

***Pathology of the
lymphatic and
hematologic
systems***

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Lymph nodes

- ✘ Normal LN soft, nonpalpable
- ✘ Lymphadenopathy – enlarged palpable LN
- ✘ Tender LN – usually in acute reaction (hyperemia, edema of LN), commonly neck
- ✘ Nontender LN – palpable firmer lump – mostly chronic reaction (neck LN, inguinal LN, ...), chronic inflammation (TB, ...), cancer
- ✘ Past medical history of the client important

Lymph nodes

- ✘ changes in size (>10 mm), shape (fused together), consistency important, must be reported
- ✘ LN in front or behind of ears, supraclavicular, pectoral – usually not affected by local inflammation – changes more suspicious

Disorders of the lymphatic system

- ✘ Lymphadenitis – inflammation of LN
- ✘ Lymphadenopathy – reactive enlargement of LN (immune reaction)
- ✘ Lymphangitis – inflammation of lymphatic vessel
- ✘ Lymphedema – increased amount of lymph fluid in soft tissue

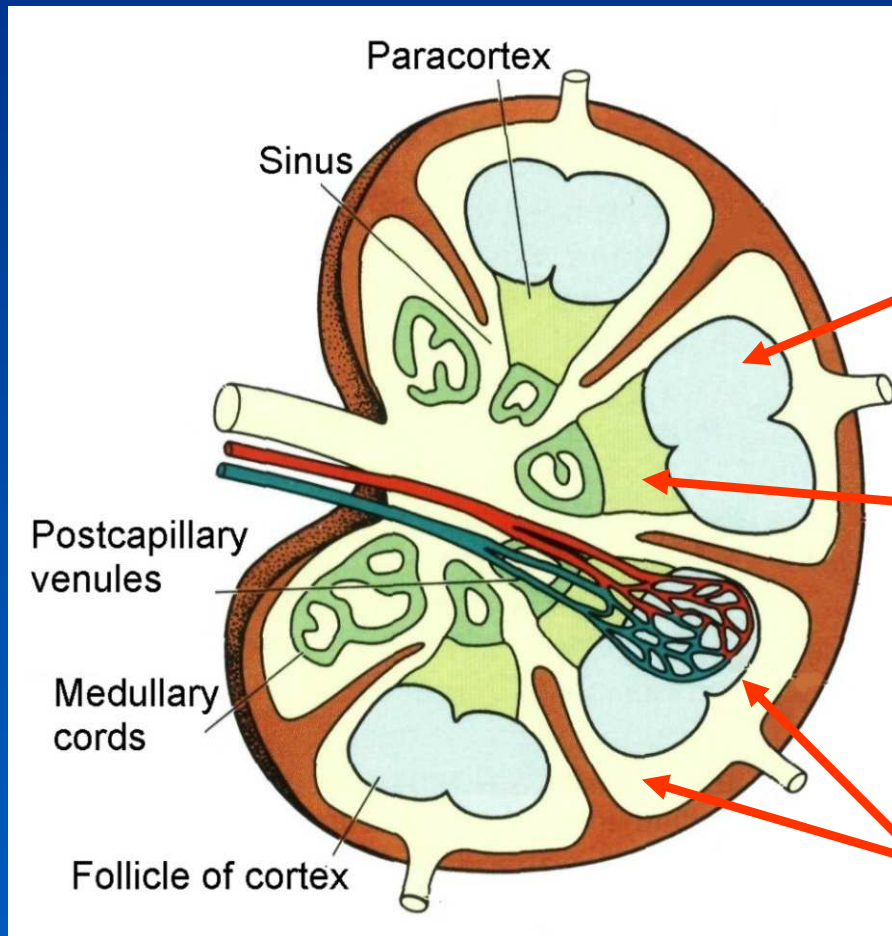
Lymphadenopathy

- ✗ LN – defense barrier
- ✗ Regional LN in focal infection /reaction, focal malignant tumor (reactive cervical lymphadenopathy in infection of oral cavity, pharynx, ears, head, skin or soft tissue)
- ✗ Generalized lymphadenopathy - ≥ 2 groups of LN; in systemic infection, immunologic reaction, spread of a malignant tumor

Non-specific reactive lymphadenopathy

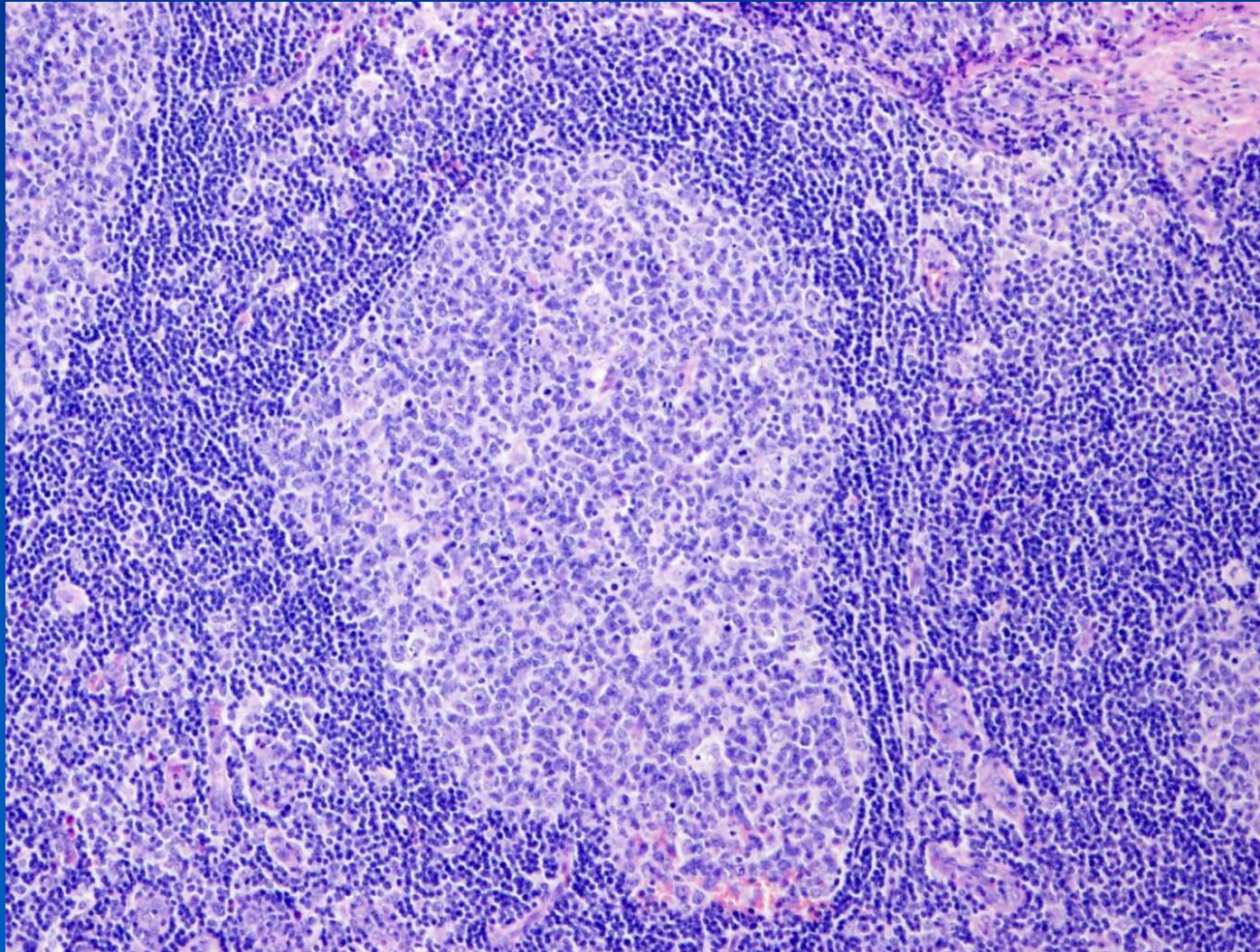
- regional or systemic response of lymphatic tissue on antigenic stimulation (inflammation, tumor, foreign material)
- Gross : acute lymphadenopathy (enlarged LN), hyperaemia, soft consistency, tender
- Micro: according to the cause – lymph. follicles activation and hyperplasia, sinus hyperplasia („histiocytosis“), T-zone activation

Reactive lymphadenopathy

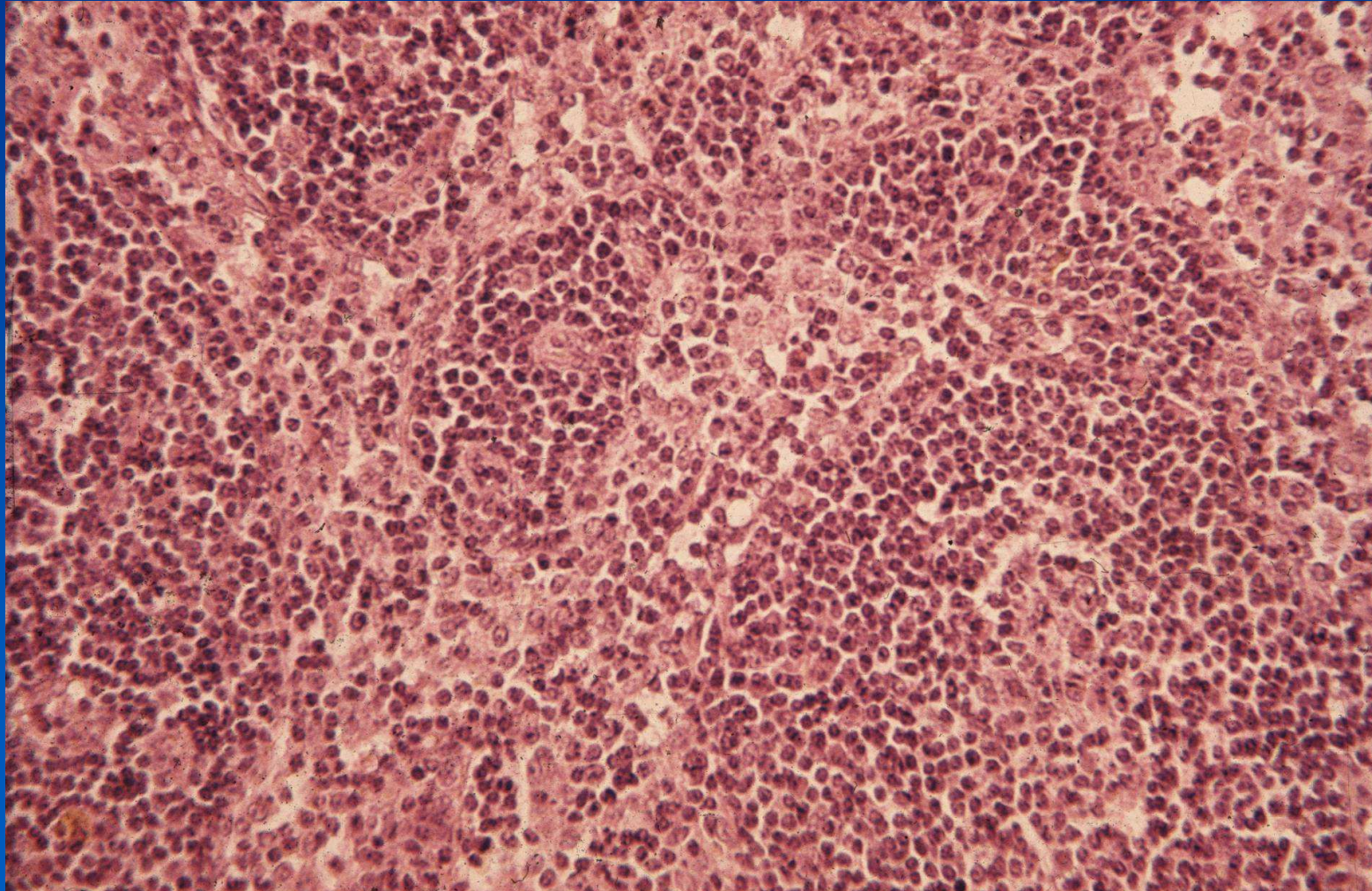


- **Reactive hyperplasia:**
 - Follicular (B)*
(bacteria, sterile inflammation)
 - Paracortical (T)*
(viruses, chronic inflammations)
- **Sinus histiocytosis**

Follicular hyperplasia - reactive



Sinus histiocytosis



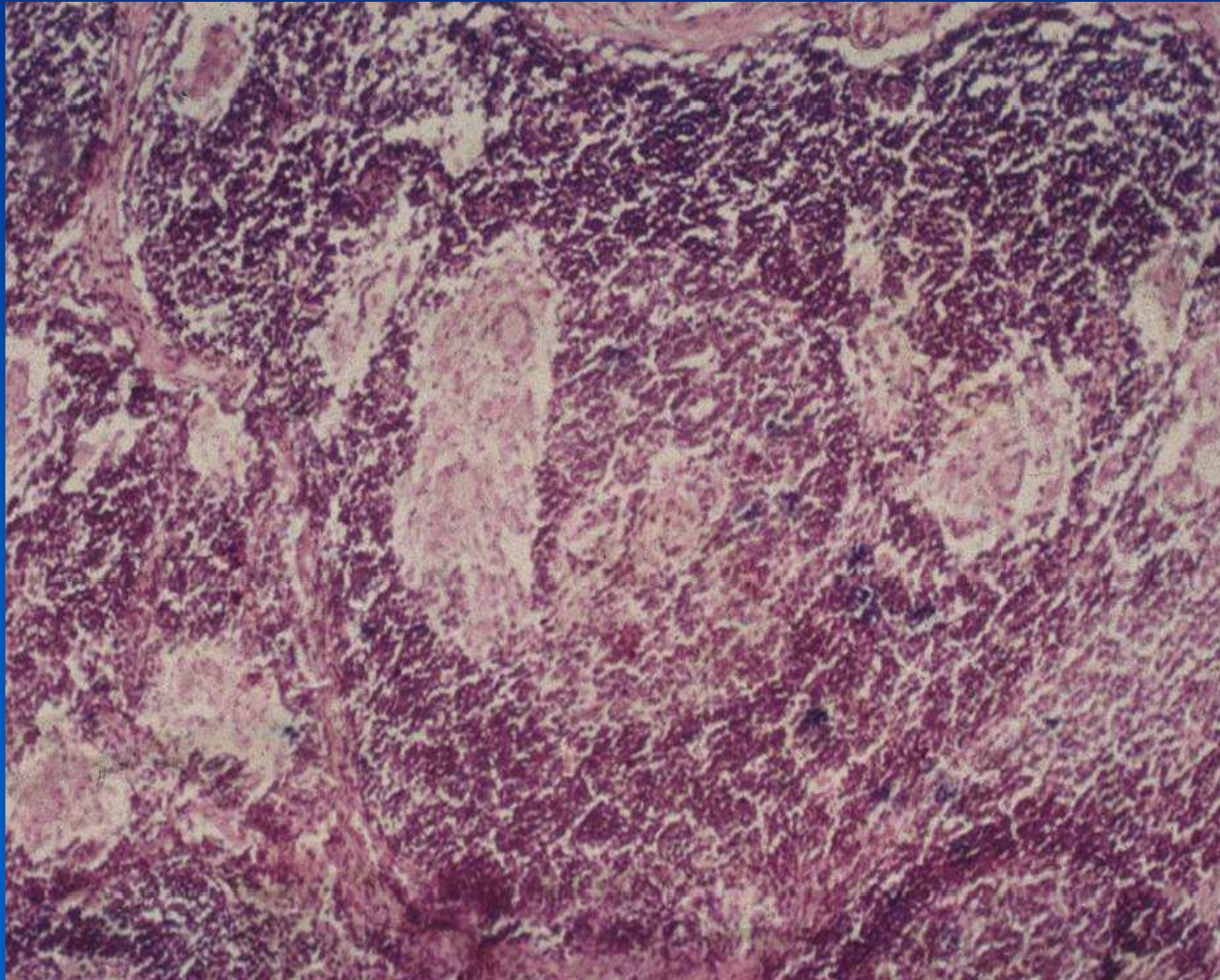
Lymphadenitis

- ✘ Acute – LN region warm, reddened, LN enlarged, tender
- ✘ Usually in more aggressive local infection, which affects even the LN (cervical in acute tonsillitis, inguinal in infection of extremities). Abscess possible.
- ✘ Short duration (approx. 2 weeks), if the cause progresses → possible transformation into chronic lymphadenitis

Lymphadenitis

- ✘ Non-specific: without specific microscopic patterns
- ✘ Specific: micro picture +/- specific for one cause
 - granulomatous inflammation (TB, sarcoidosis, mycotic infection,...)
- ✘ Chronic - LN enlarged, nontender, firmer
- ✘ Long duration, even persistent

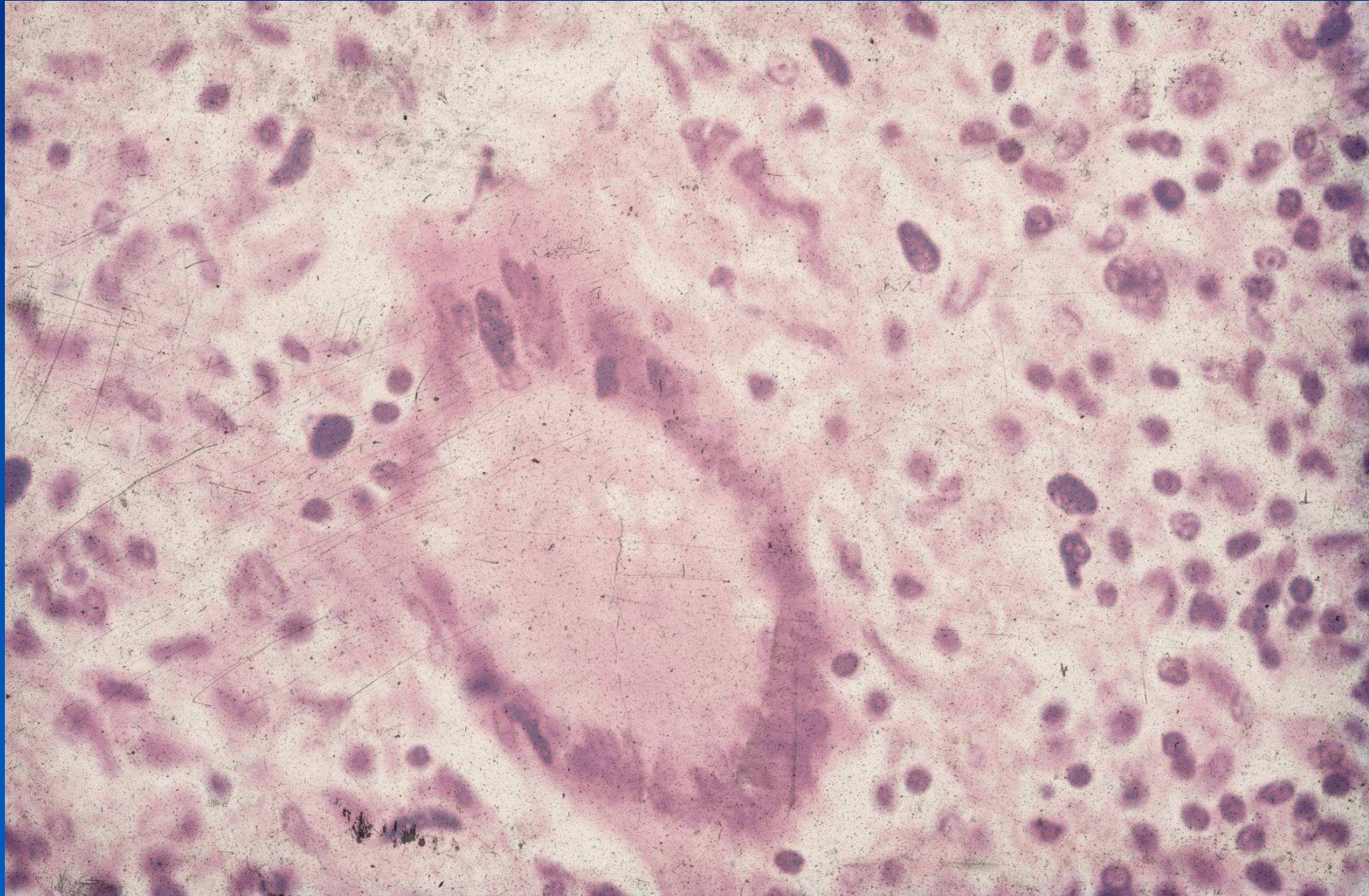
TBC lymphadenitis



Tuberculosis

- ✘ Tuberculous granuloma - basic morphology:
 - central caseous necrosis (soft), transformed epithelioid macrophages + multinucleated Langhans' giant cells (fusion of macrophages), rim of T-cells
- ✘ *Mycobacterium tuberculosis*
 - Ziehl-Neelsen staining, acid-resistant bacteria

TBC lymphadenitis



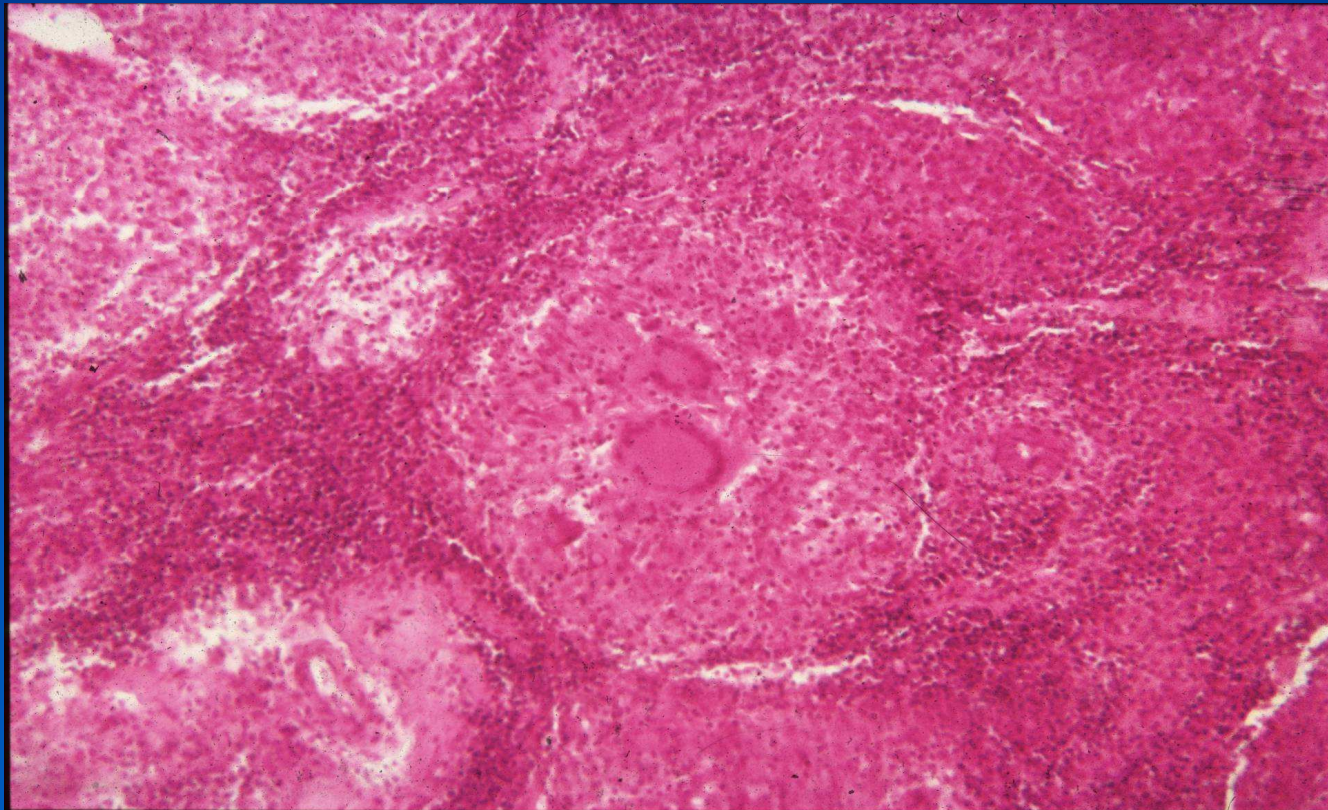
Sarcoidosis

- ✘ Chronic granulomatous inflammatory disease, direct etiology unknown
- ✘ Mostly in mediastinal LN, lung, skin, eye; any localisation possible
- ✘ Regular small „tuberculoid“ granulomas without caseous necrosis

Sarcoidosis

- ✘ May be asymptomatic, chest X-ray: bilateral lymphadenopathy (diff. dg. x lymphoma, cancer metastasis)
- ✘ Slow progression or remission + healing
- ✘ 10% mortality (lung fibrosis, cor pulmonale), 20% lung or ocular dysfunction

Sarcoidosis



Lymphangitis

- ✗ Acute inflammation of subcutaneous lymphatic vessels
- ✗ Usually from local wound/infection
- ✗ Red streak under the skin („blood poisoning“)
- ✗ Involved regional LN
- ✗ Systemic manifestation possible (fever, chills, malaise), bacteremia
- ✗ Risk of lymphedema

Lymphedema

- ✘ Swelling of the soft tissues due to accumulation of protein-rich fluid in the extracellular space
- ✘ Cause: ↓ lymphatic transport capacity and/or increased amount of lymph
- ✘ Extremities common; head, neck, abdomen, genitalia possible

Lymphedema

- ✘ Primary (idiopathic): result of lymphatic maldevelopment, rare.
 - ⇒ *May be present at birth (connatal)*
 - ⇒ *Can develop later in life without known cause*
- ✘ Secondary (acquired) more common.
 - ⇒ *Result of surgery, radiation, injury, trauma, scarring, or infection of the lymphatic system*

Secondary lymphedema

- ✘ Surgery: breast cancer, melanoma, prostate/bladder cancer, lymphoma, ovarian cancer, hip replacements
- ✘ Radiation therapy
- ✘ Drugs (steroid, etc.)
- ✘ Trauma – scarring, crush injury
- ✘ Infection: filariasis, etc.
- ✘ Chronic venous insufficiency
- ✘ Obesity
- ✘ Self-induced

Lymphedema staging

- ✘ Stage 0 – latent: reduced transport capacity, no edema present
- ✘ Stage I: pitting edema present, reversible (elevation)
- ✘ Stage II: nonpitting edema + fibrotic tissue, irreversible
- ✘ Stage III: lymphostatic elephantiasis, severe fibrotic edema, skin changes – folds, hyperkeratosis

Lymphedema



Lymphedema

- ✘ Lymphedema is a disease.
- ✘ Untreated l. is progressive
- ✘ Early diagnosis necessary
- ✘ If fully evolved, no definitive cure possible.
- ✘ Management strategies exist: treat the causing disorder;
- ✘ Proteolysis, surgery, ...
- ✘ Lymphatic drainage – manual, compression bandage, pump

Malignant complications

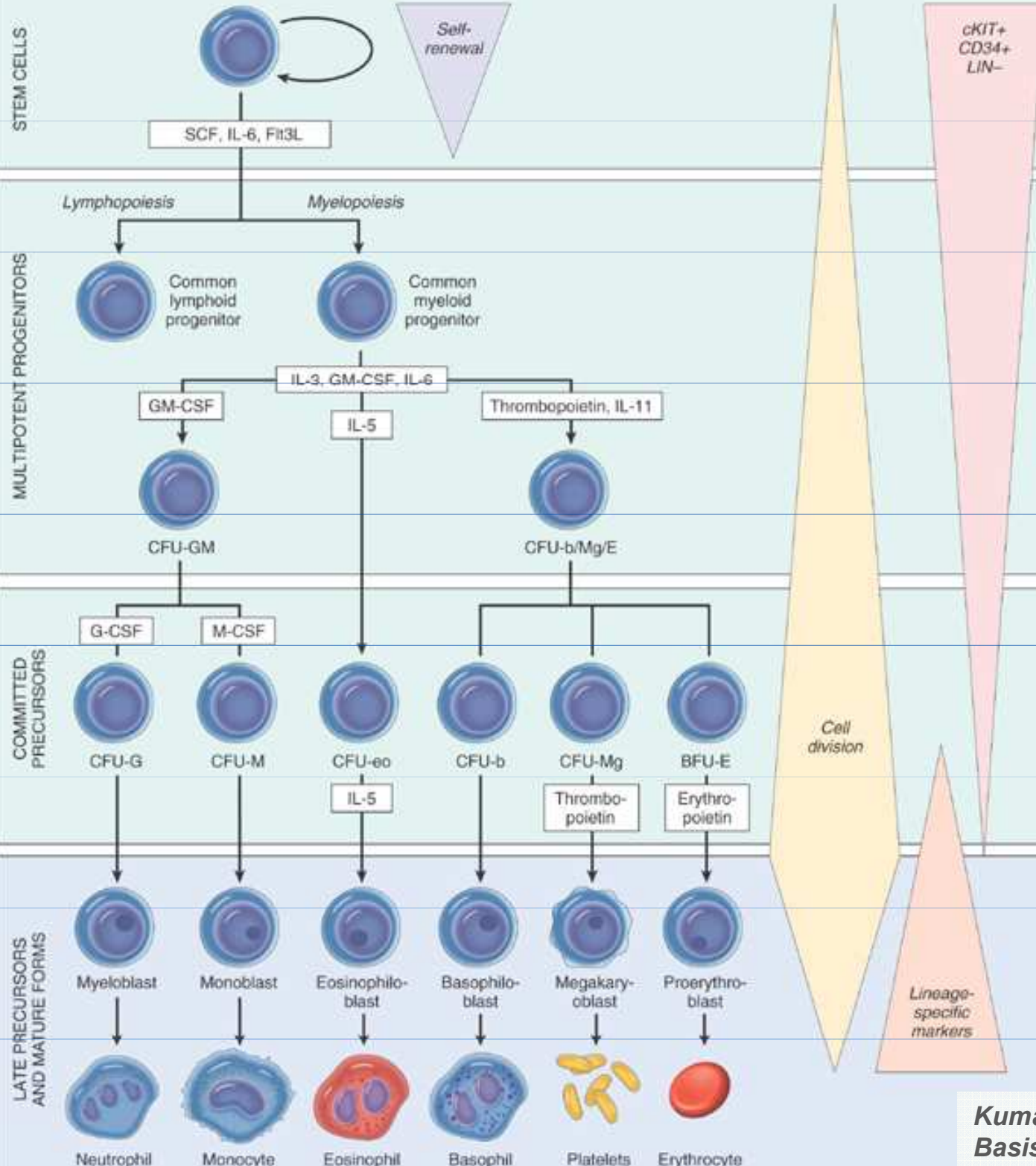
- ✘ After long-standing lymphedema possible evolution of malignant vessel tumor – angiosarcoma
- ✘ Signs: reddish-blue and dark nodules, rapid growth, bleeding, ulceration
- ✘ Bad prognosis

Tissue changes in lymphedema

- ✘ Hypoxemia, loss of functional cells
- ✘ Proliferation of connective tissue cells (fibroblasts)
- ✘ Production of collagen fibers
- ✘ Fibrotic changes, sclerosis and induration
- ✘ Fatty tissue increase

Hematopoiesis

- from **hematopoietic stem cell**
- **HSCs (Hematopoietic Stem Cells): pluripotent, ability of self-renewal (replication)**
 - ⇒ *due to asymmetric cell division variable progenitor cells arise :*
 - **phenotypically identical cells – HSCs**
 - **phenotypically different cells – multipotent cells (progenitors of myeloid cell line or progenitors of lymphoid cell line)**
 - *Regulation of hematopoiesis through specific growth factors*



Hematopoietic stem cells

- in BM (<0,1% of cells)

Multipotent progenitors

Multipotent progenitors

Committed precursors

Late precursors and mature forms

- morphologically differentiated

Possible signs of hematologic disorders

- × Congestion
- × Infarction
- × Thrombosis, embolism
- × Bleeding, bruising
- × Lymphadenopathy
- × Splenomegaly
- × Fatigue, dyspnoea
- × Edema:
 - ⇒ *lymphedema*
 - ⇒ *cerebral edema*
 - ⇒ *inflammatory edema*
 - ⇒ *pulmonary edema*

Emergency disorder

- ✘ **Shock:** acute circulatory failure causing hypoperfusion of vital organs
- ✘ **Cardiogenic or hypovolemic**
 - ⇒ *Hypotension*
 - ⇒ *Rapid, weak pulse*
 - ⇒ *Pallor*
 - ⇒ *Moist, cooler skin*
 - ⇒ *Bleeding foci possible, if shock due to bacterial toxemia (pinpoint bleeding into the skin)*

Shock

- x** Ischemic injury of multiple organs
- x** Serious clinical problem, commonly fatal
- x** Consequences:
 - ⇒ *Renal failure*
 - ⇒ *Acute pancreatitis*
 - ⇒ *Irreversible neuronal injury, risk of cerebral infarction*
 - ⇒ *Risk of myocardial infarction*
 - ⇒ *Lung insufficiency – acute respiratory distress syndrome*

Multiorgan failure (MOF) possible

Hematologic disorders

- ✘ Alteration of the oxygen-carrying capacity of the blood
- ✘ Changes of the structure, consistency of the blood
- ✘ Alteration of the blood flow

- ✘ Increased workload of the heart and/or lungs
- ✘ Alteration of tissue perfusion
- ✘ Increased risk of thrombosis
- ✘ Increased risk of bleeding

Modifications of therapy according to the blood + other tests necessary

Disorders of erythrocytes (RBC)

Anaemia

Reduction of the oxygen-carrying capacity of the blood due to decreased quantity and/or quality of RBC

- × **Posthemorrhagic**: trauma, cancer (GIT, urinary, genital, lung), ulcers, varices, coagulopathy...
- × **Hemolytic** (destruction of RBC): mechanical (artificial heart valve), autoimmune, inborn defects (of hemoglobin etc.), infection (malaria), hypersplenism
- × **Decreased production of RBC**: nutritional deficiency; bone marrow failure – due to neoplasia, drugs (antineoplastic), endocrine disorders; chronic diseases – anaemia of inflammation

Implications for the therapist

- × Diminished exercise tolerance + easy fatigability
- × Combination with other problems common (cardiovascular, renal, ...)
- × Risk of combination with bleeding disorders - !manual therapy
- × Impaired healing of wounds
- × Monitoring of vital signs and mental status necessary
- × In young athletic clients iron-deficiency anemia possible (females, dietary choices, drugs, etc.)

Disorders of leukocytes

Leukocytosis

↑ number of WBC, usually of specific group

- × Acute haemorrhage (after 1-2 hrs)
- × Infection (mostly bacterial for neutrophils, viral for lymphocytes)
- × Inflammatory reaction in tissue necrosis, trauma
- × Immune-mediated disorders (incl. allergic reaction – eosinophils)
- × Malignancies, incl. hematologic
- × Reaction to stress, incl. exercise

Disorders of leukocytes

Leukopenia

- × ↓ number of WBC ($\leq 5000/\text{ml}$)
- × Infection (HIV, other viruses – destruction of WBC)
- × Alcohol
- × Nutritional status
- × Drugs (antineoplastic, immunosuppressive, NSAID, antibiotic)
- × Malignancies incl. hematologic, carcinomas
- × Radiation therapy

Implications for the therapist

Immune deficiency – risk of infection!

Disorders of hemostasis

- × **Von Willebrand disease** – problems in formation of the primary platelet plug
- × **Hemophilia** – lack of clotting factor for secondary hemostasis; arthropathy, spontaneous bleeding, major bleeding after minor trauma
- × **Acquired coagulopathy** – common due to therapy (aspirin, antithrombotic drugs)
- × **Thrombocytopenia / thrombocytopathy** – mucosal bleeding common, easy bruising, heavy menstruation bleeding, GIT bleeding

Implications for the therapist

- ✘ Individual exercise planning according to the client stage

TUMORS of HAEMATOPOETIC and LYMPHATIC TISSUES

- ✘ Broad spectrum of entities
- ✘ **WHO classification**
 - clinical, morphologic, immunophenotypic and genetic features defining distinct diseases.

Etiopathogenesis of hematooncological diseases

- **???**
- **hereditary syndromes**
 - *Inherited genetic instability (Bloom's sy, ataxia teleangiectasia...), Down's sy, NF type I...*
- **oncogenic viruses**
 - *HTLV-1, EBV, HSV-8*
- **chronic stimulation of immune system**
 - *Helicobacter pylori, gluten-sensitive enteropathy (celiac sprue)*
- **iatrogenicity**
 - *radiotherapy, chemotherapy*
- **smoking**

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,....), tissue infiltration → organ enlargement without solid foci.*

Hematooncology

- **Lymphoma (hemoblastoma)**
 - *Neoplastic/lymphoma cells form tumor/neoplastic mass (nodal and/or extranodal)*
 - *solid tumorous foci, dissemination in form of metastasis. Usually lymphoid origin, rare histiocytic*
- ! Lymphomas may also present by leukemic infiltrates and leukemias also form solid neoplastic masses

Hematooncological diseases classification

× Myeloid neoplasms

- Monoclonal proliferations from stem cells that normally give rise to the formed blood elements
- Replacement of normal bone marrow
- 3 categories
 - acute myelogenous leukemias
 - myeloproliferative disorders
 - myelodysplastic syndromes

× Lymphoid neoplasms

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

× Histiocytic neoplasms

Hematooncology

- ✘ **Myeloid neoplasms**
- ✘ Cells of the myeloid line
(erythrocytes, granulocytes, monocytes, platelets)
- ✘ Primary involvement of bone marrow
(secondary spleen, liver and lymph nodes)

Hematooncology

✘ **General clinical signs in acute leukaemia**

rapid onset; marrow failure →

- ✘ Anaemia (fatigue, dyspnea, palor)
- ✘ Neutropenia (bacterial, fungal infection – fever, repeated oral/respiratory inflammation),
- ✘ Thrombocytopenia (bleeding, epistaxis, haematomas)

- ✘ Weight loss (increased cell turn-over)
- ✘ Hepatomegaly, splenomegaly (compression of adjacent organs)

Hematooncology

- ✘ **Acute myeloid (myeloblastic) leukaemia**
- ✘ primarily in older adults (median age 50), incidence rises with age
- ✘ leukemic infiltrates in bone marrow, liver, spleen, lymph nodes
- ✘ possible solid tumor manifestation (myeloid sarcoma)
- ✘ generally poor prognosis

Hematooncology

- ✘ **Myelodysplastic syndromes**: clonal stem cell disorders, ineffective haematopoiesis → cytopenias; dysplastic maturation. De novo or after radio/chemotherapy. Progressive marrow failure. May → AML.
- ✘ **Myelodysplastic/myeloproliferative diseases** overlapping features, variably effective haematopoiesis, dysplasia

Hematooncology

✘ **Chronic myeloproliferative diseases**

clonal stem cell disorders – hypercellular marrow with maturation, no dysplasia, effective haematopoiesis → elevated blood levels of one or more cell lines, usually hepatosplenomegaly, lymphadenopathy

✘ chronic myeloid (myelogenous) leukaemia

✘ essential thrombocythaemia

✘ polycythaemia vera (rubra) (RBC)

✘ chronic idiopathic myelofibrosis

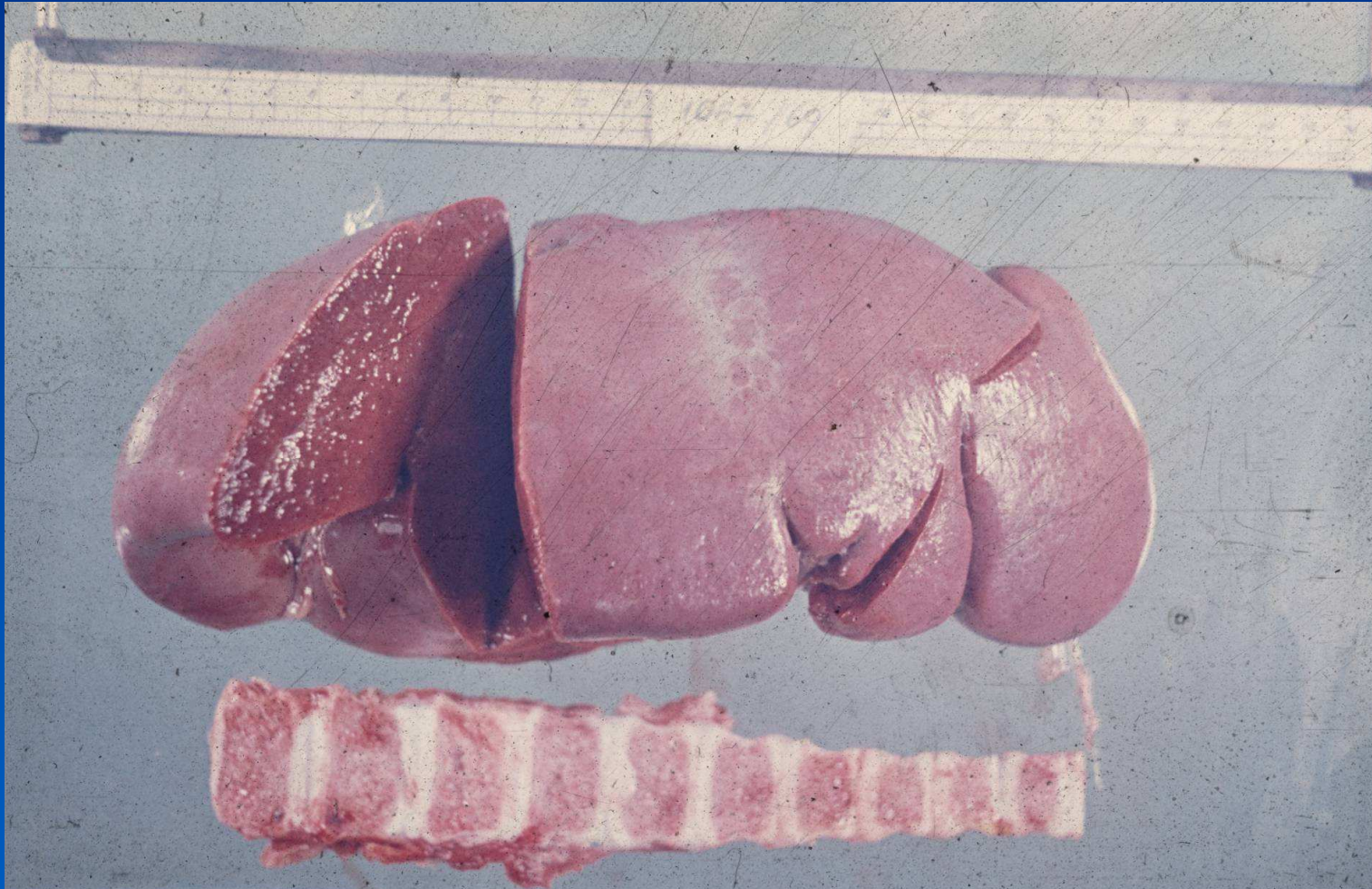
Chronic myelogenous leukemia

- × adults, peak incidence in 4th and 5th decade
- × elevated leukocyte count
- × 15-20% all leukaemias
- × huge spleen (~5-7 kg), liver enlargement
- × 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, specific drug available

CML in the liver



CML – splenomegaly, spine infiltrates



Implications for the therapist

Leukemia

Problems due to neoplasia + therapy

Immune deficiency – risk of infection!

Thrombocytopenia – bleeding

Anaemia

Other possible side effects of therapy (mood changes; muscle weakness in corticosteroid therapy)

Joint problems (arthralgia, arthritis)

Exercise necessary for improvement in health-related quality of life, mental health, reduced symptoms

Hematooncology

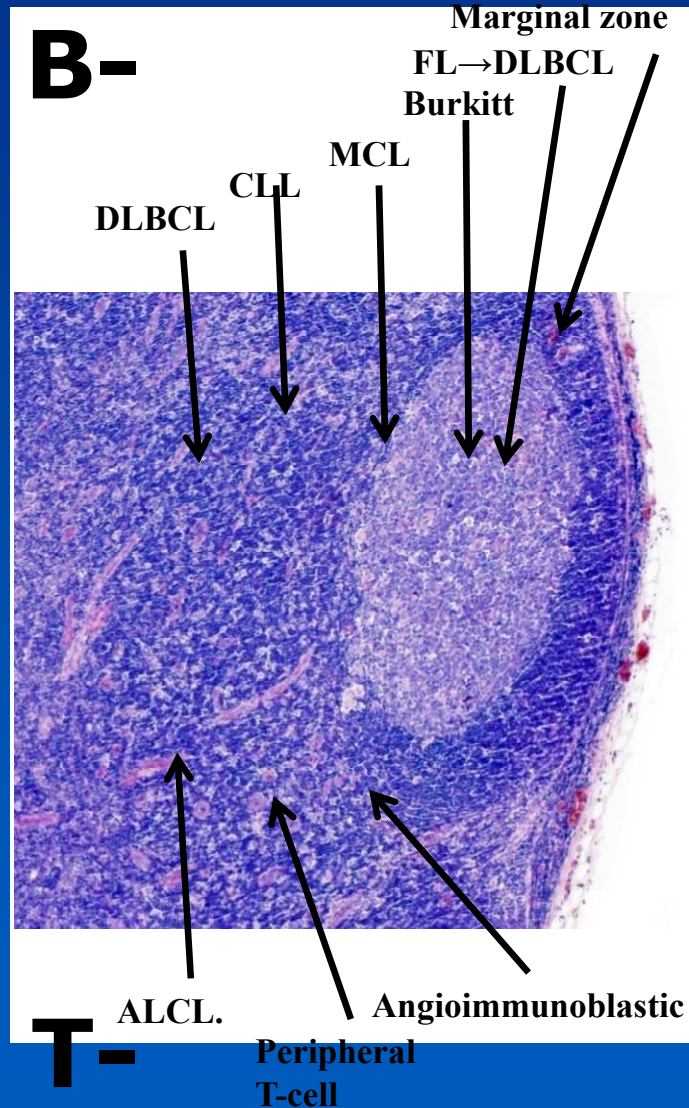
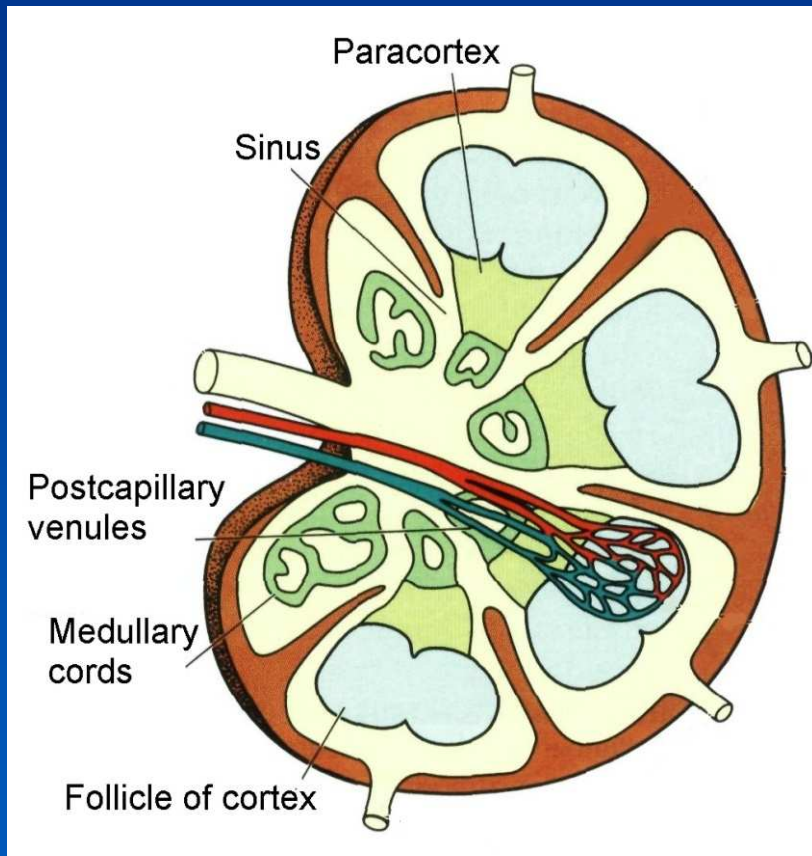
- × *Histiocytic and dendritic cell neoplasms*
- × from mononuclear phagocytes – common bone marrow precursor
- × follicular dendritic cells non-myeloid, from mesenchymal stem cell
- × true histiocytic neoplasm uncommon (Langerhans cell histiocytosis)

Non-Hodgkin lymphomas/ WHO classification

B-Cell Neoplasms	T-Cell Neoplasms
Precursor B-Cell Neoplasms - precursor B-cell leukemia/lymphoma (B-cell acute lymphoblastic leukemia)	Precursor T-Cell Neoplasms - precursor T-cell leukemia/lymphoma (T-cell acute lymphoblastic leukemia)
Peripheral B-Cell Neoplasms	Peripheral T-/NK-Cell Neoplasms

Nodal lymphomas

*different cell type/stage of immunologic maturation →
different lymphoma type*



B-cell acute lymphoblastic leukemia/lymphoma (B-ALL)

- **most frequent malignancy in children (peak at age 4)**
- Infiltration of **bone marrow, lymph nodes, liver, spleen...**
- **Highly aggressive, but chemosensitive**
(⇒ children 2 to 10 years – best prognosis)
 - ⇒ chemo-, radiotherapy generally carcinogenic in itself
 - ⇒ ! increased risk of secondary malignancy (other type of leukemia/lymphoma, lung cancer, etc.) after several years - decades

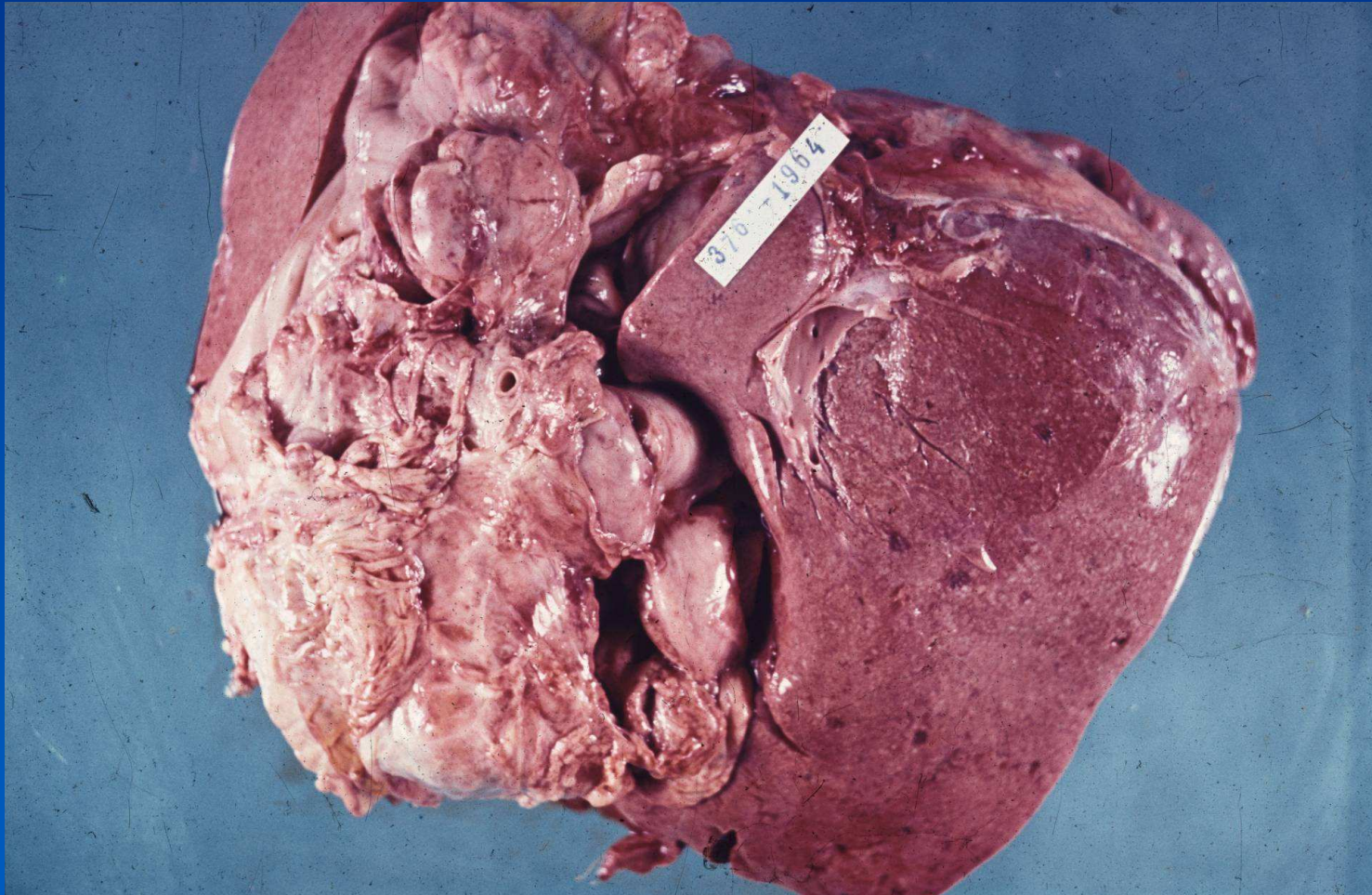
Peripheral B-cell lymphomas (selected)

- x**Chronic lymphocytic leukemia / small cell lymphoma
- x**Follicular lymphoma
- x**MALT lymphoma
- x**Plasma cell neoplasms
- x**Diffuse large B-cell lymphoma

Chronic lymphocytic leukemia (CLL)

- ✘ Mature B-cell neoplasm, same cellular morphology and genotype in small lymphocytic lymphoma (in CLL lymphocytosis in peripheral blood)
- ✘ Most common chronic leukaemia, common protracted course (~10 yrs), in >50 yrs old. Possible transformation to high grade ML
- ✘ Hypercellular bone marrow, generalised lymphadenopathy, hepatosplenomegaly

CLL- hepatic and nodal infiltrates



Follicular lymphoma

- ✗ Mature B-cell non-Hodgkin lymphoma;
- ✗ common type (40%)

- ✗ Neoplasia of follicle centre B-cells In LN - predominantly follicular pattern, sm. diffuse. May be in spleen, Waldeyer's ring,...

Follicular lymphoma

- ✘ Clinically: nontender generalised lymphadenopathy, commonly widespread disease at diagnosis (incl. liver, bone marrow), middle → late age adults.
- ✘ Low grade – longer course (5-10 years), usually incurable
- ✘ High grade – aggressive, potential for cure (remission), but possible transformation into diffuse large B-cell lymphoma

Spleen, follicular lymphoma



Extranodal marginal zone lymphoma (MALT lymphoma)

- **derived from mucosa-associated lymphatic tissue** (salivary glands, thyroid, stomach, intestine, ...)
- **chronic stimulation of immune system**
 - e.g.: chronic gastritis associated with *Helicobacter pylori* (HP) infection
 - some autoimmune inflammations (thyroiditis, salivary glands, ...)
- **low grade/aggressive lymphoma**

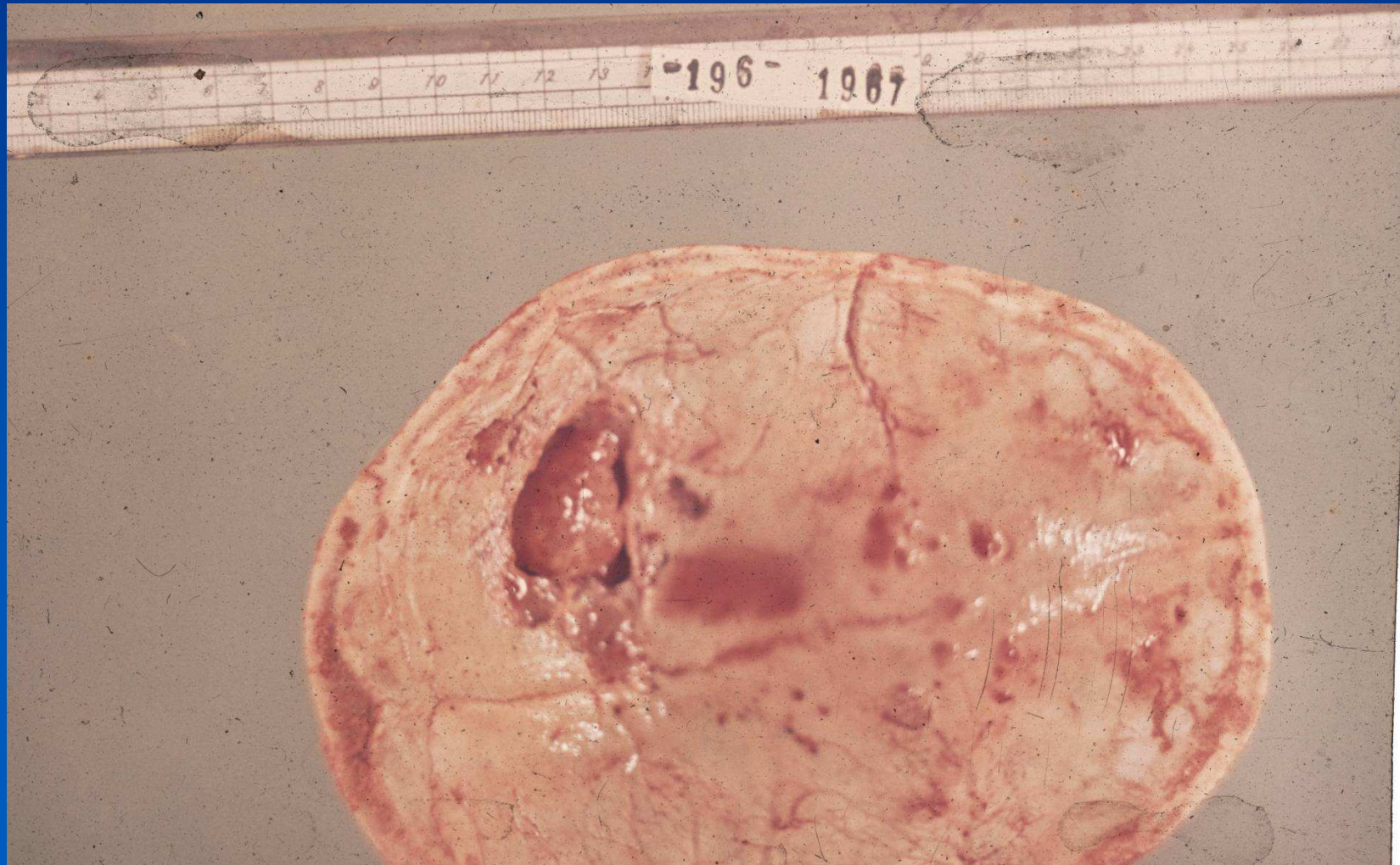
Diffuse large B-cell lymphoma *(DLBCL)*

- **older adults**, most frequent lymphoma
- **highly aggressive**
- *de novo* or high grade transformation of low grade lymphoma (CLL, FL, MALToma...)
- nodal or **extranodal** (tonsil, adenoid lymphatic tissue, GIT, skin, bones, thyroid, ...)

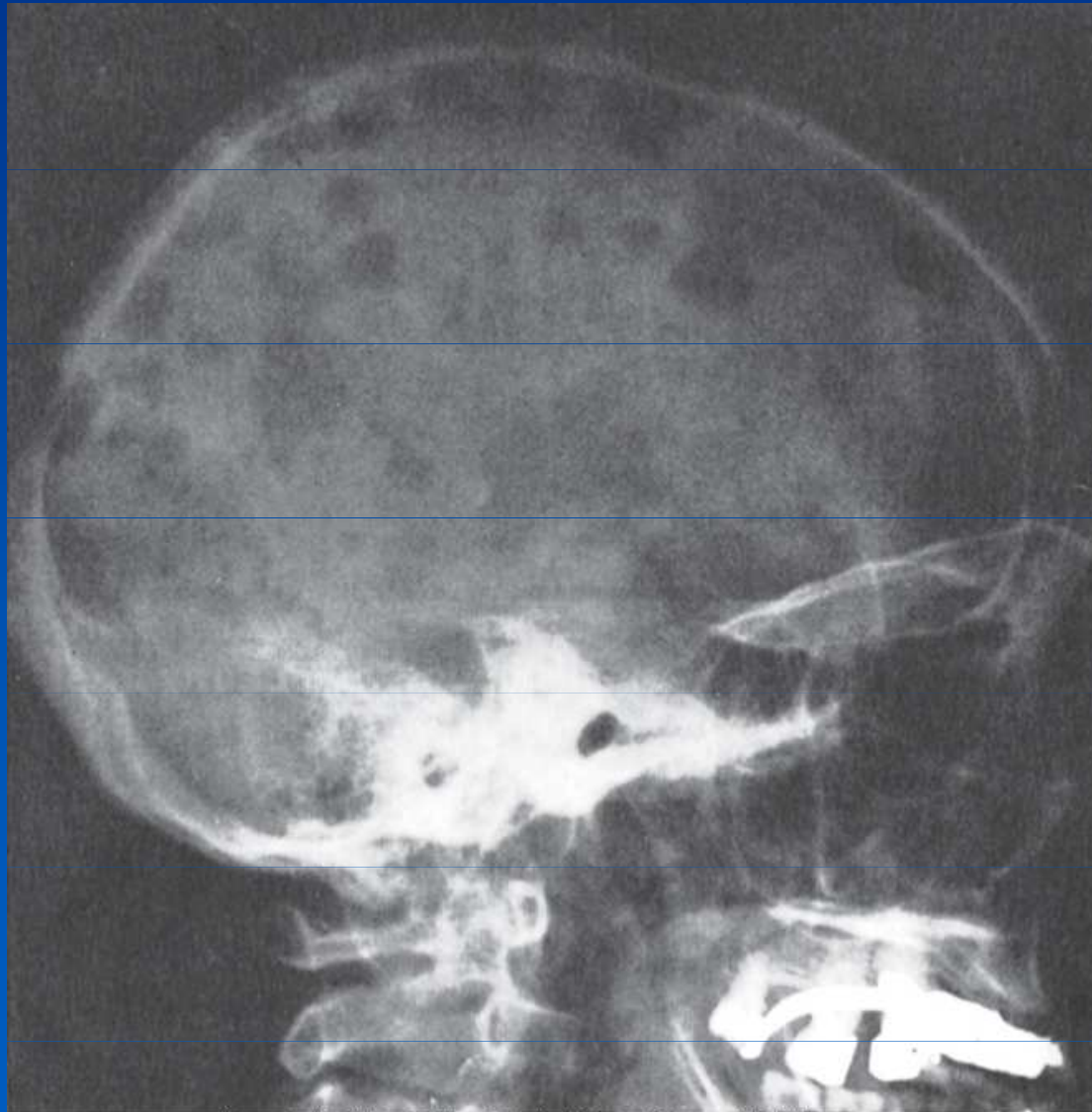
Plasma cell neoplasms

- ✘ Included in mature B cell neoplasms, clonal prolifer. of immunoglobulin secreting end-stage B cell. Most common plasma cell (multiple) **myeloma**
- ✘ Bone marrow-based, multifocal, in older adults, destructive skeletal (osteolytic) lesion, common in foci of active haematopoiesis (vertebrae, ribs, skull, ...)
- ✘ Pathological fractures, hypercalcaemia, anaemia
- ✘ Renal complications

Multiple myeloma in skull



Multiple myeloma in skull – X-ray



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.
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Multiple myeloma in spine



T-cell lymphomas

(selected entities)

- Generally uncommon
- Possible origin in the skin
 - *unusual chronic relapsing „dermatitis“*
- **Mycosis fungoides/Sézary syndrome**
 - *MF: Primary skin lymphoma*
 - *SS: leukemized, erythroderma*
- **Anaplastic large cell lymphoma**

Hodgkin lymphoma

- ✗ One of most common malignancies in young adults
- ✗ Non-tender lymphadenopathy (origin in LN), commonly cervical or axillary; usually localised at presentation (1-2 LN groups); in 30% systemic signs (high fever, night sweats, weight loss)
- ✗ Continual spread from one group of LN to the next one, diaphragm important barrier for staging, late extralymphatic spread

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

2 distinctive disease entities:

- ✘ **Nodular lymphocyte predominant HL:** 80% males, 30-50 yrs, large neoplastic „popcorn, L&H“ B cells among non-neoplastic ly
- ✘ Mostly localised at presentation, late relapse or transformation into DLBCL possible
- ✘ Stage I+II – 10 year survival in 80%

Hodgkin lymphoma

- × **classical Hodgkin lymphoma**

95% of HL, 1. peak 15-35 yrs, 2. elderly; risk factor EBV;
75% in cervical LN

- × 4. subtypes

- × variable types/numbers of neoplastic Reed-Sternberg cells in the infiltrate

- × RT, CHT → excellent prognosis, but risk of secondary malignancies (myelodysplastic sy, acute myeloblastic leukemia, lung ca)

Diagnostic cells of HL

copy



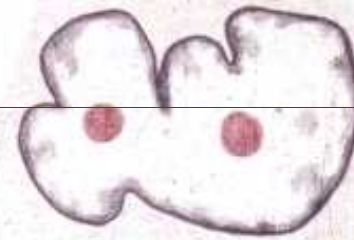
Sternberg c.



Hodgkin c.



Reed-Sternberg c.



Lacunar c.



L&H c.

Hodgkin lymphoma – splenic infiltrates



Implications for the therapist

- × Lymphadenopathy (diagnosis)
- × Infection control
- × Mobility + gait training
- × Aerobic conditioning
- × Respiratory rehabilitation
- × Lymphedema management
- × Special management in multiple myeloma: muscle wasting, risk of pathological fractures