CLASSIFICATION OF GLOMERULAR DISEASE

Wesam Ismail, MD
Pathology department
Beni-Suef University
GLOMERULAR DISEASES

Glomerulonephritis (GN), a complex syndrome encompassing a variety of individual disorders, is associated with significant morbidity and mortality (ESRD, hospitalization or death)

Rare Disease???

Initial estimates of presumed GN incidence and period prevalence in the USA

- GN may be more common than is traditionally appreciated and increase substantially with age
- Type of GN, classified as primary or secondary, is associated with both age and sex
- GN is associated with a substantial hospitalization burden, progression to ESRD, and death
- Tens of thousands of people appear to be affected by GN in the USA alone, making GN an important public health concern

GLOMERULAR DISEASES

Diseases of the glomerulus although complex have always held a special place of interest for nephrologists.

- Am I missing something?
- Should I biopsy?
- If yes, When?
- Should I treat first, then biopsy?
Classifications Based on Renal Biopsy Examination

- **Unifying the nomenclature** the ability to provide efficient communication between pathologists and between pathologists and clinicians

- **Prognosis** Implement diagnostic information with prognostic indication

- **Facilitate clinical management** guide therapeutic decisions and can be used in the follow-up of the patient

**NOT ONLY for Pathologists**
The Past
Pure morphological classifications/patterns

The Present
Based on etiology and pathogenesis

The Future
Gene Expression profiles
TABLE I. Classification of Glomerular Lesions (GL)

<table>
<thead>
<tr>
<th>I. Pathognomonic Glomerular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic Microangiopathy</td>
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<tr>
<td>Amyloidosis</td>
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<tr>
<td>Diabetic Glomerulosclerosis</td>
</tr>
<tr>
<td>Tropical ‘Membranous’ GN</td>
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<tr>
<td>Lupus Nephritis (with hematoxyphil bodies)</td>
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<table>
<thead>
<tr>
<th>II. GL in Primary Glomerular Diseases</th>
</tr>
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<tbody>
<tr>
<td>Minimal GL</td>
</tr>
<tr>
<td>Focal GL</td>
</tr>
<tr>
<td>Diffuse GL</td>
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<tr>
<td>segmental and focal proliferative GN</td>
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<tr>
<td>focal glomerular sclerosis</td>
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<tr>
<td>extramembranous GN</td>
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<tr>
<td>proliferative GN</td>
</tr>
</tbody>
</table>

from these few exceptions a pathologist should never diagnose a specific disorder from the observation of a particular lesion.

Systemic Diseases

<table>
<thead>
<tr>
<th>Schönlein-Henoch</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>periarteritis nodosa and necrotizing arteritis</td>
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</tbody>
</table>

Mixed Essential IgG-IgM Cryo-globulinaemia

Anti-GBM Nephritis and Goodpasture’s Syndrome

<table>
<thead>
<tr>
<th>IV. GL in Hereditary Nephropathies</th>
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</thead>
<tbody>
<tr>
<td>Alport’s Syndrome</td>
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<tr>
<td>Nail-patella Syndrome</td>
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<tr>
<td>Infantile Diffuse Mesangial Sclerosis</td>
</tr>
<tr>
<td>Familial NS</td>
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<tr>
<td>Partial Lipodystrophy</td>
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<tr>
<td>Amyloidosis of FMF</td>
</tr>
<tr>
<td>Storage Diseases (Fabry, etc)</td>
</tr>
</tbody>
</table>

V. Unclassified
IN > 50 YEARS

Classifying renal disease into etiology, pathogenesis, clinicopathological correlations

<table>
<thead>
<tr>
<th>Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960–present</td>
<td>Immune complex diseases, anti-GBM, lupus nephritis, post-infectious GN, IgAN</td>
</tr>
<tr>
<td>1975–present</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>1980–present</td>
<td>ANCA disease</td>
</tr>
<tr>
<td>1980–present</td>
<td>Membranous glomerulopathy pathogenesis</td>
</tr>
<tr>
<td>1990–2009</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>1990–present</td>
<td>Podocyte pathobiology</td>
</tr>
<tr>
<td>1990–present</td>
<td>Classification of diseases of the transplanted kidney</td>
</tr>
<tr>
<td>1990-present</td>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>

LUPUS GLOMERULONEPHRITIS

McCluskey 1975........ ISN/RPS Classification in 2003
Chronicity & Activity indices

ISN/RPS Classification of Lupus Glomerulonephritis
Columbia 2003

Weening, JJ, D'Agati VD, Schwartz MM et al.
The classification of glomerulonephritis in systemic lupus erythematosus revisited.
The major objective is to standardize definitions, emphasize clinically relevant lesions, and encourage uniform and reproducible reporting between centers.

**MEMBRANOUS GLOMERULOPATHY**

**Highlights**

- **Neonatal, alloimmune**: NEP
- **Early childhood MN**: BSA
- **Primary «Idiopathic» MN**
  - 70-80%: PLA₂R (+ other specificities: AR, SOD₂, enolase..?)
  - 20-30%: THSD7A, food/environmental Ag (BSA)
- **« Secondary » MN**

Prognostic significance
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

First description by Elema JD et al, 1975

Better understanding of etiology

Focal segmental glomerulosclerosis is now viewed as a group of clinical–pathologic syndromes

Identification of the podocyte as the major cellular target

Advances in the field of podocyte biology
Minimal Change Disease & FSGS
“Podocytopathies”
THE SPECTRUM OF PODOCYTOPATHIES

- No change in podocyte number
  - Minimal changes on histology
    - MCN

- Podocyte detachment/death
  - Segmental sclerosis
    - FSGS

- Podocyte proliferation
  - Low:
    - Mesangial sclerosis
      - DMS
  - High:
    - Capillary collapse
      - CG

Barisoni et al. CJASN, 2007
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Morphological Classification in 2004


Highlights

Perihilar  Tip lesion  Collapsing  Cellular

Prognostic value

Courtesy of Charles Jennette
Mesangial hypercellularity
- M0: <4 mesangial/cells/area in > 50% of the glomeruli
- M1: ≥4 mesangial cells/area in >50% of the glomeruli

Segmental glomerulosclerosis or adhesion
- S0: absent
- S1 present

Endocapillary hypercellularity
- E0: absent
- E1: present

Tubular atrophy/interstitial fibrosis
- T0: 0-25%
- T1: 26-50%
- T2: >50%
IgA NEPHROPATHY

RECOMMENDED PATHOLOGY REPORT

1- Detailed description of findings
2- Minimum prognostic data:
   Glomerular “pattern”:
   Mesangial hypercellularity in > or <50% of glomeruli (M 0/1)
   Endocapillary hypercellularity – present/absent (E 0/1)
   Segmental sclerosis/adhesions – present/absent (S 0/1)
   Tubular atrophy/interstitial fibrosis – 0-25%, 26-50%, >50% (T 0/1/2)
   In addition: Total number of glomeruli
      Endocapillary proliferation - %
      Cellular/fibrocellular crescents - %
      Necrosis - %
      Global glomerulosclerosis - %

Example: IgA nephropathy showing diffuse mesangial proliferation with focal segmental sclerosis and moderate chronic tubulointerstitial damage (M1,E0,S1,T1)

No Classes eg: I, III, V
In 1959, Gellman et al. first reported findings. Gambara et al. and Fioretto et al. made basic distinctions between typical and atypical DN. Glomerular diseases superimposed on DN. Podocytopathies. Morphological Classification in 2010 (Research committee of RPS).

TERVAERT’S PATHOLOGIC CLASSIFICATION OF DIABETIC NEPHROPATHY

I  Mild or nonspecific LM changes and EM-proven GBM thickening
IIa Mild mesangial expansion
IIb Severe mesangial expansion
III Nodular sclerosis (Kimmelstiel–Wilson lesion)
IV Advanced diabetic glomerulosclerosis

Membranoproliferative GN

Glomerular-injury pattern that is common to a heterogeneous group of diseases

New approach (pathophysiology)

immune-complex–mediated MPGN (increased levels of circulating immune complexes). . . . HCV, autoimmune dis, MG

complement mediated MPGN (disorders of the alternative pathway of complement). . . . C3 glomerulonephritis & DDD

n engl j med 366;12, 2012
MODERN APPROACH

Historical Classification

MPGN Type I

MesgP+GBM duplication

MPGN Type II/DDD

Diverse Histology

MPGN Type III

MPGN with MGN features

Modern Categories

MPGN Type I

C3 GN

C3 Glomerulopathy

DDD

C3 GN

C3 GN

MPGN Type III

C3 GLOMERULOPATHY

Morphological appearance

Disease category

GN with dominant C3

C3 Glomerulopathy

Post-Infectious GN

DDD

C3GN

Specific Genetic forms and/or autoantibodies

NOT Otherwise Specified

Specific Genetic forms e.g. CFHR5

NOT Otherwise Specified

2012 CHCC Vasculitis Nomenclature

Large Vessel Vasculitis
- Giant Cell Arteritis
- Takayasu Arteritis

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Small Vessel Vasculitis
- ANCA-Associated Vasculitis
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)
- Immune Complex Vasculitis
  - Anti-GBM Disease
  - IgA Vasculitis (Henoch-Schönlein)
  - Cryoglobulinemic Vasculitis
  - Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Variable Vessel Vasculitis (Cogan’s, Behcet’s, etc.)
Single Organ Vasculitis (cutaneous SVV, primary CNS vasculitis, etc.)
Vasculitis Associated with Systemic Diseases (e.g. Rheumatoid, Lupus, Sarcoid, etc.)
Vasculitis Associated with Probable Etiologies (e.g. HBV, HCV, drug, cancer, etc.)

ANCA GLOMERULONEPHRITIS

Highlights

Table 3. Renal outcome according to class

<table>
<thead>
<tr>
<th>Class</th>
<th>eGFR Entry</th>
<th>eGFR 12 Months</th>
<th>eGFR 12 Months*</th>
<th>eGFR 60 Months</th>
<th>eGFR 60 Months*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
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<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
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<tr>
<td>Focal</td>
<td>56.4 ± 36.8</td>
<td>63.3 ± 23.7</td>
<td>1.2 ± 10.6</td>
<td>65.6 ± 20.3</td>
<td>1.4 ± 11.8</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>15</td>
<td>15</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Crescentic</td>
<td>11.2 ± 10.9</td>
<td>32.8 ± 20.8</td>
<td>4.3 ± 17.8</td>
<td>39.5 ± 22.5</td>
<td>5.2 ± 21.1</td>
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<tr>
<td></td>
<td>55</td>
<td>40</td>
<td>40</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Mixed</td>
<td>15.4 ± 16.2</td>
<td>24.5 ± 21.4</td>
<td>-7.3 ± 15.2</td>
<td>29.9 ± 16.7</td>
<td>-9.5 ± 11.6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>10.8 ± 9.5</td>
<td>16.6 ± 15.9</td>
<td>-12.8 ± 12.4</td>
<td>20.4 ± 15.1</td>
<td>-14.6 ± 12.1</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*aCorrected for entry eGFR.
GLomerulonephritis

Classification of GN on the basis of etiology/pathogenesis

is primarily on the basis of the findings by immunofluorescence microscopy (IF) or immunohistochemistry (IHC) integrated with light microscopy (LM) and electron microscopy (EM)

The manuscript does not extend to other forms of glomerular diseases, such as membranous nephropathy, podocytopathies, and thrombotic microangiopathy
GLOMERULONEPHRITIS

On the basis of etiology/pathogenesis

*Five pathogenic types, each with specific disease entities:*

1. Immune-complex GN
2. Pauci-immune GN
3. Antiglomerular basement membrane GN
4. Monoclonal IgGN
5. C3 glomerulopathy
Table 2. Basic format of kidney biopsy report

(1) Specimen type: needle biopsy, wedge, etc.

(2) Diagnosis
   
   Primary diagnosis
   
   Disease process/pathogenic type (e.g., IgA nephropathy, lupus GN, ANCA GN, C3 GN)
   Pattern of glomerular injury (e.g., mesangial proliferative, membranoproliferative, necrotizing/crescentic, and focal and segmental sclerosing)
   Histologic scores or grade (e.g., Oxford/MEST for IgA nephropathy and ISN/RPS for lupus nephritis)
   Additional features (e.g., degree of global glomerulosclerosis, IFTA, vascular sclerosis, clinical modifiers, such as cryoglobulin/clinical HCV, bacterial endocarditis/clinical, staphylococcal cellulitis/clinical)
   Secondary diagnoses (list; e.g., acute interstitial nephritis and diabetic glomerulosclerosis); these are not felt to be part of the primary disease

(3) Comment/narrative
   
   Can be used for summarizing/clarifying morphologic basis of primary and/or secondary diagnoses or clinicopathologic correlations, providing prognostic information, discussing differential diagnosis, and providing appropriate references

(4) Summary of clinical data
(5) Gross description
(6) LM description
(7) IF/IHC
(8) EM
(9) Addendum for special studies

MEST: mesangial matrix, endocapillary proliferation (EC), subendothelial, crescent formation, interstitial fibrosis
Hepatitis C–associated immune–complex GN

**Primary diagnosis:** immune-complex GN

**Pattern of injury:** membranoproliferative GN

**Additional features:** with features of cryoglobulinemic GN (hepatitis C/clinical), focal global glomerulosclerosis (20%), moderate tubular atrophy and interstitial fibrosis (30%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis
Lupus nephritis

Primary diagnosis: (1) lupus nephritis and (2) thrombotic microangiopathy

Pattern of injury: diffuse proliferative and sclerosing GN with focal (10%) cellular crescents

Score/grade: ISN/RPS class IV-G (A/C)

Additional features: thrombotic microangiopathy associated with antiphospholipid antibodies/clinical, focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), moderate arteriosclerosis, and moderate hyaline arteriolar sclerosis
Infection-related GN

Primary diagnosis: IgA–dominant infection–related GN

Pattern of injury: diffuse exudative GN

Additional features: associated with S. aureus cellulitis infection/clinical, focal global glomerulosclerosis (30%), moderate tubular atrophy and interstitial fibrosis (30%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

Secondary diagnoses: diabetic nephropathy, moderate interstitial nephritis
Lupus nephritis

Primary diagnosis: (1) lupus nephritis and (2) thrombotic microangiopathy

Infection-related GN

Primary diagnosis: IgA–dominant infection–related GN

Secondary diagnoses: diabetic nephropathy, moderate interstitial nephritis

Commentary/notes
PROBLEMS

- Lack of inter-observer and intra-observer reproducibility
- Lack of enough validation studies
- Usually non objective selection of study groups/testable lesions
- Lumps different lesions together
- Subjective qualification and scoring systems
- Lack of precise definitions
- **When You Can’t Classify**
The challenge of functional genomics in pathology is to turn expression and sequence data into information that can be used to help diagnose disease.

Laser-assisted microdissection allowed the evaluation of mRNA expression on material fixed and processed for routine diagnostic evaluation.

**Integrated Diagnosis**
Gene expression profiles performed in parallel to routine work-up of biopsies giving independent information in the diagnostic process using microarrays.

**Add on technique**
applied to defined differential diagnostic problems after completion of the routine diagnostic work-up, e.g. FSGS vs Minimal Change
PROSPECTIVE

In the last decade

Tremendous advances have been made in our understanding of the pathology and pathophysiology of kidney disease as a result of intense collaboration between nephrologists and nephropathologists.

Over the next years

The generation of comprehensive expression profiles for the most frequent renal diseases can be expected and may allow the definition of clinical subgroups with different disease courses.
Thank You