Autoimmune Connective Tissue Diseases and Vasculitides 4.4.19

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Immunologically mediated systemic vasculitides

- Giant cell arteritis (GCA)
- Panarteritis nodosa (PAN)
- ANCA-associated vasculitides (AAV)
- many others
Pattern of involved vessels

- Aorta
- Große bis mittelgroße Arterie
- Schönlein-Henoch P. und ess. Kryoglobulinämie
- Mikroskopische Polyangiitis (Mikroskopische Polyarteriitis)
- Wegenerssche Granulomatose und Churg-Strauss-Syndrom
- Panarteriitis nodosa und Kawasaki S.
- Riesenzell-(Temporal) arteriitis und Takayasu Arteriitis
Arteritis cranialis
(sive temporalis, sive giant cell arteritis)

Clinical characteristics
- New headache in the elderly
- Constitutional symptoms (fever, sweat, weight loss, fatigue)
- Jaw claudicatio
- Polymyalgia rheumatica

Laboratory features
- high erythrocyte sedimentation rate (ESR)
- thrombocytosis
Arteritis cranialis
(sive temporalis, sive giant cell arteritis)
Duplexsonographie

Giant Cell Arteritis
(temporal artery)

Before Tx

8 wks Pred. Tx
Giant cell arteritis (GCA)

Histology of A.temporalis
Dendritic Cells in the Arterial Adventitia

A
Adventitial Dendritic Cells in Normal Arteries

B
Dendritic-Cell Activation in Arteritis
Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury

Role of T-cells in GCA?

- Implantation of bioptic material of inflamed artery in SCID-mice → depletion of tissue T-cells → stop of inflammation
  (Brack A et al., Mol Med 1997; 3: 530-43)

- Clonal expansion of CD4+ T-cells from distinct vascular lesions of the same patient → antigen-induced proliferation

- Distinct HLA-DRB1 alleles represent a genetic predisposition for GCA and PMR
  (Weyand CM et al., J Clin Invest 1992; 90: 2355-61)
Role of T-cells in GCA?

- T-cells from GCA-vessel biopsies proliferate after exposure to extracts from temporal arteries ([Martinez-Taboada V et al., Mol Med 1996; 74: 695-703])

- Relevant antigens in the arterial wall are still not identified – antigens from the Lamina elastica externa or interna?
Diagnostic imaging

• Angio – MRI (magnetic resonance imaging)
• PET (positron emission tomography)
MRI of abdominal aorta: Enlargement and edema of the vessel wall.
When do you think of GCA?

- new and sudden (unilateral) headache in the elderly
- sudden impairment of vision or blindness
- symptoms of Polymyalgia rheumatica, deterioration of general condition with or without signs of an cranial arteritis
- Fever of unknown origin (FUO) in the elderly
- high ESR (erythrocyte sedimentation rate of >100mm/hr)
Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury

Role of IL-6 in Giant Cell Arteritis

- induction of acute phase reaction (CRP, SAA) in the liver
- systemic inflammatory systemic response
- exciting therapeutic target for anti-IL-6 strategies
- prompt therapeutic response to tocilizumab (anti-IL-6R monoclonal antibody)
Before

3 months after monthly tocilizumab
Pattern of vessels involved

- Arteriole
- Kapillare
- Venole
- Vene
- kleine Arterie
- große bis mittelgroße Arterie
- Aorta

Diseases:
- Leukozytoklastische Hautvaskulitis
- Schönlein-Henoch P. und ess. Kryoglobulinämie
- Mikroskopische Polyangiitis (Mikroskopische Polyarteriitis)
- Wegenerssche Granulomatose und Churg-Strauss-Syndrom
- Panarteriitis nodosa und Kawasaki S.
- Riesenzell-(Temporal) arteriitis und Takayasu Arteriitis
Panarteritis nodosa

40 % HBV-associated

60 % Non-HBV-associated
Immunopathogenesis of PAN

- Similar to GCA, T-cell mediated (predominant infiltrates with CD4+ T-cells)
- Association with an active chronic Hepatitis B in 40%
- 10 years-survival identical between HBV-associated and non-HBV-associated disease

(Gayraud M et al., A&R 2001; 44: 666-75)
Vasculitis of medium-sized vessels
direct symptoms

- **Insult** *(brain, heart, kidney, GIT, extremities)*
- **Bleeding** *(ruptures of microaneurysmata)*
- **Pain in testis** *(spezific for PAN)*
- **Arterial hypertension** *(recent evolution)*
19-year-old man presented with a 10-month history of Raynaud’s phenomenon, fever, abdominal pain, and hypertension.

Vasculitis of medium-sized vessels
Intestine / gall bladder
Pattern of involved vessels

- Arteriole
- Kapillare
- Vene
- Vene
- kleine Arterie
- große bis mittelgroße Arterie
- Aorta
- Schönlein-Henoch P. und ess. Kryoglobulinämie
- Mikroskopische Polyangiitis (Mikroskopische Polyarteriitis)
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AASV = ANCA-associated small vessel vasculitis
ANCA (Antineutrophil cytoplasmic antibodies)

- c-ANCA
- Proteinase 3 (PR3)
- P-ANCA
- Myeloperoxidase
ANCA: IIF-Pattern

ANCA

pANCA

cANCA

+ Ladung
neutral
ANCAs

Associated antigens

Major antigen:

- Proteinase 3 (PR3)
- Myeloperoxidase (MPO)
- Other antigens: Elastase, Lactoferrin, Kathepsin G, andere?

Disease association

M. Wegener:

- Sensitivity: 73%
- Specificity: 99%

Other associations:

- Infections: i.e. endocarditis, Medi: Propylthiouracil, etc.

Microscop. Polyangiitis:

- Sensitivity: 67%
- Spezificity: 99%

Other associations:

- IBD, rheumatoid arthritis, others
- Medi: Propylthiouracil, etc.
Pathogenesis of granuloma formation in Wegener’s Disease
AASV Pathogenetically relevant therapeutic 'targets'

Pathogenesis of vasculitis in Wegener’s Disease
Direct Symptoms *(small vessel vasculitis)*

- episcleritis, scleritis, keratitis, uveitis
- hearing loss, dizziness, chronic otitis media and sinusitis
- chronic rhinitis, sinusitis
- hemoptysis, dyspnoe
- palpable purpura, skin ulceration (non spontaneously-healing, after simple injury, unusual localization)
- microhematuria, proteinuria (GN)
- mononeuritis multiplex (sensory deficits and rapidly progressive pareses)
- perimyocarditis

Target Organs:
- Eye
- Nose
- Ear
- Lung
- Skin
- Kidney
- Nerves
- Heart
Blutiges Nasensekret

Tachypnoe, Hämoptoe

Histo: keine Vaskulitis, keine Granulome

Episkleritis

Verkrustete Papeln
AASV

erythrocyte zylinders
necrotizing GN
Vasculitis - Treatment principles

For remission induction and maintenance

• systemic glucocorticoids
• +/- immunosuppressants (i.e. Methotrexate, Leflunomide, Cyclophosphamide)
• +/- biologics (i.e. rituximab in ANCA-associated vasculitides)
• Prophylaxis of infections (vaccination, co-trim)
• Prophylaxis of osteoporosis (Ca, VitD, bisphosphonates) and CVI’s (ASS in GCA)
• Treatment(adjustment) of diabetes
Autoimmune connective tissue diseases

- **Systemic lupus erythematosus (SLE)**
- Mixed connective tissue disease (MCTD)
- Sjögren’s syndrome
- Systemic sclerosis (SSc)
- Dermato/Polymyositis (DM/PM)
- Undifferentiated connective tissue disease (UCTD)
- Overlap syndrome (combination of two or more co-existing autoimmune connective tissue diseases)
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)
Genetic factors in SLE

- concordance of 14-57% in monozygotic twins
- no single gene polymorphisms/alteration
- HLA-B8; HLA-DR2; HLA-DR3; DQW1; HLA-DMA*O401; C2 deficiency (C2D); C1q deficiency; C4 (especially C4A) deficiency (C4D); C3 polymorphisms
- and many others
- Epigenetics with alterations in methylation and acetylation of DNA
Hormonal factors in SLE

- little evidence of an association between disease severity and sex hormone concentration in plasma
- use of estrogen-containing contraceptive agents is associated with an 50 percent increase in risk
- lupus flares have been associated with hyperprolactinemia
Immunopathogenesis of SLE

- SLE is primarily a disease with abnormalities in immune regulation. These abnormalities are thought to be secondary to a loss of self-tolerance.
- Autoantibodies and immune complexes they form with autoantigens.
- Autoantigens that are recognized are presented primarily on cell surfaces, particularly by cells that are activated or undergoing apoptosis.
Immunopathogenesis of SLE

- Phagocytosis and clearing of immune complexes, of apoptotic cells, and of necrotic cell-derived material are defective in SLE, allowing persistence of antigen and immune complexes.
- B cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by BlyS (BAFF) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10.
Immunopathogenesis of SLE

- This increased autoantibody persistence is not downregulated appropriately by anti-idiotypic antibodies, or by CD4+CD25hi-Foxp3+ regulatory T cells, or by CD8+ suppressor T cells.

- Some antibody/antigen complexes, particularly those containing CpG-DNA or RNA/proteins, activate the innate immune system via TLR-9 or TLR-7, respectively.
Immunopathogenesis of SLE

- Thus dendritic cells are activated and release type 1 interferons and TNFalpha. T cells release IFNgamma, IL6, IL10, while NK and T cells fail to release adequate quantities of TGFbeta. These cytokine patterns favor continued autoantibody formation.
Exogenous trigger

Multi-genetic Terrain

Neuro-Endocrine System

Sex Oestrogens Androgens

Immune-Dysregulation

Defective Clearance

Apoptotic Cells
DNA

Auto-antibodies

Immunkomplexes Complement-activation

Organ damage

Rituximab

APC

B

CTLA4-Ig

Helper Cytokine

B-cell-Suppression because of anti-idiotypic Ab and Tregs

T

B
Systemic Lupus erythematosus
Diagnostic Criteria of Lupus erythematosides

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)

Arthritis Rheum 1997;40:1725
Systemischer Lupus erythematodes

Arthralgien >90%
Jaccoud Arthritis 10%

Nierenbeteiligung 50%

Serositis 50%

ZNS-Beteiligung 40%
„Faces“ of Lupus erythematosus

- 'Butterfly' erythema
- Skin
- CDLE
- SCLE
Granular deposits of IgG and IgM at the basal membrane of the skin
**Lunge: Symptome: Dyspnoe, Husten, atemabhängige Schmerzen**

**Pleuritis** (50%)

**Pneumonitis**

**Pulmonale**

**Pulmonale Fibrose** (30% CT Veränderungen)

**Pulmonale Vaskulitis** (<5%)

**Pulmonale Hypertonie** (5-14%)

**DD**

**Lungenembolie**

**Lungenfibrose**

**Diagnostik:** Herzecho, Lungenfunktion, CT, Angio

**Therapie:** Immunsuppression

**Bakt. oder virale Infektion**

**Kardiale, renale Ursache**

**Anämie**

**Diagnostik:** ANA: oft antiRo pos. HRCT, Lungenfunktion, BAL, Biopsie

**DD:** Medikamenten induzierter SLE, MCTD, SSc, Overlap-Syndrome.

**Therapie:** Immunsuppression
Pericarditis (20-30%)  

Libman Sachs Endocarditis  
(15-60% postmortem)

clinics:  - often undetected,  
diagnostics:  - echocardiography  
therapy:  - rarely replacement of valves  
- endocarditis prophylaxis!!
Prognostic factors
Accelerated Arteriosclerosis

Causes:
• Chronic Inflammation
• Immune komplexe-Vasculitis
• Anti Phospholipid-Antibodies
• Lipid levels high (i.e. steroid - induced)
• renal failure, arterial hypertension
Lupus Nephritis (WHO Classification)

I. Minimal mesangial lesion 1%
II. Mesangial hypercellularity /GN 26%
III. Focal proliferative GN 18%
IV. Diffuse proliferative GN 38%
V. Membranous GN 16%
VI. Advanced Sklerosing GN 1-2%
• interstitial Nephritis in 50%

Immunosuppr.
1% none
26% steroids (0.5-1mg/kgKG)
18% steroids +/- MMF
38% steroids + CYC Bolus
16% steroids + CSA

Diagnostik: Klinik, 24-hr Sammelurin
Urinstatus (Blut, Eiweiss, Zylinder), Labor (+CH50, anti dsDNA, anti C1q), US Abdomen, Biopsie**
Therapie: Immunsuppression (CYC, MMF)
Immunfluoreszenz Lupus GN

- leichte Immunglobulin-Kette kappa
- leichte Immunglobulin-Kette lambda
- C5b-9
- Fibrinogen
Labordiagnostik 1

Primärdiagnostik:

Diagnose: **ANA** (antinukleäre Antikörper) wenn bei klinischem V.a. SLE positiv, dann

**ENA** (extrahierbare nukleäre Antigene)

**anti dsDNA AK** (Crithidien)
Labordiagnostik 2

Primärdiagnostik:

Aktivität:

BSG nicht sicher verwertbar

(CRP) meist normal DD: Infekt/Serositis

Komplement (CH50/C3d)

Bei aktivem SLE:

CH50 ↓, (C4 ↓, C3 ↓) C3d ↑

Klassische Komplementaktivierung
Neuropsychiatrischer SLE

Diagnostik:

- NMR
  - Marklager Hyperintensitäten
  - Territoreale Infarkte

- PET
  - Immun-Suppression
<table>
<thead>
<tr>
<th>Hämatologische Beteiligung</th>
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<tbody>
<tr>
<td><strong>Anämie</strong></td>
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<tr>
<td><strong>DD:</strong> Autoimmunhämolytisch, renal, Med. toxisch</td>
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<tr>
<td><strong>Therapie:</strong> Steroide +/- AZA, CYC, Plasmapherese (bei TTP)</td>
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<tr>
<th><strong>Leukopenie/ Lymphopenie</strong></th>
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<tr>
<td><strong>DD:</strong> SLE bedingt: 2.500-4000/µl unter 1.500/µl: z.T. Medikamenten bedingt,</td>
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<td><strong>Therapie:</strong> Meist nicht notwendig, evtl. G-CSF</td>
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<th><strong>Thrombopenie</strong></th>
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<td><strong>DD:</strong> AITP, TTP, Med toxisch</td>
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<tr>
<td><strong>Therapie:</strong> Steroide +/- AZA Danazol, ivlg, anti CD20 Plasmapherese Splenektomie</td>
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Anti-Phospholipid Syndrom

Laborkonstellation
- Phospholipid AK
- Cardiolipin-AK
- β2GPI AK
- PTT Verlängerung
- Lupus Antikoagulans

Plus klinische Symptome
- Thrombozytopenie
- wiederholte Aborte
- Thromboembolie
- Schlaganfälle
- Libman Sacks Endocarditis

Livedo reticularis

Livedo racemosa

Raynaud Phänomen

Arterielle Thromboembolie

Fingernekrosen

Apoplexia capillaris
Diagnostic autoantibodies and autoimmune diseases

- ANA Screening
- ds-DNA SLE
- Sm SLE
- Ro, La Sjögren Syndrome, SLE
- cm limited systemic sclerosis
- Scl-70 diffuse systemic sclerosis
- U1-RNP mixed connective tissue disease
- Jo-1 polymyositis/anti-synthetase syndrome
Other Autoimmune Connectivitides

- Sjögren’s syndrome
- Systemic sclerosis
- Mixed connective tissue disease (MCTD)
- Dermato/polymyositis
- Autoimmune hepatitis
- Undifferentiated connective tissue disease (UCTD)
- Overlap syndromes
Sjögren’s Syndrome

Sjogren’s Syndrome

- eye complaints
  - dryness, burning, itching, foreign body sensation
- keratoconjunctivitis sicca
  - corneal abrasions - rose bengal staining
Autoimmune connective tissue diseases

Common features

- Raynaud phenomenon
- Sicca syndrome (xerophthalmia, xerostomia)
- Serositis (pleuritis, pericarditis)
- Constitutional symptoms (fever, weight loss, sweating during night)
- Arthralgia, arthritis
- ANA positivity
Autoimmune connective tissue diseases

**Discriminating features**

- **SLE**: discoid skin lesions, skin rash (butterfly), renal insufficiency due to glomerulonephriits, CNS involvement, ds-DNA Ab, C-consumption

- **SyScl**: skin induration, sclerodaktyly, interstitial lung disease, pulmonary hypertension, acral skin ulcers, malabsorption, cm or Scl-70 Ab

- **DM/PM**: muscle weakness, skin rash, heart failure, Jo-1 Ab in the minority of cases
Autoimmune connective tissue diseases

**Discriminating features**

- **Sjögren’s syndrome**: severe autoimmune sialadenitis, SS-A and SS-B Ab
- **MCTD**: high titers of RNP Ab, on clinical terms much similarity to SLE, however much less renal involvement
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*)
Treatment principles in autoimmune connectivitides

• artificial lacrimal and salivary fluid (*Sicca-syndrome*)
• skin protection (*dryness, akral lesions*)
• infection prophylaxis upon immunosuppression (*antibiotics, vaccination*)
• active physiotherapy (*against joint contractures, loss of muscle strength, joint deviation*)
• lymphdrainage (*against lymphedema*)
• connective tissue massage (*against cutaneous fibrosis/induration and fibrosing tendovaginitis*)