

Hematologic disorders, allergic and immunologic diseases.

Markéta Hermanová

RAS (recurrent aphthous ulcerations; canker sores)

■ Primary immunodysregulation

- In ulcerative stage: decreased ratio of CD4/CD8 T lymphocytes (about 1:10); increased TCR $\gamma\delta$ +, increased TNF- α → increased activity of T cell subpopulations that mediate cytotoxic damage
- Antibody-dependent cellular cytotoxicity, T-cell mediated cytotoxicity to oral epithelial cells (Ag unknown)??? cross reactivity between Ag shared by oral streptococci and oral epithelial cells???
- Patients with cyclic neutropenia

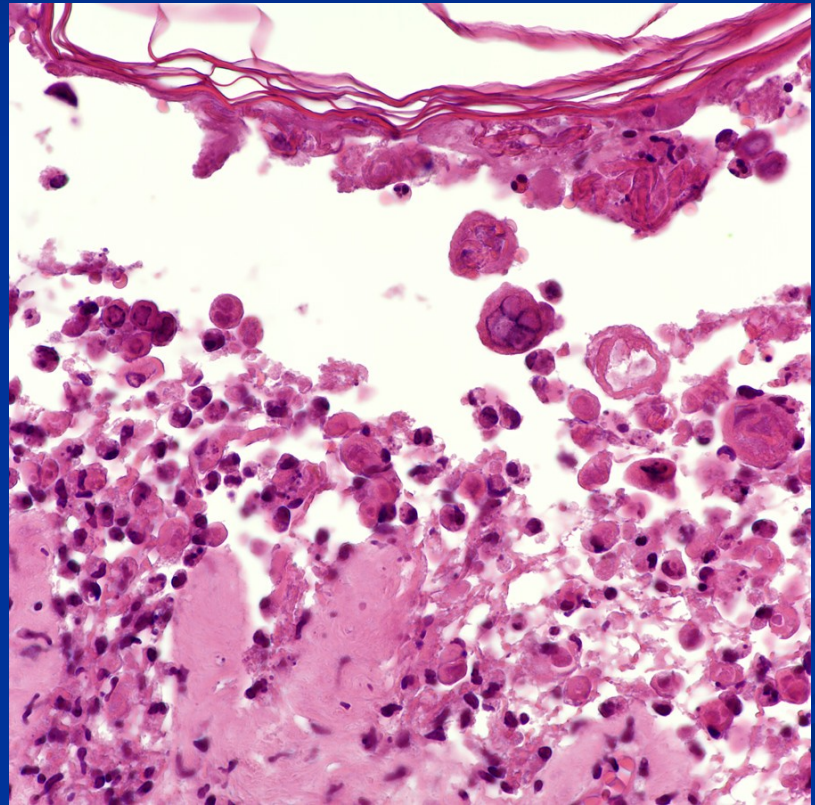
■ Decrease of mucosal barrier

■ Increase in antigenic exposure

Potential etiopathogenetic factors of aphthous stomatitis

- **Allergies**
- **Genetic predisposition** (HLA-B12, B51, Cw7)
- **Nutritional abnormalities** (B12, folate and iron deficiencies)
- **Haematological disorders** (anemia)
- **Gastrointestinal diseases** (avitaminosis B12 – atrophic oral mucosae, MAS, coeliac disease, ulcerative colitis, m. Crohn,...)
- **Hormonal influences** (pregnancy, luteal phase of MC,...)
- **Infectious agents** (L form of streptococci, HSV, VZV, CMV,...)
- **Trauma**
- **Stress**
- **Systemic disorders**

HSV infection



Systemic diseases associated with recurrent aphthous stomatitis

- Behcet's syndrome (aphthous ulcers, genital ulcers, uveitis)
- Celiac disease (gluten intolerance)
- Cyclic neutropenia (AD, *ELA2* gene - neutrophil elastase)
- Nutritional deficiencies
- IgA deficiency
- Immunocompromised conditions, incl. HIV
- Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
- PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis)
- Reiter's syndrome (arthritis, urethritis, conjunctivitis and skin lesions)

Clinical variation of aphthous stomatitis

- **Minor** (80 %)
- **Major** (10 %)
- **Herpetiform**

- **Histopathology:** ulcerative lesion covered with fibrinopurulent membrane, mixed inflammatory infiltration; spongiosis of the epithelium

Aphthous stomatitis



Behcet's disease (syndrome)

- **Recurrent oral ulceration** (minor, major or herpetiform aphthae)
- + **two of the following:**
 - Recurrent genital ulcerations
 - Eye lesions (uveitis, retinal vasculitis,...)
 - Skin lesions (erythema nodosum, pseudofolliculitis or papulopustular lesions, acneiform nodules,...)
- + arthritis, CNS involvement, cardiovascular , GIT, hematologic, pulmonary, muscular, renal systems involvement
- **HLA-B51**
- **Immunosuppressive treatment**

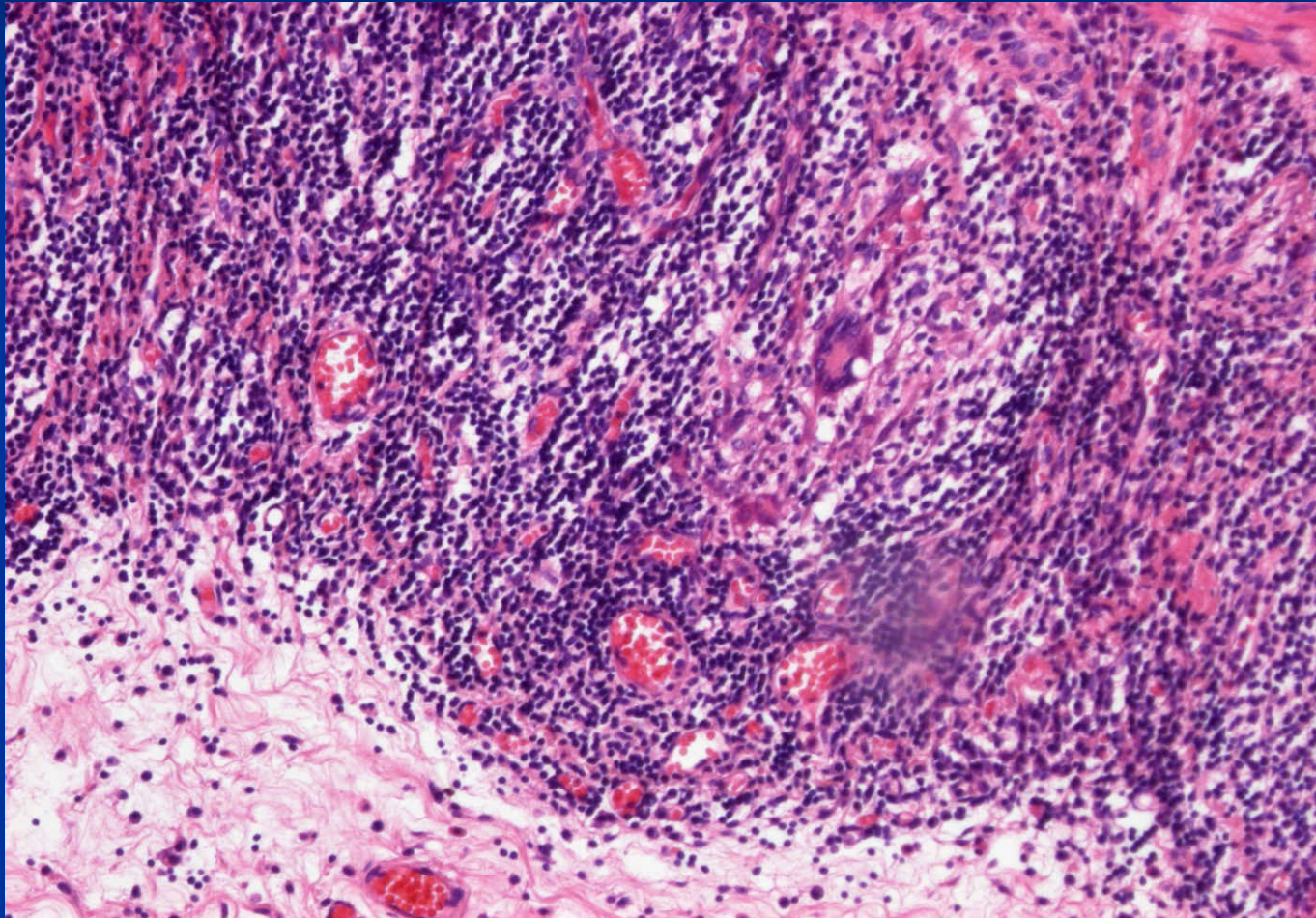
Sarcoidosis

- Multisystem granulomatous disorder of unknown cause
- Inappropriate defense response to mycobacterial infectious agents + immunodysregulation
- Lungs, lymph nodes, skin, eyes, salivary glands,....
- Any oral mucosal sites can be affected (normal in color, brownish-red, violaceous, hyperkeratotic – submucosal mass)
- Non-necrotising granulomas (accumulation of epithelioid histiocytes, Langhans' or foreign body-type giant cells, Schaumann bodies – basophilic calcifications, asteroid bodies – stellate inclusions)
- Diagnosis: clinical and radiographic presentations, biopsy-histopathology, laboratory abnormalities, Kveim test (intradermal injection of human sarcoid tissue – development of papulonodular lesion)
- Treatment: corticosteroids

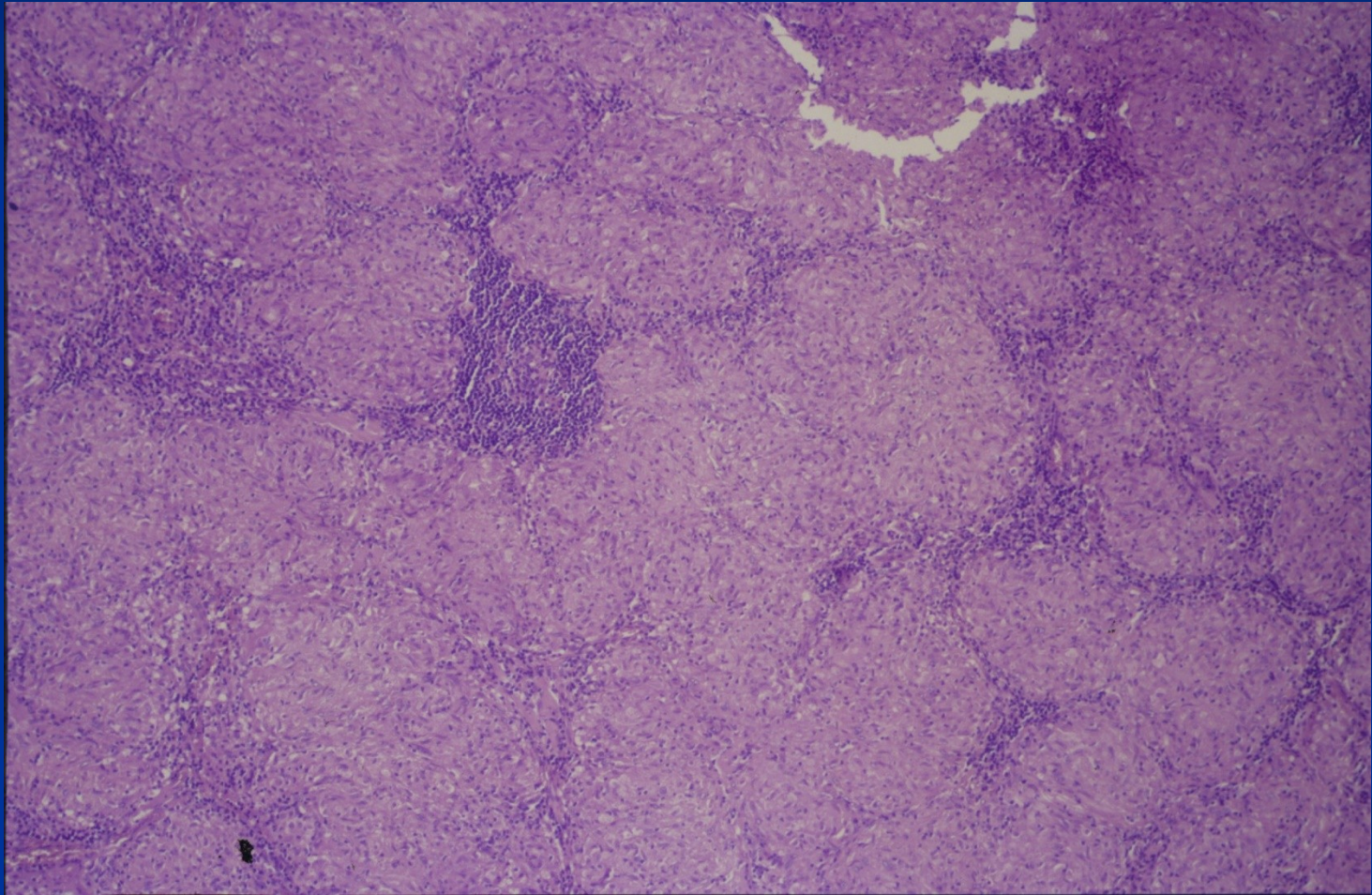
Other granulomatous disorders

- **Orofacial granulomatosis**
 - Melkersson-Rosenthal syndrome (cheilitis granulomatosa+facial paralysis+fissured tongue)
- **Wegener's granulomatosis**
- **Crohn's disease**
- **Tuberculosis**
- **Sarcoidosis**
- **Foreign body reaction, allergy**

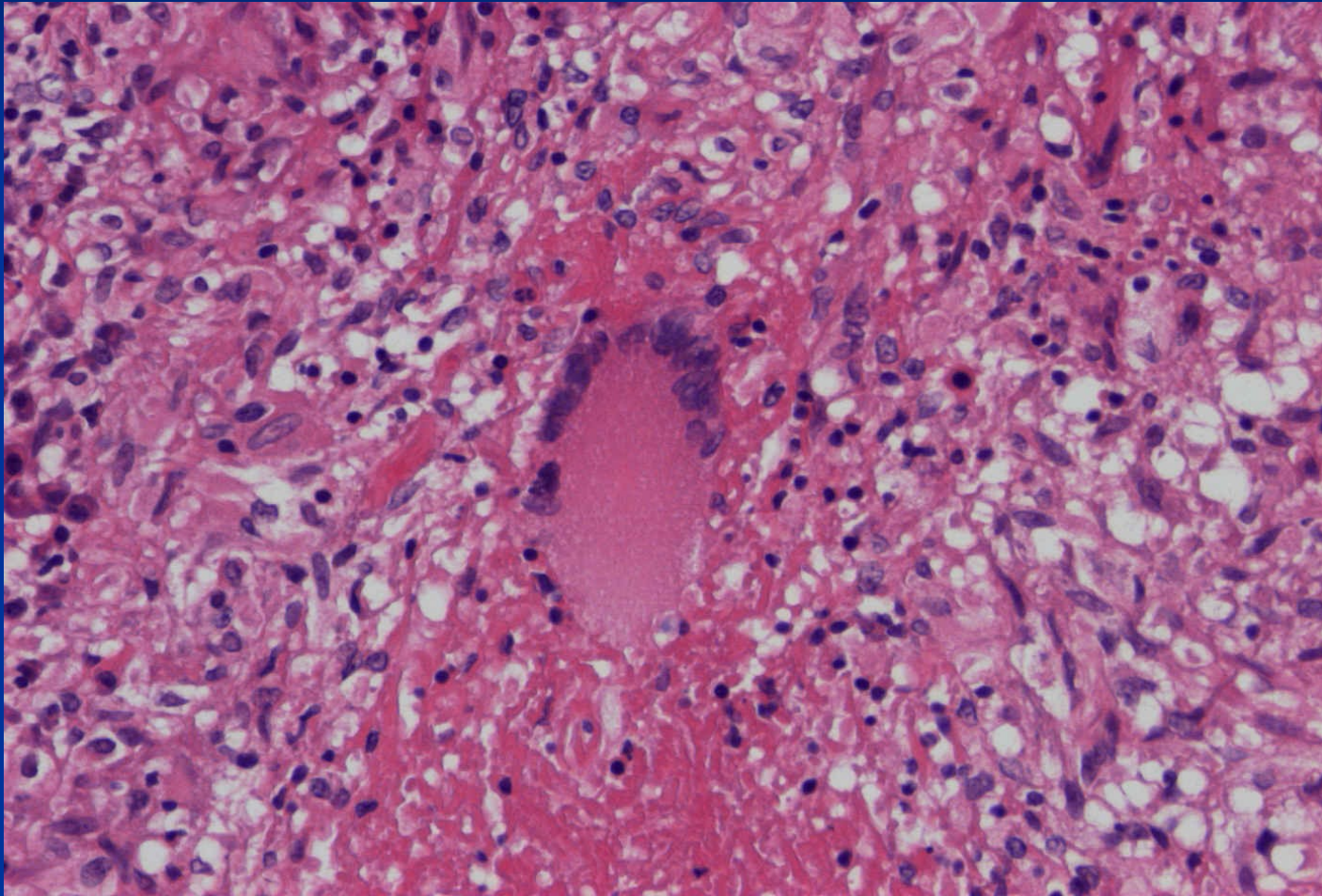
Granuloma in Crohn's disease



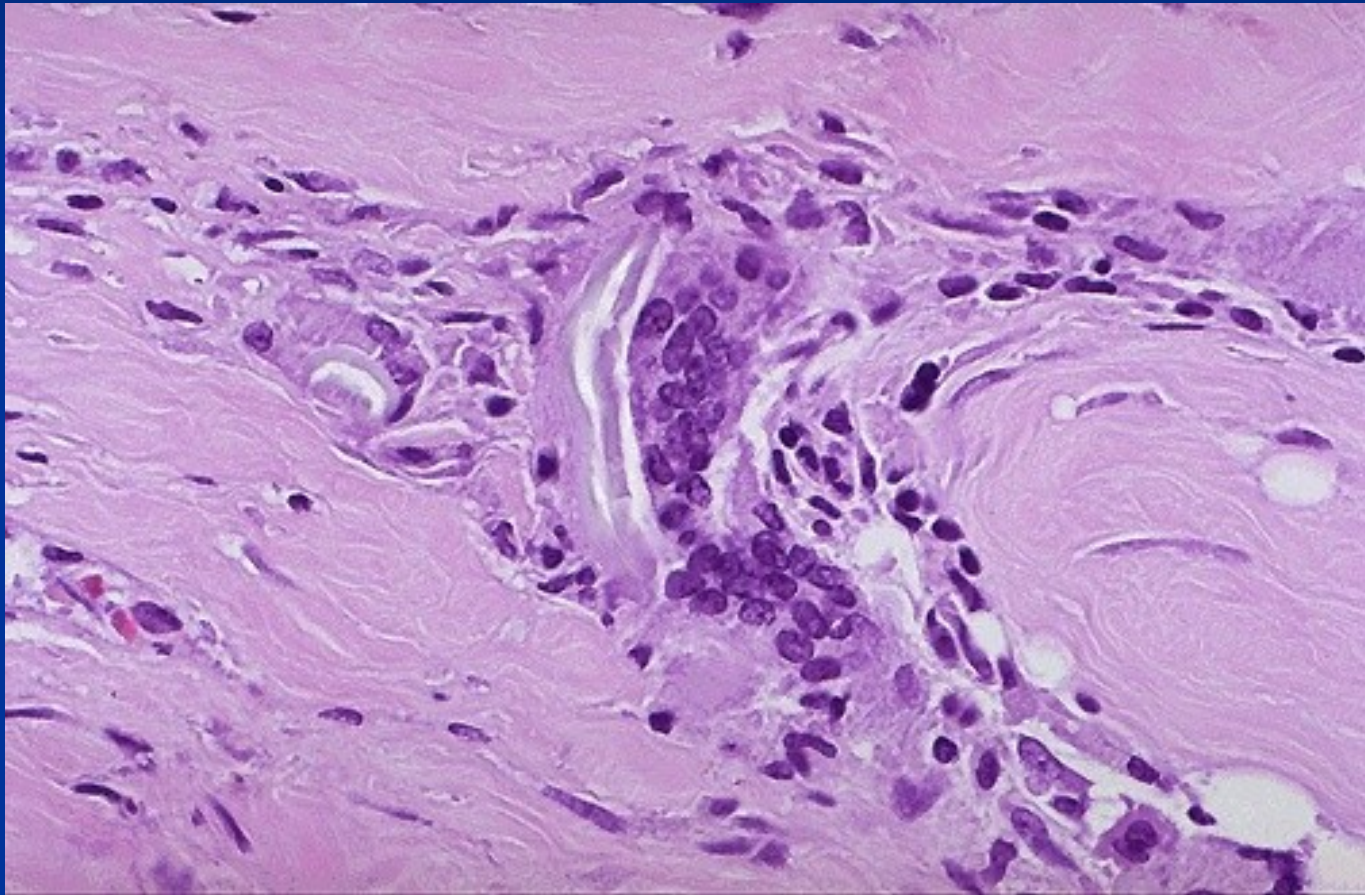
Sarcoidosis



TBC



Foreign body reaction



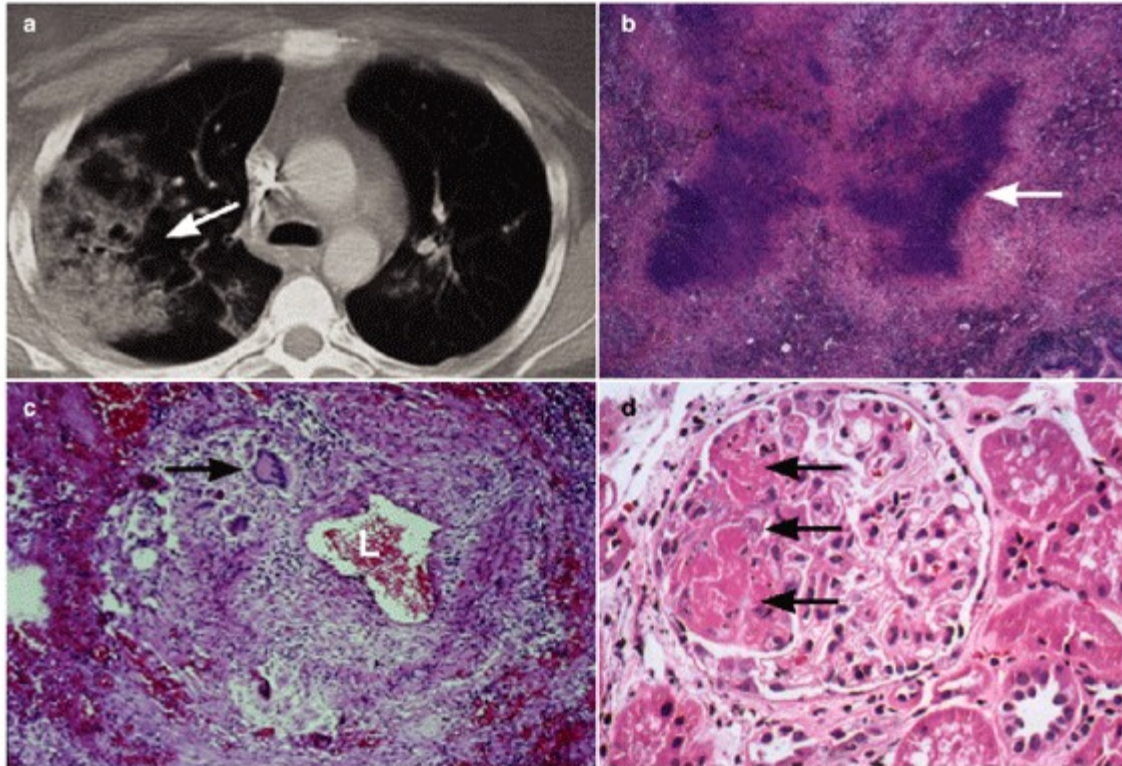
Wegener's granulomatosis

- Necrotizing granulomatous lesions of the respiratory tract
- Necrotizing glomerulonephritis
- Systemic vasculitis

Wegener's granulomatosis

- **Classic**
- **Limited** (no rapidly progressive renal lesion)
- **Superficial** (skin and mucosa affected)

- Oral lesions: strawberry gingivitis (hemorrhagic and friable), oral ulcerations, facial paralysis, labial mucosal nodules, oral-antral fistulae, poorly healing extraction sites, palatal ulcerations,.....
- cANCA autoantibodies
- Cyclophosphamide + prednisone



Features of Wegener's granulomatosis

Expert Reviews in Molecular Medicine 2005 Published by Cambridge University Press

Allergic mucosal reactions to systemic drug administration (stomatitis medicamentosa)

- **Anaphylactic stomatitis** (penicillin, sulfa drugs,...): symptoms of anaphylaxis (e.g. hoarseness, respiratory distress, vomiting), erythema and aphthous-like ulcerations in oral mucosa
- **Intraoral fixed drug reactions** (erythema, edema, vesiculoerosive lesions on labial mucosa)
- **Lichenoid drug reactions**
- **Lupus-erythematosus-like eruptions**
- **Pemphigus-like reactions**
(resemble their namesakes clinically, histopathologically and immunologically; typically posterior buccal mucosa and the lateral borders of the tongue)
- **Nonspecific vesiculoulcerative lesions**

Allergic contact stomatitis (stomatitis venenata)

- Foods, food additives, chewing gums, candies,topical anesthetics, restorative metals, acrylic denture materials,..cinnamon, amalgam
- **Acute** (burning, erythema, edema, vesicles, erosions, ulcers,...)
- **Chronic** (erythematous or white and hyperkeratotic)

■ **Perioral dermatitis**

(papules, papulopustules periorally; F>M; cosmetics, tooth-paste,...)

■ **Contact stomatitis from artificial cinnamon flavoring**

(tooth-paste, candies, chewing gums,...; mucosal enlargement, edema, erythema, circumoral dermatitis, exfoliative cheilitis,...in chronic cases a thickening of the surface epithelium)

■ **Chronic oral mucosal contact reactions to dental amalgam**

(mercury in amalgam responsible for the allergic reaction; acute or chronic; histologically and clinically resemble lichen planus – contact lichenoid reaction; posterior buccal mucosa, ventral surface of the lateral borders of the tongue affected)

■ **Angioedema (angioneurotic edema, Quinke's disease)**

- IgE-mediated hypersensitivity reactions caused by drugs (ACE inhibitors), foods, plants, dust, inhalants,...
- mast cell degranulation caused by physical stimuli (heat, cold, exercise, emotional stress, solar exposure)
- contact allergies
- activation of complement pathway (hereditary or acquired (in lymphoproliferative diseases or in patients who develop specific antibodies))
- Tissue swelling, itching, erythema (face, lips, tongue, pharynx, larynx, dermatologic involvement); involvement of GIT and respiratory tract, perioral and periorbital involvement
- Treated by oral antihistamines, corticosteroids; in laryngeal involvement – intubation and tracheostomy

Perioral dermatitis



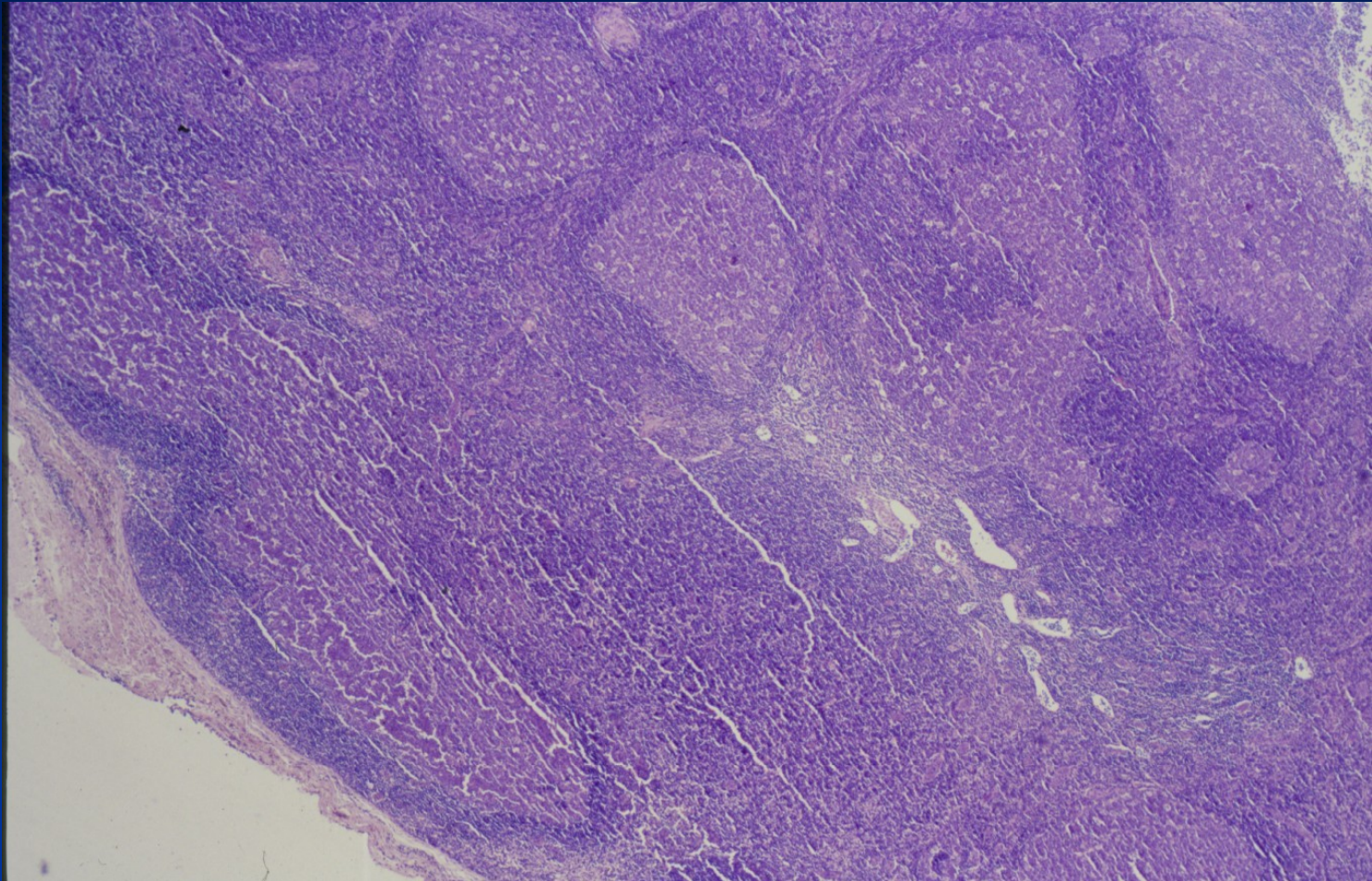
Angioedema



Hematologic disorders

- Lymphoid hyperplasia
- Hemophilia
- Anemia, sickle cell anemia, aplastic anemia
- Thalassemia
- Neutropenia, agranulocytosis, cyclic neutropenia, thrombocytopenia
- Leukemia, polycythemia vera
- Hodgkin and non-Hodgkin lymphomas
- Langerhans cell histiocytosis

Lymphoid hyperplasia – follicular hyperplasia



- Affect lymph nodes, lymphoid tissue of Waldeyer's ring, oral cavity aggregates of lymphoid tissue
- Reactive, non-neoplastic lesion: in acute infection, chronic inflammatory conditions, in HIV

Inherited bleeding disorders

(bleeding diatheses, specific clotting factor deficiency)

Type	Defect	Inheritance	Findings
Hemophilia A (classic)	Factor VIII	X-linked recessive	Abnormal PTT (partial thromboplastin time)
Hemophilia B (Christmas d.)	Factor IX	X-linked recessive	Abnormal PTT
von Willebrand disease	Abnormal von Willebrand factor, abnormal platelets	AD	Abnormal BT (bleeding time), abnormal PTT

- small oral lacerations (after minimal trauma) with significant blood loss, ecchymoses,
- deep hemorrhage after normal activities (muscles, joints, soft tissues)

Anemia

- Decrease in the volume of red blood cells (hematocrit) or in the concentration of hemoglobin
- Reduced oxygen-carrying capacity of the blood
- **Clinical features:**
 - Tiredness, headache, lightheadedness
 - Pallor of mucous membranes (oral mucosa)
 - Pallor of palpebral conjunctiva

Causes of anemia

■ Anemias with disturbed iron metabolism

- Iron deficiency
- Sideroblastic anemias

■ Megaloblastic anemias

- Pernicious anemia (avitaminosis B₁₂)
- Folic acid deficiency

■ Anemia associated with chronic disorders

- in chronic infections
- in inflammatory connective tissue disorders
- in malignancy (secondary to chronic bleeding, myelophthisic anemia)
- of uremia, of liver disease, of endocrine failure

Causes of anemia

■ Hemolytic anemias

- Extrinsic causes

- Splenomegaly
- Red cell antibodies
- Trauma in the circulation
- Direct toxin effects

- Membrane abnormalities

(paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis, hereditary ellipsocytosis)

- Disorders of the interior of the red cells

Causes of anemia

■ Disorders of hemoglobin

- sickle cell anemia (hemoglobinopathy, hereditary, abnormal shape and adherence properties of erythrocytes, fragile erythrocytes, blockage of capillaries; abnormal gene persists in human race – some degree of resistance to malarian organism)
- Thalassemias (hereditary disorders of hemoglobin synthesis; Thalassemia minor and major)

■ Aplastic anemia

- life-threatening hematologic disorder; failure of hematopoietic precursor cells in the bone marrow
- exposure to some environmental factors, drugs, certain viruses,....
- hereditary – Fanconi's anemia
- symptoms related to erythrocytes, platelets and leukocytes deficiency
- oral lesions, gingival hemorrhages, petechiae, purpura, ecchymoses, ulcerations

■ Neutropenia

- decreased number of circulating neutrophils
- congenital, hereditary; acquired (leukemia, metabolic diseases, drugs, infections,...)
- bacterial infections, oral lesions

■ Agranulocytosis

- neutrophils absent
- decreased production, increased destruction, idiopathic (some drugs?), congenital
- malaise, sore throat, swelling, fever, oral lesions – necrotizing ulcerative gingivitis

■ Cyclic neutropenia

- Idiopathic (some AD (*ELA2* gene - neutrophil elastase), ?defect in hematopoietic stem cells in the bone marrow?)
- Recurrent episodes of fever, anorexia, cervical lymphadenopathy, oral mucosal ulcerations, pharyngitis

■ Thrombocytopenia

- Decreased number of circulating blood platelets; petechiae, ecchymoses, hematomas
- Reduced production
- Increased destruction (immunologic reaction (ITP, TTP); consumption
- Splenomegaly

Hematooncology

- **Leukemia (hemoblastosis)**
 - Diffuse replacement of normal BM by leukemic cells with their subsequent variable accumulation in peripheral blood (=leukemization)
 - Infiltration of peripheral organs (liver, spleen, lymph nodes, meninges, gonads,....)

- **Lymphoma (hemoblastoma)**
 - Neoplastic/lymphoma cells form tumor/neoplastic mass (nodal and/or extranodal)

 - ! *Lymphomas may also present by leukemic infiltrates and leukemias also form solid neoplastic masses*

Hematooncology

- **Mutations that inhibit normal differentiation and maturation of progenitor cells, or mutations disrupting the regulation of progenitor and precursor cells by growth factors**
- ⇒ **Unregulated clonal expansion of immature hematopoietic cells → inhibition of normal hemopoiesis → release of immature blast into circulation, infiltration of peripheral organs**

Hematooncology

■ Myeloid neoplasms

- from stem cells that normally give rise to the formed blood elements (granulocytes, red cells, platelets)
- 3 categories
 - acute myelogenous leukemias
 - myeloproliferative disorders
 - myelodysplastic syndromes

■ Lymphoid neoplasms/lymphomas

- non-Hodgkin lymphomas
(incl. lymphocytic leukemias and plasma cell dyskrasias)
- Hodgkin lymphomas

■ Histiocytic neoplasms

Clinical features of leukemia

■ Acute myeloid leukemia

- adults, broader age range, also children

■ Chronic myeloid leukemia

- peak incidence during the 3rd and 4th decade

■ Acute lymphoblastic leukemia

- children, most common childhood malignancy

■ Chronic lymphocytic leukemia

- elderly adults

Clinical features of leukemia

■ Myelophthisic anemia

- marked reduction of normal white and red blood cells – crowding out of the normal hematopoietic stem cells by leukemic cells in bone marrow
- fatigue, easy tiring, dyspnoe, mild exertion
- lymphadenopathy, hepatomegaly, splenomegaly
- easy bruising and bleeding (due to thrombocytopenia), incl. gingival bleeding

Clinical features of leukemia

- Infections (G-, bacteria, G+ cocci, *Candida albicans*, HSV), fever
- Ulcerations of oral mucosa (due to impaired ability of the host to combat the normal microbial flora); neutropenic ulcers (deep, punched-out lesions with necrotic base)
- Infiltration of the oral soft tissues by leukemic cells (diffuse, boggy, nontender swelling, also ulcerated, also diffuse gingival enlargement or tumorlike growth)
- Infiltration of the periapical tissues

WHO classification of lymphomas

- **B-cell neoplasms**
 1. precursor B-cell neoplasms
 2. peripheral B-cell neoplasms

- **T-cell neoplasms**
 1. precursor T-cell neoplasms
 2. peripheral T-cell neoplasms

- **Hodgkin lymphomas**
 1. Classical subtypes
 2. Lymphocyte predominance

Neoplasms of immature B and T cells (precursor B and T cell neoplasms)

1. **Precursor -B-cell acute lymphoblastic leukemia/lymphoma**
 - bone marrow precursor B-cell expressing TdT and lacking surface Ig
 - children (peak at age 4), highly aggressive/chemosensitive, leukemic presentation (80 %)
 - infiltration of bone marrow, LN, liver, spleen,...
 - diverse chromosomal translocation (t(12;21))
2. **Precursor-T-cell acute lymphoblastic leukemia/lymphoma**
 - precursor T-cell (often of thymic origin) expressing TdT
 - diverse chromosomal translocations (TCR loci)
 - Adolescent males, thymic mass, variable splenic, hepatic, and bone marrow involvement; aggressive
 - B-ALL>>>T-ALL

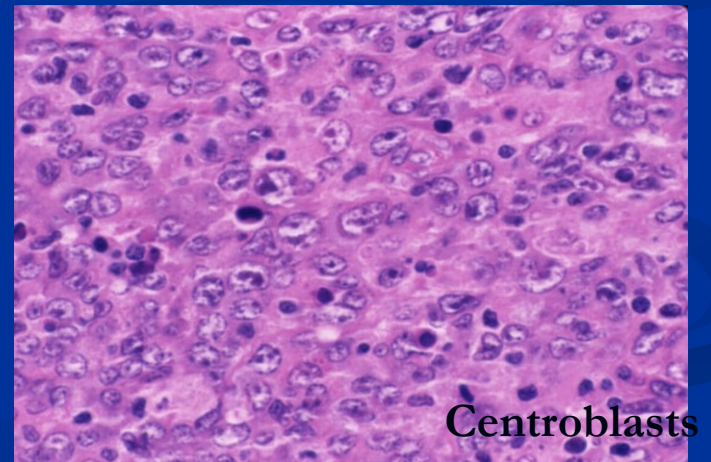
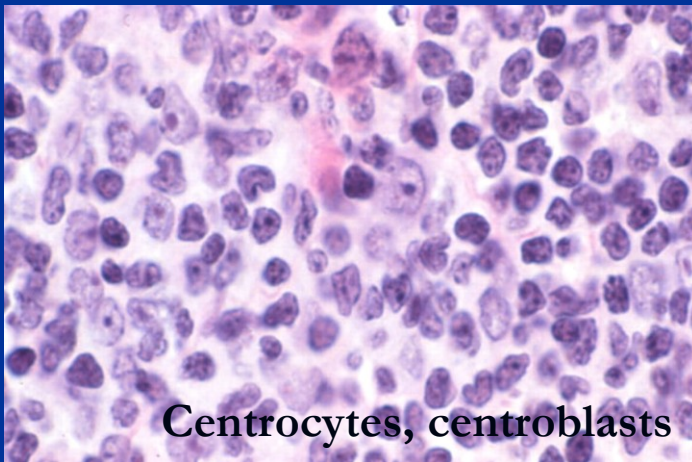
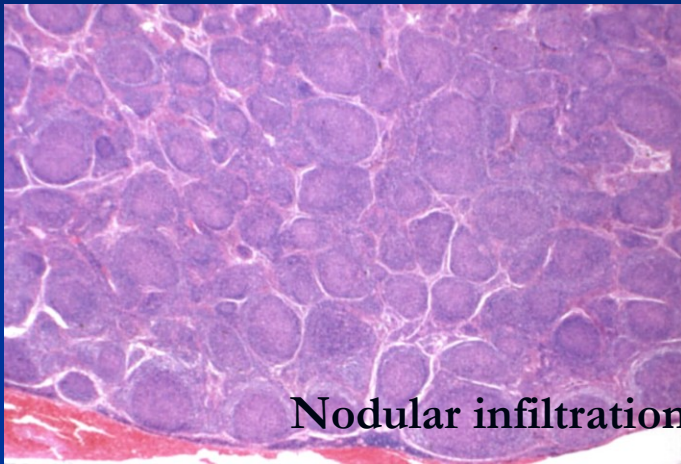
Neoplasms of mature B-cells (peripheral B cells neoplasms)

- B-chronic lymphocytic leukemia/small lymphocytic lymphoma**
 - naive B-cell or postgerminal center memory B-cell (CD5+)
 - trisomy 12, deletions 11q, 13q, 17p
 - adults; bone marrow, lymph nodes, spleen, liver; indolent; transformation into high grade lymphoma – Richter's syndrome
- Mantle cell lymphoma**
 - naive B-cell of mantles (CD5+, cyclinD1+(promotes G1 to S phase progression))
 - t(11;14); cyclinD1 locus/IgH locus
 - older males, often extranodal (lymphomatous polyposis); moderately aggressive – resistant to therapy
- Follicular lymphoma**
 - germinal center B-cell (CD10+, bcl-2+, bcl-6+): centrocytes; centroblasts and immunoblasts
 - t(14;18); bcl-2/IgH (bcl-2 (inhibitor of apoptosis) overexpression – promotion of the survival of follicular lymphoma cells)
 - adults; primary nodal, later disseminated; indolent

Spleen, follicular lymphoma



Follicular lymphoma



4. **Diffuse large B-cell lymphoma**

- germinal center or postgerminal center B-cell (centroblasts and immunoblasts)
- diverse chromosomal translocations (bcl-6 rearrangement)
- all ages, usually adults; 40 % extranodal; aggressive

5. **Burkitt lymphoma**

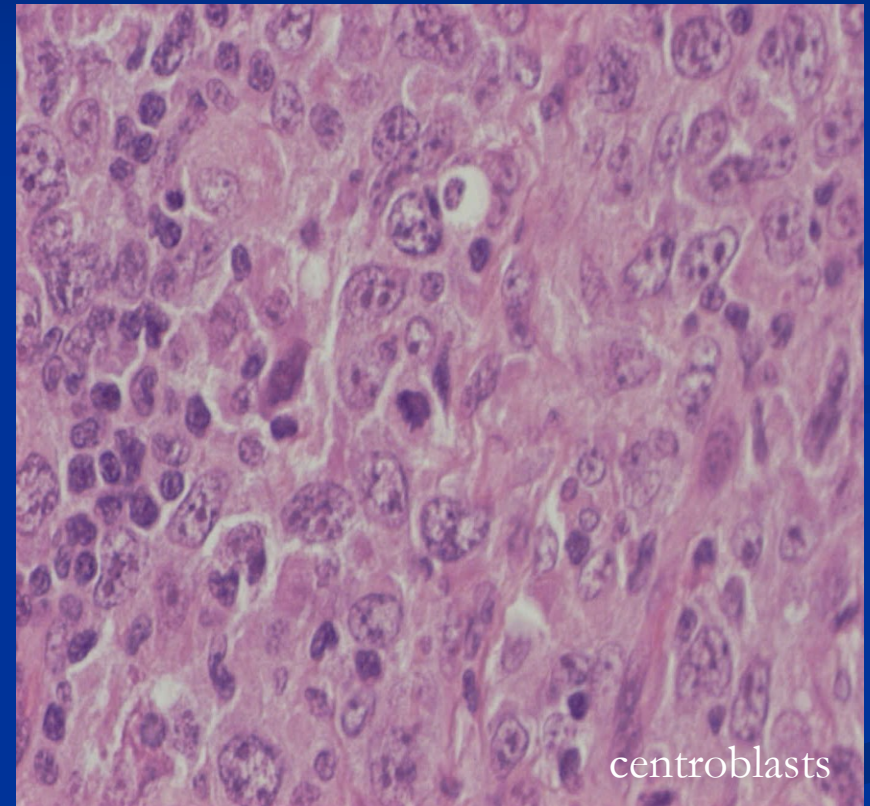
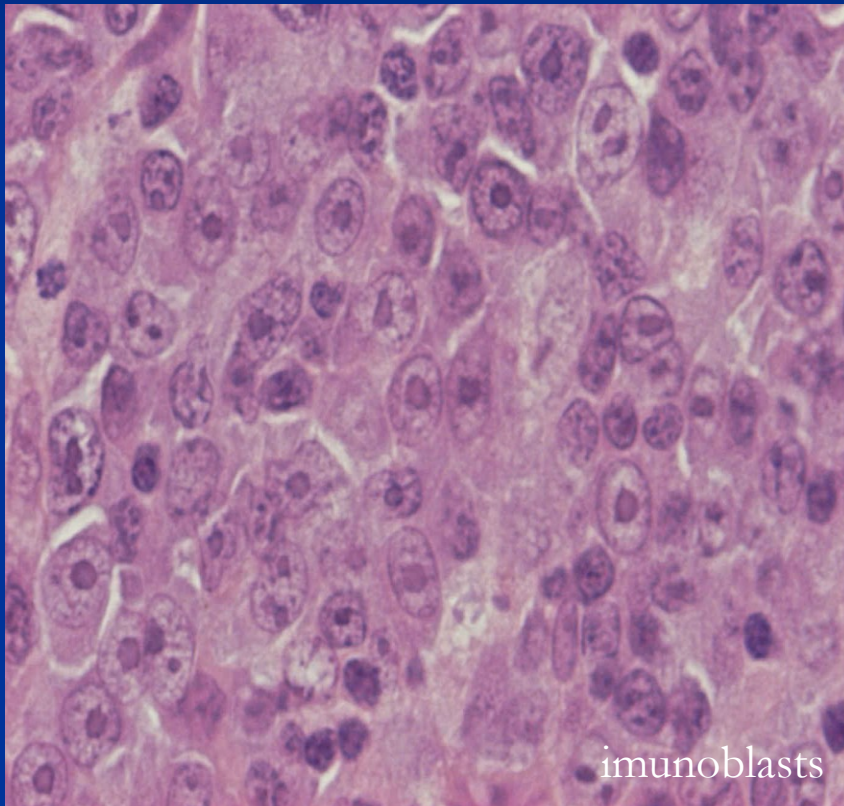
(African endemic (jaws); sporadic (intestinal); HIV+ related)

- germinal center B-cell (CD10+)?; „starry sky“ pattern; high mitotic rate, high apoptotic rate
- t(8;14) (c-myc/IgH), t(2;8) (c-myc/kappa light chains), t(8;22) (c-myc/lambda light chains)
- adolescents, young adults; aggressive, often association with EBV

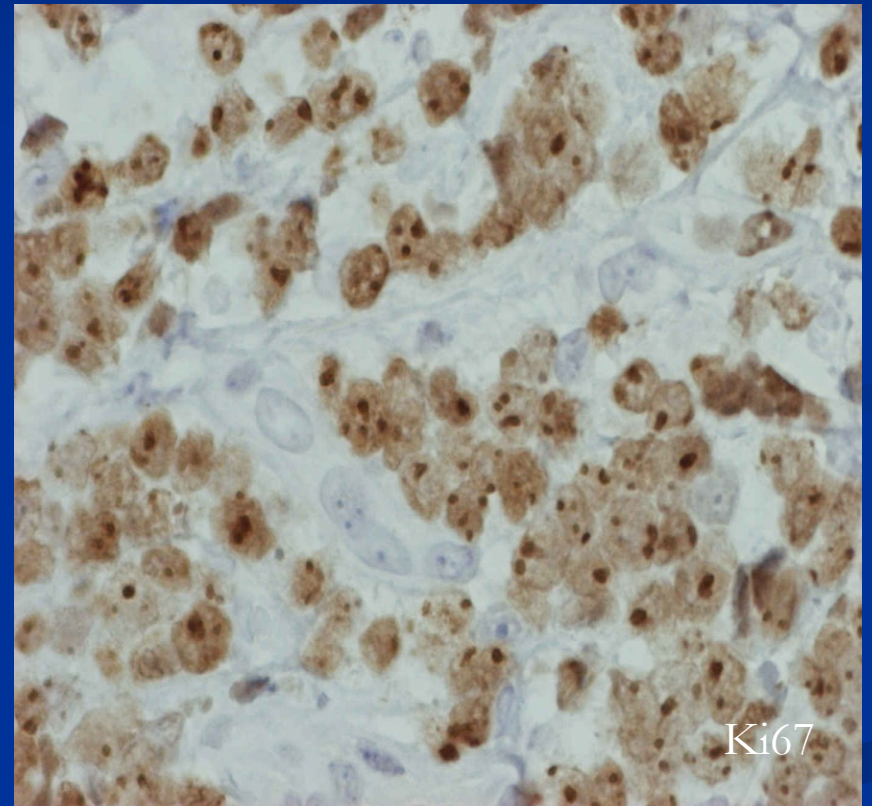
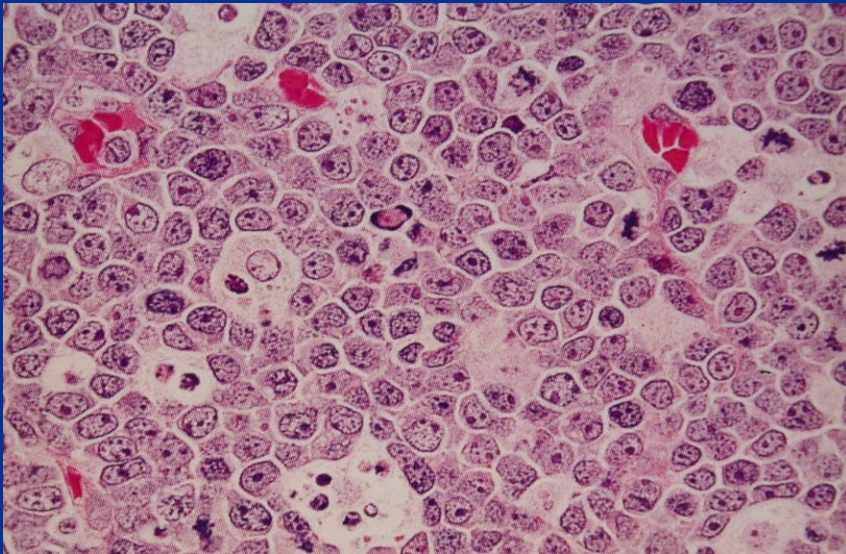
6. **Extranodal marginal zone lymphoma (MALT lymphomas)**

- postgerminal center memory B-cell
- extranodal in adults with chronic inflammation (*Helicobacter pylori* gastritis, Sjogren´s syndrome, chronic lymphocytic autoimmune thyroiditis,...); indolent, possible transformation into high grade lymphoma
- **+ nodal marginal zone B-cell lymphoma; + splenic marginal zone B-cell lymphoma**

Diffuse large B cell lymphoma



Burkitt lymphoma



7. **Hairy cell leukemia**

- postgerminal center memory B-cell (no known the physiological equivalent; hairlike projections)
- no specific chromosomal abnormality
- older males; pancytopenia, infections, bone marrow, liver and spleen infiltration, no lymph nodes involvement; indolent

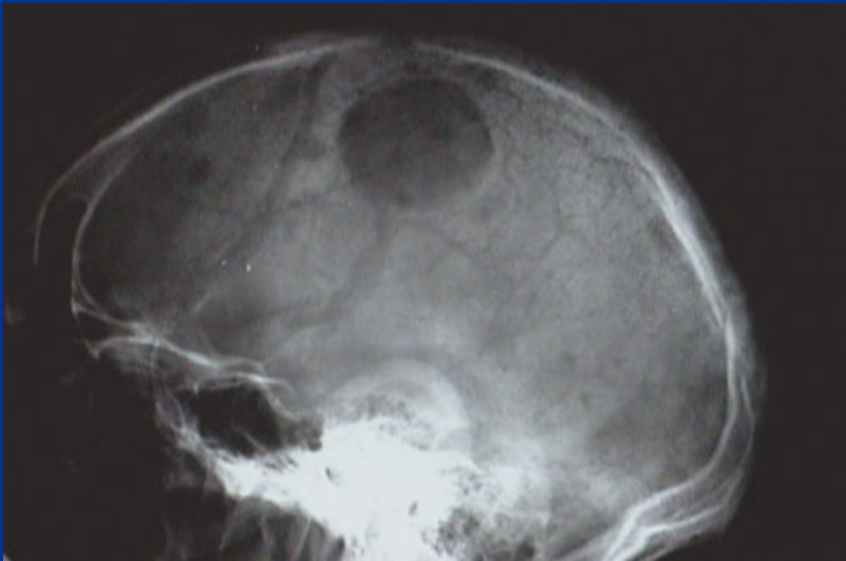
8. **Multiple (plasma cell) myeloma/plasmacytoma**

- plasma cell derived from a postgerminal center B-cell; neoplastic cell synthesizes and secretes a single homogeneous immunoglobulin or its fragments (monoclonal neoplastic proliferation of plasma cells)
- diverse rearrangements involving IgH;
- Myeloma: older adults; lytic lesions of bones, primary amyloidosis, renal failure.
- Plasmacytoma: neoplastic plasma cell masses in bone or soft tissues
- **+ monoclonal gammopathy of undetermined significance; + heavy chain disease; +extraosseal plasmacytoma; +primary or immunocyte-associated amyloidosis**

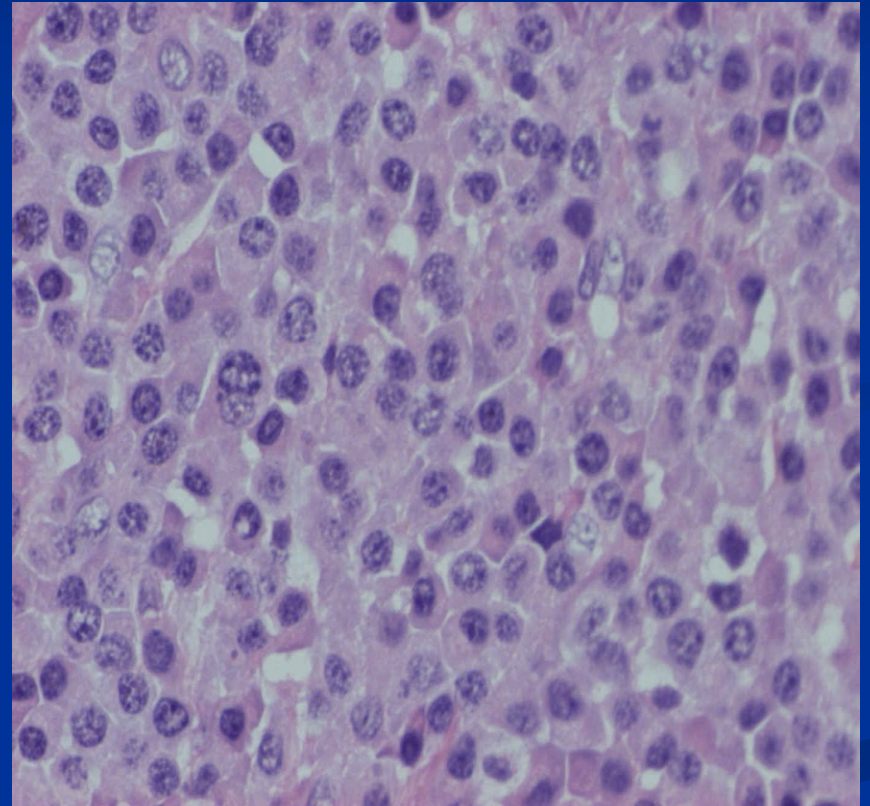
9. **Lymphoplasmacytic lymphoma**

- peripheral CD5- post-germinal center memory B-cell with activated plasma cell differentiation program ; neoplastic cells with PAS+ inclusions containing Ig (cytoplasmic Russell bodies and nuclear Dutcher bodies)
- lymph nodes, bone marrow and spleen involvement
- Waldenstrom macroglobulinemia (excess of IgM, hyperviscosity syndrome)
- Indolent

Multiple myeloma

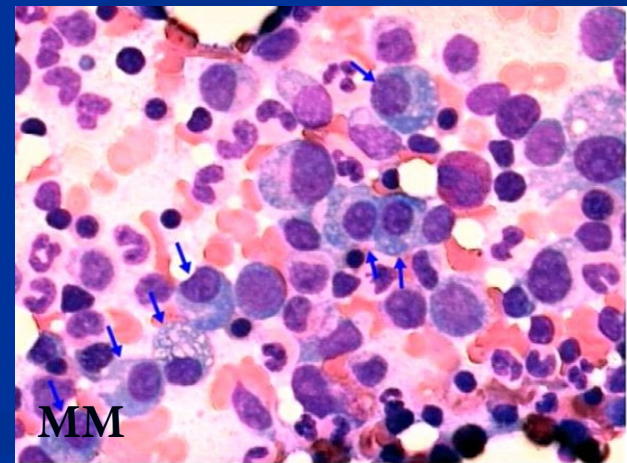
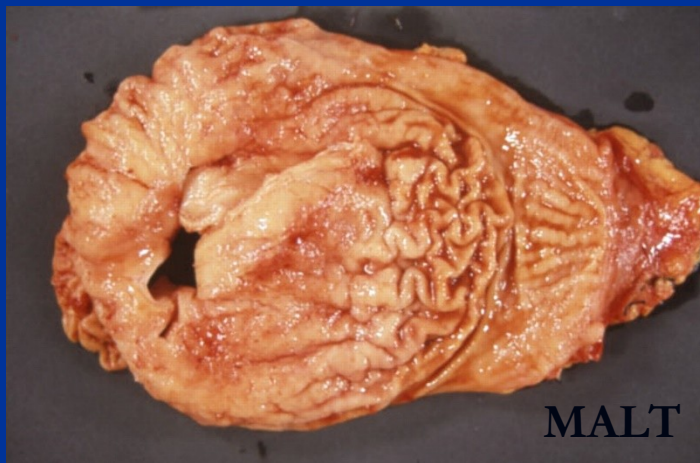
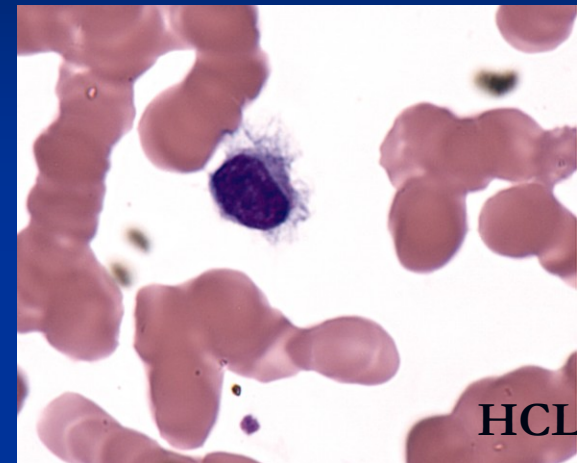
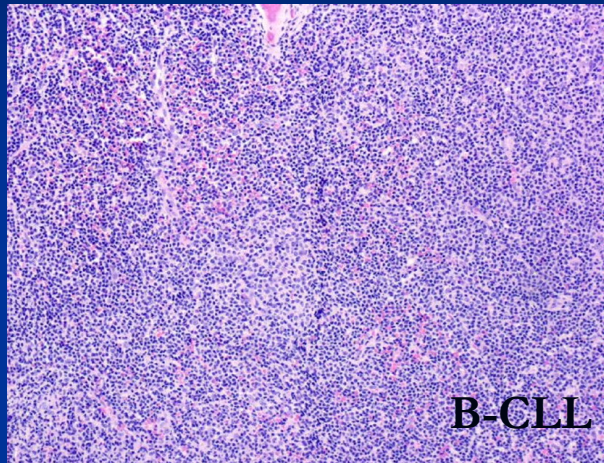


Osteolytic lesions



Infiltration by neoplastic plasma cells

Neoplasms of mature B-cells



Neoplasms of mature T-cells (peripheral T cells neoplasms)

1. **Adult T-cell leukemia/lymphoma**
 - helper T-cell (CD25+; IL-2 receptor)
 - HTLV-1 provirus in neoplastic cells
 - lymph nodes, bone marrow, hypercalcemia, osteolysis; aggressive
2. **Anaplastic large cell lymphoma T or null cell**
 - cytotoxic T cell
 - rearrangements of ALK
 - children, young adults, lymph nodes, soft tissues, skin; aggressive
3. **Extranodal NK/T cell lymphoma, nasal and nasal type**
 - NK cells, cytotoxic T cells (before WHO classification: angiocentric lymphoma)
 - nasal (lethal midline granuloma), lung (lymphomatoid granulomatosis), CNS, skin
 - aggressive, accompanied with hemophagocytic syndrome
4. **Enteropathy-type-T-cell lymphoma**
 - IEL (intraepithelial T cell; CD3+, CD4-, CD8+/-)
 - clonal rearrangement of TCR
 - often associated with CS (ulcerative jejunitis, therapy refractory sprue)
 - aggressive

5. **Peripheral T-cell lymphoma (unspecified)**
 6. **Mycosis fungoides/Sezary syndrome (leukemic)**
 - helper cells
 - no specific chromosomal abnormality
 - skin involvement (patches, plaques, nodules or generalized erythema); oral involvement - 25 cases described
 7. **T-chronic prolymphocytic leukemia**
 - splenomegaly, leukemia
 - More aggressive than B-CLL
 8. **T-cell granular lymphocytic leukemia**
 - CD8+ T cells or CD56+ NK cells (Asia, EBV)
 - splenomegaly, neutropenia, associated with autoimmune diseases – rheumatoid arthritis
 - indolent (CD8+); aggressive (CD56+)
- + angioimmunoblastic T-cell lymphoma, panniculitis-like T-cell lymphoma, hepatosplenic $\gamma\delta$ T-cell lymphoma

Differences between HL and NHL

Hodgkin lymphoma	Non-Hodgkin Lymphoma
Usually localized to a single axial group of LN (cervical, mediastinal, para-aortic)	Involvement of multiple peripheral LN
Contiguous spreading	Non-contiguous spreading
Mesenteric LN and Waldeyer ring rarely involved commonly involved
Extranodal rare	Extranodal common
Diagnostic (neoplastic) cells admixed with reactive non-malignant inflammatory cells	Neoplastic/lymphoma cells dominate
B-cell origin	B- or T-cell origin

Hodgkin lymphoma

- neoplastic cells (diagnostic cells) – minor fraction (germinal or post-germinal B-cells)
- reactive lymphocytes, macrophages, granulocytes – major fraction of tumor mass

Classical HL:

- Nodular sclerosis
- Lymphocyte-rich
- Mixed cellularity
- Lymphocyte depletion

+ Lymphocyte predominance/nodular

(diagnostic cells – the L&H (pop corn) cells- B phenotype)

Hodgkin lymphoma

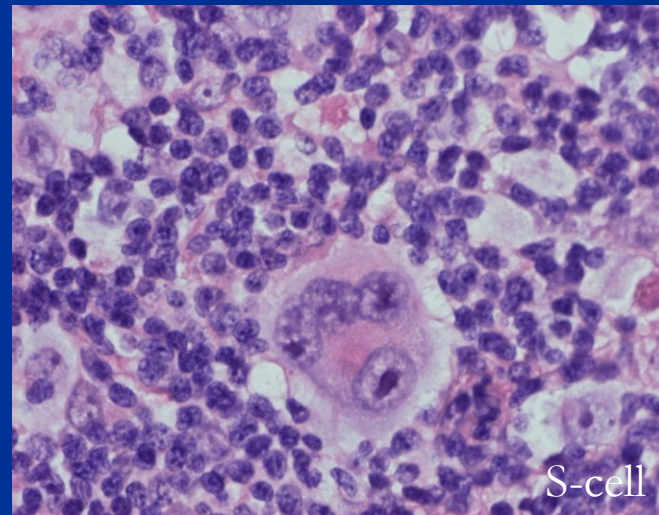
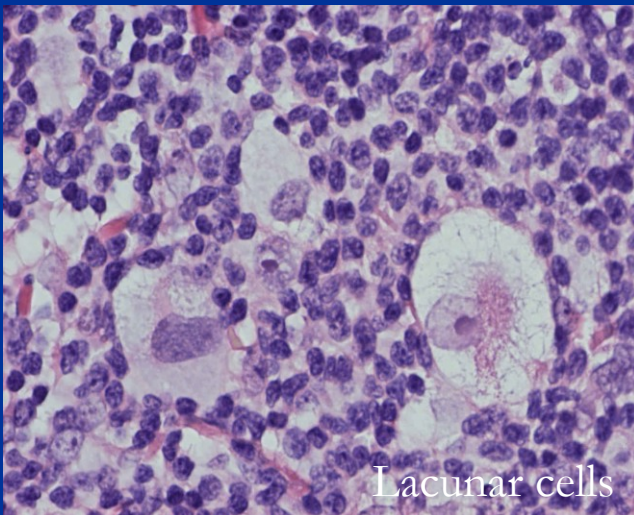
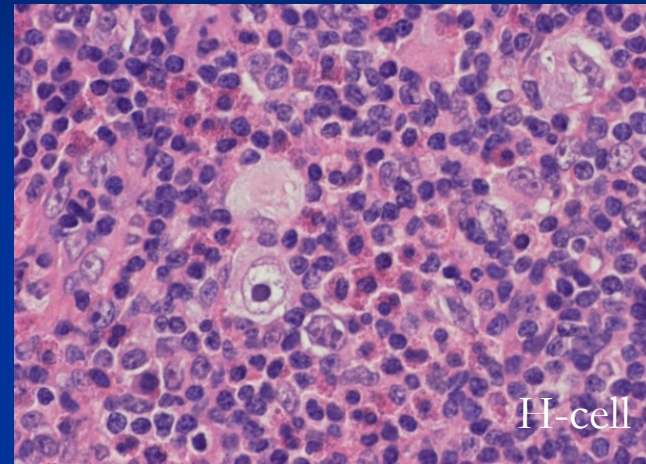
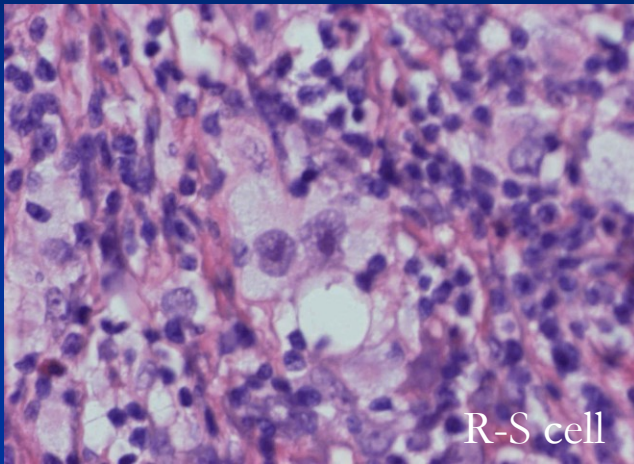
Clinical picture

- Painless enlargement of lymph nodes (cervical, mediastinal, para-aortic: often localized to single axial group with spread by contiguity); mesenteric nodes and Waldeyer ring rarely involved, extranodal involvement uncommon
- Young patients
- Night sweats, weight loss

Neoplastic cells in classical HL

- Diagnostic Reed-Sternberg and Hodgkin cells (multiple or single nucleus)
- Lacunar cells

Diagnostic cells – HL, classical



Myeloid neoplasms

- Neoplasms originated from hematopoietic progenitor/stem cells capable of giving rise to differentiated cells of myeloid series
- Cells of the myeloid series
(erythrocytes, granulocytes, monocytes, platelets)
- Primary involvement of bone marrow
(secondary spleen, liver and lymph nodes)
- 3 categories:
 1. **Acute myelogenous leukemias**
 2. **Myelodysplastic syndromes**
 3. **Chronic myeloproliferative disorders**

Acute myelogenous leukemia (AML)

- Peak incidence 15-39 years
- Replacement of normal bone marrow elements by undifferentiated elements (myeloid blasts)
- Hiatus leukemicus
- Immature blasts released into peripheral blood
- Leukemic infiltrates in bone marrow, liver, spleen, lymph nodes....
 - ⇒ Clinical signs of bone marrow failure
 - anemia (**fatigue, palor**)
 - trombocytopenia (**abnormal bleeding**)
 - **leukopenia** (infections - fever)
- Generally poor prognosis (60 % remision; 15-30 % disease free for 5 years)

AML classification

■ FAB classification

1. **M0** AML minimally differentiated
2. **M1** AML without differentiation
3. **M2** AML with maturation
4. **M3** acute promyelocytic leukemia
5. **M4** acute myelomonocytic leukemia
6. **M5** acute monocytic leukemia
7. **M6** acute erythroleukemia
8. **M7** acute megakaryocytic leukemia

■ WHO classification

1. **AML with recurrent chromosomal rearrangements/with genetic aberrations**
 - t(8;21) – favorable prognosis; inv16 - favorable; t(15;17) - intermediate; t(11q23v) – poor
2. **AML with multilineage dysplasias/with MDS-like features**
 - with prior myelodysplastic syndrome (very poor prognosis)
 - without prior myelodysplastic syndrome (poor prognosis)
3. **AML, therapy related** (alkylated agents related; epipodophyllotoxin related) – very poor prognosis
4. **AML, not otherwise specified** (M0-M7), intermediate prognosis

Myelodysplastic syndromes (MDS)

Clonal stem/progenitor cell disorder characterized by maturation defects (=ineffective maturation of myeloid progenitors) associated with ineffective hematopoiesis and an increased risk of development of AML.

- idiopathic
- therapy-related
- *Bone marrow: hypercellular or normo-cellular*
- *Peripheral blood: cytopenia of one or more cell lines*
- *Risk of transformation into AML*
(abnormal stem cell clone genetically unstable → additional mutations → AML)

Chronic myeloproliferative disorders

- Chronic myelogenous leukemia
- Polycythemia vera
- Essential thrombocytosis
- Primary myelofibrosis

Chronic myelogenous leukemia

- adults, peak incidence in 4th and 5th decade
- cell of origin: pluripotent stem cell
- acquired genetic abnormality: t(9;22); BCR-ABL fusion gene: fusion protein with tyrosinkinase activity; Philadelphia chromosome
- clinical picture: anemia, hypermetabolism due to increased cell turnover: fatigability, weakness, weight loss, anorexia.....slow progression-accelerated phase-blastic crisis (AML-like)
- poor prognosis; therapy: transplantation of bone marrow, imatinib mesylate (inhibitor of the BCR-ABL tyrosine kinase)

Chronic myelogenous leukemia

- **Elevated leukocyte count** ($>100,000$ cells μ/l)
- **Hypercellular bone marrow**
(hyperplasia of granulocytic and megakaryocytic precursors)
- **Circulating cells:** predominantly neutrophils, metamyelocytes and myelocytes, myeloblasts $<5\%$
- **Extreme hepatosplenomegaly**, spleen up to 20 kg
- Extramedullary hematopoiesis

Polycythemia vera

- Cell of origin: multipotent myeloid marrow stem cell
- increased marrow production of erythroid, granulocytic and megakaryocytic elements
- symptoms related to the increased red cell mass and hematocrit: plethora, cyanosis owing stagnation and deoxygenation, headache, dizziness, hypertension, GIT symptoms, hyperuricemia due to increased cell turnover, increased risk of major bleeding and thrombosis (epistaxis, ecchymoses, gingival hemorrhage)
- transition into myelofibrosis
- development of AML (treatment related – alkylating drugs)

Langerhans cell histiocytosis, histiocytosis X.

- Langerhans cells – dendritic mononuclear cells – Ag presenting cells
- Proliferation of histiocyte-like cells accompanied by eosinophils, lymphocytes, plasma cells, multinucleated giant cells
- **3 clinicopathologic entities:**
 - Monostotic or polyostotic **eosinophilic granuloma** of the bone (osteolytic lesions, also mandible or maxilla affected)
 - Hand-Schüller-Christian disease - **chronic disseminated histiocytosis** (bone, skin (ulcerative and proliferative mucosal lesions, proliferative gingival mass, involvement of oral soft tissues) and viscera involved)
 - Letterer-Siwe disease – **acute disseminated histiocytosis** (cutaneous, visceral, bone marrow involvement)

