Selected Topics in Clinical Immunology
- Autoimmunity-

- Biomedical Sciences
- April 12, 2018
- S. Adler
today’s menu

• vasculitis

• autoimmune connective tissue diseases

• autoinflammatory diseases
vasculitis
vasculitis

«immunreaction causing vascular inflammation with consecutive harm to affected organs»

• primary vasculitis
• secondary vasculitis

• «inflammation»
  ⇒ wall thickening / «softening»

• systemic inflammation
  ⇒ fever, tiredness, weight loss
  ⇒ night sweats, joint and muscle pain
  ⇒ serological inflammation
Chapel-Hill vasculitis classification

- **Immune Complex Small Vessel Vasculitis**
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (Henoch-Schönlein)
  - Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

- **Medium Vessel Vasculitis**
  - Polyarteritis Nodosa
  - Kawasaki Disease
  - Anti-GBM Disease

- **ANCA-Associated Small Vessel Vasculitis**
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

- **Large Vessel Vasculitis**
  - Takayasu Arteritis
  - Giant Cell Arteritis

Jennette JC, Arthritis Rheum, 2013
27 years old male
ENT problems

66 years old female
shoulder pain
Chapel-Hill vasculitis classification

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Jennette JC, Arthritis Rheum, 2013
66 years old female

Patient complains of
sudden onset of morning stiffness and pain
shoulder and hip girdle
headache
fever

Lab shows
hemoglobin ↓
ESR ↑
CrP ↑
GCA (giant cell arteritis)

affection of the temporal arteries

color coded ultrasound (Halo, flow↑)

Pfadenhauer K, Nervenarzt 2003
GCA

affection of the temporal arteries

color coded ultrasound  (Halo, flow↑)
MR-angiography
GCA

affection of the temporal arteries

color coded ultrasound (Halo, flow↑)
MR-angiography
biopsy=> histology
GCA

affection of the temporal arteries: histology
GCA pathophysiology

Dendritic Cells in the Arterial Adventitia
Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury

anti IL-6 strategy in GCA

Villiger PM, Adler S, Lancet 2016
GCA – why large vessel vasculitis?

*in at least 30% of temporal affection:*

MR angiography
GCA – why large vessel vasculitis?

*in at least 30% of temporal affection:*

MR angiography
PET-CT
GCA

complications

blindness
aortic rupture
vascular dissection
aneurysms
Chapel-Hill
Klassifikation der Vaskulitiden

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Jennette JC, Arthritis Rheum, 2013
27 years old male

*patient complains of*

nasal congestion
articular pain
red eye, visual disturbance
tired

*lab shows*

serological inflammation
anemia
urinary sediment: erythrocytes +++
specific antibodies in the blood
ANCA
antineutrophil cytoplasmatic antibodies
out of neutrophil granula and monocytic lysosomes

antigen     proteinase 3 (PR3)
proteinase 3 (PR3)
diseases     granulomatose with polyangiitis
            GPA
            myeloperoxidase (MPO)
            mikroskopic polyangiitis
            MPA

Michael Horn, Immunserologie, Inselspital Bern
27 years old male

cranial contrast-MRI
27 years old male

CT scan nasal sinuses
27 years old male

renal biopsy => histology

necrotising vasculitis
proliferations
epitheloid granuloma
negative immune stain

⇒ ANCA-associated, pauci-immune,
glomerular necrotising vasculitis, PR-3 specific:
granulomatosis with polyangiitis («Wegener ‘s disease»)

Harrison, Innere Medizin online, 18. Auflage
GPA
rapid progression of mal-perfusion (A, B)
rapid progression of mal-perfusion (A, B) to infarction (C)
autoimmune connective tissue diseases
autoimmune connective tissue disease

- systemic lupus erythematosus (SLE)
- systemic sclerosis (SSc)
- primary Sjögren’s syndrome (pSS)
- polymyositis, dermatomyositis (PM, DM)
- mixed connective tissue disease (MCTD)
- undefined connective tissue disease (UCTD)
- overlap (combination of 2 or more...)
autoimmune connective tissue disease

• systemic inflammatory affection of connective tissue
• similar morphologic changes
• affection of internal organs is frequent
• similar «features»
• arthralgias, Raynaud’s phenomenon, skin changes
• ANA anti nuclear antibodies
• women > men
• intermittently active
SLE
autoimmune diseases

multifactorial etiology

- genetic disposition
  *(i.e. HLA class I+II and other genes)*

- environmental factors
  *(infections, smoking, psychological stress)*

- hormonal dysbalance
  *(estrogen deficiency)*
basic mechanisms of autoimmunity

- break of central and/or peripheral tolerance
- genetic predisposition
  (individual pattern of HLA class I and II genes)
- gender specific factors (hormones)
basic mechanisms of autoimmunity

- **genetics** concordance 14-57% in monozygotic twins
  no single gene polymorphism
  C1q deficiency, C4 deficiency, C3 polymorphism

- **hormones** women of childbearing age
  estrogen-containing contraceptives: risk increase
**Pathogenesis of Clinical Manifestations**

- Exact etiology still obscure BUT
- Mediated directly or indirectly by antibodies / antigens
- Creation of immune complexes (IC)
- IC deposition $\Rightarrow$ complement activation $\Rightarrow$ tissue damage

- Autoantigens that are recognized are presented primarily on cell surfaces, particularly by cells that are activated or are undergoing apoptosis
pathogenesis of clinical manifestations

- IC deposition $\Rightarrow$ complement activation $\Rightarrow$ tissue damage

Granular deposits of IgG and IgM at the basal membrane of the skin
pathogenesis of clinical manifestations

- IC deposition $\Rightarrow$ complement activation $\Rightarrow$ tissue damage

immune deposits kidney
non-bacterial thrombotic endocarditis

Libman Sachs endocarditis (15-60% postmortem)

clinics: - often undetected,
diagnostics: - echocardiography
therapy: - rarely replacement, endocarditis prophylaxis!!
Anti-Phospholipid Syndrome

lab
- phospholipid ab
- cardiolipin-Ab
- β2GPI ab
- PTT prolongation
- Lupus Antikoagulans

symptoms
- thrombocytopenia
- repetitive abortion
- thrombosis/embolism
- insults
- Libman Sacks endocarditis

livedo reticularis
livedo racemosa
Raynaud phenomenon
apoplexia capillaris
arterial thromboembolism
exogenous trigger

multi-genetic terrain

neuro-endocrine system

sex estrogens androgens

immune-dysregulation

defective clearance

apoptotic cells DNA

auto-antibodies

immunocomplexes complement-activation

organ damage

Rituximab, Belimumab

B-cell-suppression ↓ because of anti-idiotypic Ab and Tregs ↓

APC

B

CTLA4-Ig

Helper-Cytokine

T
diagnostic criteria of SLE

1. butterfly erythema
2. discoid skin lesions
3. photosensitivity
4. orale ulcerations
5. arthritis
6. serositis
7. renale disturbances
   - proteinurie
   - cellular zylinders
8. neurological symptoms
   - seizures, psychosis
9. hematological disturbances
   - hemolytic anemia
   - leukopenia
   - lymphopenia
   - thrombozytopenia
10. immunological disturbances
    - anti-dsDNA
    - anti-Sm, anti-C1q
11. antinuclear antibodies (ANA)
Treatment principles in autoimmune connectivitides

- antiinflammatory drugs (*NSAIDs, glucocorticoids*)
- antimalarial drugs (*background drug, skin, joints*)
- antimetabolites (*methotrexate, azathioprine*)
- alkylating agents (*cyclophosphamide for severe renal and CNS disease*)
- T-cell inhibitors (*ciclosporine A, mycophenolate mofetil*)
- biologics (*B-cell depletion by rituximab/anti-CD20 and inhibition of T-cell co-stimulation by CTLA4-Ig*)
autoinflammatory diseases
Classification of Inflammatory Processes

- Pathogen
  - yes
    - Infection
  - no
    - Auto-Antigen
      - Autoreactive T/B cells
      - Autoantibodies
        - yes
          - Autoimmunity
        - no
          - Autoinflammation
gout
The Inflammasome and gout

Il-1 beta can be blocked by anankinra

Martinon et al., JCI 2006
Cryopyrin-associated periodic fever syndromes (CAPS)

Clinical Presentations

Nature Reviews Rheumatology

NOMID/CINCA

www.hopkinsarthritis.org/
Cryopyrin-associated periodic fever syndromes (CAPS)

Therapy

NOMID/CINCA
Deficiency of IL-1 Receptor Antagonist (DIRA)
Monogenetic Autoinflammatory Diseases (Hereditary Periodic Fever Syndromes)
«autoinflammatory diseases«

- may be genetically linked (hereditary fever syndromes)
- many exhibit enhanced NALP3 / inflammasome activity
- holds true (in part) for crystal-induced arthritis (gout)
- mostly IL-1 driven

=> therapy with IL-1 blocking agents as strategy