HARRISON'S BASED GENERAL MEDICINE

PART - 4

CONTENT

RHEUMATOLOGY & IMMUNOLOGY

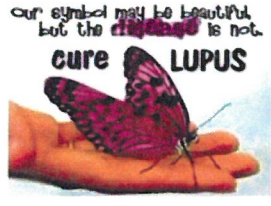
SLE : ETIOPATHOGENESIS

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.

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).

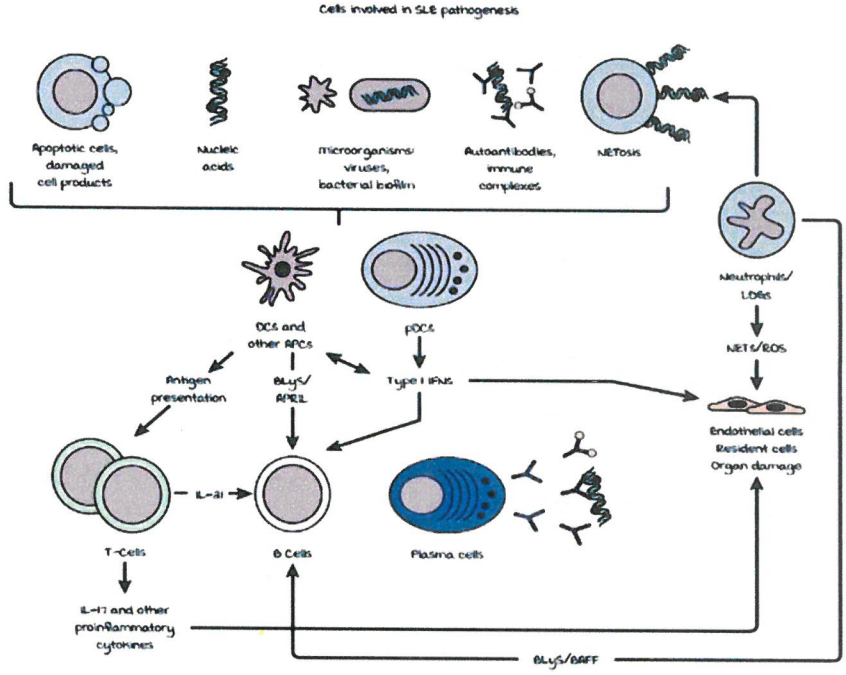
HLA $DR\ B_1\ 03$, $DR\ B_1\ 02$.

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_a TH_{17}

↓

Predominant lineage : TH_a

$TH_a > TH_1 > TH_{17}$

↓

IL-4, IL-5, IL-10, IL-13.

↓

Secondarily activates B cells.

↓

Produce antibodies.

↓

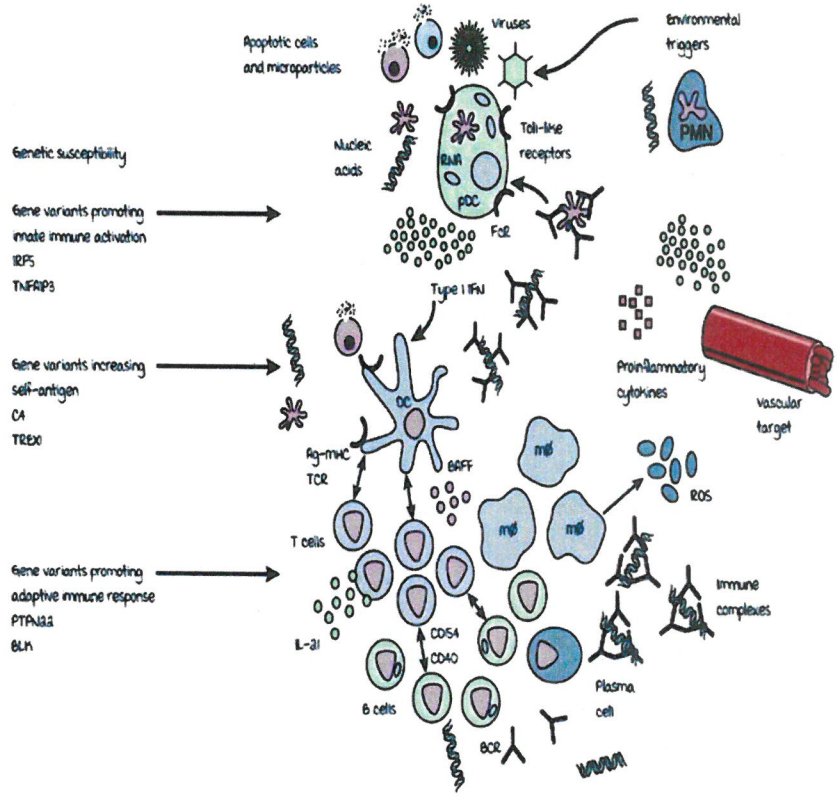
Immune complexes get deposited in various organs.

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 U1 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 U1 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 U1RNP	
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	

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.

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.

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.

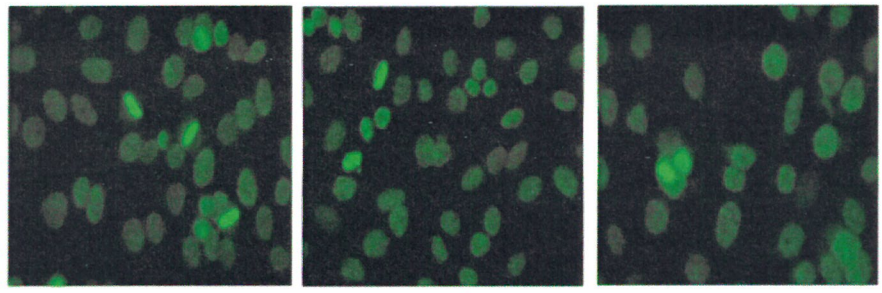
Nucleolar pattern :

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

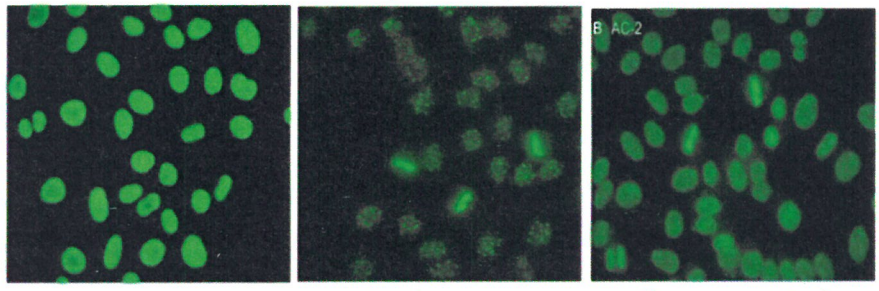
ANA and ANA profile in a lupus patient should not be repeated periodically because they just help in classifying the disease as SLE and not useful as prognostic markers.

Biomarkers in SLE 00:41:55

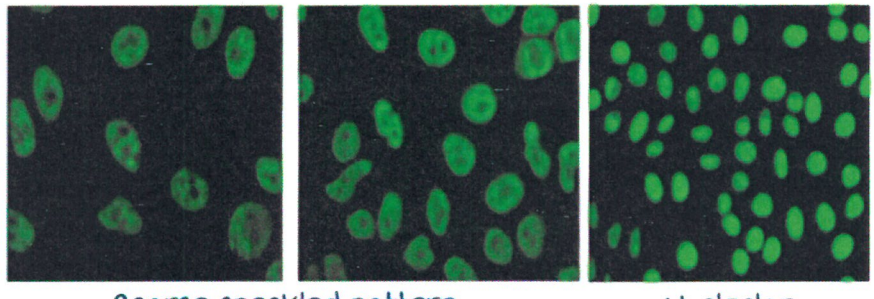
- ESR :
  Non-specific elevation.
  Almost 90% of lupus have an increased ESR.
  Can monitor disease activity.
- CRP : Low in active lupus (due to the presence of anti-CRP antibody and suppression of CRP by TNF α).
- Anti-ds DNA antibody : To assess the disease activity/ flare.
- Anti C1 Q antibodies : 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.

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.

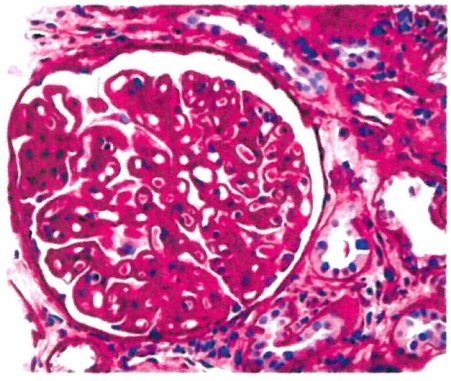
Within days to weeks develops renal failure .

high coloured urine +.

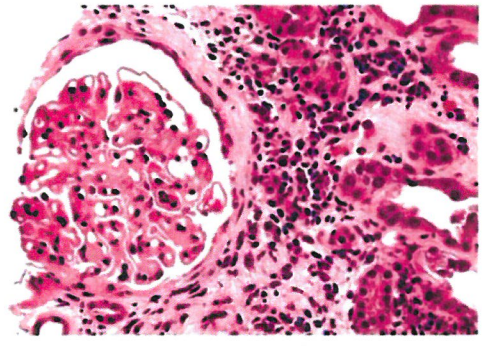
within week :

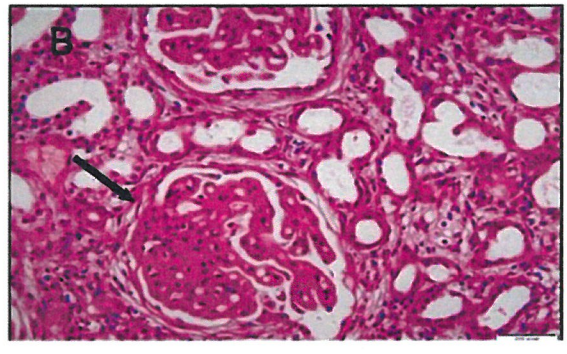
reduced urine output .

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.

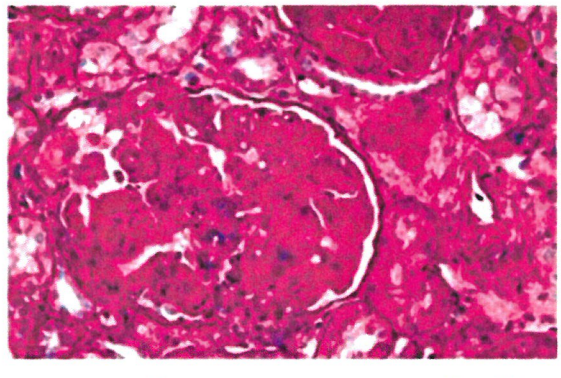


membranous nephropathy with thickened glomerular basement membranes (thick capillary loops).





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.