Vasculitides, Autoimmune Connective Tissue Diseases and Autoinflammatory Disorders
30.3.2017
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RIAl Department of Rheumatology, Immunology and Allergology
Immunologically mediated systemic vasculitides

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

- Arteriole
- Kapillare
- Venole
- Vene

- kleine Arterie
- große bis mittelgroße Arterie
- Aorta

- 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
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)
Doppler sonography

Giant Cell Arteritis
(temporal artery)

Before Tx

8 wks Pred. Tx

Halo
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

T1 pre-contrast  T1 contrast-enhanced
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)
Figure A: Survival rates for relapse and prednisolone dose.

Survival rates:
- Tocilizumab + prednisolone: 50 (46-54)
- Placebo + prednisolone: 25 (11-38)

Mean time to relapse:
- Tocilizumab + prednisolone: 25 (11-39)
- Placebo + prednisolone: 25 (11-39)

P-value: 0.0005

Number at risk:
- Tocilizumab + prednisolone: 20, 17, 17, 17
- Placebo + prednisolone: 10, 5, 2, 2

Figure B: Survival rates for prednisolone dose.

Survival rates:
- Tocilizumab + prednisolone: 38 (35-42)
- Placebo + prednisolone: 50 (46-54)

Mean time to prednisolone dose:
- Tocilizumab + prednisolone: 12 (7-17)
- Placebo + prednisolone: 12 (7-17)

P-value: <0.0001

Number at risk:
- Tocilizumab + prednisolone: 20, 18, 18, 3
- Placebo + prednisolone: 10, 7, 5, 4

Villiger PM et al., Lancet 2016, published online March 4 http://dx.doi.org/10.1016/S0140-6736(16)00560-2
Before 3 months after monthly tocilizumab
Pattern of vessels involved

- Kapillare
- Venole
- Vene
- Arteriole
- kleine Arterie
- große bis mittelgroße Arterie
- Aorta
- Leukozytoklastische Hautvaskulitis
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Panarteritis nodosa

40 % HBV-associated

60 % Non-HBV-associated
Immunopathogenesis of PAN

• Similar to GCA, T-cell mediated (predominantly 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
- Vene
- Venule
- Kapillare

**Arteries**
- große bis mittelgroße Arterie
- kleine Arterie

**Conditions**
- 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
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**
<table>
<thead>
<tr>
<th>ANCAs</th>
<th>associated antigens</th>
<th>disease association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Major antigen:</strong></td>
<td><strong>M. Wegener:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Proteinase 3 (PR3)</strong></td>
<td>Sensitivity: 73 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spezificity: 99 %</td>
</tr>
<tr>
<td></td>
<td><strong>other antigens:</strong></td>
<td>other associations:</td>
</tr>
<tr>
<td></td>
<td>Elastase, Lactoferrin, Kathepsin G, andere?</td>
<td>infections: i.e. endocarditis, Medi: Propylthiouracil, etc.</td>
</tr>
<tr>
<td></td>
<td>Microscop. Polyangiiitis:</td>
<td>Sensitivity: 67 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spezificity: 99 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other associations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IBD, rheumatoid arthritis, others</td>
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**Fluorescence pattern**

- c-ANCA
- p-ANCA
Pathogenesis of granuloma formation in Wegener’s Disease
Pathogenetically relevant therapeutic 'targets'

Pathogenesis of vasculitis in Wegener‘s Disease
AASV

Pathogenetically relevant therapeutic 'targets'

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 localisation)
- microhemaaturia, 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 cylinders  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 autoantigens form immune complexes.
- Autoantigens that are recognized are presented primarily on cell surfaces, particularly by cells that are activated or are 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 CpGDNA 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 IFN gamma, IL6, IL10, while NK and T cells fail to release adequate quantities of TGF beta. These cytokine patterns favor continued autoantibody formation.
Release of neutrophil extracellular traps (NETs) by neutrophils and the activation of plasmacytoid dendritic cells direct the chronic interferon-α production observed in SLE.

1. Type I interferons prime the neutrophils for NETosis, with translocation of LL-37 (an antimicrobial peptide) to the surface. NETosis begins by the binding of surface LL-37 by anti–LL-37 autoantibodies.

2. NETs released from dying neutrophils are taken up by plasmacytoid dendritic cells as a NET-associated LL-37–DNA immune complex, together with anti–LL-37 or anti-DNA autoantibodies.

3. NET-associated self DNA engages toll-like receptor 9 (TLR9) in endosomes, leading to interferon release and additional neutrophil priming. Moreover, neutrophil-derived antimicrobial peptides such as LL-37 are used as B-cell autoantigens in combination with DNA. As a result, abundant NET creation may also prompt autoreactive B-cell activation, possibly through the capacity of NETs to engage B-cell receptors and TLR9 in B cells, leading to the release of anti–LL-37 and anti-DNA autoantibodies.

IFNAR denotes type I interferon-α receptor.
Exogenous trigger

Multi-genetic Terrain

Neuro-Endocrine System

Sex Oestrogens Androgens

Immune-Dysregulation

Defective Clearance

Apoptotic Cells
DNA
Auto-antibodies

Immunocomplexes Complement-activation

Organ damage

Rituximab, Belimumumab

CTLA4-Ig

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

Helper ↑ Cytokine

B

APC

T
Systemic Lupus erythematosus
Diagnostic Criteria of Lupus erythematosus

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)
Arthralgien >90%
Jaccoud Arthritis 10%

Nierenbeteiligung 50%
Serositis 50%

ZNS-Beteiligung 40%

Systemischer Lupus erythematodes
"Faces" of Lupus erythematosus

- 'Butterfly' erythema
- SCLE
- CDLE

Skin images showing various types of lupus rash.
Granular deposits of IgG and IgM at the basal membrane of the skin
**Heart**

**Pericarditis** (20-30%)  
**Libman Sachs Endocarditis**  
(15-60% postmortem)

- **Clinics:** often undetected,
- **Diagnostics:** echocardiography
- **Therapy:** rarely replacement of valves
  - endocarditis prophylaxis!!
# Kidney

**Lupus Nephritis (WHO Classification)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Minimal mesangial lesion</td>
<td>1%</td>
<td>none</td>
</tr>
<tr>
<td>II. Mesangial hypercellularity /GN</td>
<td>26%</td>
<td>26% steroids (0.5-1mg/kgKG)</td>
</tr>
<tr>
<td>III. Focal proliferative GN</td>
<td>18%</td>
<td>18% steroids +/- MMF</td>
</tr>
<tr>
<td>IV. Diffuse proliferative GN</td>
<td>38%</td>
<td>38% steroids + CYC Bolus</td>
</tr>
<tr>
<td>V. Membranous GN</td>
<td>16%</td>
<td>16% steroids + CSA</td>
</tr>
<tr>
<td>VI. Advanced Sklerosing GN 1-2%</td>
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<tr>
<td>• interstitial Nephritis in 50%</td>
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**Diagnostics:**
- clinics, 24-hr urine collection
- urine status (ery, protein), laboratory (C3/4, anti dsDNA, anti C1q), US abdomen, renal biopsy

**Therapy:**
- immunosuppression (CYC, MMF)
Neuropsychiatric SLE

Diagnostics:

MRT

- subcortical hyperintensity
- territorial insults

PET

Immunosuppression
Anti-Phospholipid Syndrome

**Laboratory**
- phospholipid ab
- cardioplin-Ab
- β2GPI ab
- PTT prolongation
- Lupus Antikoagulans

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

**Imaging**
- livedo reticularis
- livedo racemosa
- Raynaud phenomenon
- arterial thromboembolism
- necrosis of finger tips
- apoplexia capillaris
# Hematological manifestations

<table>
<thead>
<tr>
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<th>DD:</th>
<th>Therapy:</th>
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<tbody>
<tr>
<td><strong>anemia</strong></td>
<td>autoimmunehemolytic, renal, drug-induced</td>
<td>steroids +/- AZA, CYC, plasmapheresis (with TTP)</td>
</tr>
<tr>
<td><strong>leukopenia/lymphopenia</strong></td>
<td>SLE-induced, drug-induced</td>
<td>mostly not necessary, G-CSF</td>
</tr>
<tr>
<td><strong>thrombopenia</strong></td>
<td>AITP, TTP, drug-induced steroide +/- AZA</td>
<td>danazol, ivlg, anti CD20, plasmapheresis, splenectomy</td>
</tr>
</tbody>
</table>
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:

- C3
- C3a
- Klassische Komplementaktivierung
- C3b
- C3d

Bei aktivem SLE:

- CH50 ↓
- (C4 ↓, C3 ↓)
- C3d ↑
- Anti dsDNA Antikörper
- Immunkomplex
- CRP (meist normal)
- DD: Infekt/Serositis

Komplement (CH50/C3d)

BSG nicht sicher verwertbar
Diagnostic autoantibodies and autoimmune diseases

- **ANA** Screening
- **ds-DNA** SLE
- **Sm** SLE
- **C1q** SLE; if absent, renal disease is very unlikely
- **SS-A/B** 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
Sjogren’s Syndrome

- eye complaints
  - dryness, burning, itching, foreign body sensation
- keratoconjunctivitis sicca
  - corneal abrasions - rose bengal staining
R. H. 1929  Aufn. vom 29.9.05
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 glomerulonephritits, CNS involvement, ds-DNA Ab, C-consumption

- **SyScI**: 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)
• alkylation 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*)
Classification of Inflammatory Processes

Pathogen

yes

Infection

no

Auto-Antigen
Autoreactive T/B cells
Autoantikörper

yes

Autoimmunity

no

Autoinflammation
Allocation of the Innate and Adaptive Immune System to Autoinflammation and Autoimmunity

**Auto-Antigen**
**Autoreactive T/B cells**
**Autoantibodies**

- **yes**
  - **Autoimmunity**
    - **Adaptive Immune System**

- **no**
  - **Autoinflammation**
    - **Innate Immune System**
Cryopyrin-associated periodic fever syndromes (CAPS)

Clinical Presentations

Nature Reviews Rheumatology


NOMID/CINCA

http://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)
Pathogenesis
Gouty inflammation
The Inflammasome and gout

Martinon et al., JCI 2006
MSU crystals

CD14

MYD88

NALP3

Caspase 1

ASC

Pro-IL1β

NFκB mediated cell activation

phagocytosis

Endothelium/leucocyte

IL1β

caspase-1

monocyte

Anakinra (Kineret®)

endothelial activation

Endothelium/leucocyte

TLR2/4
Key Messages 'Autoinflammatory Diseases'

- Autoinflammatory syndromes may be genetically-linked diseases (*hereditary periodic fever syndromes*) many of which exhibit enhanced NALP3/inflammasome activity.
- This is also true for crystal-induced arthritis (*gout*).
- Autoinflammatory syndromes are mostly IL-1 driven and can successfully be treated with anti-IL-1 strategies (i.e., IL-1 receptor antagonist, IL-1β monoclonal antibody).