Overview of glomerular diseases

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*Endothelial cells are fenestrated

*Glomerular basement membrane (GBM) is mainly composed of:
- Collagen IV
- Laminin
- Proteoglycans...polyanionic
- Fibronectin
...etc

= filtration slit ...bridged by thin slit diaphragm...mainly composed of: nephrin from adjacent foot processes

Nephrin & its partner proteins (e.g., podocin) are very important in the selective permeability of the filtration barrier

GBM: lamina densa inside & lamina rara on each side (interna & externa)
Glomerular diseases

= Glomerulopathies

- Most 1ry & many 2ry glomerular diseases are immune-mediated
  - circulating Ag-Ab complexes that deposit in the glomerulus
  - in situ deposition of antibodies
    - Fixed antigens
    - Planted antigens
  - anti-GBM antibody-mediated GN

These are called in general: glomerulonephritis (GN)...because they are immune-mediated glomerular injury

Kidney is the only or main organ involved

Kidney is involved additionally to other organs

Glomerulopathies Secondary to Systemic Diseases

- Lupus nephritis (systemic lupus erythematosus)
- Diabetic nephropathy
- Amyloidosis
- GN secondary to multiple myeloma
- Goodpasture syndrome
- Microscopic polyangiitis
- Wegener granulomatosis
- Henoch-Schönlein purpura
- Bacterial endocarditis–related GN
- Thrombotic microangiopathy

Hereditary Disorders

- Alport syndrome
- Fabry disease
- Podocyte slit-diaphragm protein mutations

GN, glomerulonephritis; IgA, immunoglobulin A.

Elsevier. Kumar et al. Robbins basic pathology 9th...modified
From the previous table...The following entities are the main immune-mediated glomerulopathies that you will hear about:

- Anti-GBM antibody-mediated glomerulonephritis and Goodpasture syndrome
- Postinfectious (or) Poststreptococcal glomerulonephritis
- Membranous nephropathy
- Mambranoproliferative glomerulonephritis I (MPGN I) & dense deposit disease
- IgA nephropathy and Henoch-Schonlein purpura
- Lupus nephritis
Regarding immune-mediated glomerulopathies (Glomerulonephritides)

- circulating Ag-Ab complexes that deposit in the glomerulus

or

- in situ deposition of antibodies

or

- anti-GBM antibody-mediated GN

The antigen can be:
- exogenous...e.g., streptococcal or antigens of other microbes, e.g., HBV, Plasmodium falciparum, Treponema pallidum
or
- endogenous...e.g., lupus nephritis
or
- unknown...e.g., Membranoproliferative GN (MPGN)

Remember: membranous nephropathy

Exogenous...e.g., endostroptosin in poststreptococcal glomerulonephritis

Endogenous...e.g., lupus nephritis
Regarding immune-mediated glomerulopathies (Glomerulonephritides):

We have an immune reaction with the following events occur at different quantities, patterns and combinations according to the disease we are talking about:

- Leukocyte infiltration in the glomerulus
- Antibody deposition in the glomerulus
- Complement deposition in the glomerulus
- Mesangial proliferation
- Endothelial cell proliferation
- Epithelial (visceral or parietal) cell proliferation
- Fibrin deposition...remember that there is also a role of platelets and thrombin
Now we said that in immune-mediated glomerulopathies we may have deposition of immunoglobulins or complement... Where can we detect this deposition (mainly using immunofluorescence)?

- 3 possible sites of deposition:
  - mesangium
  - between endothelium & BM (subendothelial)
  - between podocytes & BM (subepithelial)

 Deposits may be located at more than one site in a given case.
You will hear about some names that are **“Renal clinical syndromes”**

...which means that each of these syndromes is a group of symptoms/signs/lab results that points to a renal disease

...each of these syndromes can be caused by more than one disease

...The main 3 renal clinical syndromes associated with glomerular diseases are “Nephritic syndrome”, “Nephrotic syndrome” & “Rapidly progressive glomerulonephritis”

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**• Nephrotic syndrome:**

-4 main manifestations:
  ...heavy proteinuria...>3.5gm/day (=nephrotic range proteinuria)
  ...hypoalbuminemia and consequent severe edema
  ...hyperlipidemia
  ...lipiduria

-4 main diseases:
- Minimal change disease (MCD)
- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy
- Membranoproliferative glomerulonephritis I (MPGN I)
  (+ Dense deposit disease (DDD))

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**• Nephritic syndrome:**

- Main manifestations:
  ...hematuria (usually gross) with RBC casts
  ...oliguria & azotemia of acute onset
  ...hypertension
  ...the proteinuria if present is non-nephrotic range
  ...edema

- Main diseases:
  ...Poststreptococcal glomerulonephritis (PSGN)
  ...IgA nephropathy
  ...Alport
Other renal clinical syndromes

- Asymptomatic hematuria, non-nephrotic proteinuria, or both:
  - mild glomerular abnormalities

- Rapidly progressive glomerulonephritis (RPGN):
  - severe glomerular injury
  - loss of renal function in a few days or weeks
  - manifested by:
    - microscopic hematuria
    - dysmorphic RBCs & RBC casts
    - mild to moderate proteinuria
  - characterized microscopically by crescentic change in the glomeruli
    - remember that the microscopic counterpart of RPGN is: Crescentic glomerulonephritis
    - What is this?
Other renal clinical syndromes, cont’d

- **Acute kidney injury (AKI)**...previously called acute renal failure (ARF):
  ...dominated by oliguria or anuria
  ...recent onset of azotemia/uremia
  ...can result from any acute condition affecting any part of the nephron (not always glomerular disease is the cause...remember that the most common cause of AKI is tubular)

- **Chronic kidney disease**:
  ...prolonged symptoms and signs of uremia
  ...the result of progressive scarring in the kidney from any cause
  ...may culminate in end-stage kidney disease
  ...can result from any chronic condition affecting any part of the nephron

Remember:
- Increased urea and creatinine without symptoms = azotemia
  ...with symptoms = uremia
## Complications of uremia

<table>
<thead>
<tr>
<th>Fluid and Electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
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<tr>
<td>Calcium Phosphate and Bone</td>
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<tr>
<td>Hyperphosphatemia</td>
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<tr>
<td>Hypocalcemia</td>
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<tr>
<td>Secondary hyperparathyroidism</td>
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<tr>
<td>Renal osteodystrophy</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Anemia</td>
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<td>Bleeding diathesis</td>
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<td>Cardiopulmonary</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Pulmonary edema</td>
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<tr>
<td>Uremic pericarditis</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Bleeding</td>
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<tr>
<td>Esophagitis, gastritis, colitis</td>
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<tr>
<td>Neuromuscular</td>
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<tr>
<td>Myopathy</td>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Encephalopathy</td>
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<tr>
<td>Dermatologic</td>
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<tr>
<td>Sallow color</td>
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<tr>
<td>Pruritus</td>
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<tr>
<td>Dermatitis</td>
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</tbody>
</table>
Other renal clinical syndromes, cont’d

These are not glomerular...

- *Urinary tract infection* is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic, and it may affect the kidney (*pyelonephritis*) or the bladder (*cystitis*) only.
- *Nephrolithiasis* (renal stones) is manifested by renal colic, hematuria (without red cell casts), and recurrent stone formation.
Immunofluorescence (IF)

• When the nephrologist or pediatrician takes a kidney biopsy, he takes 3 samples (one fresh for IF, one in formalin for light microscopy, and one in glutaraldehyde for electron microscopy)

• We take frozen sections of the kidney sample that was fresh and put them on slides

• We use antibodies labelled by fluorochrome

• The targets of these antibodies are IgG, IgA, IgM, C3, C4...etc.
...for example: in one slide we direct anti-IgG to the tissue, in another one we direct anti-C3...and so on
...if a disease for example is characterized by IgG deposition, the slide that we directed labelled anti-IgG to it will show positivity in the fluorescence microscope
IF, cont’d

• Now the positivity is as the following:

- Capillary (BM) VS Mesangial

- Granular VS Linear
Granular VS Linear IF patterns

Typical for: Anti-GBM GN

*The deposition in these 2 examples is mainly a capillary deposition...not mesangial
A brief note on Anti-glomerular basement membrane antibody–mediated glomerulonephritis

...α3 chain of the type IV collagen of the GBM is the target here

...Sometimes the anti-GBM antibodies cross-react with basement membranes of lung alveoli, resulting in simultaneous lung and kidney lesions...this is called???

...less than 1% of GN cases but:
Many instances are characterized by very severe glomerular damage with necrosis and crescents and the development of the clinical syndrome of rapidly progressive GN
A note to remember

• Any renal disease (glomerular or nonglomerular) that destroys sufficient nephrons to reduce the GFR to 30-50% of normal...adaptive responses in the remaining renal tissue occur and this may be complicated by FSGS followed by global sclerosis entering a vicious cycle of nephron loss and maladaptation causing progressive glomerulosclerosis
Thank You