Clinical Nephrotic and Nephritic Syndromes

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## Anatomy of the Renal Block

<table>
<thead>
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<th>Physiology</th>
<th>Pathophysiology</th>
<th>Urology</th>
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<td>Body Fluids</td>
<td>Glomerular Diseases – 3</td>
<td>Histology Lab</td>
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<tr>
<td>GFR, Clearance</td>
<td>Acute Kidney Injury – 1</td>
<td>Malignancy – 1</td>
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<td>Sodium / Diuretics</td>
<td>Chronic Kidney Disease – 3</td>
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<td>Potassium</td>
<td>Renal Lab -2</td>
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<td>Acid</td>
<td>Transplant Pathology-1</td>
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<tr>
<td>Water</td>
<td>Vascular Diseases – 1/2</td>
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<td>Steady State</td>
<td>Plumbing- 1/2</td>
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Learning Objectives (3)

• Review the basic structure and function of the normal glomerulus

• Understand the pathophysiology and clinical presentation of patients with nephrotic and nephritic syndromes

• Formulate a differential diagnosis of a patient with glomerular disease
Outline

• Normal Glomerulus

• Nephrotic Syndrome

• Nephritic Syndrome(s)
Afferent Arteriole

Efferent Arteriole

Capillary Loop

E

A

CL
Three Glomerular Cell Types

- Podocyte
- Mesangial cell
- Endothelial cell
Three Glomerular Cell Types

• Endothelial cells
  – Restrict filtration of cells and macromolecules through fenestrae
  – Make inflammatory mediators in response to injury

• Mesangial cells
  – Regulate vascular tone
  – Make mesangial matrix
  – Response to injury as effector cells

• Podocytes
  – Maintain impermeability to protein filtration (prevent proteinuria)
Outline

• Normal Glomerulus

• Nephrotic Syndrome

• Nephritic Syndrome(s)
Case 1

• 30 yo M presents with periorbital and lower extremity edema, 10 kg weight gain and foamy urine
• Physical exam: BP 120/80, pitting edema
• Laboratory:
  – Cr 0.9 mg/dL
  – Urinalysis: 3+ protein, no RBC, no WBC
  – Urine protein/Cr = 4 (normal < 0.15)
The Nephrotic Syndrome

Proteinuria (>3.5g/day)
Hypoalbuminemia
Hyperlipidemia
Lipiduria
Edema
Slit diaphragm
The Nephrotic Syndrome

Structural abnormality common to all nephrotic syndromes is diffuse “fusion” of the foot processes of the podocytes
Hyperlipidemia

• Poorly understood but clinically relevant

• Hypercholesterolemia
  – Decreased oncotic pressure stimulates hepatic lipoprotein synthesis

• Hypertriglycerideridemia
  – Impaired metabolism
Lipiduria

Maltese Cross
Mechanisms of Edema

• “Underfill”
  – Low oncotic pressure (hypoalbuminemia) leads to plasma volume depletion (water moves from plasma to interstitial compartment)

• “Overfill”
  – Sodium retention
  – Poorly understood
Hypercoagulable State

• Urinary losses of antithrombin III, Protein C & S, increased platelet activation, hyperfibrinogenemia

• 10-40% develop arterial or venous thromboembolism
The Nephrotic Syndrome

- Proteinuria (>3.5g/day)
- Hypoalbuminemia
- Hyperlipidemia
- Lipiduria
- Edema
The Nephrotic Syndrome

- Primary renal disease
  - Focal segmental glomerulosclerosis
  - Membranous nephropathy
  - Minimal Change Disease

- Systemic disease
  - Diabetes mellitus
  - Amyloidosis
  - Systemic lupus erythematosus (SLE)
Focal Segmental Glomerulosclerosis (FSGS)
Focal Segmental Glomerulosclerosis (named for the histology)
Epidemiology

- Most common cause of nephrotic syndrome in adults in the United States

- Patients less than 40

- African-Americans
Major Causes of FSGS

- Idiopathic/Primary
- Familial

- Secondary
  - Infection (e.g. HIV)
  - Drugs (e.g. heroin)
  - Obesity (hyperfiltration)
  - Reduced nephron number (hyperfiltration)
    - Reflux nephropathy, unilateral renal agenesis, sickle cell disease, advanced renal disease
Pathogenesis

• Not completely understood

• Possible circulating glomerular permeability factor in primary FSGS that targets the podocyte

• Disease of the podocyte
  – Familial forms localized to podocyte-specific genes, including APOL1 (in African Americans)
FSGS

Disease of the podocyte
Membranous Nephropathy
Epidemiology

• Most common cause of nephrotic syndrome in Caucasian adults and > 60 yrs

• Incidence increases with age

• Men > women
Major Causes
Membranous Nephropathy

• Idiopathic/Primary  80%
  – Antibodies to Phospholipase A$_2$ receptor (PLA2R)
• Secondary  20%
  – Solid tumors
    • Bowel, breast, lung
  – SLE
  – Infections
    • Hepatitis B/C, malaria, syphilis
  – Rheumatoid arthritis
    • Drugs
      – Penicillamine
      – Gold
Pathogenesis

- Autoantibody to glomerular antigens causing in situ immune complex formation
  - Phospholipase A2 receptor
M-type Phospholipase A2 receptor
(NEJM 2009)

Foot processes

Fenestrated endothelium
Minimal Change Disease
Epidemiology

• Most common cause of nephrotic syndrome in children
Major Causes
Minimal Change Disease

• Idiopathic/Primary

• Secondary
  – NSAID (fenoprofen)
  – Malignancy
    • Hodgkin’s disease
    • Leukemia
Diabetic Nephropathy
Epidemiology

- Most common cause of end-stage renal disease (ESRD)

- 30-40% of type 1 and 15-20% of patients with type 2 diabetes mellitus develop diabetic nephropathy after 10 –20 years
Amyloidosis
Amyloidosis

- Older patients

- Variety of proteins form β-pleated sheets
  - Immunoglobulin light chains in primary (AL)
  - Amyloid AA secondary to chronic inflammation (e.g. rheumatoid arthritis)

- Poor prognosis

- Deposition in the heart, liver, GI tract
The Nephrotic Syndrome

• Primary renal disease
  – Focal segmental glomerulosclerosis (adults)
  – Membranous nephropathy (older)
  – Minimal Change Disease (younger)

• Systemic disease
  – Diabetes mellitus (common disease with renal involvement)
  – Amyloidosis (rare disease with renal involvement)
  – Systemic lupus erythematosus (SLE)
Case 1 – Nephrotic Syndrome

- 30 yo M presents with periorbital and lower extremity edema, 10 kg weight gain and foamy urine
- Physical exam: BP 120/80, pitting edema
- Laboratory:
  - Cr 0.9 mg/dL
  - Urinalysis: 3+ protein, no RBC, no WBC
  - Urine protein/Cr = 4 (normal < 0.15)
The Nephrotic Syndrome

Proteinuria (>3.5g/day)
Hypoalbuminemia
Hyperlipidemia
Lipiduria
Edema
History and Physical Clues

- NSAID use (gold, penicillamine)
- History of malignancy
- History of diabetes, HIV
- Age
  - Children: Minimal change disease
  - Adults: FSGS and Membranous
- EDEMA
- Foamy urine
The Nephrotic Syndrome
Laboratories

- Focal segmental glomerulosclerosis
  - HIV antibody
- Membranous nephropathy
  - Hepatitis B surface antigen, Hepatitis C antibody, RPR (for syphilis)
- Minimal Change Disease
- Diabetes mellitus
- Amyloidosis
  - SPEP, UPEP (serum and urine protein electrophoresis)
- Systemic lupus erythematosus (SLE)
  - ANA, anti-DNA, serum complements (C3, C4)
Diagnosis: Nephrotic Syndrome

- Kidney biopsy is required in most cases to establish the diagnosis
Outline

• Normal Glomerulus

• Nephrotic Syndrome

• Nephritic Syndrome(s)
The Nephritic Syndrome

Proteinuria < 3.5 grams/day

Edema

Hematuria  (red cell casts, dysmorphic RBCs)

Hypertension

Renal Failure
Nephritic Syndrome(s)

- Focal Nephritic
  - Mild, benign

- Diffuse Nephritic
  - Moderate level of disease
  - Rapidly progressive glomerulonephritis (RPGN)
Case 2

- 30 yo M presents with
  - Ankle edema in the evenings
  - Intermittent “coca-cola” colored urine 3 days after upper respiratory infection (over 10 years)

- Physical exam: BP 110/70, trace ankle edema

- Laboratory
  - Cr 0.9 mg/dL
  - Urinalysis: 1+ protein, 10-20 RBC, no WBC
  - Urine protein/Cr = 0.5
Macroscopic Hematuria

Coca-cola urine
Red Blood Cell cast in the urine
Dysmorphic RBCs
Focal Nephritic Syndrome

• Pathology
  – Inflammatory lesions < 50% of glomeruli

• Clinical
  – RBCs, RBC casts, mild proteinuria (< 1.5 g/day)
  – Mild or no edema, hypertension, renal failure
Focal Nephritic Syndrome

• Primary renal disease
  – IgA Nephropathy
  – Alport’s Syndrome
  – Thin Basement Disease

• Systemic disease
  – SLE (focal /mesangial)
  – Henoch Schonlein Purpura (HSP)
IgA Nephropathy
Epidemiology

Percent of patients with GN

Singapore: 52%
Japan: 41%
Australia: 30%
Southern Europe: 20-28%
United Kingdom: 24%
Germany: 16%
USA: 12%
Canada: 8%
IgA Nephropathy
Clinical and laboratory features at presentation

Male/female 2:1; age usually 20-40 years

- Microscopic hematuria
- Macroscopic hematuria
- Proteinuria > 1 g/d
- Proteinuria > 3 g/d
- Elevated creatinine
- Elevated BP
- Loin pain
- Infection-related exacerbations
- Familial history
Pathogenesis

IgA1 complexes
Increased renal delivery
Impaired MPS clearance

Liver
Asialo-glycoprotein receptor

Spleen

Inflammatory mediators
Cytokines
Growth factors
Oxidants
Proteases
Matrix components

Mesangial cell localization
## Differential Diagnosis – Focal, Nephritic

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gross Hematuria</th>
<th>Frequency</th>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>Yes</td>
<td>Variable</td>
<td>No</td>
</tr>
<tr>
<td>Alport’s</td>
<td>Yes</td>
<td>1:50,000 live births</td>
<td>Males X-linked 15% - none</td>
</tr>
<tr>
<td>TBMD</td>
<td>&lt;10%</td>
<td>5-9% of population</td>
<td>No</td>
</tr>
</tbody>
</table>
Case 3

- 30 yo M presents
  - 2-3 weeks periorbital and pitting edema to mid-calf
  - Dark urine

- Physical exam: BP 195/110
  - Purpura on thighs, pitting edema to knees

- Laboratory
  - Creatinine 2.3 mg/dL (from 0.9 last year)
  - Urinalysis: 3+ protein, 50-100 RBC, 10-20 WBC
  - Urine protein/Cr = 3
Purpuric skin lesions
## Nephrotic vs. Nephritic Syndrome

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Nephritic</th>
<th>Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>RBCs, RBC casts</td>
<td>Lipid, fatty casts, Oval fat bodies</td>
</tr>
<tr>
<td>Protein excretion</td>
<td>&lt; 3.5 g/day</td>
<td>&gt; 3.5 g/day</td>
</tr>
<tr>
<td>BP</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>GFR</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
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</table>
Diffuse Nephritic Syndrome

• Hypocomplementemic (low C3, C4) disorders
  – Postinfectious glomerulonephritis
  – Membranoproliferative glomerulonephritis
    • Cryoglobulinemia (HCV)
    • Systemic lupus erythematosus (SLE)

• Normal complement (normal C3, C4) disorders
  – Anti-GBM disease or Goodpasture syndrome
  – Vasculitis (ANCA-related)
  – IgA nephropathy
Postinfectious Glomerulonephritis
Post infectious Glomerulonephritis

- Post streptococcal
- Bacterial endocarditis
- Shunt (ventriculo-peritoneal shunt) nephritis
- Nephritis with visceral abscesses
Poststreptococcal Glomerulonephritis

- Children > adults
- Streptococcus, group A beta-hemolytic (types 1, 4, and 12)
- Dark urine (hematuria)
- Sore throat - 10 to 14 days earlier
- No long-term sequelae in most patients
Membranoproliferative Glomerulonephritis
Membranoproliferative GN

- Types I, II and III
- Children and young adults
- Nephrotic and nephritic

- Secondary forms - older adults
  - Most commonly associated with hepatitis C, cryoglobulinemia, SLE
Rapidly Progressive Glomerulonephritis

Rapidly progressive decline in renal function

Active urine sediment characterized by an inflammatory process

Formation of cellular crescents within Bowman’s space
Anti-glomerular Basement Membrane (anti-GBM) Disease
Anti-GBM Disease and Goodpasture’s Syndrome

Pulmonary hemorrhage, iron deficiency anemia, RPGN
Age 15-30 yrs or 60-70 yrs, 6:1 male
Pulmonary toxins: cigarettes, hydrocarbons, influenza
Lab: Positive anti-GBM antibody
Biopsy: Crescents; linear IgG, C3
Pathogenesis of Anti-GBM Nephritis

Antibody to Type IV Collagen, Alpha-3 chain, NC1 domain
The Nephritic Syndrome

Proteinuria < 3.5 grams/day

Edema

Hematuria (red cell casts, dysmorphic RBCs)

Hypertension

Renal Failure
History and Physical Clues

- Sore throat
- Rash
- Liver disease
- Pulmonary symptoms
- Hypertension
- Dark urine
- Edema
Nephritic Syndrome

- Hypocomplementemic Disorders (low C3, low C4)
  - Postinfectious glomerulonephritis
    - ASO titer
  - Systemic lupus erythematosus (SLE)
    - ANA, anti-DNA
  - Membranoproliferative glomerulonephritis
    - Hepatitis C
  - Cryoglobulinemia (HCV)
    - Cryoglobulins

- Normal complement disorders
  - Anti-GBM disease or Goodpasture syndrome
    - Anti-GBM antibodies
  - Vasculitis (ANCA-related)
    - ANCA (Anti-Neutrophil Cytoplasmic Antibody)
  - IgA nephropathy
Diagnosis of Nephritic Syndrome

• Kidney biopsy is usually needed
A word or two about Systemic Lupus Erythematosus (SLE)…
Systemic Lupus Erythematosus (SLE)

- SLE Can Present as All Forms of Glomerular Disease
  - Nephrotic syndrome
  - Nephritic syndrome
    - Diffuse or more severe, RPGN

- SLE Affects All Three Glomerular Cell Types
SLE Affects All Three Glomerular Cell Types

Mesangial Cell

Podocyte

Endothelial Cell
Systemic Lupus Erythematosus

• Immune complex GN
  – Anti-DNA

• Classification
  – Type I Normal Kidney
  – Type II Mesangial
  – Type III Focal proliferative
  – Type IV Diffuse proliferative
  – Type V Membranous
Pathogenesis of Glomerular Injury

Immune dysregulation

- Genetic influence
- Inflammation
  - Resolution
  - Variable rate of progression
- Scarring

Genetic influence

Renal Failure
Three Glomerular Cell Types

• Endothelial cells
  – Restrict filtration of cells and macromolecules through fenestrae
  – Make inflammatory mediators in response to injury

• Mesangial cells
  – Regulate vascular tone
  – Make mesangial matrix
  – Response to injury as effector cells

• Podocytes
  – Maintain impermeability to protein filtration (prevent proteinuria)
Summary
<table>
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<tr>
<th>Primary renal disease</th>
<th>Nephritic Syndrome</th>
<th>Nephrotic syndrome</th>
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<tbody>
<tr>
<td>Post infectious</td>
<td></td>
<td>Minimal change</td>
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<tr>
<td>IgA nephropathy</td>
<td></td>
<td>Focal sclerosis</td>
</tr>
<tr>
<td>MPGN</td>
<td></td>
<td>Glomerulosclerotic (FSGS)</td>
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<tr>
<td>Anti-GBM</td>
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<td>Membranous nephropathy (MPGN)</td>
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<tr>
<th>Systemic disease</th>
<th>Vasculitis</th>
<th>Diabetes</th>
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<tbody>
<tr>
<td>- SLE</td>
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<td>Amyloid</td>
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<tr>
<td>- HSP</td>
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<td>SLE</td>
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<tr>
<td>- Microscopic polyangiitis</td>
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<tr>
<td>- Cryoglobulinemia</td>
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<td></td>
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<tr>
<td>- Wegener’s granulomatosis</td>
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# Differential Diagnosis by Age

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<tr>
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<th>&lt; 15 years old</th>
<th>15-40 years old</th>
<th>&gt; 40 years old</th>
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<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>MCD</td>
<td>MCD (MCD)</td>
<td>(FSGS)</td>
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<td>FSGS</td>
<td>FSGS</td>
<td>(FSGS)</td>
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<td></td>
<td></td>
<td>Membranous</td>
<td>Membranous</td>
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<td></td>
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<td>Diabetes</td>
<td>Diabetes</td>
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<tr>
<td></td>
<td></td>
<td>SLE</td>
<td>Amyloid (&gt;60)</td>
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<td><strong>Focal nephritic</strong></td>
<td>Postinfectious</td>
<td>IgA</td>
<td>IgA</td>
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<td>IgA</td>
<td>Alport’s</td>
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<td>Alport’s</td>
<td>Thin BMD</td>
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<td>ANCA Vasculitis</td>
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• Formulate a differential diagnosis of a patient with glomerular disease