Diseases of the immune system

Lecture II.
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Autoimmune diseases

• **Definition:**
  – immune reaction to *self-antigens*

• **Pathomechanism:**
  – failure of *self-tolerance*

• **Consequence**
  – inflammation - tissue damage,
  – loss of function /rarely: increased function due to cell activation, cell proliferation

• **Self tolerance**
  – No immun reaction against self antigens=*anergy*:
Development of self-tolerance

Tolerance = unresponsiveness

CENTRAL TOLERANCE
develops in primary lymphoid organs

PEERIPHERAL TOLERANCE
1. anergy
2. suppression by regulatory T cells
3. apoptosis
Failure of self-tolerance

= Presence of self-reactive B, T lymphocytes

GENETIC background:
Inheritance of susceptibility genes: HLA, immun regulatory genes,
example: HLA-DR4 linked to rheumatoid arthritis

INFECTIONS:
1. Molecular mimicry - rheumatic fever
2. Breakdown of T-cell anergy - infections upregulate APCs

TISSUE INJURY:
Tissue injury can release or change self-antigens:
Traumatic uveitis (sympathetic ophthalmia), orchitis.
Autoimmune diseases

• **Systemic diseases**
  affect principally the connective tissue and blood vessels: "collagen vascular" or "connective tissue" disorders

• **Organ specific**
  directed against one particular organ or cell type, that results in localized tissue damage
In general

- Female predominance
- Young adults
- Chronic course
- Immunsupression
- Intercurrent infections
- Autoantibodies
- Overlapping syndromes (systemic forms)
Most important systemic autoimmune diseases

- Systemic lupus erythematosus- SLE
- Systemic sclerosis- SS
- Rheumatoid arthritis- RA
- Dermatomyositis
Systemic Lupus Erythematosus (SLE)

- **Common disease**: 1 case per 2500, female predominance 9:1
- **Any organ can be affected**: skin, kidneys, serosal membranes, joints, and heart.
- **Discoid lupus**: only skin involvement
- **Genetic predisposition**: HLA-DR2 or HLA-DR3 3-5 xrisk
- **Clinical presentation variable**, overlaps with other autoimmune diseases (rheumatoid arthritis, polymyositis, and others)
Mechanism of autoantibody production

- Inherited susceptibility genes
  - Class II MHC
  - Complement
  - Other

- Environmental triggers (e.g., UV irradiation)

  - Cellular apoptosis

  - Nuclear proteins, other self-antigens

  - Defective clearance of nuclear antigens

  - Activation of helper T cells and B cells specific for self-antigens

  - IgG autoantibody production

  - Immune complex and autoantibody-mediated tissue injury

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• Autoantibodies:
  – **Antinuclear antibodies (ANAs)** against DNA, histones, nucleolar antigens - immune complex formation - **type III hypersensitivity**
  – **Cell surface antibodies** against blood cells, including red cells, platelets, and lymphocytes - cytopenias - **type II hypersensitivity**
  – **Antiphospholipid antibody** (cell membrane component) "lupus anticoagulants" (prolonged clotting time) prothrombotic state - venous and arterial thromboses - **type II hypersensitivity**
  – **Anticardiolipin antibody** - false + test for syphilis
Vasculitis caused by type III hypersensitivity

Organs involved: kidneys, joints, skin and small blood vessels in many tissues.

Acute necrotizing vasculitis with fibrinoid necrosis
Skin

- Butterfly rash over the face
  - immunocomplex deposition
- Photosensitivity
  - UV light causes apoptosis

Heart

- Fibrinous pericarditis
- Libman-Sacks endocarditis
  - immunocomplex deposition
  - sterile vegetations = small thrombus
Kidney - Lupus nephritis

- Chronic glomerulonephritis

  - Histology:

  Membranous glomerulonephritis

  Proliferative

**Immunofluorescence microscopy**

- deposition of immunocomplexes in the capillary walls
Joints, serosal membranes, CNS

- **Arthritis**: nonspecific
- **Serositis**: serous effusions to fibrinous exudates, pericarditis
- **CNS involvement**: Seizures-vascular lesions caused by microthrombuses- ischemia or multifocal cerebral microinfarcts (antiphospholipid antibodies)

**Major causes of death:**
1. Renal failure,
2. Intercurrent infections,
3. Diffuse CNS involvement
(5 year survival :95%)
Clinical diagnostic criteria: at least 4 out of 11 symptoms

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1. Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
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<td>2. Discoid rash</td>
<td>Erythematous raised patches with adherent keratic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
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<td>3. Photosensitivity</td>
<td>Rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
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<td>4. Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
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<td>5. Arthritis</td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
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<td>6. Serositis</td>
<td>Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion</td>
</tr>
<tr>
<td>7. Renal disorder</td>
<td>Persistent proteinuria &gt;0.5 g/mL or &gt;3 if quantitation not performed or Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td>8. Neurologic disorder</td>
<td>Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)</td>
</tr>
<tr>
<td>9. Hematologic disorder</td>
<td>Hemolytic anemia—with reticulocytosis, or Leukopenia—≤4.0 × 10^9 cells/L (4000 cells/mm³) total on two or more occasions, or Lymphopenia—≤1.5 × 10^9 cells/L (1500 cells/mm³) total on two or more occasions, or Thrombocytopenia—≤100 × 10^9 cells/L (100 × 10^12 cells/mm³) in the absence of offending drugs</td>
</tr>
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<td>10. Immunological disorder</td>
<td>Anti-DNA antibody to native DNA in abnormal titer, or Anti-Sm—presence of antibody to Sm nuclear antigen, or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM antiphospholipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative Treponema pallidum immobilization or fluorescent treponemal antibody absorption test</td>
</tr>
<tr>
<td>11. Antinuclear antibody</td>
<td>An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome</td>
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*This classification, based on 11 criteria, was proposed for the purpose of identifying patients in clinical studies. A person is said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

Rheumatoid Arthritis

- 1% of the population
- F/M : 3-4/1
- Symmetric chronic arthritis, principally affecting the small joints

- Systemic disease: extra-articular involvement: skin, heart, blood vessels, muscles, and lungs- RA may resemble SLE or scleroderma

proximal interphalangeal and metacarpophalangeal joints
Chronic inflammatory synovitis

**Pathomechanism:** Type IV hypersensitivity
CD4+ helper T cell mediated

**Activation:** macrophage
endothelial cells
B-cell

**Production of autoantibodies:**
*rheumatoid factor* (RF)- *IgM/ IgG* against Fc portions of their own (self) IgG

*HLA-DR4*
- **Chronic inflammatory synovitis**
  - **Pannus**: proliferating synovial-lining cells admixed with inflammatory cells, granulation tissue, and fibrous connective tissue;

- **Rheumatoid subcutaneous nodules**
  - **Granulomas** ~2 cm diam. with necrobiotic center.

- **Serositis**: fibrinous pleuritis or pericarditis
Late consequences:

- **Progressive joint destruction** leading to disability after 10-15 years.

Ankylosis: loss of flexibility due to fibrosis and calcification

- **Ulnar deviation**

- 5-10% **amyloidosis** (chronic inflammation) therapy: cytokine (TNF) antagonists
Systemic Sclerosis/ SS Scleroderma

- Fibroblast activation with excessive fibrosis, microvascular injury

1. Limited scleroderma: Skin

2. Diffuse scleroderma: Skin+ gastrointestinal tract, lungs, kidneys, heart, and skeletal muscles
Pathomechanism: CD4+ T cell activation

Autoantibodies ANAs

Immune complex

Type III Hypersensitivity

PDGF, TGFβ
IL1, FGF

Damage periadventitial fibrosis and narrowing ischemic injury

Inflammation, fibrosis, atrophy

Type IV Hypersensitivity
Limited Scleroderma - CREST syndrom

The limited symptoms of scleroderma are referred to as CREST:

- **C**alcinosis - calcium deposits in the skin
- **R**aynaud's phenomenon - spasm of blood vessels in response to cold or stress
- **E**sophageal dysfunction - acid reflux and decrease in motility of esophagus
- **S**clerodactyly - thickening and tightening of the skin on the fingers and hands
- **T**elangiectasias - dilation of capillaries causing red marks on the surface of the skin
Limited scleroderma-Skin

Raynaud's phenomenon: In 70% of the patients this is the first symptom
Induced by cold, emotion
Results: vasoconstriction, hypoxia ➔ ulcers, gangrene

EARLY phase

LATE phase

ULCERS

Sclerosis, atrophy
Skin involvement:

1. Involvement of the fingers and hands to wrist - acrosclerosis
   Face - mask like
   Fingers: sclerodactily

2. Proximal extremity: ascending sclerosis including the forearm

3. Sclerosis at the trunk.
Diffuse scleroderma - visceral involvement

Gl tract involvement: in 90% of the patients
Tongue: sclerosis of the frenulum
Oesophagus: dysmotility: fibrosis, gastroesophageal reflux- Barrett metaplasia

Lung: 50% of the patients
Interstitial fibrosis- pulmonary hypertension

Diagnosis: serology, detection of autoantibodies:
  - Diffuse Scleroderma specific ANA:
    • DNA-topoisomerase (70%)
  - Limited scleroderma specific ANA:
    • anticentromere antibody (90%)
Sjögren syndrome

- Dry eyes - keratoconjunctivitis sicca
- Dry mouth - xerostomia
- Pathomechanism: Type IV. HS, CD4+ T
- **Diagnosis:**
  - Histology of small salivary glands: lymphocytic infiltration, fibrosis
  - Serology: SS-A, SS-B- anti-ribonucleoprotein antibodies (70%-reumatoid factor)
Xerostomia

• **Causes:**
  – Sjögren’s,
  – radiation therapy
  – medications! (anticholinergic, antidepressant/antipsychotic, diuretic, antihypertensive, sedative)

• **Consequence:**
  – atrophy of the papillae of the tongue, with fissuring and ulcerations,
  – dental caries, candidiasis,
  – difficulty in swallowing and speaking.
Organ-specific autoimmune diseases

- **Liver**: autoimmune hepatitis, PBC, PSC
- **Pancreas**: autoimmune pancreatitis
- **Suprarenal gl**: autoimmune adrenalitis
- **Thyroid gland**: Hashimoto thyroiditis, Graves disease
Autoimmune hepatitis

- **Pathomechanism:** CD4+ helper T cell mediated reaction
  - Association with other autoimmune diseases (60%): RA, IBD, Sjögren sy.
- **Female** predominance (70%)
- **Clinical picture:** Mild-severe chronic hepatitis, 5% of the cases progress to cirrhosis and death.
- **Diagnosis:** Presence of autoantibodies: anti-SMA, liver/kidney microsomal antibodies.
Primary biliary cirrhosis - PBC

Chronic, progressive liver disease - middle aged women

**Diagnosis:**
- Serology, anti-mitochondrial antibodies – AMA - 90%
- Histology: Chronic cholangitis, cholestasis (green liver), micronodulare cirrhosis
Primary sclerosing cholangitis PSC

-Chronic cholestatic liver disease associated with destruction of intra- and extrahepatic bile ducts of all size, leading to secondary biliary cirrhosis

-Association with ulcerative colitis (70%)

Diagnosis: Histology, cholangiography
Addison disease

- **Primary insufficiency of the adrenal cortex**
  - Autoimmune adrenalitis: 60-70% of primary adrenal insufficiency
  - Other causes of adrenal insufficiency: TBC, AIDS, metastasis-lung cancer

- **Cause**: genetic: mutation of the autoimmune regulator gene, FAILURE OF CENTRAL SELF-TOLERANCE

- **Histology**: lymphocytic infiltration,

- **Symptoms**: weight loss, fatigue, anorexia, depression, skin hyperpigmentation
Hashimoto thyreoiditis

- CD8+ and CD4+ T-cell and antibody mediated tissue injury (*anti-thyroglobulin antibodies*)
- Histology: lymphocytic infiltration with germinal centers
Graves disease- diffuse goiter

- Mediated by anti-TSH receptor stimulating antibodies- TYPE II. HS
- Clinical symptoms (triad):
  - Symmetric enlargement of the gland + hyperthyroidism
  - Exophtalmus
  - Pretibial myxoedema
IMMUNODEFICIENCY

• **primary**
  – **inherited defects** affecting immune system development **SEVERE**

• **secondary**
  – effects of other diseases
    • 1. infections/sepsis **SEVERE-MODERATE**
    • 2. immunosuppressiv therapy-transplantation!
    • 3. chemotherapy
    • 4. malignant tumors
    • 5. autoimmunity
    • 6. aging **MILD**
    • 7. malnutrition
    • 8. chronic diseases (liver, kidney)
Primary immunodeficiency

• Early diagnosis (6 month-2 years)
• Pathological T cell, B cell development and mixed diseases
• Clinical symptoms: Infections
  – T cell deficiency: Viral (herpes, varicella/zoster), fungal (candida, cryptococcus), protozoal (toxoplasma) intracellular bacteria (tuberculosis).
  – B cell def.: streptococcus, staphylococcus, haemophilus
X-Linked Agammaglobulinemia: Bruton Disease

- Failure of B cell differentiation
- X-linked disease - women are carriers
- Underdevelopment of lymphoid tissues,
- Absence of immune globulins, normal T cell-mediated responses
- Bacterial infections
- Increased risk for autoimmune diseases
Thymic Hypoplasia: DiGeorge Syndrome

- **Congenital defect in thymic development with deficient T cell maturation.**
- **Infections:** Viral (varicella/zoster), fungal (candida, cryptococcus), and protozoal (toxoplasma) infections and infection with intracellular bacteria (tuberculosis).
- **Treatment:** transplantation of thymic tissue
Severe combined immundeficiency (SCID)

- Different genetic background (mutation of the immun regulatory molecules - IL)
- Hypoplasia of all lymphoid tissues
- Early death due to infections
- Opportunistic infections: candida, pneumocystis, CMV, pseudomonas.
Wiskott-Aldrich syndrome combined immundeficiency with thrombocytopenia and ecema

• X-linked recessive disease-males
  – Mutation of the Wiskott-Aldrich syndrome protein- links several membrane receptors to the cytoskeleton

• Progressive age-related combined immundeficiency
  – depletion of T lymphocytes, decreased antibody production-

• Early death- infections, malignant lymphoma
Isolated IgA Deficiency

- Most common, 1:700
- Block of differentiation of B cells to IgA secreting plasma cells
- Lack of IgA- weakened mucosal defenses predispose patients to recurrent sinopulmonary infections and diarrhea.
- Increased risk for autoimmune diseases
Acquired Immuno deficiency Syndrome

- Infection: human immunodeficiency virus (HIV) human retrovirus (RNA)
- depletion of CD4+ T lymphocytes, and by profound immunosuppression leading to -
  - secondary neoplasms,
  - opportunistic infections
  - neurologic manifestations
- 95% of HIV infections are in developing countries
- 35 million people infected, new infections 5 million/ year
- new anti-retroviral drugs!
Transmission

CLOSE CONTACT NEEDED
Exchange of blood or body fluids (seminal fluid) that contain the virus or virus-infected cells

• Sexual Transmission - homosexual and heterosexual contacts-increasing!
• Parenteral Transmission - intravenous drug abusers, (recipients of blood transfusion)
• Mother-to-Infant Transmission (>10%)
• Through nonintact skin - health care workers
  – accidental needle-stick injury or exposure of nonintact skin to infected blood
  – seroconversione rate about 0.3% per accidental exposure- antiretroviral drugs!!!
Infection

CD4 molecule - high-affinity receptor for the virus
Infected cells: CD4+ T cells, macrophages, dendritic cells.
Disease course

1. Latent infection (3-6 week):
   - HIV proviral cDNA in quiescent T cells
   - Dividing T cells: integrated into the host genome

2. Acut phase/productive infections (influenza-like syndrome):

3. Chronic phase (silent): lymph nodes and the spleen are sites of continuous HIV replication and cell destruction

4. AIDS - decline in the number of CD4+ T cells >200/µl blood
Opportunistic infections

- **Viral**: Herpes simplex, herpes zoster, cytomegalovirus
- **Bacterial**: tuberculosis-mycobacterium avium intracellulare
- **Fungal**: Candidiasis, pneumocystis, cryptococcus, aspergillus
- **Protozoon**: toxoplasma
Viral infections

Herpes labialis
Herpes simples virus 1

Herpes zoster varicella

Oral hairy leukoplakia EBV
Bacterial infections

Atypical mycobacteriosis: mycobacterium avium intracellulare complex (MAC)
Disseminated disease - lungs+GI
No granulomatosus reaction

Acid-fast staining - Ziehl-Nielsen
Fungal infections

**Candidiasis**: *candida albicans*

Soor oris  oesophagitis

PAS reaction
Pneumocystis jiroveci pneumonia

Foamy exudate - cysts with silver stain

Grocott
PROTOZOAL INFECTION
Toxoplasma encephalitis

*Toxoplasma gondii* -is one of the most common causes of neurologic (focal and diffuse) symptoms and morbidity in persons with AIDS

Endogen reinfection

Obligate intracellular protozoon

Source: cat

Histology: abscess:
Increased risk for malignancy

• Kaposi-sarcoma
  – Brownish macules, nodules on the skin
  – Low malignancy, dermal vascular tumor (endothelial cells)
  – Localisation: head, face, ears, neck, oral cavity

• Non-Hodgkin lymphoma
Graveyard in Africa- 250000 dead/ 1 year
ORGAN TRANSPLANTATION

• **Allografts**-between same species/human-human (xeno- different species)

• **History**: 1st. 1954-kidney identical twins, 1962 in Hungary

• **Transplanted organs**: kidney, liver, pancreas, lung, heart, bone marrow

• **Source**: brain-dead individuals kept on respiratory machine (2% alive donors-kidney, liver)
Complications of transplantation

- **Rejection** of the organ (host versus graft)
  – Cell- and antibody-mediated hypersensitivity reactions directed against HLA molecules on the foreign graft
- **Graft versus host disease** - bone marrow transplantation- skin, GI tract, liver
- **Infections** due to immununsuppression (secondary immundeficiency)
- Late: post-transplant lymphoproliferative disease (PTLD)
TYPES OF GRAFT REJECTION

Hyperacut rejection - in minutes
Humoral reaction: - mediated by preformed antidonor antibodies

Akut rejection - 0-3 month,
1. Cellular (90%) - mediated by CD8+, CD4+ T cells and NK cells against HLA antigens
2. Humoral (10%) - HLA, endothelial antigens IgG+complement aktivation.

Chronic rejection - month, years
Cellular - T cell reaction/ cytokines
Morphologic patterns of graft rejection

Hyperacute Vasculitis - Fibrinoid necrosis, thrombosis

Acute cellular Tubulitis - T cell and macrophage infiltration

Acute humoral Vasculitis - T cell and granulocytes

Chronic Arteriolosclerosis, Fibrosis mediated by cytokines