The electron micrograph represents the portion of the glomerulus primarily responsible for which one of the following functions?

A. control of renin release  
B. filtration of plasma  
C. reabsorption of water  
D. secretion of H+ and ammonium to regulate pH

Format

• Examples - 32 questions  
• Connections & buzz words  
• Relevant explanations, focusing on problem areas  
• Not covered? – write to mpicken@lumc.edu or mpicken@luc.edu
The nephrotic syndrome is characterized by severe proteinuria, decreased serum albumin level, and edema. This result from damage to one or more components of the glomerular capillary wall. In particular, the glomerular basement membrane is essential for maintaining serum oncotic pressure. In nonpathologic states, which of the following properties of the glomerular basement membrane prevent albumin from being freely filtered into the urine?

- (A) A combination of small pore size and negatively charged pore-forming molecules prevents albumin filtration
- (B) A combination of small pore size and positively charged pore-forming molecules prevents albumin filtration
- (C) Albumin is freely filtered across the basement membrane but is readily reabsorbed along the nephron
- (D) The positive charge of proteoglycans in the basement membrane repels albumin
- (E) The small size of the glomerular basement membrane pores excludes albumin molecules

An 8-year-old boy presents with headaches, dizziness, and malaise. He was seen for a severe sore throat 2 weeks ago. Physical examination reveals facial edema. The blood pressure is 180/110 mm Hg. A 24-hour urine collection demonstrates oliguria, and urinalysis shows hematuria. Which of the following best describes this patient’s medical condition?

- (A) Acute nephritic syndrome
- (B) Hereditary nephritis
- (C) minimal change disease
- (D) IgA nephropathy
- (E) Alport syndrome
A 13-year-old boy is brought to the emergency department with periorbital edema, hypertension and tea-colored urine. His parents say that he had a sore throat about 3 weeks ago. Urinalysis shows RBCs. A positive antistreptolysin O titer and decreased levels of complement are also noted. What findings would be expected in this patient's glomeruli?

- (A) no deposits detectable
- (B) Linear subendothelial pattern
- (C) Mesangial deposits
- (D) IgA deposits
- (E) Subepithelial humps

In post-infectious glomerulonephritis

1. Infected elicits antibody response (immunoglobulin G, IgG)
2. Immune complexes form in circulation (antigen + IgG + complement)
3. Deposition of immune complexes in the capillary wall elicits inflammatory reaction leading to structural damage ("Swiss cheese") with hematuria and proliferation
4. However, immune complexes are also formed in situ leading to formation of big sub-epithelial deposits "humps" (white arrow) which are unique to postinfectious glomerulonephritis and therefore diagnostically useful. The humps contain SpeB (streptococcal exotoxin B) and streptococcal glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which reaches the sub-epithelial aspect of the glomerular basement membrane owing to its cationic charge – here the antigen is not intrinsic but "planted antigen"
An 8-year-old boy presents with headaches, dizziness, and malaise. He was seen for a severe sore throat 2 weeks ago. Physical examination reveals facial edema. The blood pressure is 180/110 mm Hg. A 24-hour urine collection demonstrates oliguria, and urinalysis shows hematuria. What test(s) may be helpful in the differential diagnosis in this child?

a. ASO (antistreptolysin O antibody)
b. Complement level
c. both
d. neither

A 16-year-old boy comes to the physician with a 1-year history of intermittent, painless hematuria without dysuria on increased frequency of micturition. He says he has also had several respiratory infections and adds that the hematuria increased within a couple of days of the infections. Which of the following is most likely to be found in his kidney biopsy?

- (A) Increased antistreptolysin O titer
- (B) Mesangial IgG deposits
- (C) Mesangial IgA deposits
- (D) Proteinuria exceeding 3.5 gm/24 h
- (E) Subepithelial deposits
A 32-year-old man complains of recurrent hematuria since his youth. The hematuria typically occurs following upper respiratory tract infections. Vital signs are normal. Urinalysis shows hematuria and mild proteinuria. Laboratory studies disclose normal levels of BUN and creatinine. Which of the following is the most likely diagnosis?

- (A) Alport syndrome
- (B) IgA nephropathy
- (C) Hereditary nephritis
- (D) pneumonia
- (E) Postinfectious glomerulonephritis

A 20-year-old male was found to have hematuria via pre-employment testing. Also his scr (serum creatinine) was elevated at 2.5 mg/dL [n=0.7-1.5]. He has been otherwise healthy. Several members of his family, mostly males, were diagnosed with chronic renal failure by age 50 years. Which best applies to this patient:

a. recommend repeated testing at age of 50
b. eye testing may be needed, no hearing testing needed
c. only hearing testing needed
d. he has IgA nephropathy
e. eye and hearing testing may be needed
Hereditary nephritis - pathology:
- paraffin sections: normal, non-diagnostic
- immunofluorescence: negative
- electron microscopy diagnostic: lamina densa splitting & lamination, "basket weave"

A 30-year-old man with a history of smoking suddenly develops oliguria, hematuria and hemoptysis. Serologic studies reveal antibodies to the glomerular basement membrane. Which of the following pathologic changes is visible by light microscopy in this biopsy specimen?

• (A) Crescents in the urinary space
• (B) Leukocytic infiltrates in the glomeruli
• (C) Mesangial cell proliferation
• (D) Thickening of the glomerular basement membrane
• (E) Thrombi in glomerular capillaries
Rapidly progressive glomerulonephritis - pathology:
- proliferation of parietal epithelial cells with formation of crescents,
- breaks in glomerular basement membrane with blood and fibrin in urinary space

Pathogenesis variable:
- anti-glomerular basement membrane (RPGN type I)
- circulating immune complex glomerulonephritis (RPGN type II)
- pauci-immune crescentic glomerulonephritis (RPGN type III)
May be limited to kidney or systemic

A 35-year-old man with a history of smoking presents with hematuria and bloody sputum. Over the next 2 days, he develops oliguria and renal failure, after which he is placed on dialysis. A renal biopsy is stained with antihuman IgG, and the results are shown. Which of the following best described the pattern of direct immunofluorescence observed on this photomicrograph?

- [A] Discontinuous and mesangial
- [B] Finely granular along the perimesangial reflections
- [C] Linear along the glomerular basement membrane
- [D] Mesangial
- [E] Peripheral granular humps

Goodpasture Syndrome: antibody cross-reactivity with pulmonary alveolar basement membrane

Linear IgG deposits along glomerular and alveolar basement membranes

Antigen: noncollagenous protein (NC1); normally encrypted and does not elicit antibody response

Clinically: rapidly progressive glomerulonephritis with hematuria + pulmonary hemorrhage (hemoptysis) = pulmonary-renal syndrome
antibodies against antigens within glomerular basement membrane

- linear stain for IgG (antibody) = damage along the entire length
- severe damage to the GBM with multiple areas of necrosis, “sieve-like” effect with big holes big leaking large number of RBCs with GROSS hematuria

Human disease: anti-glomerular basement membrane antibody disease

RPGN type II:
- a subset of patients with immune complex glomerulonephritis
  (<1% of postinfectious glomerulonephritis, IgA nephropathy, SLE) develops exuberant damage to glomerular basement membrane with necrosis, breaks and leakage of blood and fibrin to the glomerular urinary space and proliferation of the parietal epithelial cells and formation of crescents

Except for the severity and the presence crescents, the other diagnostic pathology = the same as in the corresponding forms of glomerulonephritis not complicated by crescents:
- granular IgG C3 in postinfectious glomerulonephritis
- granular IgG C3 in lupus nephritis
- granular IgA C3 in IgA nephropathy

Treatment: underlying process
Example: lupus nephritis with crescents treated with a more aggressive immunosuppression

Rapidly progressive glomerulonephritis type II
A 16-year-old boy comes to the physician with a 3-year history of intermittent, painless hematuria without dysuria and an increased frequency of micturition. He says he has also had several respiratory infections and adds that the hematuria increased within several days of the infections. Which of the following is most likely?

- (A) Increased antistreptolysin O titer
- (B) Mutation in basement membrane protein gene
- (C) IgA mesangial deposits
- (D) Proteinuria exceeding 3.5 gm/24 h
- (E) Subepithelial humps deposits

A 68-year-old female complains of nasal obstruction, bloody nose, cough and bloody sputum. A chest x-ray displays cavitating lesions and multiple nodules within both lung fields. Urinalysis reveals 3+ hematuria and red blood cells casts. Laboratory studies show anemia and elevated serum levels of c-ANCA (antineutrophil cytoplasmic antibody). Peripheral eosinophils are not increased. A renal biopsy exhibits focal glomerular necrosis with crescents and vasculitis affecting arterioles and venules. What is the appropriate diagnosis?

- (A) EGPA (eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome)
- (B) Goodpasture syndrome
- (C) Hypersensitivity vasculitis
- (D) Postinfectious glomerulonephritis
- (E) GPA (granulomatosis with polyangiitis, microscopic angiitis & granulomatosis)

**GPA – granulomatosis with polyangiitis (aka microscopic angiitis and granulomatosis, aka Wegener granulomatosis):**
- Pulmonary vasculitis with granuloma-like morphology
- Crescentic pauci-immune glomerulonephritis
- PR3-ANCA (c-ANCA)
Pulmonary-renal syndrome:

- Anti-GBM antibody mediated
- ANCA mediated

Rapidly progressing glomerulonephritis – summary

<table>
<thead>
<tr>
<th>RPGN type I</th>
<th>Linear antibody immunofluorescence</th>
<th>Antibody against collagen in glomerular and alveolar basement membrane</th>
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<tbody>
<tr>
<td></td>
<td>Goodpasture</td>
<td>Hematuria = hemoptysis, Classically young adult male</td>
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<thead>
<tr>
<th>RPGN type II</th>
<th>Granular immune complex deposits</th>
<th>Poststreptococcal in rare patients</th>
<th>Severe immune complex deposition, 1-shot (postinfectious), Chronic immune complex disease</th>
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<tr>
<td></td>
<td>IgA in rare patients</td>
<td>Severe Lupus nephritis</td>
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<table>
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<tr>
<th>RPGN type III</th>
<th>Negative immunofluorescence</th>
<th>Type <em>Immune</em></th>
<th>Pulmonary angitis and granulomatosis (Wegener) = p-ANCA</th>
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<tr>
<td></td>
<td>GPA - Pauci-immune arthritis and granulomatosis (Wegener)</td>
<td>EGBA - Microscopic angitis-Churg Strauss</td>
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Crescentic glomerulonephritis type versus age @ diagnosis

<table>
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<tr>
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Rapidly progressing glomerulonephritis – summary

- RPGN type I: Linear antibody immunofluorescence
  - Goodpasture
  - Antibody against collagen in glomerular and alveolar basement membrane
  - Hematuria = hemoptysis
  - Classically young adult male

- RPGN type II: Granular immune complex deposits
  - Poststreptococcal in rare patients
  - IgA in rare patients
  - Severe Lupus nephritis
  - Severe immune complex deposition, 1-shot (postinfectious)
  - Chronic immune complex disease

- RPGN type III: Negative immunofluorescence
  - GPA - Pauci-immune arthritis
  - EGBA - Microscopic angitis-Churg Strauss
  - Pulmonary angitis and granulomatosis (Wegener) = p-ANCA
  - Microscopic angitis & Churg Strauss = p-ANCA
  - Eosinophils & asthma in Churg Strauss

Crescentic glomerulonephritis type versus age @ diagnosis

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A 54-year-old woman with squamous cell carcinoma of the lung develops bilateral pitting edema of the lower extremities. Laboratory studies show hyperlipidemia, hypalbuminemia, and 4+ proteinuria. Urinalysis reveals no inflammatory cells or RBCs. Renal biopsy in this patient would most likely show which of the following patterns of glomerular disease?

- (A) Berger disease (IgA nephropathy)
- (B) Goodpasture syndrome
- (C) Membranous glomerulopathy
- (D) Minimal change glomerulopathy
- (E) Nodular glomerulosclerosis

The pathogenesis of the clinical syndrome in the patient described in the previous question is the best characterized by which of the following mechanisms of disease?

- (A) Deposition of anti-glomerular basement membrane antibody
- (B) Deposition of IgA in the mesangium
- (C) Expansion of the glomerular basement membrane with PAS-positive glycoproteins
- (D) Subendothelial electron dense deposits
- (E) Subepithelial electron dense deposits
Membranous nephropathy - subepithelial electron dense deposits

Injury to visceral epithelial cells with effacement of foot processes - PROTEINURIA

with little to no inflammatory reaction "nephropathy" rather than "nephritis"

Autoimmune antibodies to renal auto-antigen or planted antigen

Association between nephrotic syndrome and malignancy - secondary membranous nephropathy - paraneoplastic syndrome

Planted cancer antigens eliciting in-situ immune complex formation

In-situ immune complex formation: antibody against glomerular antigens

Antibody binding on basal surface of podocytes leads to injury to podocytes with loss of slit diaphragms and foot process effacement which in turn lead to severe proteinuria

There is NO cellular reaction because complexing takes place in the distal zone of the filtration barrier

Evidence:
1- the terminal complement membrane attack complex (C5b-9) is detected in urine because complement deposition and activation occurs in the urinary space after the immune complex has been formed in-situ
2- experimental model
A 24-year-old woman complains of swelling of her legs and puffiness around her eyes. Her abdomen has become protuberant and she feels short of breath. Physical examination reveals generalized edema and ascites. Total serum protein is 5.2 g/dl (reference = 5.5-8.0 g/dl), and albumin is 3.1 g/dl (reference = 3.5-5.1 g/dl). Serum cholesterol is elevated at 310 mg/dl. There are 5 g of protein in a 24-hour urine collection. The urinary sediment contains many hyaline casts but no RBCs or inflammatory cells. A renal biopsy stained by direct immunofluorescence for IgG is shown. Which of the following is the most likely diagnosis?

- (A) Amyloid nephropathy
- (B) focal segmental glomerulosclerosis
- (C) membranoproliferative glomerulonephritis
- (D) Membranous glomerulopathy
- (E) Minimal change disease

Membranous nephropathy

- Young adults
- Second most common nephrotic syndrome in adults ~ 30% of primary glomerular diseases, children ~ 5%
- Podocyte injury via immune mechanism: granular subepithelial deposits, GBM thickening, loss of foot processes
- No complement drop (chronic, relatively slowly progressing)
- Primary: autoimmune response against aPLA2R, THSD7A, NFB renal antigens (aka “primary”)
- Secondary: hepatitis, lupus, diseases, malignancies, SLE
- Edema, proteinuria, loss of anti-thrombin III, infections...
- In elderly can cause episode of cardiac failure...
- Secondary: hyperlipidemia: with increase in total cholesterol and low density lipoproteins (LDL) cholesterols, accelerated atherogenesis
- Progressive disease... difficult to treat, does NATF respond well to steroids...

PLA2R = phospholipase A2 receptor
Immunofluorescence patterns

Granular along basement membrane
THINK: MEMBRANOUS

Linear along basement membrane
THINK: ANTI-GLomerular BASEMENT MEMBRANE GLOMERULONEPHRITIS
Aka type I RPGN (rapidly progressive glomerulonephritis)

“lumpy-bumpy” on immunofluorescence
“hump-like” by electron microscopy
think postinfectious glomerulonephritis

Mesangial
THINK: IgA nephropathy

Deposits
- texture: linear, granular (finely, lumpy-bumpy)
- location: mesangial, basement membrane, mixed
A 3 yo boy presented with periorbital and generalized edema. He has been otherwise healthy. His urinalysis showed 2.5 gm/24 hr proteinuria, no RBCs or inflammatory cells. His pediatrician is most likely to do the following:

A. Order a kidney biopsy  
B. Recommend a supportive treatment  
C. Prescribe treatment with steroids  
D. biopsy will show sub-epithelial immune complex deposits  
E. Will warn the parents that there is a high likelihood of progression to renal failure

For the patient described in the previous question, electron microscopy of a kidney tissue prior to treatment would most likely demonstrate which of the following abnormalities?

• (A) Duplication of capillary basement membranes  
• (B) Electron-dense immune deposits in the capillary basement membrane  
• (C) Electron-dense immune deposits in the mesangium  
• (D) Fusion of podocyte foot processes  
• (E) splitting of the lamina densa
Which of the following is the most likely outcome of diseases in the patient described in the previous question?

- (A) slowly progressing renal failure
- (B) development of nephritic syndrome
- (C) transition into recurrent hematuria
- (D) recovery without serious consequences
- (E) transition into acute renal failure

A 10 yo boy presented with a nephrotic syndrome. He has a 5 year history of relapsing nephrotic syndrome, initially responding to steroids, subsequently became steroid-dependent and steroid-resistant. His serum creatinine is raising. Which would be the most appropriate choice:

A. He will be treated without a biopsy
B. He will be scheduled for a biopsy
C. He will require hearing testing
D. His biopsy will show membranous nephropathy
E. His biopsy will show minimal change disease

A 30-year-old man with a history of drug addiction presents with a 6-month history of progressive swelling in his ankles and abdomen. Urinalysis shows heavy proteinuria (>4g/24 hours) but no evidence of inflammatory cells or RBCs. Laboratory studies reveal hyperlipidemia and hypoproteinemia. Serum creatinine level is normal. The blood test for ANCA is negative. The patient responds well to treatment with corticosteroids, but edema and proteinuria recur the following year. The steroid treatment is repeated with the same results. Upon the third recurrence of edema and proteinuria, the patient becomes steroid-resistant. A renal biopsy is shown. Which of the following is the most likely diagnosis for this patient's glomerulopathy?

- (A) Acute glomerulonephritis
- (B) Diabetes
- (C) Crescentic glomerulonephritis
- (D) Diffuse proliferative glomerulonephritis
- (E) focal and segmental glomerulosclerosis
FSGS

- Segmental obliteration of glomerular capillaries – collapse of capillary loops, increase in mesangial matrix, adhesions with Bowman’s capsule
- Initially only some segments of some glomeruli involved (i.e. focal & segmental), sampling of juxtamedullary glomeruli
- Progressively more glomeruli involved, progression to global sclerosis = tubular atrophy + interstitial fibrosis
- Uninvolved glomeruli = normal by histology
- By electron microscopy: All glomeruli show effacement of the epithelial cell foot processes & loss of slit diaphragm
- FSGS = the most frequent morphologic manifestation of glomerular injury seen in human biopsy material, continues to increase, adults 35%, children 10%
- Hispanic, AA patients
- Clinical: nephrotic syndrome, higher incidence of hematuria, reduced GFR, HTN, non-selective proteinuria more often
- Poor response to steroids, progression to renal failure
- Shared pathogenic pathway – different etiologies leading to similar type of injury, primary versus secondary

Nephrotic syndrome = clinical syndrome

- Proteinuria >3.0/3.5 gm/day
- Children – body surface
- Hypoalbuminemia, <3 gms/dl
- Edema
- Hyperlipidemia & lipuria – lipid droplets/casts in urine!
- Antithrombin III – thrombotic & thromboembolic complications
- Primary versus secondary

- DDx
  - Primary: minimal change, FSGS, membranous nephropathy
  - Secondary: diabetes, lupus (10%), amyloidosis

Minimal change disease and FSGS:

- one disease at opposite ends of a spectrum
- OR
two different diseases

?
DIABETES:
nonenzymatic glycosylation
of vascular basement membrane

DIABETES
nonenzymatic glycosylation of vascular basement membrane
efferent arteriole > affected efferent
high glomerular filtration pressure
Hyperfiltration
microalbuminuria
nephrotic syndrome
ACE inhibitors – to slow progression

Amyloidosis = TISSUE DIAGNOSIS
H&E (left upper) = “homogeneous”
Congo red (right upper) viewed under polarized light
(right upper) = “apple green” birefringence
Left - by electron microscopy = fibrillar
Amyloid can be detected in subcutaneous fat typically from periumbilical abdomen - Screening as well as diagnosis!

Amyloidosis in plasma cell dyscrasia/multiple myeloma
From: Amyloid and related disorders in Surgical Pathology, Picken et al, Springer 2015

70%
Nephrotic syndrome

Renal Amyloidoses
AL: ~85%
Non-AL: ~15%

- Derived from immunoglobulin light chain
- Plasma cells with proliferation
- Anti-plasma cell chemotherapy...

AA
- Derived from SA
- Chronic inflammatory process
- Anti-inflammatory

-AA: 1 has specific therapy

Hereditary:
- Liver transplantation
- Chaperone (transthyretin amyloidosis)
- Genetic testing
Primary abnormality: proteinuria, secondary: hypoalbuminemia, edema

Pathogenesis – podocyte injury:
- immune complex (membranous)
- non-immune complex (minimal change disease, FSGS)

Membranous nephropathy:
- autoimmune, intrinsic renal or planted antigen
- resistant to steroids, variable outcome

Minimal Change Disease:
- pathogenesis?
- most common nephrotic syndrome in children, responds to steroids, excellent prognosis

FSGS:
- idiopathic (pathogenesis?) or secondary (diverse), most common biopsy diagnosis in adults, resistant to therapy, progression to end stage kidney disease

Secondary nephrotic syndrome:
- diabetes, 10% SLE, amyloidosis

Nephrotic syndrome - summary

<table>
<thead>
<tr>
<th>PRIMARY GLOMERULAR DISEASES</th>
<th>CHILDREN %</th>
<th>ADULTS %</th>
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</thead>
<tbody>
<tr>
<td>membranous</td>
<td>~5</td>
<td>30</td>
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<tr>
<td>Minimal change disease</td>
<td>65</td>
<td>10</td>
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<tr>
<td>FSGS</td>
<td>10</td>
<td>35</td>
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<td>MPGN</td>
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<td>10</td>
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<td>other</td>
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</table>

Nephrotic syndrome - prevalence

<table>
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<tr>
<th>PRIMARY GLOMERULAR DISEASES</th>
<th>CHILDREN %</th>
<th>ADULTS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary glomerular diseases</td>
<td>95</td>
<td>60</td>
</tr>
<tr>
<td>Secondary to systemic disease</td>
<td>5</td>
<td>40</td>
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A 32 yo computer programmer presents with generalized edema and unintentional weight gain. In general he has been healthy. Only recently he complained of a lower back pain during a period requiring long hours at the computer. However, the pain was relieved with some over the counter meds. His urinalysis shows 3+ protein, his serum creatinine is 5.0 mg/dl (n=0.7-1.5). You are suspecting that …

a. His biopsy will show crescents
b. His biopsy will look normal by light microscopy
c. His biopsy will show subepithelial deposits
d. He most likely has interstitial nephritis and minimal change disease
e. He has postinfectious glomerulonephritis
Acute drug-induced interstitial nephritis

- Rash – 25%
- Acute renal failure – 50%, older patients
- Treatment: drug withdrawal
- An IgE- and T cell-mediated immune reaction to a drug, characterized by interstitial inflammation, often with abundant eosinophils and edema

synthetic antibiotics, diuretics, NSAIDs, miscellaneous

NSAIDs:
- acute hemodynamic (inhibition of prostaglandin synthesis)
- acute hypersensitivity interstitial nephritis
- Interstitial Nephritis + Minimal Change Disease (nephrotic syndrome + renal failure)

Chinese herb nephropathy: Aristolochic acid
- Interstitial fibrosis with relative paucity of leukocytes
- Increased incidence of urothelial carcinoma

A 26 yo female is discovered to have elevated serum creatinine level. She has been healthy, well nourished. In fact she has been trying to shed some weight but with no great success...

a. You suspect cancer as a cause of her renal failure
b. You ask her about all her prescription medications
c. She probably has reflux nephropathy
d. She has acute pyelonephritis
e. You ask her about her about herbal preparations
TIN: tubulo-interstitial nephritis
Inflammatory disease primarily involving the renal tubules and interstitium
1) infectious: acute or chronic pyelonephritis (UTI), reflux nephropathy, etc
2) drugs induced interstitial nephritis: IgE and T-cell mediated immune reaction to a drug (antibiotics, NSAIDs)
3) metabolic diseases (urate, oxalate, hypercalcemia), multiple myeloma (light chain cast nephropathy)

In general, tubules and interstitium are frequently involved together, either from the beginning or subsequently, with disease progression. Thus, in metabolic diseases in particular, initially, mainly tubules are affected (acute uric acid nephropathy, light chain cast nephropathy). However, with progression of the disease process there is also involvement of the interstitium.

A 7 yo boy developed malaise followed by bloody diarrhea. He was previously healthy with a good appetite and he really enjoyed his hamburger, which his father bought him from a street stand... His mother noticed that his urine turned red and was also diminished in volume... His kidney biopsy will show:

- Subepithelial hump-like deposits
- IgA deposits in glomeruli
- Crescents in >50% of glomeruli
- IgA deposits in glomeruli and skin capillaries
- Thrombi in glomerular capillaries

Fibrin thrombi in glomeruli and small vessels
Injury to endothelial cells with apoptosis, platelet activation
His clinical studies most likely will show:

a. renal failure,
b. thrombocytopenia,
c. schistocytes (fragmented red blood cells) in peripheral blood smears
d. all of the above (a-c)
e. crescents in the glomeruli

Thrombotic microangiopathies

Clinical various syndromes with overlap
Morphology similar: widespread thrombosis in the microcirculation
microangiopathic hemolytic anemia, thrombocytopenia, renal failure (some)

Hemolytic-uremic syndrome (HUS):
childhood HUS – endothelial injury by STEC (Shiga toxin producing E. coli)
atypical HUS – mutation, rare
secondary HUS = HUS-like, drug toxicity, malignant HTN, scleroderma

Thrombotic thrombocytopenic purpura (TTP):
- acquired autoantibodies
- inherited (familial) defects in von Willebrand factor with thrombosis & platelets consumption

A 63-year-old man was diagnosed with urothelial carcinoma. Treatment consisted of neoadjuvant chemotherapy with Gemcitabine/Paclitaxel, followed by radical cystoprostatectomy. During his fourth dose of neoadjuvant chemotherapy his creatinine increased to 6.25 mg/dL from a baseline of 1.6 mg/dL; proteinuria, 0–3 red blood cells (RBCs) on urinalysis, normal complement levels, and negative serologies [anti–nuclear antibody (ANA), anti–double stranded (ds) DNA, ANCA]. He had thrombocytopenia and his peripheral blood smear showed abnormal red blood cell morphology (schistocytes, spherocytes, segmented RBCs).

Which is the main pathogenetic mechanism of his kidney failure?

A. ANCA (anti-neutrophil cytoplasmic antibodies)
B. Endothelial injury
C. Malignant hypertension
D. Immune complex deposits
E. Shiga toxin-producing E. coli exposure
Drug-induced TMA [DITMA] - 2 mechanisms
- immune-mediated reactions and
- dose- or duration-related toxic reactions

A 73 year old male presented with acute on chronic back pain, in the context of metastatic castrate-resistant prostate cancer with known pulmonary and skeletal metastases. He was day 3 into his first cycle of cabazitaxel. Within 24 hours of admission, he acutely deteriorated with progressive drowsiness and the development of an acute kidney injury. During this period, he developed acute thrombocytopenia and hemolytic anemia. He was subsequently diagnosed with an atypical hemolytic uremic syndrome. NO DIARRHEA

Many patients with DITMA are found to have an underlying genetic complement defect

atypical HUS [aHUS] = complement mediated TMA
Unregulated/excessive activation of the alternative complement pathway leading to complement-mediated injury: transformation from low-grade physiologic activity (“tick-over”) to unrestrained hyperactivity
- triggers: excessive complement activation after minor vascular injuries
- acquired autoantibodies against complement components
- inherited abnormalities of complement regulatory proteins

Human diseases: glomerular = dense deposit disease/C3 glomerulonephritis (lecture II)
Systemic: aHUS

TTP – platelet aggregation due to von Willebrand factor-cleaving protease (ADAMTS13)
Deficiency leading to formation of unusually large von Willebrand factor multimers leading to excessive thrombosis
- absence/deficiency of ADAMTS13, the von Willebrand factor cleaving metalloprotease
- acquired due to autoimmune antibody to ADAMTS13, or
- hereditary
- massive platelet thrombi

Complement system
Components (numbered C1-C9) present in plasma in inactive forms, each activated by proteolysis to acquire own proteolytic activity, thus setting up enzymatic cascade

Classical
- trigger: Ab+Ag

Mannose-binding lectin (MBL)
- trigger: lectin to mannose of bacteria

Both classical & lectin pathway begin with engagement of early complement components C1(C2, C4, C2a) MASP (Mannose-binding lectin-Associated Serine Protease), very similar to C1 molecules of the classical complement pathway
Glomerular diseases caused by complement activation in the absence of antibody:

Unregulated/excessive activation of the alternative complement pathway leading to complement-mediated injury – transformation from low-grade physiologic activity (“tick-over”) to uncontrolled hyperactivity

Triggers: excessive complement activation after minor vascular injuries
- acquired autoantibodies against complement components
- inherited abnormalities of complement regulatory proteins

Human diseases
Glomerular: dense deposit disease/C3 glomerulonephritis (lecture II)
Systemic (with significant renal manifestations): thrombotic microangiopathies (lecture III)

A 6-year-old boy presented with upper respiratory tract infection. After two days, he developed an erythematous, nonpruritic rash that progressed proximally from both feet to thighs and upper extremities and subsequently abdominal pain associated with melena.

On physical examination, there was pharyngeal erythema, and nontender, nonblanching purpuric rash involving both upper and lower extremities with a mild pedal edema.

Laboratory tests showed mild leukocytosis (WBC: 10,900/microL) and a macroscopic hematuria on urinalysis; Hb: 13.5 g/dL [N: 11.5-15.0]; Hct: 41.2%; [N:35.0-45.0]; serum Creatinine: 0.9 mg/dL[N: 0.5-1.0mg/dL]; stool for occult blood: positive

His kidney biopsy is likely to show:
A. Thrombi in glomeruli
B. Basket weave on electron microscopy
C. Postinfectious glomerulonephritis with “humps”
D. Thrombi in glomeruli associated with positivity for IgA
E. Mesangial IgA deposits

IgA nephropathy with extra-renal symptoms (systemic IgA) = Henoch-Schönlein purpura (HSP):

- mainly children, 3-8 yo
- kidney, skin, gastrointestinal, joints
- hematuria, purpuric skin lesions, abdominal pain & gastrointestinal bleeding, arthralgia
- small vessel vasculitis in affected sites
An infant is diagnosed with an enlarged left kidney – shown. Most likely:

a. This lesion will respond to chemotherapy
b. This is a premalignant lesion
c. This is a congenital disorder and genetic testing is diagnostic
d. Kidney parenchyma shows cysts and immature tubules and cartilage
e. Kidney sections show undifferentiated malignant blastema, tubules and stroma
Disorganized parenchyma distorted by cysts of various sizes lined by flattened to cuboidal epithelium. Immature mesenchyme, cartilage (10-20%), immature collecting ducts with fibromuscular collars.

Kidneys and lungs

- Agenesis, bilateral dysplasia
- Oligohydramnios (decreased amniotic fluid)
- Hypoplastic lungs
- Potter sequence...
Bilateral renal agenesis: 
Potter sequence (aka Potter’s syndrome): 
Lung hypoplasia

GLIHYDRAMNOS

Flat face with low set ears, extremities developmental defects

INCOMPATIBLE WITH LIFE

### Cystic diseases

<table>
<thead>
<tr>
<th></th>
<th>FEMALE DYSPLASIA</th>
<th>CHRONIC ADPKD</th>
<th>ADULT ADPKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1:1000-2000</td>
<td>1:20,000</td>
<td>1:500-1,000</td>
</tr>
<tr>
<td>Bilateral</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Segmental</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reniform shape</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ureter abnormalities</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver abnormalities</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other abnormalities</td>
<td>Potter’s</td>
<td>berry aneurysm</td>
<td>mitral valve prolapse</td>
</tr>
</tbody>
</table>

ADPKD: intracranial aneurysm “berry aneurysm” = the most serious possible complication of PKD 3–7%
Aneurysm = bulging blood vessel due to weakening of the blood vessel wall
Rupture with intracranial bleeding
A 2 yo boy is brought to pediatrician because his mother palpated “a bulging mass” while bathing him. What best applies to this case?

a. This tumor most likely is composed of clear cells
b. This tumor typically shows loss of short arm of chromosome 3
c. This tumor is most likely highly chemoresistant
d. This tumor is chemosensitive
e. Tumor morphology will show cysts, immature tubules and cartilage

Wilms’ tumor triphasic: malignant undifferentiated blastema (undifferentiated small round blue cells), abortive tubules and fibroblast-like stroma

Cystic dysplasia versus Wilms tumor

<table>
<thead>
<tr>
<th>Feature</th>
<th>Wilms tumor</th>
<th>Cystic dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformation</td>
<td>Increased risk</td>
<td>100%</td>
</tr>
<tr>
<td>Histogenesis</td>
<td>Attempts to recapitulate nephrogenesis</td>
<td>Aberrant nephrogenic differentiation</td>
</tr>
<tr>
<td>Histology</td>
<td>Undifferentiated blastema, “embryonal”, “small blue cells”, malignant</td>
<td>Immature, persistent abnormal structures benign</td>
</tr>
<tr>
<td>Metastatic potential</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cysts</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetics</td>
<td>Mutations, somatic, germ line some sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5-10%</td>
<td>Potter’s syndrome</td>
</tr>
</tbody>
</table>
Wilms’ tumor

- Pediatric, most common
- Children <10 yo; 2-5 yo
  - undifferentiated blastema (undifferentiated small round blue cells)
  - abortive glomeruli-tubules
  - spindle cell stroma
- Chemosensitive
- Clinical presentation: mass, syndromic

Risk of WT (Wilms tumor) increased with groups of congenital malformations associated with distinct chromosomal loci (10% of WT):

Syndromic tumors -- 10%
1. WAGR syndrome: WT, aniridia, genital anomalies, and mental retardation; WT in ca 33%
2. Denys-Drash syndrome: gonadal dysgenesis, early onset of nephropathy
3. Beckwith-Wiedemann syndrome: an overgrowth disorder usually present at birth, increased risk of childhood cancer and certain congenital features: macroglossia (large tongue), macrosomia (above average birth weight and length), microcephaly, midline abdominal wall defects
Wilms Tumor and hepatoblastoma

Wilms Tumor
Cystic dysplasia
Wilms tumor biology:
- relationship between malformations and neoplasia
- Histologic similarities between organogenesis and oncogenesis
- The two-hit theory of recessive tumor suppressor genes
- The role of premalignant lesions
- Treatment with 85% cure rate

Cancers of infancy and childhood versus cancers in adulthood:
1. Incidence and type of tumor
2. Relatively close relationship between abnormal development (organogenesis) and tumor induction (oncogenesis)
3. Prevalence of underlying familial or genetic alterations
4. Tendency of fetal or neonatal malignancies to regress or cytodifferentiate
5. Improved survival or cure of many childhood tumors

HISTOLOGY:
- Primitive (embryonal) rather pleomorphic-anaplastic
- Sheets of "small blue cells"
- Frequently features of organogenesis specific to the site of tumor origin ("blastoma")
- "Round blue cell tumors"

During a radiologic workup for gall bladder stones, a 65 yo male was found to have a 5 cm mass in his right kidney.

a. This is most likely oncocytoma
b. This is a benign tumor
c. Chemotherapy is effective
d. Surgery will be scheduled
e. Tumor's morphology shows abortive glomeruli/tubules and stroma
Clear cell RCC

- 70-80%
- Clear cytoplasm
- 3p, somatic mutation/hypermethylation induced inactivation of the VHL gene (tumor suppressor gene)
- Loss of VHL gene results in accumulation of the transcription factor HIF-1α and over-expression of HIF-1α target genes, which facilitate cellular adaptation to tissue hypoxia
- VHL gene in development of both sporadic and familial clear cell RCC

GENES TO KNOW:

- APKD1, APKD2 - adult polycystic kidney disease
- TSC 1 and TSC2 - tuberous sclerosis complex, benign tumors, kidney tumor = angiomylipoma
- VHL (3p) - von Hippel Lindau, renal cell carcinoma, clear cell type
- WT1 - Wilms Tumor

A retired dentist developed a sudden onset of a severe flank pain radiating to the back with nausea and vomiting. Urinalysis showed 10–15 red blood cells per high power field. He denied any history of alcohol or recreational drug use. His past medical history includes type 2 diabetes and hypertension. What should be considered in the differential diagnosis?

a. Nephrolithiasis
b. Acute tubulointerstitial nephritis
c. Acute tubular injury
d. Acute pyelonephritis
Patient described in the previous question passed spontaneously a stone. What would be the best choice?

a. Send stone to pathology for chemical analysis
b. Send stone to pathology for photographic analysis
c. Most likely atheromatous stone
d. Give back stone to patient for safe keeping
e. Discard the stone if patient is not interested in keeping it

Questions?
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Thank you
Good luck!