Hematologic disorders, allergic and immunologic diseases.

Markéta Hermanová

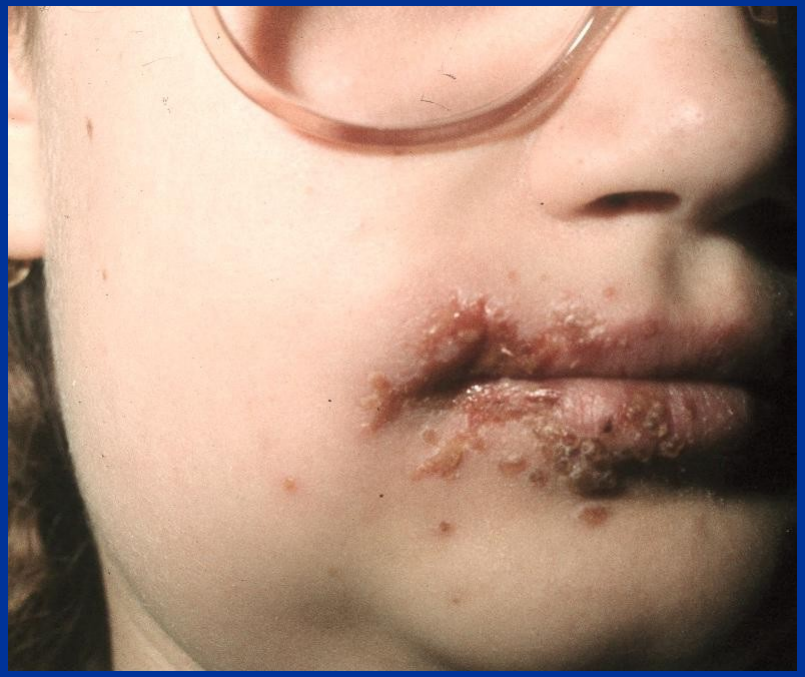
RAS (recurrent aphthous ulcerations; canker sores)

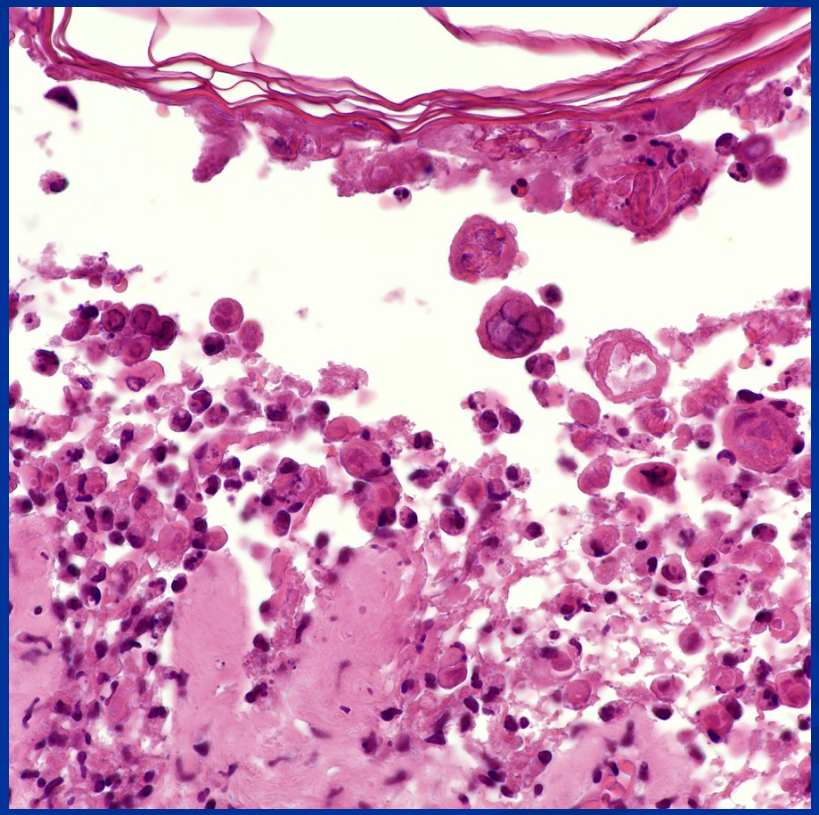
- **Primary immunodysregulation**
  - In ulcerative stage: decreased ratio of CD4/CD8 T lymphocytes (about 1:10); increased TCRγδ+, increased TNF-α → increased activity of T cell subpopulations that mediate cytotoxic damage
  - Antibody-dependent cellular cytotoxicity, T-cell mediated cytotoxicity to 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 deficiences)
- **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

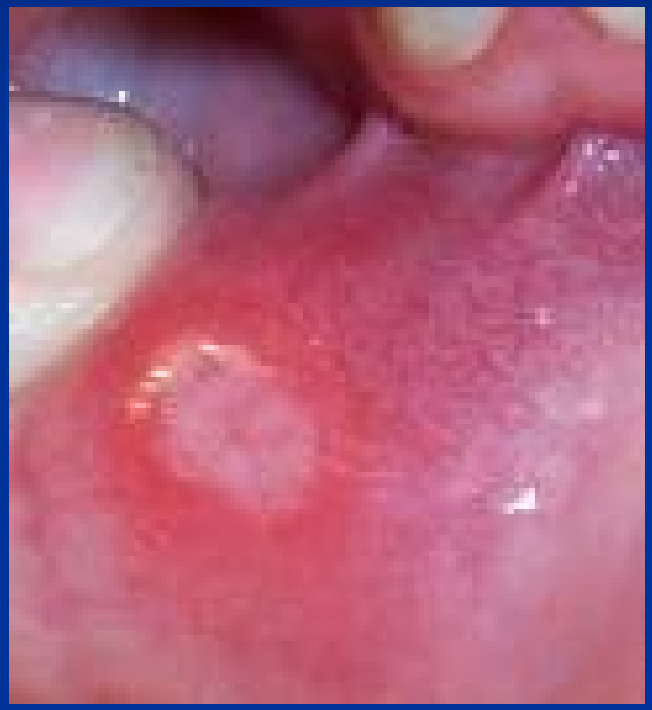
- Behcet´s syndrome (aphtous ulcers, genital ulcers, uveitis)
- Celiac disease (gluten intolerance)
- Cyclic neutropenia (AD, *ELA2* gene - neutrophil elastase)
- Nutritional deficiencies
- IgA deficiency
- Immunocompromised conditions, incl. HIV
- Inflammatory bowel disease (ulcerative colitis, Crohn´s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

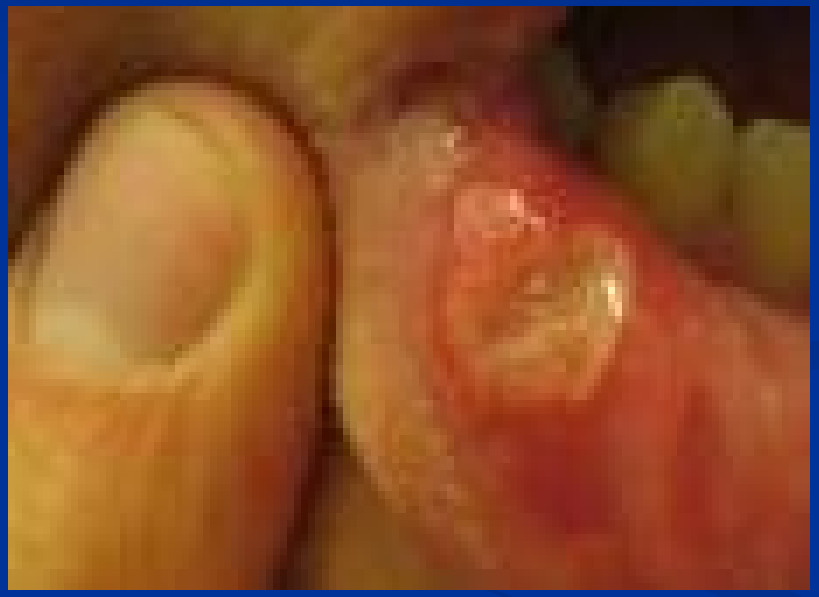
Clinical variation of aphthous stomatitis

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

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

Aphtous 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**
- **Immunosuppresive treatment**

Sarcoidosis

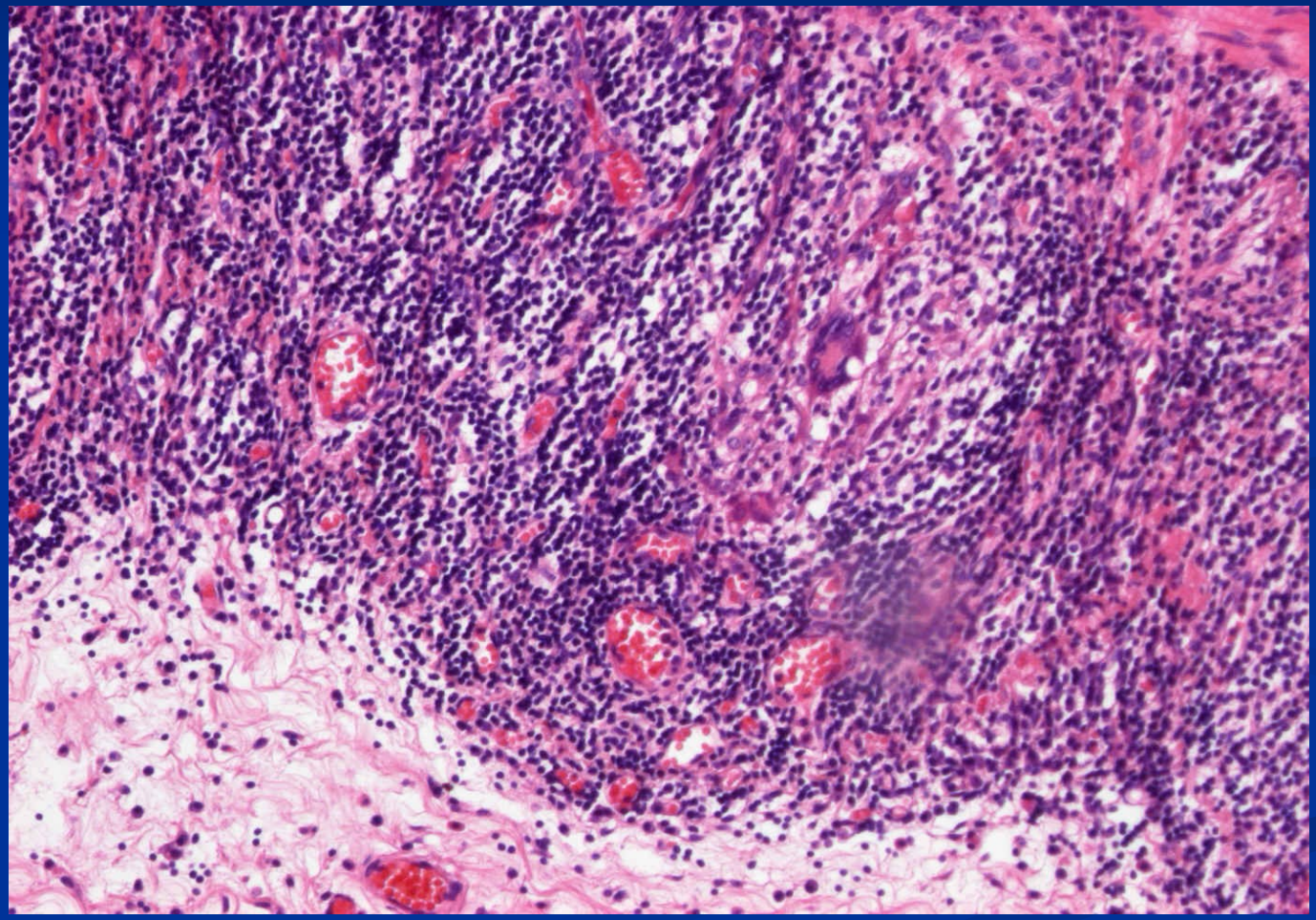
- Multisystem granulomatous disorder of unknown cause
- Inappropriate defense response to mycobacterial infectious agents + immunodysregulation
- Lungs, lymph nodes, skin, eyes, salivary glands,….
- Any oral mucosal sites can be affected (normal in color, brownish-red, violaceous, hyperkeratotic – submucosal mass)
- Non-necrotising granulomas (accumulation of epitheloid 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

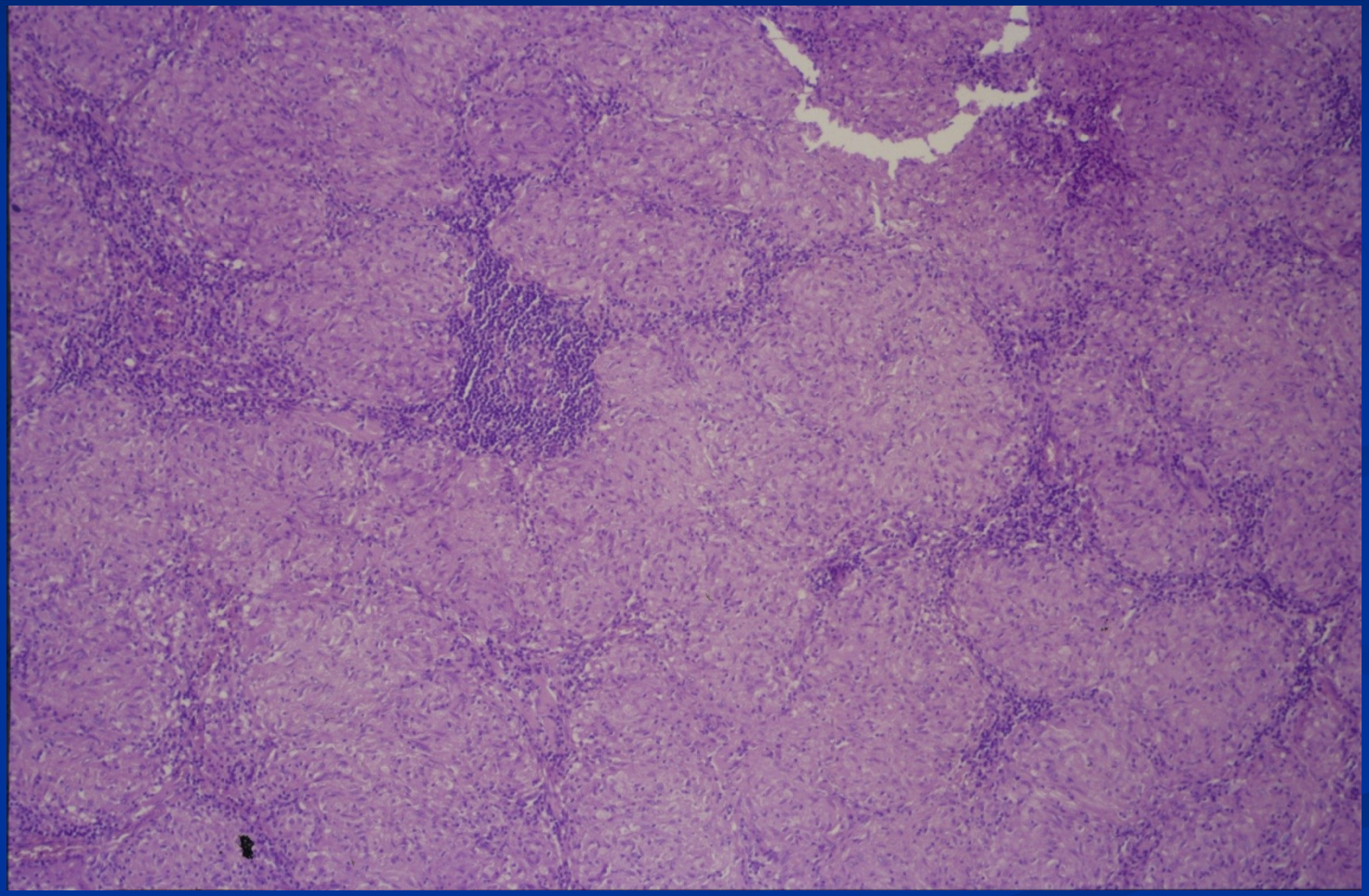
- **Orofacial granulomatosis**
  - Melkersson-Rosenthal syndrome (cheilitis granulomatosa+facial paralysis+fissured tongue)

- **Wegener´s granulomatosis**
- **Crohn´s disease**
- **Tuberculosis**
- **Sarcoidosis**
- **Foreign body reaction, allergy**

Granuloma in Crohn´s disease



Sarcoidosis



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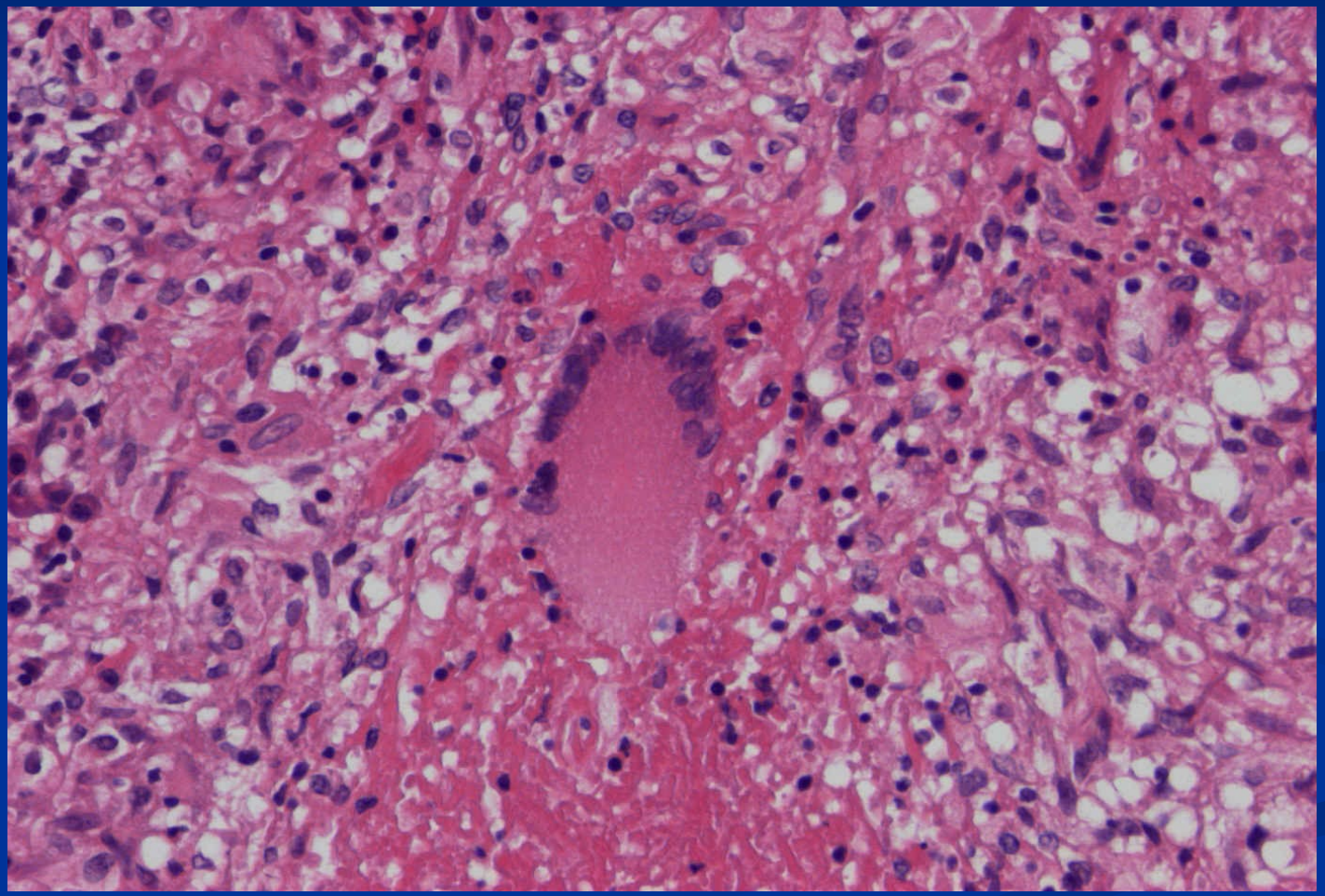
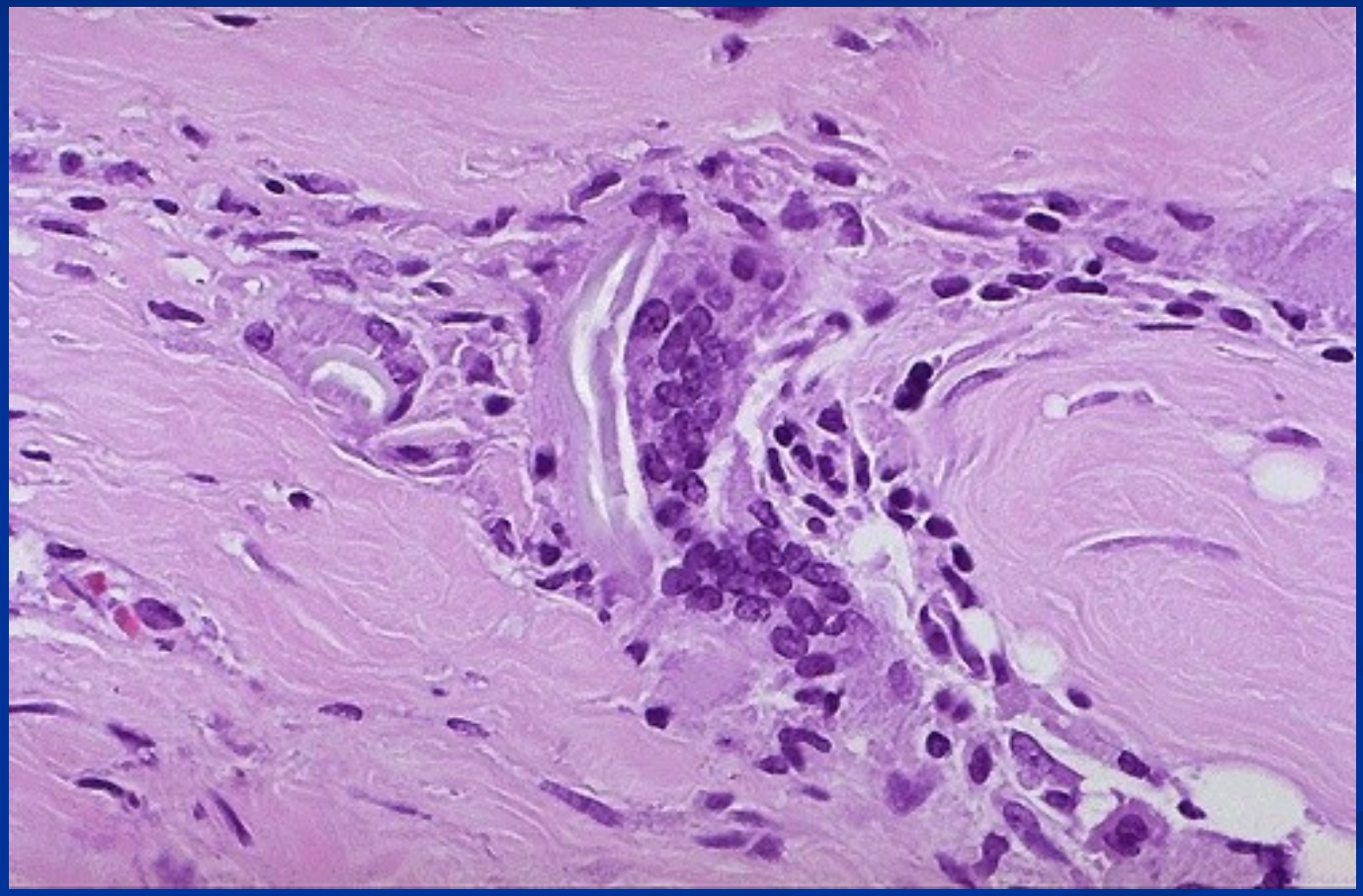


Foreign body reaction



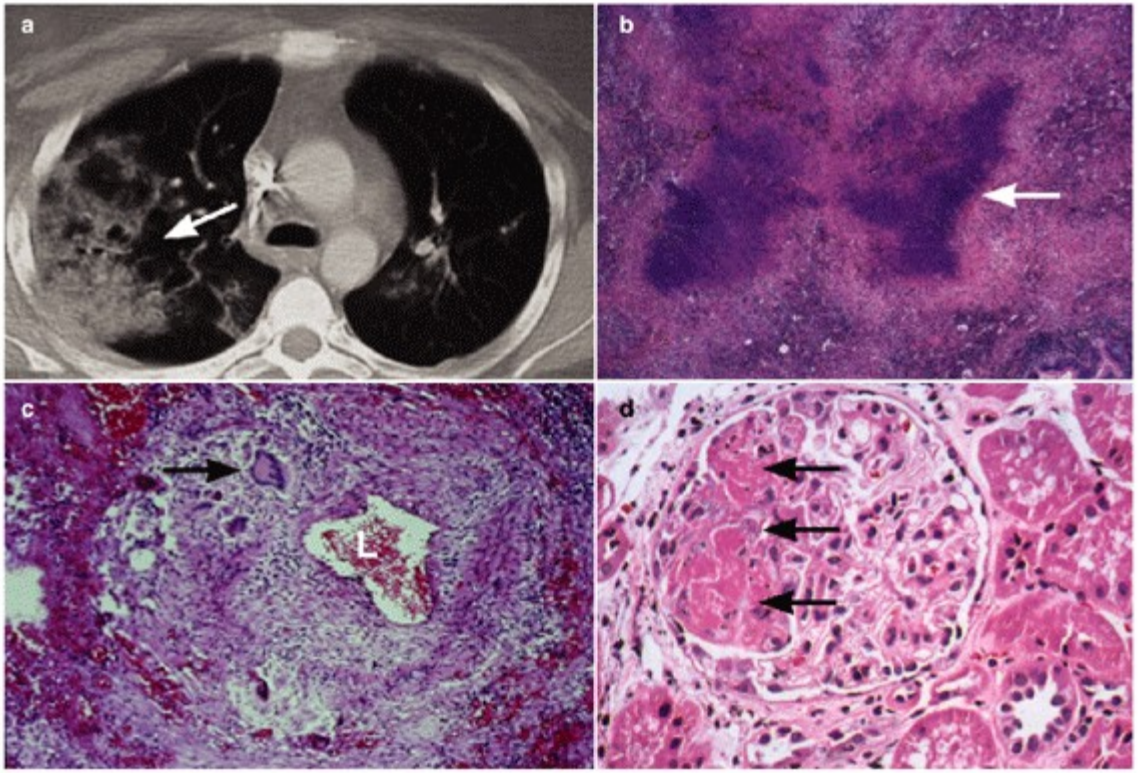
Wegener´s granulomatosis

- 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,…): symtoms of anafylaxis (e.g. hoarseness, respiratory distress, vomiting), erytema 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 imunologically; typically posterior buccal mucosa and the lateral borders of the tongue)
- **Nonspecific vesiculoulcerative lesions**

Allergic contact stomatitis (stomatitis venenata)

- Foods, food aditives, chewing gums, candies, ……topical anesthetics, restorative metals, acrylic denture materials,…cinnamon, amalgam

- **Acute** (burning, erythema, edema, visicles,erosions, ulcers,…)

- **Chronic** (erythematous or white and hyperkeratotic)

- **Perioral dermatits**

  (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)

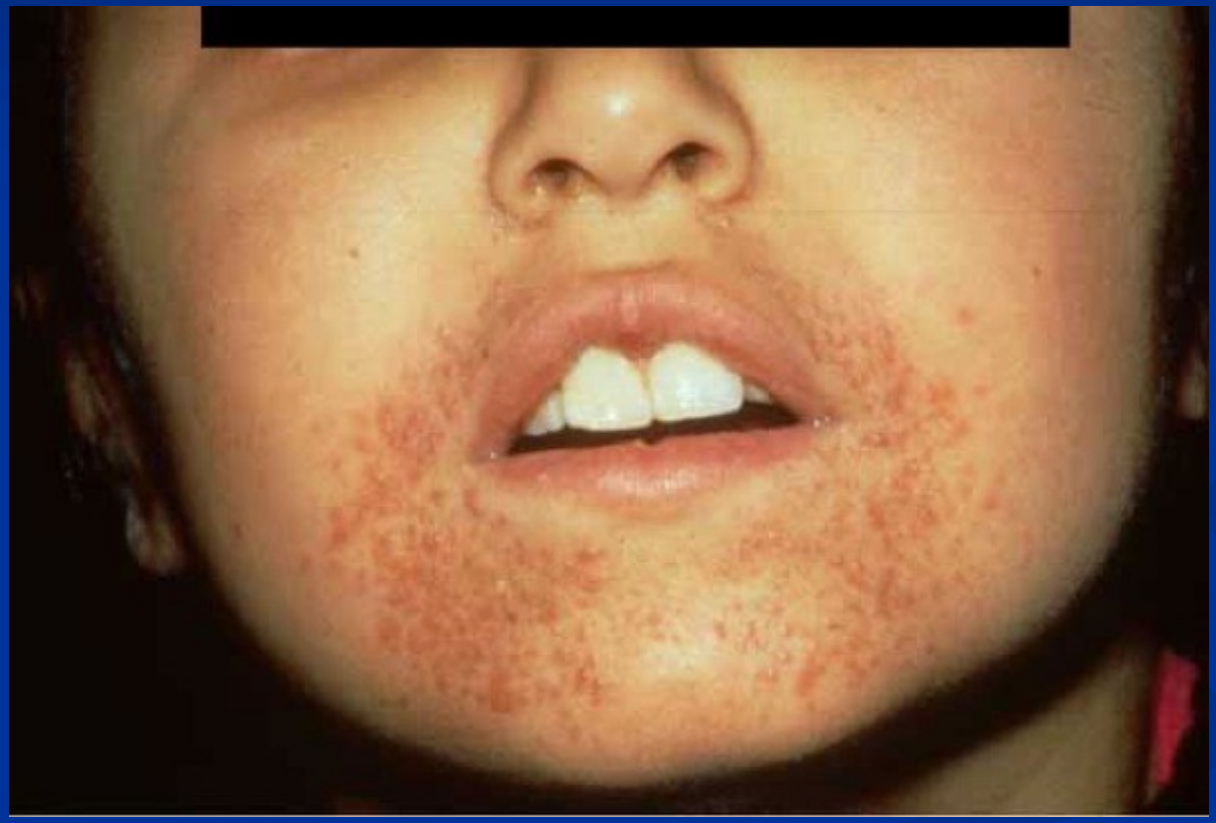
- **Chronic oral mucosal contact reactions to dental amalgam**

  (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)

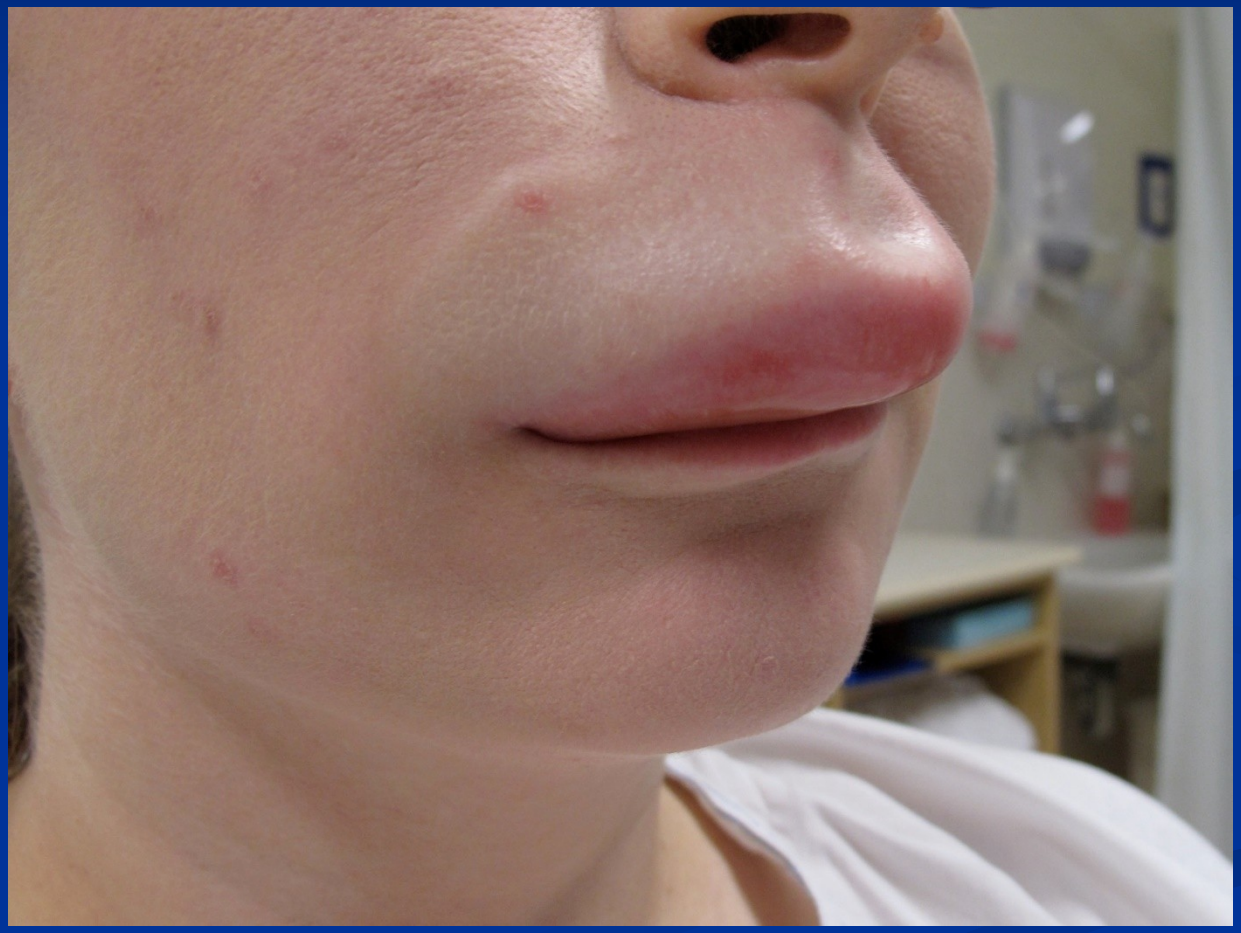
- **Angioedema (angioneurotic edema, Quinke´s disease)**

- 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



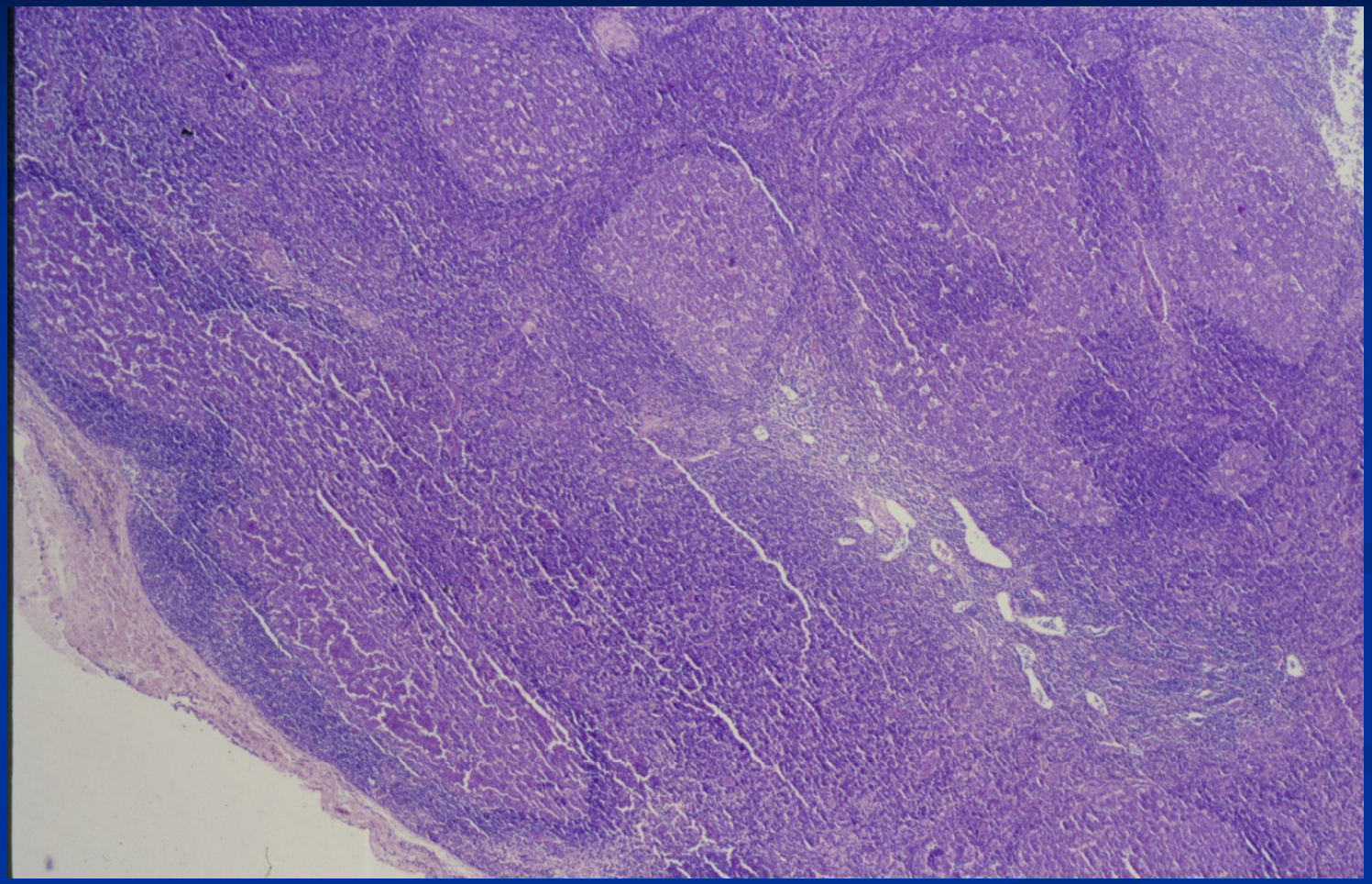
Angioedema



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 tromboplastin 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, eccchymoses,
- deep hemorhage 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 conjuctiva

Causes of anemia

- **Anemias with disturbed iron metabolism**
- Iron deficiency
- Sideroblastic anemias

- **Megaloblastic anemias**
- Pernicious anemia (avitaminosis B_{12})
- 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, plateles and leukocytes deficiency
- oral lesions, gingical 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); consuption
  - 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 massess***

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 enlargemenr 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)

1. **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

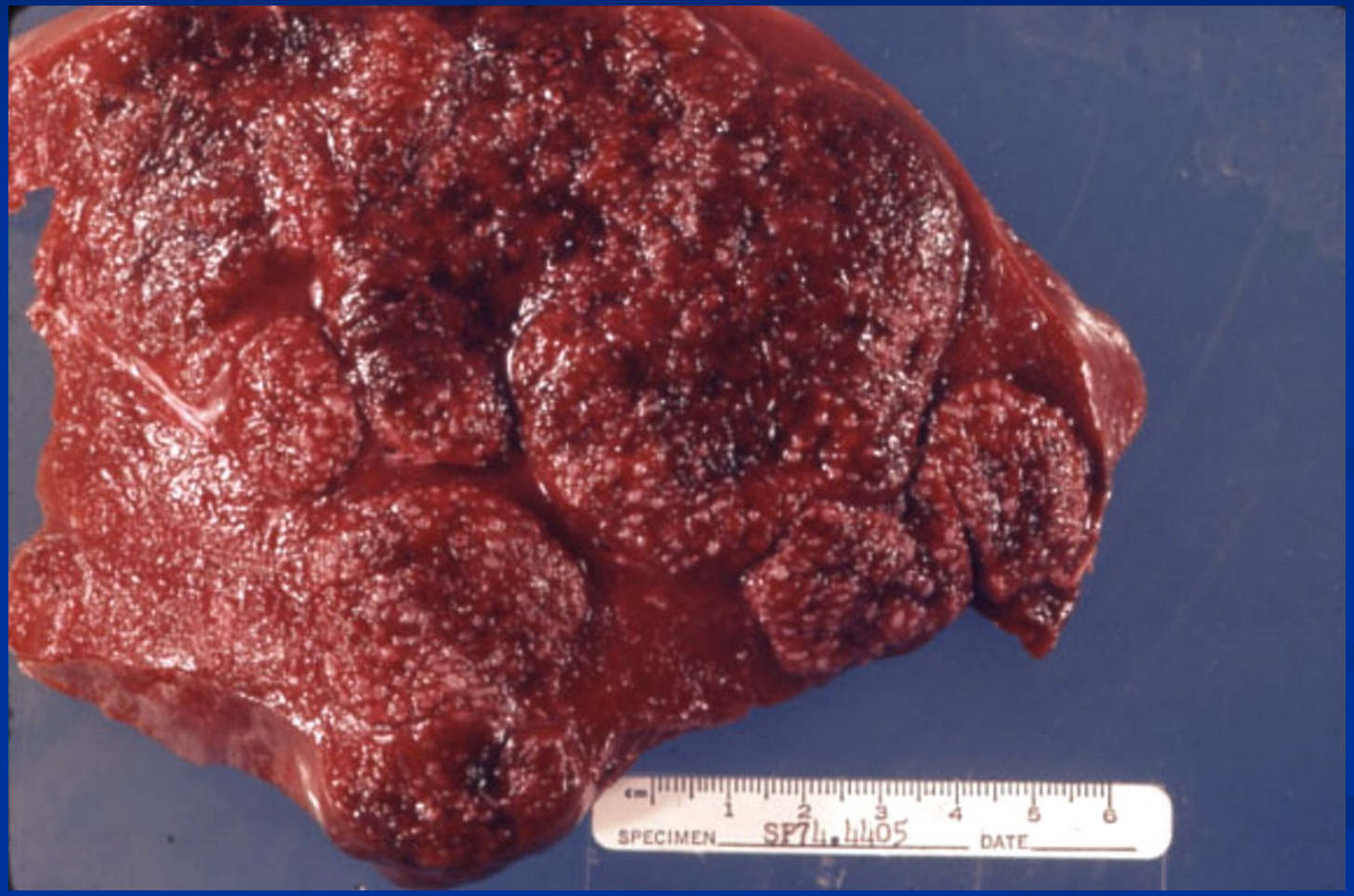
2. **Mantle cell lymphoma**

- naive B-cell of mantles (CD5+, cyclinD1+(promotesG1 to S phase progression)
- t(11;14); cyclinD1 locus/IgH locus
- older males, often extranodal (lymphomatous polyposis); moderately aggressive – resistent to therapy

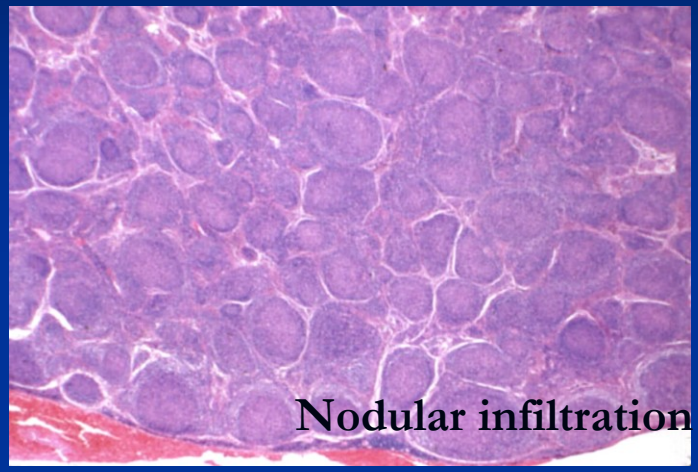
3. **Follicular lymphoma**

- 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

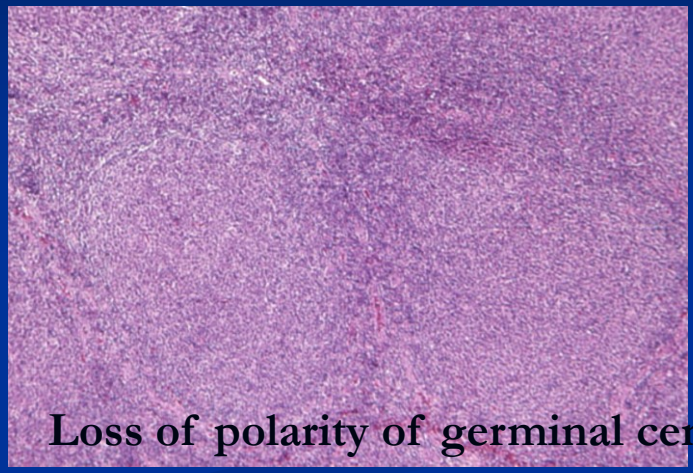
Spleen, follicular lymphoma



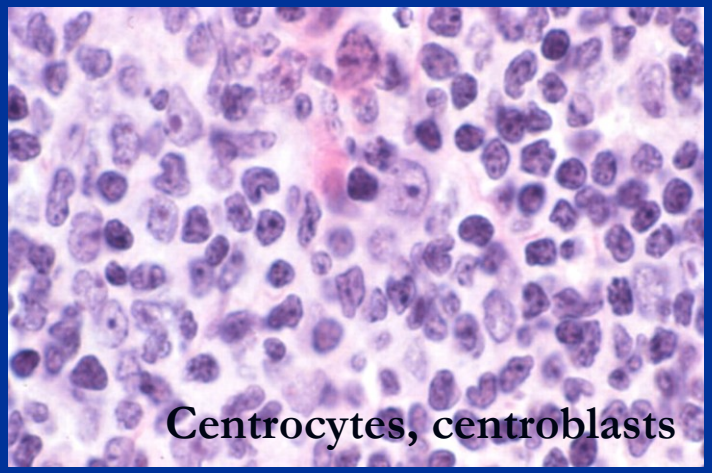
Follicular lymphoma



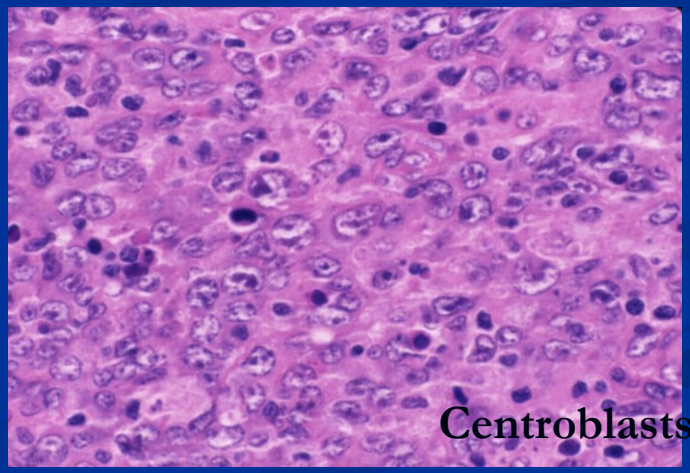
Nodular infiltration



Loss of polarity of germinal centers



Centrocytes, centroblasts



Centroblasts

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**

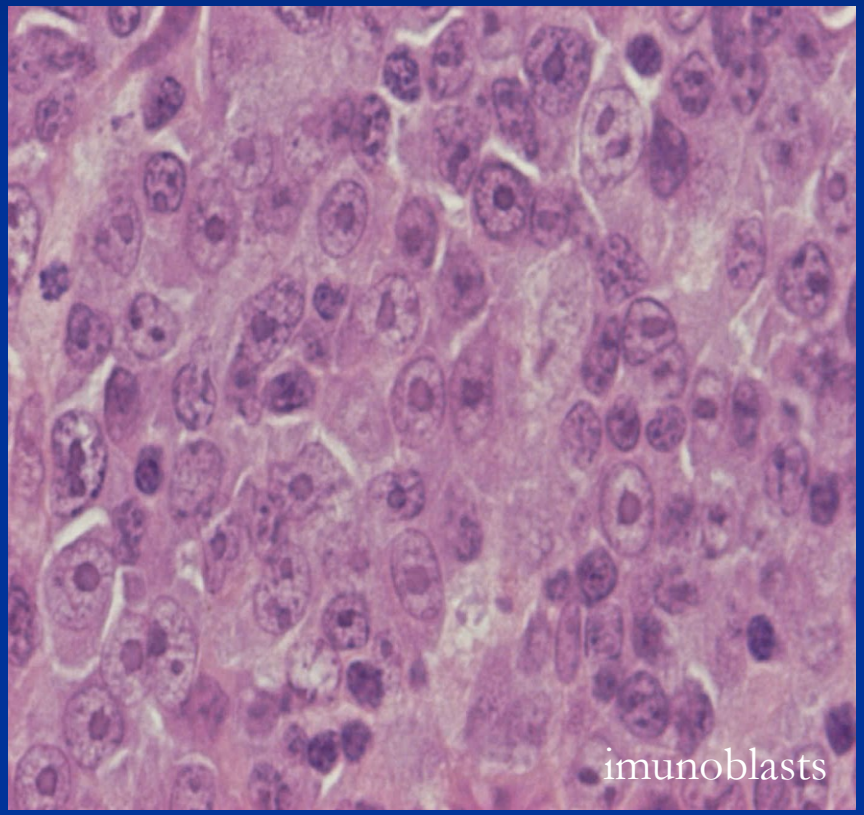
(African endemic (jaws); sporadic (intestinal); HIV+ related)

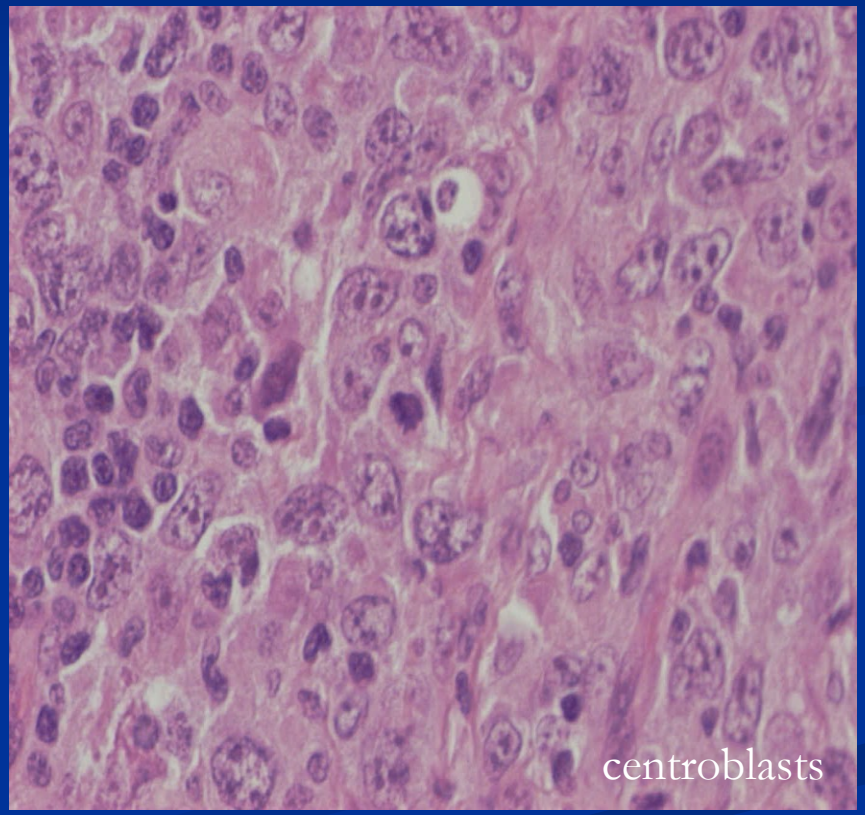
- germinal center B-cell (CD10+)?; „starry sky“ pattern; high mitotic rate, high apoptotic rate
- t(8;14) (c-myc/IgH), t(2;8) (c-myc/kappa light chains), t(8;22) (c-myc/lambda light chains)
- adolescents, young adults; aggressive, often association with EBV

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

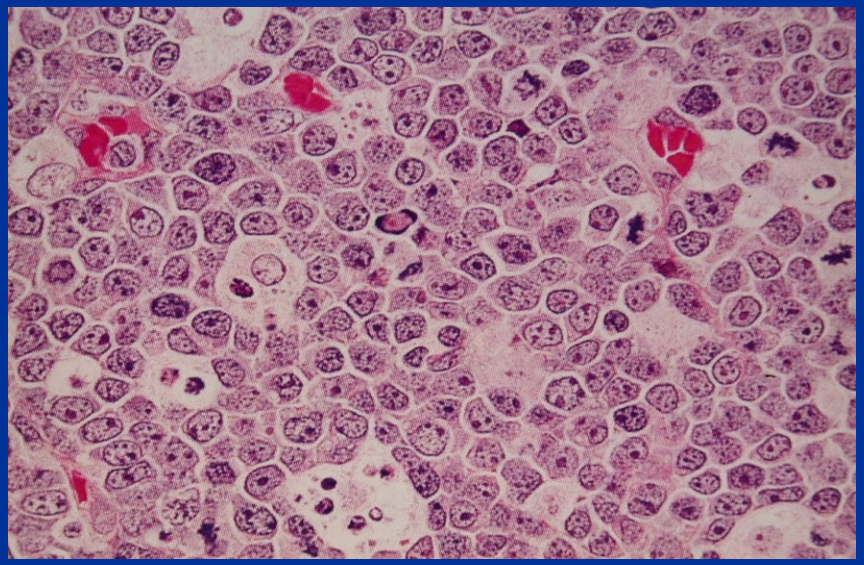
- postgerminal center memory B-cell
- extranodal in adults with chronic infalmmation (*Helicobacter pylori* gastritis, Sjogren´s syndrome, chronic lymphocytic autoimmune thyreoiditis,…); indolent, possible transformation into high grade lymphoma
- **+ nodal marginal zone B-cell lymphoma; + splenic marginal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

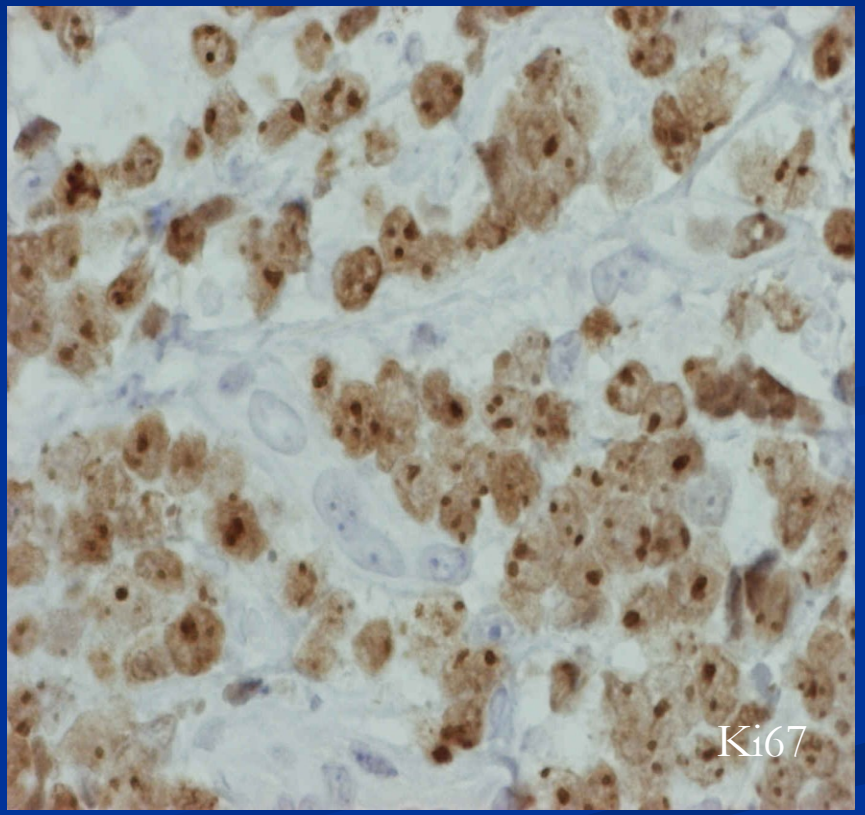
Diffuse large B cell lymphoma





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

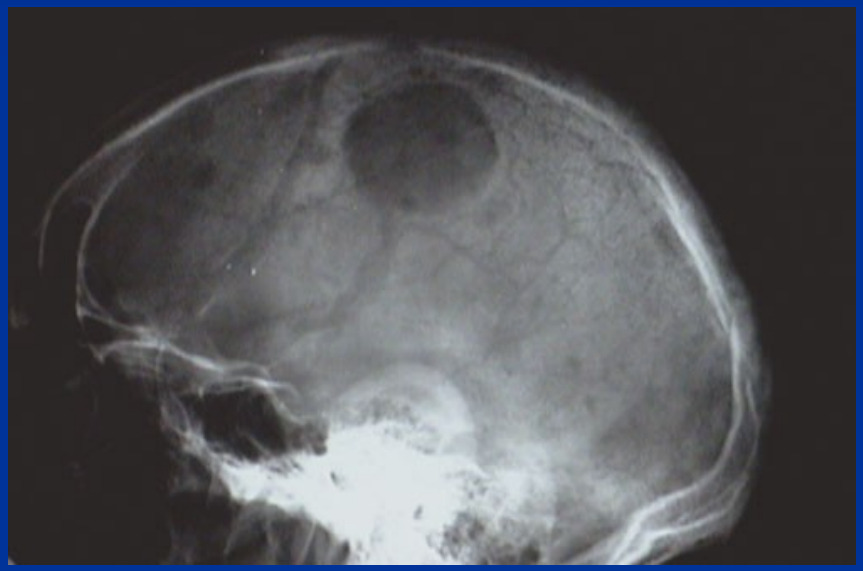
8. **Multiple (plasma cell) myeloma/plasmacytoma**

- 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 reaarangements involving IgH;
- Myeloma: older adults; lytic lesions of bones, primary amyloidosis, renal failure.
- Plasmacytoma: neoplastic plasma cell masses in bone or soft tissues
- **+ monoclonal gammapathy of undetermined significance; + heavy chain disease; +extraosseal plasmacytoma; +primary or immunocyte-associated amyloidosis**

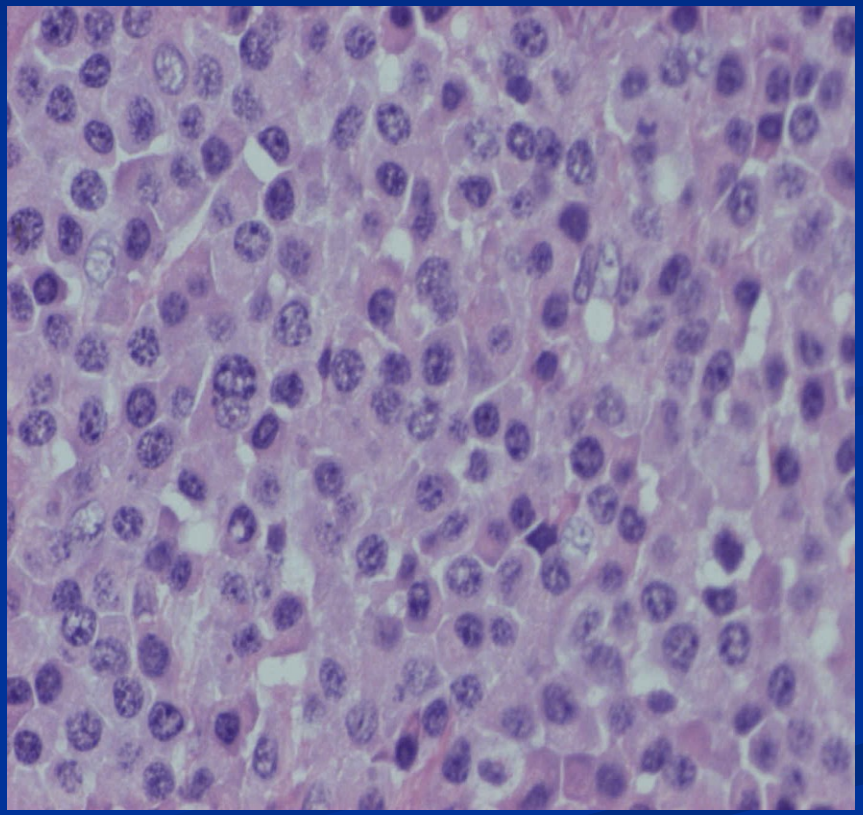
9. **Lymphoplasmacytic lymphoma**

- 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

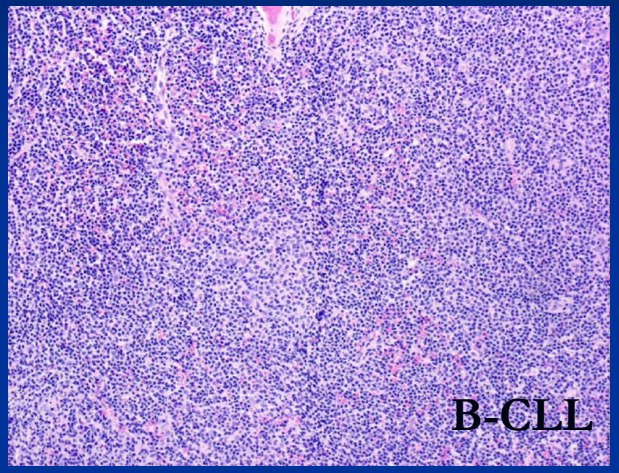


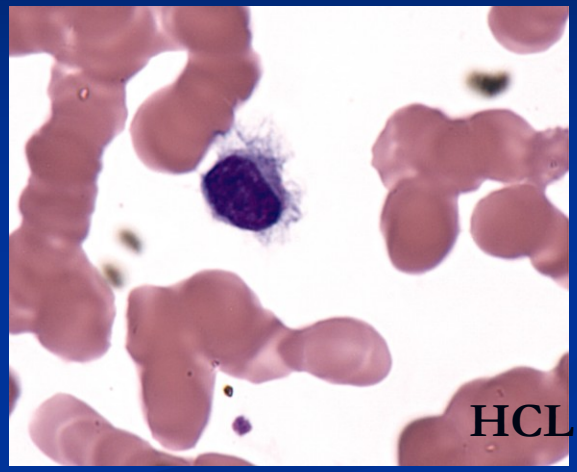
Osteolytic lesions

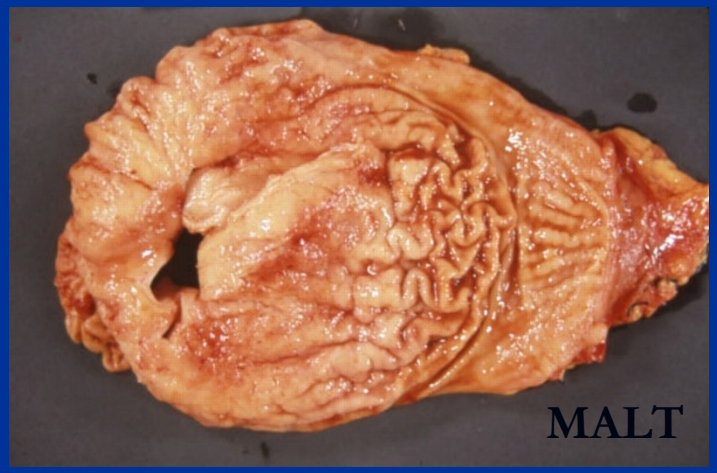


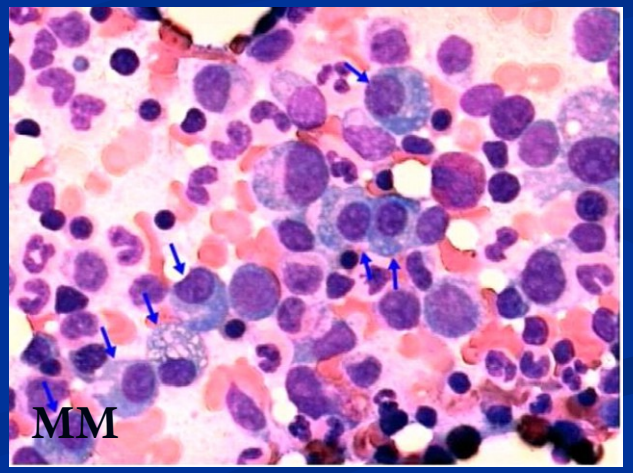
Infiltration by neoplastic plasma cells

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, osteolysus; aggressive

2. **Anaplastic large cell lymphoma T or null cell**
- cytotoxic T cell
- rearangements of ALK
- children, young adults, lymph nodes, soft tissues, skin; aggressive

3. **Extranodal NK/T cell lymphoma, nasal and nasal typ**
- 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 reaarangement 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 – reumatoid arthritis
- indolent (CD8+); aggressive (CD56+)

+ angioimmunoblastic T-cell lymphoma, panniculitis-like T-cell lymphoma, hepatosplenic γδ 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

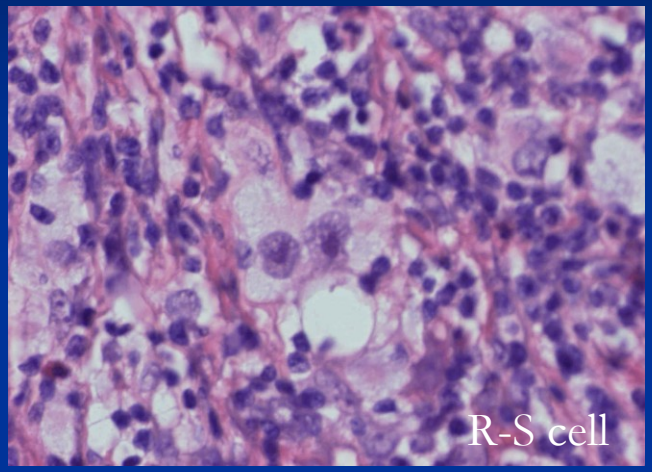
Clinical picture

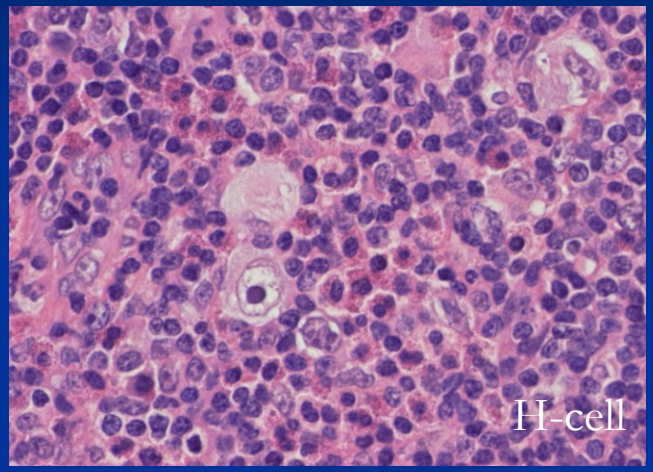
- Painless enlargement of lymph nodes (cervical, mediastinal, para-aortic: often localized to single axial group with spread by contiguity); mesenteric nodes and Waldeyer ring rarely involved, extranodal involvement uncommon
- Young patients
- Night sweats, weight loss

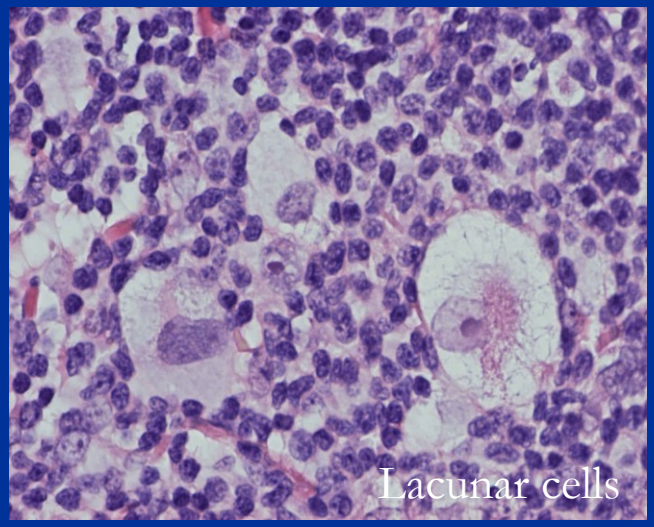
Neoplastic cells in classical HL

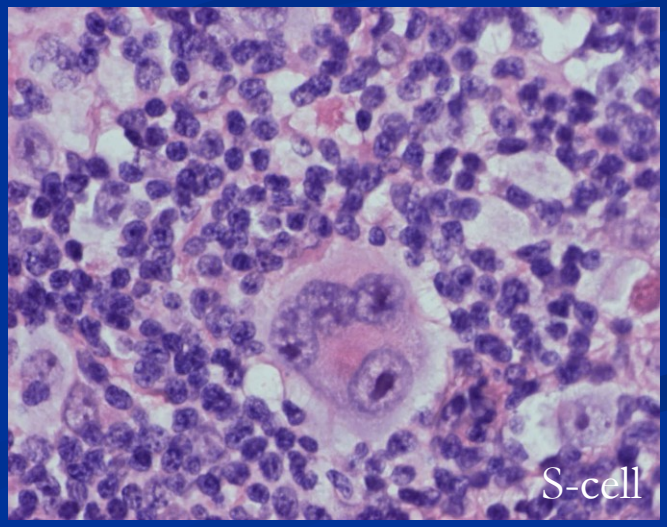
- Diagnostic Reed-Sternberg and Hodgkin cells (multiple or single nucleus)
- Lacunar cells

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 neutrofils, 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)

Thank you for your attention …