Lupus Nephritis

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A typical Lupus Nephritis Case

- 35-years old woman presented with malar rash, fever, arthritis and hypertension (BP 190/100 mmHg)
- Labs showed Hb=9.5g/l, ESR=80mmFHR, CRP=3.5mg/dl, Creatinine = 2.1, Proteinuria (2+), RBC in urine = 15
- Subsequent labs showed ANA + Homogenous pattern, dsDNA 3+
- Renal Biopsy showed Focal segmental glomerulosclerosis with high activity index. Immunofluroscence was positive for C3, IgG and IgM

Lupus Nephritis Pathologic Classification
An Evolving Paradigm

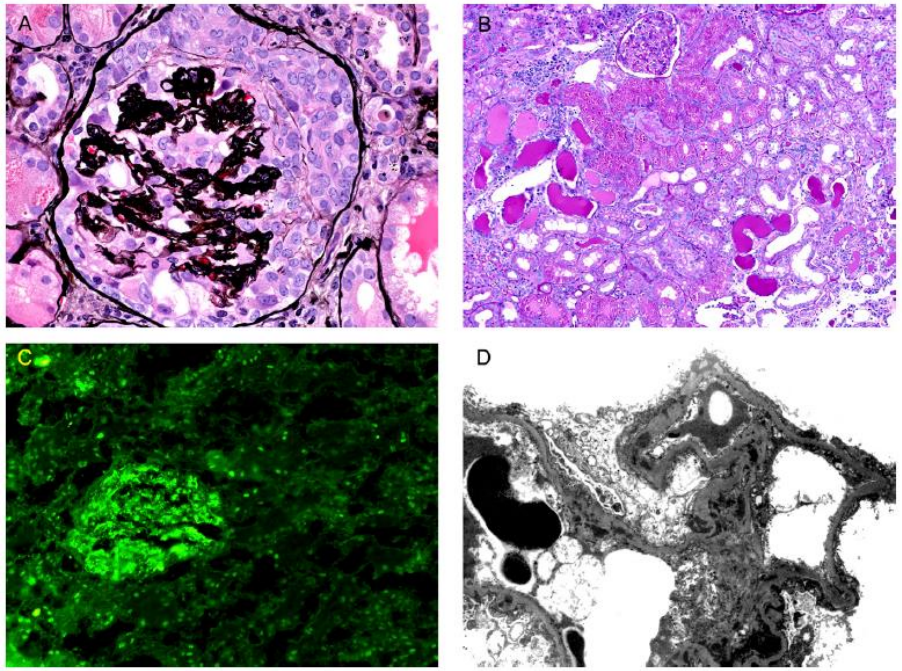
2003 Classification (fundamental) most people are familiar with:

Table 4. Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis[a]
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class V	Membranous lupus nephritis[c]
Class VI	Advanced sclerosing lupus nephritis

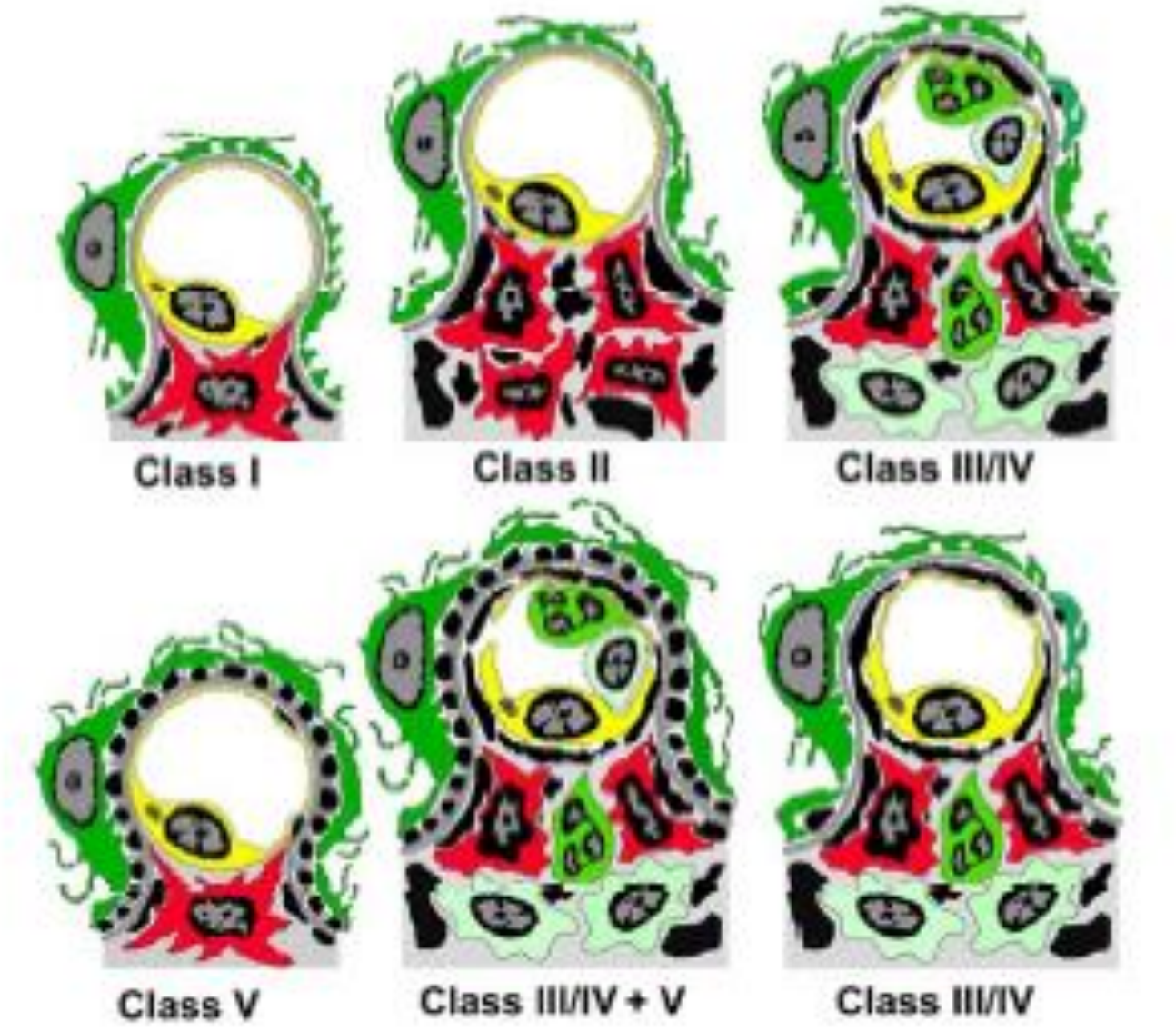
Class III and IV: Active / Chronic

Next slide shows what the classification means



J Am Soc Nephrol. 2013.

Ultrastructural Features of a Single Glomerular Capillary affected by Lupus Nephritis



Class I: mesangial immune deposits (black) but no mesangial cell (red) hypercellularity or influx of PMNs.

Class II: mesangial immune deposits and mesangial cell hypercellularity but no influx of PMNs.

Class III/IV (U.R.): mesangial and capillary influx of PMNs

Class III/IV (L.R): subendothelial capillary wall immune deposits that can be seen by LM and mesangial but no capillary influx of PMNs (dark green neutrophils and light green monocytes/macrophages);

Class III/IV + V with influx of PMNs and numerous subepithelial immune deposits in addition to subendothelial deposits

Class V with numerous subepithelial immune deposits
but no influx of leukocytes

(podocyte = outer green cell, endothelial cell = yellow cell, mesangial cell = red cell, neutrophil = green cell with segmented nucleus, monocyte/macrophage = light green cell)

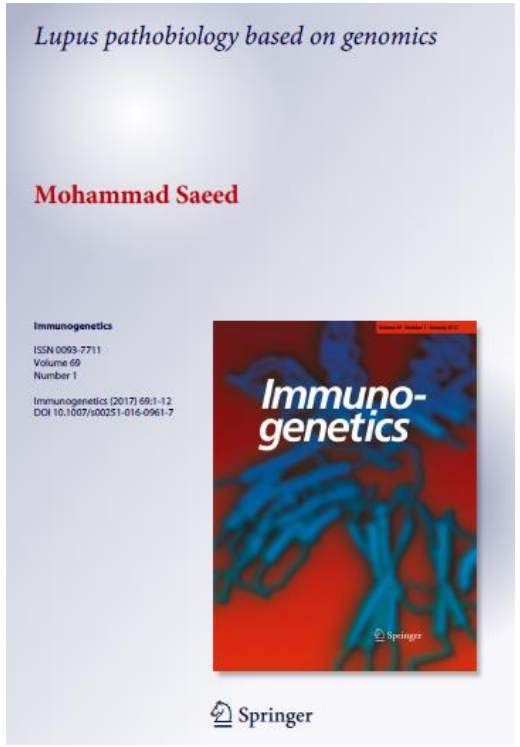
Bajema IM, et al. Kidney Int. 2018 PMID: 29459092.

Summary: Lupus Nephritis Pathologic Classification 2018

Classification system has become progressively based on cellular components rather than histological observations

- Proposed elimination of Class VI
- Segmental and Global terms eliminated
- Crescents redefined as involving glomerular capsular circumference of >10% (down from previous 25%)
- Collapsing GN to be separately classified
- The need to include Vascular (Thrombotic microangiopathy (TMA) and vasculitis) and Tubulointerstitial lesions
- Certain histologic terms changed to mean definite cell types (Endocapillary Proliferation to Hypercellularity – as the histologic effect is due to inflammatory cell infiltration)
- Activity and Chronicity Indices refined and included

Bajema IM, et al. Kidney Int. 2018
PMID: 29459092.



Molecular Pathogenesis

Immunogenetics

January 2017, Volume 69, Issue 1, pp 1–12 | Cite as

Lupus pathobiology based on genomics

Authors | Authors and affiliations

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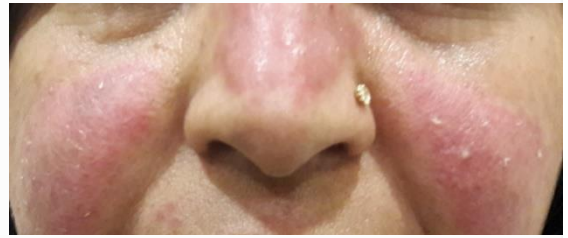
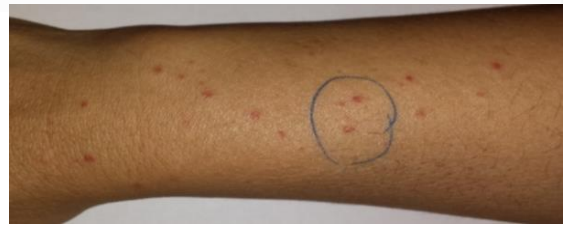
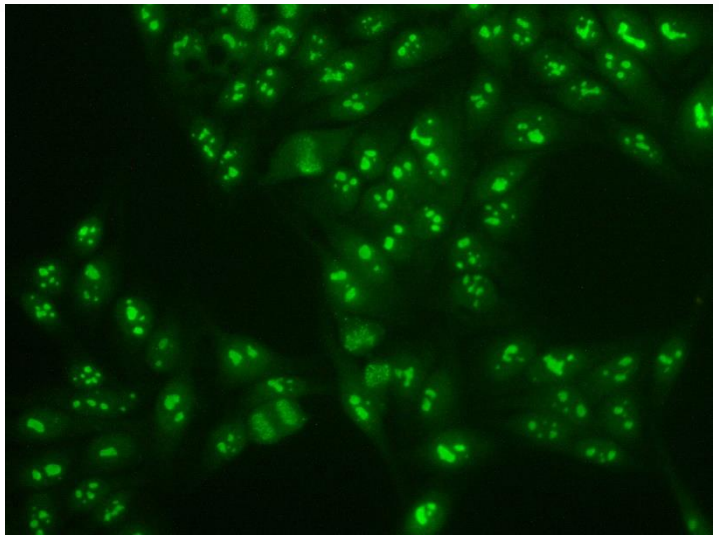
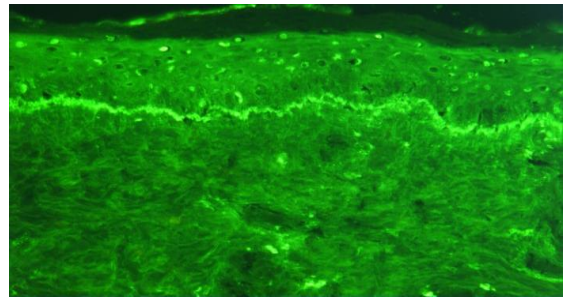








For detailed overview please refer to my review above (available as open access) with direct links at: www.immunocure.pk

Lupus Pathobiology based on Genomics – How Drugs work in SLE

Mohammad Saeed. Immunogenetics 2017; 69: 1-12.

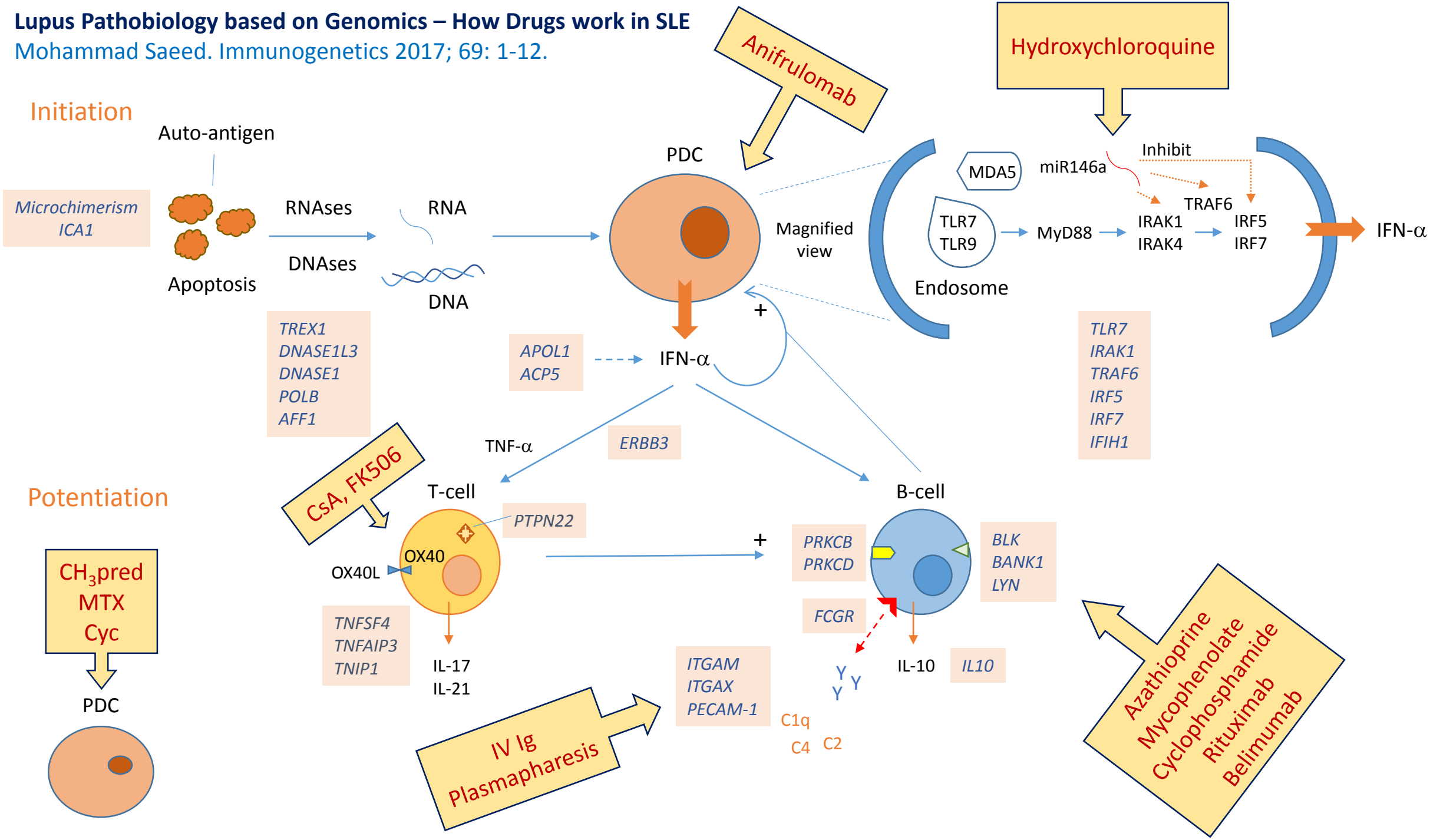


Table 1. Pathomechanisms of LN inside the kidney

Glomerular Pathology	Tubulointerstitial Pathology
Mesangial and subendothelial, immune complex deposits, complement activation	Immune complex deposits in periglomerular vessels
Fc, Toll-like, and complement receptor activation	Complement activation
Activation of renal cells and infiltrating leukocytes (subepithelial IC causes LN class V and podocyte injury with massive proteinuria)	Activation of endothelial cells, luminal adhesion molecules
Local cytokine expression	Leukocyte recruitment
Recruitment of leukocytes	Local antibody production by B cells including tertiary lymphoid organ formation
Proliferation of endothelial and mesangial cells	Cytotoxic and Th17 T cells
Filtration barrier damage causing proteinuria and hematuria	Proapoptotic cytokines
Renal cell necrosis causing focal scaring	Proximal tubular cell damage causing proteinuria
Proliferation of parietal epithelial cells and crescent formation	Tubular/vascular atrophy
Periglomerular inflammation	Hypoxia → inflammation
Global glomerulosclerosis	Insufficient tubular and vascular repair plus ischemia promotes interstitial fibrosis

Similar to mechanisms outside the kidney in SLE

Lech M, Anders HJ. The pathogenesis of lupus nephritis. J Am Soc Nephrol. 2013. PMID: 23929771.

Antibodies in Lupus Nephritis

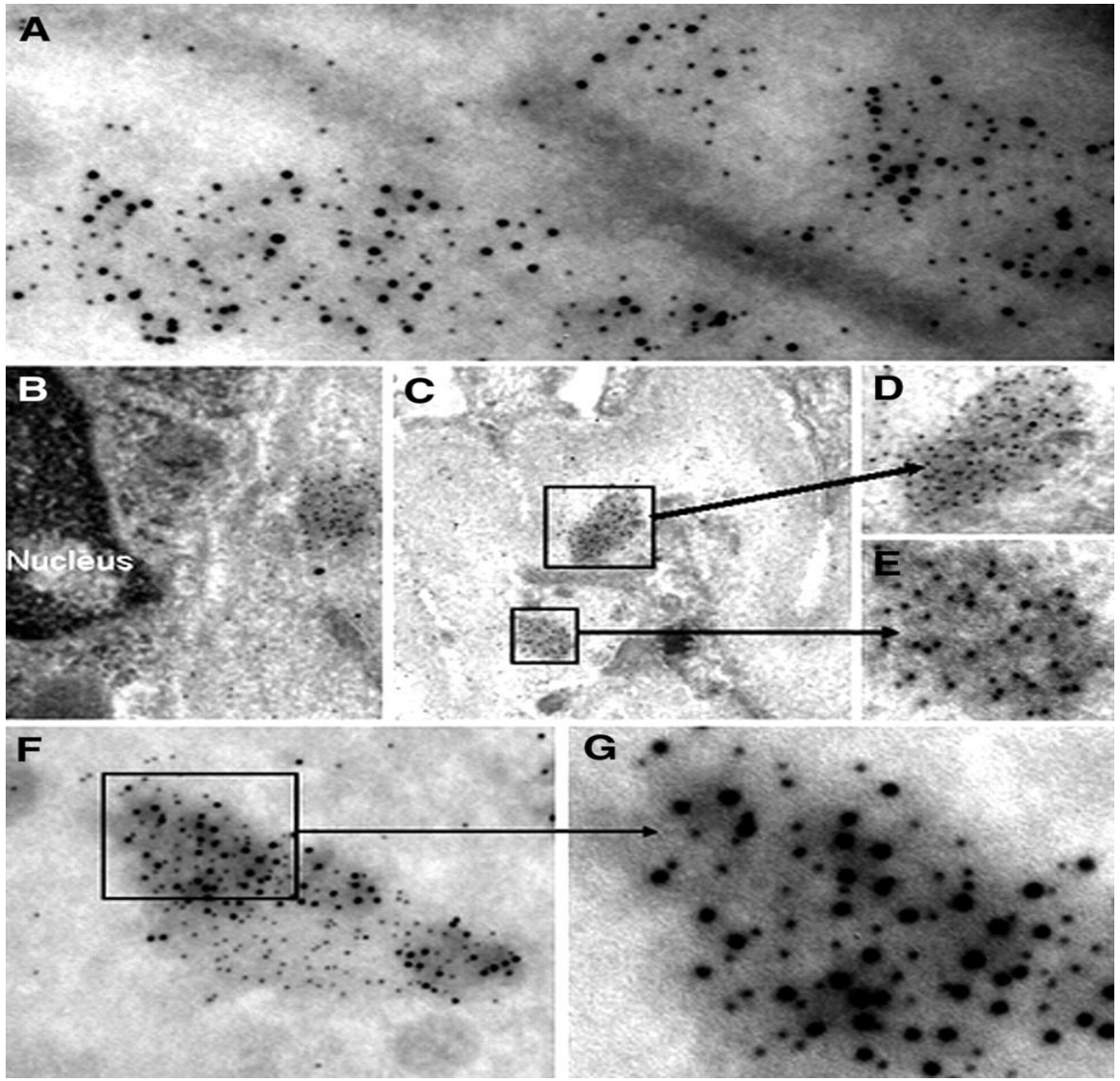
Immune Electron Microscopy

Ab localized to GBM where electron dense structures (EDS) are deposited NOT in surrounding tissue.

EDS are oligo-nucleosomes resulting from aberrant apoptosis

EDS bind anti-dsDNA antibodies

NZB/W F1 mice



Passive transfer of anti-dsDNA Ab do not cause LN.

Lupus GN develops in mice without serum ANA, dsDNA and IgG eluted from kidney homogenates.
(J Exp Med 2004).

Immunoglobulin from autopsy lupus kidneys had max reactivity < 40% against 14 different antigens. (J Rheumatol 2003).

15–26% of antibodies polyreactive between a diverse antigen panel that included ssDNA, dsDNA, LPS, and insulin. (Semin Immunol 2007).

JASN

Mortensen E S , Rekvig O P JASN 2009;20:696-704

Collapsing GN in SLE

JASN
BRIEF COMMUNICATION www.jasn.org

Apolipoprotein L1 Risk Variants Associate with Systemic Lupus Erythematosus-Associated Collapsing Glomerulopathy

Christopher P. Larsen,*† Marjorie L. Beggs,* Mohammad Saeed,* and Patrick D. Walker*†

APOL1 associated strongly with Collapsing Glomerulopathy in SLE [P<0.001, CI $_{95\%}$ =2.4 to 12.1]

Two APOL1 risk alleles conferred 5.4-fold in African Americans

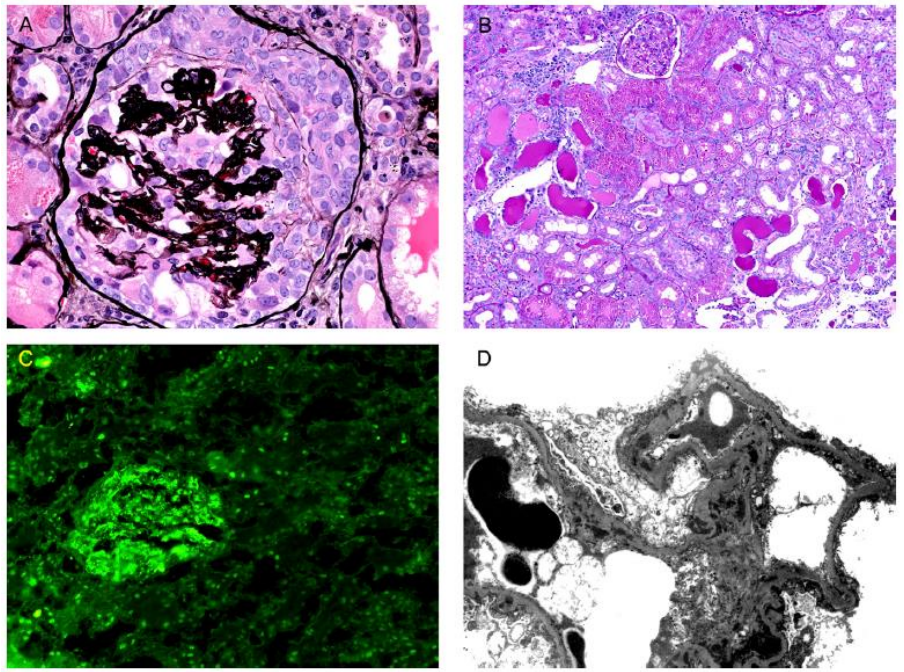
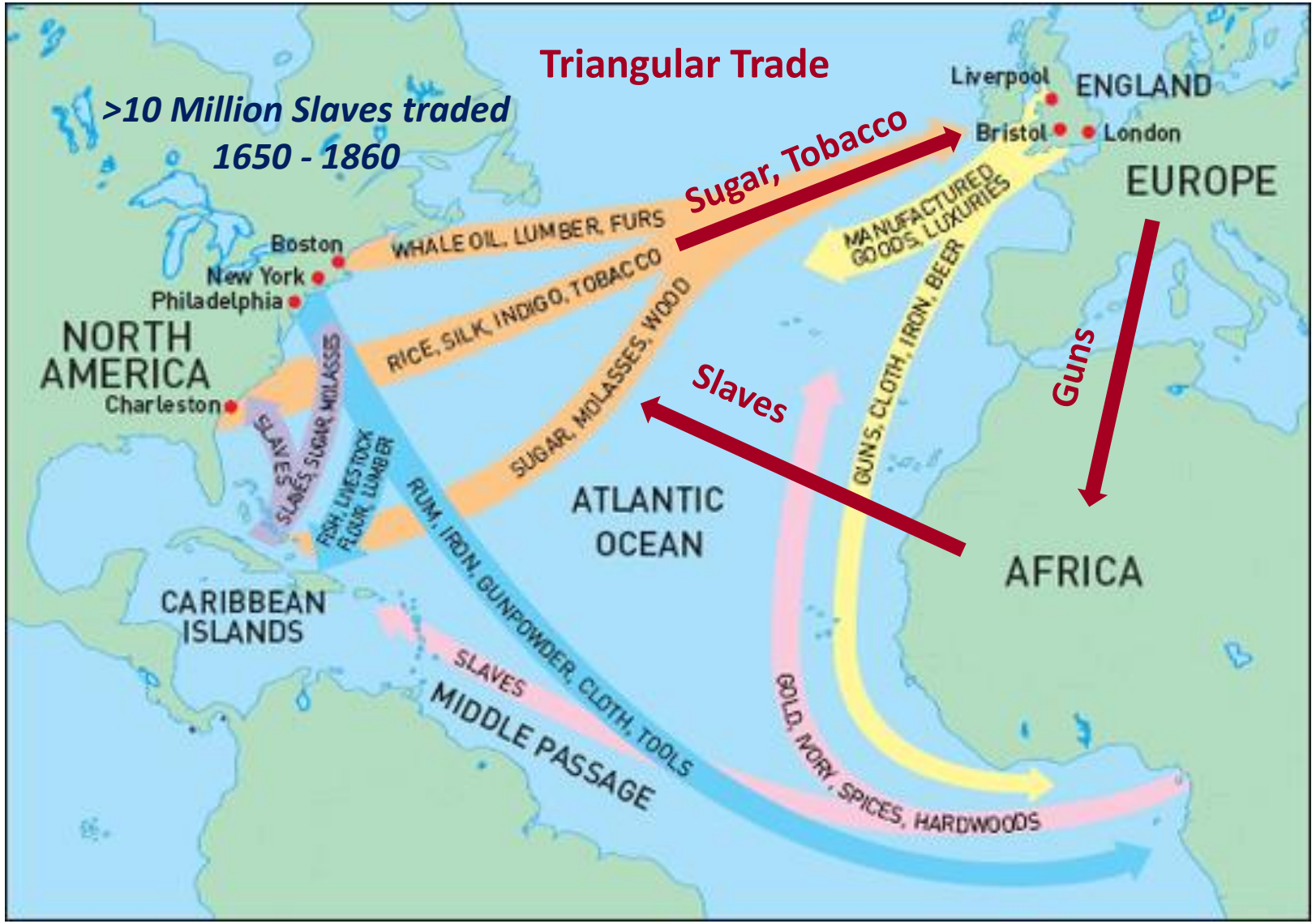


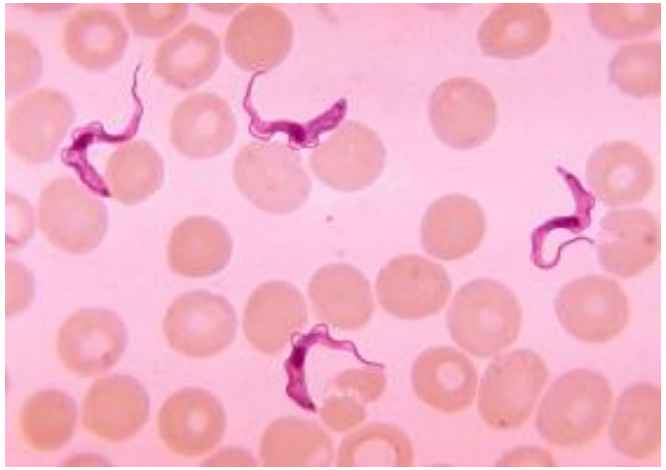
Figure 1. Morphology of SLE-associated collapsing glomerulopathy.
(A) Glomerular tuft collapse with overlying epithelial hypertrophy and hyperplasia inBowman's space
(B) Characteristic tubulointerstitial changes – tubular dilation / hyaline casts
(C) Positive staining for IgG is present in glomeruli
(D) Transmission electron photomicrograph diffuse foot process effacement and mesangial / subepithelial deposits

"Top 10 Developments in Lupus Nephritis"
Curr Rheumatol Rep (2013) 15:358

Sleeping Sickness, Slave Trade and Kidney Disease



Trypanosomes



APOL1 kills trypanosomes following pH-dependent anionic-pore formation in the endocytic system, which disrupts ionic homeostasis.

APOL1 G1/G2 variants adept at killing Trypanosomes

These variants are common in West Africa

Membranous GN and PLA2R

Genes & Immunity

Genes and Immunity (2014), 1–6

www.nature.com/gene

ORIGINAL ARTICLE

PLA2R-associated membranous glomerulopathy is modulated by common variants in *PLA2R1* and *HLA-DQA1* genes

M Saeed, ML Beggs, PD Walker and CP Larsen

Membranous glomerulopathy (MG) is most commonly caused by autoantibodies directed against the podocyte phospholipase A2 receptor (PLA2R1) and common variants in this gene are associated with MG. Here for the first time, we carried out a large case–control association study ($n = 1512$) of PLA2R-positive and -negative MG to determine the extent of association in these pathologic subtypes. We performed four separate sets of analyses to determine significance of the single-nucleotide polymorphisms (SNPs) and their haplotypes followed by joint analysis and trans-ethnic mapping to increase power. The *PLA2R1* SNP rs35771982 was most strongly associated with PLA2R-positive MG ($P = 1.4 \times 10^{-14}$, odds ratio (OR_{GG}) = 1.98). The associations of other SNPs in *PLA2R1* could be explained because of linkage disequilibrium with the G-allele. Haplotypes in *PLA2R1* did not exceed the significance of rs35771982 even after 10 000 permutations. *PLA2R1* variants were only associated with PLA2R-positive MG and predominantly in Caucasians. PLA2R1 variants did not associate with MG in African Americans (AA). There was strong epistasis between *HLA-DQA1* SNP rs2187668 and the *PLA2R1* variant rs35771982. Thus, common variants in the *PLA2R1*, particularly rs35771982, modulate PLA2R-positive MG with *HLA-DQA1* in Caucasians. PLA2R-negative MG especially in AA, may provide a novel opportunity to discover new genes underlying MG.

Genes and Immunity advance online publication, 4 September 2014; doi:10.1038/gene.2014.50

Figure S1: Immunogenicity analysis of PLA2R protein for the H300D substitution introduced by SNP rs35771982 (C>G)

NP_001007268.1 300_His (C Allele)

NP_001007268.1 300_Asp (G allele)

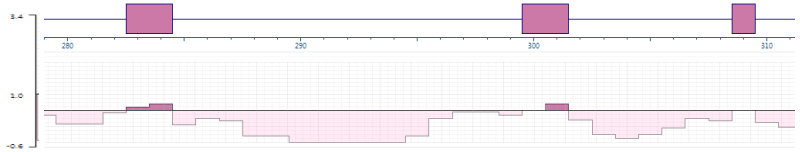


Figure S1 PLA2R protein with and without rs35771982 which replaces the His at position 300 with Asp. The alteration in the amino acid sequence created an area of increased antigenicity.

Saeed M, Beggs ML, Walker PD, Larsen CP. PLA2R-associated membranous glomerulopathy is modulated by common variants in PLA2R1 and HLA-DQA1 genes. **Genes Immun. 2014** Dec;15(8):556-61. PubMed PMID: 25187357.

Membranous GN and PLA2R

PLA2R1 gene variants associated with SLE (PMID: 26645973)

APOL1 variants in PLA2R+ MGN accelerates disease and is a risk factor for collapsing GN (AJKD 2014. PMID: 24731740 – Dr. Mohammad Saeed*)

PLA2R antibodies in Lupus Nephritis (Lupus. March 2019. PMID: 30760090)

- ~ 200 SLE patients surveyed
- 5% had PLA2R Ab
  - SLE MGN 19% were PLA2R +
  - Renal Biopsy >70% PLA2R +
  - Indicated worse prognosis / aggressive disease

PLA2R Ab present before clinical onset of MGN (PMID: 27181779)

PLA2R Antibody + predicts response to RTX (PMID: 25804280, 29571438, 27352623, 26413273)

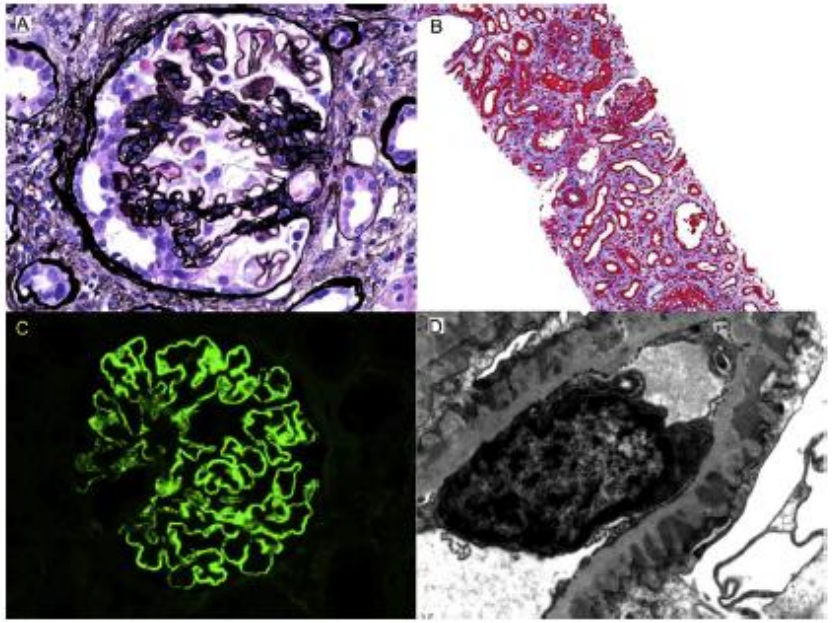


Figure 1. Collapsing glomerulopathy in a patient with PLA_2R-positive membranous glomerulopathy. (A) Jones methenamine silver stain shows glomerular tuft collapse with overlying epithelial hypertrophy and hyperplasia in Bowman space (original magnification, ×400). (B) Tubulointerstitial changes are evident from lower power, including acute tubular injury, interstitial inflammation, and early interstitial fibrosis (Masson trichrome; original magnification, ×100). (C) Glomerulus with granular capillary loop staining for PLA_2R (indirect immunofluorescence; original magnification, ×400). (D) Transmission electron photomicrograph shows diffuse foot-process effacement and numerous subepithelial deposits (unstained; original magnification, ×12,000).

PMID: 24731740

PLA2R antibody Immunofluorescence Blood Test

ImmunoCure

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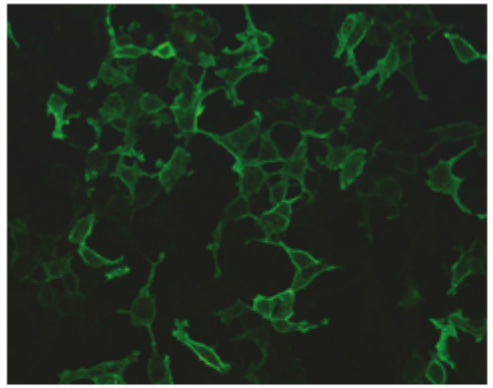
13 Mar 2019

admin Autoimmune Disease / Patient Care, Laboratory

New Blood Test: PLA2R antibody for Membranous Glomerulonephritis

Home Blood Draw / Sample collection: 0334-2121-232



Membranous Glomerulopathy (MG) MG is a morphologic pattern of glomerulonephritis in which immune complexes deposit along the subepithelial aspect of the glomerular basement membrane. The molecular etiology of MG was recently discovered to be Podocyte Phospholipase A2 receptor (PLA2R) and its genetic susceptibility mutation was identified by Dr. Mohammad Saeed and colleagues (Saeed et al. 2014).

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Now Available in Pakistan at ImmunoCure, Karachi

EULAR LN Guidelines 2012

Indications for first renal biopsy in SLE [indispensable in most cases]

Any sign of renal involvement:

- Proteinuria ≥0.5g/24-hr
- Hematuria
- Cellular casts

Treatment Goal [6 to 12 months]:

Complete renal response with UPCR <50mg/mol and normal or near-normal (±10% of normal GFR) renal function.

Partial renal response, defined as ≥50% reduction in proteinuria to sub-nephrotic levels and normal or near-normal renal function.

van der Heijde *et al* Ann Rheum Dis 2016,75:3-15

Practical Issues

Renal damage predicts mortality in SLE (Bruce, 2015). Renal biopsy guides therapy.

Absence of an early Rx response (6 months) is poor long-term prognostic factor (Tamirou; 2016).

Target proteinuria < 0.7-0.8 g/day at 1-year is a favorable long-term predictor (Dall'Era, 2015).

Induction therapy CRR at 6 months: < 30%
Recurrence rate on maintenance Rx: ~ 30%

Induction Therapy for LN

Regimens

i) NIH IV CYC (0.75-1g/m2 monthly x 6) combined with IV methylprednisolone and oral GCs (Austin, 1986; Boumpas, 1992; Gourley, 1996; Illei, 2001);

ii) Euro-Lupus IV CYC (500 mg every two weeks x 6) combined with pulse IV methylprednisolone (3 daily pulses of 750 mg) and oral GCs (prednisolone 0.5 mg/kg/d) (Houssiau, 2002)

iii) MMF (2-3 g/day) (Chan, 2000; Ginzler, 2005; Ong, 2005; Appel, 2009).

All RCTs comparing NIH IV CYC to MMF concluded that the two regimens are equally toxic and efficacious, at least in the short and medium term, even for severe LN patients (Tang, 2008; Rovin, 2013; Appel 2009; Ginzler 2005).

In pure class V RTX or CsA recommended for non responders

RTX also recommended for CYC, MMF failures or in consideration of drug ADRs

Maintenance Therapy for LN

Regimens

Two drugs are mainly used for maintenance therapy in LN:

- AZA (ideally 2-2.5 mg/kg/day)
- MMF (usually 2 g/day).

Patients planning pregnancy should not use MMF which is absolutely contraindicated, at least during the first 3 months.

In the absence of data it seems prudent to maintain AZA or MMF [in combo with Pred 5 to 7.5mg (EULAR 2012)] for at least several years (min 3-years per EULAR 2012) after remission, or at least very good disease control, is achieved.

Gradual drug withdrawal, glucocorticoids first, can then be attempted.

Adjunct treatment for LN

- ACE-inhibitors or ARB for proteinuria (UPCR >50mg/mmol) or hypertension
- Statins for persistent dyslipidemia (target LDL=100 mg/dL)
- Hydroxychloroquine to decrease renal flares and limiting the accrual of renal and cardiovascular damage.
- Aspirin for antiphospholipid antibodies positive patients
- Calcium and vitamin D supplementation
- Immunizations with non-live vaccines

Monitoring and Follow-up of LN

Active lupus nephritis should be regularly monitored

Follow-up scheduled q2-4 weeks for the first 2-4 months after diagnosis or flare
Monitoring for both renal and extra-renal disease activity should be life-long at least every 3-6 months.

Each visit:

- body weight, blood pressure*
- complete blood cell count*
- serum creatinine and eGFR*
- Proteinuria*, urinary sediment (microscopic evaluation),
- serum albumin,
- serum C3 and C4, serum anti-dsDNA antibody levels
- Anti-phospholipid antibodies and lipid profile at baseline and monitored intermittently.

*predictors of long term outcome in lupus nephritis

Repeat renal biopsy in case of worsening or refractoriness to treatment

- failure to decrease proteinuria by ≥50%
- persistent proteinuria > 1-year
- worsening of GFR

Renal Biopsy informs:

- Class Switch
- Activity / Chronicity Index
- Other Pathology

Summary: EULAR Optimal care for Lupus Nephritis

Early detection and complete baseline evaluation, including renal biopsy
Education on the long-term risks and the treatment goals
Follow-up in specialized Lupus Clinics
Identification of non-adherence to therapy
Minimize glucocorticoids
Early treatment switch in case of insufficient response after 6 months
Optimal renal protection (BP: ≤120/80 mm Hg; antiproteinuric therapy)
Prevention of cardiovascular disease (smoking cessation, weight control, BP control, lipids)
Prevention of GC-induced bone loss
Immunization (HPV, influenza, Streptococcus pneumoniae)

Lupus Nephritis

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