Hematologic disorders, allergic and immunologic diseases.

Markéta Hermanová

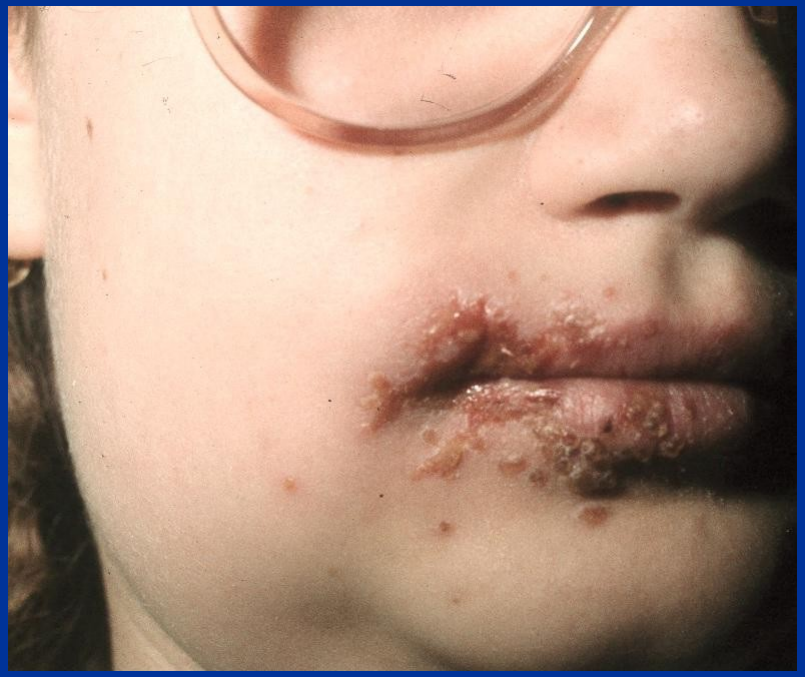
RAS (recurrent aphthous ulcerations; canker sores)

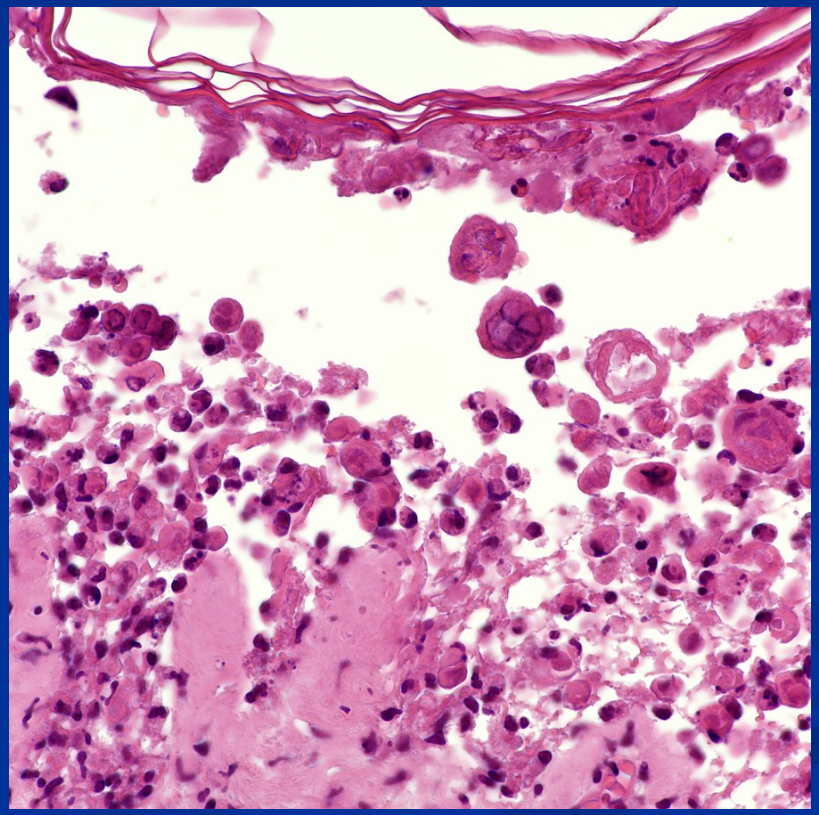
- **Primary immunodysregulation**
  - In ulcerative stage: decreased ratio of CD4/CD8 T lymphocytes (about 1:10); increased TCRγδ+, increased TNF-α → increased activity of T cell subpopulations that mediate cytotoxic damage
  - Antibody-dependent cellular cytotoxicity, T-cell mediated cytotoxicity to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

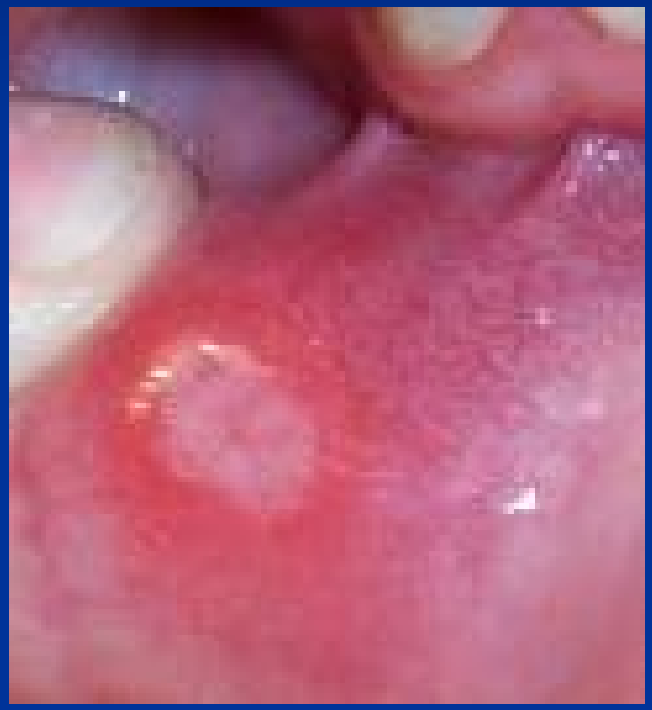
- Behcet´s syndrome (aphtous ulcers, genital ulcers, uveitis)
- Celiac disease (gluten intolerance)
- Cyclic neutropenia (AD, *ELA2* gene - neutrophil elastase)
- Nutritional deficiencies
- IgA deficiency
- Immunocompromised conditions, incl. HIV
- Inflammatory bowel disease (ulcerative colitis, Crohn´s 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)

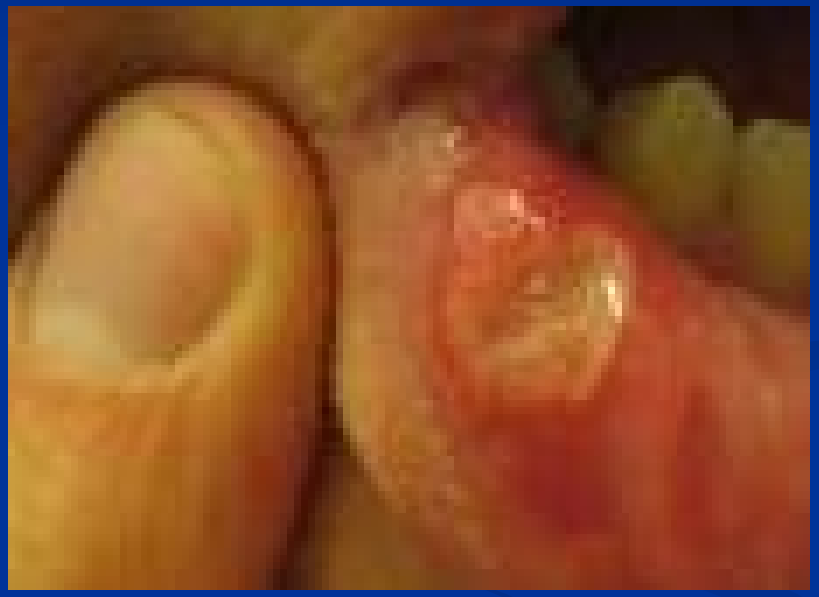
Clinical variation of aphthous stomatitis

- **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

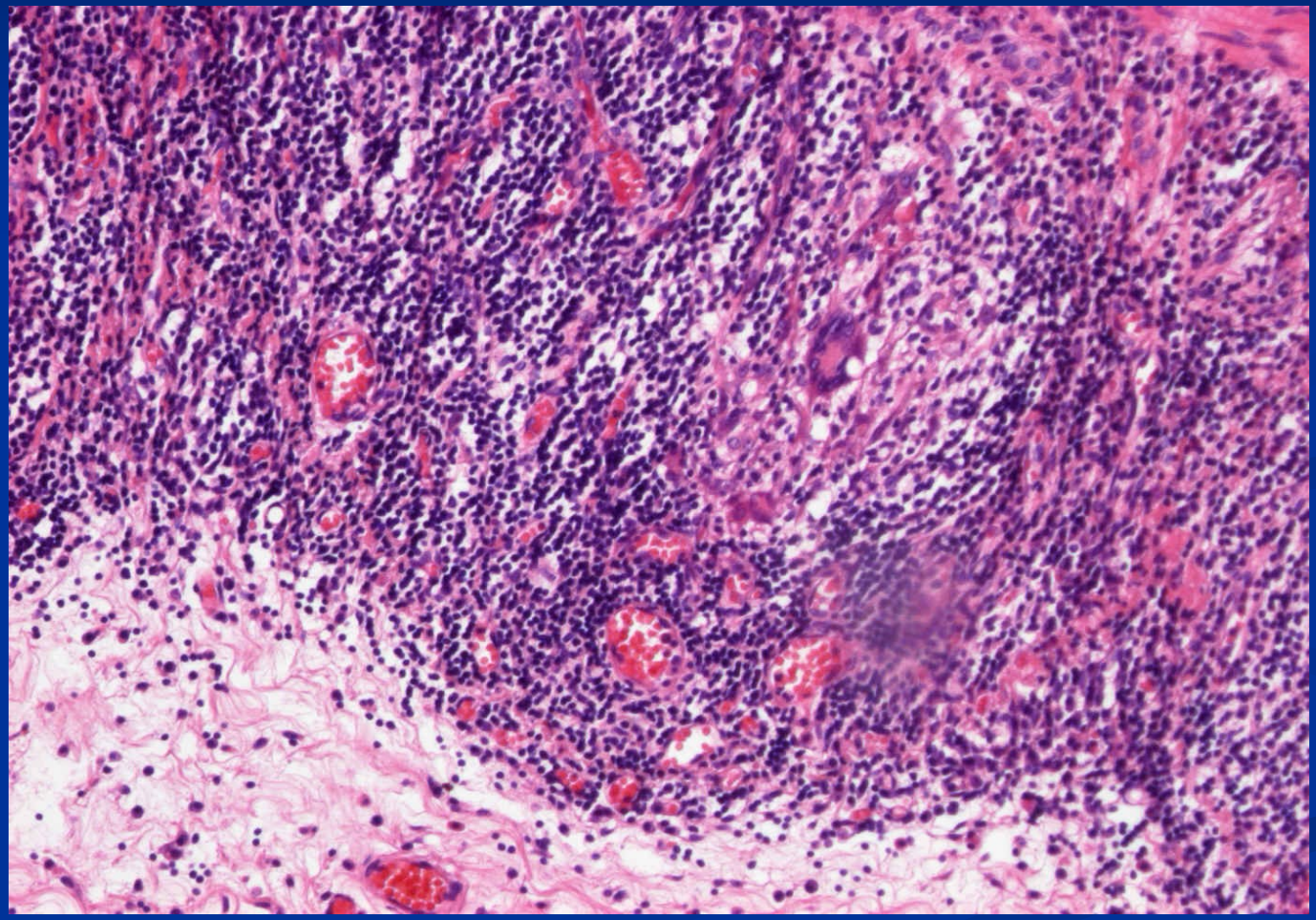
- Multisystem granulomatous disorder of unknown cause
- Inappropriate defense response to mycobacterial infectious agents + immunodysregulation
- Lungs, lymph nodes, skin, eyes, salivary glands,….
- Any oral mucosal sites can be affected (normal in color, brownish-red, violaceous, hyperkeratotic – submucosal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

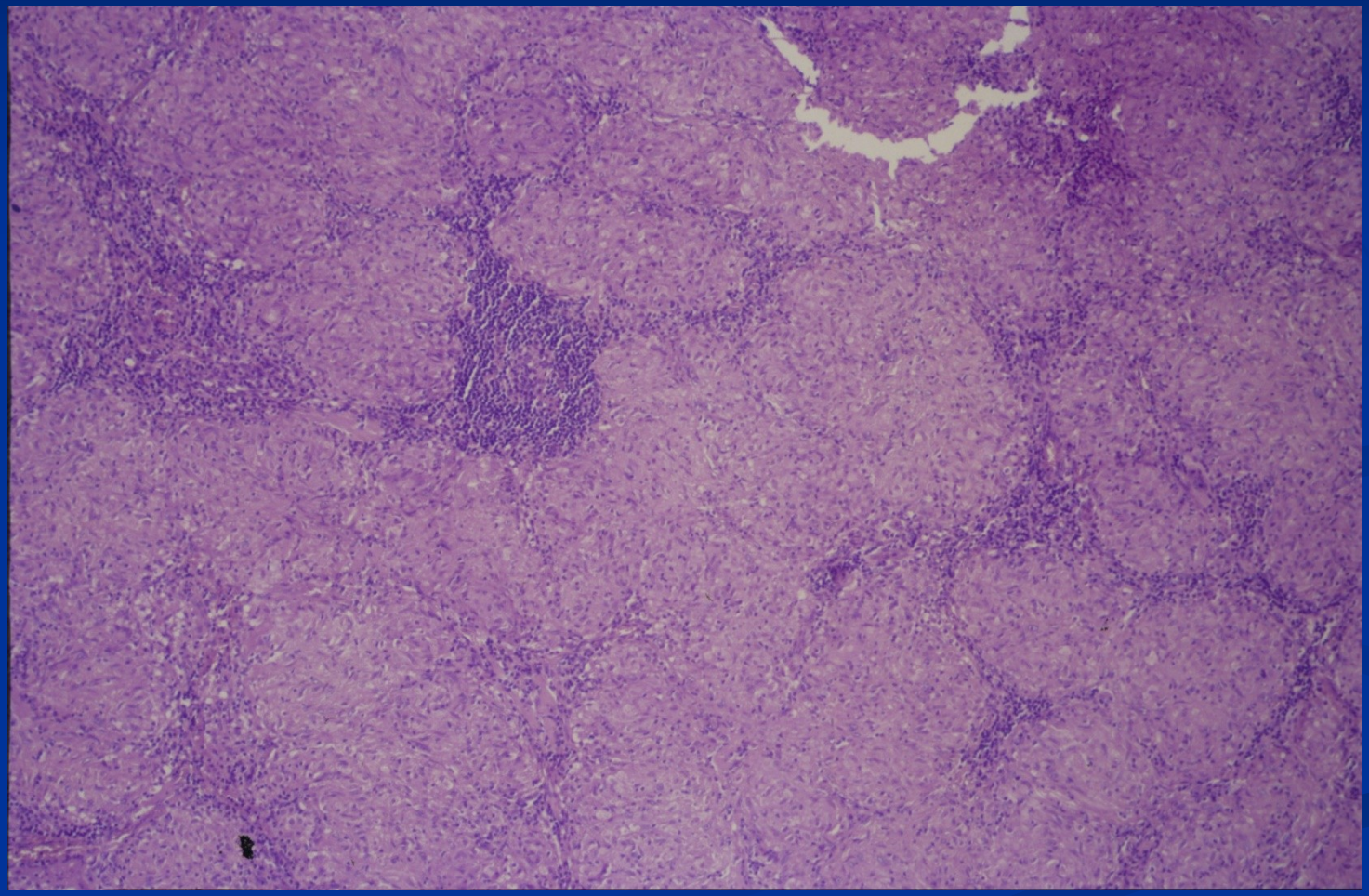
- **Orofacial granulomatosis**
  - Melkersson-Rosenthal syndrome (cheilitis granulomatosa+facial paralysis+fissured tongue)

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

Granuloma in Crohn´s disease



Sarcoidosis



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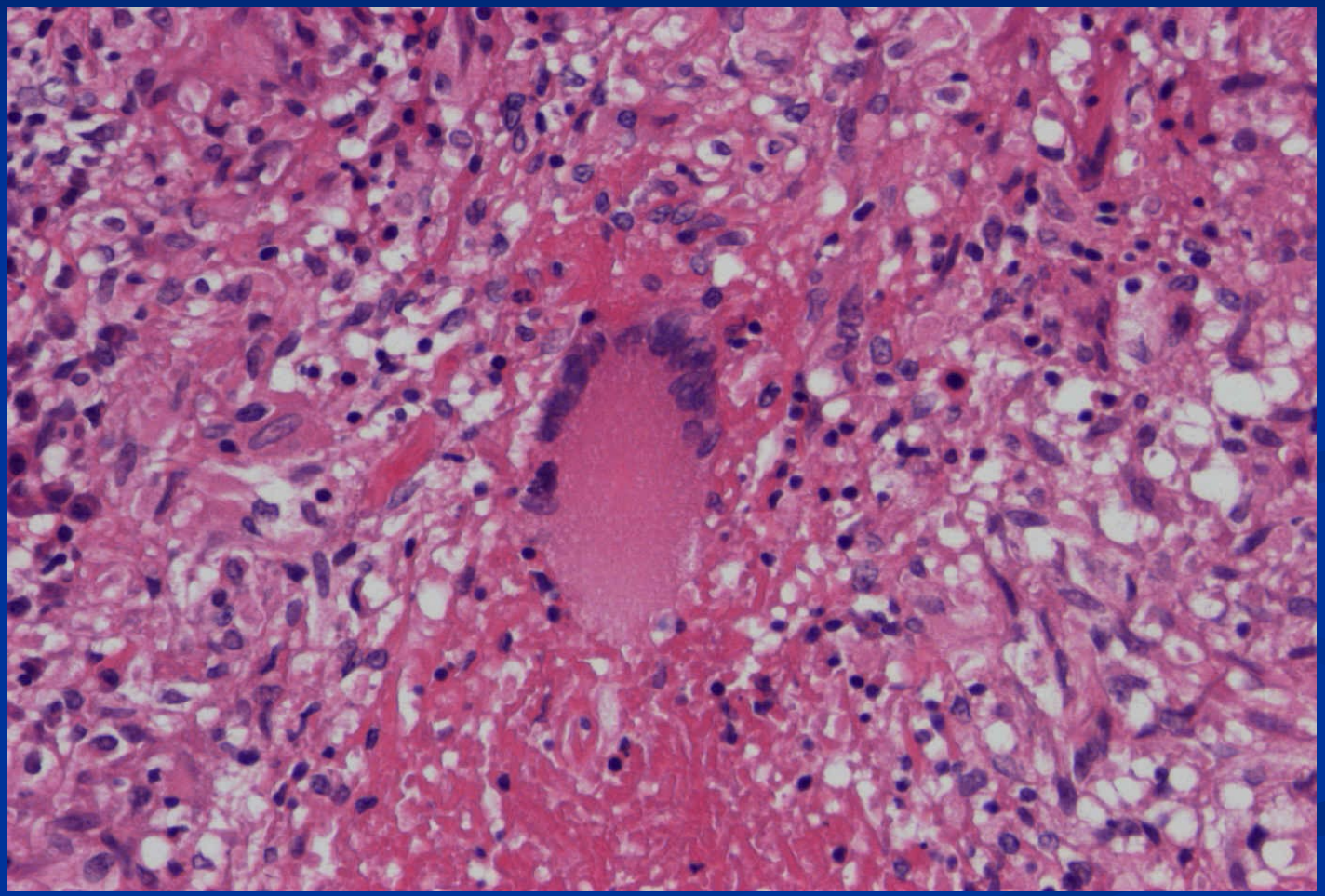
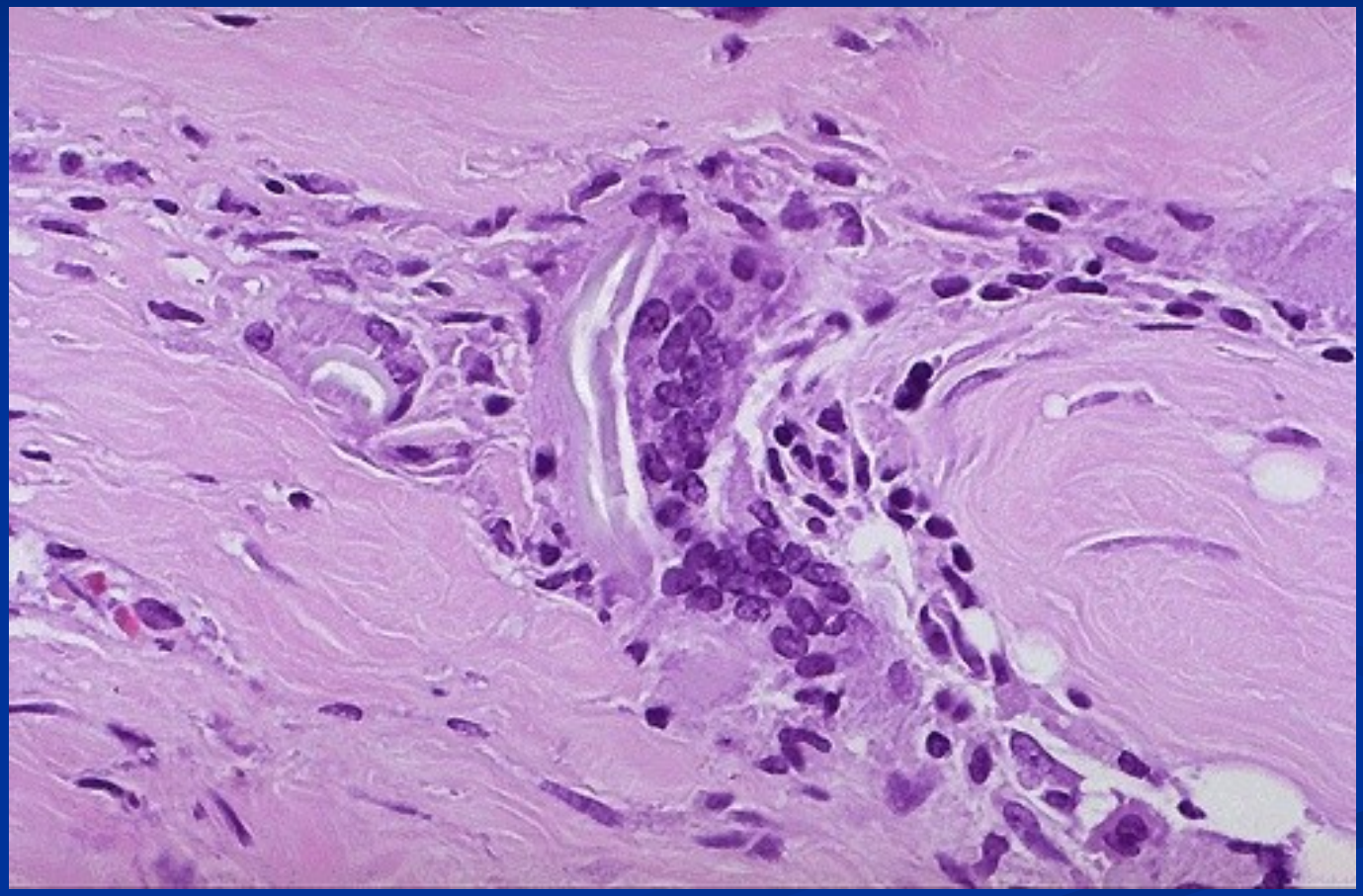


Foreign body reaction



Granulomatosis with polyangitis (Wegener´s granulomatosis)

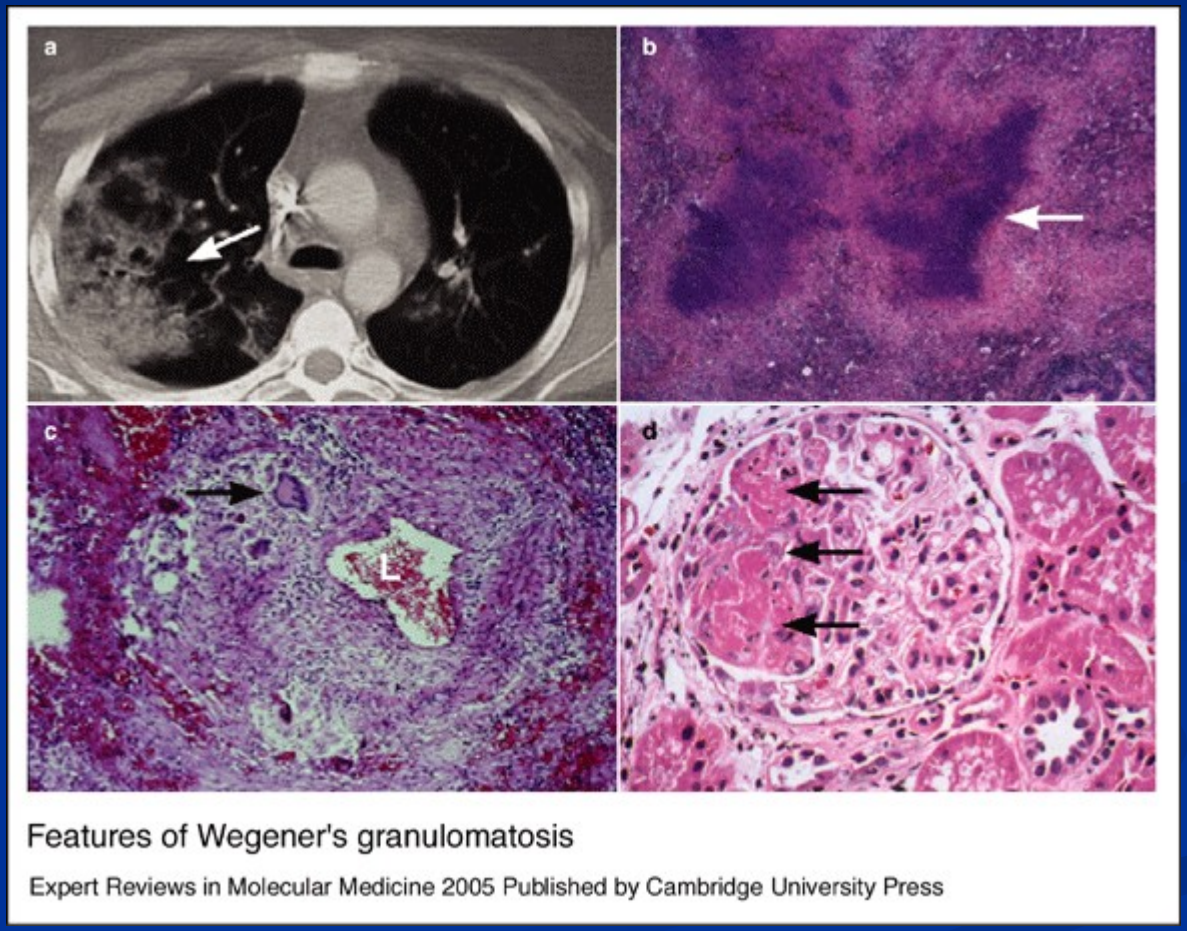
- Necrotizing granulomatous lesions of the respiratory tract
- Necrotizing glomerulonephritis
- Systemic vasculitis

Granulomatosis with polyangitis (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

Granulomatosis with polyangitis (Wegener´s granulomatosis)



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)

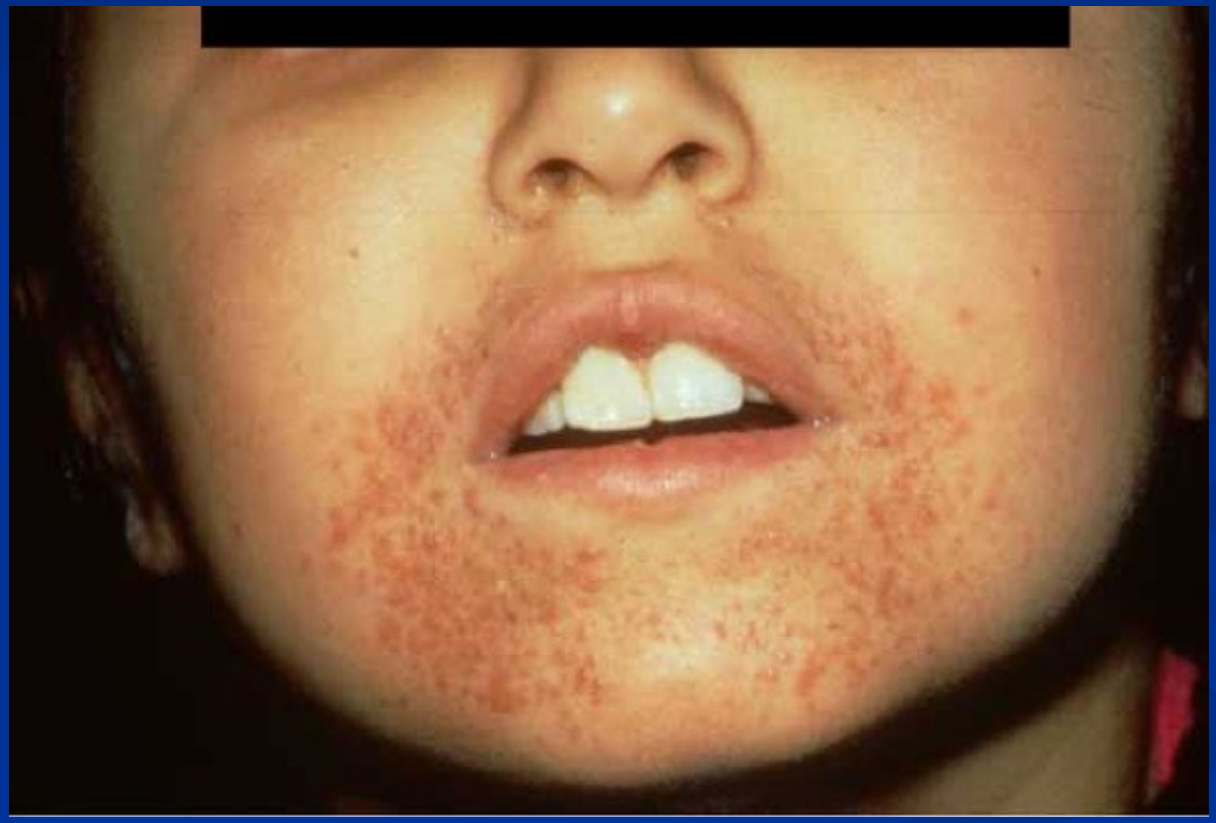
- **Chronic oral mucosal contact reactions to dental amalgam**

  (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)

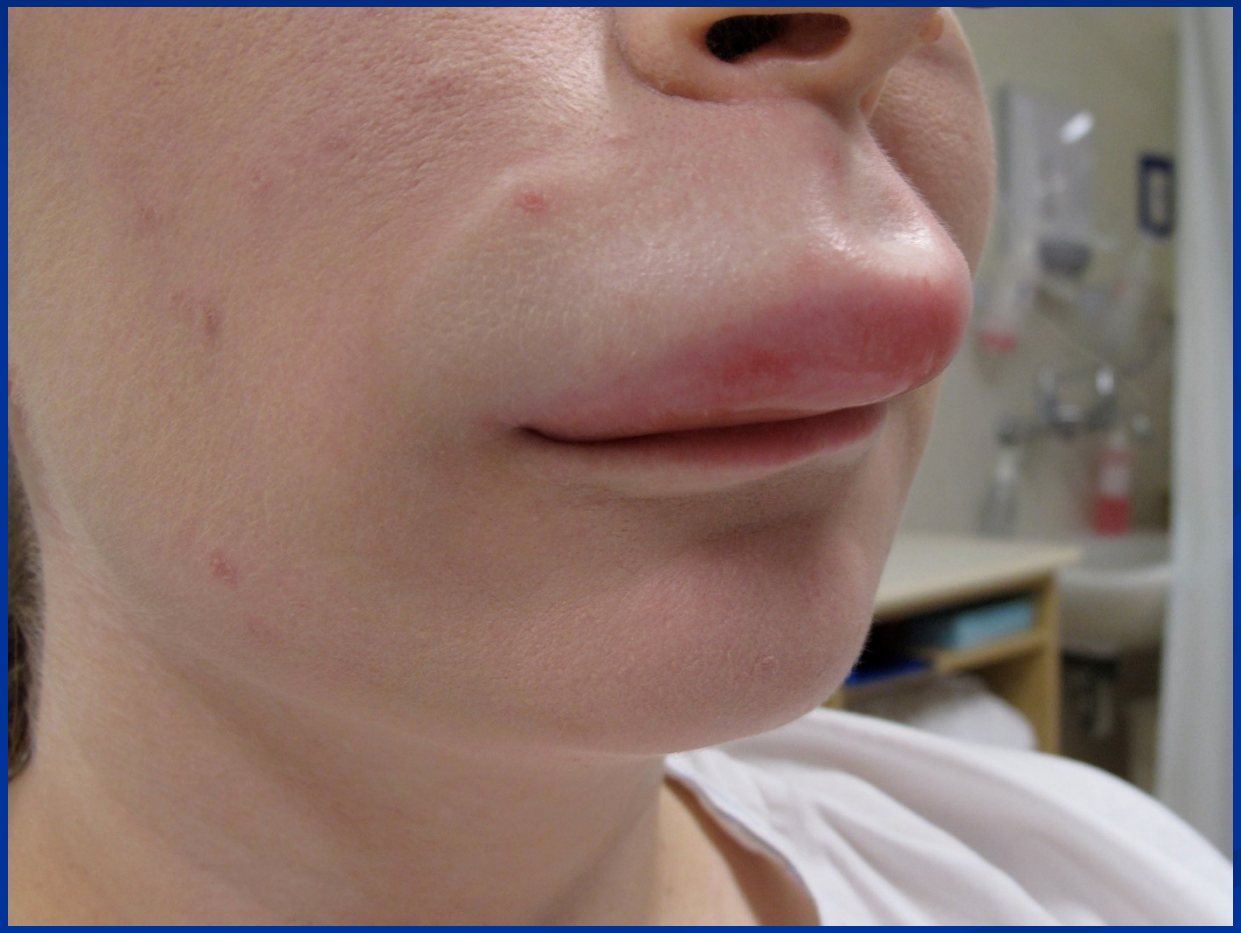
- **Angioedema (angioneurotic edema, Quinke´s disease)**

- 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



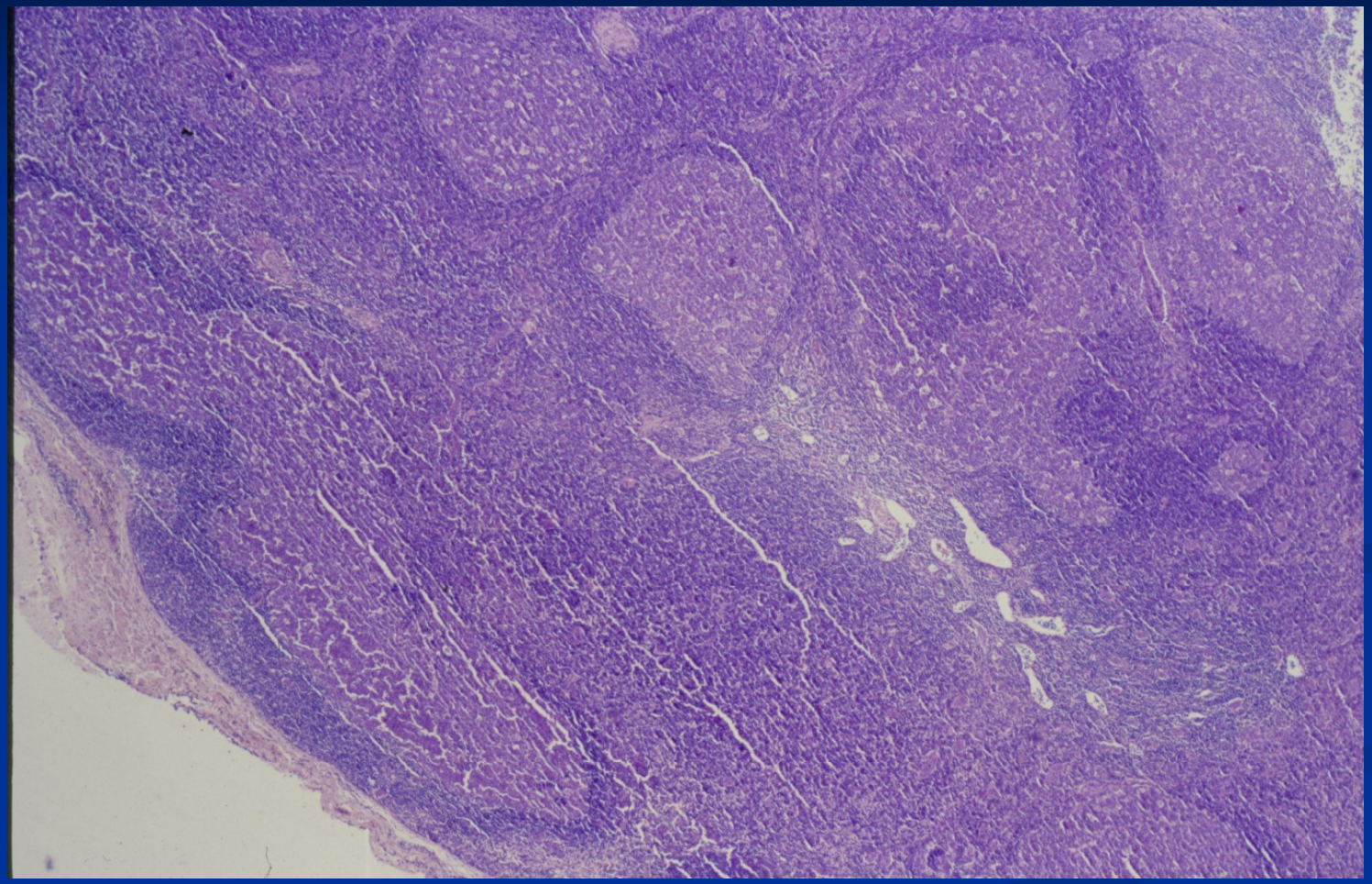
Angioedema



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

Leukaemias

Neoplastic proliferation of white blood cell precursors

Diffuse replacement of normal BM by leukaemic cells with their subsequent variable accumulation in peripheral blood (=leukaemization)

Infiltration of peripheral organs by leukaemic cells (liver, spleen, lymph nodes, meninges, gonads,….)

Consequence, particularly in acute leukaemias: bone marrow failure with anaemia, neutropenia and thrombocytopenia

Lymphomas

Neoplastic/lymphoma cells form tumor/neoplastic mass (primary nodal and/or extranodal)

Lymphomas may also present by leukaemic infiltrates and leukaemias also form solid neoplastic massess

See the pathology lecture…….

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)

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

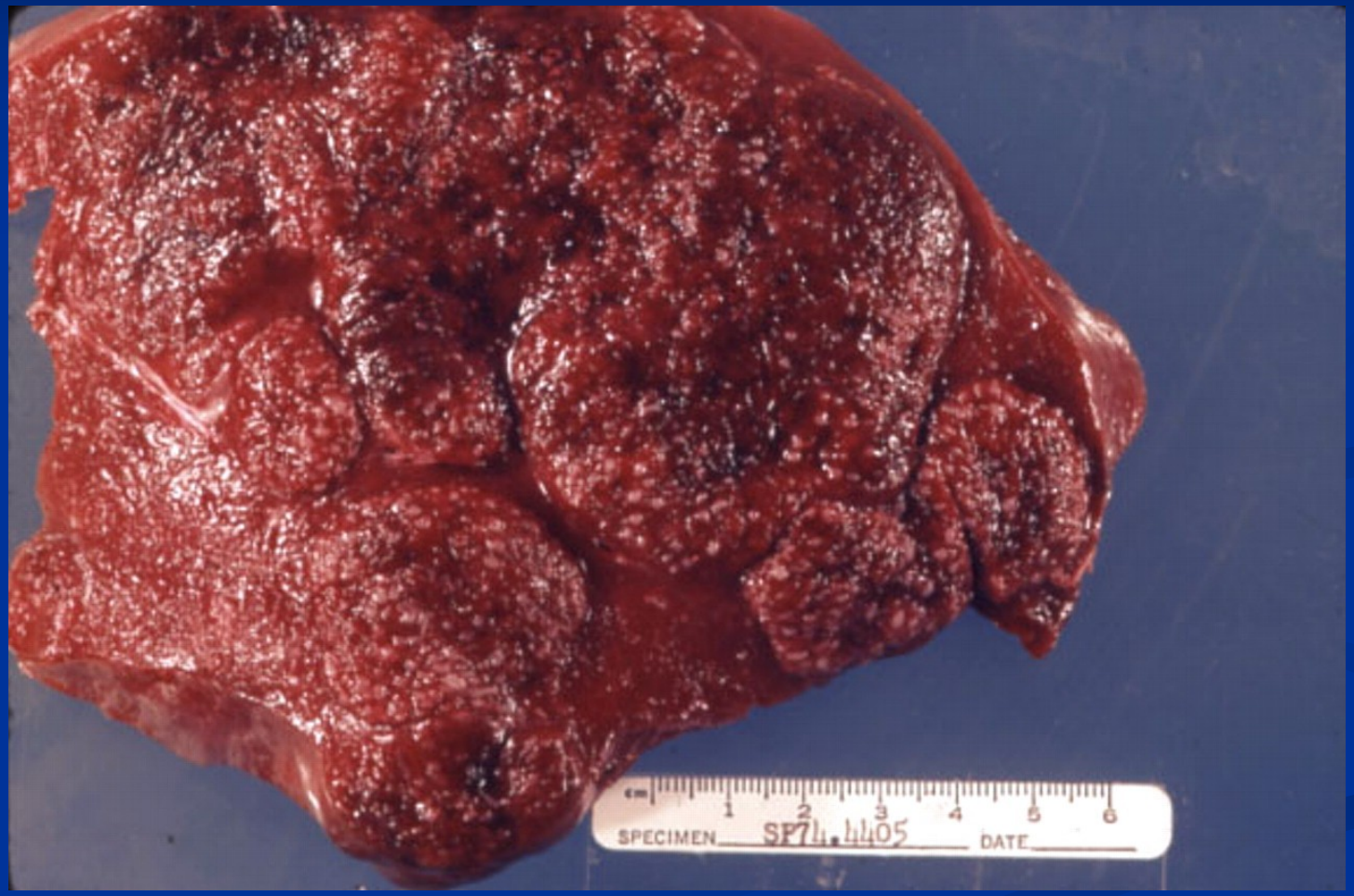
2. **Mantle cell lymphoma**

- 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

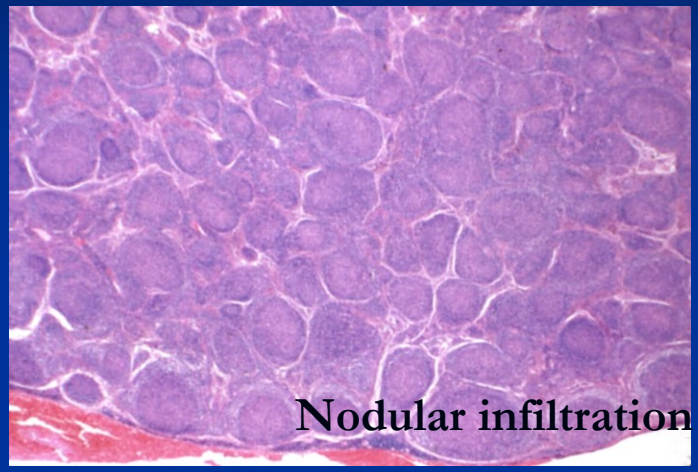
3. **Follicular lymphoma**

- 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

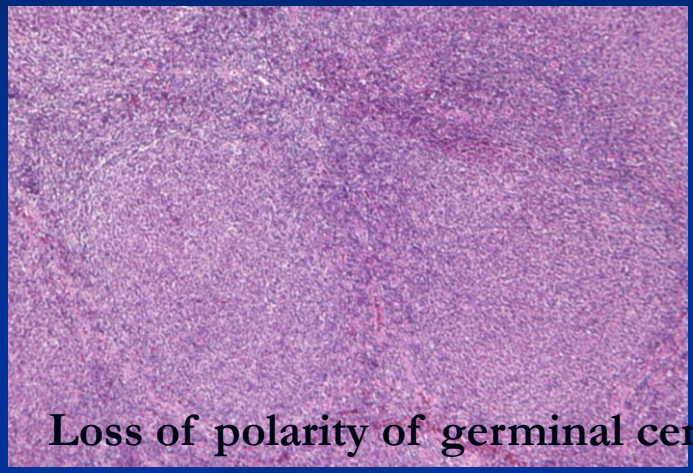
Spleen, follicular lymphoma



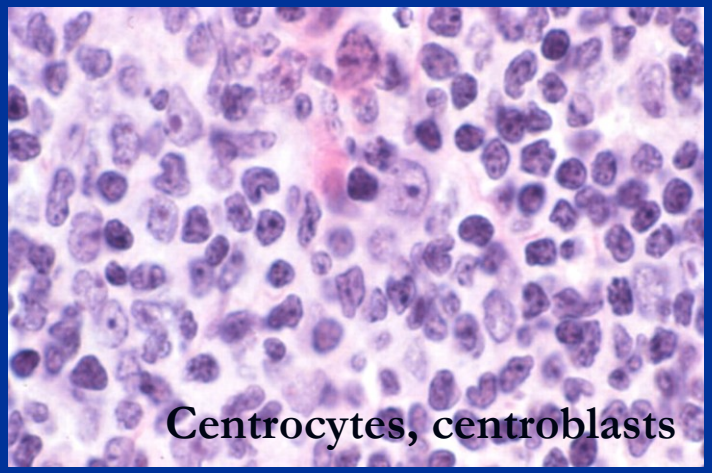
Follicular lymphoma



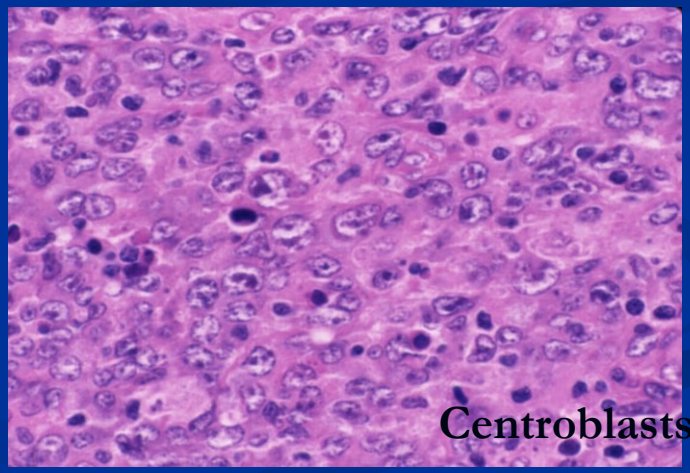
Nodular infiltration



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**

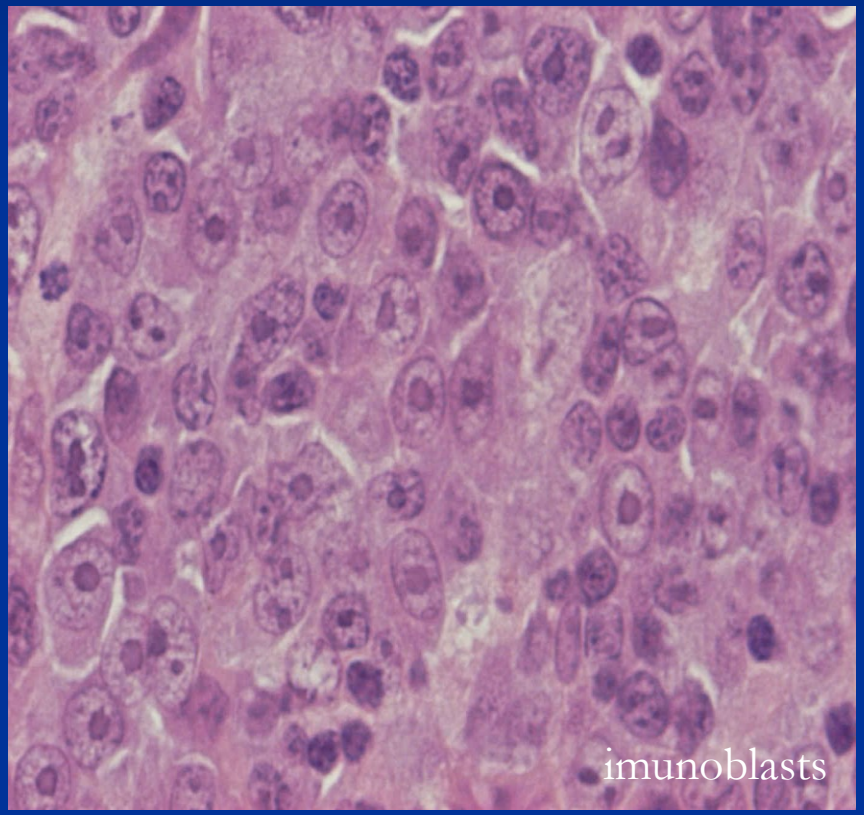
(African endemic (jaws); sporadic (intestinal); HIV+ related)

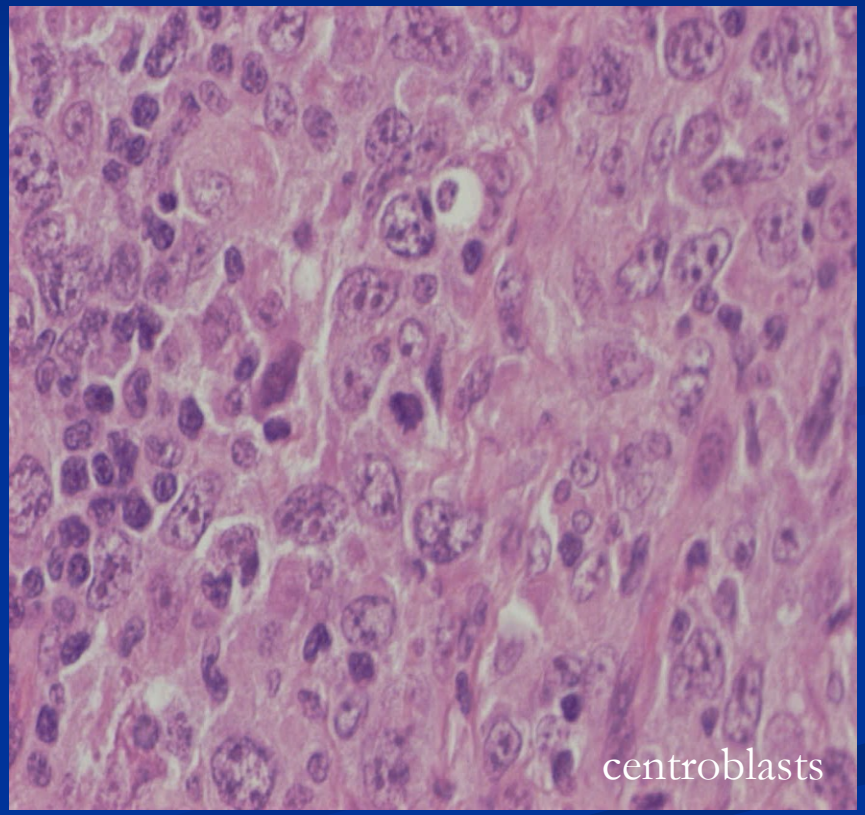
- germinal center B-cell (CD10+)?; „starry sky“ pattern; high mitotic rate, high apoptotic rate
- t(8;14) (c-myc/IgH), t(2;8) (c-myc/kappa light chains), t(8;22) (c-myc/lambda light chains)
- adolescents, young adults; aggressive, often association with EBV

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

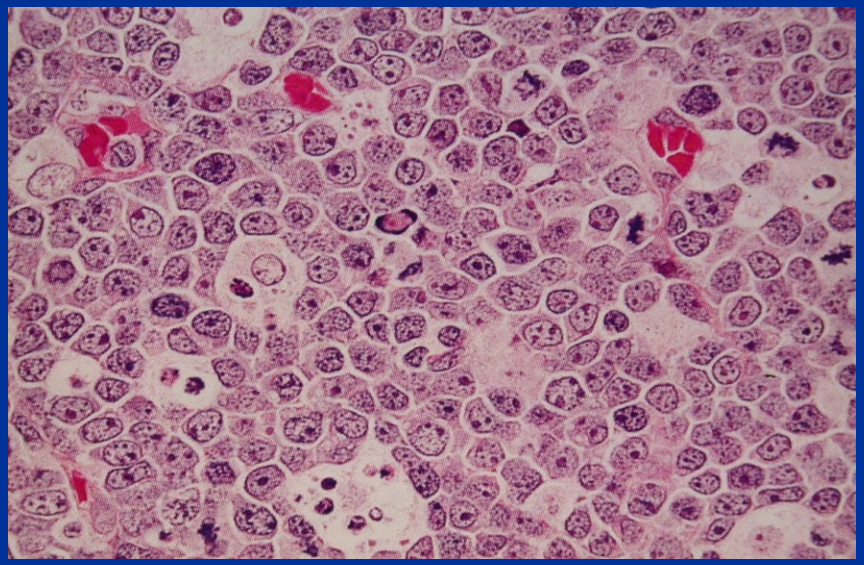
- postgerminal center memory B-cell
- extranodal in adults with chronic infalmmation (*Helicobacter pylori* gastritis, Sjogren´s syndrome, chronic lymphocytic autoimmune thyreoiditis,…); indolent, possible transformation into high grade lymphoma
- **+ nodal marginal zone B-cell lymphoma; + splenic marginal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

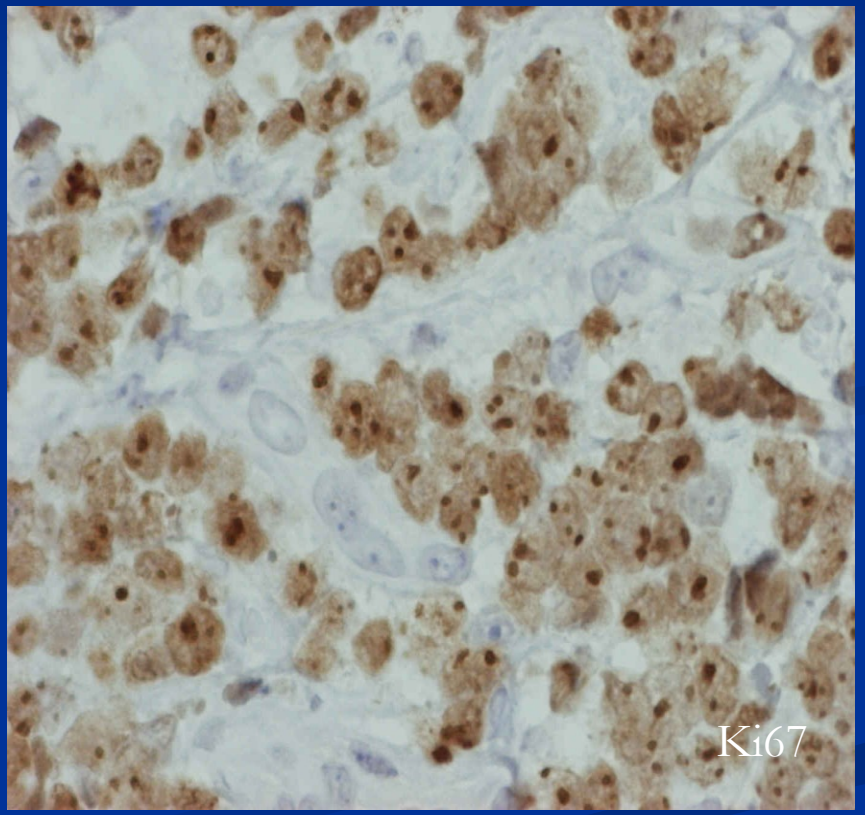
Diffuse large B cell lymphoma





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

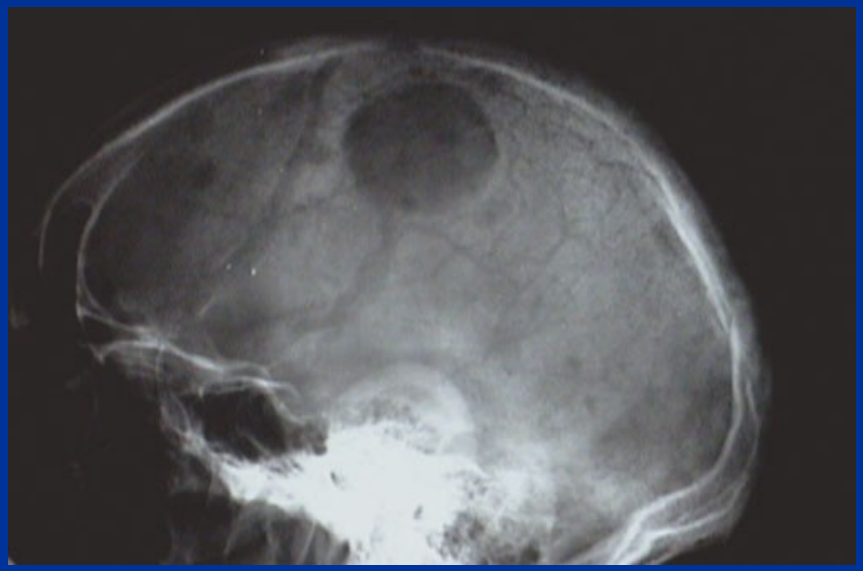
8. **Multiple (plasma cell) myeloma/plasmacytoma**

- 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**

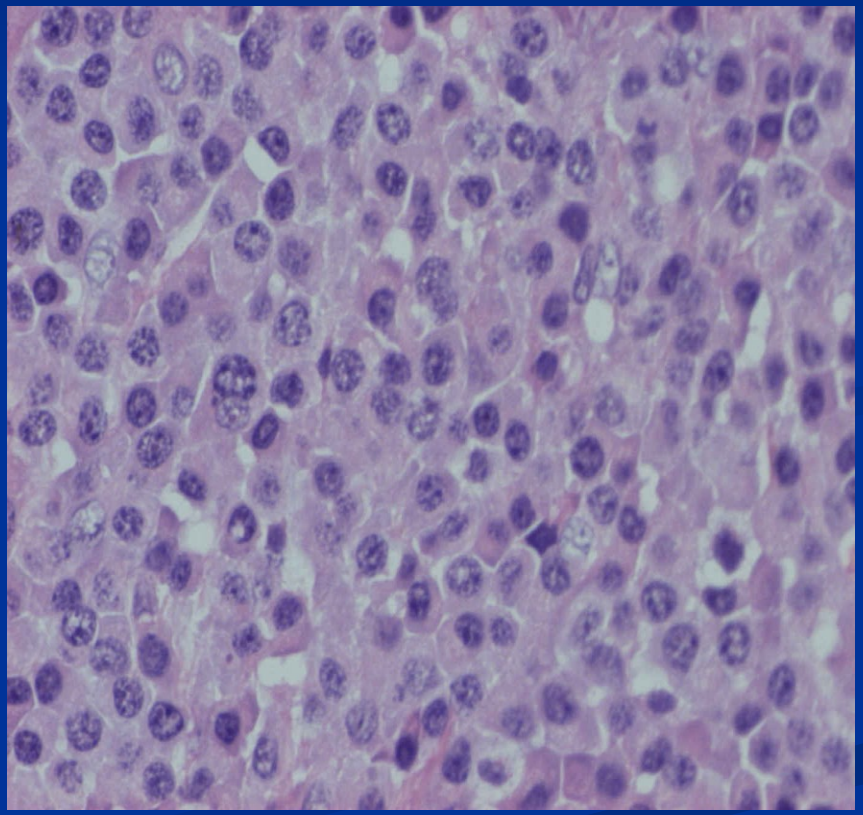
9. **Lymphoplasmacytic lymphoma**

- 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

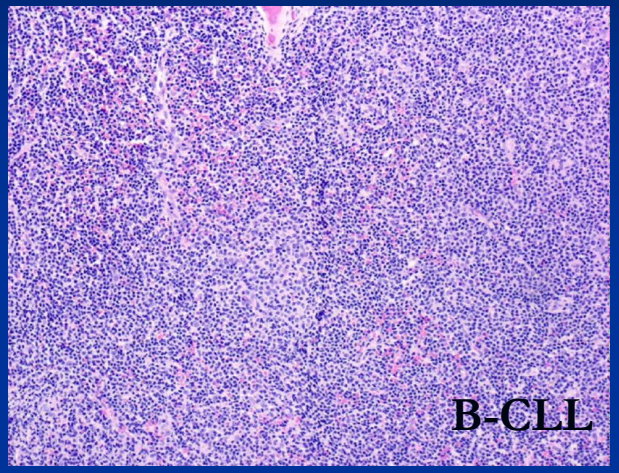


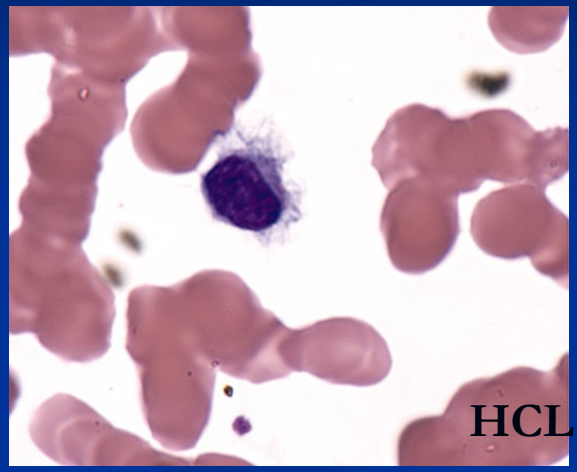
Osteolytic lesions

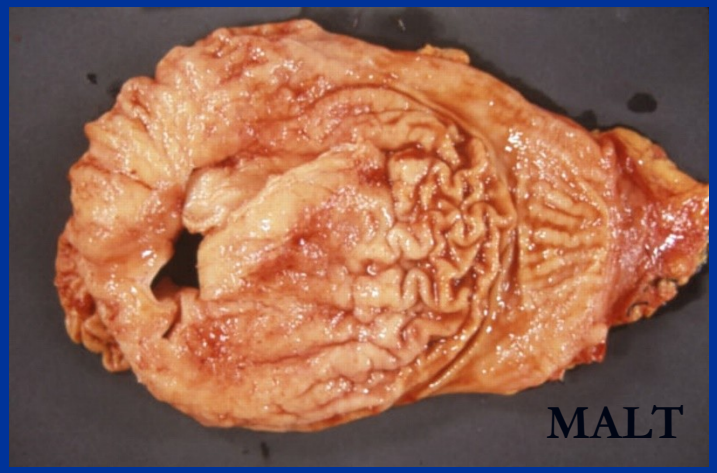


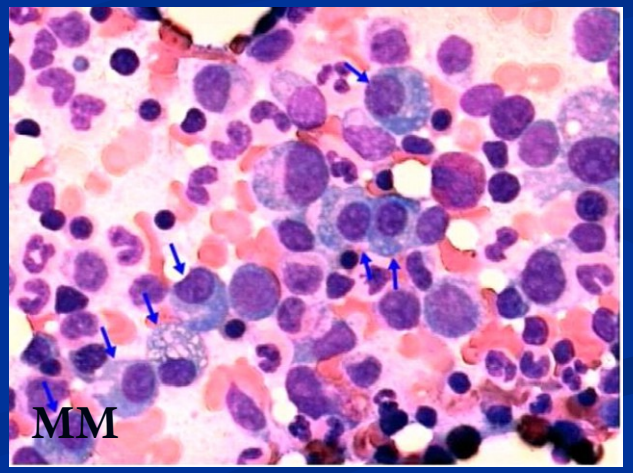
Infiltration by neoplastic plasma cells

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, osteolysis; 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

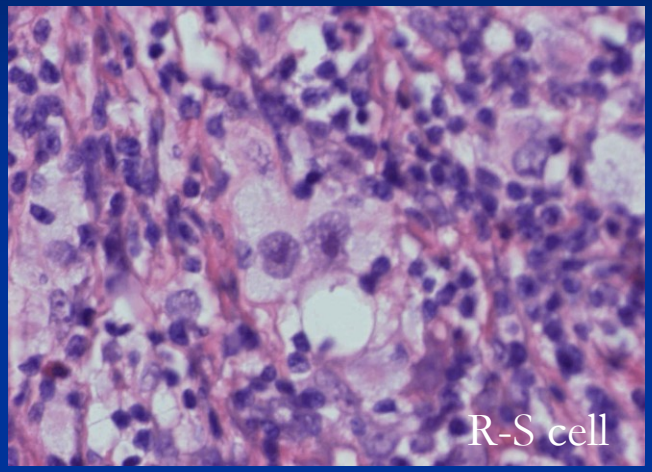
Clinical picture

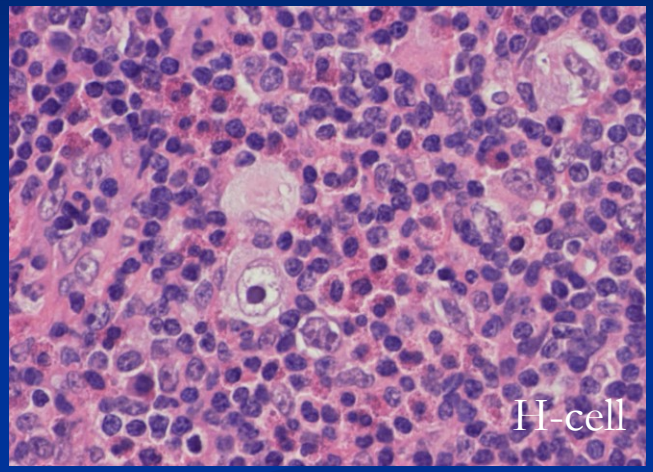
- Painless enlargement of lymph nodes (cervical, mediastinal, para-aortic: often localized to single axial group with spread by contiguity); mesenteric nodes and Waldeyer ring rarely involved, extranodal involvement uncommon
- Young patients
- Night sweats, weight loss

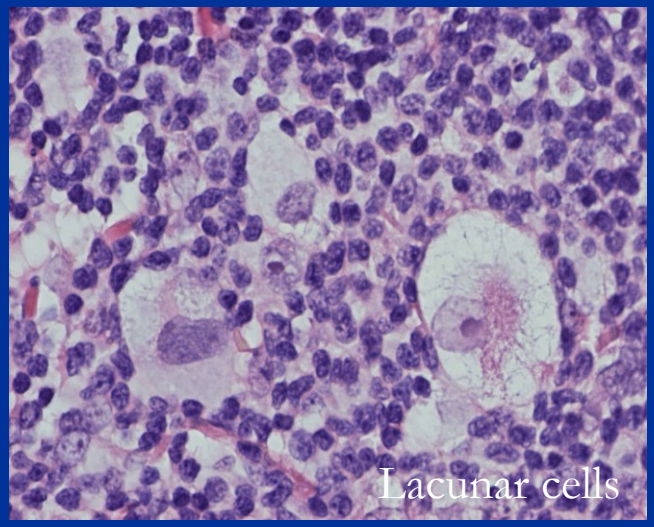
Neoplastic cells in classical HL

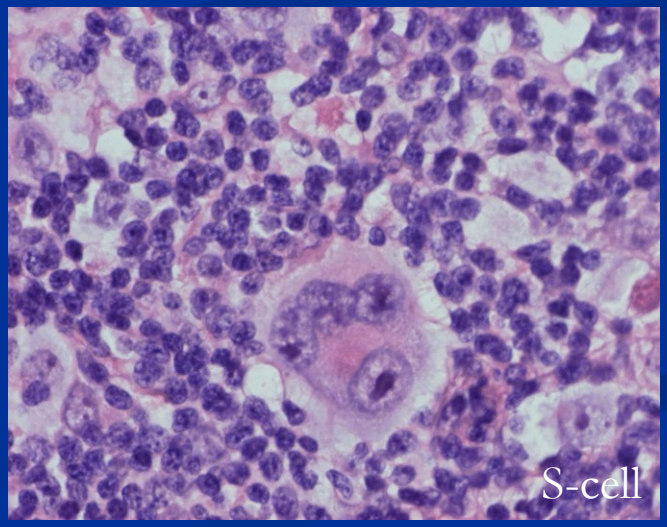
- Diagnostic Reed-Sternberg and Hodgkin cells (multiple or single nucleus)
- Lacunar cells

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 myeloid leukeamia (AML)

Associated with diverse aquired mutations that lead to abnormal expression of transcription factors, which interfere with myeloid differentiation; often assoc. with mutations in genes encoding GFR signaling pathways components or regulators of the epigenome

Replacement of normal bone marrow elements by immature myeloid blasts

Hiatus leukemicus

Immature myeloid lineage blasts released into peripheral blood

Leukaemic infiltrates in bone marrow, liver, spleen, lymph nodes….

Clinical signs of bone marrow failure

→ anemia **(fatigue, palor)**
→ trombocytopenia **(abnormal bleeding)**
→ granulocytopenia **(bacterial infections - fever)**

Peak incidence 15-39 years
Generally poor prognosis (60 % remision; 15-30 % disease free for 5 years)

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.

de novo or following genotoxic exposures; frequently harbor mutations in splicing factors, epigenetic regulators, and transcription factors

Primary/idiopathic (six categories based on morphological and cytogenetic features in the WHO classification)
Secondary/therapy-related

Predominantly in older adults

Clinically: weakness, infections, hemorrhages due to pancytopenia

Treatment: allogeneic HSC transplantation (in younger patients), supportive treatment with ATB and blood products transfusion, thalidomide-like drugs and DNA methylation inhibitors in some patients

Bone marrow: *hypercellular or normocellular or (hypocellular)*
Dysplastic differentiation of erythroid, granulocytic, monocytic and megakaryocytic lineages to various degree
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

- presence of mutated constitutively activated tyrosine kinases or other aberrations in signaling pathways that lead to growth factors independence

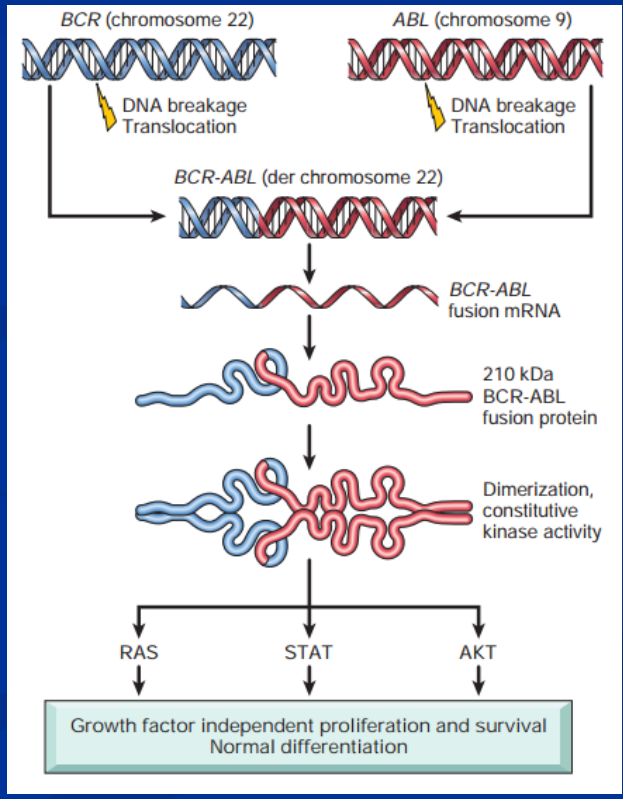
Chronic myeloid leukaemia, BCR-ABL1-positive

Polycythaemia vera

Essential thrombocythaemia

Primary myelofibrosis

Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Myeloid leukaemia, unclassifiable



Chronic myeloid leukaemia (CML)

presence of aquired genetic abnormality: t(9;22); BCR-ABL fusion gene: fusion protein with tyrosinkinase activity; Philadelphia chromosome;

BCR-ABL preferentially drives the proliferation of granulocytic and megakaryocytic progenitors, abnormal release of immature granulocytes from the marrow into blood

adults, peak incidence in 5th and 6th decade

Clinical features:
- anemia, hypermetabolism due to increased cell turnover: fatigability, weakness, weight loss, anorexia
- slow progression-accelerated phase-blast crisis (AML-like)

Therapy:
- transplantation of bone marrow
- imatinib mesylate (inhibitor of the BCR-ABL tyrosine kinase)

Chronic myeloid leukaemia (CML)

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

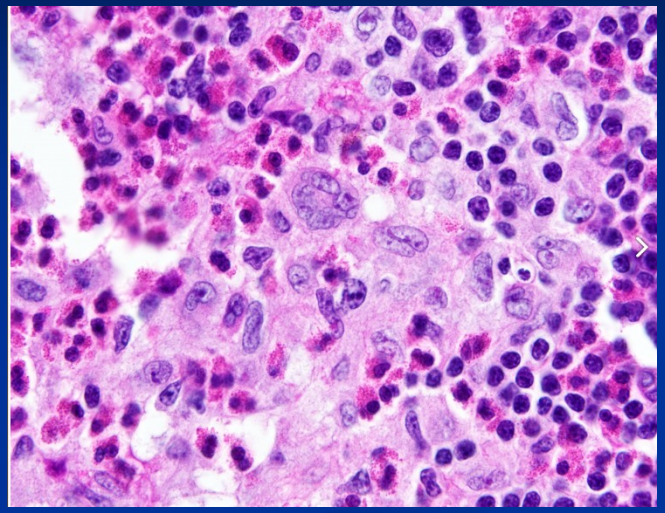
Polycythemia vera

- the transformed progenitor cells have markedly decreased requirements for erythropoietin and other hematopoietic growth factors due to activating mutations in the tyrosine kinase JAK2
- increased marrow production of red cells, granulocytes and platelets (panmyelosis)
- symptoms related to the increased red cell mass and hematocrit: plethora, cyanosis owing stangnation and deoxygenation, headache, dizziness, hypertension, GIT symptoms, hyperuricemia due to increased cell turnover, abnormal blood flow and platelet function lead to increased risk of major bleeding and thrombosis
- transition into myelofibrosis, accompanied by increased extramedullary haematopoiesis
- transformation to AML in 2 % of patients

Histiocytic and dendritic cell neoplasms

- derived from mononuclear phagocytes (macrophages and dendritic cells (antigen presenting cells) or histiocytes

- rare tumours, <1% of tumours presenting in lymph nodes and soft tissues



Langerhans cell histiocytosis (histiocytosis X)

Immunophenotype: CD1a+, langerin+, S100+; ultrastructurally cytoplasmic tennis–racket shape Birbeck granules)

- *monoostotic* (solitary osteolytic lesion (eosinophilic granuloma), involvement of adjacent soft tissues)
- *polyostotic* (multifocal osteolytic lesion (Hand-Schüller-Christian d.), involvement of adjacent soft tissues)
- *disseminated and multisystem* (Letterer-Siwe disease; skin, bones, liver, spleen and bone marrow affected)

Pulmonary Langerhans cell histiocytosis – special category, in smokers, reactive?, neoplastic? (BRAF mutated in some lesions)

Oral pathology in Langerhans cell histiocytosis:

- osteolytic lesions, alco mandible or maxila affected
- ulcerative and proliferative mucosal lesions, proliferative gingival mass, involvement of oral soft tissues

Thank you for your attention …