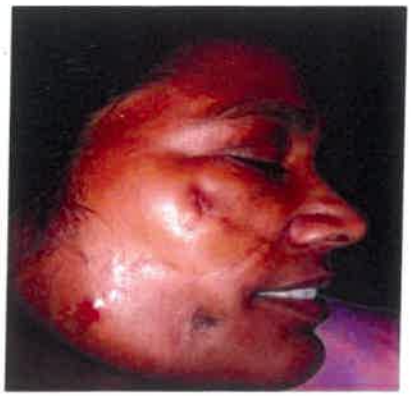


Papulosquamous lesions

Other lupus specific skin lesions :



Chillblain LE



Lupus panniculitis

Lupus profundus

Joint manifestations 00:18:42

Arthritis → Inflammatory
Arthritis → Non inflammatory

Inflammatory arthritis ⟶ Look for site.

Features	SLE
Arthralgia/ Arthritis	Only pain or inflammation (redness, tenderness &swelling) >, can be arthritis or only arthralgia.
morning stiffness & change with activity	Seen in SLE, activity decreases the stiffness (inflammatory).
ESR	High (since inflammatory in SLE)
Upper/ lower limb ?	Upper limb
Small joint/ large joint ?	Small joint
mono/ oligo (1-4) or Polyarthralgia arthritis	Polyarthralgia/ arthritis.
Symmetrical/ Asymmetrical ?	Symmetrical
Axial skeleton	Not involved.

SLE joint manifestations :
Arthritis or arthralgia which is bilaterally symmetrical.
Predominantly involving upper limb peripheral small joint.
Polyarthritis/polyarthralgia without the involvement of axial skeleton.

SLE is an example of Jaccoud arthropathy :

It is non erosive and can be deforming arthritis (laxity of ligaments).

D/d : Rheumatoid Arthritis/ RA (similar features).
RA is erosive arthritis which also leads to deformities.
Investigation : Anti-CCP.

Clinical scenario :

1. An SLE patient who was diagnosed in 2019 and on treatment is presently in remission. She presented with acute painful red hot swelling of left knee joint. Has history of on & off fever. Her general condition is good with no other muco-cutaneous involvement.

This episode is not related to SLE as red hot swelling is not seen in SLE and as other features of SLE are not present.
This is a case of acute mono arthritis.
Any case of acute mono arthritis is septic arthritis unless proven otherwise (other posibility is gout).
Cause : Immunosupression due to steroidal treatment of SLE.

2. An SLE patient diagnosed 3 months ago on tapering dose of treatment. Presents with hip joint pain and difficulty in walking and movement of hip (especially internal rotation).
Investigation to be done ?
This is a case of avasular necrosis which presents with hip joint pain & difficulty in movement (internal rotation).
Cause : Steroid treatment.
Investigation : MRI.

SLE : ORGAN SYSTEMS

Vascular involvement 00:00:31

Most common cause of death in SLE : Acute Coronary Syndrome (ACS).

ACS in SLE is due to :

- Accelerated atherosclerosis.
- Association with anti-phospholipid antibodies syndrome → 1/3rd of patients have APLA → Increased chance of thrombosis.
- Coronary vasculitis.

Increased risk of TIA, stroke and MI.
It is an MI equivalent.

Lung involvement 00:04:38

Brunt of the disease falls on kidneys in SLE and on lungs in rheumatoid arthritis.
Lung parenchyma is not involved → Interstitial lung disease not seen.

Pleura gets involved.
Most common lung manifestation : Pleuritis with or without effusion.
Pleural effusion is usually small and bilateral.

When a patient diagnosed of SLE 2 months back, comes with pleuritic chest pain and X-ray showing bilateral small pleural effusion, the diagnosis of SLE related pleural effusion is made only after evaluation.
Diagnostic pleural tap has to be done and Light's criteria is to be applied.

Light's criteria : To assess of the pleural fluid is exudate or transudate.

Pleural fluid protein/serum protein > 0.5.

Pleural fluid LDH/serum LDH > 0.6.

Pleural fluid LDH > 2/3rd the upper limit of normal.

Any one of the three-criterion met → Exudate.
All criteria not met → Transudate.

Exudative effusion can be due to :

- TB.
- Malignancy.
- Pneumonia.
- Connective tissue disease (CTD).

Pleural fluid should be sent for :
Gene Xpert to assess for TB.

Cytological examination of pleural fluid for malignancy.

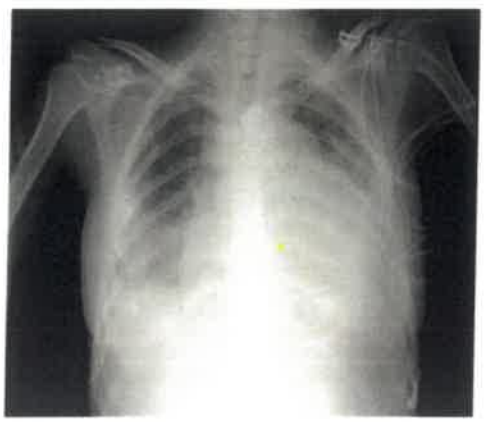
Check for pneumonia like symptoms.

CTD is diagnosed after ruling out the other common causes for exudative pleural effusion.
Usually exudative effusions are unilateral, except for SLE which is bilateral.

To differentiate between pleural effusion of RA and SLE → pleural fluid glucose.

Pleural fluid glucose is normal in SLE.

Pleural fluid glucose is low in RA (<30 g/l).

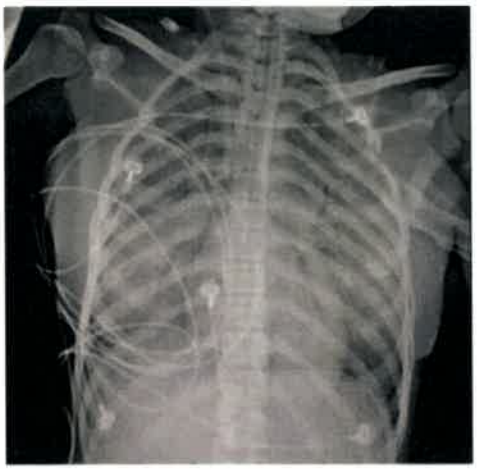


Not seen in SLE :

- Elevated CRP.
- ILD.
- PAH.

Shrinking lung syndrome : Associated with anti- Ro in SLE.

Q. A 22-year-old female diagnosed with SLE since 4 months. She is on steroid and mycophenolate. She complains of cough since 4-5 days, accompanied by 3-4 episodes of hemoptysis. No history of fever or cardiac ailments. She complains of fatigue since last week. On examination, she is pale. Chest has scattered crepts. X- ray shows bilateral air space opacification, which is predominantly lower lobe.



For this patient, assess the levels of :

- Anti-ds DNA titers.
- Serum C3.
- Serum C4.
- Serum CRP.

Low serum C3, C4, CRP and high titers of anti-ds DNA → lupus activity → DAH (diffuse alveolar hemorrhage) → patient should be actively immunosuppressed.

Otherwise, not due to SLE. May be community acquired pneumonia.

In case the patient has SLE in the above scenario :

- Lupus pneumonitis.
- DAH.

In DAH : Bronchoscopy shows blood in air spaces.

Hemosiderin laden macrophages in bronchoalveolar lavage and sputum.

DLCO (diffusing lung capacity for CO) increased.

Biomarker	Diagnosis	Flare
ESR	✗✗✗	✓✓✓
C- Reactive Protein	✗✗✗	✗✗✗
Antinuclear Antibody	✓	✗✗✗
ANA Profile By Immunoblot	✓	✗✗✗
Anti ds DNA	✓✓	✓✓/✗✗
Complements – Low C3 and Low C4	✓✓	✓✓

Cardiac and other system involvement 00:19:40

Most common cardiac involvement : Pericarditis without tamponade (50%).

Libmann-Sacks endocarditis : Vegetations on undersurface of the valve.

Valvular involvement : MR > AR.

Lupus myocarditis → Anti Ro-Sa.

Blood manifestations :

- Anemia of chronic disease is seen.
- Lupus with progressive anemia → Hemolytic anemia.
- Hemolytic anemia associated with warm antibody autoimmune hemolytic anemia that is IgG based.
- Leukopenia/Lymphopenia.
- Risk for diffuse large B-cell lymphoma.
- Recurrent thrombocytopenia due to anti-platelet antibodies → 2° ITP.

Ophthalmological manifestations :

Most common manifestation : Dry eye → 2° Sjogren syndrome.

Uveitis is not seen.

GIT manifestations :

- Lupus hepatitis/autoimmune hepatitis type I.
- Lupus enteropathy → Presents as small bowel diarrhea.

CNS manifestations :

- Increased risk for stroke.
- Most common manifestation : Cognitive decline.
- Can sometimes have psychosis, depression.

The patient can die in the first 10 years due to infection.
Sometimes can die due to vasculitis (not common).

DAH.

CNS vasculitis.

Mesenteric vasculitis.

TREATMENT OF SLE

New classification : SLICC

00:00:28

Sytemic Lupus International Classification Criteria (SLICC) :

Clinical manifestations	Immunological
1. Acute cutaneous lupus. 2. Chronic cutaneous lupus. 3. Oral or nasal ulcers. 4. Non scarring alopecia. 5. Arthritis. 6. Serositis. 7. Renal. 8. Neurological. 9. Hemolytic anemia. 10. Leukopenia. 11. Thrombocytopenia (< 1 lakh/cumm).	1. ANA. 2. Anti-DNA. 3. Anti-Sm. 4. Antiphospholipid antibody. 5. Low complement (C3, C4, CH50). 6. Direct coombs test (do not count in presence of hemolytic anemia).

Diagnosis : ≥ 4 criteria (at least one clinical and one laboratory criteria) or biopsy proven lupus nephritis with positive ANA or anti-DNA.

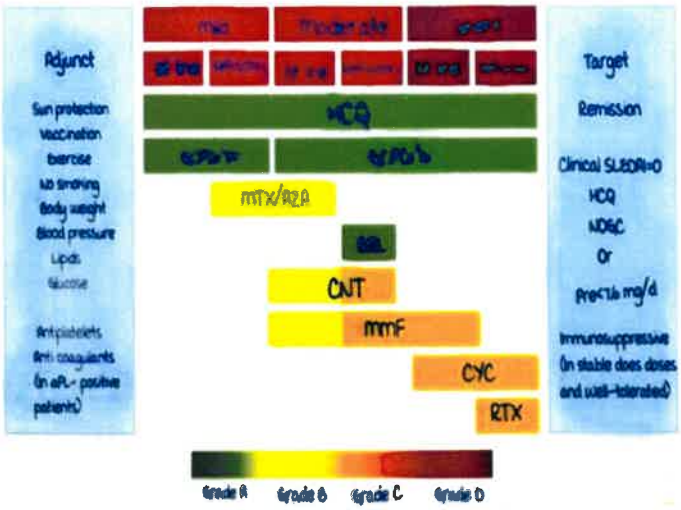
Mild SLE : Constitutional symptoms, skin disease, mild arthritis.

Moderate SLE : Constitutional symptoms, skin disease, severe arthritis.

Severe SLE : Organ system involvement including vasculitis.

SLEDAI score : Indicates severity.

Non- renal systemic lupus erythematous



Management :

1. Mild SLE :

   Oral steroid 1 mg/kg/day followed by tapering dose after 6 weeks.

   Minimum dose to achieved by 3 months.

   Hydroxychloroquine (HCQ) (adverse effect : 1% irreversible retinal toxicity). QT interval to be monitored.

2. Moderate SLE :

   Treatment of mild SLE + Methotrexate/Azathioprine (based on severity of arthritis).

   Belimumab : Anti Blyss (B lymphocyte stimulator) can be tried for mild to moderate SLE.

   Class V lupus nephritis :

   Poor response to steroids.

   Urine protein >1g : Steroids + MMF.

   Urine protein <1g : Steroids + ACE-I.

3. Severe SLE :

   IV steroids for 3 days (methylprednisolone 0.5-1g) pulse therapy followed by oral steroid 1 mg/kg/day and tapered.

   Eurolupus regime : 6 doses IV cyclophosphamide 500 mg/ m^2 once every two weeks or MMF 2-3g/day oral.

Cyclophasphamide :

Alkaline agent, has the tendency to produces secondary malignancy.

Low counts.

Gonadal toxicity.

Reassess at the end of 3 months.

Complete remission : ACR criteria.

- S. creatinine normal.
- Urine protein creatinine ratio normal (< 0.2).
- Urine sediment inactive.

- Only 50 % on an average go into remission.
- 50% relapse following reduction/cessation of treatment, hence maintenance is required.
- At the end of 3 months, if no or partial response, change from cyclophosphamide to MMF and vice versa.
- At the end of 6 months, reassess if still active : Resistant lupus.

Treatment of resistant lupus (repeat biopsy) :

1. Rituximab 4 doses (375 mg/m^2).
2. Mixed regimen : MMF + Calcineurin inhibitors.

MMF is the preferred drug.

Maintenance treatment 00:14:38

At least for 2-3 years.

Low dose oral steroids + MMF > Azathioprine.

Newer drugs :

Anifrolumab : Anti IFN alpha.

Epratuzumab : Anti CD22.

Ocrelizumab : Humanised Anti CD20.

DRUG INDUCED SLE

Drug induced SLE 00:00:17

Also known as Drug Induced Lupus Erythematosus (DILE).
Drug induced lupus is typically characterised by rash with arthritis (skin + joint involvement).
Male : Female = 1 : 1.
Good prognosis.
Renal system and CNS never involved in drug induced lupus.
Pleuritis, pericarditis or serositis can occur.

Causes :
Mnemonic : CHIMP.
C : Carbamazepine, Chlorpromazine.
H : Hydralazine.
I : Isoniazid, Interferon, Infliximab.
M : methyldopa.
P : Procainamide, Phenytoin, Propylthiouracil.

Antipsychotic drug causing SLE : Chlorpromazine.
Most drugs causing SLE are safe in lupus patients.

Diagnosis:

- ANA : positive in 100% of patients.
  Homogenous pattern : Antihistone antibodies.
- Antihistone antibody test positive.
- Anti Ds DNA negative.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) 00:00:12

Earlier known as Anti Phospholipid Antibody syndrome (APLA).

1/3rd of patients with SLE have APS.

Association of SLE with APS results in thrombosis.

Types of APS :

P° APS

- Not associated with other connective tissue disorders.
- Associated with HLA DR w 53 & DR 4.

a° APS (50%).

- most commonly associated with SLE.

Thrombosis in APS →

1. Antibodies against phospholipid binding protein :
   - β_a glycoprotein I is a phospholipid binding protein (most important BaGpI).
   - Others include prothrombin, annexin, phosphatidyl serine etc.
   - Phosphatidyl serine, commonly present intracellulary, reaches the surface of the platelet and binds to β_a glycoprotein leading to apoptosis of the platelet.
   - Antibodies in APS are directed towards phospholipid binding protein, resulting in inhibition of apoptosis & activation of platelets.
   - Activates complement cascade & leads to thrombosis.
2. Resistance for activated protein C by competing for phospholipid binding.

Thrombocytopenia :

- Lupus anticoagulant (LAC) causes endothelial injury (1st hit), resulting in trapping of platelets.
- Platelet count with APS → 50,000- 100000 /mL.
- Classical presentation → Thrombocytopenia + Thrombosis.
- No bleeding.
- Most common cause of acquired thrombophilia : APS.

- Venous thrombosis > Arterial thrombosis.
- m/c cause of inherited thrombophilia → Factor V leiden mutation.

2nd hit : Due to

- Estrogen.
- Smoking.
- Obesity.
- Prothrombotic states.

Diagnosis of APS 00:06:08

Laboratory criteria :

Any out of three antibodies, positive twice over a period of 12 weeks.

1. Anti β_2 glycoprotein Antibody :
   - Detected by ELISA (IgG, IgM, IgA).
2. Anticardiolipin antibody :
   - Done by ELISA (IgG, IgM or IgA).
   - most sensitive test.
3. Lupus anticoagulant (LAC) :
   - most specific.
   - Correlates with maximum risk of thrombosis.
   - LAC in vitro inhibits clotting factor-phospholipid binding and prolongs aPTT.
   - Cannot be detected directly.
   - Detected indirectly by the prolongation of :
     aPTT.
     dRVVT (Diluted Russels Viper Venom test).
     KCT (Kaolin Clotting Time).

Clinical criteria :

Pregnancy criteria →

Before 10 weeks, 3 or more miscarriages.

- After 10 weeks, even 1 miscarriage (2nd trimester abortion).
- Premature delivery (<34 weeks) of a morphologically normal neonate due to pre eclampsia/ eclampsia/ HELLP syndrome.

Adult criteria :

Thrombosis → Arterial & venous thromboses.

Venous thrombosis

- Livedo reticularis → Lacy network pattern due to veno dilatation caused by venous obstruction.
- Budd Chiari syndrome.

Arterial thrombosis

- Stroke.
- Rarely ACS.

Revised sapporo classification criteria 00:18:52

Clinical criteria :

1. Vascular thrombosis →
- One or more clinical episodes of arterial venous or small vessel thrombosis in any tissue or organ.

2. Pregnancy morbidity →
- One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
- One or more premature births of a morphologically normal neonate before 34th week of gestation because of eclampsia, severe pre eclampsia or recognized features of placental insufficiency or
- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities & paternal and maternal chromosomal causes excluded.

Laboratory criteria :

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis & hemostasis.

2. Anticardiolipin antibody of immunoglobulin IgG & or IgM isotype in serum or plasma , present in medium or high titer (> 40 GPL or MPL, or >99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.

3. Anti β_2 glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer >99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.

Definite antiphospholipid syndrome (APS) → At least one of the clinical criteria & one of the laboratory criteria are met.
Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive antiphospholipid antibody test and the clinical manifestation.
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Other features :
Cardiac valve disease (vegetations or thickening) : Libmann sacks's ensocarditis.
multiple sclerosis like syndrome.

Clinical manifestations of APS

00:23:31

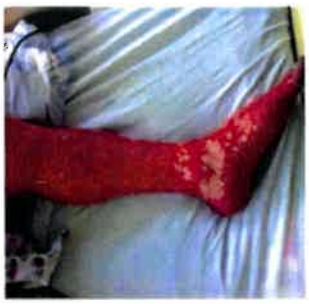
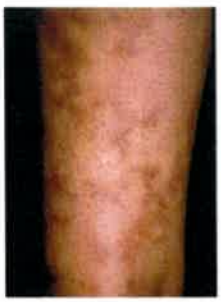
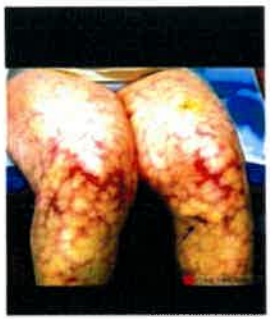
manifestation	%
Venous Thrombosis & related consequences	
Deep vein thrombosis.	39
Livedo reticularis.	24
Pulmonary embolism.	14
Superficial thrombophlebitis.	12
Thrombosis in various other sites.	11
Arterial Thrombosis & related consequences	

Stroke.	20
Cardiac wall thickening/ dysfunction and /or Libman sacks endocarditis.	14
Vegetations.	11
Transient ischemic attack.	10
Myocardial ischemia (infarction or angina) & coronary bypass graft thrombosis.	9
Leg ulcers and/or digital gangrene.	7
Arterial thrombosis in extremities.	7
Retinal artery thrombosis/ amaurosis fugax.	6
Ischemia of visceral organs or avascular necrosis of bone.	3
Multi infarct dementia.	20
Neurologic manifestations of uncertain etiology	
Migraine.	7
Epilepsy.	1
Chorea.	1
Cerebellar ataxia.	0.5
Transverse myelopathy.	3
Renal manifestations due to various reasons (renal artery/ renal vein/ glomerular thrombosis/ Fibrous intima hyperplasia).	
Musculoskeletal manifestations (Jacourd's arthropathy)	
Arthralgias.	39
Arthritis.	27
Obstetric manifestations (referred to the number of pregnancies).	
Pre-eclampsia.	10
Eclampsia.	4
Fetal manifestations (referred to the number of pregnancies).	
Early fetal loss (< 10 weeks).	35
Late fetal loss (≥ 10 weeks).	17
Premature birth among the live births.	11
Hematologic manifestations	
Thrombocytopenia.	30
Autoimmune hemolytic anemia.	10

- Thrombosis: Venous > arterial.
- DVT : most common clinical manifestation.
- Stroke : most common manifestation in arterial thrombosis.

- DVT/Budd chiari syndrome more common presentation than arterial thrombosis.
- Sneddon's syndrome : Triad of
  - Livedo reticularis.
  - Hypertension.
  - Stroke.
- Autoimmune hemolytic anemia + thrombocytopenia without bleeding
- Renal site of lesion : Small vessels (catastrophic APS).
- Adrenal dysfunction : Addison like features (Catastrophic APS).
- Placental thrombosis/ IUGR/ Implantation is affected.

Livedo reticularis

Catastrophic APS :

Criteria :

1. Evidence of involvement of three or more organs, systems or tissues.
2. Development of manifestations simultaneously or in less than 1 week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of Lupus anticoagulant/ anti cardiolipin/ anti β_2 glycoprotein I antibodies.

Definite catastrophic APS:

- All four criteria.

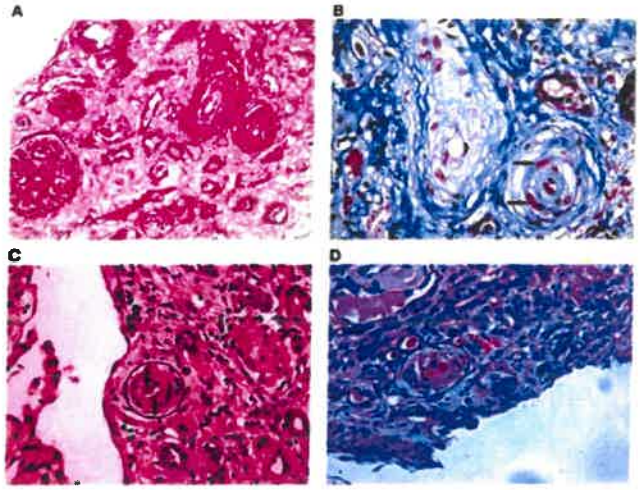
Probable catastrophic APS:

- Criteria 2 through 4 & two organs, systems, or tisssues involved.
- Criteria 1 through 3, except no confirmation 6 weeks

apart owing to early death of patient not tested before catastrephic episode.

- Criteria 1, 2 & 4.
- Criteria 1, 3 & 4 and development of a third event more than 1 week but less than 1 month after the first, despite anti coagulation.

Antiphospholipid syndrome nephropathy histologic lesions :



A. Luminal narrowing due to circumferential myointimal thickening of the wall of arteriole & one interlobular artery. Glomerulus exhibiting ischemic features with wrinkling of the glomerular capillary basement membrane.
B. An interlobular artery and an arteriole showing luminal narrowing due to pale mucoid intimal thickening and myointimal cellular proliferation. Additionally the arteriole reveals fibrin insudation within the wall (black arrow)(masson trichrome 400x).
C. Arteriole showing luminal thrombus (HE 400X).
D. Arteriole showing TMA with platelet fibrin thrombus occluding the lumen & nuclear debris in the arterial wall.

Management of antiphospholipid syndrome 00:40:28

Clinical circumstances	Recomendation
Adult patient diagnosed with APS	Heparin (5000 u IV Q6H) or LWMH (1 mg/kg S/C BD overlapped with warfarin to get INR 2.5-3.

Venous thrombosis.	Warfarin INR 2.5-3.
Arterial thrombosis.	Warfarin INR 2.5-3.
Recurrent thrombosis.	Warfarin INR 3-4 ± Low dose aspirin.
Asymptomatic.	No treatment.
Pregnancy	
First pregnancy.	No treatment.
Single pregnancy loss at < 10 week.	No treatment.
≥ Fetal or ≥ 3 (pre) embryonic losses, no thrombosis/ premature delivery/ miscarriage > 10 weeks	Prophylactic heparin + low dose aspirin throughout pregnancy, discontinue 6-12 weeks postpartum.
Thrombosis regardless of pregnancy history.	Therapeutic heparin or low dose aspirin throughout pregnancy, warfarin postpartum.
Valve nodules or deformity.	No known effective treatment : Full anti coagulation if emboli or intracardiac thrombi demonstrated.
Thrombocytopenia > 50000/ mm^3.	No treatment.
Thrombocytopenia < 50000/ mm^3	Prednisolone, IVIG, Rituximab.
Catastrophic antiphospholipid syndrome.	Anti coagulation + Corticosteroids + IVIG or Plasmapheresis.

SJOGREN'S SYNDROME

2nd most common multisystem autoimmune chronic inflammatory disease.

Female to male ratio is 9 : 1.

Seen in 40 - 60 years old middle aged females.

1° Sjogren syndrome :

Not associated with any other connective tissue disease.

HLA DR3 > DR2.

2° Sjogren syndrome :

Associated with other connective tissue diseases.

Associated with :

Rheumatoid arthritis > SLE.

Inflammatory muscle diseases.

Granulomatosis with polyangiitis.

Clinical features

00:05:14

Glandular Sjogren disease : Keratoconjunctivitis sicca. (dry eye) + xerostomia (dry mouth).

Extra glandular Sjogren disease :

Seen in 50% of patients.

Multisystem manifestations seen.

Autoimmune lymphocytic exocrinopathy → Involves glands with ducts.

Not an endocrinopathy.

Can involve an endocrine gland : Thyroid gland.

In exocrine glands → CD4+ T helper cells infiltrates & deposits around the ductal epithelium and blood vessels → Periductal and perivascular infiltration.

Presentation includes :

- Dry eye.
- Dry mouth.
- Dry throat.
- Dry skin.
- Dry vagina.

The lymphocytic infiltration causes activation of ductal epithelium causing :

Immune destruction → Destruction of ductal epithelium.

Immune inhibition → Inhibits M3 cholinergic receptors responsible for ductal secretion.

No role for virus infection.
(CMV is a salivary gland virus but not associated with Sjogren syndrome).

T > B cell mediated with CD4+ T helper cells predominantly involved.

Th1 > Th17.

Associated salivary gland enlargement seen due to IL-18 positive macrophages involvement.

Antibodies associated with Sjogren syndrome :
Anti- M3 antibodies.
Anti- α- fodrin antibodies.

Dry eye 00:13:31

It is a non- specific symptom.

Schirmer test:
Defective tear production is assessed.
<5mm is diagnostic of dry eye.

Aqueous and mucin layers of the tear film are involved, with mild involvement of the lipid layer as well.