General Medicine

Volume - 4

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Volume - 4

Rheumatology and Immunology

Respiratory Disorders

Acid Base Regulation

ECG

Biostatistics

SLE : ETIOPATHOGENESIS

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Connective tissue disorders

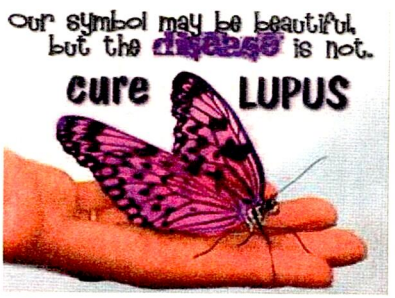
00:01:10

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 because SLE is driven by estrogen.

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.

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Risk factors of SLE

00:16:18

Genetic risk factors :

Complement deficiency :

- Strongest genetic risk factor of SLE : Early component deficiency : $C_{1q} > C_2 > C_4$.
- TREX gene mutation (present on chromosome 3).
- HLA DR B_1 03 , DR B_1 02.
- HLA DR3 : Subacute cutaneous lupus.

Note : late complement deficiency predispose to Neisseria and Toxoplasma infection.

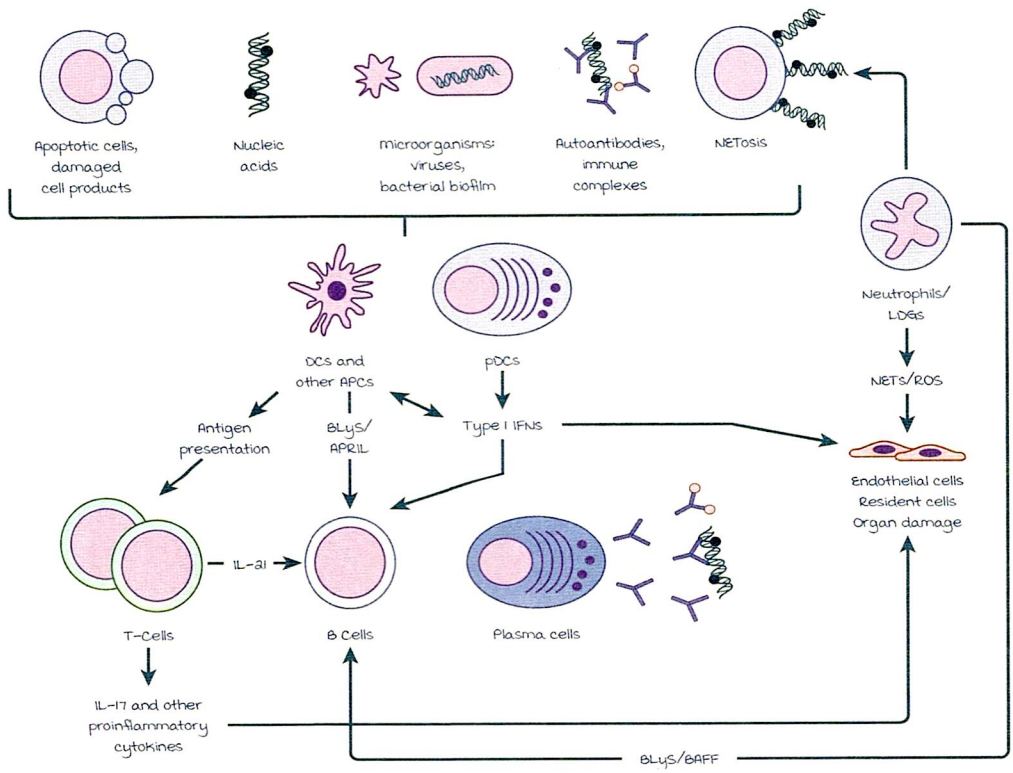
Environmental risk factor :

Important only in people affected with any genetic risk factors.

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

Pathogenesis of SLE

00:21:31



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Immune dysregulation :

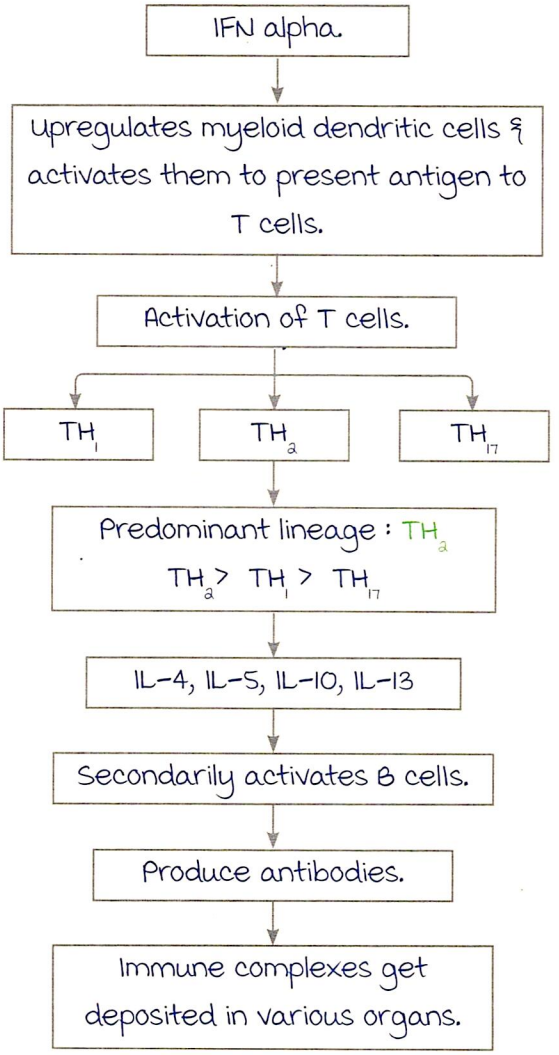
Type 3 hypersensitivity reaction (Immune complex mediated disease)

1. Defective clearance of apoptotic debris or defective lymphocytic phagocytosis.
2. Inefficient degradation of DNA containing neutrophil extracellular traps (NET) : Defective NETosis.
3. 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.



Vessel wall : Vasculitis.

Joints : Arthritis.

Glomeruli : Glomerulonephritis.

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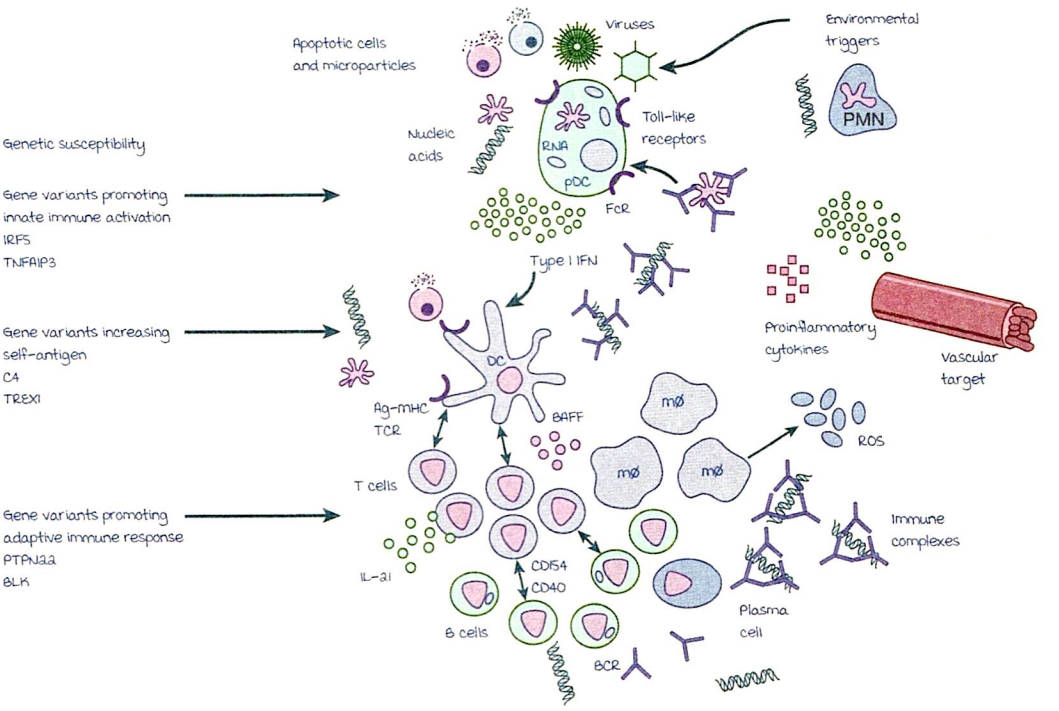
Contributors to systemic lupus erythematosus (SLE) pathogenesis



Activation of B cell

00:33:32

T cell activates B cell by multiple pathways :

- IL 4 pathway.
- IL 12/21 pathway.
- 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.
- Autoantibodies in SLE : Antinuclear antibodies (98%), anti-dsDNA (70%), Anti-Sm (25%), anti-RNP, Anti-Ro (SS-A), Anti-La (SS-B), Antihistone, Antiphospholipid, Antierythrocyte, Antiplatelet, Antineuronal (includes antiglutamate receptor), Antiribosomal P.
- Antinuclear antibodies forms the best screening tests for all autoimmune diseases, repeated negative tests make SLE unlikely.

ANA/Anti nuclear antibodies

00:01:11

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.

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 DNA.

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.

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ANA pattern :

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

- Homogenous pattern : anti-ds DNA.
- Coarse speckled pattern : anti-Smith.
- Dense fine speckled pattern (DFS pattern) : r/o CTD.
- Fine speckled pattern : Sjogren's syndrome.

Antibodies checked under ANA profile

Anti Sm	Specific
Anti UIRNP	
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 I	
Anti Mi 2	
Anti Ku	Lupus association
Anti PCNA	Lupus association
Anti Pm Scl	

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

Antibody	Specific disease
Anti Sm	Specific for Lupus(10-44%)
Anti- UI RNP	MCTD
Anti SSA (anti Ro)	Sjogrens
Anti SS B (anti La)	Sjogrens
Anti Scl 70	Scleroderma
Anti Jo I	myositis

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).

m/c 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 secondary Sjogren's syndrome.
- Indicates good prognosis (Associated with decreased risk for nephritis and vasculitis).
- In pregnancy, it indicates the risk for neonatal lupus with congenital heart block.

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- Associated with subacute cutaneous lupus erythematosus/SCLE (photosensitive).
- Associated with shrinking lung synrdome.
- 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 antiphospholipin syndrome/APS.
- 1/3rd of the patients with SLE have APS (thrombosis).

Anti - RBC/erythrocyte antibody 00:24:25

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

Antiplatelet antibody 00:31:14

Idiopathic thrombocytopenic purpura/ITP : Patient presents with thrombocytopenia and bleeding.

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

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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 : m/c antibody seen in neuro SLE.
- Antiribosomal-P antibody : Correlates with depression/ psychosis in CNS lupus (helps to differentiate b/w depression d/t neuro lupus & functional depression in SLE).

m/c neurological manifestation in SLE : Cognitive dysfunction.

Reading an ANA report :

- Methodology : Indirect immunoflorescence.
- Standard dilution : 1:80 <<.
  Intensity : 1+, 2+, 3+, 4+.
- Pattern : Coarse speckled, cytoplasmic staining.

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 00:41:56

- 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 INF α).

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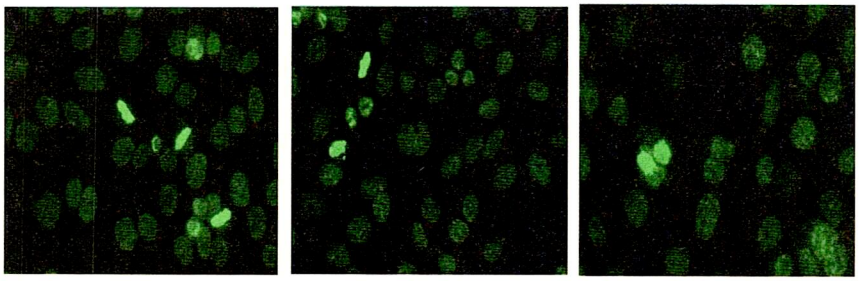
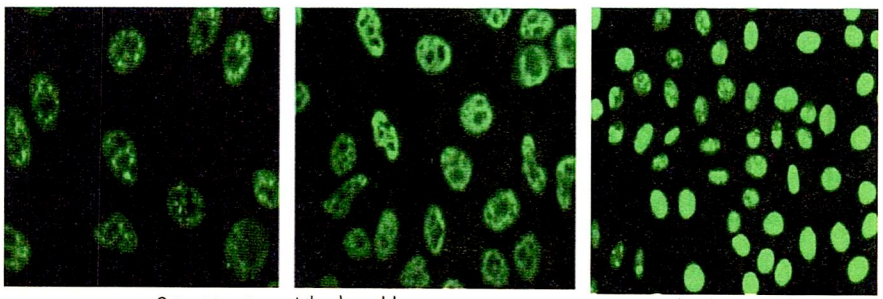
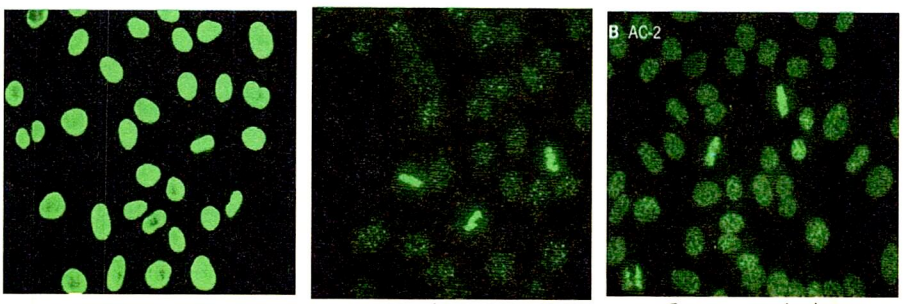
- Anti-ds DNA antibody : To assess the disease activity/flare.
- Anti C1 Q antibodies : To assess nephritis.
- Complement C3 and C4 : SLE is charecterised by low C3 and C4.
- ANA profile : To diagnose SLE.
- ENA profile : To diagnose SLE.



Dense speckled pattern



Coarse speckled pattern | Nucleolar pattern



Homogenous pattern | Centromere pattern | Fine speckled pattern

Anti-ds DNA :

3 major methodology :

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

m/c pattern in SLE : Homogenous pattern.

Most specific pattern in SLE : Homogenous/coarse speckled pattern.

m/c pattern in CTD : Fine speckled pattern.

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SLE : LUPUS NEPHRITIS

Lupus nephritis

00:01:15

50 to 60% of SLE patients 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 :
  - Commonly Seen.
  - Mainly Involved.
- Tubulo Interstitial component : Rare .

Glomerular involvement in lupus nephritis .

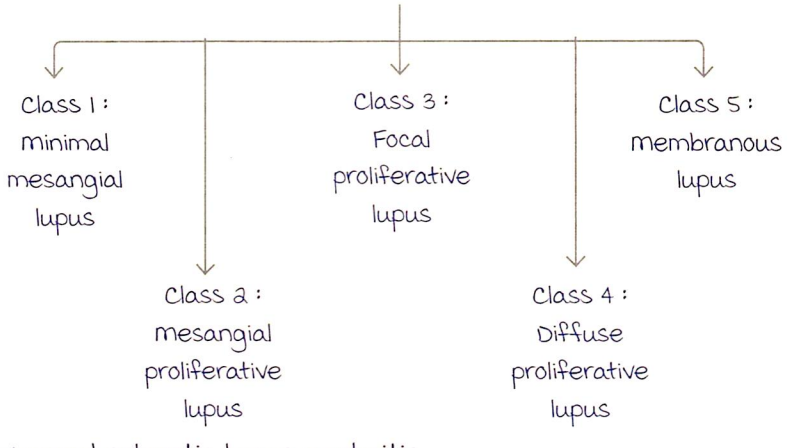
Indication for biopsy :

Urine > 1g/day protein or 500 mg/dl with microscopic hematuria (≥ 3 RBC per HPF after urine centrifugation).

On suspicion of nephritis :

- The patient have to be assessed on URE (urine routine examination).
- URE to be done in all follow ups.

Classification of lupus nephritis (based on biopsy) :



Class 6 : Advanced sclerotic lupus nephritis

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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 .

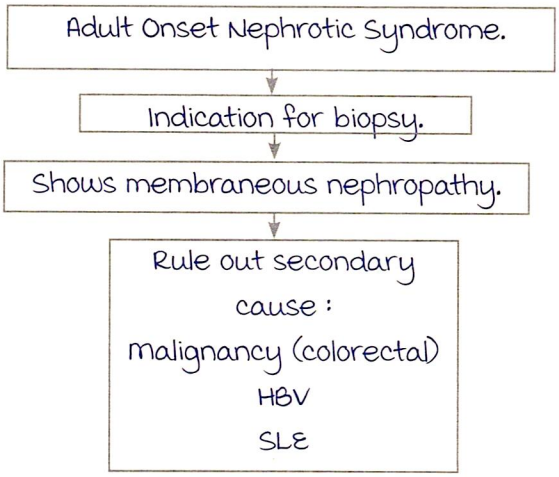
Immunofluorescence in both Class 1 & Class 2 : Mesangial Immune Complex deposition seen and hence cannot be differentiated.

Class 5 :

- Membranous Lupus.
- Difficult to treat.
- Steroid refractory.
- Better prognosis than class 4 as lesser chance for CKD.
- Presentation : Adult Onset Nephrotic Syndrome.

Manifestations :

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



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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 .

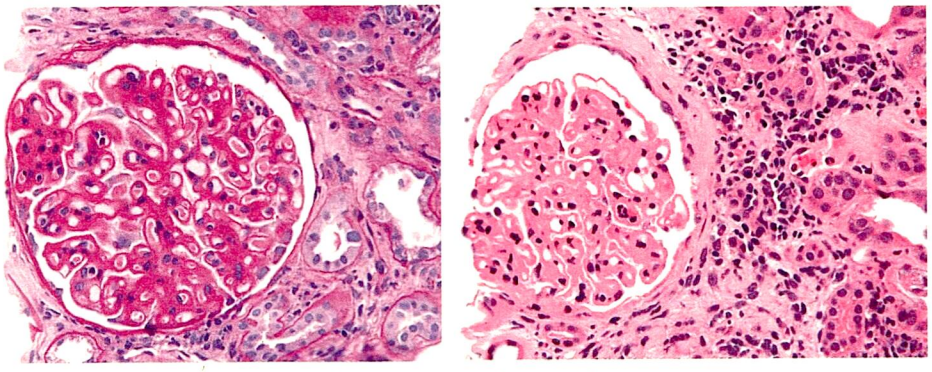
Global : Entire complete involvement.

Segmental : In part involvement.

Presents with Type 2 RPGN.

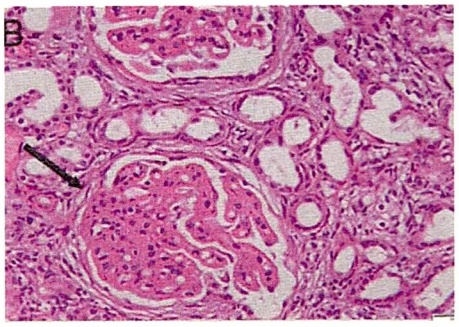
- Within days to weeks develops renal failure.
- High coloured urine +.
- Within week : Facial puffiness, pedal edema develops & progresses, reduced urine output.

Membranous nephropathy : Thickened glomerular basement membranes (thick capillary loops) :

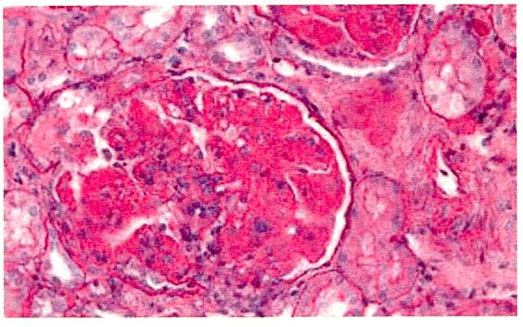


Membranous nephropathy

Class IV : Glomerulus showing thickened capillary loops and membranes.



Membranous nephropathy



Diffuse proliferative lupus nephritis (class IV)

Case HP :

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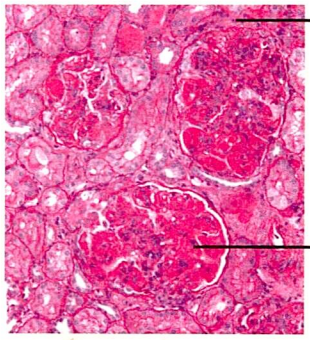
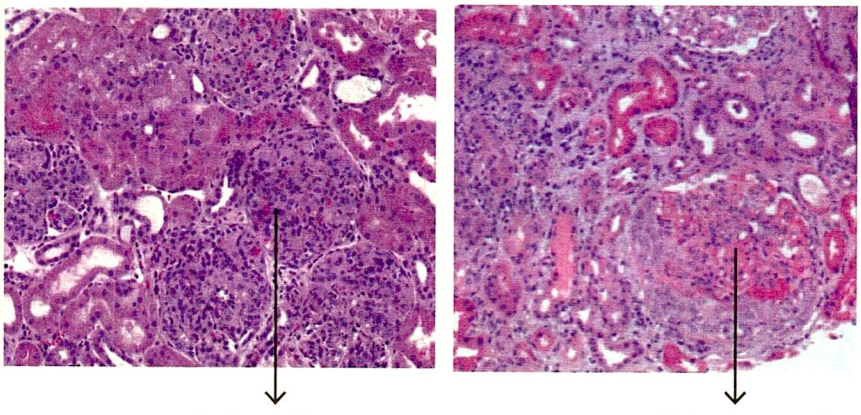
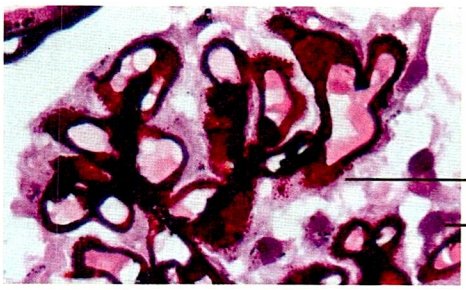


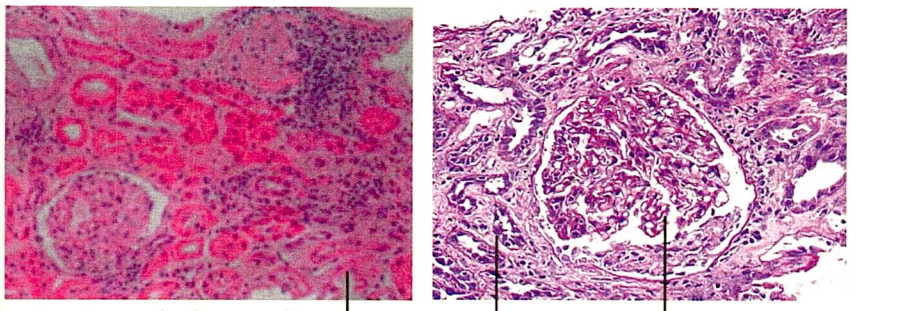
Complete proliferation :



RPGN class IV



Membranous nephropathy



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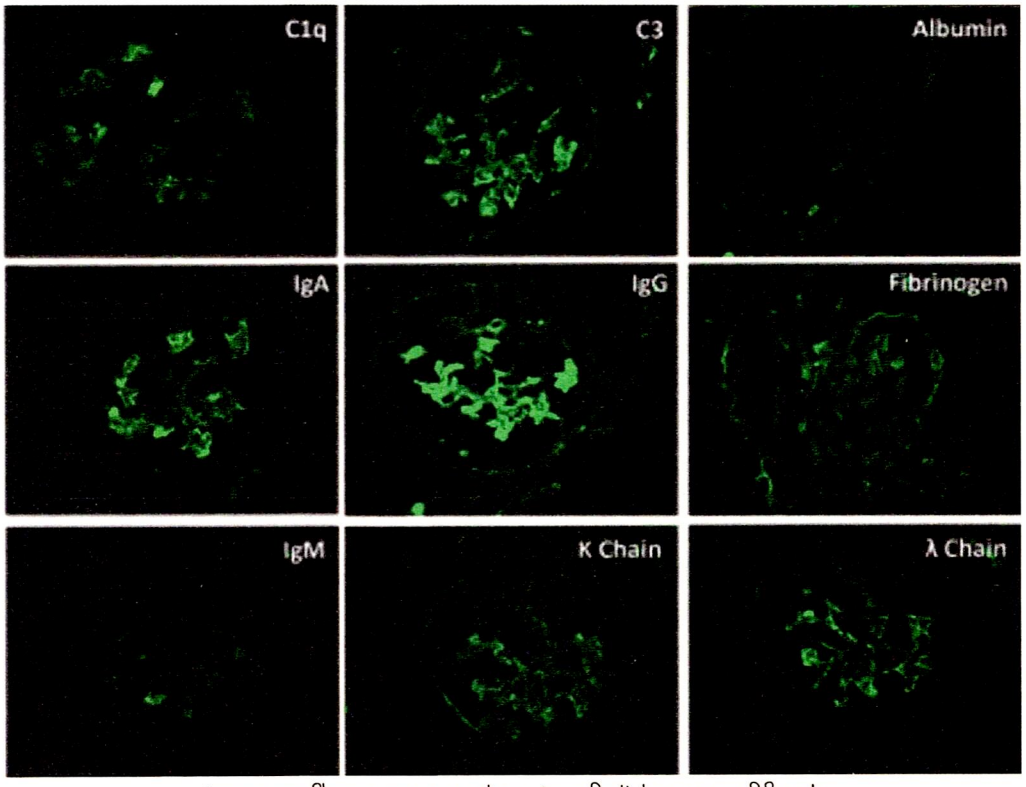
In class 3 & 4 SLE : IgG, IgA, Kappa Lambda, C_1q, C_3.



Immunofluroscence showing full house effect

In Class 4 : wire loop due to subendothelial deposition.

most specific finding : In electron microscopy hematoxylin bodies of gross.

R/o 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.