The spectrum of lupus nephritis: Therapeutic implications
Disclosures

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Consultancy fees: GSK, Novartis, Janssen, Kezar
Renal involvement in SLE: How you define lupus nephritis?

LN dissected by histological classes

LN dissected by histological activity

LN dissected by specific molecular features

Therapy responsive versus non-responsive LN

The „nephritic flare“ of LN

The „proteinuric flare“ of LN

LN = CKD and treating „LN“ is only a minor aspect in treating CKD

Call to action
Renal involvement in SLE: How you define lupus nephritis?

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Renal involvement in SLE: How you define LN?
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HCQ-induced podocytopathy a renal complication of SLE treatment
M. Fabry as rare comorbidity to SLE/LN
Renal involvement in SLE: How you define LN?

- Homozygous nephrin mutation = unrelated podocytopathy
- APOL1 G1/G2 = APOL1 podocytopathy
- C3 glomerulopathy = genetic or sec. acquired?
- C3 TMA = genetic or sec. acquired?
- incident ANCA vasculitis = sec. acquired?
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Call to action
**HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS**

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal Mesangial Lupus Nephritis</strong></td>
<td><strong>Mesangial Proliferative Lupus Nephritis</strong></td>
</tr>
<tr>
<td>- Deposition of immune complexes detectable by immunofluorescence techniques.</td>
<td>- Mesangial hipercellularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal Lupus Nephritis</strong></td>
<td><strong>Diffuse Lupus Nephritis</strong></td>
</tr>
<tr>
<td>- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving &lt;50% of all glomeruli.</td>
<td>- Active or inactive diffuse, segmental or global endo/extracapillary glomerulonephritis involving ≥50% of all glomeruli. Subendothelial diffuse immune deposits, with or without mesangial alterations, are common.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class V</th>
<th>Class VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Membranous Lupus Nephritis</strong></td>
<td><strong>Advanced Sclerosis Lupus Nephritis</strong></td>
</tr>
<tr>
<td>- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.</td>
<td></td>
</tr>
<tr>
<td>- It can occur in combination with class III or IV and it can manifest advanced sclerosis.</td>
<td>- Lupus Nephritis with terminal prognosis.</td>
</tr>
<tr>
<td>- 90% of the glomeruli in global sclerosis.</td>
<td></td>
</tr>
</tbody>
</table>
LN dissected by histological classes

- Confirms immune complex GN, proliferative vs. membranous GN
- Confirms CKD, IFTA indicates amount of lost nephrons (prognosis)

- Outdated by concept
- No unbiased classification validated by outcome, e.g. Oxford classification for IgAN

  Clinically no pendant of clinical RF as in other kidney diseases, e.g. IgAN

  Often confused with stage of LN

  Focal versus diffuse proliferative LN?

  Lupus podocytopathy, e.g. Class II with nephrotic syndrome

  Lesion patterns unrelated to pathophysiology or specific treatment targets
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LN dissected by histological activity

HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS

Class I
**Minimal Mesangial Lupus Nephritis**
- Deposition of immune complexes detectable by immunofluorescence techniques.

Class II
**Mesangial Proliferative Lupus Nephritis**
- Mesangial hipercellularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.

Class III
**Focal Lupus Nephritis**
- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving <50% of all glomeruli.
- Manifestations include active lesions (A), chronic inactive lesions (C) or active and chronic lesions (A/C)

Class IV
**Diffuse Lupus Nephritis**
- Active or inactive diffuse, segmental or global endo/extracapillary glomerulonephritis involving ≥50% of all glomeruli. Subendothelial diffuse immune deposits, with or without mesangial alterations, are common.
- This class is also divided in diffuse segmental (IV-S), when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when ≥50% of the involved glomeruli have global lesions.
- It can also manifest A, C or A/C lesions.

Class V
**Membranous Lupus Nephritis**
- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.
- It can occur in combination with class III or IV and it can manifest advanced sclerosis.

Class VI
**Advanced Sclerosis Lupus Nephritis**
- Lupus Nephritis with terminal prognosis.
- 90% of the glomeruli in global sclerosis.

Weening, et al. JASN 2003
LN dissected by histological activity

**First biopsy:** Activity is the target of immunosuppressive therapy

**Repeat biopsy:** Potential to define immunological remission

Membranous LN?
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LN dissected by specific molecular features

Membranous nephropathy
- All comers

PLA2R
- Negative
- Positive → PLA2R positive membranous nephropathy
  - 20-30%, but much higher in MLN
  - 70% - 80% in all comers

De novo transplant
- IgG4 related disease
  - Stop until there’s antigenic targets to test for

IgG pattern
- Global
- Segmental

Autoimmune history
- Or mesangial deposits
- Or full house staining

EXT1/2 18% MLN

THSD7A 1-5%
- Lacks C3 staining
- All may have an association with neuropsychiatric lupus

NELL1 ~4%
- Older patients ~5%

NCAM1 6-7% MLN

SEMA3B
- Rare antigen overall, but ~10% of pediatric membranous

Children
- Monotypic
  - IgG kappa (masked or unmasked)
  - Other subtypes
    - IgG subclass restricted

SAP
- Positive
- Negative
  - Requires a hematologic workup

Monoclonal membranous

MGMID
- Very rare
- Membranous-like glomerulopathy with masked IgG kappa deposits

*Percentages in blue are of the PLA2R negative cases*
LN dissected by specific molecular features

IFNopathies

Complementopathies

DNAse/RNAse-deficiencies

Autoimmune Lymphoproliferative Syndrome (ALPS), ...
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Call to action
- Response to first-line treatment is generally a good marker of outcome
- How to define response to treatment?
- Proteinuria is a marker for many things
  - Activity
  - Glomerular hyperfiltration
  - Persistent damage
- Sediment is difficult
- What matters is immunological response -> Repeat biopsy
Therapy-responsive versus non-responsive LN

Per-protocol repeat kidney biopsy in incident cases of lupus nephritis

2003 ISN/RPS class III/IV (A or A/C) ≥ V
2003 ISN/RPS class V

Eligibility

Randomisation

Treatment

MMF or ELP IV CYC* IV and oral CC ACEI and/or ARB HCQ

Part I: SOC* Part II - Intervention arm: Repeat kidney biopsy at M12 (N = 103)
Clinical assessment Primary endpoint CRR Major 2 yr endpoint Renal impairment
Histological assessment
Intensity ≥ 3 if AI ≥ 3*

Part I: SOC* Part II - Control arm: No repeat kidney biopsy (N = 103)
Clinical assessment Primary endpoint CRR Major 2 yr endpoint Renal impairment

BL M12 M24 M60

*Add-on therapies will be allowed, including drugs within the frame of 12-month lasting clinical trials.

*Applies for 2003 ISN/RPS class III/IV (≥ V) LN at baseline. For pure membranous (2003 ISN/RPS class V) LN at baseline, individual assessment of the repeat biopsy at the site should steer the decision of treatment.

Part I (BL–M12): Observational Part II (M12–M60): Interventional
Therapy-responsive versus non-responsive LN

The mighty „Refractory LN“

- If its LN, it should respond to immunosuppression

- If it doesn`t:
  - Drug non-adherence
  - Drug dose?
  - Second round of diagnostics (extended labs, podocytopathy repeat biopsy, genetics/APOL1)
  - Causes of hyperfiltration, BMI?, ACEi?, sodium-free diet?

Not sure, if „refractory LN“ really exists
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The „nephritic flare“ of LN

Suspected remission

Initial diagnostic biopsy

Partial response re-biopsy

Protocol re-biopsy

Withdrawal re-biopsy

around 1 year (?)

Suspected disease activity

Initial diagnostic biopsy

Flare re-biopsy

CKD progression re-biopsy

Anders HJ. Ann Transl Med. 2018
The „nephritic flare“ of LN

<table>
<thead>
<tr>
<th>Repeat biopsy</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>15</td>
<td>8</td>
<td>40</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>13</td>
<td>26</td>
<td>25</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>29</td>
<td>34</td>
<td>158</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>11</td>
<td>9</td>
<td>37</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>VI</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mixed II + V</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mixed III + V</td>
<td>0</td>
<td>6</td>
<td>7</td>
<td>21</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Mixed IV + V</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>11</td>
<td>9</td>
<td>1</td>
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Distribution of the ISN/RPS classes at the first and repeat renal biopsies in 686 well-documented published cases of patients with repeat biopsy performed only on clinical indications.

Mixed III + V: 79,0%
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Call to action
Obesity and/or diabetes affect the kidney like a permanent pregnancy!

= persistent hemodynamic overload to the remnant nephrons of a LN kidney
= single nephron hyperfiltration = podocyte stress and loss
= proteinuria, sec. FSGS, CKD progression

Anders HJ, et al. Nat Rev Nephrol 2018

The "proteinuric flare" of LN
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**Criteria for CKD (either of the following present for > 3 months)**

<table>
<thead>
<tr>
<th>Markers of kidney damage (one or more)</th>
<th>Albuminuria (AER $\geq$ 30 mg/24 h; ACR $\geq$ 30 mg/g ($\geq$ 3 mg/mmol))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine sediment abnormalities</td>
</tr>
<tr>
<td></td>
<td>Electrolyte and other abnormalities due to tubular disorders</td>
</tr>
<tr>
<td></td>
<td>Abnormalities detected by histology</td>
</tr>
<tr>
<td></td>
<td>Structural abnormalities detected by imaging</td>
</tr>
<tr>
<td></td>
<td>History of kidney transplantation</td>
</tr>
</tbody>
</table>

| Decreased GFR | GFR $< 60$ ml/min per 1.73 m$^2$ (GFR categories G3a-G5) |

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; GFR, glomerular filtration rate.
LN = CKD

- First priority: CV mortality (BP, lipids, diabetes, smoking)
  Infection mortality (minimize steroids, vaccinate, hygiene)

- Minimize hemodynamic and metabolic overload of the remnant nephrons
  - Keep or reach BMI <25
  - Low-salt diet
  - Avoid dihydropyridine calcium channel blockers
  - With maximal RAS inhibition (effect +)
  - Plus SGLT2 inhibitor (no studies, effect likely +++)
  - Be careful with pregnancies, they can destroy CKD kidneys

- Avoid all nephrotoxins, namely smoking, NSAIDs and cyclosporin A, (PPIs)

- Avoid blood sampling in from potential shunt veins

- Avoid blood transfusions (HLA sensitization)
If your patients have (West-) African ancestors:

Determine APOL1 genotype (prevalence up to 30%)

1 or 2 APOL1 risk alleles represent a dose-dependent weakness of the kidney to HTN and any kidney disease

Patients with LN and 1 or 2 APOL1 risk alleles are rapid CKD progressors unresponsive to IS treatment

Maximize the control of glomerular hyperfiltration to prolong kidney lifespan!
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Call to action
A call to action

IC-GN is only one of many forms of kidney disease in SLE

Unbiased classification for LN is needed

Treatment targets activity!!! Classification by activity?

Pathophysiology is heterogeneous and classes I-VI do not indicate that

There is no “refractory LN“: Adherence?, repeat diagnostics

„Nephritic flare“: Mostly undertreatment, no biopsy needed

„Proteinuric flare“: Mind causes of glomerular hyperfiltration, SGLT2 inhibitors (?)

LN = CKD and must be treated as CKD, SGLT2 inhibitors (?)