Diseases of blood vessels affecting renal system

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- เมื่อสิ้นสุดการเรียนการสอน นักศึกษาสามารถ
  ○ จำแนกประเภทของโรคในกลุ่ม renovascular diseases ได้
  ○ อธิบายพยาธิกำเนิดของโรคในกลุ่ม renovascular diseases ได้
  ○ อธิบายพยาธิสภาพของโรคในกลุ่ม renovascular diseases ได้
  ○ ประยุกต์ความรู้พื้นฐานไปใช้ในทางคลินิกได้
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Benign nephrosclerosis

- Renal pathology associated with sclerosis of renal arterioles and small arteries
- Focal ischemia of parenchyma supplied by vessels with thickened walls and consequent narrowed lumens.
- Parenchymal effects → reduction in functional renal mass
  - Glomerulosclerosis
  - Chronic tubulointersstitial injury
Benign nephrosclerosis

- Nephrosclerosis at autopsy is associated with increasing age, more frequent in blacks than whites, and may be seen in the absence of hypertension.
- Hypertension and diabetes mellitus increase the incidence and severity of the lesions.
Benign nephrosclerosis

• Pathogenesis
  ◦ Two processes participate in inducing the arterial lesions
    • Medial and intimal thickening
      • Response to hemodynamic change, aging, genetic defects or combination
    • Hyaline deposition in arterioles
      • Extravasation of plasma proteins through injured endothelium
      • Increased deposition of basement membrane matrix
Benign Nephrosclerosis: Hyaline Arteriolarsclerosis

**HYALINE ARTERIOLAR SCLEROSIS**

- **ARTERIES**
  - Accelerates ARTERIOSCLEROSIS; POTENTIATES ATEROMA

- **ARTERIOLES**
  - Hyaline thickening

**LUMEN**
- Narrow but open
Benign nephrosclerosis

- **Morphology**
  - **Gross**
    - Normal or moderately reduced in size
    - 110 to 130 gm
    - The cortical surfaces have a fine, even granularity that resembles grain leather.
    - The loss of mass is due mainly to cortical scarring and shrinking.
Benign nephrosclerosis

- **Histologic examination**
  - Narrowing of the lumens of arterioles and small arteries
    - Thickening and hyalinization of the walls (hyaline arteriolosclerosis)
- **Corresponding to the fine surface granulations**
  - Microscopic subcapsular scars with sclerotic glomeruli and tubular dropout, alternating with better preserved parenchyma.
Benign nephrosclerosis

- In addition, the interlobular and arcuate arteries show a characteristic lesion
  - Medial hypertrophy
  - Reduplication of the elastic lamina
  - Increased myofibroblastic tissue in the intima
  - This change, called fibroelastic hyperplasia
  - Often accompanies hyaline arteriolosclerosis and increases in severity with age and in the presence of hypertension
Benign nephrosclerosis

- Consequent to the vascular narrowing
  - There is patchy ischemic atrophy consisting of
    - Foci of tubular atrophy and interstitial fibrosis
  - Variety of glomerular alterations: collapse of the GBM, deposition of collagen within the Bowman space, periglomerular fibrosis, and total sclerosis of glomeruli.
Benign nephrosclerosis

- Clinical feature of benign nephrosclerosis
  - Unusual for uncomplicated benign nephrosclerosis to cause renal insufficiency or uremia.
  - Moderate reductions in renal blood flow, but the GFR is normal or only slightly reduced.
  - On occasion, there is mild proteinuria.
Benign nephrosclerosis

- Three groups of hypertensive patients with benign nephrosclerosis are at increased risk of developing renal failure:
  - African descent people
  - People with more severe blood pressure elevations
  - Persons with a second underlying disease, especially diabetes.
Malignant nephrosclerosis

- Associated with the malignant or accelerated phase of hypertension
- May occasionally develop in previously normotensive individuals
- Often superimposed on
  - Pre-existing essential benign hypertension
  - Secondary forms of hypertension
  - Underlying chronic renal disease
    - Glomerulonephritis or reflux nephropathy
Malignant nephrosclerosis

- Malignant hypertension is relatively uncommon, occurring in 1% to 5% of all patients with elevated blood pressure.
- In its pure form, it usually affects younger individuals, with a high preponderance in men and in blacks.
Malignant nephrosclerosis

Pathophysiology

- Unclear
- The initial insult seems to be some form of vascular damage to the kidneys.
  - Result from long-standing benign hypertension,
    - Eventual injury to the arteriolar walls
- The initiating injury may spring de novo from arteritis, a coagulopathy, or some injury causing acute exacerbation of the hypertension.
Malignant nephrosclerosis

- Increased permeability of the small vessels
  - To fibrinogen and other plasma proteins, endothelial injury, focal death of cells of the vascular wall, and platelet deposition

- → fibrinoid necrosis of arterioles and small arteries, swelling of the vascular intima, and intravascular thrombosis.

- Mitogenic factors from platelets (e.g., PDGF), plasma, and other cells cause hyperplasia of intimal smooth muscle of vessels → hyperplastic arteriolosclerosis
Malignant nephrosclerosis

- Markedly ischemic kidney
  - With severe involvement of the renal afferent arterioles, the renin-angiotensin system receives a powerful stimulus
- Markedly elevated levels of plasma renin.
- Angiotensin II causes intrarenal vasoconstriction, and the attendant renal ischemia perpetuates renin secretion.
- Other vasoconstrictors (e.g., endothelin) and loss of vasodilators (nitric oxide) may also contribute to vasoconstriction.
Malignant nephrosclerosis

- Aldosterone levels are also elevated, and salt retention contributes to the elevation of blood pressure.
- The consequences of the markedly elevated blood pressure on the blood vessels throughout the body are known as malignant arteriosclerosis, and the renal disorder is malignant nephrosclerosis.
Malignant nephrosclerosis

Morphology

- Gross
  - Flea bitten appearance due to pinpoint petechiae on cortical surface

- Micro
  - Fibrinoid necrosis of arterioles
  - Hyperplastic arteriolitis (onion skinning) due to concentric layering of collagen;
  - Necrotizing glomerulitis,
  - Wrinkling and collapse of capillary walls
  - Small crescents
Malignant Nephrosclerosis
Flea bitten Kidney
In malignant nephrosclerosis, the kidney demonstrates focal small hemorrhages. This is due to an accelerated phase of hypertension in which blood pressures are very high.
Malignant Nephrosclerosis

FIBRINOID necrosis of vessel wall and thrombosis, especially affecting kidney and abdominal viscera

Necrotic media infiltrated by fibrin
Cellular reaction
Lumen occluded by thrombus
Malignant hypertension leads to fibrinoid necrosis of small arteries as shown here. The damage to the arteries leads to formation of pink fibrin, hence the term "fibrinoid".
Thickening of the arterial wall with malignant hypertension also produces a hyperplastic arteriolitis. The arteriole has an "onion skin" appearance.
Malignant nephrosclerosis

- Symptoms
  - Systolic pressures > 200 mmHg and diastolic pressures >120 mmHg
  - Papilledema
  - Retinal hemorrhages
  - Encephalopathy
  - Cardiovascular abnormalities
  - Renal failure
Malignant nephrosclerosis

- Early symptoms are related to increased intracranial pressure
  - Headaches, nausea, vomiting, and visual impairments, particularly scotomas or spots before the eyes
- “Hypertensive crises”
  - Episodes of loss of consciousness or even convulsions
- At the onset of rapidly mounting blood pressure
  - Marked proteinuria
  - Microscopic or sometimes macroscopic hematuria
  - No significant alteration in renal function
- Soon, renal failure makes its appearance.
Malignant nephrosclerosis

- The syndrome is a true medical emergency
  - Requiring the institution of aggressive and prompt antihypertensive therapy to prevent the development of irreversible renal lesions
Renal artery stenosis

• Unilateral renal artery stenosis is a relatively uncommon cause of hypertension
  ◦ 2% to 5% of cases
  ◦ Important because it represents a potentially curable form of hypertension with surgical treatment.
Renal artery stenosis

- Pathophysiology
  - Occlusion of the renal artery causes ischemia, which then causes an elevation of blood pressure by triggering the release of renin.
  - Increased renin levels help in the conversion of angiotensin I to angiotensin II, causing severe vasoconstriction, aldosterone release.
  - Aldosterone-mediated sodium and water retention
Renal artery stenosis

- Chronic renal ischemia
  - Atrophy of tubules and glomeruli, capsular fibrosis and arteriosclerosis
- In RAS, the GFR is dependent on angiotensin II and other modulators that maintain the balance between the afferent and efferent arteries.
Renal artery stenosis

- However, when perfusion pressure decreases below 70-85 mm Hg
  - Maintaining an adequate GFR may no longer be possible.
- Significant functional impairment of autoregulation
  - Decrease in the GFR
  - Not likely to be observed until arterial luminal narrowing exceeds 50%.
Renal artery stenosis

- Two main morphologic alterations
  - Atherosclerotic disease
    - Affects mainly the proximal third of the main renal artery
    - Most common among older men
  - Fibromuscular dysplasia (FMD)
    - Involves the distal two thirds and branches of the renal arteries
    - Most common among younger women
    - Intimal, medial and adventitial hyperplasia
Renal artery stenosis

- Morphology
  - The ischemic kidney is usually reduced in size and shows signs of diffuse ischemic atrophy
  - Crowded glomeruli, atrophic tubules, interstitial fibrosis, and focal inflammatory infiltrates
  - Mild arteriolosclerosis of arterioles in the ischemic kidney
  - Contralateral nonischemic kidney → more severe arteriolosclerosis
Renal artery stenosis

- Clinical course
  - Presenting with essential hypertension
  - Abdominal bruit
  - Elevated plasma or renal vein renin, response to angiotensin-converting enzyme inhibitor
Renal Vasculitis

- The kidney is involved in many types of systemic vasculitis
- Glomerulonephritis is a local form of vasculitis that affects glomerular capillaries
Renal Vascular Involvement in Vasculitides

- Large-vessel vasculitis
  - Granulomatous arteritis in a patient >50 years
  - Giant cell arteritis
- Medium vessel vasculitis
  - Granulomatous arteritis in a patient <50 years
  - Takayasu arteritis
- Small-vessel vasculitis
  - Necrotizing arteritis without mucocutaneous lymph node (MCLN) syndrome
  - Polymyalgia nodosa
  - Kawasaki disease

- Immune complexes in vessel walls with immunofluorescent (IF) staining for immunoglobulins
  - Other sources for immune complexes
  - Cryoglobulins in blood and vessel walls
  - IgA-dominant deposits in vessel walls
  - Systemic lupus erythematosus or rheumatoid arthritis
  - No asthma or granulomas

- Circulating antineutrophil cytoplasmic antibodies (ANCA) with paucity of vascular immunoglobulin staining
  - Granulomas and no asthma
  - Eosinophilia, asthma, and granulomas
  - GPA (Wegener)
  - EGPA (Churg-Strauss)
Renal Vasculitis

- **Large Vessel Vasculitis**
  - Giant cell arteritis and Takayasu arteritis
  - Affect the aorta and its major branches
  - Renovascular hypertension
  - Renal ischemia
  - Stimulates increased renin production and consequent hypertension
Giant cell arteritis
Takayasu arteritis
Renal Vasculitis

- **Medium-sized vessel vasculitides**
  - Affect arteries, but not arterioles, capillaries, or venules
  - Polyarteritis nodosa, which occurs mainly in adults
  - Kawasaki disease, which principally afflicts young children
  - Rare causes of renal dysfunction
Renal Vasculitis

- Necrotizing arteritis
- Involve renal arteries
  - Lead to pseudoaneurysm formation
- Renal thrombosis, infarction, and hemorrhage
Polyarteritis nodosa

- Here is a vasculitis of a renal arterial branch.
- Lymphocytes are scattered in and around the vessel.
- This happens to be the classic form of polyarteritis nodosa (PAN), a systemic vasculitis that most often affects the kidneys.
- The ANCA serology is often negative.
Renal Vasculitis

- **Small Vessel Vasculitis**
  - Affects small arteries, arterioles, capillaries, and venules.
  - Glomerulonephritis is a frequent component of small vessel vasculitides.
  - Other common manifestations include purpura, arthralgias, myalgias, peripheral neuropathy, and pulmonary hemorrhage.
  - Immune complexes, anti-basement membrane antibodies or ANCA can cause small vessel vasculitides.
ANCA associated vasculitis

- Wegener's Granulomatosis
  - Necrotizing granulomatous inflammation, usually in the respiratory tract
- Churg-Strauss syndrome
  - Eosinophilia and asthma
- Microscopic polyarteritis
  - No asthma or granulomatous inflammation
<table>
<thead>
<tr>
<th>Type</th>
<th>Antigen</th>
<th>Associated Diseases</th>
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<tbody>
<tr>
<td>PR3-ANCA (c-ANCA)</td>
<td>Proteinase-3 (PR3)</td>
<td>Wegener's granulomatosis</td>
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<tr>
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<td>Microscopic polyarteritis</td>
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<td>Churg-Strauss syndrome</td>
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<td>MPO-ANCA (p-ANCA)</td>
<td>Myeloperoxidase (MPO)</td>
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<td>Necrotizing and crescentic GN</td>
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<td></td>
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<td>Churg-Strauss syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Classic polyarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wegener's granulomatosis</td>
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<td>SLE, RA, Chronic IBD</td>
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<td>Nonspecific, or lactoferrin, lysozyme, beta-glucuronidase, cathepsin G</td>
<td>Primary sclerosing cholangitis</td>
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<td>Primary biliary cirrhosis</td>
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<td>SLE, RA</td>
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C-ANCA pattern  P-ANCA pattern
Normal blood vessel

Cells lining the inner surface (endothelial cells)
Blood plasma (liquid with proteins)
Neutrophil type of white blood cell
Other type of white blood cell
Red blood cell
Basement membrane surrounding the vessel
Pathogenesis of ANCA associated vasculitis

**Neutrophil** type of white blood cell

**ANCA (Anti-Neutrophil Cytoplasmic Autoantibody)**

Blood vessel wall

Inflammation of the vessel wall (**vasculitis**) caused by white blood cells that have been stimulated by ANCA
Differential Diagnosis of Small-Vessel Vasculitis

Small-vessel vasculitis

ANCA–associated small-vessel vasculitis
  - Wegener’s granulomatosis
  - Microscopic polyangiitis
  - Churg-Strauss syndrome

Granuloma present?*

Yes
  - Asthma and eosinophilia present?
    - Yes
      - Churg-Strauss syndrome
    - No
      - Microscopic polyangiitis

No
  - Microscopic polyangiitis

Non-ANCA–associated small-vessel vasculitis
  - Henoch-Schönlein purpura

Serum cryoglobulin?†

Yes
  - Ig-A dominant immune deposit†
  - Henoch-Schönlein purpura

No
  - Serum cryoglobulin?†
    - Yes
      - Cryoglobulinemia
    - No
      - Other “Non-ANCA” vasculitis (e.g., inflammatory bowel disease vasculitis)
ANCA associated vasculitis

Wegener’s Granulomatosis, Micropolypolyarteritis and its renal-limited variant share similar morphological lesions and are therefore considered as one pathological entity with different systemic involvement.

Focal or diffuse necrotizing extracapillary glomerulonephritis is the histological hallmark of ANCA-associated Vasculitis.
Wegener granulomatosis

Segmental necrotizing vasculitis with leukocytoclasia in the vasa recta from renal medulla of a patient with WG
Wegener granulomatosis

- This is a renal biopsy at low magnification in which there is a focal lesion centered around a blood vessel.
- Thus, a vasculitis is present.
- The one glomerulus at the right center appears normal.
Wagener granulomatosis

- At high power, the vasculitis is seen to involve a renal artery branch. This is a necrotizing granulomatous vasculitis.
- In this case, the anti-neutrophil cytoplasmic autoantibody (ANCA) serology was positive and a diagnosis of Wegener granulomatosis was made.
Microscopic polyarteritis

- Necrotizing arteritis in the renal cortex of a patient with microscopic polyarteritis
Thrombotic microangiopathy

- Hemolytic Uremic Syndrome (HUS)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Glomerular thrombosis
- Scleroderma, renal crisis
- Malignant hypertension
Thrombotic microangiopathy

- A group of disorders with overlapping clinical manifestations
- Characterized morphologically by thrombosis in capillaries and arterioles throughout the body
- Clinically by microangiopathic hemolytic anemia, thrombocytopenia, and, in certain conditions, renal failure.
Thrombotic microangiopathy

- The renal failure is associated with platelet or platelet-fibrin thrombi in the interlobular renal arteries, arterioles, and glomeruli together with necrosis and thickening of the vessel walls.
- Schistocytes (fragmented red cells) in peripheral blood smears
- Normal coagulation times and normal or only slightly elevated fibrin split products.
Thrombotic microangiopathy

Classifications

- Typical HUS (synonyms: epidemic, classic, diarrhea-positive)
  - Most frequently associated with consumption of food contaminated by bacteria producing Shiga-like toxins
Thrombotic microangiopathy

- Atypical HUS (synonyms: non-epidemic, diarrhea-negative), associated with
  - Inherited mutations of complement-regulatory proteins
  - Diverse acquired causes of endothelial injury
    - Antiphospholipid antibodies
    - Complications of pregnancy and oral contraceptives
    - Vascular renal diseases such as scleroderma and hypertension
    - Chemotherapeutic and immunosuppressive drugs
    - Radiation
Thrombotic microangiopathy

- TTP, which is often associated with inherited or acquired deficiencies of ADAMTS13
  - Plasma metalloprotease that regulates the function of von Willebrand factor (vWF)
Thrombotic microangiopathy

- Pathogenesis
  - Endothelial injury
  - Platelet aggregation
Thrombotic microangiopathy

- Endothelial injury
  - In typical HUS, \( \rightarrow \) Shiga-like toxin
  - In inherited forms of atypical HUS \( \rightarrow \) excessive, inappropriate activation of complement
  - The endothelial injury in HUS \( \rightarrow \) cause platelet activation and thrombosis within microvascular beds
Thrombotic microangiopathy

- Reduced endothelial production of prostaglandin I$_2$ and NO (both inhibitors of platelet aggregation) and increased endothelin
  - Promote vasoconstriction
- Finally, adhesion molecules expressed on injured endothelium result in the recruitment of leukocytes → thrombosis
Thrombotic microangiopathy

- Platelet Aggregation
  - In TTP the initiating event appears to be platelet aggregation
    - Induced by very large multimers of vWF
    - Deficiency of ADAMTS13
      - Plasma protease that cleaves vWF multimers into smaller sizes
  - Deficiency of ADAMTS13 is most often caused by autoantibodies that inhibit ADAMTS13 function
Thrombotic microangiopathy

- Less commonly, a chronic relapsing and remitting form of TTP is associated with inherited deficiencies of ADAMTS13.
- Very large vWF multimers can bind platelet surface glycoproteins and activate platelets spontaneously.
- Providing a pathophysiologic explanation for the microthrombi that are observed in vascular beds.
Classic (Childhood) Hemolytic-Uremic Syndrome

- 75% of cases occur in children after intestinal infection with verocytotoxin-producing *E. coli* (e.g., type O157:H7).
- Verocytotoxins are similar to *Shiga* toxins produced by *Shigella*.
- Some epidemics have been traced to ingestion of infected ground meat (as in hamburgers).
Classic (Childhood) Hemolytic-Uremic Syndrome

- Characterized by
  - Sudden onset of bleeding manifestations (especially hematemesis and melena)
  - Severe oliguria
  - Hematuria
  - Microangiopathic hemolytic anemia
  - Prominent neurologic changes

- Hypertension is present in about half the patients
Classic (Childhood) Hemolytic-Uremic Syndrome

- Pathogenesis
  - Shiga-like toxin
    - Increased adhesion of leukocytes
    - Increased endothelin production and loss of endothelial nitric oxide
    - Presence of cytokines, such as tumor necrosis factor, endothelial lysis
    - Thrombosis and vasoconstriction
    - Microangiopathy
Classic (Childhood) Hemolytic-Uremic Syndrome

• Morphology
  ◦ Gross appearance
    • Patchy or diffuse renal cortical necrosis
  ◦ Microscopic examination
    • Thickening and splitting of capillary walls
    • Endothelial and subendothelial swelling
    • Deposits of fibrin-related materials in the capillary lumens, subendothelially, and in the mesangium.
    • Mesangiolysis
    • Fibrinoid necrosis and intimal hyperplasia of arterioles and are often occluded by thrombi.
Classic (Childhood) Hemolytic-Uremic Syndrome
Adult Hemolytic-Uremic Syndrome

- In association with infection
  - Typhoid fever, *E. coli* septicemia, viral infections, and shigellosis
- In the antiphospholipid syndrome
- As complications of pregnancy or the postpartum period
- Associated with vascular renal diseases
- In patients treated with chemotherapeutic and immunosuppressive drugs
Idiopathic TTP

- Causes of TTP
  - Usually without prodromal syndrome
  - Idiopathic
  - Autoimmune: SLE

- Systemic manifestation of TTP
  - Cerebral symptoms
  - Hemorrhage
  - Cardiac failure
  - Renal failure
Idiopathic TTP

- A small platelet-fibrin thrombus is seen in a glomerular capillary above the arrow. This occurred in a patient with thrombotic thrombocytopenic purpura (TTP).
Thrombotic microangiopathy

- Glomerular thrombosis
  - Disseminated intravascular coagulation
    - Gram negative sepsis (shock)
    - Obstetric complications (incomplete abortion)
    - Massive tissue injuries (burn)
    - Neoplasms (pancreatic CA)
    - Hyperacute allograft rejection
    - Toxin (snake venom)
Diffuse Cortical Necrosis

- Uncommon condition
- After an obstetric emergency, septic shock, or extensive surgery
- When bilateral and symmetric, it can be fatal in the absence of supportive therapy
- Patchy cortical necrosis may permit survival.
- The cortical destruction has the features of ischemic necrosis.
Diffuse Cortical Necrosis

- Glomerular and arteriolar microthrombi are found in most cases.
- Morphologic features have considerable overlap with thrombotic microangiopathy and disseminated intravascular coagulation
- The pathogenetic sequence of events in this injury remains obscure.
Diffuse Cortical Necrosis

- **Morphology**
  - Ischemic necrosis are sharply limited to the cortex.
  - May be patchy, with areas of coagulative necrosis and apparently better-preserved cortex.
  - Intravascular and intraglomerular thromboses
  - Hemorrhages occur into the glomeruli, together with the formation of fibrin plugs in the glomerular capillaries.
Renal infarction

- Kidney: end-organ nature of blood supply
- Extremely limited collateral circulation from extrarenal sites
- Embolism: most common cause
- Morphology: white (anemic infarct), wedge shape, coagulative necrosis
Renal infarction