Renal Pathology
Lecture III

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Outline

• Glomerular involvement in systemic diseases
• Thrombotic microangiopathies
• Summary


• Introduction to glomerular diseases recorded
• Urinary tract histology – part II (recorded)

Goals:

1. Explain glomerular pathology in the context of systemic diseases
2. Explain thrombotic microangiopathies
Objectives:
1. Name systemic diseases associated with significant glomerular involvement
2. Identify differences between nephrotic syndrome in primary glomerular diseases versus nephrotic syndrome associated with systemic diseases
3. Contrast and compare glomerular involvement in different systemic diseases
4. Explain the general pathomechanism underlying diabetic nephropathy and how it correlates with renal and systemic symptoms
5. Explain how to diagnose and treat amyloidosis?
6. Explain the role of kidney biopsy in management of patients with systemic lupus erythematosus
7. Explain the different pathomechanisms of thrombotic microangiopathies
8. Contrast and compare typical versus atypical hemolytic uremic syndrome
9. Contrast and compare pathomechanisms of HSP (Henoch-Schönlein purpura) versus HUS (hemolytic-uremic syndrome)

Lecture III

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Disease</th>
<th>Pathogenesis</th>
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<tbody>
<tr>
<td>Acute nephritic syndrome</td>
<td>Recurrent hematuria</td>
<td>IgA nephropathy</td>
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<td>IgA immune complex circulating</td>
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<td>Type I</td>
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<td>Membranous nephropathy</td>
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<td>Minimal change disease</td>
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<td>Focal &amp; segmental glomerular sclerosis</td>
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Nephrotic syndrome

<table>
<thead>
<tr>
<th>Children %</th>
<th>Adults %</th>
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<tr>
<td>Primary glomerular diseases</td>
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<tr>
<td>Secondary to systemic disease</td>
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</table>
Kidney involvement in systemic diseases
- Diabetic nephropathy
- Amyloidosis
- SLE – Systemic Lupus Erythematosus
- Thrombotic microangiopathies

Diabetic nephropathy
Diabetic nephropathy is the most common cause for ESRD (End Stage Renal Disease) in the USA
see also separate lecture

New Cases of Kidney Failure by Primary Cause
- Diabetes, 44%
- HTN, 38.4%
- GN, 13.5%
- Other, 13.7%

Kidney disease = a leading cause of mortality in patients with diabetes

- Diabetes is pandemic
- Globally, diabetes affects up to half a billion people
- In the US, one in 10 people have diabetes
- Americans born in the year 2000, have a 25% - 45% lifetime risk of diabetes

A person diagnosed with diabetes mellitus at age 50 years old dies 6 years earlier than a person without diabetes.

Better understanding of diabetic kidney disease essential to decrease:
- the number of ESRD (end stage renal disease) patients
- diabetes-associated mortality

Diabetic nephropathy

Clinical syndrome characterized by:
- proteinuria,
- progressive decline in GFR (glomerular filtration rate), and
- hypertension

Glomerular lesions
Atherosclerosis & arteriosclerosis
Pyelonephritis acute & chronic

Diabetic Glomerulosclerosis

Diabetes:
nonenzymatic glycosylation of the vascular basement membrane resulting in hyaline arteriosclerosis
DIABETES nonenzymatic glycosylation of vascular basement membrane

ACE (angiotensin-converting enzyme) inhibitors – to slow progression

Diabetic glomerulosclerosis = progressive thickening of glomerular basement membrane and increase in mesangial matrix eventually forming KW (Kimmelstiel-Wilson) nodules

Pathologic-based staging of DKD:

Class I = glomerular basement membrane thickening
Class II = > 25% expansion of the mesangial space, class III = nodular sclerosis, class IV = global sclerosis

Diabetic glomerulosclerosis underlies the clinical syndrome of diabetic nephropathy (proteinuria, progressive decline in GFR, and hypertension)

DIABETIC NEPHROPATHY:

overt nephropathy correlates with retinopathy

Kidney biopsy NOT done if course typical
> 5 years since onset of diabetes
Amyloidoses
Abnormal protein folding diseases
Robbins pages 182-187, separate recording

Amyloid: what is it and why it forms
Name = misnomer: “amyloid” means starch but deposits of amyloid contain predominantly protein
Amyloidoses = amyloid diseases

Fibrillogenesis
- α helix
- β pleated sheet
- Conformational shift to β-pleated sheet 2nd structure

Amyloidoses – protein folding disorders
- hydrophobic, insoluble
- non-functional
- resistant to degradation
- sticky
- extracellular

All amyloid deposits have same morphology:
- not beta-pleated sheet
- Congo red positive with green birefringence under polarized light
Amyloidoses – protein folding disorders

**AMYLOIDOSES:**
1. >32 protein types, many more variants
2. Localized, systemic or systemic and/or localized
3. Most prevalent versus rare versus exceedingly rare
4. Specific organs, i.e. cerebral, endocrine organs...
5. Treatable versus not-treatable, genetics...
6. Most common:
   - **AL** (amyloid light chain)
   - **AA** (amyloid A protein)
   - **Aβ** (amyloid β protein)
   - **ATTR** (amyloid derived from transthyretin)... hereditary

Cerebral Amyloidosis: β-amyloid protein (Aβ) Alzheimer’s disease (AD)
Systemic amyloidosis - 1

1. Typical clinical presentation:
   - multisystem
   - nephrotic syndrome, cardiac, peripheral nerve
   - beware of external signs - relatively rare but can be very helpful: periorbital purpura, submandibular swelling, shoulder pad, nail lesions

2. Epidemiology:
   - rare, underdiagnosed

3. Etiology/pathogenesis: protein folding disorders - β pleated sheet
   - plasma cell dyscrasia, AL (light chain derived)
   - underlying chronic inflammation, AA amyloidosis
   - genetic predisposition: mutation in the protein (transthyretin, other...)
   - other/unknown...

Separate recording....

AL – amyloid Light chain
derived from immunoglobulin light chain

Clonal proliferation of plasma cells synthesizing abnormal immunoglobulin
- plasma cell dyscrasia (small clone, low tumor burden ["small dangerous clones"] aka "primary", ca 85% of AL
- multiple myeloma (overt plasma cell malignancy) 5-15%
- derived from immunoglobulin λ or κ light chain, λ > κ
- intrinsic properties of the light chain

AL = amyloidosis derived from immunoglobulin light chain:
- most prevalent type of systemic amyloidosis in the developed world (85%)
- 2,000 – 3,000 new cases each year in the US
- clonal plasma cell proliferation in the bone marrow
- monoclonal protein in blood and deposits are systemic

Aggressive chemotherapy with stem cell rescue
**Reactive systemic amyloidosis – AA amyloidosis**
- derived from SAA protein (serum amyloid A protein)
- secondary to associated inflammatory condition
- long standing inflammation leads to a sustained elevation of SAA levels
- rheumatoid arthritis
- inflammatory bowel disease (Crohn diseases)
- heroin abusers, “skin-poppers”
- deposits mainly in kidneys, liver, spleen

**Familial AA**
Familial Mediterranean fever (FMF) – “polyserositis”
FMF is an autoinflammatory disease caused by mutations in MEFV gene, which encodes pyrin which is involved in the regulation of innate immunity
episodic fever, arthritis, pleuritic, peritonitis
FMF usually occurs in people of Mediterranean origin: Sephardic Jews, Armenians, Arabs, Greeks, Turks, Italians
Colchicine for prevention of attacks of fever

**Pathogenesis of amyloidosis**

<table>
<thead>
<tr>
<th>INCREASED PRODUCTION OF PRECURSOR</th>
<th>NORMAL PRODUCTION OF MUTANT</th>
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<tr>
<td>Acquired mutations leading to Intrinsic instability</td>
<td>Chronic inflammation</td>
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<td>Monoclonal plasma cells</td>
<td>Macrophage activation</td>
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<tr>
<td>Immunoglobulin light chain</td>
<td>Incomplete proteolysis</td>
</tr>
<tr>
<td>incomplete proteolysis</td>
<td>aggregation</td>
</tr>
<tr>
<td>Al. amyloidosis</td>
<td>AA amyloidosis</td>
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**Amyloidosis derived from transthyretin - ATTR**

ATTR mutant: polynuropathy, cardiac
V122 – 4% African Americans

ATTR wild type: even normal transthyretin is prone to misfolding (β-sheet age)
- mainly cardiac, aka “Cardiac Alzheimer’s”
- carpal tunnel
Systemic amyloidosis - 2

4. Pathology:
- Kidney involvement in 70%, cardiac, peripheral nerves
5. Laboratory tests:
- Tissue diagnosis: biopsy of an affected organ or a "surrogate" site

Differential diagnosis of proteinuria/nephrotic syndrome in adults:
1. Focal and Segmental Glomerular Sclerosis/Minimal change disease
2. Membranous nephropathy
3. Diabetes
4. Amyloidosis!!!

Cardiac amyloidosis – heart failure, arrhythmia, long list of differential
Pain recurrence – sensory and autonomic disturbances, long list of differential
Amyloid deposits are unevenly distributed in tissues

"Surrogate" site biopsy

Amyloid can be detected in subcutaneous fat
Fat biopsy typically from periumbilical abdomen for diagnosis and screening of patients at risk (i.e., known plasma cell dyscrasia)
Systemic amyloidosis - 3

6. Prognosis:
   - amyloid type and stage dependent, delay in diagnosis...
   - amyloid typing: immuno stains & proteomics

7. Treatment:
   - amyloid protein type dependent
   - aggressive chemotherapy with stem cell rescue
   - treatment of underlying inflammation,
   - liver transplantation, pharmacologic clinical trials stabilizers, gene silencing...

Renal Amyloidoses

AL: ~85%
- derived from monoclonal light chain
- pathogenesis: clonal plasma cell proliferation
- pathology: systemic, kidney, heart...
- treatment: anti-plasma cell therapies...

Non-AL: ~15%
- derived from SAA (serum amyloid-associated)
- pathogenesis: chronic inflammation, synovial & serosal
- pathology: systemic, kidney, liver, gastrointestinal
- treatment: anti-inflammatory

hereditary: avoid misdiagnosis as AL
- derived from various mutated proteins; transthyretin, other peripheral nerves, spinal
- kidney: chronic inflammation, renal failure
- clinical trial
- genetic testing

SLE – Systemic Lupus Erythematosus, separate labs/lectures

Kidney biopsy:
- to determine the severity of kidney involvement and potential for reversibility of lesions
- to determine treatment options
- for prognosis
### Systemic lupus erythematosus - 1

1. **Typical clinical presentation:**
   - multisystem
   - edema, skin lesions, arthritis
2. **Epidemiology:**
   - primarily young women
3. **Etiology/pathogenesis:**
   - autoimmune: anti DNA, erythrocytes, platelets
   - genetic predisposition: familial, HLA association, other genes
   - environmental triggers

*Separate lectures/small groups etc….*

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### LUPUS NEPHRITIS

Glomerular involvement ranging from mild to severe proliferative glomerulonephritis (class III/IV) with necrosis and crescents and clinically with nephritic syndrome, some may be rapidly progressive.

About 10% of patients develop lupus membranous nephropathy (class V) with nephrotic syndrome.

![Image of kidney section](image)

**A – E**  
Class IV lupus nephritis

Abundant immune complex deposits
Systemic lupus erythematosus - 2

4. Pathology:
   - kidney involvement in 60-70% by light microscopy
   - different patterns (class I-V)
   - abundant immune complex deposits
5. Laboratory tests:
   - autoantibodies: ANA’s, anti-Sm, anti-dsDNA
6. Prognosis:
   - kidney involvement significant
7. Treatment:
   - variable level of immunosuppression largely dependent on activity of kidney involvement

Separate lectures, small groups

Vascular diseases:
Benign nephrosclerosis (separate lecture)
Hypertension (separate lecture)
Atherosclerosis, atheroemboli (separate lecture)
Vasculitis (separate lecture)
Thrombotic microangiopathies

Thrombotic microangiopathies TMA
- umbrella term for various clinical syndromes with:
  - thrombosis (widespread platelet-rich thrombi) in the microcirculation
  - thrombocytopenia (consumption of platelets)
  - microangiopathic hemolytic anemia (narrowing of blood vessels by thrombi)

Clinical:
  • microangiopathic hemolytic anemia (MAHA)
  • thrombocytopenia
  • renal failure
1. Typical clinical presentation:
   - microangiopathic hemolytic anemia (MAHA), thrombocytopenia, renal failure (some)
   - various clinical syndromes with clinical overlap
   - diarrhea in typical HUS [hemolytic uremic syndrome], no diarrhea in atypical HUS, TTP [thrombotic thrombocytopenic purpura]

2. Epidemiology:
   - children
   - adults

3. Etiology/pathogenesis: endothelial injury with platelet activation & aggregation
   primary TMA:
   - typical hemolytic-uremic syndrome [HUS]
   - atypical HUS (aHUS) - uncontrolled complement activation
   - thrombotic thrombocytopenic purpura (TTP), platelet aggregation due to ADAMTS13 deficiency
   secondary TMA:
   - malignant hypertension, scleroderma
   - drug toxicities (chemotherapy), antiphospholipid antibodies (SLE), pregnancy, contraceptives...

Infection associated TMA
STEC-HUS (Shiga toxin E. coli)
aka “typical HUS”, 75%

<table>
<thead>
<tr>
<th>atypical HUS (complement-mediated HUS)</th>
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<tr>
<td>- acquired or hereditary complement</td>
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<tr>
<td>abnormalities with uncontrolled</td>
</tr>
<tr>
<td>activation of complement</td>
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</tbody>
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TTP
- acquired or inherited deficiencies in ADAMTS13

Secondary TMA
- malignant HTN, scleroderma
- Drug-mediated TMAs (DITMA)

Thrombotic microangiopathy - pathology

- thrombocytopenia - excessive platelet consumption
- microangiopathic hemolytic anemia due to mechanical injury (shearing) of red cells as they pass through vascular channels narrowed by thrombi

Fibrin thrombi in glomeruli and small vessels; endothelial injury
typical HUS:
- associated with infection with E. coli producing Shiga toxin (STEC-HUS)
- one of the main causes of acute kidney injury in children

Clinical studies:
- recent diarrhea, melena (blood in stool)
- renal failure
- thrombocytopenia
- schistocytes (fragmented red blood cells) in peripheral blood smears

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/decrease of ADAMTS13, the von Willebrand factor cleaving metalloprotease
- acquired due to autoimmune antibody to ADAMTS13, or
- hereditary
- massive platelet thrombi

Thrombotic microangiopathies – 2

4. Pathology:
- widespread thrombosis in small vessels
- similar morphology despite differences in pathogenesis

5. Laboratory tests:
- thrombocytopenia
- schistocytes (fragmented red blood cells) in peripheral blood smears
- ADAMTS13 (TTP)

6. Prognosis:
- serious

7. Treatment:
- supportive
- underlying disease
- Eculizumab antibodies against complement (C5) in atypical HUS
- plasma exchange to replace ADAMTS13
Drug-induced TMA [DITMA] - 2 mechanisms

- Immune-mediated reactions
- 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.

Malignant hypertension and TMA:

- Arteries and arterioles with fibrinoid necrosis narrowing the lumen
- Microangiopathic hemolytic anemia due to mechanical injury (shearing)
- Renal function and MAHA usually recover with management of blood pressure

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:

a. Subepithelial hump-like deposits
b. IgA deposits in glomeruli
c. Crescents in >50% of glomeruli
d. IgA deposits in glomeruli and skin capillaries
e. Thrombi in glomerular capillaries
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 IgA vasculitis in affected sites

Review abdominal pain and kidney syndromes in children:
HUS versus HSP

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<th>HSP (IgA vasculitis)</th>
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<td>Preceding infection – upper respiratory</td>
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<td>Renal failure</td>
<td>Hematuria</td>
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<td>NO</td>
<td>Rash/purpura</td>
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<td>joint pain/swelling (knees, ankles)</td>
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<td>Thrombocytes</td>
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HUS – E.coli infection, endothelial injury

HSP - IgA vasculitis
Review abdominal pain and kidney syndromes in children: HUS versus HSP

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Hereditary nephritis - pathology:
- paraffin sections: normal, non-diagnostic
- immunofluorescence: negative
- electron microscopy diagnostic: lamina densa splitting & lamination, “basket weave”

Postinfectious glomerulonephritis

think postinfectious glomerulonephritis
### Lecture III - summary

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<td>Acute nephritic syndrome</td>
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<td>via rapidly progressive glomerulonephritis</td>
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<td>Scleroderma</td>
<td>Endothelial injury, platelet activation, toxins</td>
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