Pathology of noninfectious vasculitides

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Systemic noninfectious vasculitides

Vasculitis = a general term for inflammation of vessel walls

Any type of vessel in all locations can be affected in practice – overwhelming number of clinical symptoms and problems

- **Clinical manifestation:** very variable, the disease has attacks and spontaneous remissions
- **the diagnosis is difficult**

The vasculitides are often serious diseases, prompt recognition and therapy.

Patients suffer from *symptoms of systemic inflammation* (such as fever, arthralgias, myalgias, weight loss), and can simultaneously have *symptoms of local system involvement*. They can develop *local mass lesion* which can lead to the diagnosis of malignant tumor.
Historical development of names of vasculitides

1. description of necrotizing arteritis (PAN) Rokitanský (1852)
   Periarteritis nodosa (1866 Kussmaul, Maler)

   1890 Hutchison GCA
   1908 Takayasu
   1934 Horton GCA

   1942 Rich, hypersen. angiitis
   1978 Fauci, hypersen.a.
   mainly skin involvement,

   1903 Osler SLE
   1936 Wegener
   1948-52 Zeek, hypersens. angiitis
   small vessel vasculitis
   1951 Churg- Strauss
   1954 Godman and Churg (MPA x PAN)
   1982 Davis, ANCA antibodies

For decades PAN was the term used for virtually any patient with necrotizing arteritis
First description of necrotizing arteritis with aneurysmata (PAN, 1852)

Karel Rokitansky

- Karel Rokitansky was born in Hradec Královc, started his medicine study in Prague under Purkyně.
- When Purkyně left in r. 1823 for Wroclaw, Rokitansky went to Vienna.
- Aneurysmal lesions in numerous arteries in a 23-year-old shoemaker (without histology)
- Eppinger: histological confirmation
- 1866; Kussmaul and Maier: 27-year-old tailor; periarteritis nodosa with histology (with the involvement of gli)

Death of colleague Dr. Koletscko, who succumbed the sepsis after injury at autopsy room, has inspired Dr. Ignaz Semmelweis (a pioneer in antiseptic medical practice).
Karl, baron von Rokitansky, (born Feb. 19, 1804, Königratz, Austria—died July 23, 1878, Vienna), Austrian pathologist whose endeavours to establish a systematic picture of the sick organism from nearly 100,000 autopsies—30,000 of which he himself performed—helped make the study of pathological anatomy a cornerstone of modern medical practice and established the New Vienna School as a world medical centre during the latter half of the 19th century.

A professor of pathological anatomy (1844–74) at the Vienna General Hospital, he inspired the Bohemian student Ignaz Semmelweis, later a martyr to the cause of antiseptic medical practice, to take up the study of medicine (1846) and afterward supported him in his struggle to eliminate childbed fever by cleaning up Europe’s maternity wards.

First to detect bacteria in lesions of malignant endocarditis, an often rapidly fatal inflammation of the membrane lining the inner walls of the heart, Rokitansky created the basis for a differentiation of lobar pneumonia (originating in the lower lobe of the lung) and lobular pneumonia, or bronchopneumonia (originating in the finer subdivisions of the branched bronchial tree). He made a fundamental study of acute yellow atrophy of the liver (now known as Rokitansky’s disease; 1843), established the micropathology of pulmonary emphysema (a condition of the lung characterized by
2012 revised international CHCC nomenclature of vasculitides

**Medium vessel v.**
- PAN
- Kawasaki disease

**ANCA-associated small vessel v.**
- GPA (Wegener g.)
- MPA (microscopic polyangitis)
- EGPA (Churg-Strauss sy)

**Immune complex small vessel v.**
- Anti-GBM
- IgA v. (HSP)
- Cryoglobulinemic v.

**Large vessel vasculitis**
- Takayasu a.
- Giant cell a.

Nomenclature noninfectious vasculitides

1. Large vessel vasculitis: GCA a Takayasu
2. Medium vessel vasculitis: PAN a Kawasaki
3. Small vessel vasculitis (arteries, arterioles, venules, veins):
   a) ANCA-associated vasculitis (most frequent vasculitis of adults!!!)
   b) immune complex:
      IgA v.(Henoch-Schönlein), anti-GBM (ANCA : anti-GBM = 100 : 1),
      cryoglobulins, hypocomplementemic urticarial (anti-C1q) v., serum sickness
4. Variable vessel vasculitis (Cogan’s, Behcet’s, etc.)
Single organ vasculitis (cutaneous SVV, primary CNS vasculitis, etc.)
Vasculitis associated with systemic diseases (e.g. Rheumatoid, Lupus, Sarcoid, etc.)
Vasculitis associated with probable etiologies (e.g. HBV, HCV, drug, cancer, etc.)
Large Vessel Vasculitis, 2012 CHCC definition

Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected.

1. Takayasu arteritis

Patients: women under 50, rare in the Czech Rep.
- Morphology: shares histological features of GCA (granulomatous arteritis), no fibrinoid necrosis

2. Giant cell (temporal) arteritis (GCA)

- Patients: over 50, common (with polymyalgia rheumatica)

The distinction between the two entities is made on the basis of a patient’s age!!!
PAN, 2012 CHCC definition

• Necrotizing arteritis of medium or small arteries \textit{without} \textit{glomerulonephritis} or vasculitis in arterioles, capillaries, or venules; and \textit{not associated with ANCA}.

• Very rare

No GN !!!
Kawasaki disease; 2012 CHCC definition

- Arteritis associated with the *mucocutaneous lymph node syndrome*, predominantly affecting medium and small arteries.
- *Coronary arteries are often involved*. Aorta and large arteries may be involved.
- Usually occurs in infants and young children.
Small vessel vasculitides

1. ANCA-associated small vessel v.
   • GPA (Wegener g.)
   • MPA (microscopic polyangitis)
   • EGPA (Churg-Strauss sy)

2. Immune complex small vessel v.
   • Anti-GBM
   • IgA v. (HSP)
   • Cryoglobulinemic v.
   • Hypocomplementemic urticarial v.
ANCA antibodies (Anti-Neutrophil Cytoplasmatic Antibody)

- ABs specific to antigens of neutrophil granules and to lysosomes of monocytes;
- c-ANCA (cytoplasmatic)  p-ANCA (perinuclear)
- Many different antigens in the group c- or p- (proteinasa 3, myeloperoxidasa-MPO, lactoferin, cathepsin G, elastasa, lysosym, azurocidin atld.)
- ANCA positive vasculitides: c-ANCA: PR3 (proteinasa 3),
  p-ANCA: MPO (myeloperoxidasa)
  IF determine the group c or p
  ELISA distinguishes the precise antigens (PR3 or MPO) which are associated with AAV

- New methods for identification of specific epitopes (MALDI-TOF/TOF-MALDI-MS)
  Epitope specificity defines pathogenicity

ANCA associated vasculitis:

• very aggressive disease; systemic involvement (joints, skin, ENT, lungs, kidneys)
• May occur at any age, typical onset between 5th-7th decades of life
• The most common form of systemic vasculitis in adulthood

• Estimated incidence $>15\text{-}23$/million
  age over 65: 53/million
• Geographical variation: c ANCA more frequent in northern Europe, p ANCA more frequent in southern Europe, Asia and Japan

Prognosis of untreated GPA (c ANCA) is worse than the prognosis of the majority of tumors; and the mortality rate at 1 year is 80%

Rapid dg is critical
Occurrence of systemic involvement

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The concept that MPO- and PR3-AAV are genetically distinct diseases with phenotypic overlap and that studies and clinical practice may benefit from clustering according to serotype.

ANCA-associated vasculitides

- Any organ may be afflicted (kidney, lungs, ENT...)

- **Kidney involvement:**
  - pauciimmune necrotizing crescentic (rapidly progressive) glomerulonephritis
  - 75% of patients with GN have systemic vasculitis

- Renal biopsy:
  - Gold standard to confirm the diagnosis
  - To assess the prognosis
  - Not absolutely required, but recommended whenever possible
ANCA-associated GN: morphology: gli
pauciimmune necrotizing GN with crescents

**Acute lesions**: necrosis + crescents
**Typically scattered** with normal gli or their parts, later with combination of acute and chronic lesions
ANCA-associated GN: morphology: gli
Crescents: epithelial/cellular, fibro-epithelial, fibrotic
ANCA-associated GN: morphology
vessels & interstitium
ANCA-associated GN: morphology of advanced disease
Time period during the course of vasculitis in morphology
When it is difficult to diagnosed AAV

**In a kidney biopsy:**
- Early acute lesion: normal morphology; sampling error
- Advanced lesion (destruction and high number of crescents)
- Chronic scaring lesions
- Combinations: with IgA and or other diseases (modify the morphological features); anti-GBM, DM, SLE: mainly MPA with slow progression with segmental sclerotic lesions

**In other locations/organs:**
- More difficult to diagnose vasculitis (often second opinion can help)
Case no. 1.: 63-year-old woman

- Autumn 2002 worse hearing, ENT in normal range, CT showed inflammation in the middle ear
- She visited internist in January next year
- She requested lungs examination, normal
- February: artralgias of small joints, susp.
- May: S-Cr 197 umol/l, microhematurie
- June: S-Cr 273 umol/l;
- only then she is sent to nephrologist
- Weight loss: 6 kg

AAV advanced morphological features (MPA, p-ANCA)
Case no. 2.: a 25-year-old woman

- During the last year: recurrent otitis media and sinusitis
- 5 weeks she is not feeling well, fever
- Admitted to the hospital at pulmonary department
- Dg.: pulmonary infiltrates, fever
- c-ANCA ++++, treated with ATB
- S-Cr 143 μmol/l (1.61mg/dl)
- urine: numerous ery

Successful treatment, S-Cr 90umol/l, PU less than 1g/day, after 5 years: a healthy child
Now, 14 years after renal manifestation, during 2 last years: relapse in ENT and lungs location
Case no. 3.: 28-year-old man

- 5 mths of non-specific symptoms: myalgia, artralgia, unintended weight loss (10 kg)
- chronic otitis media with hypacusis l. sin.

  acute polyneuropathy: hypoesthesia and paresthesia

- mild hematuria and proterinuria (1 g/day), sterile pyuria
- CRP 45 mg/dl, sCr 120μmol/l; 1.36 mg/dl, Hb 99
- US and CT: mass of left kidney – exploratory surgery
- firm and whitish appearance;
- perioperative biopsy – no malignant cells, granulomatous inflammation
- mass seemed malignant – nephrectomy completed
Case no. 3.: nephrectomy specimen
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Case no. 3.: nephrectomy specimen
Case no. 3.

- diagnosis of **granulomatosis with polyangiitis** confirmed by c-ANCA positive (IF and ELISA)
- treated with corticoids and cyclophosphamide until complete recovery
- remission in the **follow-up (14 years)** – **normal renal function** (S-Cr 76μmol/l; 0.86 mg/dl), ANCA negative, only mild proteinuria (0.6 g/day)
- maintainence therapy – low-dose azathioprine
AAV, systemic involvement

nodulus imitates metastasis

stomach

skin
Czech Registry of ANCA-associated vasculitides (AAV)

- Local database of AAV in Prague since 1993
- National level & online data collection since 2009
- Main aims:
  - To obtain consistent epidemiologic and clinical data on patients with AAV in the Czech Republic
  - To support modern therapeutic strategies in (young and/or refractory) AAV patients

16 centres in 7 cities:

9x Nephrology
4x Rheumatology
2x Immunology
1x Pediatrics
Results

n = 689 patients:
Male/Female: 330/359 (48/52%)
Median age at dg: 58 (range 11 – 89) years
No of patients alive: 510 ; → Prevalence 48.5 pmp

Age distribution:
ANCA type (ever) ELISA and/or IIF

- c/anti-PR3: 57%
- p/anti-MPO: 38%
- Atypical, N/A: 2%
- Negativní: 3%
- others: 0%
Cumulative organ involvement (n: 689)
Causes of death

2.9x increased risk of death due to cardiovascular cause, in patients aged 15-64 years: 10x increased risk of mortality (all causes)
In morphological point of view, ANCA vasculitis should be considered when:

- Chronic inflammation in ear and/or repeated sinusitis
- Skin vasculitic lesions: painful
- Ischemic ulcers in GIT
- Pauciimmune necrotizing GN
- Lungs: hemoptysis and changing infiltrates ("GPA" can imitate tumor and older patients are sometimes treated with cytostatic drugs)
- Unexplained chronic inflammatory disease

Rare: PAN, Kawasaki, Takayasu

"More frequent": GCA, drugs associated vasculitis (mainly skin lesions)

ANCA associated vasculitis is the most common form of systemic vasculitis of adults.
Nephropathology for the nephrologists

Introduction to renal pathology and approach to diagnosis (clinic-pathology correlations)

When to add molecular pathology to the diagnosis of kidney diseases (Helen Liapis, US)

Clinical up-data of membranous nephropathy: Is it time to change the guidelines? (Pierre Ronco)

Should the patients with a clear diagnosis of AAV be biopsied? (V. Tesař)

How I treat a patient with AAV (3 case reports)

Interpretation of renal allograft biopsies: an algorithmic approach with up-grade of Banff classification system (A. Perkowska-Ptasińska)