Mackenzie Health

Lupus Nephritis

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Objectives

- Review the pathogenesis of lupus nephritis
- Review the different histologic subtypes of lupus nephritis
- Discuss the management of lupus nephritis
- Explore issues related to lupus and pregnancy

Case: J.J.

- 22 F with thrombocytopenia, hypocomplementemia, arthralgias and nephrotic syndrome. ANA and dsDNA positive. 24h urine 7g/d protein

- She was diagnosed with systemic lupus erythematosis (SLE) with renal involvement.

- A renal biopsy was performed for diagnosis and to guide subsequent therapy.

Systemic Lupus Erythematosus (SLE)

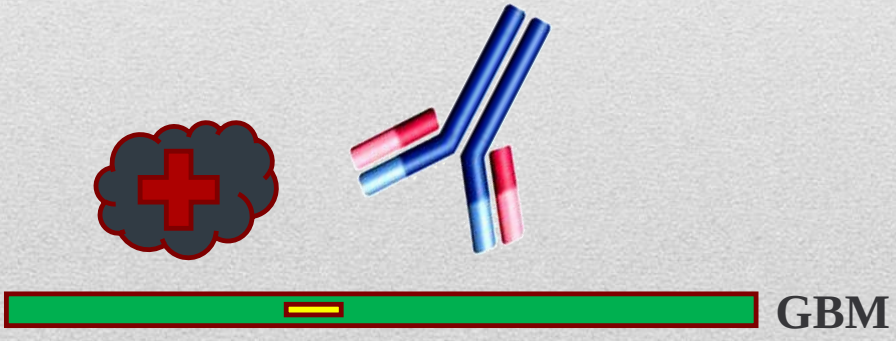
- Multifaceted systemic autoimmune disease characterized by production of pathogenic immunoglobulins
- Kidneys -- major target organ
  - Up to 60% of adult SLE patients
  - 10 year overall survival:
    - 88% renal involvement
    - 94% no renal involvement

Systems Involved	Prevalence in Patients, %
Hematologic	100
MSK	90
Skin	85
Renal	60
CNS	50
GI	21

Robbins: Pathologic Basis of Disease 6th Ed, p220

Pathogenesis of Lupus Nephritis

- Seropositive lupus is characterized by the presence of autoantibodies against self antigens – in particular nuclear antigens
- In lupus nephritis, circulating positively charged nuclear self antigens binds to negatively charged heparan sulfate on GBM
- This deposition of DNA is followed by insitu formation of DNA-anti-DNA complexes within glomeruli



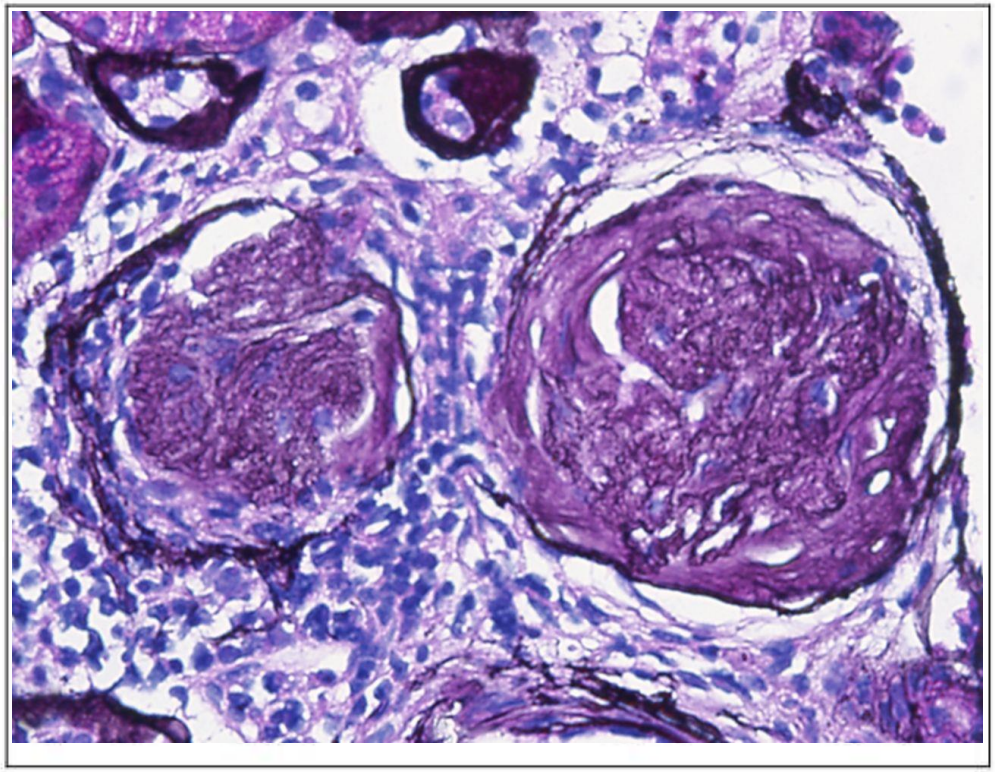
Pathogenesis of Lupus Nephritis

- These immune complex deposition leads to complement activation and inflammatory response ensues
- Depending on the location and the extent of the deposition, it may lead to different histologic subtypes

Table 1: The 2003 International Society of Nephrology and International Pathology Society Classification of lupus nephritis

- Class I: Minimal mesangial lupus glomerulonephritis (LGN)
- Class II: Mesangial proliferative LGN
- Class III: Focal LGN (< 50% glomeruli)
- Class IV: Diffuse LGN (≥ 50% glomeruli)
  - Class IV-S: Predominantly segmental
  - Class IV-G: Predominantly global
- Class V: Membranous LGN

Class VI: Advanced sclerotic LGN (> 90% sclerotic glomeruli)



Therapeutic Goals in Lupus Nephritis

- To achieve renal remission promptly
- Avoid flares/relapses
- Avoid renal dysfunction
- Fulfill the above with minimal toxicity
  - Metabolic (diabetes, accelerated atherosclerosis)
  - Bone (osteoporosis, AVN)
  - Infection
  - Premature ovarian failure

Concept of Induction and Maintenance Treatment

- Induction treatment:
  - Highly efficacious drugs at the expense of more potential toxicity to turn off inflammation and achieve remission quickly, followed by
- Maintenance treatment:
  - Lower doses of toxic regimens, and/or
  - Use of sequential therapies with alternative less toxic agents for use over long term to maintain control of inflammation

Lupus Nephritis Treatment Overview

- Treatment depends on ISN Classification

- **Class I, II (Mesangial); VI (Advanced Sclerotic)**
  - conservative Rx ACE/ARB, BP control
  - immunosuppression dictated by extrarenal manifestations

- **Class III, IV (Focal and Diffuse Proliferative LN)**
  - Immunosuppression with induction and maintenance Rx
  - Details to follow

- **Class V (Membraneous LN)**
  - Non nephrotic range proteinuria, preserved kidney function: conservative ACE/ARB, BP control
  - Pure class V and persistent nephrotic range proteinuria (>3.5g/d): Steroids + 1 of CYC/CNI/MMF/AZA

- **All Classes**
  - Hydroxychloroquine (Plaquenil) unless contraindicated

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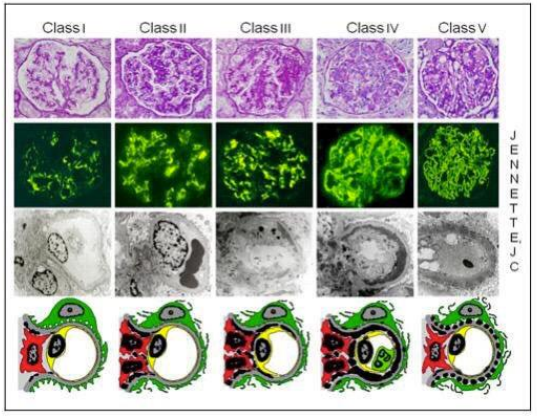
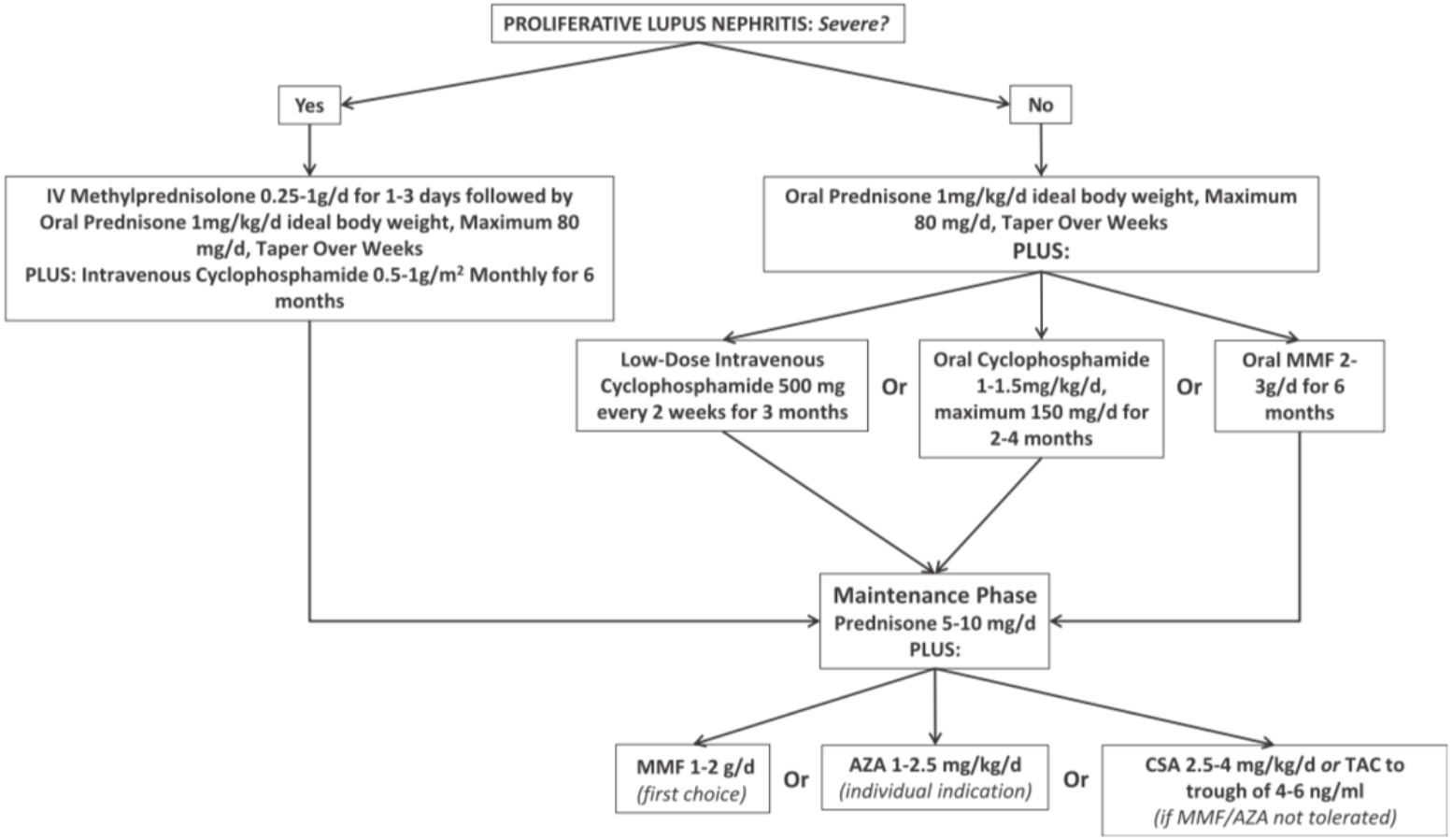


Induction and Maintenance for Proliferative (class III/IV) Lupus Nephritis



Rovin et al. Clin J Am Soc Nephrol 12: 825–835, 2017.

Treatment of Resistent Disease

- Only 60-70% of severe lupus nephritis will have complete or partial remission, often requiring 6 months or more induction therapy
- Renal relapses: 8-10 relapses per 100 treated patient per year for the first 5 years after induction.
- Cumulative toxicity of these induction regiments contribute significantly to morbidity and mortality
- Beware of medication non adrenance

Treatment of Resistant Disease

- For patients treated with CYC, use MMF
- For patients treated with MMF, use CYC
- Rituximab: 60-80% CRR + PRR but relapses are common 15-30%. No benefit in RPGN w crescent. Watch for late onset leucopenia and infusion reactions. Contraindicated if concomitant Hep B viral infection (can reactivate viral replication)
- Other reported but less favorable options:
  - Add tacrolimus to MMF
  - Abatacept, leflunomide
  - IVIG
  - Plasmapheresis
  - Stem cell transplant
- Consider Rebiopsy
  - see how much fibrosis and if change in disease course

Adjunctive Therapy

- BP Control
- Management of Proteinuria with ACEi/ARB
- Chloroquine (Plaquenil)
- Modification of Cardiac risk factors:
  - Dyslipidemia
  - Stop smoking
  - Diabetes glycemic control
- Aspirin for CV protection
- Anticoagulation for those at high risk for DVT/APLS
- Calcium, Vit D, +/- Bisphosphonates
- Prophalaxis: Septra/PPI
- Gonadal rescue: GnRH/Harvesting

Lupus Nephritis (LN) Treatment

Induction, Maintenance and Adjunct Medication

Henry Chen, Renal Pharmacist

September 2019

Case: J.J

- Renal biopsy: Class IVa diffuse proliferative lupus nephritis with membraneous features

Case: J.J

- 2010 Prednisone 1mg/kg (60mg) x 2 months followed by taper, Cellcept (MMF) 1.5g bid x 2 years then tapered off, Ramipril 10mg bid initially then decreased to off due to low BP.
- In complete remission for 2 years
- Feb 2015: Flareup Hand and knee stiffness, proteinuria, dsDNA high and low C4. She was managed with Prednisone 20mg daily and cellcept 750mg bid with improvement. Cellcept and prednisone decreased
- Feb 2016: Increased edema. Prednisone increased back up to 30mg daily and cellcept increased to 1g bid. She responded well and prednisone tapered to 12.5mg daily over time and cellcept remains at 1g bid. Refused Plaquenil

Case 4: J.J.

- August 2017: Increased edema and alopecia. No joint symptoms. Went to ER and Prednisone increased to 40mg daily but she did not comply. She only took 25mg for fear of heartburn symptoms. She continues on Cellcept 1g bid. dsDNA 8, low C3, normal C4. Albumin 28. Cr 50. Platelets 344. Nov 2017 24 h urine protein 1.32g/day. Continues to refuse plaquenil. BP 129/85.

- Feb 2018: Cr 47. 24h urine protein 2.47g/d. Self titrated down cellcept to 250mg bid and prednisone to 5mg daily. Agrees to start Plaquenil but did not fill (and still not started). Given worsening proteinuria, renal biopsy was repeated to assess for chronicity vs active inflammation to guide therapy.

- March 2018 Renal biopsy: Class V lupus membraneous nephritis with little fibrosis. No endocapillary proliferation. Decreased prednisone and stopped cellcept, again asked to start plaquenil Added cyclosporin. Cr 44 24 h urine protein 2.02g/d

- July 2018: Cr 50 24 h urine protein 0.88g/day Still not on plaquenil (patient defers now to until after ophthalmology assessment after August 2018). Prednisone 5mg daily, Cyclosporin 100mg po bid. (did not do the other serology tests I asked for)

Case 4: JJ

Enrolled in our GN clinic and multidisciplinary counselling and support was provided

- Oct 2018 – present:
  - remission 24 h urine 0.49g/day, Cr 57
  - Doing well clinically

Lupus Nephritis

- young women of childbearing age

- Be mindful of:
  - Unplanned pregnancy
  - Contraception counselling
  - Fertility preservation
  - Medication adherence
  - Lost to followup
  - Disease can change course

Lupus nephritis and Pregnancy

- Pregnancy should be planned:
  - Contraception counselling
    - Estrogen containing contraception is contraindicated if patient has vascular disease (ie HTN/CKD). Increases thrombosis & high BP/protienuria risk
    - Suggest to use progesterone only pill/IM injection; or IUD
    - Barrier method should not be sole method used
  - Ideally:
    - Renal function should be stable
    - Proteinuria is less than 500mg/day
    - "stabilization of rapid progression where possible and minimization of proteinuria using pregnancy safe drugs"
    - Drugs and pregnancy:
      - Unsafe: cyclophosphamide, MMF, ACE/ARB, methotrexate
      - Hydroxychloroquine (plaquenil) should be continued
      - MMF → change to azathioprine
      - ECASA 81mg daily to prevent fetal loss
      - If > 5g/d proteinuria: advisable for anticoagulation to prevent thrombosis

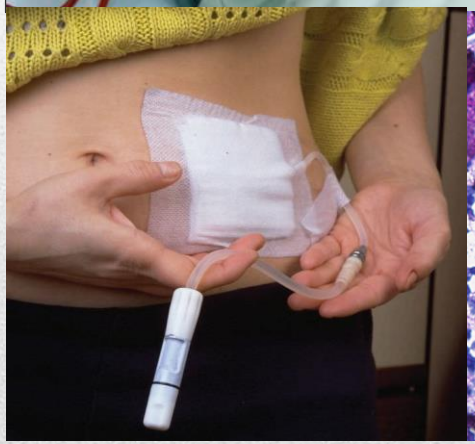
Lupus and Pregnancy Outcomes

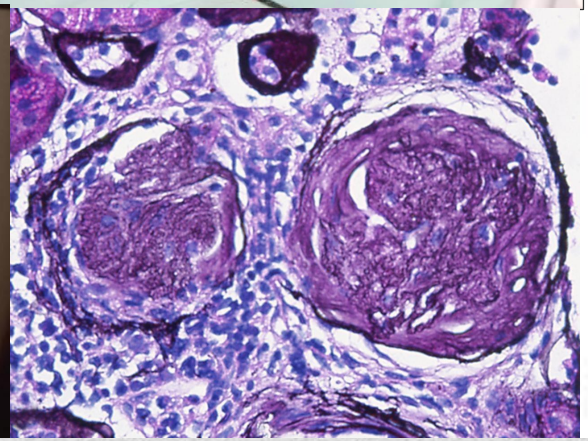
- CKD increases maternal and fetal risk
  - Maternal: worsen renal function, proteinuria, hypertension/preeclampsia
  - Fetal: increase risk of fetal loss, IUGR, preterm delivery

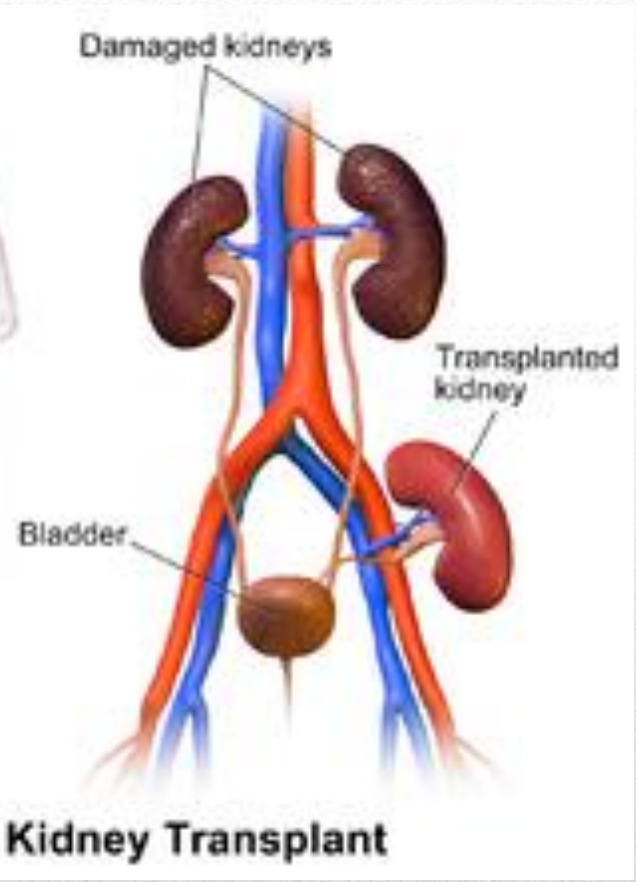
  - Risk of maternal lupus flare during pregnancy:
    - Extrarenal: 26%
    - Renal: 16%

  - Outcomes excellent in patients with inactive disease:
    - Patients with Cr <106 umol/L and urine protein less than ~ 1g/day, 81% had uneventful pregnancies
    - Severe maternal flares were rare (2.5% in second trimeter, 3% in 3rd trimester)

  - High Risk:
    - Severity of preexisting disease
    - Non white ethnicity
    - Presence of anticardiolipin antibody (APLA)
    - Hypertension







Management of ESRD in Lupus Nephritis

Lupus Nephritis and ESRD

- 10-30% of patients with proliferative LN progress to ESRD
- In patients with severe and progressive renal impairment
  - No indication for immunosuppression from renal standpoint
  - However, extrarenal lupus flares may sometimes require reintroduction of immunosuppressive therapy

Renal Replacement Therapy

- Patient survival similar with either HD or PD
  - 21-22% overall mortality over 3 years
  - Similar in overall, CV and infection related morality
  - Survival similar to general population of patients with ESRD except there is an increased risk of death during first 3 months of dialysis primarily due to sepsis

Renal Transplantation

- Treatment of choice in lupus patients with ESRD
  - Transplant 70% reduction in all cause mortality (from CV death and infection), across all ethnic groups
- As successful in the lupus nephritis patients as in general population
  - Similar overall 5 and 10 year graft survival rates between patients with lupus compared with those with other ESRD etiology
- Recurrence of LN in transplanted kidney:
  - 2- 11%, treatable. Incidence of graft loss due to recurrent disease is 2-4% over 5-10 years
  - Any time: 1st week after transplant to 16 years after transplant
- Antiphospholipid antibiodies are screened for prior to transplant: increased risk for thrombotic events

In Summary

- Lupus nephritis affects ~ 60% of patients with lupus in varying degrees
- Treatment depends on ISN class
- 10-30% progress to ESRD
- Renal transplantation has survival advantage over dialysis and patients do as well as patients with other etiologies of ESRD

WE THE NURSE

Pharmacists, Dietians, Social Workers, Docs and Techs

URINE GOOD HANDS

Thank You For Your Attention