Medical renal biopsy for the small biopsy exam

Sean Chang
SA Pathology, Royal Adelaide Hospital
Exam-oriented approach

- Typical exam cases

- Focus on the most obvious & diagnostic features
  - Not about rare interesting cases
  - Not about latest advances

- Flexible use of clinical, LM, IF and EM data

- Categorisation of entities
  - Must know clinical well!
Medical renal biopsy

- Clinical
- Light microscopy (LM)
  - H&E
  - ABPAS
  - Methenamine silver-PAS
  - Trichrome: Mallory’s etc
- Compartments
  - Glomeruli
  - Tubules
  - Interstitium
  - Blood vessels
- Immunofluorescence (IF)
  - IgG, IgA, IgM
  - C3, C1q
  - Ig light chains: kappa, lambda
  - Albumin, fibrinogen
- Electron microscopy (EM)
Clinical presentation of GN

- Nephrotic syndrome
- Nephritic syndrome
- Asymptomatic proteinuria +/- or haematuria
- Rapidly progressing GN (RPGN)
  - Rapid severe nephritic + acute kidney injury (AKI)
- Chronic kidney disease (CKD)
- Primary: “idiopathic”
- Secondary: associated with other diseases
Nephrotic syndrome

- Proteinuria > 3 g/day
- Serum albumin < 30 g/L
- Oedema
- Hypercholesterolaemia
- Complications: effusion, thrombosis etc

**Underlying GN (mostly non-proliferative)**
- Minimal change
- Membranous: primary, secondary
- Focal segmental glomerulosclerosis (FSGS) – primary, secondary
- Diabetic nephropathy
- Amyloid
Nephritic syndrome

- Haematuria (tea or coca-cola colour): dysmorphic rbc
- Proteinuria
- Oedema
- Hypertension
- Renal impairment

**Underlying GN (mostly proliferative)**
- Post-infectious GN
- Mesangiocapillary GN
- Focal/diffuse proliferative GN: SLE
- Early crescentic GN
- IgA nephropathy / Henoch-Schönlein purpura
Asymptomatic proteinuria +/or haematuria

- IgA nephropathy
- Thin membrane disease (no proteinuria)
- Alport's syndrome
- Early/mild stages of other GNs: eg. SLE

RPGN

- Crescentic GN
- Acute deterioration of other GN (often those causing nephritic syndrome)

In older patients (> 60 years), think monoclonal Ig-mediated nephropathies
Tubular pole (proximal tubule)

Vascular pole

Distal tubule

Peripheral capillary wall (PCW)

Endothelium

Mesangium

Bowman's space

Parietal epithelium

Visceral Epithelium (podocyte)

Capillary lumen
ABPAS

- BM
  - GBM, TBM
  - Bowman’s capsule
- Mesangium
- Insudation (plasma protein)
- Cryoglobulin
- Immune deposits
- PT brush borders
- Hyaline cast (Tamm-Horsfall protein)
- Vascular hyalinosi
Methenamine silver

• BM
  – GBM, TBM
  – Bowman’s capsule
• Mesangial sclerosis
• Vascular elastic laminae

Negative
• Insudation
• Amyloid, light chains
Trichrome

- Interstitial fibrosis

Red
- Immune deposit
- Plasma protein
- Fibrin thrombi, cryoglobulin
- Fibrinoid necrosis
- Light chain cast
- Vascular hyalinosis

Jhaveri et al. Kidney Int 84: 34, 2013
LM definitions

- **Diffuse**: > 50% glomeruli involved
- **Focal**: < 50% glomeruli involved
- **Global**: entire glomerulus involved
- **Segmental**: only part of glomerulus involved
Assessing the glomerulus

• Cellularity: if increased, which cells?
• Mesangium: expansion, nodules
• Capillary wall: thickening, spikes, double contours
• Capillary lumina: obliterated?
  – Collapse, sclerosis, cells (endothelium, inflammatory), “thrombi”
LM classification of glomerular changes

A. Normal

B. Non-proliferative: normocellular
   • Normal light microscopy
   • Abnormal capillaries: lumina, wall
   • Abnormal mesangial matrix

C. Proliferative: hypercellular
   • Mesangial → Mesangioproliferative
   • Endothelial → Endocapillary
   • Inflammatory cells (monocytes, neutrophils) → Exudative
   • Parietal epithelial → Crescentic
   • (Podocyte / visceral epithelial)
Proliferative changes: definitions

- **Mesangioproliferative**: > 3 nuclei per mesangial area
  - away from the vascular pole
  - capillary lumina patent

- **Endocapillary**: endothelial proliferation or swelling
  - capillary lumina obliterated

- **Exudative**: inflammatory cells (monocytes, neutrophils)

- **Crescentic**: parietal epithelial cells (> 2 layers)
Mesangial

Fogo
Endocapillary
Exudative

Fogo

renalpathology.wordpress.com
Crescentic
Normal glomeruli by LM

**Nephrotic**
- Minimal change
- Early membranous
- Early amyloidosis
- FSGS (undersampling)

**Haematuria**
- Thin GBM disease
- Alport’s
- Early IgAN

Adapted from Zhou
Abnormal capillaries or matrix

Thick capillary wall
- Normal mesangium
  - Membranous
- Mesangial expansion, deposits
  - Diabetic nephropathy
  - Amyloid, MIDD
  - Fibrillar
  - Immunotactoid

Capillary luminal occlusion
- TMA
- Cryoglobulinaemia
- Amyloid

Sclerosis, capillary collapse
- FSGS
  - including collapsing variant
- Ischaemic obsolescence
- End stage kidney

Adapted from Zhou
Proliferative

Mesangial
• IgAN
• Lupus class II
• Resolving PIGN

Endocapillary
• PIGN
• MCGN
• Lupus class III-IV
• IgAN

Crescentic
• Immune deposits
• Anti-GBM
• Pauci-immune

Adapted from Zhou
Capillary lumen
Endothelium
Podocyte
Mesangium
rbc
Capillary lumen
Foot processes
Important EM features (for this exam)

• Immune complexes
  – Mesangial / paramesangial
  – Subepithelial, intramembranous
  – Subendothelial

• Deposits: fibrillary, granular
• Podocyte foot process effacement
• GBM thickening / thinning
Proliferative glomerular diseases
Case 9

Male 54 years old.
Long-standing microscopic haematuria.
Recent onset hypertension and worsening of proteinuria.
Clinical consideration

• Asymptomatic haematuria, now progressed?
• Asymptomatic haematuria, now second disease (double diagnosis)?

Asymptomatic proteinuria +/- or haematuria
• IgA nephropathy
• Thin membrane disease
• Alports syndrome
• Early/mild stages of other GNs: eg. SLE
IgA
Diagnosis

IgA glomerulonephritis / nephropathy
IgA nephropathy

- Commonest immune-mediated GN

- Many clinical presentations
  - Asymptomatic haematuria/proteinuria
  - Classic: synpharyngitic macrohaematuria
  - CRF
  - Less common: nephritic, nephrotic, AKI

- **Henoch Schonlein purpura**: “systemic IgAN”
  - Children-adolescents
  - Purpuric rash (IgA+ LCV), arthritis, abdominal pain

- Defined by IF
IgA nephropathy - LM

Classic: Mesangiproliferative GN

- **Mesangial proliferation**: > 3 nuclei per mesangial area
- **Mesangial expansion**: increased mesangial matrix
- Assess away from the vascular pole
- Normal capillary walls

- Other changes: endocapillary proliferation, segmental sclerosis, crescents, interstitial fibrosis / tubular atrophy
IgA nephropathy - LM

Oxford classification (MEST-C)

- **Mesangial cellularity**: % glom (50%)
- **Endocapillary proliferation**: +, -
- **Segmental glomerulosclerosis**: +, -
- **Tubular atrophy/interstitial fibrosis**: extent
- **Crescents**: % glom (0, 25%)
IgA nephropathy

Defined by IF

IF
• Dominant IgA (by definition) + C3 (usually)
  – Other Ig negative or weak
  – Lambda > kappa (reversal of normal pattern)
• Granular on mesangial +/- adjacent capillary wall

EM
• Mesangial/paramesangial immune complex deposits
  – +/- Subendothelial deposits
• Mesangial proliferation and expansion
Case 6

Male 13 years old.
Recent foot infection.
Acute renal impairment, active urine sediment, proteinuria, hypertension.
Clinical consideration

Nephritic syndrome
• Post-infectious GN
• Mesangiocapillary GN
• Focal/diffuse proliferative GN: SLE
• Early crescentic GN
• IgA nephropathy / Henoch-Schonlein purpura

• “Recent” foot infection: clue!
• How recent?
IgG, C3
Inflammatory cells in capillary lumina
Subepithelial humps
Diagnosis

Acute post-infectious GN
(Diffuse endocapillary exudative GN)
Acute post-infectious GN

- Classically streptococcus
  - also Staphylococcus, virus etc
- Children to young adults
- Follows URTI or skin infection (2-4 weeks later)
- Acute nephritic syndrome, AKI (RPGN)
- Clinical clue: low serum C3
Acute post-infectious GN: LM

Classic: Diffuse exudative endocapillary GN
• Global endocapillary and mesangial proliferation
• Exudative: neutrophils

Others
• +/- Crescents
• +/- MCGN
• Late: mesangioproliferative only
Acute post-infectious GN

IF

- Dominant C3, + IgG
  - IgM/A negative or minimal (mimicked by C3 GN)
- Granular on capillary wall, mesangium
  - May be coarse granular
  - Patterns: Starry sky, garland, mesangial (late)
- Trap: Staph-related GN often IgA-dominant (mimic IgAN)

EM

- Subepithelial humps (classic)
  - +/- subendothelial, mesangial
- No BM reaction (unlike membranous GN)
Case 10

Clinical consideration

Nephritic syndrome
• Post-infectious GN
• Mesangiocapillary GN
• Focal/diffuse proliferative GN: SLE
• Early crescentic GN
• IgA nephropathy / Henoch-Schonlein purpura

• Hepatitis C: clue!
• Purpuric rash: clue!
• Low serum C4, normal C3: clue!
Diagnosis

Mesangiocapillary GN type 1 with cryoglobulinaemia (cryoglobulinaemic GN)
Mesangiocapillary GN (MCGN)

- Nomenclature

<table>
<thead>
<tr>
<th>US</th>
<th>UK/Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranoproliferative (MPGN)</td>
<td>Mesangiocapillary (MCGN)</td>
</tr>
<tr>
<td>Mesangiocapillary (rarely used)</td>
<td>MCGN type 1</td>
</tr>
</tbody>
</table>
Mesangiocapillary GN (MCGN)

- Heterogenous diseases with common LM
- **Proliferation**: mesangial, endocapillary, exudative
- Mesangial expansion
- **Accentuated lobularity** with cellular nodules
- **Capillary wall**: thickened, **double contours** (tram track)
  - interposition of mesangial and mononuclear cells between endothelium and GBM
MCGN subclassification

- Traditionally by **EM** (use this for the exam)
- Newer by **IF** (reflects immunopathogenesis)

**EM subtypes:** by location of immune complexes
- **Type 1:** Mesangial + subendothelial
  - commonest by far
- **Type 2:** Dense deposit disease
- **Type 3:** Type I + subepithelial
  - Heterogeneous: sub-subtypes (!), IF overlaps with type I
MCGN: IF subtypes

**Immune complex-mediated**
- **Classical** pathway activation
  - Serum: low C4, normal C3
- IF: Ig + C3, on mesangium & capillary wall
  - types of Ig depends on aetiology
- EM: type I

**Complement-mediated MCGN**
- **Alternate** pathway activation (C3 glomerulopathy, GP)
  - Serum: low C3, normal C4
- IF: C3 only (no/minimal Ig), on mesangium & capillary wall
- EM: Dense deposit disease (type II), C3 GN (type I or III)
MCGN type 1

- **Idiopathic**: children / young adult
- **Infections**: HCV (+/- cryoglobulinaemia)
- **Other infections**: HBV, chronic infections (SBE, shunt nephritis, abscess, osteomyelitis), syphilis
- **Autoimmune**: SLE
- **Plasma cell dyscrasia**: cryoglobulinaemia type 1
MCGN type 1

**IF**
- Chunky deposits on mesangium, capillary wall
- Idiopathic, HCV: IgG/M + C3
- SLE: full house (IgG, IgA, IgM, C3, C1q)

**EM**
- Mesangial + subendothelial immune complexes
- Mesangial/inflammatory cell interposition
  - + new inner GBM
Subendothelial deposits
Cryoglobulinemia

- Serum Ig which precipitate in the cold but re-dissolve when re-warmed
- Monoclonal (type 1), mixed (types 2, 3)

**Clinical**: Purpura (LCV), GN, arthritis, peripheral neuropathy, low C3/C4 (+/-)

**Type 1** (< 5%)
- Monoclonal: multiple myeloma (usually IgG), Waldenstroms (IgM)
- Look for kappa / lambda restriction in IF

**Type 2** (2/3)
- Monoclonal IgM against IgG (rheumatoid factor) + polyclonal IgG
- HCV (95%), HBV, EBV

**Type 3** (1/3)
- Polyclonal anti-IgG IgM (rheumatoid factor) + polyclonal IgG
- Chronic inflammation, autoimmune diseases, HCV
Cryoglobulinaemia

LM
• MCGN
• Hyaline thrombi in capillary lumina: strong PASD +ve (IgM)
• Vasculitis (+/-)
Cryoglobulinaemia

**IF**
- Like MCGN type 1, usually IgM dominant
- Also +ve in thrombi
- May be monoclonal (eg. type 1 cryoglobulinaemia)

**EM**
- Like MCGN type 1
- *Organised / crystalline* deposits and thrombi: short fibrils or tubules
MGCN type 2: Dense deposit disease

- Association: partial lipodystrophy (sunken face)

**LM**
- MCGN
- Thick refractile capillary wall (*string of sausages*): PAS +ve

**IF**
- Chunky C3 (no Ig) on capillary wall +/- mesangium

**EM** (*characteristic*)
- Dense ribbon in GBM (lamina densa)
- MCGN changes
Case 8

Male 64 Years Old.
Acute renal impairment, active urine sediment.
Recent nose bleed and haemoptysis.
Clinical consideration

• RPGN / acute nephritic

RPGN

• Crescentic GN
• Acute deterioration of other GN (often those causing nephritic syndrome)

• Nose bleed and haemoptysis: clue!
IF

- All negative
Diagnosis

Pauci-immune crescentic GN
(probably ANCA-related: Wegeners granulomatosis)
Crescentic GN: LM

- **Definition**: active crescents in >= 50% glom
  - But must mention ANY active crescents in report

- **Cellular (active)**:
  - parietal epithelial cell proliferation (> 2 cell layers)
  - fibrinoid necrosis, inflammatory cells

- **Fibrocellular, fibrous (chronic)**

- **Rupture** → inflammation, granulomas
- **Adjacent glomerular tuft**: collapsed, fibrinoid necrosis
- **Look AWAY from crescents**
  - Assess non-crescentic glomeruli
  - Arteries: necrotising arteritis (fibrin)
- **Acute interstitial infiltrate, ATN (non-specific)**
Crescentic GN: IF

• Active crescent: Fibrinogen +/- complement
  – no diagnostic value
• Look AWAY from crescent

Further classification by IF

• Immune complex GN: IF depends on underlying GN
  – Look in non-crescentic glom (eg PIGN, IgAN, MCGN, lupus)

• Pauci-immune: IF negative
  – Mostly ANCA-associated vasculitis (90%)

• Anti-GBM disease (Goodpasture’s disease)
Crescentic GN: EM

- Crescent: fibrin, cells (epithelial, inflammatory, fibroblasts) – no diagnostic value
- Look AWAY from crescent

- Immune complex GN: depends on underlying GN
  – Look in non-crescentic glom (eg PIGN, IgAN, lupus)

- Pauci-immune: no immune complexes

- Anti-GBM disease: no immune complexes
ANCA-associated vasculitis

- Usually elderly
- Small vessel vasculitis (Chapel Hill consensus, 2012)
- ANCA = antineutrophil cytoplasmic antibody

Types
- c-ANCA (cytoplasmic): against proteinase 3 (PR3)
- p-ANCA (perinuclear): against myeloperoxidase (MPO)

<table>
<thead>
<tr>
<th></th>
<th>Wegeners</th>
<th>CS</th>
<th>MPA</th>
<th>Renal-limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-ANCA</td>
<td>75%</td>
<td>5%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>20%</td>
<td>40%</td>
<td>50%</td>
<td>65%</td>
</tr>
</tbody>
</table>
ANCA-associated vasculitis

Wegeners granulomatosis (Granulomatosis with polyangiitis, GPA)
• Vasculitis, necrosis, granulomas (uncommon in kidney bx)
• Upper respiratory tract: sinusitis, nose bleed, otitis media etc
• Lower respiratory tract: lung infiltrate, cavitating lesion
• Flu-like symptoms, purpura, neuropathy, eye disease

Churg-Strauss syndrome (eosinophilic GPA)
• Pathology like Wegeners but eosinophil-rich (uncommon in kidney bx)
• Asthma, peripheral eosinophilia

Microscopic polyangiitis (MPA)
• Vasculitis, necrosis but no granulomas
• Flu-like symptoms, purpura, neuropathy, lung involvement
ANCA-associated (pauci-immune) GN

**LM**
- Crescentic and necrotising GN
- Non-crescentic glomeruli: ~ normal
- Necrotising arteritis: uncommon
- Tubulointerstitial nephritis, ATN

**IF:** Negative

**EM:** No immune complexes
Anti-GBM disease

Goodpastures

- **Syndrome:** renal impairment + haemoptysis
- **Disease:** syndrome due to antibodies against glomerular and lung capillary BM
  - Autoantibody to **alpha 3 (IV) collagen** (most abundant in GBM and lung capillary BM)

Clinical

- All ages, common in young adults
- May occur in transplant recipients with Alport’s syndrome
Anti-GBM disease

**LM**
- Fibrinoid necrosis with GBM breaks
- Crescents all ~ same stage
- Non-crescentic glomeruli: ~ normal
- Tubulointerstitial nephritis, ATN; no arteritis

**IF**
- Linear IgG (always) + C3 (usually) along GBM (+/- TBM)
  - NOT granular (cf membranous)
  - DDx: diabetes, MIDD (no C3)

**EM**
- No immune complexes or deposits
  - Antigen is diffusely distributed throughout GBM
- GBM breaks
Case 5

Female 35 years old.
Acute renal impairment.
Microscopic haematuria, active urine sediment, proteinuria.
Anaemia, thrombocytopenia.
Clinical consideration

• Nephritic, +/- RPGN?

• Anaemia, thrombocytopenia: clue!
  – Autoimmune?
  – Thrombotic microangiopathy?
  – Malignancy (especially myeloma)?
    • Less likely in a 35 year old
  – Unrelated?
Diagnosis

Lupus nephritis class IV
Systemic lupus erythematosus

- Typically young female, East Asian or West African descent
- Rash (eg. malar), photosensitivity, mucosal ulcers
- Arthritis, effusions
- Renal
- Haem: anaemia (AIHA), thrombocytopaenia (ITP)
- Neuro: seizure, psychosis etc

Antibodies
- Antinuclear Ab (ANA): sensitive but less specific
- Anti-dsDNA: specific but less sensitive
- Others: antiphospholipid etc
- Clue: low serum C3 & C4
Lupus GN: clinical

Mild: class I, II
• Normal or asymptomatic proteinuria, haematuria
• Seldom biopsied

Severe: class III, IV (proliferative GN)
• Nephritic, nephrotic, RPGN, CKD

Membranous: class V
• Nephrotic

Chronic: class VI
• CKD, ERKD
Lupus GN:
ISN/RPS (2002) classification

Class I: Minimal mesangial GN
• LM: ~ normal
• IF/EM: mild mesangial deposits only

Class II: Mesangial proliferative GN
• LM: mesangial proliferation / expansion only
• IF/EM: mesangial deposits only
Lupus GN –
ISN/RPS (2002) classification

Class III: Focal proliferative GN (< 50% glom)
- LM: proliferative, necrotising, sclerosing lesions
- IF/EM: subendothelial & mesangial deposits
- Subclass: active (A), chronic (C), mixed (A/C)

Class IV: Diffuse proliferative GN (> 50% glom)
- LM: proliferative, necrotising, sclerosing lesions
- IF/EM: subendothelial & mesangial deposits
- Subclass: active (A), chronic (C), mixed (A/C)
- Subclass: G (> 50% global), S (> 50% segmental)
Lupus GN – ISN/RPS (2002) classification

Class V: membranous GN
- LM: diffuse **membranous** GN, +/- mesangial changes
- IF/EM: extensive subepithelial +/- mesangial deposits
  - > 50% capillary loops of > 50% glomeruli
- May co-exist with class III, IV

Class VI: advanced sclerotic GN
- LM: > 90% glomerulosclerosis, no active lesions
- IF/LM: +/- residual deposits
Class IV lupus GN: LM

“MCGN pattern + extras”

MCGN
• Accentuated lobularity with cellular nodules
• Proliferation: mesangial, endocapillary, exudative
• Capillary wall: tram track (double contours)

Extras
• Wire loops: marked irregular thickening of capillary wall
  – due to confluent immune deposits
• Luminal “hyaline thrombi”
  – due to massive subendothelial deposits
• Crescent, fibrinoid necrosis, sclerosis
Class IV lupus GN: IF, EM

**IF**
- **Full house**: IgG (dominant), IgA, IgM, C3, C1q
- Coarse granular on capillary wall, mesangium

**EM**
- Abundant large deposits at multiple sites
  - Subendothelial, mesangial, subepithelial deposits
  - May appear crystalline (~ cryoglobulin)
- Tubuloreticular bodies in endothelium (not specific)
Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices

Kidney Int 93(4):789-796, 2018
### Table 2 | Proposed modified NIH lupus nephritis activity and chronicity scoring system

<table>
<thead>
<tr>
<th>Modified NIH activity index</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocapillary hypercellularity</td>
<td>Endocapillary hypercellularity in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>0-3</td>
</tr>
<tr>
<td>Neutrophils/karyorrhexis</td>
<td>Neutrophils and/or karyorrhexis in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>0-3</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>Fibrinoid necrosis in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>(0-3) x 2</td>
</tr>
<tr>
<td>Hyaline deposits</td>
<td>Wire loop lesions and/or hyaline thrombi in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>0-3</td>
</tr>
<tr>
<td>Cellular/fibrocellular crescents</td>
<td>Cellular and/or fibrocellular crescents in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>(0-3) x 2</td>
</tr>
<tr>
<td>Interstitial Inflammation</td>
<td>Interstitial leukocytes in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) in the cortex</td>
<td>0-3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>0-24</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified NIH chronicity index</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total glomerulosclerosis score</td>
<td>Global and/or segmental sclerosis in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>0-3</td>
</tr>
<tr>
<td>Fibrous crescents</td>
<td>Fibrous crescents in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of glomeruli</td>
<td>0-3</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>Tubular atrophy in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) of the cortical tubules</td>
<td>0-3</td>
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<tr>
<td>Interstitial fibrosis</td>
<td>Interstitial fibrosis in &lt;25% (1+), 25%-50% (2+), or &gt;50% (3+) in the cortex</td>
<td>0-3</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>0-12</strong></td>
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</table>
Other renal involvements in SLE

- ANCA-associated GN (c-ANCA)
- Thrombotic microangiopathy (antiphospholipid Ab)
- Necrotising vasculitis
- Acute tubulointerstitial nephritis

Remember full house IF and clinical
Non-proliferative glomerular diseases
Minimal change GN

Clinical
- Children to young adults Nephrotic
- Usually no haematuria, HT or renal failure
- Associations
  - Drugs esp NSAIDs (clue: interstitial infiltrate with eos)
  - Hodgkins, bee sting, venom, viral
  - Very steroid responsive in children (less in adults)

LM: normal
IF: normal
EM: diffuse (> 80%) podocyte foot process effacement & microvillous transformation
  - If < 50%, unlikely to be MCD (may be secondary / adaptive FSGS)
Minimal change GN

Microvillous transformation

Foot process effacement

Normal

Effaced
Case 4

Male 70 years old.
Nephrotic syndrome for months.
Inactive urine sediment.
Clinical consideration

Nephrotic syndrome
• Minimal change
• Membranous: including lupus class V
• Focal segmental glomerulosclerosis (FSGS)
• Diabetic nephropathy
• Amyloid
Stiff lumina
Thick capillary wall
IgG, C3
Diagnosis

Membranous glomerulonephritis
(Stage 2-3)
Membranous GN

Clinical
• Nephrotic +/- haematuria, HT, renal failure

• Primary
  – +/- anti-phospholipase A2 receptor Ab (serum, IHC)

• Secondary
  – Malignancy (especially older patients)
  – Hepatitis B, chronic malaria, syphilis
  – Autoimmune disease: SLE, Hashimoto
  – Drugs: gold, penicillamine
Membranous GN: LM

• Stiff lumina, *capillary wall thickening*

• GBM reaction to deposits (*silver* stain):
  – Seen from side: *spikes*, ladder / tram track
  – Seen en face: *holes* / Swiss cheese

• Mesangium may appear expanded

• Typically *no proliferation*

• Rare proliferation (mesangial, crescents): suspect secondary causes (eg lupus)
Membranous GN

**IF**
- **Granular IgG, C3** on capillary wall (NOT linear)
  - Mesangial staining: suspect secondary causes
  - “Full house”: suspect lupus

**EM**
- **Subepithelial** deposits
  - Mesangial deposits: suspect secondary causes
  - Foot process effacement
Membranous GN

EM staging

• 1: small subepithelial deposits, no GBM reaction
• 2: subepithelial deposits + GBM reaction (spikes)
• 3: intramembranous deposits (completely surrounded by GBM reaction)
• 4: deposits resorbed → lucent area
Stage 2

Foot process effacement

Stage 3

Spikes
Focal segmental glomerulosclerosis (FSGS)

• Pattern of glomerular reaction due to podocyte injury

Primary
• Idiopathic
• Familial: abnormalities in podocyte proteins (many types)

Secondary
• Other GN: IgAN, lupus, TMA etc (indicates chronicity)
• Adaptive (to increased “demand”)
  – Oligomeganephronia: especially indigenous patients
  – Single kidney: agenesis, dysplasia, nephrectomy, Tx
  – Obesity, hypertension etc
• Virus: HIV, parvovirus B19
• Drugs: pamidronate
FSGS

Clinical
• Nephrotic + haematuria, HT, renal failure
• Poor steroid response
• Primary FSGS may recur in Tx: +/- within hours

Variants: hierarchical classification
• Collapsing
• Tip
• Cellular
• Hilar
• NOS
Figure 1 Kidney biopsies algorithm for the morphologic Columbia classification of FSGS in the variants COLL (collapsing); CELL (cellular); GTL (tip lesion); PHG (perihilar) and NOS (not otherwise specified).
FSGS, NOS – LM

- **Focal**, starts *juxtamedullary* (adequate sampling important)
  - 1 affected glomerulus enough for Dx
  - Uninvolved glomeruli normal (unless has underlying GN)
  - Undersampled cases misdiagnosed as “minimal change disease”
  - **Clue**: interstitial fibrosis (disproportionate for age), glomerulomegaly

- **Segmental sclerosis**
  - Capillary *lumina obliteration*, foam cells
  - Increased mesangial *matrix*: silver positive
  - **Hyalinosis** (plasma protein insudation): silver negative
  - **Synechiae**: adhesion to Bowman’s capsule
  - Podocyte hyperplasia; no other proliferation

- Uninvolved segments normal
- Interstitial fibrosis, tubular atrophy
FSGS NOS

**IF**
- Sclerotic segment: IgM, C3 (non-specific trapping)
  - Exception: FSGS in other GN
- Non-sclerotic segment: Negative

**EM**
- Diffuse (> 80%) podocyte foot process effacement
  - Even in non-sclerotic segments
  - Adaptive FSGS may have milder, more focal changes (< 50%)
- **No immune deposits** (except FSGS in other GN)
- Sclerotic segment: increased mesangial matrix, hyaline (homogenous electron-dense), lipid, podocyte hyperplasia
Collapsing FSGS

Classic associations
- HIV (esp African ethnicity), parvovirus B19
- Pamidronate

Clinical: Severe proteinuria, rapidly progressing CKD

LM
- Often diffuse and global
- Capillary tuft collapse, podocyte hyperplasia, protein droplets
- Little sclerosis, hyalinosis, adhesions
  - (Neither focal, segmental nor sclerotic!)
- Diffuse tubular damage (microcystic), interstitial infiltrate
Collapsing FSGS

**IF**
- Like FSGS NOS

**EM**
- FSGS NOS + GBM wrinkling / collapse
- HIV: tubuloreticular bodies
Nodular glomerulopathies

- Diabetic nephropathy
- Amyloid nephropathy
- Monoclonal Ig deposition disease (MIDD)
- Fibrillary GN
- Immunotactoid GN
Diabetic nephropathy

LM
• Glomerulomegaly
• Thick capillary wall (GBM thickening)
• Mesangial expansion & proliferation
• Mesangiolysis (fraying) → capillary microaneurysms

• Nodular DN: Kimmestiel-Wilson lesion
  – Mesangial sclerosis: PAS +ve, silver +ve
    • Nuclei pushed to periphery of nodule
  – Plasma protein **insudate** (fibrin cap, capsular drop)
    • Bright eosinophilic (glassy), PASD +ve, silver –ve
  – Lipid, foam cells, Bowman’s capsule BM thickening
Mesangiolysis, microaneurysm
Hyaline droplets
Diabetic nephropathy

**LM**

- Blood vessels
  - *Arteriolar hyalinosis*: afferent & efferent
  - Arteriosclerosis: intimal fibroplasia
- Interstitial fibrosis, tubular atrophy, TBM thickening
Diabetic nephropathy

**IF**
- Linear accentuation of IgG, albumin of GBM
  - +/- also TBM, Bowman’s capsule BM
- C3 -ve (cf anti-GBM disease)

**EM**
- Thick GBM (widened lamina densa)
- Mesangial expansion & proliferation
- No immune complexes
  - Hyaline only
IgG, albumin
Case 1

Male 64 years old.
Nephrotic syndrome 3 months.
Inactive urine sediment.
No relevant past medical history.
Clinical consideration

Nephrotic syndrome
- Minimal change
- Membranous: including lupus class V
- Focal segmental glomerulosclerosis (FSGS)
- Diabetic nephropathy
- Amyloid
Diagnosis

AL amyloid nephropathy
**Amyloid**

**Definition:** protein which forms beta-pleated sheets

**Systemic amyloidosis** with renal involvement
- **AL** (monoclonal light chain): plasma cell dyscrasias
  - Very rare: AHL, AH amyloid (heavy chain)
- **AA** (amyloid A): chronic inflammation
  - Chronic infection: osteomyelitis, TB, bronchiectasis etc
  - Rheumatoid arthritis
- “Senile” cardiac amyloidosis (transthyretin)
- **Familial:** many types (eg. transthyretin)
Amyloid

- Renal: nephrotic, proteinuria
  - Clue: CKD with normal / large kidneys
- Neuro: peripheral neuropathy, postural hypotension
- Infiltration: cardiac failure, macroglossia, carpal tunnel syndrome, hepatomegaly
- Purpura, bruising

AL amyloid
- Serum/urine paraprotein: monoclonal band (M spike)
  - protein electrophoresis, immunofixation
- Serum free light chain
- Urine Bence-Jones protein
Amyloid

LM

- Amorphous pale eosinophilic nodules
  - PAS weak, silver -ve
  - Congo red: apple green birefringence with polarised light
- Capillary wall thickening
  - “feathery spikes” with silver (“eyelashes”)
- No proliferation

- Other deposits: vessels, tubules, interstitium
- AL amyloid: light chain cast nephropathy
- IHC: amyloid P (all amyloid), light chain (AL), amyloid A (AA), transthyretin
Amyloid

**IF**
- **AL:** clonal Ig light chain (usually lambda)
  - Ig, C3, C1q: Negative
- Other types: All negative

**EM**
- Randomly oriented non-branching **fibrils:** 8-12 nm diameter
- In GBM, mesangium, vessel wall, interstitium
Monoclonal Ig deposition disease (MIDD)

**Associations**
- Plasma cell dyscrasias
- B cell lymphoma

**Clinical**
- Proteinuria/nephrotic, hematuria, HT, renal impairment
- Extrarenal: cardiac, liver etc

**Types**
- Light chain (LCDD): 90%
- Light & heavy chain (LHCDD): < 10%
- Heavy chain (HCDD): very rare
LCDD

- Diagnosis rests on IF and EM
- LM very variable (need high index of suspicion)

LM
- Nodules
  - PASD +ve, silver weak +ve
  - Congo red -ve
  - Nuclei scattered in nodule

- +/- Proliferative: mesangial, MCGN, crescents

- Deposits on TBM (thick: ribbon-like), vessels, interstitium
- Light chain cast nephropathy
Proliferation only
LCDD

**IF**
- Monoclonal light chains on GBM +/- mesangium
  - 90% kappa
- Ig, C3, C1q: Negative
- Also TBM, interstitium, vessels

**EM**
- Granular or amorphous deposits: non-fibrillary
- On GBM (inner aspect), TBM (outer aspect), vascular BM, mesangial nodules
Case 2

Female, 43 years old.  
Nephrotic syndrome, microscopic haematuria, renal impairment.  
No relevant past medical history
Clinical consideration

Nephrotic syndrome
• Minimal change
• Membranous: including lupus class V
• Focal segmental glomerulosclerosis (FSGS)
• Diabetic nephropathy
• Amyloid
PAS +ve
Diagnosis

Fibrillary glomerulopathy
Fibrillary GN

Diagnosis rests on IF and EM

Clinical
• Usually Caucasian
• Nephrotic, haematuria, CKD, RPGN

LM
• Looks like mesangial expansion or FSGS but “not quite right”
  – PAS +ve but silver –ve
• Congo red –ve
• Variable proliferation: mesangial, MCGN, crescents
• “Hard to categorise by LM”
• Potential marker: DNAJB9 (IHC developed)
Fibrillar GN

**IF**
- IgG, C3, light chains on mesangium + capillary wall
  - Pseudolinar: “ribbon-like”
  - May show kappa restriction
- IgA, IgM, C1q: negative

**EM**
- Randomly oriented non-branching fibrils: 15-30 nm diameter
- GBM (subepithelial to subendothelial), mesangium
Immunotactoid GN

- ?? Related to fibrillary GN but much rarer
- Associated with monoclonal gammopathy, lymphomas
- Diagnosis rests on **IF and EM**

**LM:** like fibrillary GN

**IF**
- Chunky IgG, C3, light chains: mesangium & capillary wall
- May show IgM, IgA kappa restriction

**EM**
- Parallel microtubules (20-60 nm diameter): “stacked wood”
- Mesangium, GBM (subendothelial)
IgG
Non-glomerular pathologies
Case 3

Female 71 years old. Previously well.
Recent diarrhoea.
Acute renal impairment with severe hypertension.
IF

• All negative
Diagnosis

Thrombotic microangiopathy – possibly haemolytic uraemic syndrome
Thrombotic microangiopathy (TMA)

• Heterogeneous disorders with common pathogenesis
• Endothelial injury $\rightarrow$ activation of coagulation system
• Generally identical histopathological findings
TMA: Clinical syndromes

- Haemolytic uraemic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- **Antiphospholipid syndrome**
  - Isolated or a/w SLE
  - CVA, recurrent abortions
  - Lupus anticoagulant (prolonged APTT), anti-cardiolipin
- Accelerated (malignant) hypertension, (pre)-eclampsia, scleroderma renal crisis
- Drugs: VEGF inhibitors
- Transplant: vascular rejection, calcineurin inhibitors
HUS / TTP

Classic HUS (D+)
- Epidemic / sporadic, often children
- E coli O157:H7 etc, Shigella
- Bloody diarrhoea, AKI, hypertension, thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), high LDH

Atypical HUS (D-)
- Alternative complement pathway activation
- Pregnancy, drugs (quinine, clopidogrel, ticlopidine), malignancy, HIV, familial/recurrent

TTP
- Low ADAMTS13 activity (vWF cleavage protein)
- Predominantly neuro (CVA); also renal, MAHA, thrombocytopenia
TMA: LM

Acute Glomeruli

- Luminal occlusion: endothelial swelling (*endotheliosis*), fibrin/platelet *thrombi*, fragmented rbc
- Capillary wall “thickening” (subendothelial widening)
- Hypocellular “bloodless” glomeruli
- Fibrinoid necrosis, crescents

Vessels (arterioles, arteries)

- Luminal occlusion: *thrombi*, endothelial swelling
- Mucoid intimal hyperplasia (oedema), fragmented rbc, fibrinoid necrosis
Fibrinoid necrosis

Bloodless glomerulus
Vessels
• Thrombus
• Fragmented rbc
• Mucoid intimal hyperplasia
TMA: LM

Chronic (days)

Glomeruli
• Mesangiolysis, microaneurysms, sclerosis
• Ischaemia: thick wrinkled capillary wall, double contouring, loop collapse
• MCGN

Vessels
• Luminal stenosis, recanalised thrombus
• Onion-skin intimal fibrous thickening
• Arteries: duplication of internal elastic lamina

Interstitial fibrosis / tubular atrophy
- Mesangiolysis, microsneurysm
- Capillary wall double contouring
- Artery: intimal fibroplasia (onion skin)
TMA

IF
• Essentially negative
• Fibrinogen: glom, vessel walls
• No Ig, complements (non-specific trapping only)

EM
• Fibrin thrombi, rbc fragments, platelets
• Endothelial swelling
• Subendothelial widening and fibrils (fibrin)
  – Endothelium separates from BM
• Mesangiolysis
Can the cause of TMA be diagnosed from the renal bx?

Generally no

• Scleroderma renal crisis: involve large vessel
• Antiphospholipid syndrome: more thrombi, involve large vessel
• (Pre)-eclampsia: marked endotheliosis

But much overlap
Depend on clinical correlation
Case 7

Male 56 years old.
Acute renal impairment.
Recent bone pain.
Diagnosis

Myeloma light chain cast nephropathy
Light chain cast nephropathy


LM
- Proteinaceous cast: Ig light chain + Tamm-Horsfall protein
- Usually distal & collecting tubules
- Fractured, lamellated, weak PASD stain
- Histiocytic & giant cell reaction
- Tubular damage & rupture → inflammation, granuloma
- Other myeloma-related renal diseases (amyloid, MIDD)
Light chain cast nephropathy

**IF**

- Monoclonal light chains (50%): usually kappa
  - “kappa kills the kidney”
- Abnormal light chain may fail to label (altered antigenicity)
- May label with both kappa & lambda (appear polyclonal) due to non-specific
- +/- IgA, IgM: non-specific

**EM**

- Casts: variable electron density, cell fragments, debris
Hyaline cast

Myeloma cast
Monoclonal Ig-mediated nephropathies

- AL amyloidosis (rarely AH, AHL)
- LCDD (rarely HCDD, LHCDD)
- Cryoglobulinaemic GN (type 1 & 2)
- Light chain cast nephropathy

- Rare
  - Proliferative GN with monoclonal deposits
  - Light chain proximal tubulopathy
  - etc
Miscellaneous classic pathologies
Alport syndrome

- Defect in type IV collagen synthesis
  - Many types: alpha 1-6 chains
- Most commonly X-linked dominant (worse in males)
- Asymptomatic haematuria +/- proteinuria, CKD
- Hearing loss, eye abnormalities

**LM:** non-specific
- Glomerulosclerosis, interstitial fibrosis, foam cells

**IF:** absent staining for specific alpha chains

**EM:** characteristic GBM changes
- Irregular thinning and thickening
- Basket weave (lamellated appearance)
Fabry disease

- X-linked recessive
- *Alpha-galactosidase A deficiency* → glycosphingolipid accumulation

**Clinical**
- Polyuria, proteinuria, CKD
- Skin (diffuse *angiokeratoma*, haemangioma etc), painful *neuropathy*, eye abnormalities

**LM**
- *Cytoplasmic vacuolation* (esp podocytes, parietal epithelial cells)

**IF**: non-specific

**EM**
- *Myelin bodies*: lamellated inclusions in lysosomes
Some books

- Fogo et al. Diagnostic Atlas of Renal Pathology (3e, 2016)
- Lager et al. Practical Renal Pathology (1e, 2013)
- Zhou et al. Silva’s Diagnostic Renal Pathology (2e, 2017)
- Colvin et al. Diagnostic Pathology: Kidney diseases (2e, 2016)
- Jennette et al. Heptinstall’s Pathology of the Kidney (2 vol) (7e, 2015)
Good luck!