LUPUS NEPHRITIS
THE MANY FACES OF A RARE DISEASE
BY DR. LINDOKUHLE MAHLASE
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CASE 1

- 13 YEAR OLD GIRL FROM MOZAMBIQUE PRESENTED TO BASE HOSPITAL WITH SEIZURES AND HYPERTENSION, SHE WAS TREATED AS A MENINGITIS IN VIEW OF THE HIGH CRP AND FITS.

- SHE WAS THEN REFERRED TO CMJAH FOR CT SCAN, WHERE NEPHROLOGY WAS CONSULTED FOR HYPERTENSION WORK UP.

- EXAMINATION SHOWED A PATIENT WITH VASCULITIC LESIONS, PERIPHERAL OEDEMA AND HYPERTENSION

UDIPSITX: 3+ PROTEINS, 3+ BLOOD

MICROSCOPE SHOWED ACTIVE SEDIMENT WITH GRANULAR CAST AND RBC CASTS
CASE 1

- U&E: SHOWED A PATIENT IN ACUTE RENAL FAILURE (HD FOR 6 WEEKS)
- LUPUS WORK UP WAS POSITIVE
- BIOPSY SHOWED A CLASS 3 LUPUS NEPHRITIS (TREATED AS SUCH)
- SHE DEFAULTED FOLLOW UP AND DEMISED AT HOME
CASE 2

• 11 YEAR OLD CAUCASIAN GIRL WHO PRESENTED WITH MIGRAINES AND DEPRESSION WITH ANXIETY DISORDER. CLINICAL EXAMINATION REVEALED SIGNS IN KEEPING WITH LUPUS.

• SHE HAD NORMAL RENAL FUNCTION BUT THE URINE DIPSTIX REVEALED NEPHROTIC RANGE PROTEINURIA

• IMMUNOLOGY WAS POSITIVE FOR LUPUS

• SHE WAS TREATED AS A SEVERE LUPUS DUE TO MRI FINDING OF NEURO INVOLVEMENT

• BIOPSY SHOWED CLASS 1 LUPUS NEPHRITIS
CASE 2

- DEFAULTED FOLLOW UP WITH CMJAH AND SELF REFERRED TO PRIVATE NEPHROLOGIST WHERE SHE IS DOING WELL.
INTRODUCTION

• SLE IS CHRONIC AUTOIMMUNE DISEASE AFFECTING MULTIPLE ORGAN SYSTEMS, INCLUDING SKIN, CNS, HEART, BLOOD, KIDNEYS AND SEROUS MEMBRANES.

• RENAL INVOLVEMENT POSES THE GREATEST RISK OF MORTALITY AND MORBIDITY.

• RENAL MANIFESTATION ARE HIGHLY VARIABLE AND ARE PRESENT IN 30 — 60% OF THE PATIENTS WITH SLE.
PATHOPHYSIOLOGY

• NOT FULLY UNDERSTOOD BUT INVOLVES AUTOIMMUNITY AT THE CENTER OF THE DISEASE.
• THIS INVOLVES COMPLEX PROCESSES LIKE:
  - LOSS OF SELF TOLERANCE
  - DYSREGULATED APOPTOSIS AND INADEQUATE REMOVAL OF APOPTOTIC CELLS
  - FORMATION OF ANTIBODIES THAT TARGET TISSUE-SPECIFIC ANTIGENS
PATHOPHYSIOLOGY

• POOR CLEARANCE: PATIENTS WITH SLE HAVE POOR CLEARANCE MECHANISM FOR CELLULAR DEBRIS, THIS INCLUDE DYSFUNCTIONAL COMPLEMENT SYSTEM.

• THIS RESULTS IN PROLONGED EXPOSURE OF SELF ANTIGEN TO THE AUTOIMMUNITY!
PATHOPHYSIOLOGY

• IMMUNE SYSTEM VS THE KIDNEY:

1. ANTIGEN THAT ARE DIRECTED AGAINST NUCLEOSOMES CROSS REACT WITH THE GLOMERULAR BASEMENT MEMBRANE

2. AUTOANTIBODES HAVE HIGH AFFINITY FOR VASCULAR ORGANS LIKE GLOMERULI

3. CATIONIC AUTOANTIBODES VS ANIONIC BASEMENT MEMBRANE
ETIOLOGY

• GENETIC FACTORS

• ENVIRONMENTAL

• HORMONAL
GENETIC PREDISPOSITION PLAYS AN IMPORTANT ROLE IN THE DEVELOPMENT OF BOTH SLE AND LUPUS NEPHRITIS. MULTIPLE GENES HAVE BEEN IMPLICATED WITHOUT CONCLUSIVE EVIDENCE IN ANIMAL STUDIES.

- MONOZYGOUS TWINS 20-40 PERCENT OF DEVELOPING SLE IF ONE TWIN IS AFFECTED
- DIZYGOUS TWINS 2-5 % RISK
- HLA-DR2 AND DR3 ARE ASSOCIATED WITH SLE
- HLADR4 APPEARS TO BE PROTECTIVE AGAINST SLE
ENVIRONMENTAL FACTORS

• TOXINS:
  - LARGACTIL
  - ISONIAZID
  - QUINIDINE
  - HYDRALAZINE
ENVIROMENTAL FACTORS

• INFECTIONS : EBV (CAUSE VS ASSOCIATION)

**CAUSE:** ANTI RO ANRIBODIES CROSS REACT WITH EBNA-1

MICE IMMUNIZED WITH EBNA-1 ANTIGEN DEVELOP CLINICAL LUPUS SYMPTOMS

**ASSOC:** SLE IS AN IMMUNOSUPPRESSIVE CONDITION, COULD LEAD TO SEROCONVERSION OF THE LATENT EBV INFECTION.
ENVIRONMENTAL FACTORS

- UV LIGHT EXPOSURE
- SMOKING
- ALCOHOL
- SILICA DUST
CLINICAL PRESENTATION

- ASYMPTOMATIC PROTEINURIA OR HAEMATURIA
- DIPSTIX IN ALL PATIENTS AT ALL CLINIC VISITS
- FULL WORK UP AND REFERRAL OF PATIENTS WITH ASYMPTOMATIC PROTEINURIA AND HAEMATURIA
CLINICAL PRESENTATION

• ACTIVE NEPHRITIS
  - OEDEMA
  - HEADACHE, DIZZINESS, SEIZURES

NEPHRITIS SYMPTOMS ARE USUALLY RELATED TO HYPERTENSION AND POOR RENAL
CLINICAL PRESENTATION

- NEPHROTIC SYNDROME

- ALL PATIENTS WITH NEPHROTIC SYNDROME HAVE TO HAVE LUPUS WORK UP
Table 2. Prevalence of clinical manifestations in patients with lupus nephritis

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Approximate Prevalence, %</th>
</tr>
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<tbody>
<tr>
<td>Proteinuria</td>
<td>100</td>
</tr>
<tr>
<td>Nephrotic range proteinuria/nephrotic syndrome</td>
<td>50</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>80</td>
</tr>
<tr>
<td>Macroscopic hematuria</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Urinary red blood cell casts</td>
<td>30</td>
</tr>
<tr>
<td>Other urinary cellular casts</td>
<td>30</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>60</td>
</tr>
<tr>
<td>Rapid decline in kidney function</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
</tr>
<tr>
<td>Tubular abnormalities</td>
<td>70</td>
</tr>
</tbody>
</table>
INVESTIGATION

BASELINE LABORATORY:
URINE DIPSTIX
URINE MICROSCOPE
URINE PCR
FBC, DIFF, SMEAR

ACUTE PHASE REACTANTS (CRP, ESR)
ALBUMIN
CHOLESTEROL
U&E, CMP

IMMUNOLOGY:
ANA, ANT-DS DNA, C3, C4
RENAL BIOPSY

- INDICATIONS:
  - PROTEINURIA > 500MG/DL WITH OR WITHOUT ACTIVE CLINICAL LUPUS DISEASE
  - PERSISTENT DECLINE IN RENAL FUNCTION IN A LUPUS PATIENT
  - PERSISTENT MICROSCOPIC HAEMATURIA
  - ACTIVE SEDIMENT ON MICROSCOPE (WCC & RBC CASTS, GRANULAR)
CLASSIFICATION OF LUPUS NEPHRITIS
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Normal glomeruli (by light microscopy, immunofluorescence, and electron microscopy)</td>
</tr>
<tr>
<td>Class II</td>
<td>Purely mesangial disease</td>
</tr>
<tr>
<td></td>
<td>a. Normocellular mesangium by light microscopy but mesangial deposits by immunofluorescence or electron microscopy</td>
</tr>
<tr>
<td></td>
<td>b. Mesangial hypercellularity with mesangial deposits by immunofluorescence or electron microscopy</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal proliferative glomerulonephritis (&lt;50%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse proliferative glomerulonephritis (≥50%)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous glomerulonephritis</td>
</tr>
<tr>
<td>Class</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Class I</td>
<td>Minimal mesangial lupus nephritis</td>
</tr>
<tr>
<td>Class II</td>
<td>Mesangial proliferative lupus nephritis</td>
</tr>
<tr>
<td>Class III</td>
<td>Focal lupus nephritis(^a)</td>
</tr>
<tr>
<td>Class IV</td>
<td>Diffuse segmental (IV-S) or global (IV-G) lupus nephritis(^b)</td>
</tr>
<tr>
<td>Class V</td>
<td>Membranous lupus nephritis(^c)</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced sclerosing lupus nephritis</td>
</tr>
</tbody>
</table>
CLASS I – MINIMAL MESANGIAL LUPUS NEPHRITIS:

• NORMAL GLOMERULI BY LIGHT MICROSCOPY
• MESANGIAL IMMUNE DEPOSITS BY IMF/EM
Immunofluorescence microscopy shows mesangial positivity for immunoglobulin G.
CLASS II – MESANGIAL PROLIFERATIVE LUPUS NEPHRITIS:

- PURELY MESANGIAL HYPERCELLULARITY OF ANY DEGREE OR MESANGIAL MATRIX EXPANSION BY LIGHT MICROSCOPY WITH MESANGIAL IMMUNE DEPOSITS
Class II: Mild, global mesangial hypercellularity

Immunofluorescence microscopy shows deposits of IgG confined to the mesangium.

Jennette et al. Hepinstall’s Pathology of the kidney, 6th Ed
CLASS III – FOCAL LUPUS NEPHRITIS:

- ACTIVE OR INACTIVE FOCAL, SEGMENTAL, AND/OR GLOBAL ENDOCAPILLARY AND/OR EXTRACAPILLARY GN INVOLVING < 50% OF ALL GLOMERULI, TYPICALLY WITH FOCAL SUBENDOTHELIAL IMMUNE DEPOSITS, WITH OR WITHOUT MESANGIAL ALTERATIONS
Lupus nephritis class III;
Segmental crescent with mild
mesangial hypercellularity
Segmental capillary necrosis with sparing of the remainder of the capillary tuft

Segmental rupture of the GBM with mesangial hypercellularity
CLASS IV – DIFFUSE LUPUS NEPHRITIS:

• ACTIVE OR INACTIVE DIFFUSE, SEGMENTAL OR GLOBAL ENDO- OR EXTRACAPILLARY GLOMERULONEPHRITIS INVOLVING 50% OF ALL GLOMERULI, TYPICALLY WITH DIFFUSE SUBENDOTHELIAL IMMUNE DEPOSITS, WITH OR WITHOUT MESANGIAL ALTERATIONS.
Lupus nephritis class IV: Endocapillary hypercellularity, subendothelial deposits and karyorrhectic debris

Circumferential crescent
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 LUPUS NEPHRITIS MAY OCCUR IN COMBINATION WITH CLASS III OR IV
Lupus nephritis class V. There is regular thickening and rigidity of the glomerular capillary walls accompanied by global mesangial hypercellularity.

Subepithelial deposits with formation of spikes.
CLASS VI - ADVANCED SCLEROSING LUPUS NEPHRITIS:

- 90% OF GLOMERULI GLOBALLY SCLEROSED WITHOUT RESIDUAL ACTIVITY
Lupus nephritis class VI. Extensive glomerular sclerosis with fibrous crescents. The global sclerosis affects more than 90% of glomeruli.

Jennette et al. Hepinstall’s Pathology of the Kidney, 6th Ed
WHY CLASSIFY?

ANSWER: TREATMENT
TREATMENT

• GOAL:
  - PREVENT ESRD
  - ACHIEVE COMPLETE REMISSION OR MINIMAL RELAPSE EPISODES
  - MINIMIZE SIDE EFFECTS
TREATMENT

• INDUCTION

• ADJUVANT THERAPIES

• MAINTNANCE
TREATMENT

- CLASS 1 & 2

TREATMENT IS DICTATED BY THE SEVERITY OF THE EXTRARENAL LUPUS
NO LONG-TERM ASSOCIATION WITH ERSD
MAY REQUIRE MANAGEMENT OF PROTEINURIA AND SHORTER COURSE OF CORTICOSTEROIDS
TREATMENT

- CLASS 3&4
Pulse MP 0.5-1.0 g/m² for 3 days then prednisone (PD) 0.5-1.0 mg/kg/day
tapered after 10-12 weeks to lowest effective dose x 6 months

PLUS

IV Cyclophosphamide (CYC)
Low dose (0.5 g/m²/day)  
Every 2 weeks x 6  
Improved  
Maintenance therapy
MMF 600 mg/m²/day  
or  
AZA 2 mg/kg/day  
+/− daily PD

Oral Mycophenolate Mofetil (MMF)
High dose (1.0 g/m²/day)  
every month x 6  
Not Improved

1200 mg/m²/day x 6 month
Not Improved

CYC (low or high dose) plus

Pulse MP 500 mg/m² plus and daily PD

MMF 1200 mg/m²/day x 6 months
Not Improved

Rituximab

CL + PD

Improved

MP then daily PD

Improved
TREATMENT

• CLASS V:

GENERALLY TREATED WITH PREDNISONE FOR 1-3, THEN TAPERING FOR 1-2 YEARS DEPENDING ON THE RESPONSE

OTHER IMMUNOSUPPRESSANTS ARE ADDED IF THEY ARE ASSOCIATED WITH ANOTHER PROLIFERATIVE CLASS
CLASS VI

• Treat with corticosteroids and other immunosuppressive agents as dictated by the extrarenal symptoms

• Dialysis

• Transplant once the disease is burnt out
TAKE HOME POINTS

• KEEPS HIGH INDEX OF SUSPICION
• URINE DIPSTIX IS IMPORTANT SCREENING TOOL
• CONSULT NEPHROLOGY TIMEOUSLY
• GOD LOVES YOU
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