Immune system pathology

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Physiologic function

Protection + defence against external and/or internal noxae

- Defence against infection incl. toxic products
- Autotolerance against body-own antigenes
- Immunologic internal control (removal of old, defective, some mutated cells)

Failure possible due to inadequate immune function and/or too violent (event. evasive) noxae

Disorders of the immune system

Exaggerated immune reaction

- Hypersensitivity reactions
- Autoimmune disorders

Transplantation immunopathology

Defective immune reaction

- Immunodeficiency (primary, secondary)

Hypersensitivity

Hypersensitivity reactions

- sensitisation (previous exposition to an antigen) + repeated exposure → possible pathologic (excessive) response: hypersensitivity – imbalance between effector mechanisms of immune responses and control (+limiting) mechanisms
- antigens exogenous (chemicals, organic substances incl. microorganisms, …); endogenous (autoimmune diseases)
- association with inheritance of particular susceptibility genes (HLA, non-HLA)
- abnormal – excessive/misdirected/poorly controlled reaction to common not harmful antigenes and/or self antigenes
- same effector mechanisms as in normal immune reaction

Hypersensitivity

Classification according to the immunologic mechanism (→ mode of tissue injury and disease, manifestations) + time of response

Commonly multiple mechanisms in any one disease

- Antibody-mediated allergies are immediate and subacute hypersensitivities
- The most important cell-mediated allergic condition is delayed hypersensitivity

Hypersensitivity reactions

Immediate (type I) hypersensitivity

- Rapid immunologic reaction occurring within minutes after the combination of an antigen with IgE bound to mast cells in individuals previously sensitized to the antigen („allergen“).
- Systemic disorder or local reaction.
- Anaphylaxis; allergies; bronchial asthma (atopic forms)
- Vascular dilatation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation

Immediate (type I) hypersensitivity

- Anaphylaxis: systemic reaction mostly after injection of an antigen into a sensitized individual. In minutes → shock (may be fatal).
- Causes: foreign proteins, polysaccharides, drugs (penicillin), food (nuts, shellfish), insect toxins
- Starts with itching, hives, and skin erythema
- Contraction of bronchioles → respiratory distress. Laryngeal edema → hoarseness
- Vomiting, abdominal cramps, diarrhea
- Vascular shock, widespread edema

Immediate (type I) hypersensitivity

- Local reactions: diverse, according to the entry of the allergen. Localized cutaneous swellings (skin allergy, hives);

  nasal and conjunctival discharge (allergic rhinitis and conjunctivitis);

  hay fever; bronchial asthma;

  allergic gastroenteritis (food allergy).

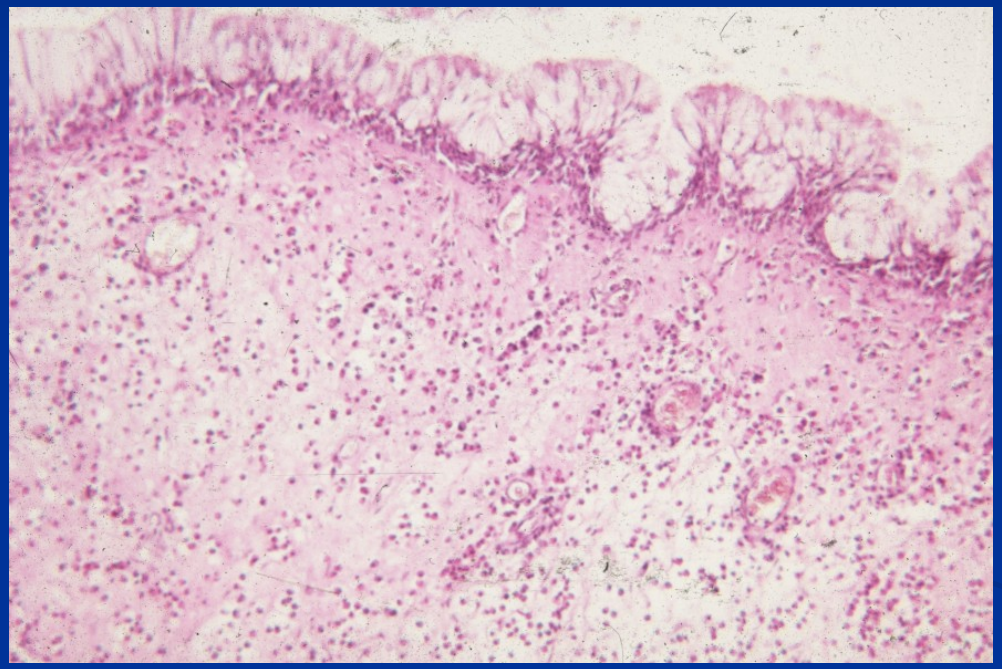
Immediate (type I) hypersensitivity

- The immediate or initial reaction: IgE production +T_H2 response → release of preformed mediators of mast cells (histamin, etc.)→ vasodilation, vascular leakage, edema, smooth muscle spasm or glandular secretions (mucus production)
- Evident within 5 - 30 minutes after exposure to an allergen, usually ↓ in 60 minutes

Immediate (type I) hypersensitivity

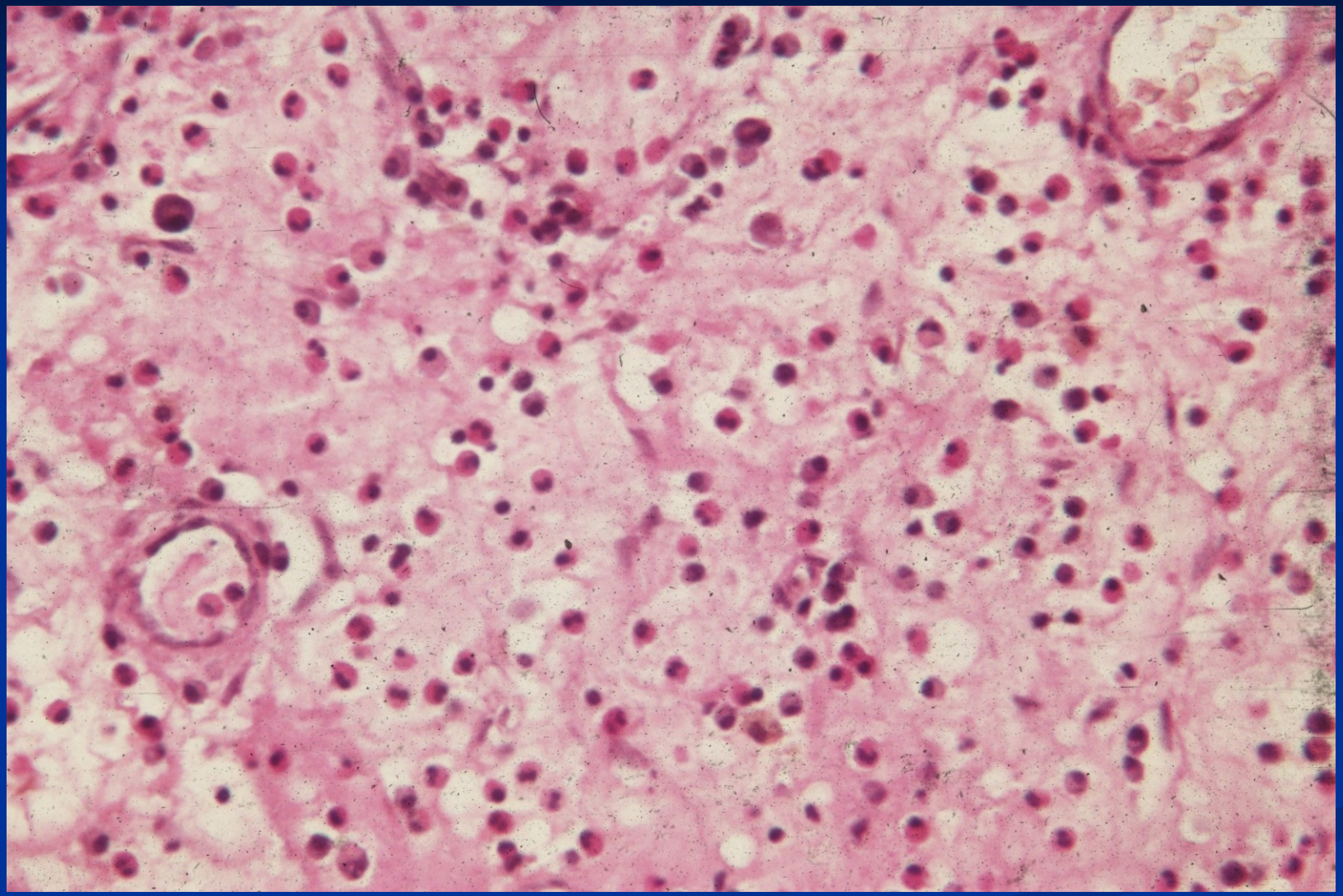
- Late-phase reaction (e.g., allergic rhinitis and bronchial asthma) in 2 - 24 hours later
- Without additional exposure to antigen, inflammatory reaction sustained by reactive cells recruited by sensitised T-cells, may last for several days.
- Infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells; tissue destruction (mucosal epithelial cell damage by major basic protein MBP, etc.).

Allergic rhinitis



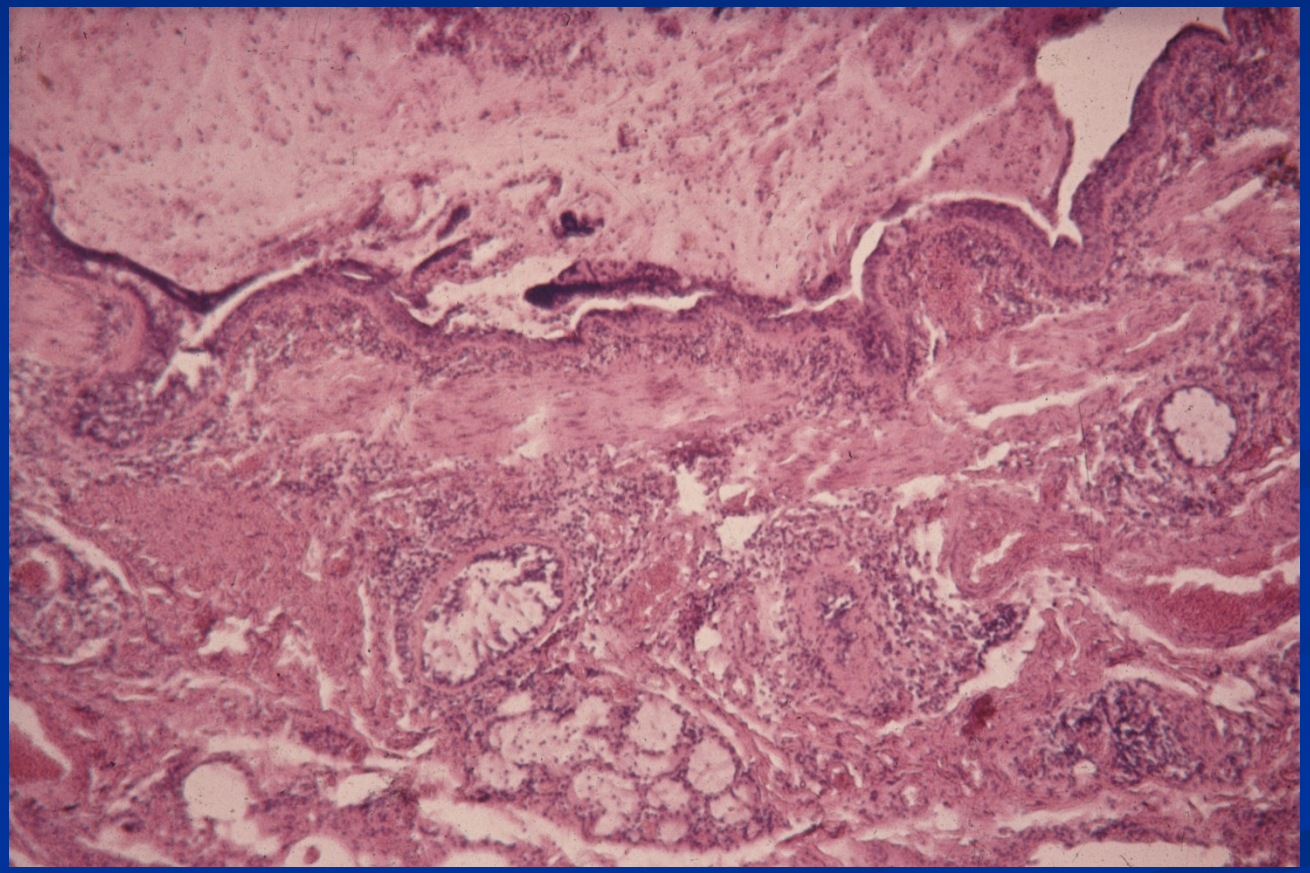
Hyperemia + edema, mucus hyperproduction, reactive cells

Allergic rhinitis



Reactive infiltrate with eosinophils, mast cells, neutrophils, lymphocytes

Bronchial asthma



Smooth muscle and mucus glands hypertrophy, mucus hyperproduction, reactive infiltrate

Atopy

- **Genetically determined susceptibility to immediate hypersensitivity reactions.**
- **Atopy:** predisposition to develop localized immediate hypersensitivity reactions to a variety of inhaled and ingested allergens.
- ↑ serum IgE levels, ↑ IL-4–producing TH2 cells
- Positive family history of allergy in 50% of atopic individuals.
- Atopic eczema, allergic rhinitis, asthma (+ secondary hyper-responsiveness of bronchial mucosa to non-specific irritants, e.g. cold, tobacco smoke,… secondary neural triggering.)

Antibody-mediated (type II) hypersensitivity

- Onset usually slow (1–3 hours) after antigen exposure
- Production of IgG, IgM → binding to antigen on target cell or tissue → phagocytosis or lysis of target cell (by activated complement, etc.); recruitment of leukocytes
- Inflammation
- In some diseases functional problems without cell or tissue injury (type V hypersensitivity – Graves‘ disease)

Antibody-mediated (type II) hypersensitivity

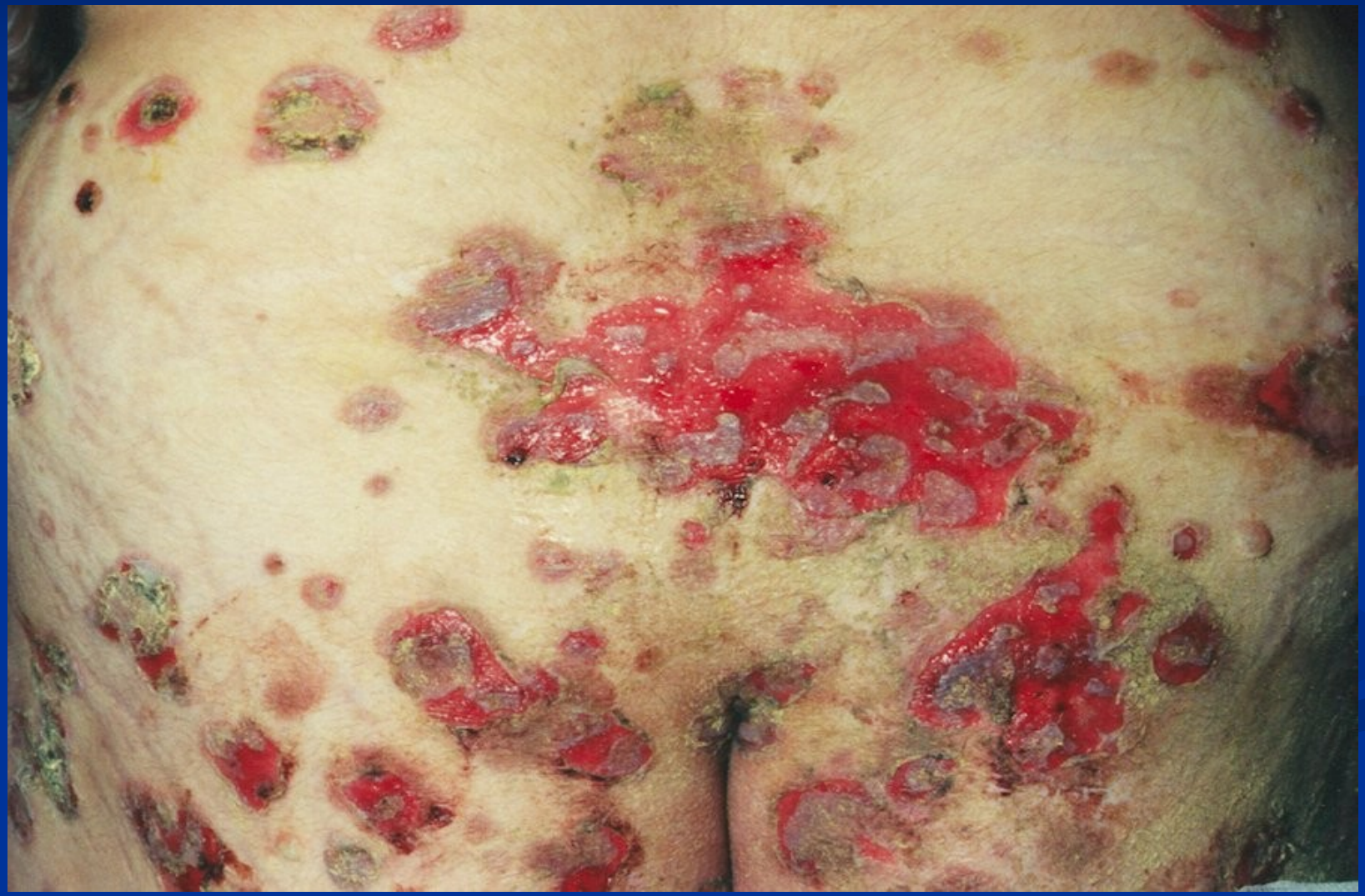
- Transfusion reactions: preformed antibody in the host
- Hemolytic disease of the newborn (fetal erythroblastosis): IgG from the mother cross the placenta → destruction of fetal red cells
- Part of drug reactions: drug attaching to the cell surface proteins, AB x drug-membrane protein complex
- Autoimmune blood cells destruction → anemia, purpura (bleeding)

Antibody-mediated (type II) hypersensitivity

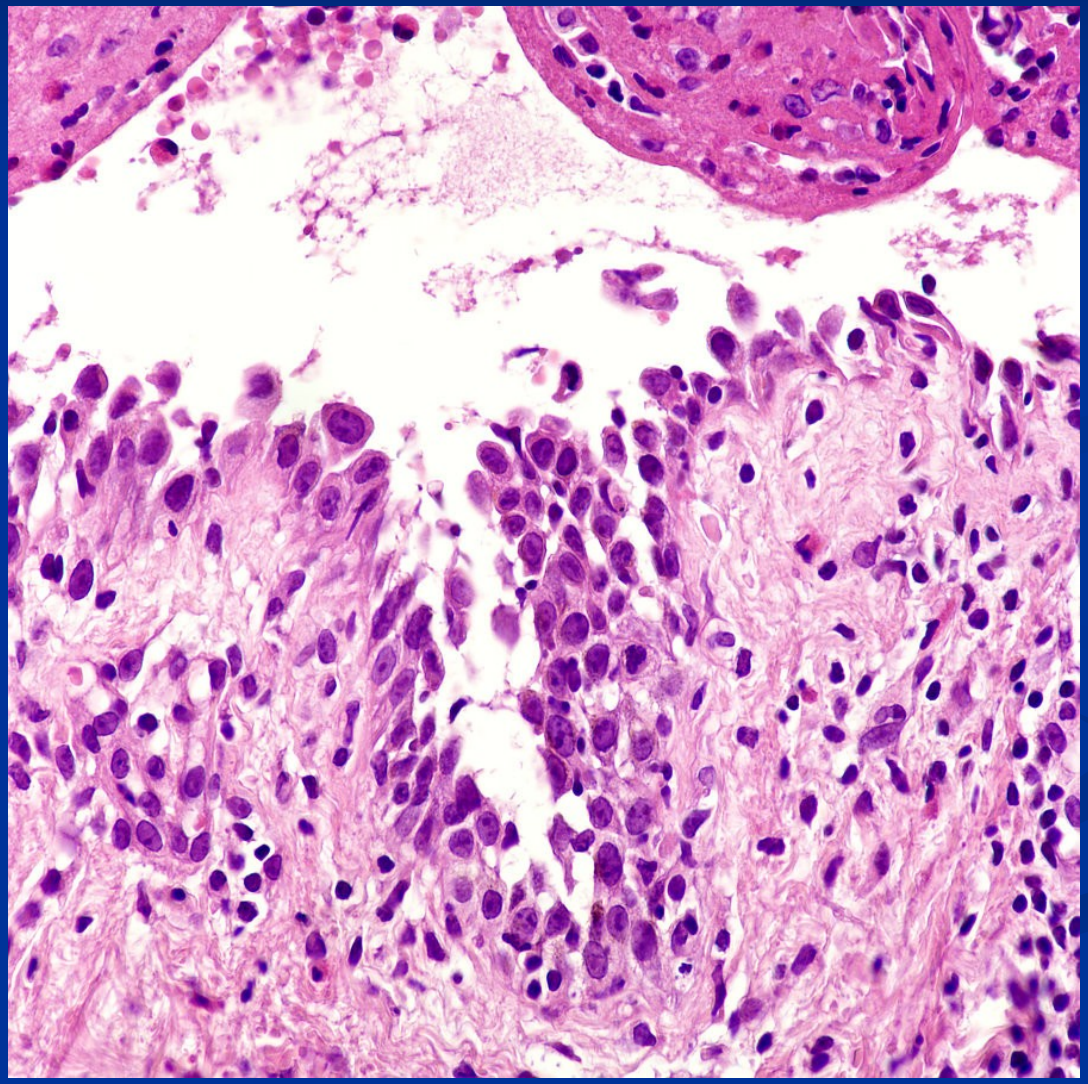
Inflammation

- Pemphigus vulgaris: Target proteins in intercellular junctions of epidermal cells (epidermal cadherin) → antibody-mediated activation of proteases, disruption of intercellular adhesions → skin vesicles (bullae)
- Vasculitis caused by ANCA: → neutrophil degranulation and inflammation → vasculitis (see the special lecture on vasculitis)

Pemphigus vulgaris



Pemphigus vulgaris – acantholytic bulla



Antibody-mediated (type II) hypersensitivity

- Goodpasture syndrome: target protein in basement membranes of kidney glomeruli and lung alveoli → nephritis, lung hemorrhage
- Acute rheumatic fever: Streptococcal cell wall antigen; antibody cross-reaction → myocarditis, arthritis
- Insulin-resistant pre/diabetes: Insulin receptor as target
- Acute vascular rejection in organ grafts

Antibody-mediated (type II) hypersensitivity

Cellular dysfunction – metabolism affected

- Graves disease (hyperthyroidism): target TSH receptor → antibody-mediated stimulation of TSH receptors → hyperthyroidism

Hypersensitivity reactions

Immune complex–mediated (type III) hypersensitivity

Antigens widely distributed through the body or blood → stimulation, production of IgG, circulating/local antigen-antibody complexes.

- Deposition of antigen-antibody complexes (vessel wall)→ complement activation → recruitment of leukocytes → release of enzymes and other toxic molecules

Immune complex–mediated (type III) hypersensitivity

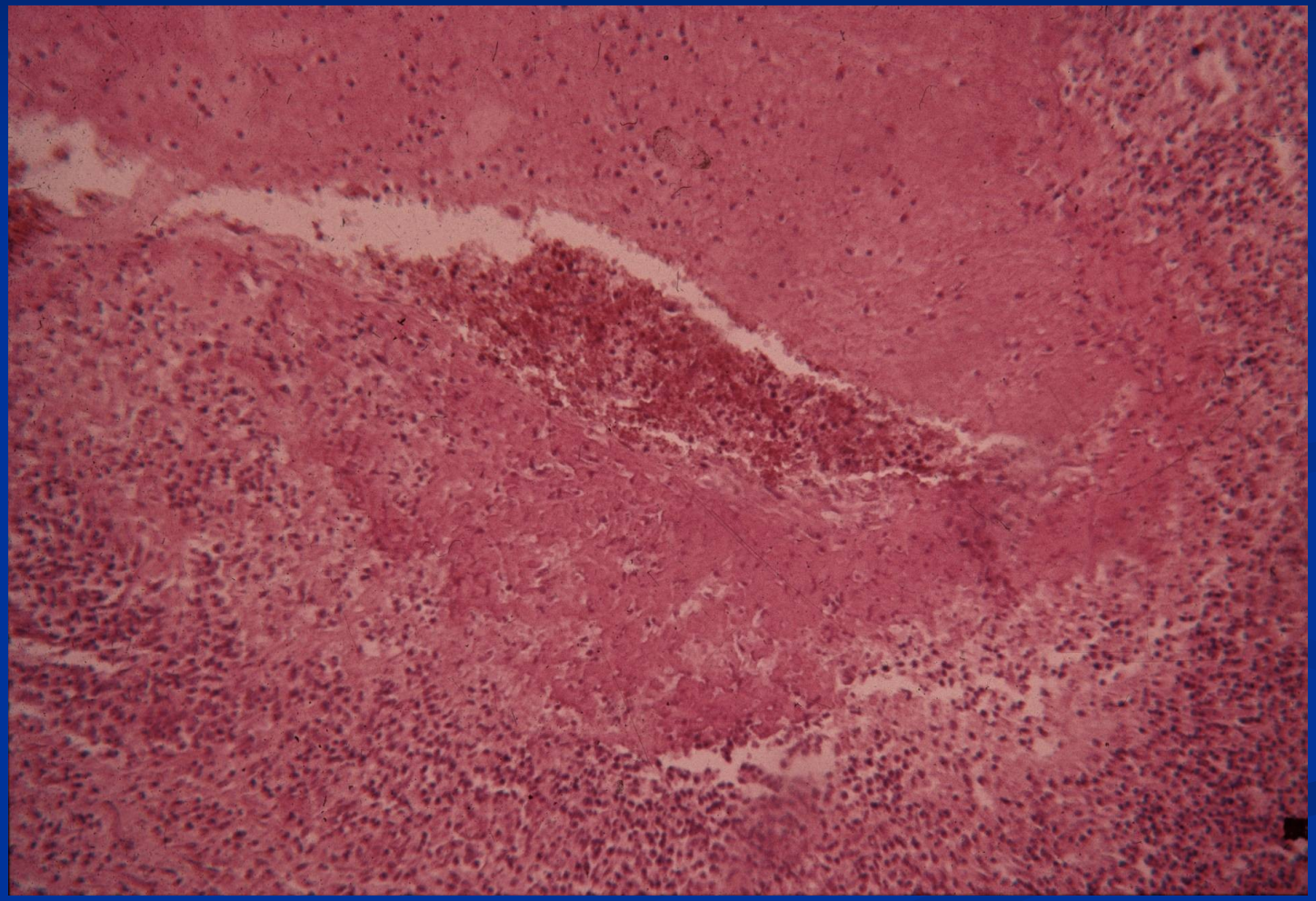
Morphology:

- acute necrotizing vasculitis: necrosis of the vessel wall + neutrophilic infiltration.
- necrotic tissue + deposits of immune complexes, complement, and plasma protein → eosinophilic deposits - **fibrinoid necrosis**

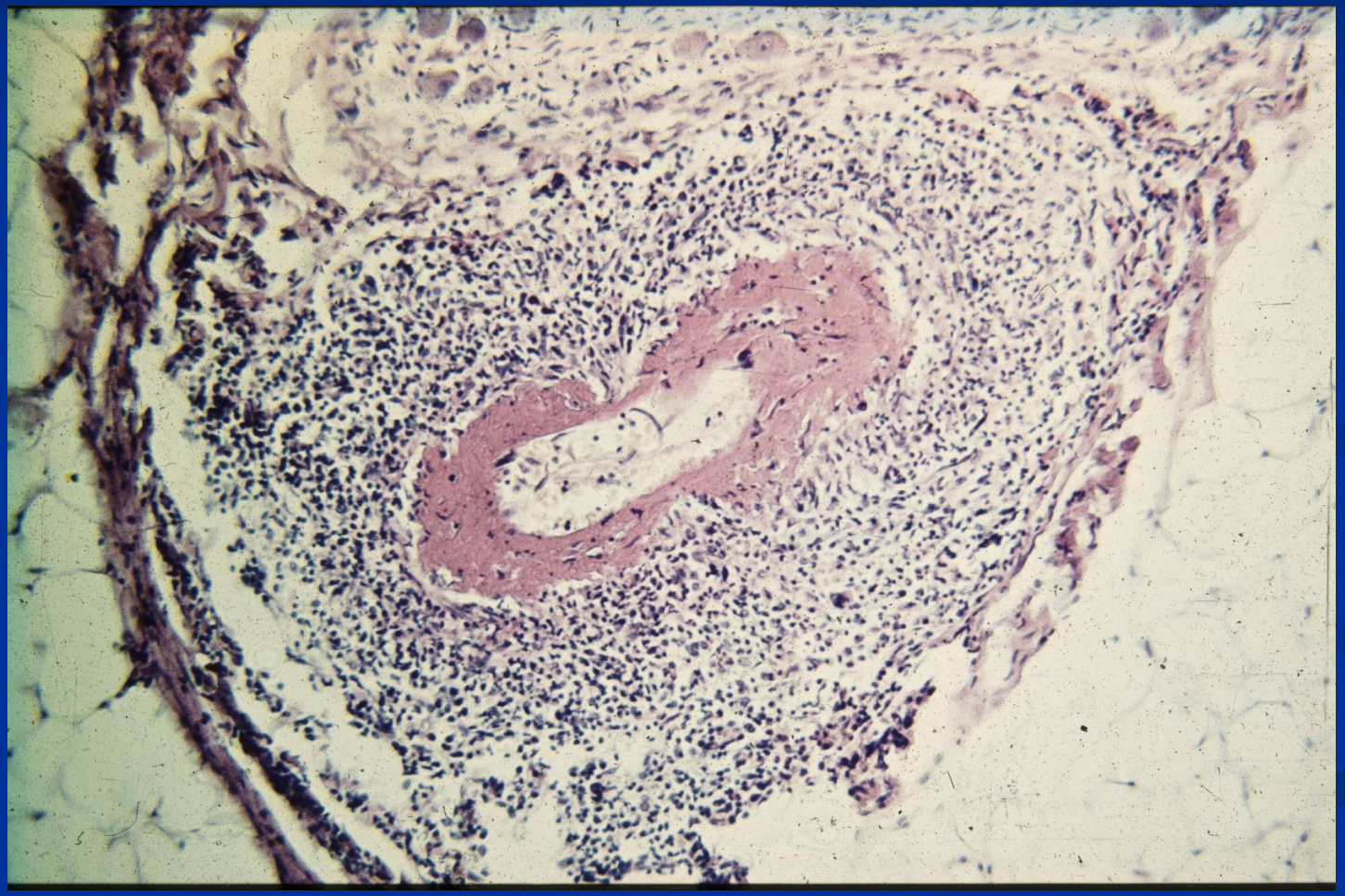
Immune complex–mediated (type III) hypersensitivity

- Systemic lupus nuclear antigens; nephritis, skin lesions, arthritis, others
- Acute (poststreptococcal) glomerulonephritis streptococcal cell wall antigen(s); may be „planted“ in glomerular basement membrane; formation of local IC → nephritis
- Chronic immune complex nephritis (persistent antigen exposure, abnormal immune response incl. local factors)
- Some forms of vasculitis

Polyarteriitis nodosa - acute



Polyarteriitis nodosa - healing



Hypersensitivity reactions

T cell–mediated (type IV) hypersensitivity

- Initiated by antigen-activated (sensitized by primary exposure) T lymphocytes, including CD4+ and CD8+ T cells.
- CD4+ cytokines → inflammatory reaction in a few days (approx. 3).
- Possible cause of chronic inflammatory disease, incl. autoimmune diseases.
- CD8+ cells may also be involved. esp. following viral infections,

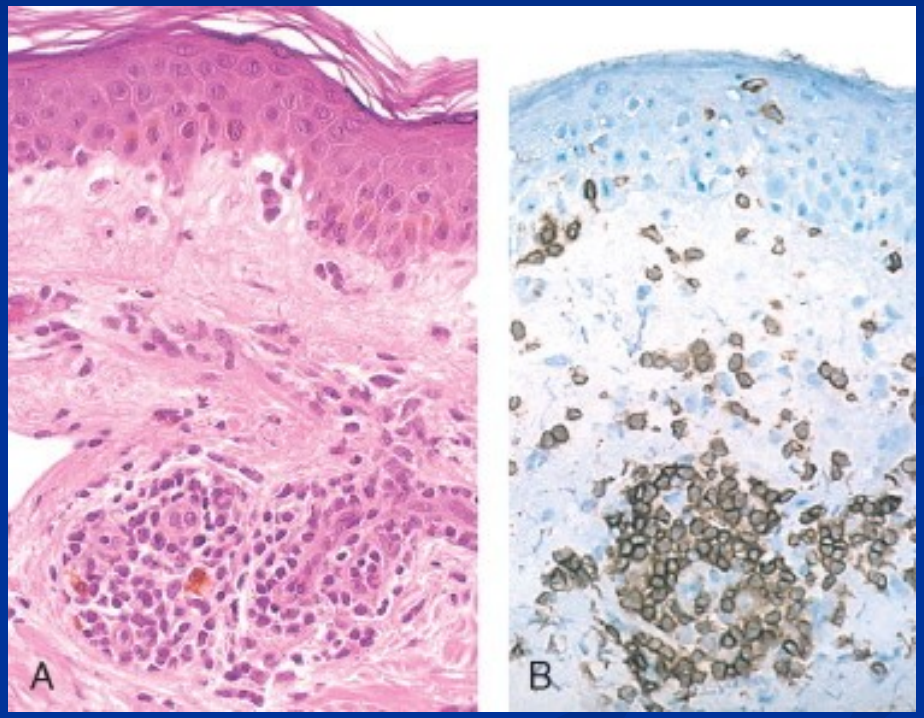
T cell–mediated (type IV) hypersensitivity

- Perivascular cellular infiltrates (T-cells, macrophages, eosinophils possible); edema; granuloma formation; cell destruction

- Contact dermatitis; type I diabetes; multiple sclerosis; rheumatoid arthritis; inflammatory bowel disease (i.e. Crohn disease); tuberculosis

Delayed-type hypersensitivity

- Perivascular infiltration by T cells and mononuclear phagocytes.
- Immunohistochemistry: predominantly perivascular cellular infiltrate CD4+.



from Robbin's Pathologic Basis of Disease

T cell–mediated (type IV) hypersensitivity

- Contact dermatitis:
- Induction phase: sensitising small exogenous molecules (chemicals, etc.) – immunogenic + intrinsic protein carrier → bound by antigen-presenting Langerhans cells → induction of T-cells
- Elicitation phase upon re-exposure, effector T-cells migrate into skin – inflammation with blisters – vesicular dermatitis
- Patch testing response after approx. 3 days

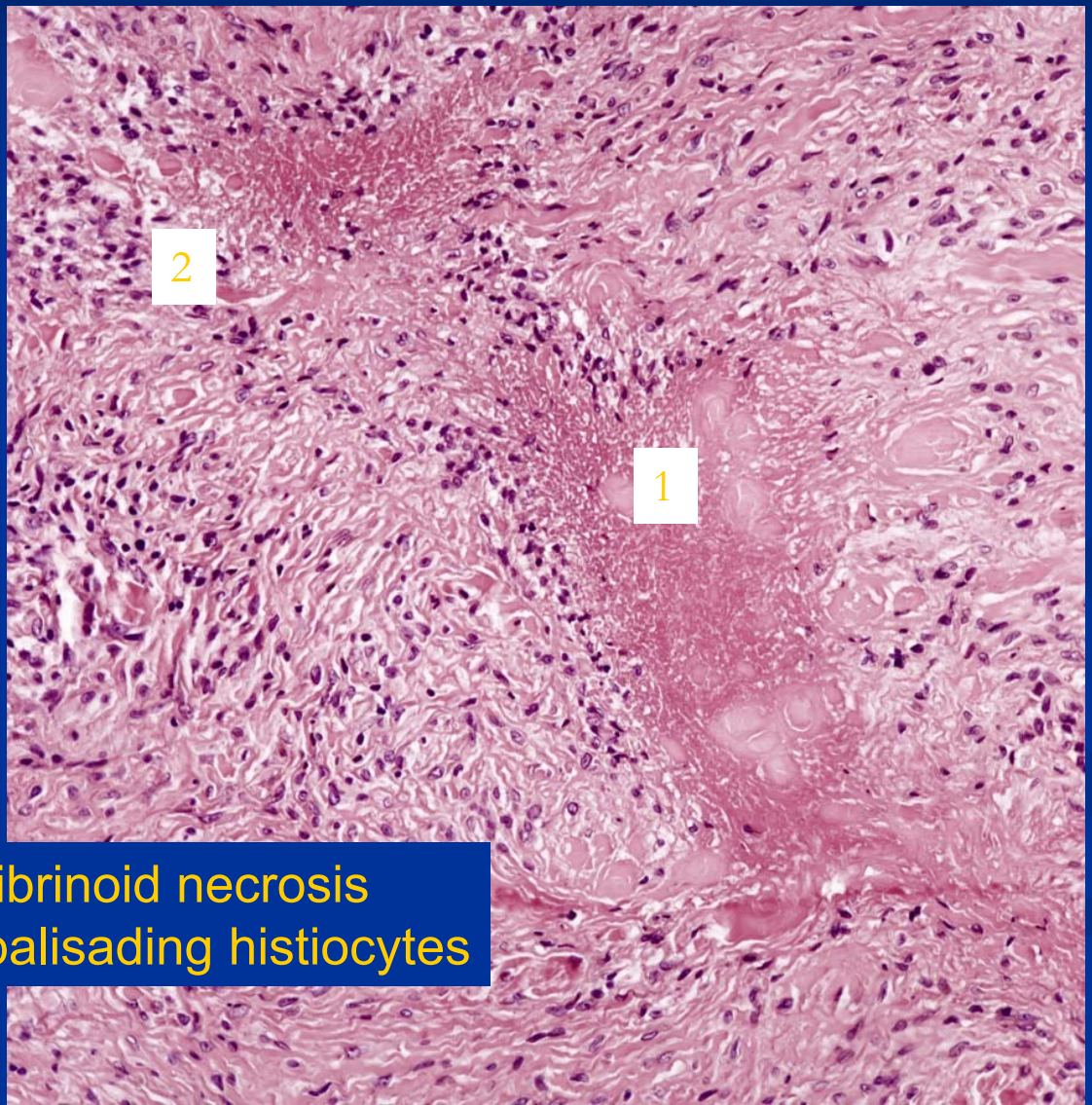
T cell–mediated (type IV) hypersensitivity

- Type 1 diabetes mellitus: antigens of pancreatic islet β cells; insulitis (chronic inflammation in islets), destruction of β cells; diabetes
- Multiple sclerosis: protein antigens in CNS myelin; demyelination in CNS with perivascular inflammation; paralysis, ocular lesions, etc.

T cell–mediated (type IV) hypersensitivity

- Rheumatoid arthritis: chronic arthritis with inflammation, destruction of articular cartilage and bone
- Crohn disease: unknown antigen; role for commensal bacteria; chronic intestinal inflammation, obstruction

Rheumatoid nodules



1 fibrinoid necrosis
2 palisading histiocytes

Granulomatous inflammation

- Persistent or nondegradable antigens (tb bacilli, …)
- Infiltrate dominated by macrophages in 2-3 weeks.
- Activated macrophages transform into epithelium-like cells epithelioid cells.
- Granuloma: microscopic aggregation of epithelioid cells usually surrounded by a layer of lymphocytes.
- Granulomatous inflammation typically associated with strong T-cell activation with cytokine production

Cell-mediated cytotoxicity

- **Reactions of CD8+ T cells:**
- CD8+ T-Ly kill antigen-bearing target cells.
- Important component of many T cell–mediated diseases (type 1 diabetes).
- T-Ly directed against cell surface histocompatibility antigens: important role in graft rejection.
- Reactions against viruses: virus-infected cell killing → elimination of the infection + cell damage (viral hepatitis).
- Tumor-associated antigens presented on the cell surface, T-Ly involved in tumor rejection

AUTOIMMUNITY

- Norm: ability of immune system to differentiate between self and non-self antigens
- Pathology: immune system response against self antigens

Autoimmune diseases

- *Autoimmunity arises from a combination of the inheritance of susceptibility genes (contribute to the breakdown of self-tolerance), and environmental triggers, (infections, tissue damage), promoting the activation of self-reactive lymphocytes.*
- Autoantibodies (AA) in clinically normal people.
- Physiologic AA in removal of breakdown products after tissue damage (antigen-antibody complex removed by macrophages)
- Imbalance between control mechanisms (normally preventing pathologic self-reactivity) and pathways leading to the generation and activation of pathogenic effector lymphocytes.

Autoimmune diseases

- Pathologic autoimmunity: presence of immune reaction specific for self-antigen
- + primary pathogenic, not secondary to tissue damage
- + absence of other cause
- ev. similar to experimental models of AI.
- Commonly uncertain „pure“ autoimmunity – term immune-mediated inflammatory diseases

Autoimmune diseases

Changes in self-antigens, that make them look like non-self to the immune system

prolongated expression/persistence od antigenes normally cleared out

posttranslational transformation of antigenes – „neoantigenes“ not recognized

Factors influencing autoimmune disease

Internal triggering factors

- genotype / HLA
- cytokines
- apoptosis genes
- hormones

External triggering factors

- infections
- UV
- drugs
- chemicals (including food)
- stress

Autoimmune diseases

- *Most autoimmune diseases: complex multigenic disorders*
- Many autoimmune diseases associated with infections, clinical flare-ups often preceded by infectious prodromes (stimulation of lymphocytes by preexisting innate immune reaction)
- Many infectious diseases similar to autoimmune disease in pathology (Lyme disease)

Breakdown of tolerance

(Bypass of helper T cell tolerance

Imbalance of suppressor-helper T cell function

Genetic factors

Polyclonal lymphocyte activation)

Autoimmune diseases

- Progressive tendency (ev. sporadic relapses and remissions)
- Epitope spreading: tissue damage → self-antigen release + epitopes exposure (antigens normally concealed from the immune system) → continual activation of lymphocytes recognizing previously hidden epitopes;
- These epitopes not expressed normally – no lymphocytic tolerance

Mechanisms of tissue injury

- Auto-antibodies circulating in blood or at site of tissue injury
- Autoreactive B and T cells in blood and at site of tissue injury
- Hypersensitivity reactions occurring at sites of tissue injury
- Histology: chronic inflammation
- Pathway for apoptosis

Autoimmune diseases

- Different autoimmune diseases show substantial clinical, pathologic, and serologic overlaps.
- Precise phenotypic classification often problematic.

Autoimmune diseases

- **DISEASES MEDIATED BY ANTIBODIES AND IMMUNE COMPLEXES**

Organ-specific autoimmune diseases (examples)

Autoimmune hemolytic anemia
Autoimmune thrombocytopenia
Graves disease
Goodpasture syndrome

Systemic autoimmune diseases

Systemic lupus erythematosus (SLE)

Autoimmune diseases

DISEASES MEDIATED BY T-CELLS

Organ-specific autoimmune diseases

Type 1 diabetes mellitus
Multiple sclerosis

Systemic autoimmune diseases

Rheumatoid arthritis RA (+ possible role of antibodies)
Systemic sclerosis (+ possible role of antibodies)
Sjogren syndrome (+ possible role of antibodies)

Diseases caused by autoimmunity or by reactions to microbial antigens

Inflammatory bowel disease (Crohn disease, ulcerative colitis)

Incidence of autoimmune diseases

- RA 1-3%
- Sjögren´s sy 1/20 000
- Vasculitis 1/100 000

- Prevalence of autoimmune diseases

5-7% of population

Diagnosis

clinical picture

laboratory

autoantibodies

autoreactive lymphocytes

autoantigens

related genes

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Chronic systemic autoimmune disease
- Cause unknown
- Loss of normal self-tolerance
- Affects almost any organ(s)
- Characterized by chronic inflammation
- Auto-antibodies formed against variety of self antigens
- Immune circulating complexes deposit in tissues

SLE

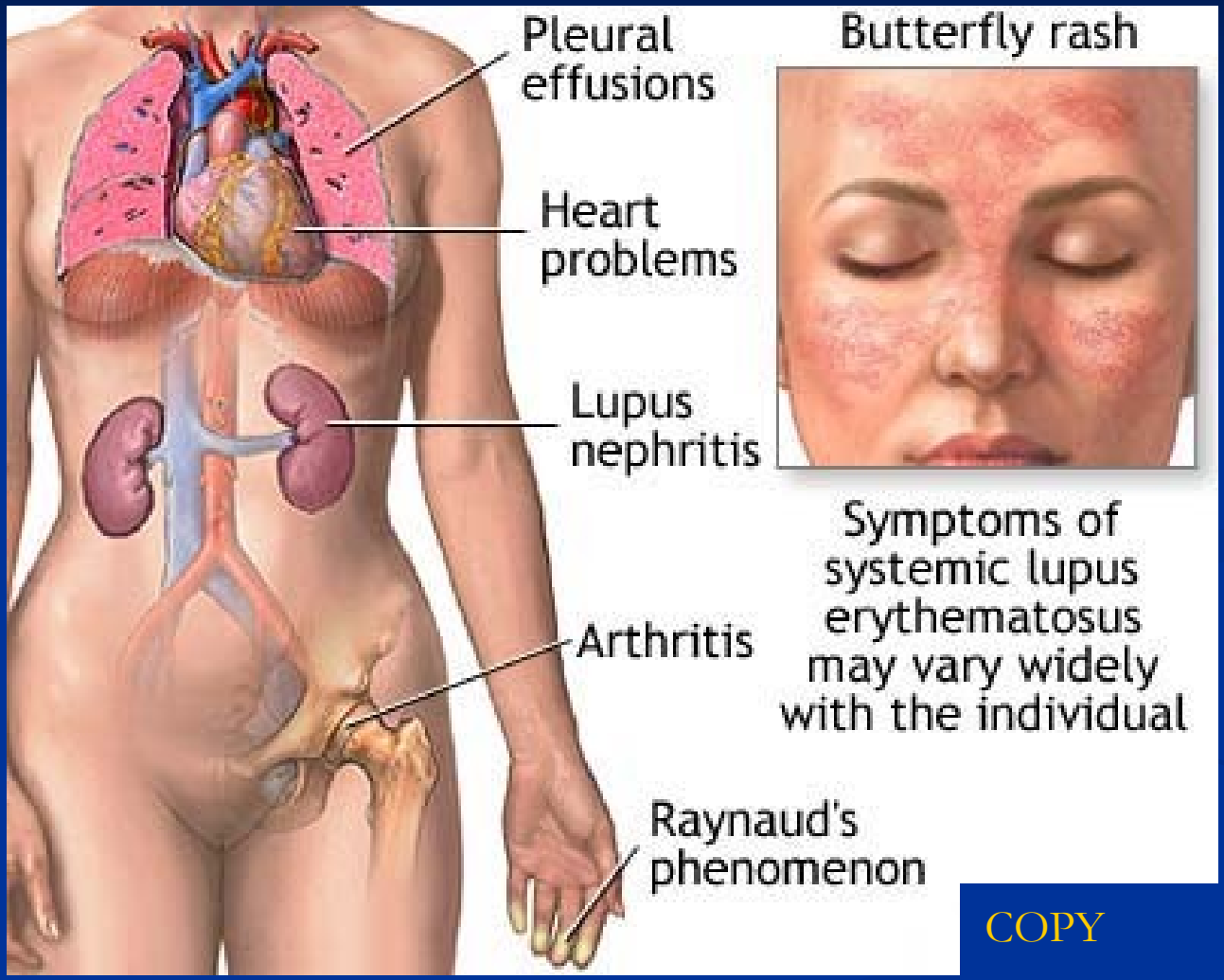
- The course of the disease is variable and unpredictable.
- Rare acute cases result in death within weeks to months.
- Appropriate therapy: flare-ups and remissions, years or even decades.
- *The most common causes of death are renal failure and intercurrent infections.*

SLE – typical case

young woman with some of the following features:

- a butterfly rash over the face,
- fever,
- pain but no deformity in one or more peripheral joints (feet, ankles, knees, hips, fingers, wrists, elbows, shoulders),
- pleuritic chest pain
- photosensitivity

SLE


Pleural effusions
Heart problems
Lupus nephritis
Arthritis
Raynaud's phenomenon
Butterfly rash
Symptoms of systemic lupus erythematosus may vary widely with the individual

COPY

SLE

- Acute necrotizing vasculitis involving capillaries, small arteries and arterioles may be present in any tissue.
- Arteritis with fibrinoid deposits in the vessel walls.
- Chronic stages: fibrous thickening of vessels with luminal narrowing.

Selected SLE manifestations

serous membranes (common)

pleuritis

respiratory disease

pneumonitis

progressive interstitial fibrosis

CNS disease

life threatening complication

- vasculitis leading to hemorrhage infarction
- thromboembolic complications

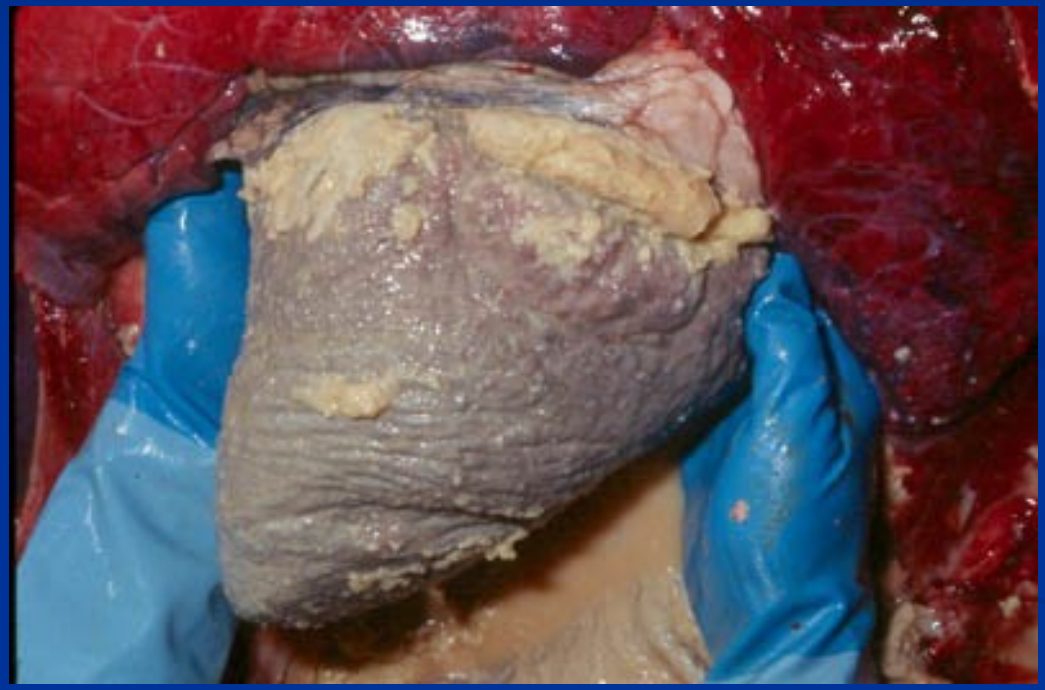
cardiac manifestations

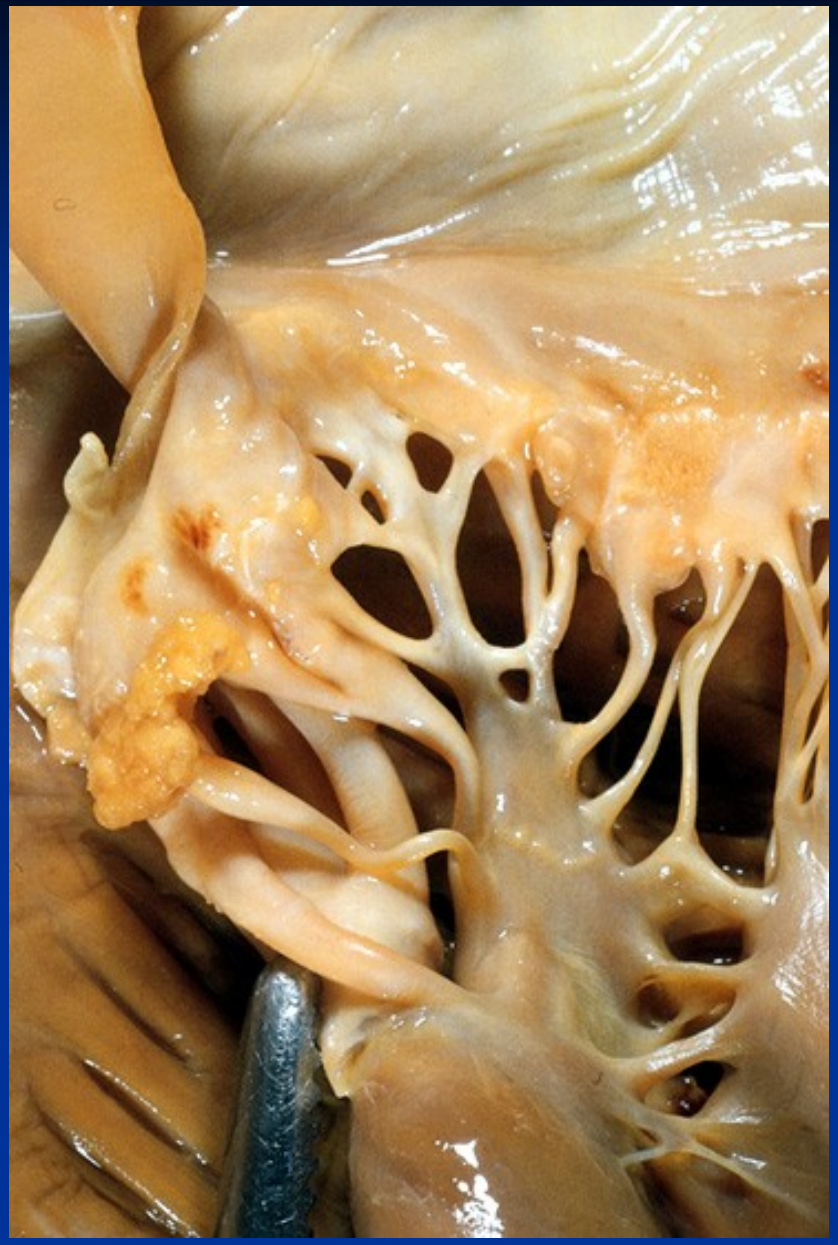
pericarditis (most common finding)

Libman-Sacks endocarditis

- sterile vegetative growths on valves

SLE pericarditis

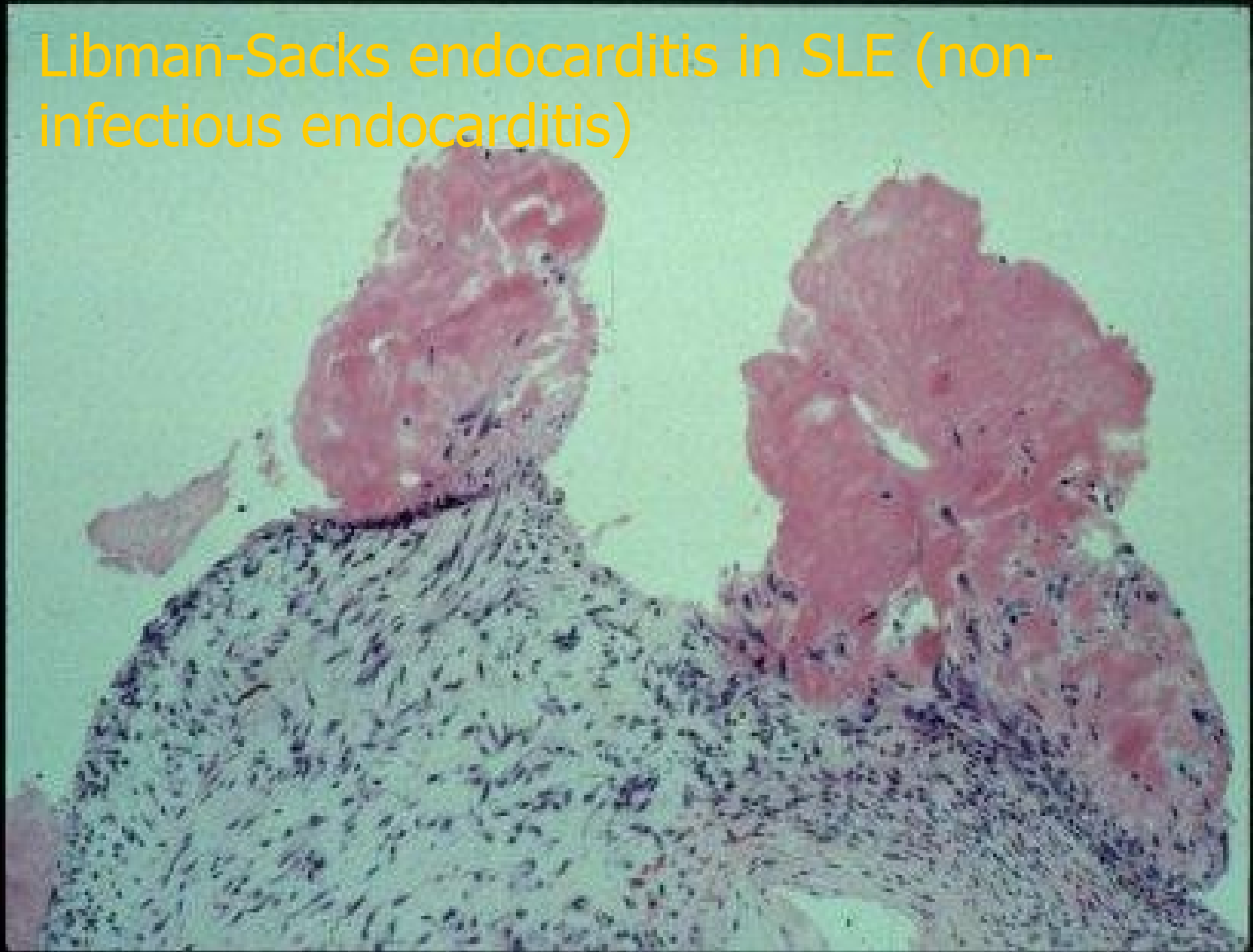




Libman-Sacks endocarditis of the mitral

(From Robbins Basic Pathology, 2003)

Libman-Sacks endocarditis in SLE (non-infectious endocarditis)

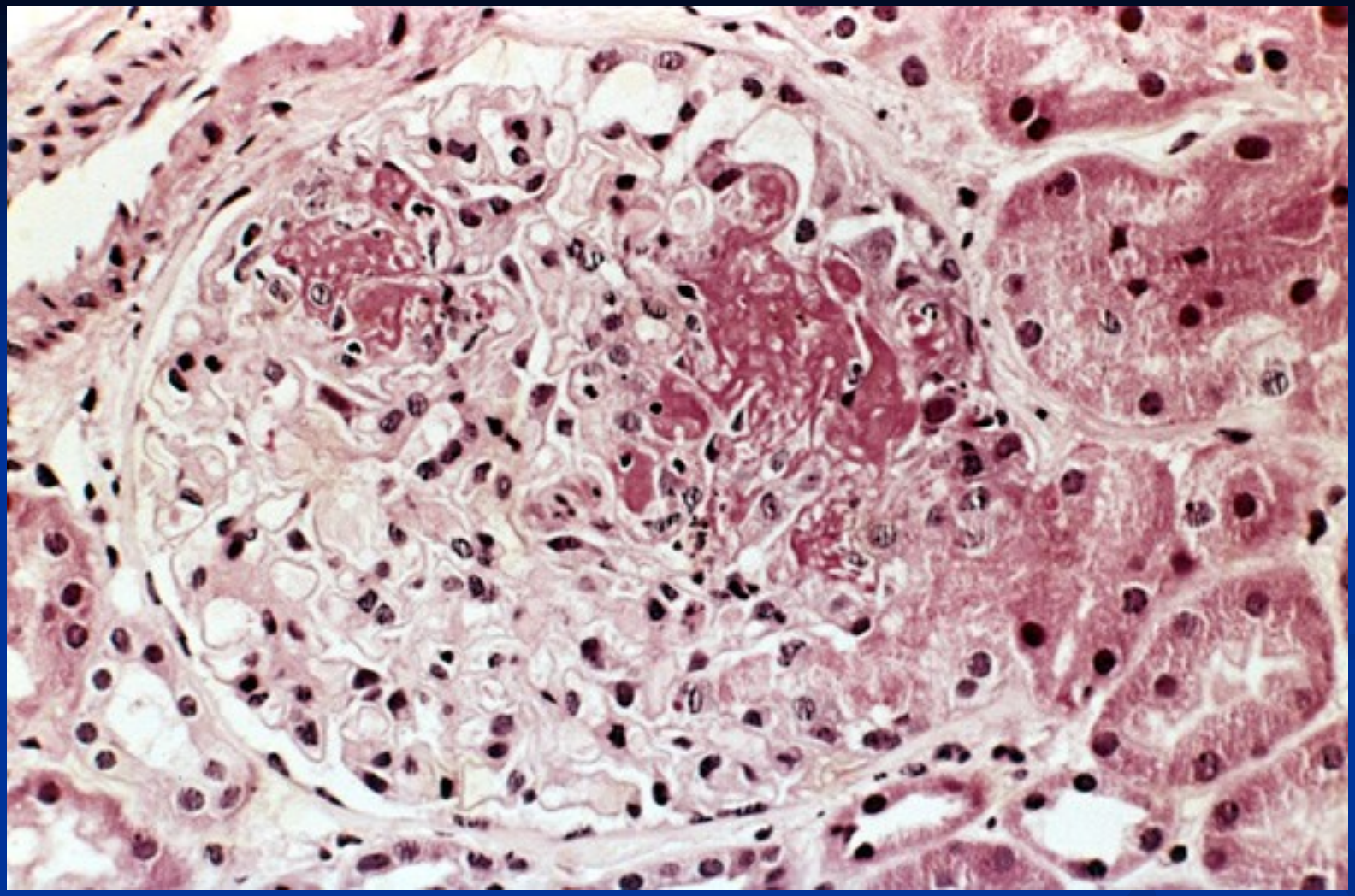


Joint disease > 90% SLE patients have polyarthralgia

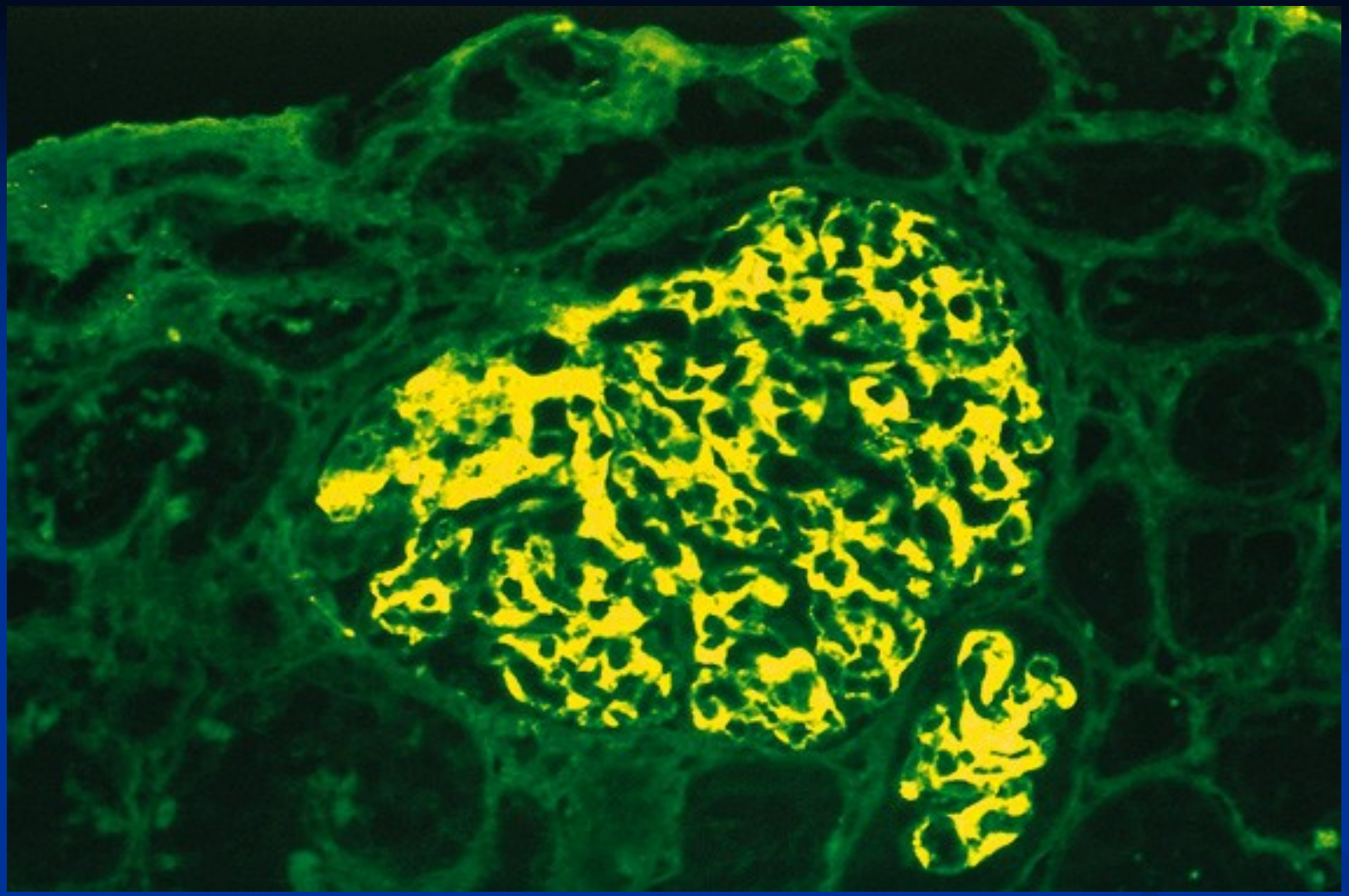
- inflammatory synovitis +/- joint destruction (as in RA)

Renal disease

~ 75% have glomerulonephritis, variable morphology possible



Lupus nephritis. (From Robbins Basic Pathology, 2003)



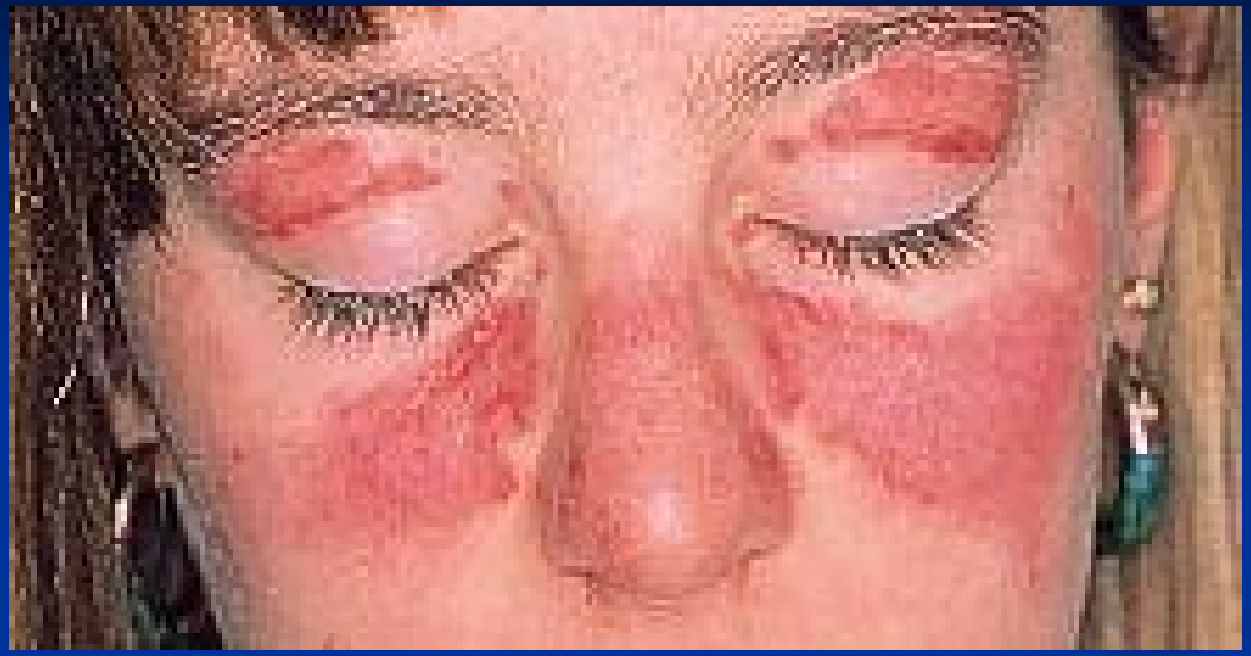
Immunofluorescence with anti-IgG mesangial and capillary wall deposits of IgG.

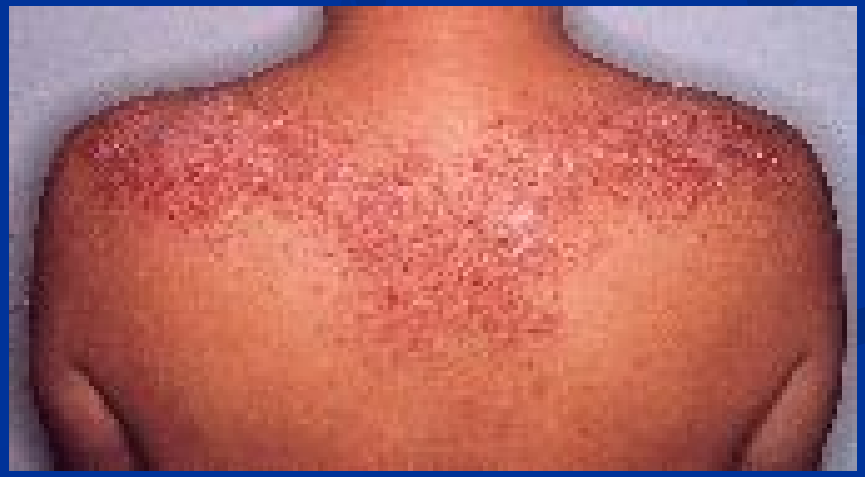
(From Robbins Basic Pathology, 2003)

SLE

- ***Skin.*** Characteristic erythema affecting the facial „butterfly“ area (bridge of the nose and cheeks) in approximately 50% of patients, similar rash on the extremities and trunk.
- Urticaria, bullae, maculopapular lesions, ulcerations
- **Exposure to sunlight starts or worsens the erythema.**

Clinical features of SLE





Chronic discoid lupus

- Skin manifestations may mimic SLE, but systemic manifestations rare.
- Later may be progression into systemic SLE in a minority of patients
- Skin plaques with varying degrees of edema, erythema, scaliness, follicular plugging, and skin atrophy surrounded by an elevated erythematous border.

Rheumatoid arthritis

- Systemic autoimmune disease (joints, skin, blood vessels, heart, lungs, muscles)
- Etiology unknown, combination of gen. predisposition, environment (trigger), autoimmunity
- Rheumatoid factor (RF) – AA to a part of IgG, in 80%

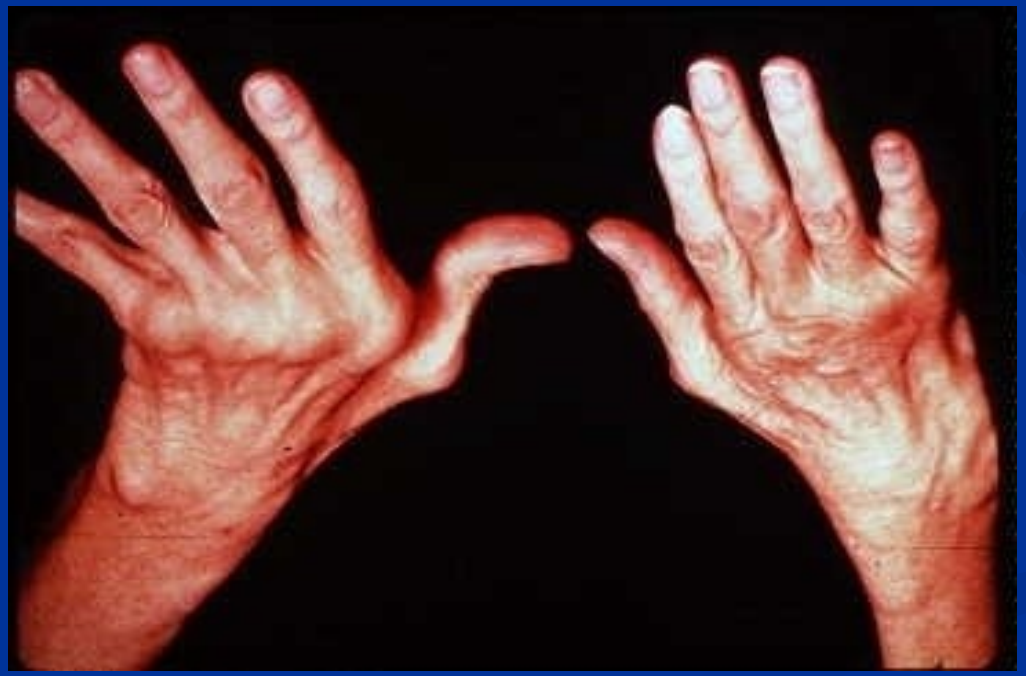
Rheumatoid arthritis

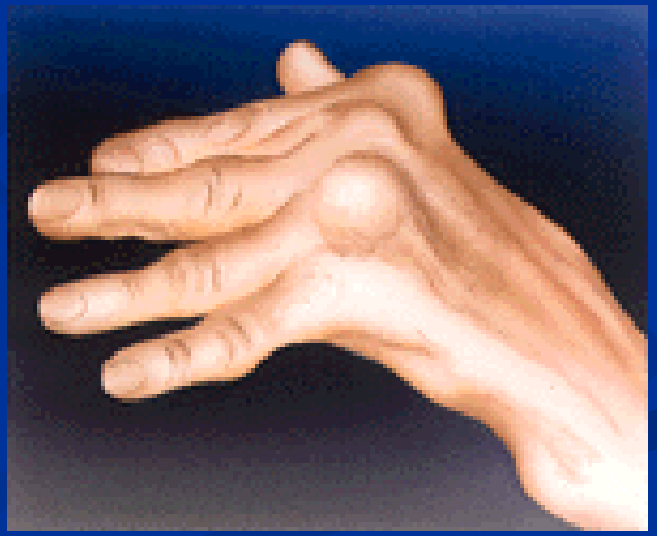
- Chronic nonpurulent proliferative inflammation of synovial joints
- Proliferation of synovial lining cells, oedema, fibrin deposition → pannus (synovial cells + granulation tissue + inflammatory cells) →
- Erosion of articular cartilage and adjacent bone (osteoclasts) →
- Fibrous ankylosis → bony ankylosis

Rheumatoid arthritis

- Variable course, usual start in hands or other small joints.
- Arthritis + morning stiffness
- Worsening limitation of motion
- Rheumatoid nodules in organs or tissues – skin, lungs (!x ca), myocardium,…

RA





IgG4-related disease

- IgG4-associated systemic sclerosing disease
- Combination of variable immune-mediated disorders
  - Type 1 autoimmune pancreatitis
  - Sclerosing sialoadenitis (mimicking tumor)
  - Orbital disease – pseudotumor – eye protrusion
  - Retroperitoneal fibrosis
  - IgG4 related sclerosing cholangitis
  - Nephritis
  - Others

IgG4-related disease

- More commonly middle-aged and older men
- Dense lymphoplasmocytic infiltrate, predominance of IgG4+ plasma cells – bioptic diagnosis
- Commonly elevated serum IgG4 levels
- Good response to corticosteroids

Sjögren syndrome

- chronic disease characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia) due to destruction of the lacrimal and salivary glands.
- More often in association with another autoimmune disease (secondary form). Associated rheumatoid arthritis most common, possible SLE, thyroiditis
- Possible vaginal dryness

Sjögren syndrome

- Women between the ages of 50 and 60.
- Keratoconjunctivitis → blurring of vision, burning, and itching
- Xerostomia → difficulty in swallowing solid foods, decrease in the ability to taste, cracks and fissures in the mouth,
- Emergence of a dominant B cell clone → development of a marginal zone lymphoma (in the setting of chronic lymphocytic inflammation). 5% of Sjögren patients develop lymphoma, incidence 40x greater than normal.

Systemic sclerosis

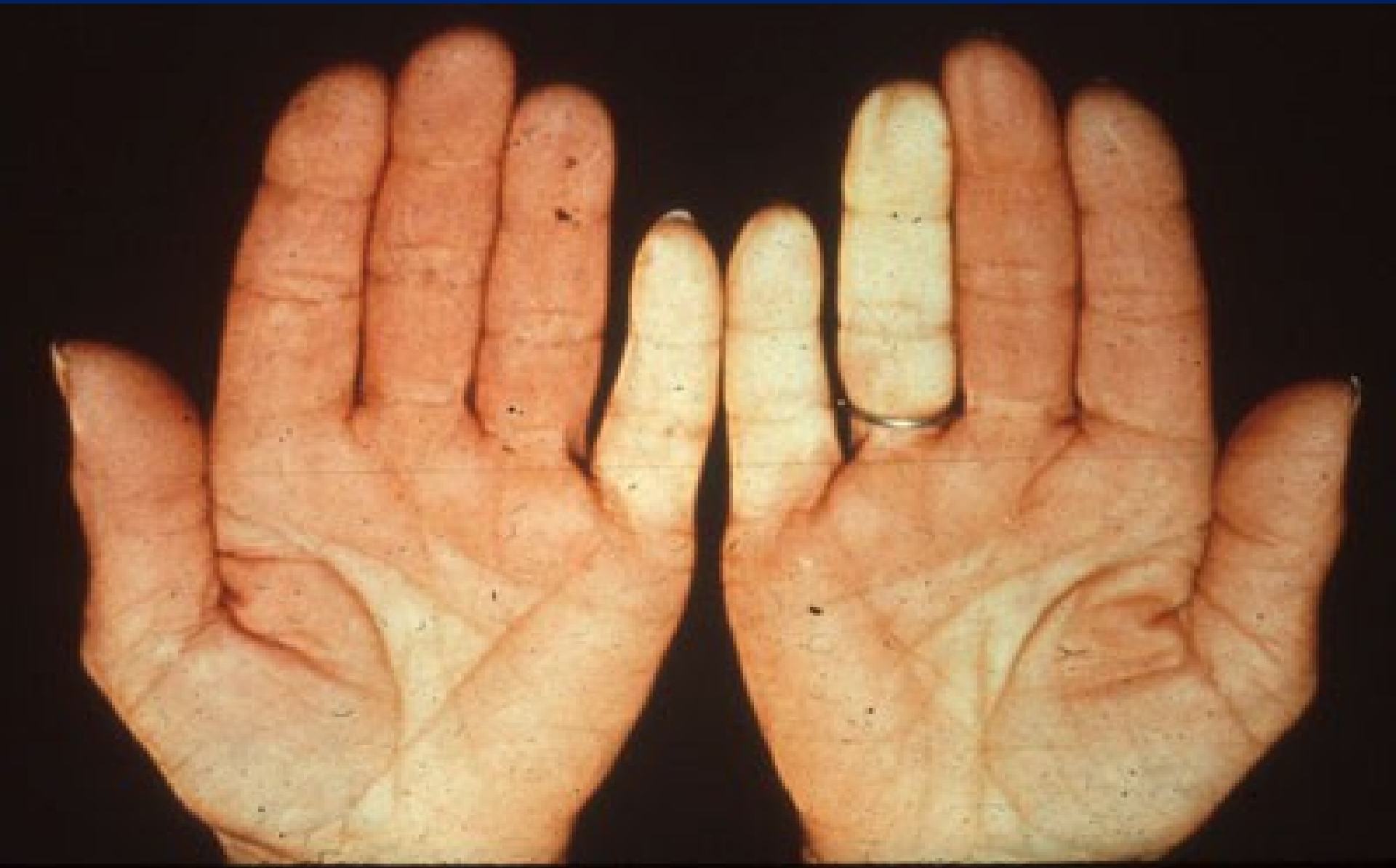
- chronic inflammation thought to be the result of autoimmunity,
- damage to small vessels
- later progressive interstitial and perivascular fibrosis in the skin and multiple organs
- gastrointestinal tract, kidneys, heart, muscles, lungs (interstitial fibrosis)
- death from renal failure, cardiac failure, pulmonary insufficiency, or intestinal malabsorption

- ! it's not multiple sclerosis (CNS demyelinating disease)

Systemic sclerosis

- female-to-male ratio of 3 : 1, peak incidence 50-60
- Raynaud's phenomenon: episodic vasoconstriction of the arteries and arterioles of the extremities
- Dysphagia due to esophageal fibrosis and its resultant hypomotility

Raynaud's phenomenon



Noninfectious vasculitis

- commonly in form of:

necrotizing inflammation of the walls of blood vessels and showing strong evidence of an immunological pathogenetic mechanism

- The general term *noninfectious vasculitis*

- See the lecture on vascular diseases

Organ-specific autoimmune diseases

Endocrine system

- Autoimmune (Hashimoto's) thyroiditis
- Hyperthyroidism (Graves' disease; thyrotoxicosis)
- Type I diabetes mellitus (insulin-dependent or juvenile diabetes)
- Insulin-resistant diabetes
- Autoimmune adrenal insufficiency (Addison's disease)
- Autoimmune oophritis

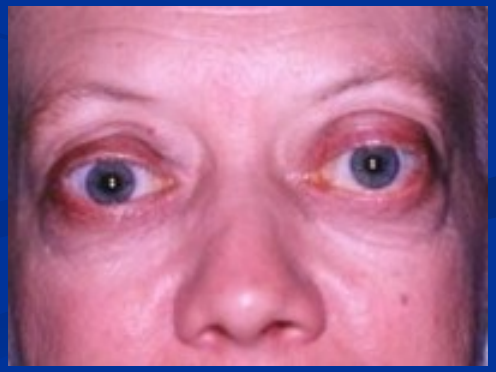
Autoimmune diseases of thyroid

Hashimoto´s thyroiditis

- hypofunction of thyroid
- autoantibodies against thyroglobulin and microsomes of follicular cells

Graves-Basedow´s disease

- hyperfunction of thyroid, thyrotoxicosis
- autoantibodies against TSH receptor: LATS – long acting thyroid stimulants



Type 1 diabetes (T1D)

- Also known as
  insulin-dependent diabetes mellitus (IDDM) or
  juvenile-onset diabetes
- Organ-specific autoimmune disorder (pancreatic islets)
- Hyperglycaemia results from:
  - specific auto-destruction of insulin-secreting β-cells in the islets of Langerhans in the pancreas
- Etiology and pathogenesis of autoimmune diabetes largely unknown

Organ-specific autoimmune diseases

Hematopoietic system

- Autoimmune haemolytic anemia
- Autoimmune thrombocytopenia
- Autoimmune neutropenia
- Pernicious anemia

Organ-specific autoimmune diseases

Neuromuscular system

- Autoimmune polyneuritis
- Multiple sclerosis
-

Multiple sclerosis

- autoimmune disorder, genetic (HLA etc.) + environmental factors (infection as trigger), amount of UV/ vitamin D, demyelinisation
- plaque (active, inactive), astrocytic proliferation, gliosis – sclerosis
- muscular weakness, paraesthesia, sensoric dysfunction (ocular), etc.

Organ-specific autoimmune diseases

Skin

- Pemphigus and other bullous diseases

Organ-specific autoimmune diseases

GIT

- Chronic ulcerative colitis
- Malignant pernicious anaemia with chronic atrophic gastritis
- Autoimmune hepatitis, AI pancreatitis
- Primary biliary cholangitis

Organ transplantation
Rejection

Organ transplantation

- Selection of most suitable donor and recipient - AB0-system most important, complete match necessary
- HLA-system: match in major antigenic determinants

- Ultimate goal: most possible immunologic tolerance

Tolerance

see Immunology for details

selected mechanisms of peripheral tolerance:

- clonal deletion (apoptosis of T cells) in long functional grafts
- suppressor T cells or other host factors
- dendritic cell from the donor surviving in the host → imunologic chimerism donor + recipient

Rejection

- complex immunologic process, cellular and humoral reaction, may be in combination
- **Factors** – genetic diversity, type of tissue (vascularisation, number of antigen presenting cells), host immune system activity (immunosuppression), graft condition
- Rejection in reaction on presence (+ demasking grade) of foreign antigenes.

Hyperacute rejection

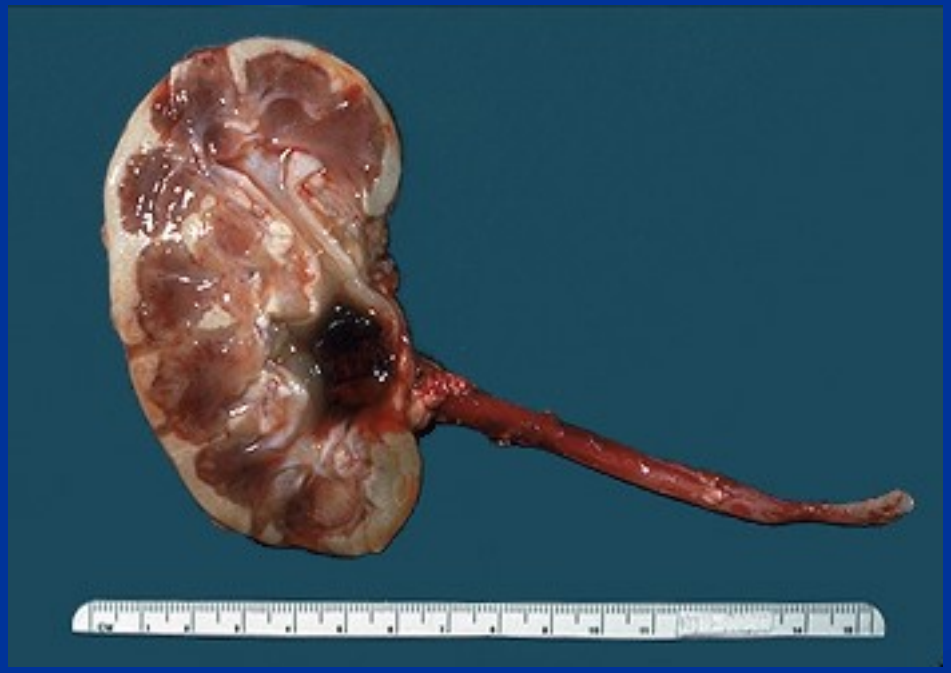
- Rare, within minutes or hours after transplantation.
- Preexisting antibodies for graft endothelial cells– part of antibody-mediated rejection
- Due to previous exposure of the host to foreign antigenes (transfusion, transplantaion, pregnancy)
- A hyperacutely rejecting kidney rapidly cyanotic, mottled, flaccid, + excretion of a few drops of bloody urine.
- The kidney cortex necrotic (infarction), nonfunctioning kidneys have to be removed.
- Similar in other organs

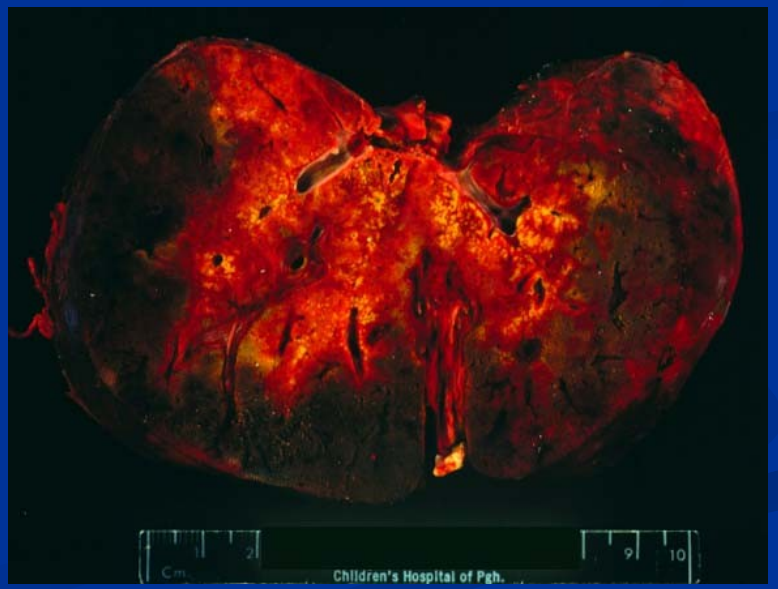
Hyperacute rejection

- Ig binding, complement acivation, endothelial injury + fibrin-platelet thrombi
- Neutrophil accumulation in arterioles, glomeruli, and peritubular capillaries.
- Changes diffuse and intense: thrombotic occlusion of the glomerular capillaries, fibrinoid necrosis in arterial walls
- Ischemic necrosis of the graft
- Necessity of cross-match test

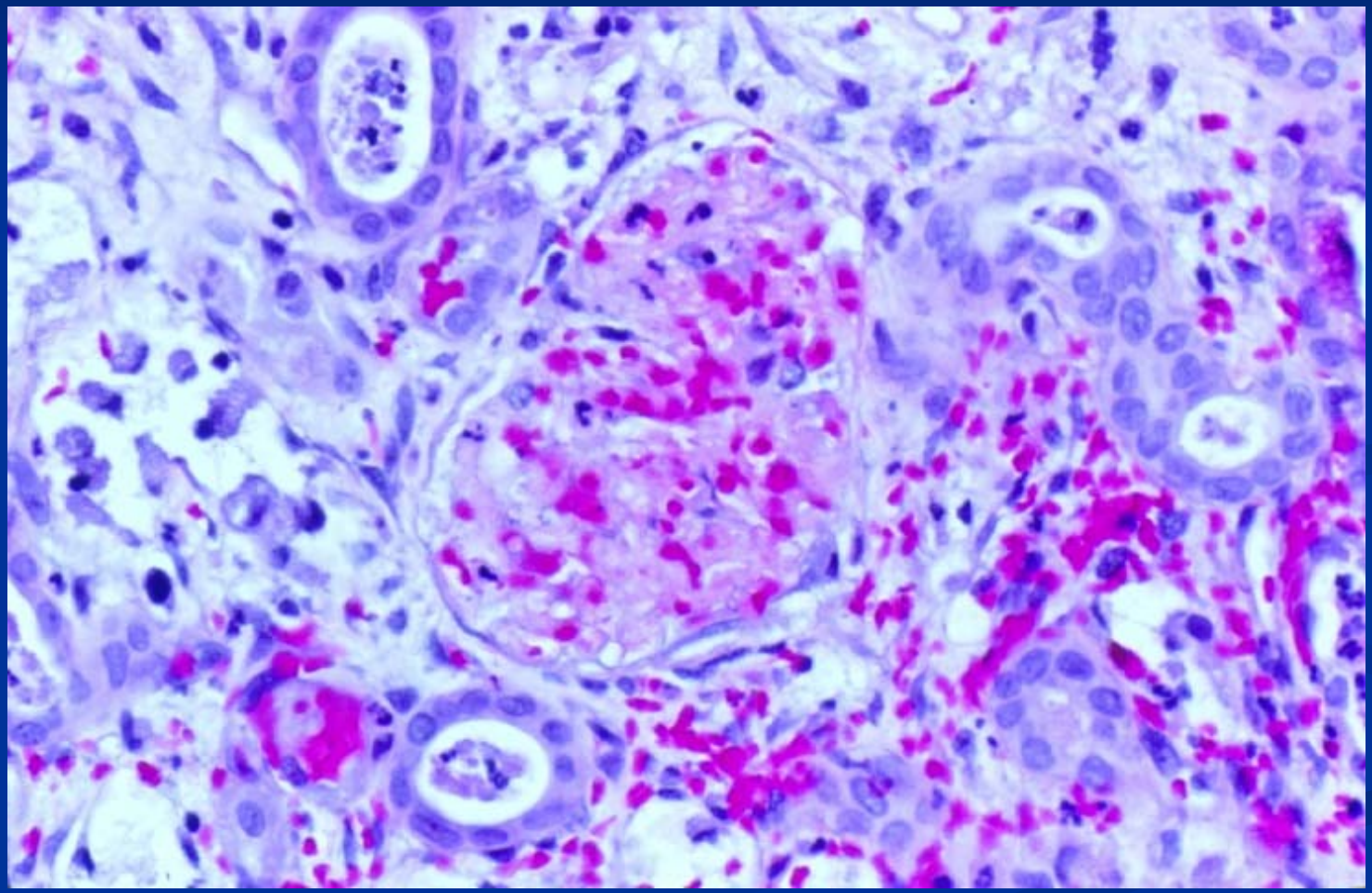
Hyperacute rejection

- ischemic necrosis of kidney, liver

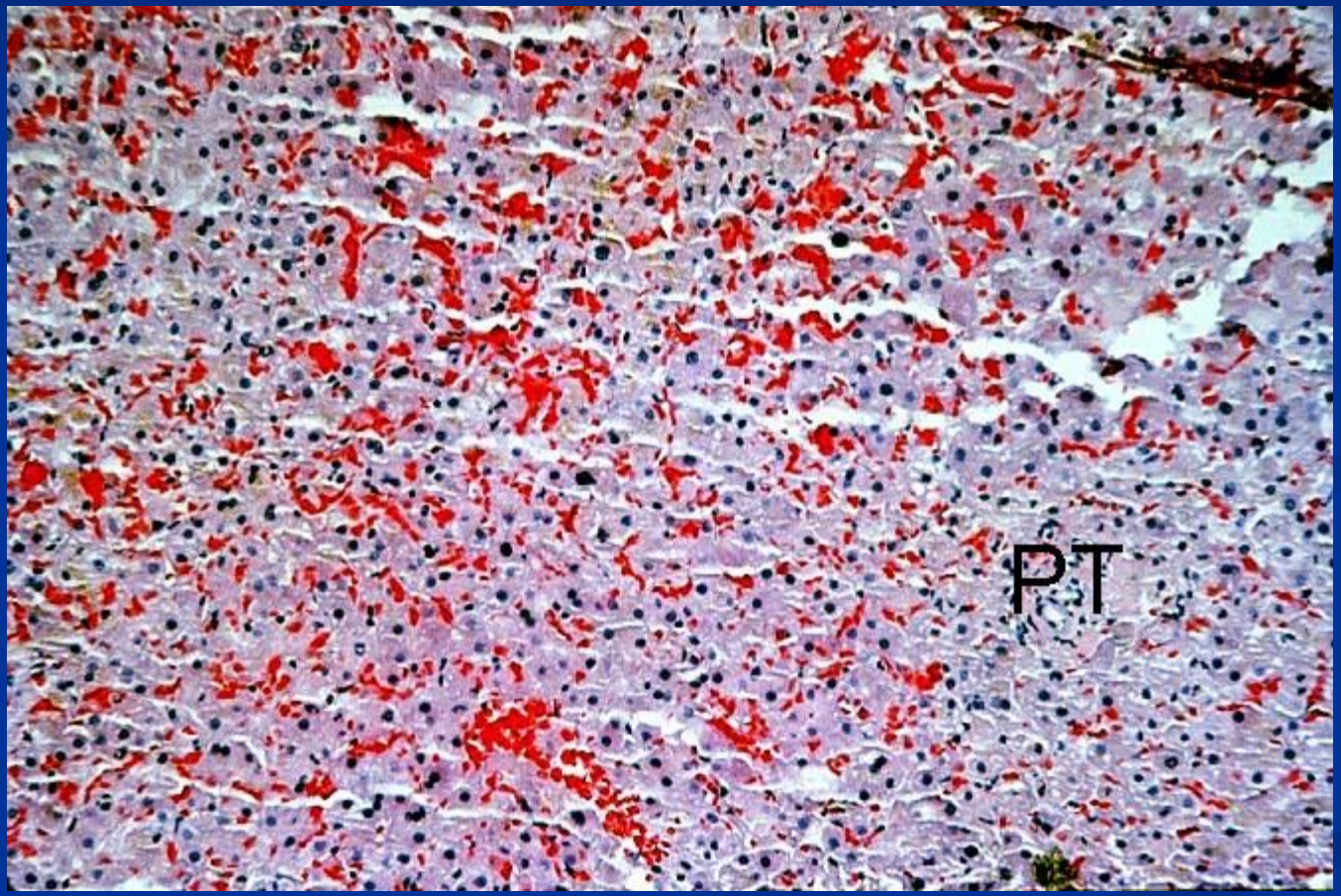




Hyperacute rejection - glomerulitis



Hyperacute rejection -liver



Acute rejection

- Within days of transplantation in the untreated recipient, or may appear suddenly months or even years later (↓ immunosuppression, other factors).
- In any one patient, cellular, antibody-mediated immune mechanisms may predominate, or combine.

Acute antibody-mediated (humoral) rejection (AMR)

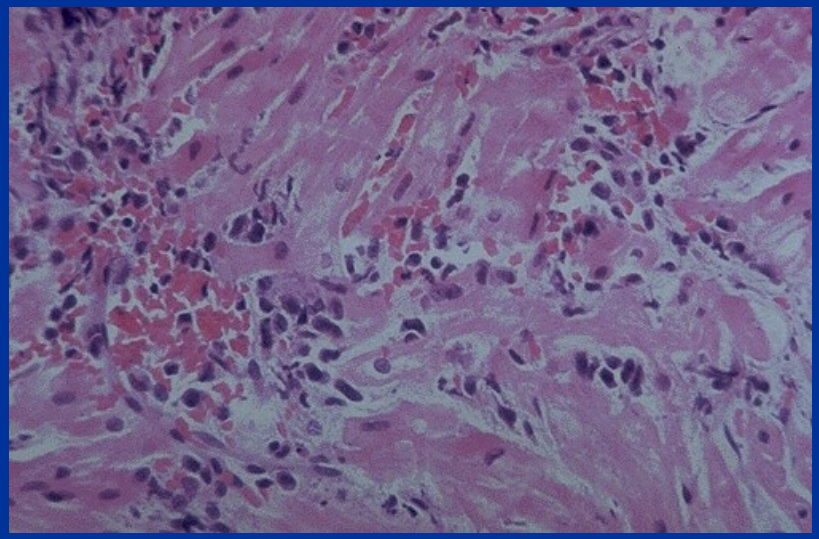
- Mediated by antidonor antibodies, manifestation mainly by damage to the blood vessels.
- Necrotizing vasculitis with endothelial cell necrosis, neutrophilic/macrophagic infiltration, deposition of Ig, complement and fibrin, thrombosis, interstitial oedema possible.
- Subacute vasculitis possible : thickening of the intima with proliferating fibroblasts, myocytes, foamy macrophages.

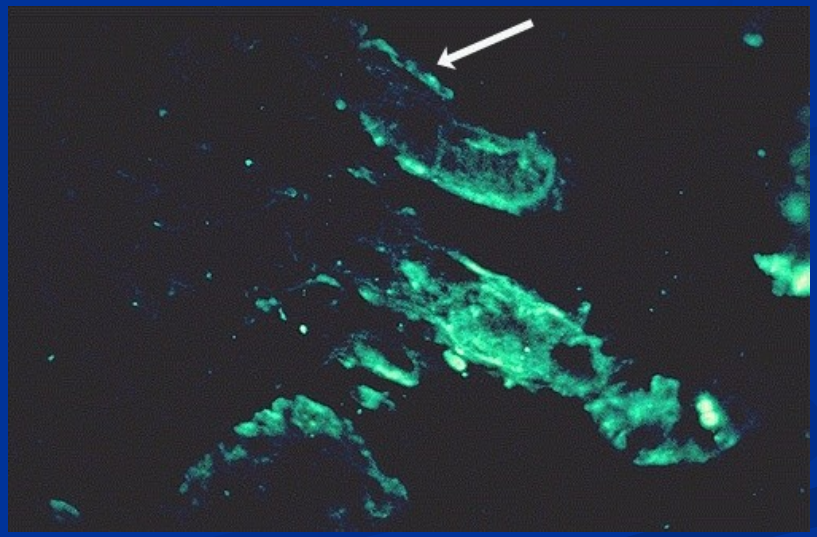
Antibody-mediated (humoral) rejection (AMR)

- Deposition of the complement breakdown product C4d in allografts - indicator of possible humoral rejection. C4d produced during activation of the complement system
- Affected patients treated with B cell–depleting agents, plasmapheresis.
- Proliferative vascular lesions mimic arteriosclerotic thickening , proliferation of vascular smooth muscle cells – progression into chronic rejection.

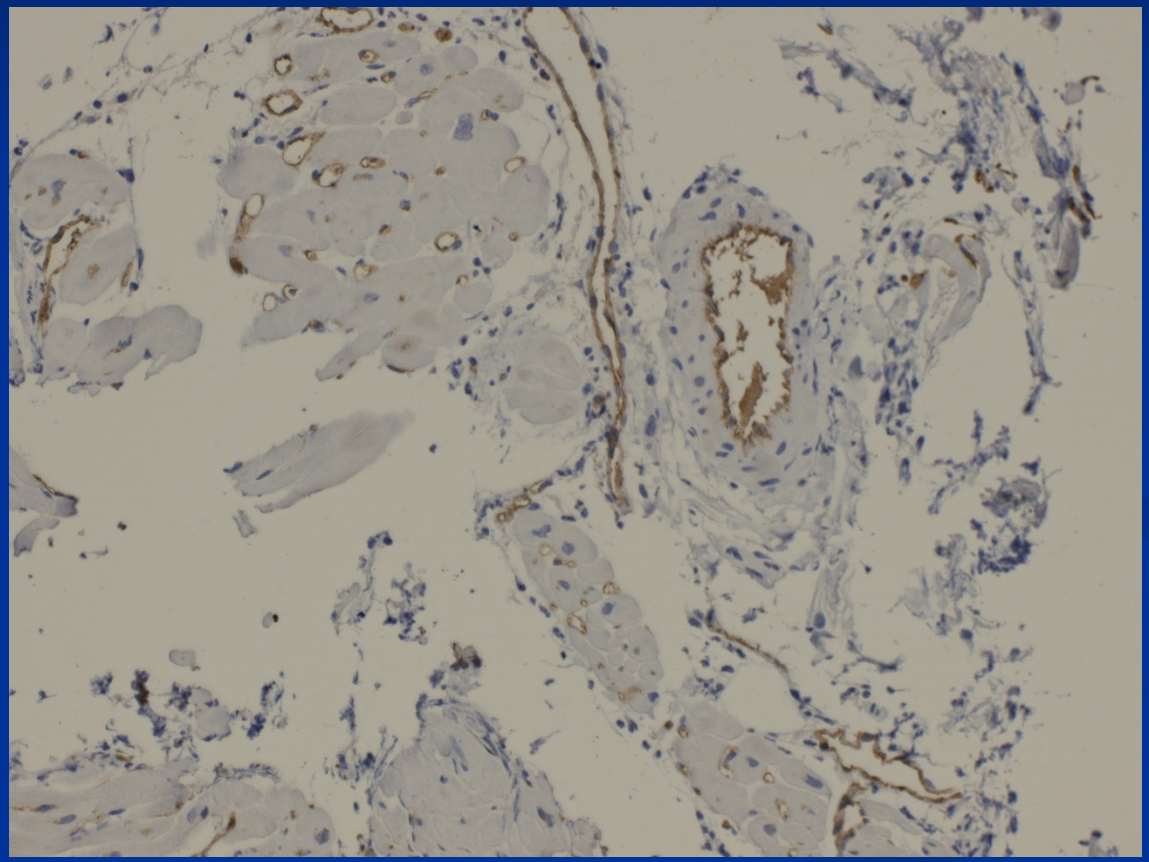
Acute antibody-mediated (humoral) rejection (AMR)

- Vasculitis, thrombosis
- C4d deposits - immunofluorescence



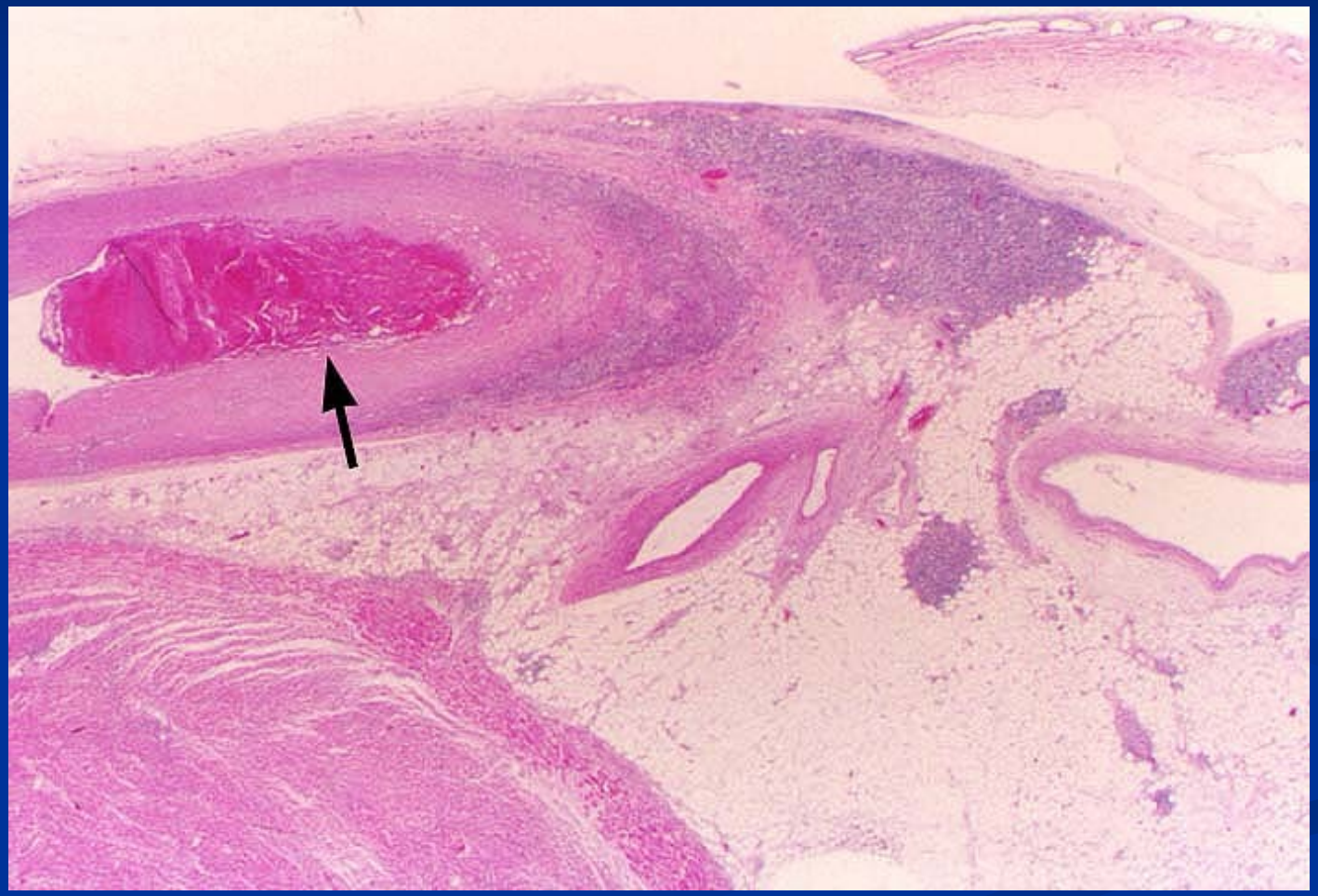


Acute antibody-mediated (humoral) rejection (AMR)



C4d immunohistochemistry – luminal intravascular positivity, myocardium

Acute antibody-mediated (humoral) rejection (AMR)



vasculitis + thrombosis

Acute cellular rejection

- Most common within the initial months after transplantation
- Clinical and biochemical signs of organ failure common
- Histology: CD4+ and CD8+ T lymphocytes, edema, mild interstitial hemorrhage possible
- Focal tubular/ductal necrosis
- More severe: necrotic hepatocytes, cardiomyocytes

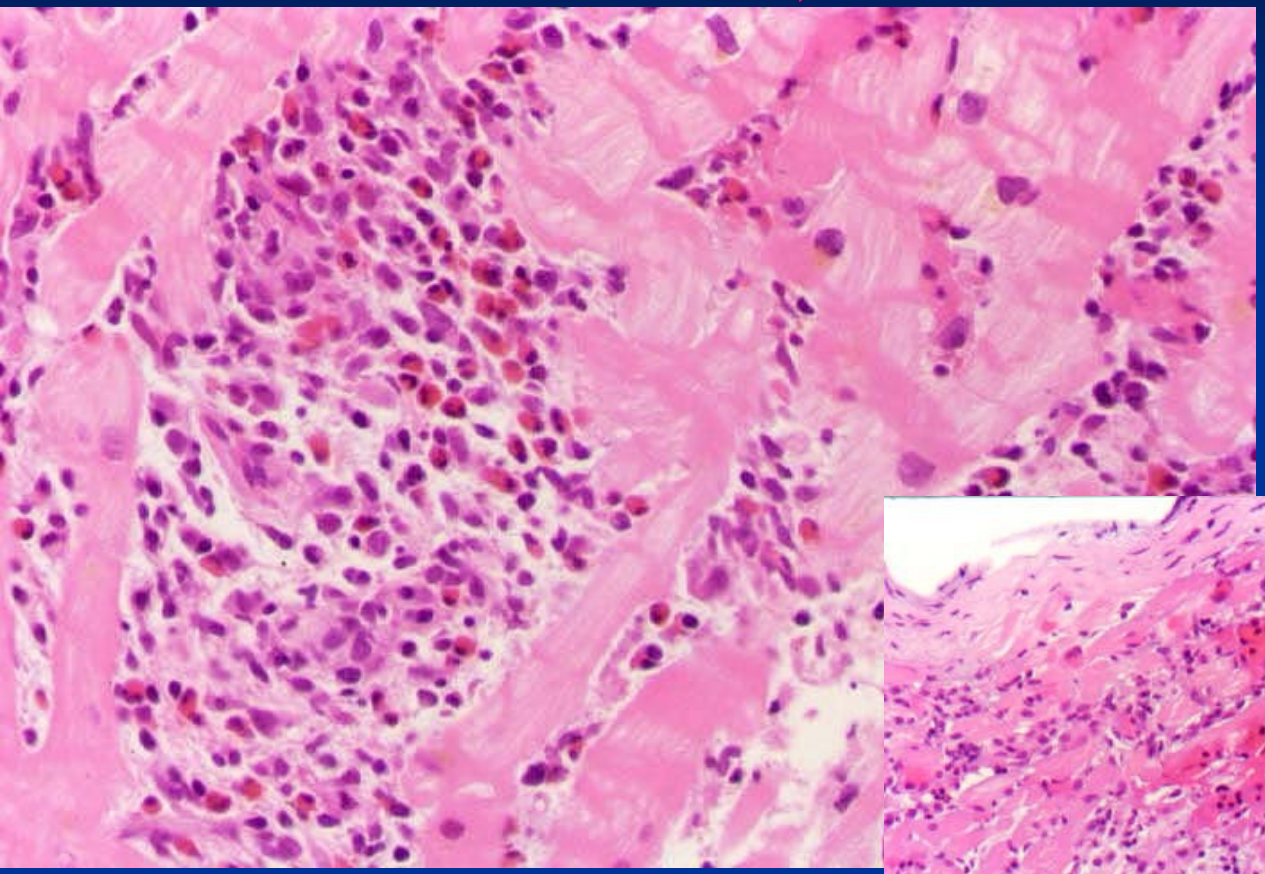
Acute cellular rejection

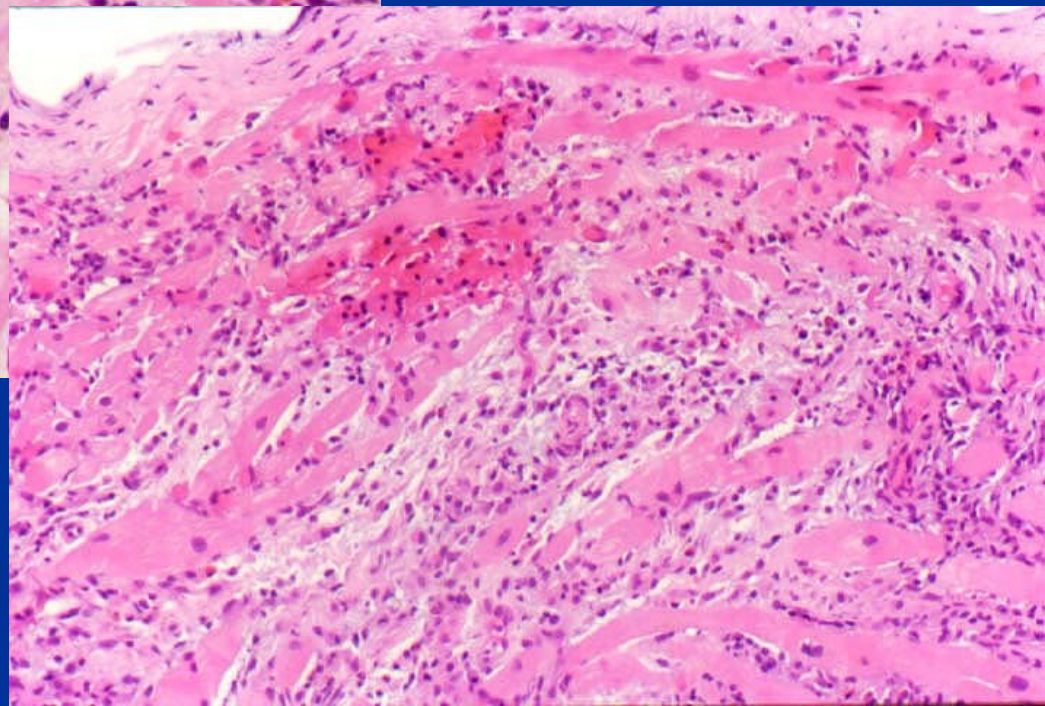
- Endotheliitis: endothelial cells injury, T- cells between the endothelium and the vessel wall.
- The recognition of cellular rejection important, patients respond well to immunosuppressive therapy.
- Untreated ACR may lead to the graft failure and/or chronic rejection

Acute cellular rejection (ACR)

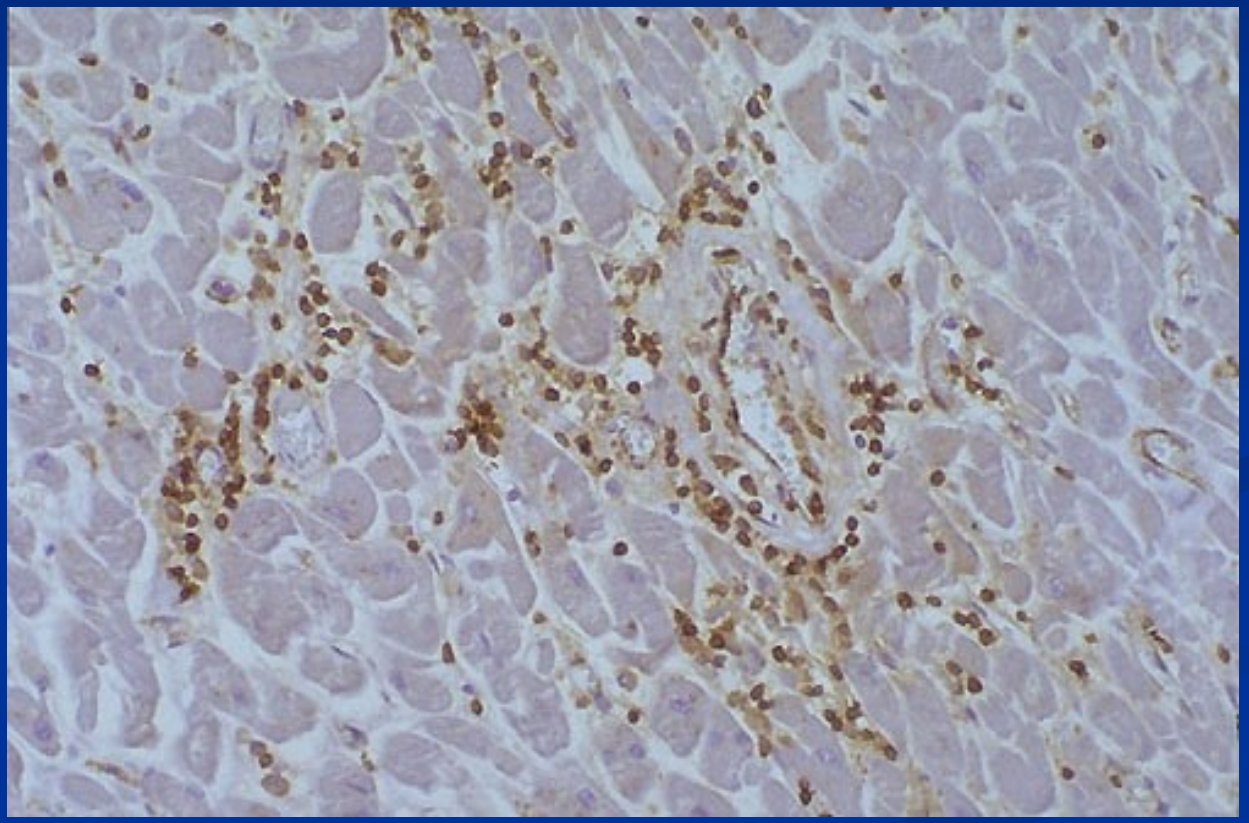
- Classification: organ specific indexes for establishing the rejection presence and activity (RAI – rejection activity index in liver grafts)
- Rejection grade – mild – moderate – severe → therapy
- Diff. dg. x other pathol. lesions (ATN in kidney; oportunistic or recurrent infections in liver, …).
- Possible co-existence of pathol. changes (rejection + infection, rejection + preservation injury, …)

Acute cellular rejection - myocardium





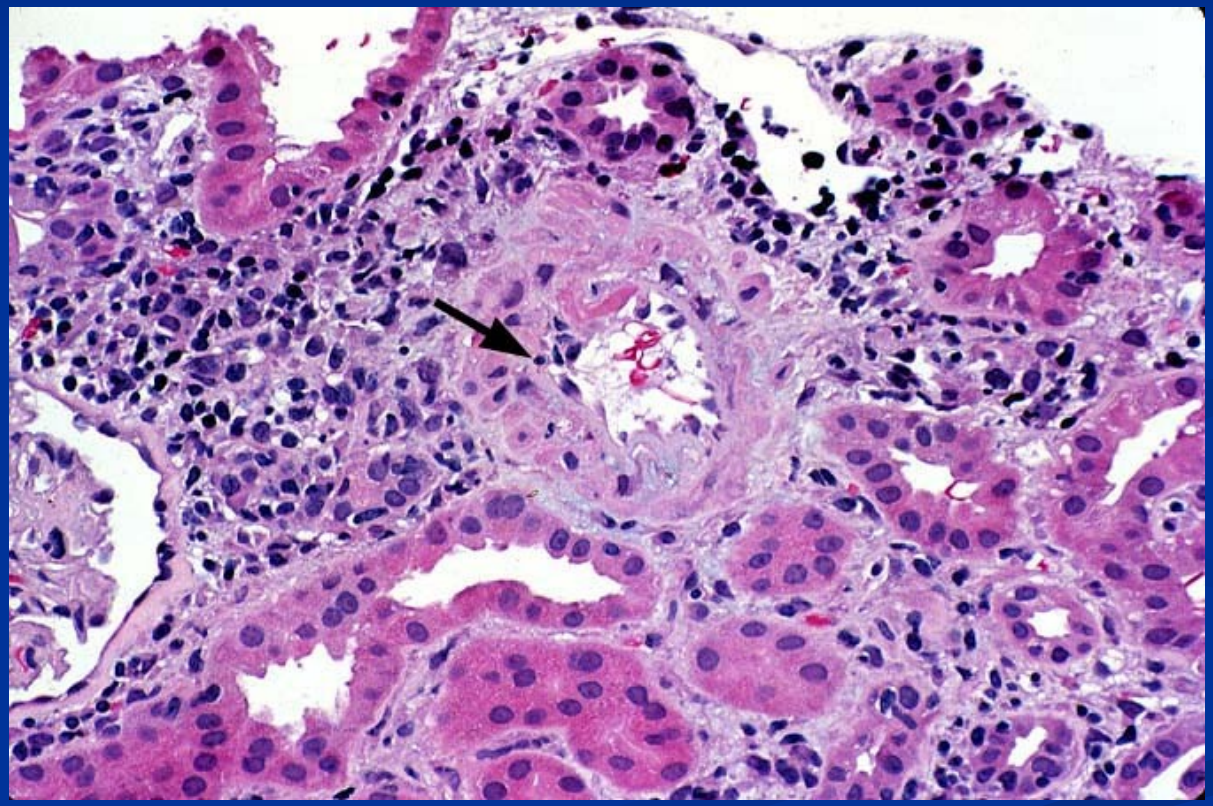
Acute cellular rejection - myocardium



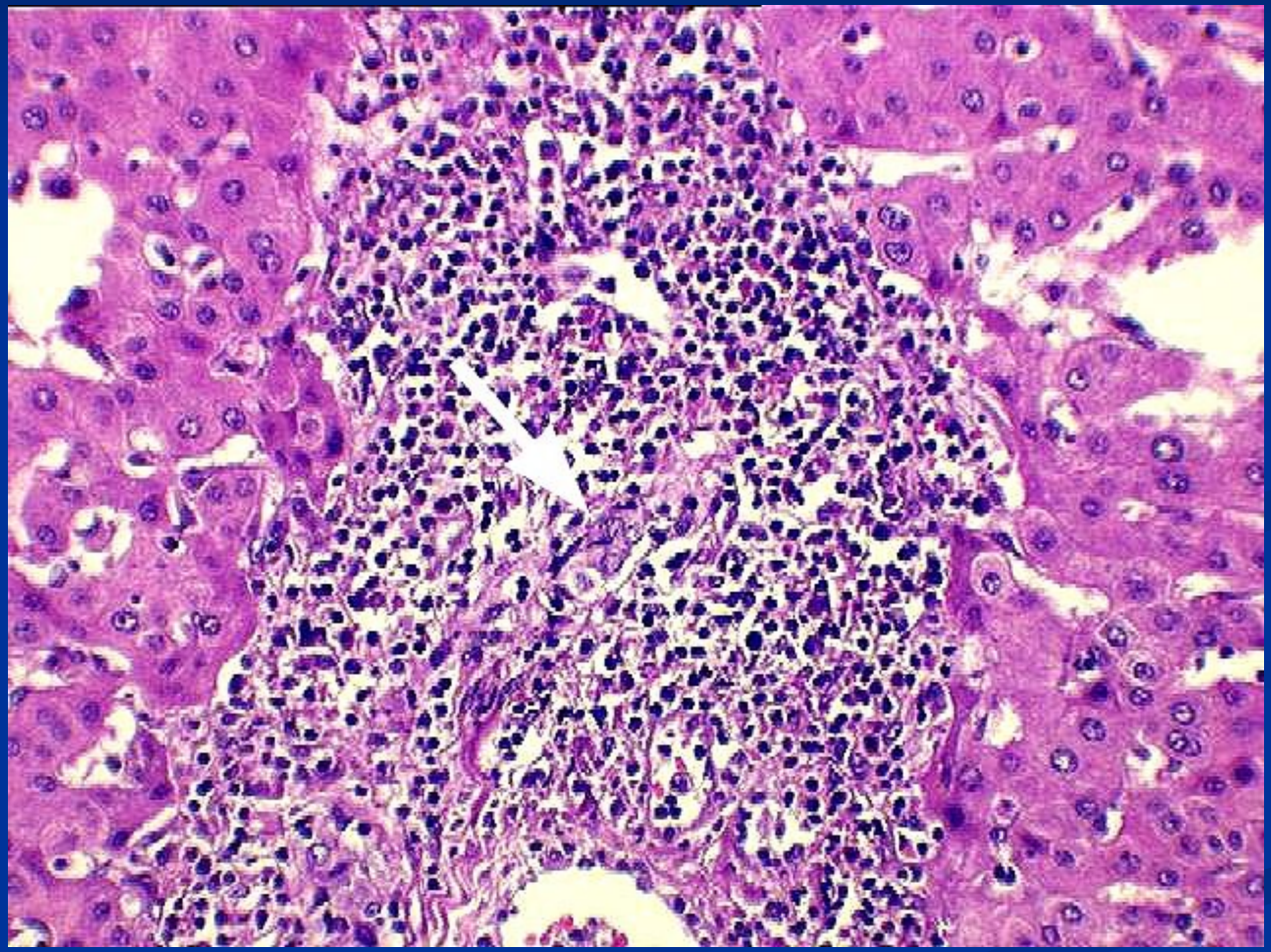
IHC: CD3+ T-cells infiltrate in interstitium

Acute cellular rejection

- endothelialitis + tubulitis + infiltrate



Acute rejection -liver



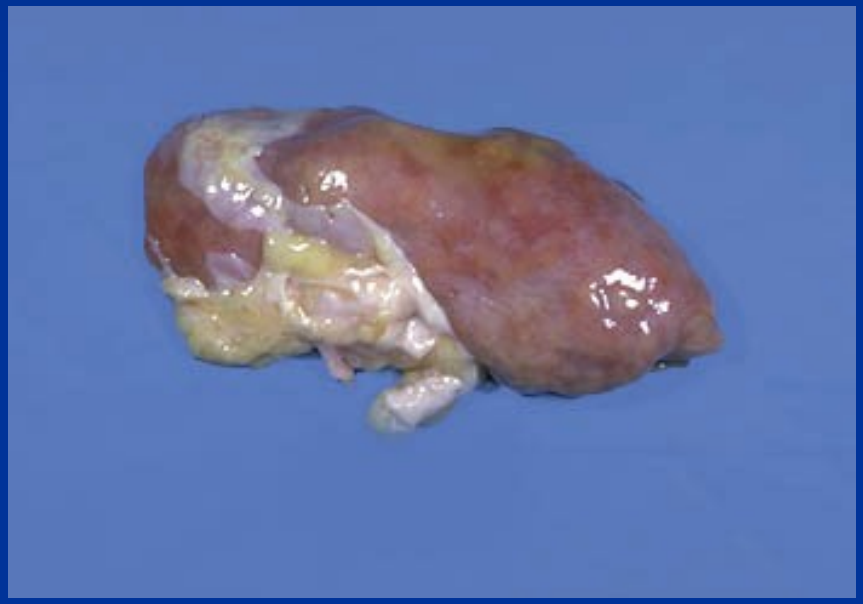
Chronic rejection

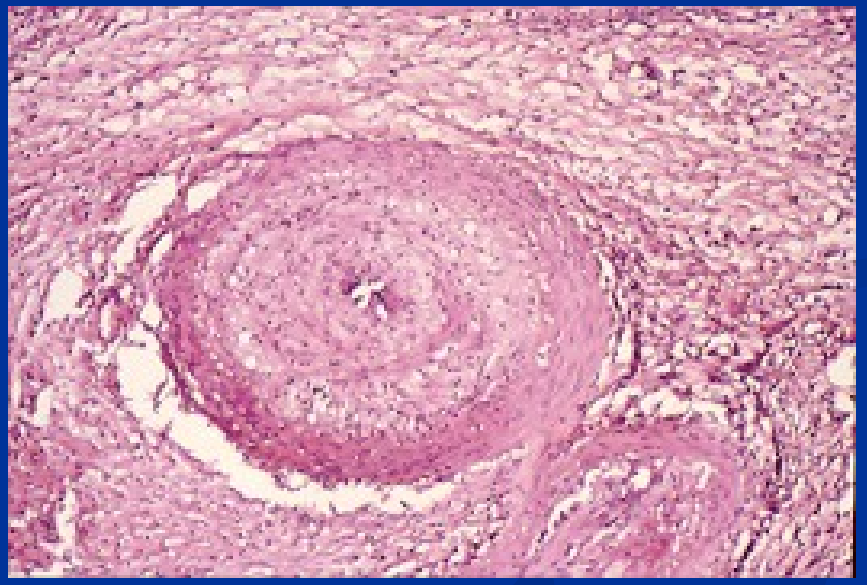
- Important cause of graft failure, multifactorial (ac. rej. persistence, viral infections, chronic ischemia).
- Patients with chronic rejection - progressive organ failure presentation.
- Chronic rejection dominated by vascular changes, interstitial fibrosis, and tubular/ductal atrophy with loss of parenchyma.

Chronic rejection

- **Vascular changes:** dense, obliterative intimal fibrosis + macrophagic reaction („accelerated arteriosclerosis“)→ ischemia, loss of parenchymal cells, interstitial fibrosis and tubular/ductal atrophy, shrinkage of the parenchyma.

Chronic rejection

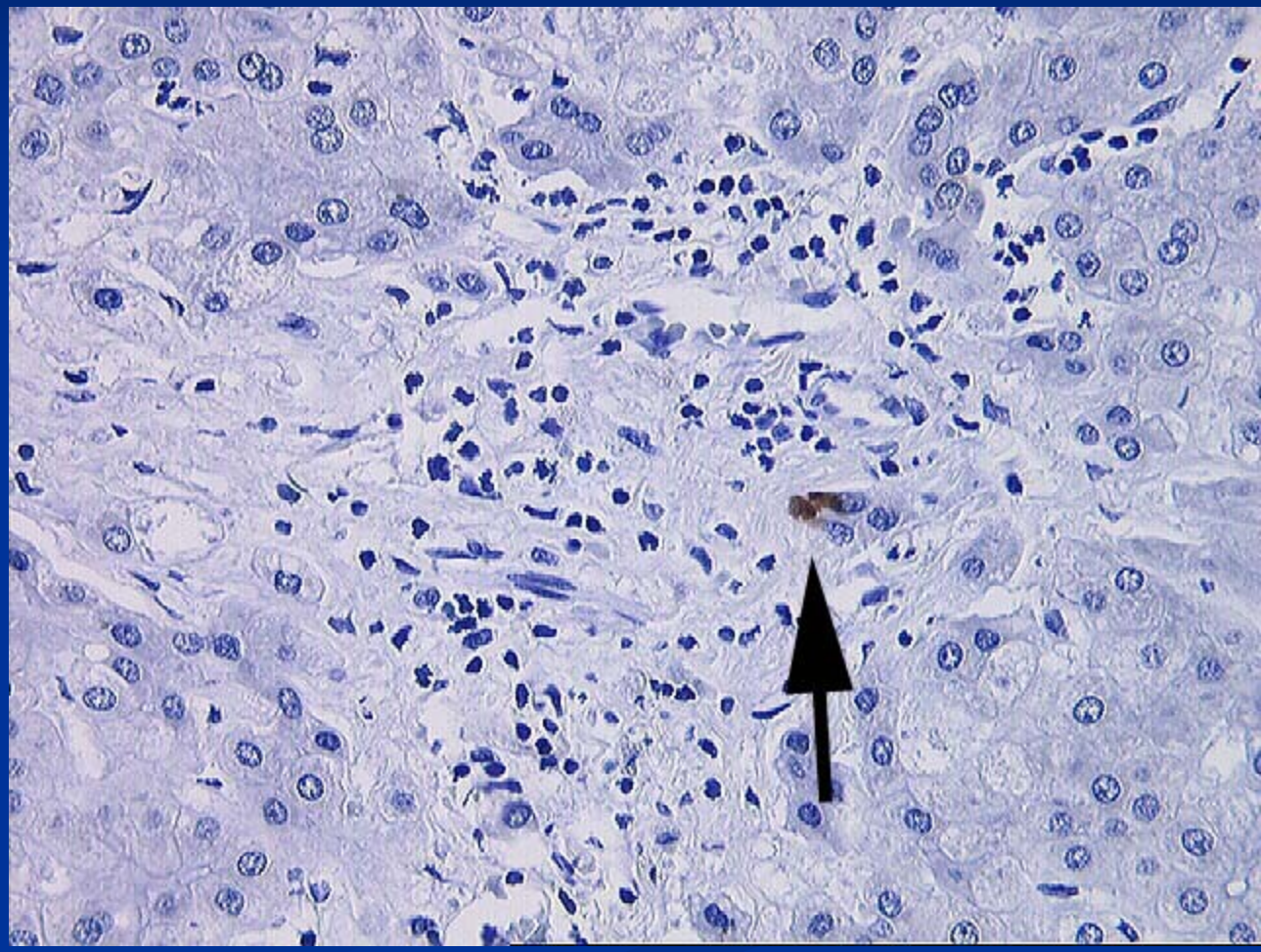


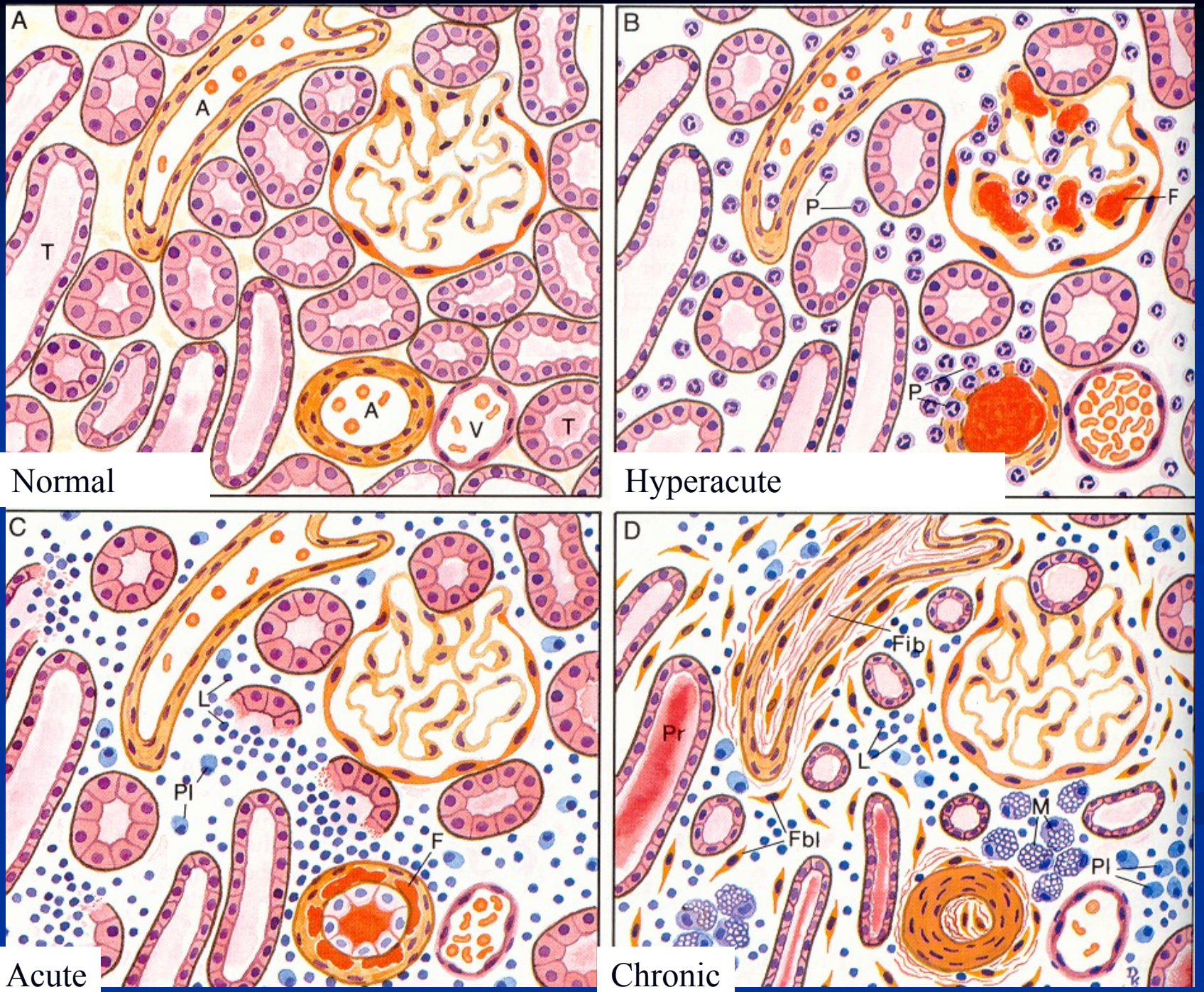


Failed atrophic renal graft, rejection vasculopathy

Chronic rejection – ductopenic

- liver graft – IHC CK7: duct loss

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Chronic

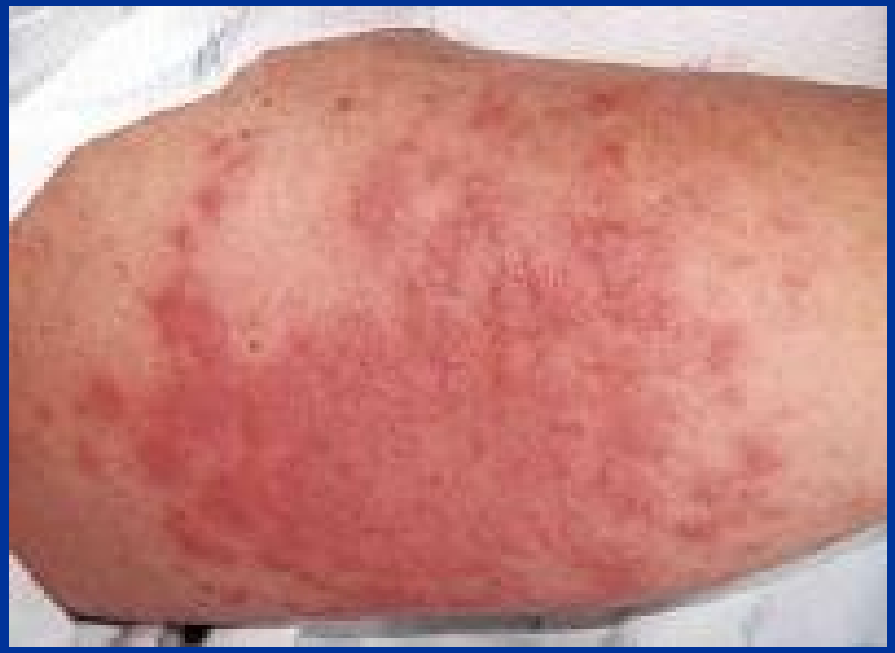
GVHD

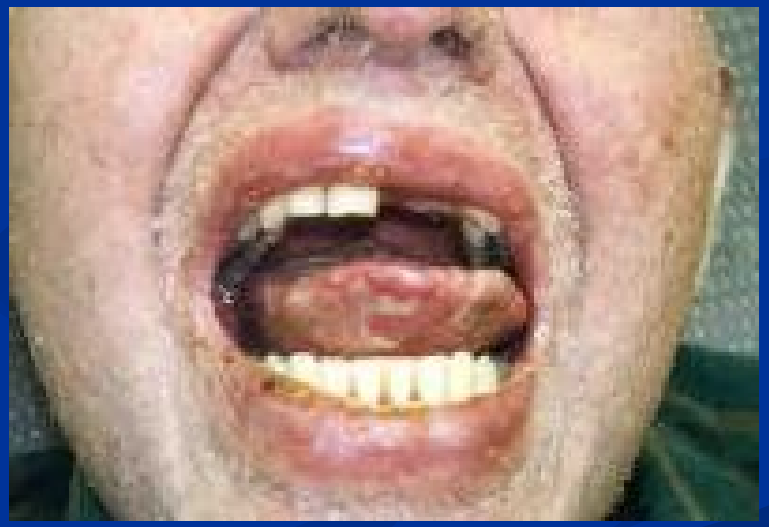
- Graft-versus-host disease: immunologically competent cells or their precursors transplanted into immunologically non-functioning recipients, the transferred cells recognize/attack alloantigens in the host
- Direct cytotoxicity (CD8+ T-cells) + cytokines

GVHD

- Graft-versus-host disease – most patient with bone marrow transplantation, possible in organs with higher amount of lymph. tissue – intestine, liver (immunologic competent T cells + precursors → in immunodeficient host)
- precise HLA typization/match necessary
- hyperacute few days, fever, generaliz. erythrodermia
- acute –skin rash, mucosal ulceration, liver cholestatic lesions, thrombocytopenia, anaemia
- chronic – chron. lichenoid lesions + atrophy of skin, mucosa, bronchiolitis obliterans, chron. hepatitis,…

GVHD





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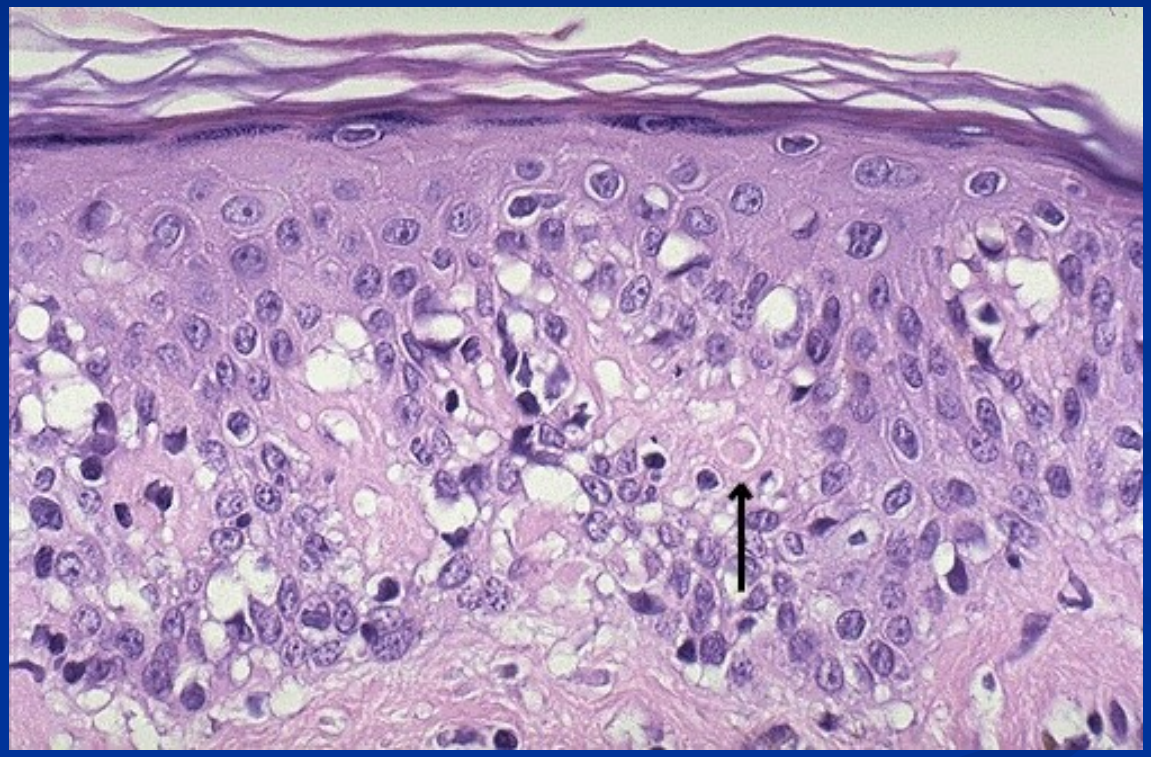
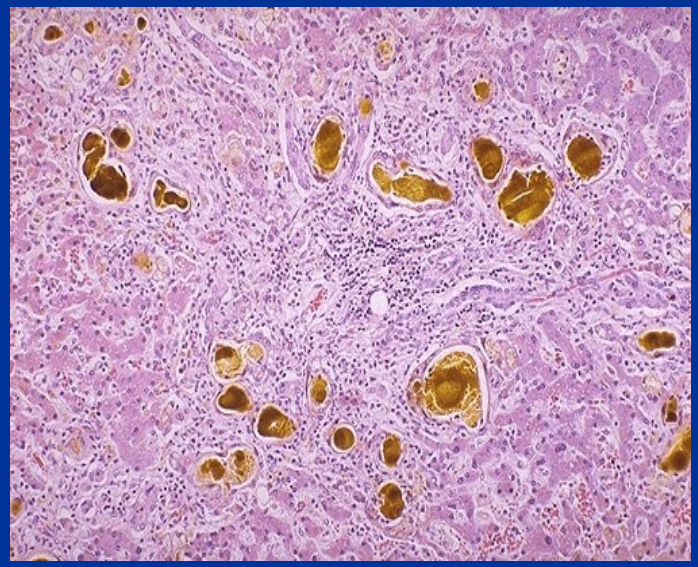
GVHD

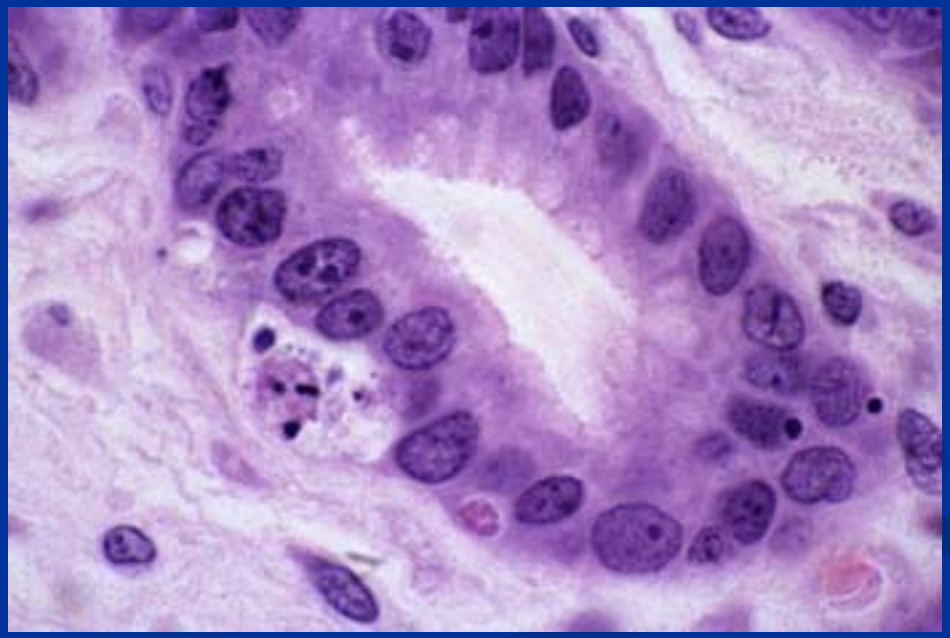


Apoptosis of keratinocytes

GVHD

- Liver cholestasis
- Apoptosis in intestinal mucosa

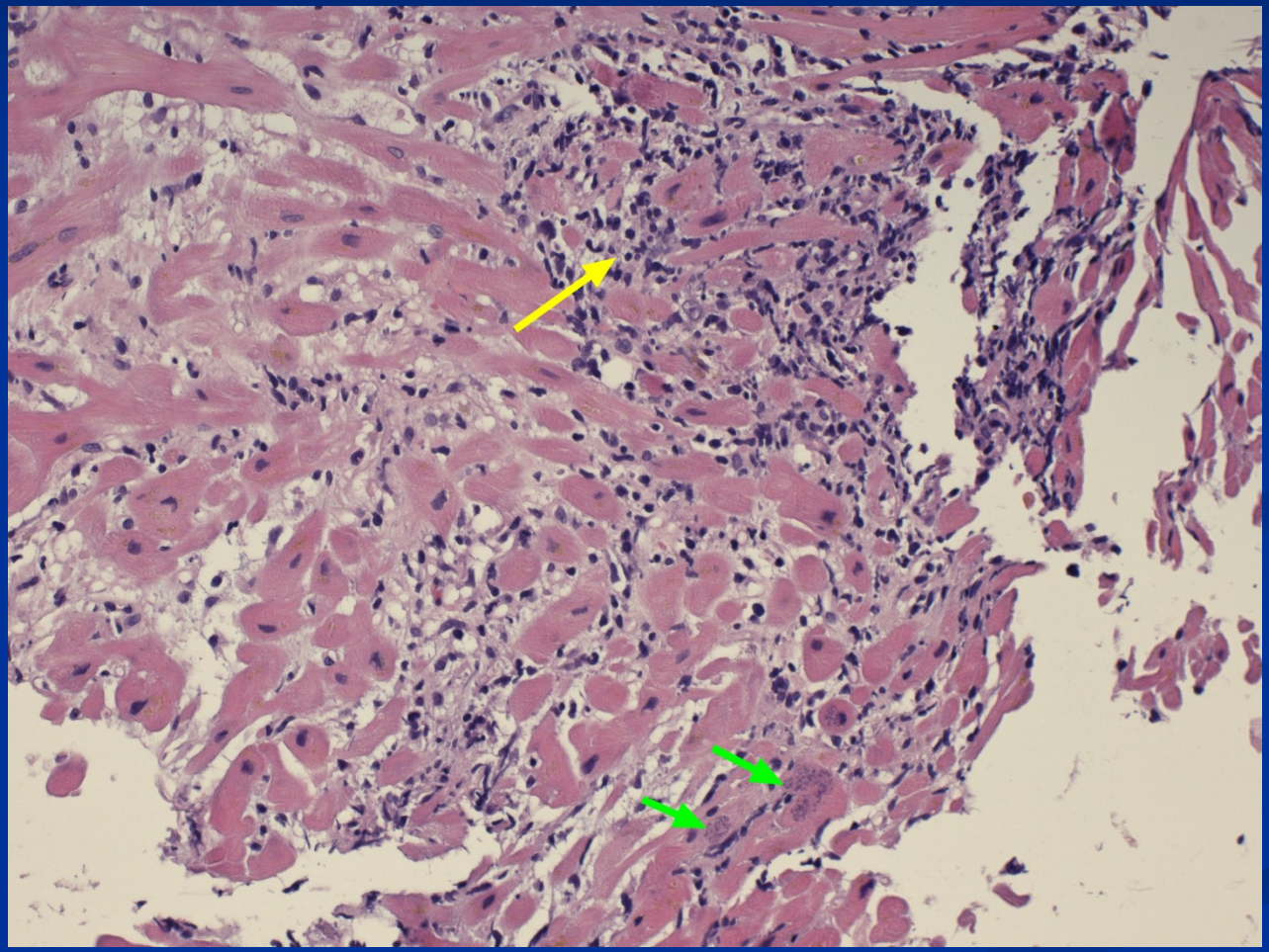




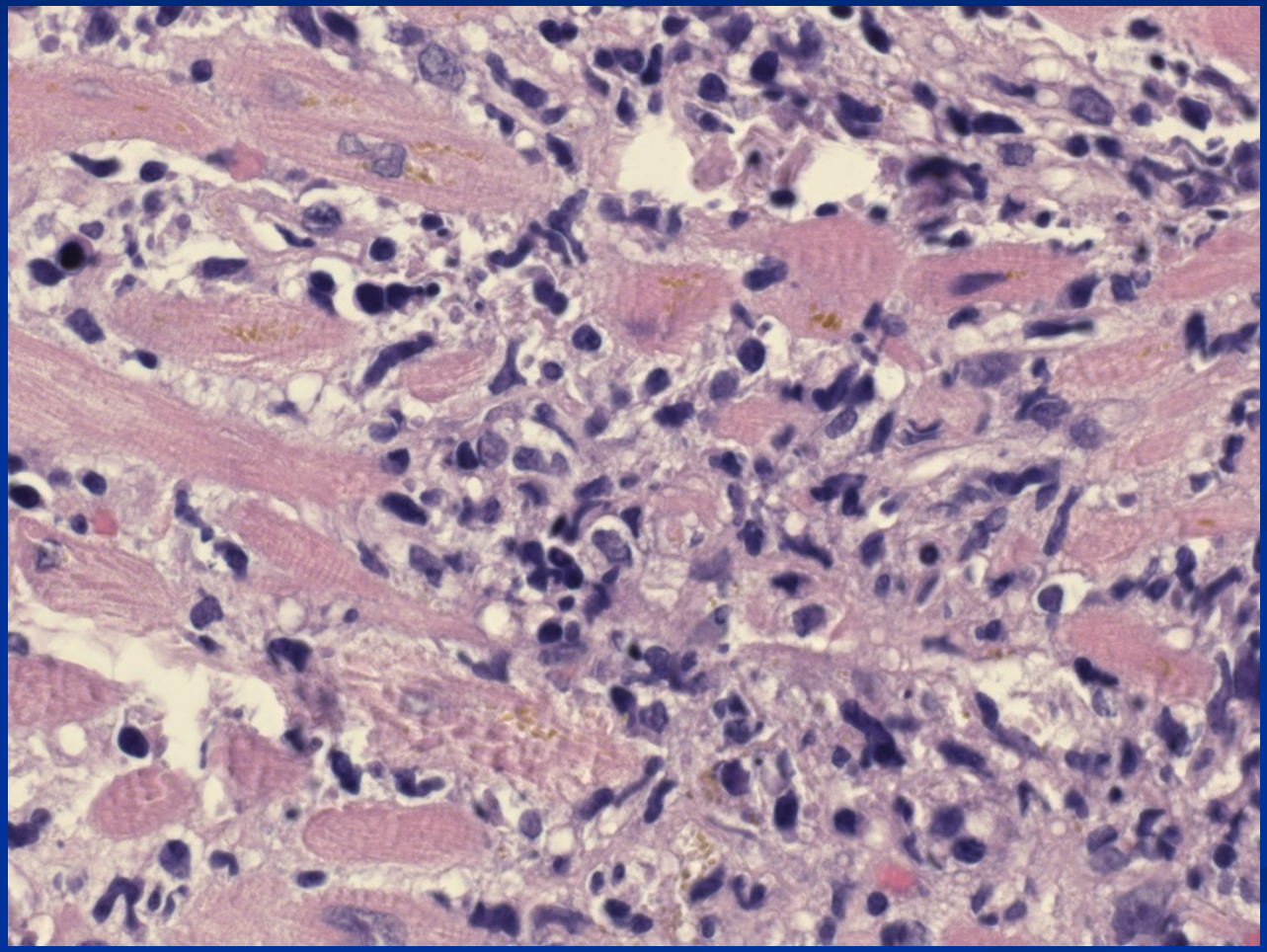
Other problems in transplantation

- alone or in combination
- surgical problems
- opportunistic and other infections
- drug toxicity
- neoplasia

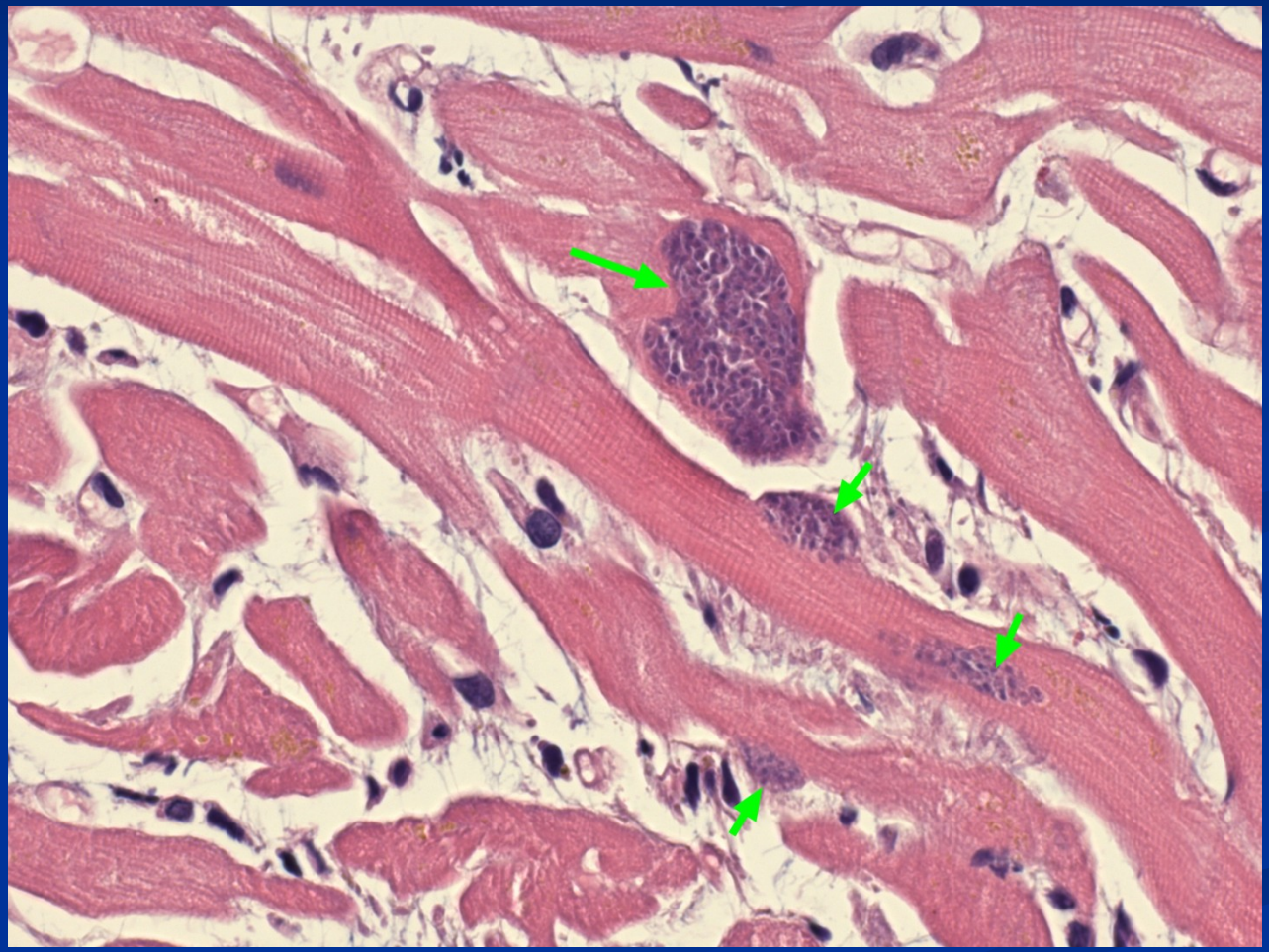
Acute rejection + infection in immunodeficient host



Acute rejection + infection in immunodeficient host



Acute rejection + infection in immunodeficient host



Toxoplasmosis

Immunodeficiency

- Next week...