Kidney involvement in systemic diseases

Diabetes

Diabetes will be covered by separate lecture(s). In this lecture only the main features of diabetic nephropathy are discussed.

Diabetic nephropathy is the most common cause for ESRD (End Stage Renal Disease) in the USA. Diabetes causes about 44% of new cases of kidney failure in the US. **Kidney disease is a leading cause of mortality in patients with diabetes.** Diabetes is pandemic and globally affects up to half a billion people. In the US, one in 10 people have diabetes and Americans born in the year 2000, have a 25% - 45% lifetime risk of diabetes. On average, 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 is essential to decrease the number of ESRD (end stage renal disease) patients and diabetes-associated mortality.

Diabetic nephropathy is a clinical syndrome characterized by:
- proteinuria,
- progressive decline in GFR (glomerular filtration rate), and
- hypertension

Pathology includes glomerular lesions, atherosclerosis & arteriosclerosis, as well as acute and chronic pyelonephritis.

As a consequence of a nonenzymatic glycosylation of the vascular basement membrane there is thickening of the vascular basement membranes (“hyaline arteriosclerosis”) throughout the body affecting, in particular, small blood vessels. Thickening of the glomerular arterioles, in particular of the efferent arteriole, leads to increased glomerular filtration pressure, which, in turn, leads to microalbuminuria, which ultimately progresses to nephrotic syndrome.

Diabetic glomerulosclerosis is a consequence of the progressive thickening of the glomerular basement membrane and an increase in the mesangial matrix, eventually forming KW (Kimmelstiel-Wilson) nodules.

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

Most patients do not need a kidney biopsy to establish diabetic kidney disease. Diabetic nephropathy correlates with retinopathy.

Amyloidosis

Amyloidosis is a consequence of the deposition of abnormally folded protein, which acquires a β-pleated sheet conformation. Although many (>32) different proteins have been shown to form deposits of amyloid, all deposits of amyloid share the same staining pattern, with an affinity to Congo red dye and a fibrillar ultrastructural appearance.
Among the various amyloidoses, some are localized while other may be either systemic or systemic and/or localized. Only a few amyloidosis types are seen in the majority of patients, some amyloidoses are rare or exceedingly rare. In clinical practice, the most important are those which are treatable versus not-treatable; hereditary amyloidoses also require genetic counselling. The most common amyloidoses include: AL (amyloid light chain), AA (amyloid A protein) and Aβ (amyloid β protein); hereditary amyloidoses are rarer. Aβ, associated with Alzheimer’s disease is an example of a localized amyloidosis limited to the central nervous system. It will be discussed in some detail during the neuropathology lectures.

Among the various amyloid types, 85% of patients develop amyloidosis as a result of the deposition of monoclonal immunoglobulin light chains (AL); AL is associated with an underlying clonal proliferation of plasma cells. These plasma cells produce an abnormal immunoglobulin light chain, which circulates in the blood and can form deposits in various organs, typically the kidney, the heart, and peripheral nerves.

AA amyloidosis, also referred to as a reactive systemic amyloidosis, is derived from SAA protein (serum amyloid A protein). This diseases is secondary to an associated, long-standing, inflammatory condition leading to a sustained elevation of SAA levels. In the US, and other developed countries, such diseases include rheumatoid arthritis and inflammatory bowel disease (Crohn diseases); heroin abusers may also be affected. Deposits of amyloid are systemic but target primarily the kidneys, liver and spleen.

AA amyloidosis is a serious complication in a subset of patients affected by autoinflammatory diseases that are secondary to mutations in genes encoding proteins that are involved in the regulation of innate immunity. The best know example of these diseases is Familial Mediterranean fever.

Hereditary amyloidoses are individually rare but collectively contribute almost 10% of systemic amyloidoses. In these diseases, the amyloid protein itself is affected by a mutation. The most prevalent is amyloidosis derived from a mutant of transthyretin, ATTR.

Interestingly, even a normal transthyretin (wild type), is prone to undergo fibrillogenesis in older individuals, mainly males. ATTR affects primarily the heart and peripheral nerves.

ALect2: amyloid derived from leukocyte chemotactic factor 2 has recently emerged as a systemic amyloidosis with predominantly renal involvement, affecting predominantly Mexican Americans. Currently, no treatment is available for this disease and it is important to avoid its misdiagnosis as AL.

Diagnosis of amyloidosis is based on pathologic examination of tissue. In routinely stained sections, more advanced deposits appear amorphous, “hyaline-like”, and Congo red stain is required for diagnosis. While the kidney is frequently involved, fat biopsy may be used for screening patients.
Correct identification of the amyloid protein type is critical since treatments are based on the protein type. For patients with light chain amyloidosis treatment strategies involve aggressive chemotherapy with bone marrow transplant. Patients with AA amyloidosis are treated with various anti-inflammatory drugs. Patients with hereditary amyloidoses have been treated with liver transplantation as a form of a “surgical gene therapy”. However, recently, pharmacologic treatments have emerged and are currently available in clinical trials.

**Systemic lupus erythematosus:**
This disease will be covered more extensively later and will involve separate lectures as well as small groups. Here the discussion is limited to the basics of pathologic evaluation.

1. Typical presentation: very diverse, multisystem but renal involvement with edema is common
2. Epidemiology: primarily young women
3. Etiology/pathogenesis: immune DNA-anti DNA complexes
4. Pathology: kidney involvement is seen in 60-70% of patients by light microscopy and involves different patterns (class I – V) most of which are associated with abundant immune complexes and a variable proliferative activity.
5. Laboratory tests involve testing for various autoantibodies including ANAs, anti-Sm, anti-dsDNA, etc
6. Prognosis is largely dependent on the severity of kidney involvement and the response to treatment
7. Treatments involve variable levels of immunosuppression, largely dependent on the activity of kidney involvement. Kidney biopsy is, therefore, frequently performed to assess the activity and the potential for reversibility of renal involvement and, thereby, to guide the intensity of treatment

**Diseases of blood vessels:** several diseases, including benign nephrosclerosis, malignant hypertension, atherosclerosis, renal artery stenosis, thromboembolic diseases and vasculitides are covered by separate lectures. In this lecture I will discuss thrombotic microangiopathies.

**Thrombotic microangiopathy (TMA)** is an 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)

Thus the clinical picture consists of:

- microangiopathic hemolytic anemia (MAHA)
- thrombocytopenia
- renal failure

1. Typical clinical presentation of TMA:
   - microangiopathic hemolytic anemia, thrombocytopenia, renal failure (some)
   - various clinical syndromes with clinical overlap (HUS, TTP)
   - 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 and aggregation
   - primary TMA:
     typical hemolytic-uremic syndrome (HUS), 75% of cases, infection with E. coli producing Shiga toxin E. coli (STEC- HUS)
     atypical HUS (aHUS)- uncontrolled complement activation
     thrombotic thrombocytopenic purpura (TTP), platelet aggregation due to von Willebrand factor-cleaving protease (ADAMTS13) deficiency leading to formation of unusually large von Willebrand factor multimers
   - secondary TMA:
     drug toxicities (chemotherapy)
     malignant hypertension, scleroderma
     antiphospholipid antibodies (SLE), pregnancy, contraceptives…

4. Pathology: widespread thrombosis in small vessels and injury to endothelial cells; 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 in TTP to replace ADAMTS13

**PRIMARY TMA**

**Typical HUS** is a primary TMA associated with infection with E. coli producing Shiga toxin (STEC-HUS) and is one of the main causes of acute kidney injury in children. Clinically there is a history of recent diarrhea, melena (blood in stool), renal failure, thrombocytopenia and schistocytes (fragmented red blood cells) in peripheral blood smears

Typical case of infection associated HUS:

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…

Clinical studies: renal failure, thrombocytopenia, schistocytes (fragmented red blood cells) in peripheral blood smears

Clinical diagnosis: acute renal failure associated with bloody diarrhea, typical HUS
atypical HUS [aHUS] is complement mediated TMA
There is unregulated/excessive activation of the alternative complement pathway leading to complement-mediated injury. In short, there is transformation from low-grade physiologic activity (“tick-over”) to unrestrained hyperactivity.
Triggers: excessive complement activation after minor vascular injuries owing to either
- acquired autoantibodies against complement components or
- inherited abnormalities of complement regulatory proteins
Examples of human diseases include glomerular dense deposit disease/C3 glomerulonephritis (lecture II) and a systemic disease atypical HUS (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

SECONDARY TMA:

Drug-induced TMA [DITMA]: 2 mechanisms
- immune-mediated reactions and
- dose- or duration-related toxic reactions

Typical example:
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 (MAHA) due to mechanical injury (shearing)
- renal function and MAHA usually recover with management of blood pressure
REVIEW: abdominal pain and kidney involvement in children: HUS versus HSP (Henoch Schönlein purpura):

<table>
<thead>
<tr>
<th>HUS:</th>
<th>HSP:</th>
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<tbody>
<tr>
<td>Shiga toxin producing <em>E. coli</em></td>
<td>IgA vasculitis</td>
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<tr>
<td>Poorly prepared food</td>
<td>Preceding infection – upper respiratory</td>
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<td>Abdominal pain, recent diarrhea</td>
<td>Abdominal pain, blood in stool</td>
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<tr>
<td>Renal failure</td>
<td>Hematuria</td>
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<tr>
<td>NO rash</td>
<td>Rash/palpable purpura</td>
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<tr>
<td>NO</td>
<td>Joint pain/swelling (knees, ankles)</td>
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<tr>
<td>thrombocytopenia</td>
<td>NO</td>
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<td>Anemia with schistocytes</td>
<td>NO</td>
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SUMMARY:

In this lecture we reviewed 4 systemic diseases which typically are associated with significant renal involvement:

1. diabetes which is associated with nonenzymatic glycosylation of basement membrane
2. amyloidoses – diseases associated with abnormal folding of proteins
3. systemic lupus erythematosus – disease associated with autoimmunity
4. thrombotic microangiopathies – diseases associated with endothelial injury (via different mechanisms) leading to thrombosis