Leukemia. Lymphomas. (WHO classification)

Markéta Hermanová

- **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

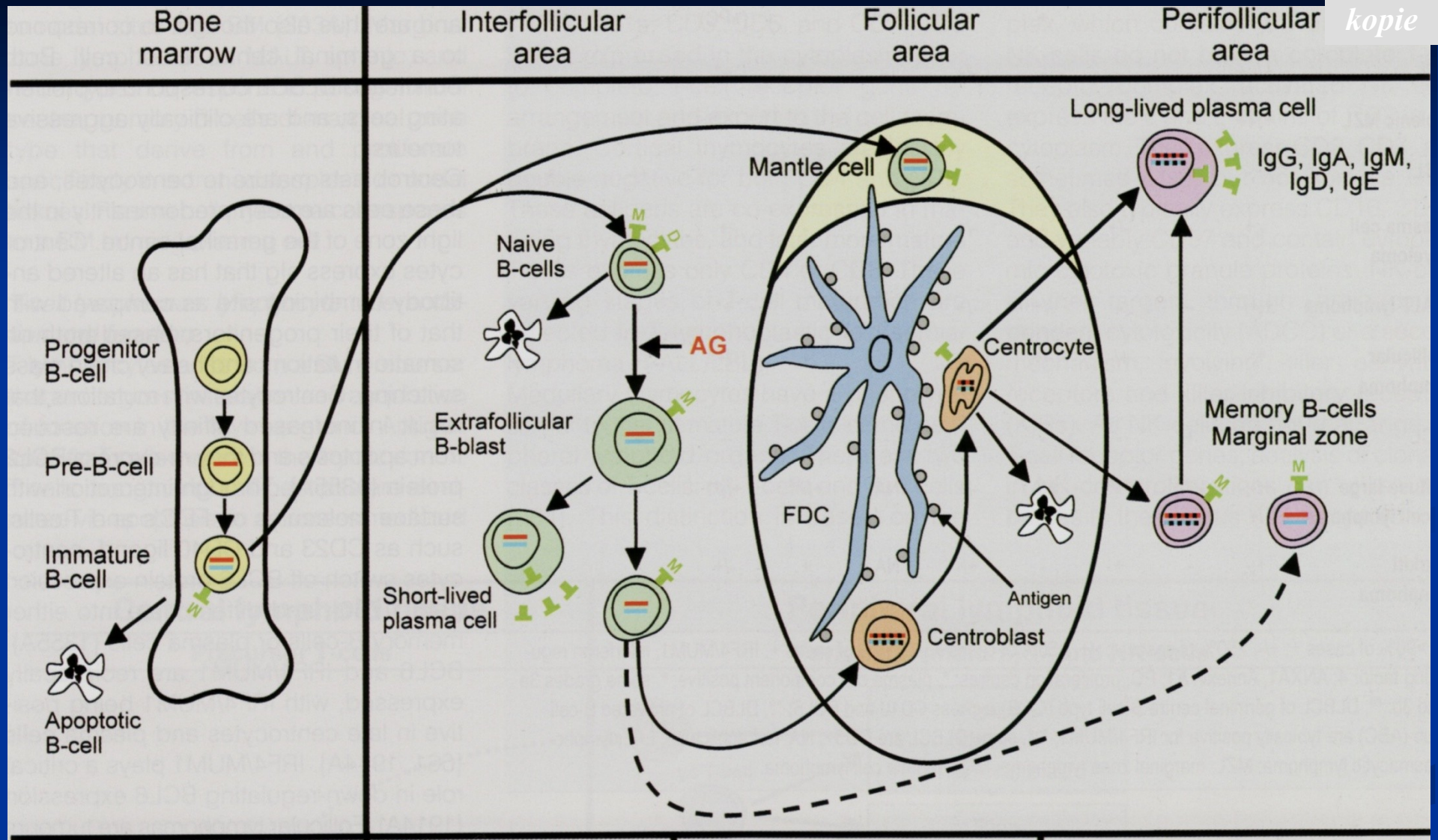
→ **acute myelogenous leukemias**
→ **myeloproliferative disorders**
→ **myelodysplastic syndromes**

- **Lymphoid neoplasms/lymphomas**

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

- **Histiocytic neoplasms**

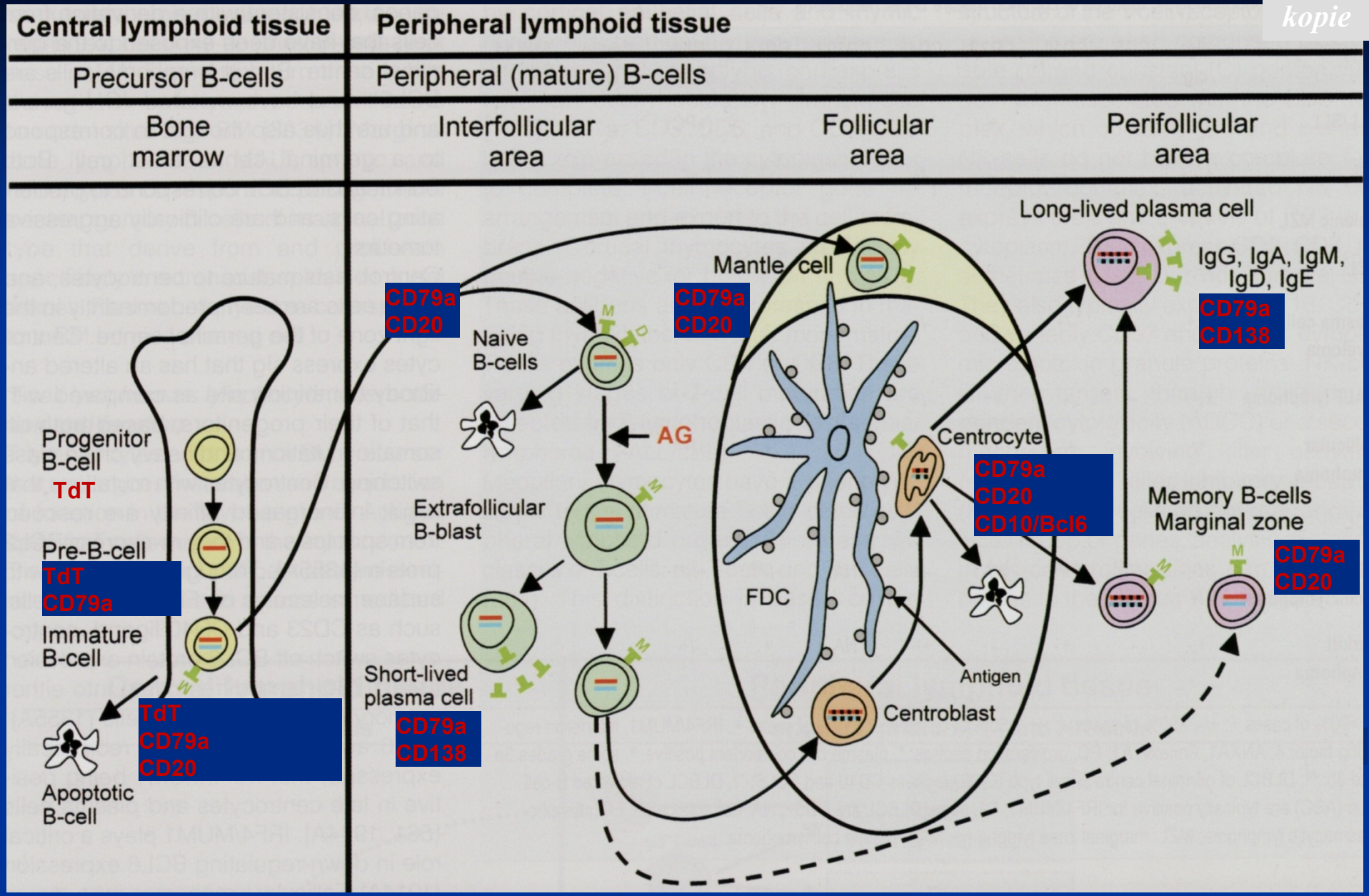
LYMPHOID NEOPLASMS (B-cell) – cells of origin



Precursor B-cell neoplasms	Pre-GC neoplasm	GC neoplasms	Post-GC neoplasms
B lymphoblastic leukaemia/lymphoma	Mantle cell lymphoma	Follicular lymphoma Burkitt lymphoma DLBCL (some) Hodgkin lymphoma	Marginal zone & MALT lymphoma Lymphoplasmacytic lymphoma CLL/SLL, DLBCL(some) Plasma cell myeloma

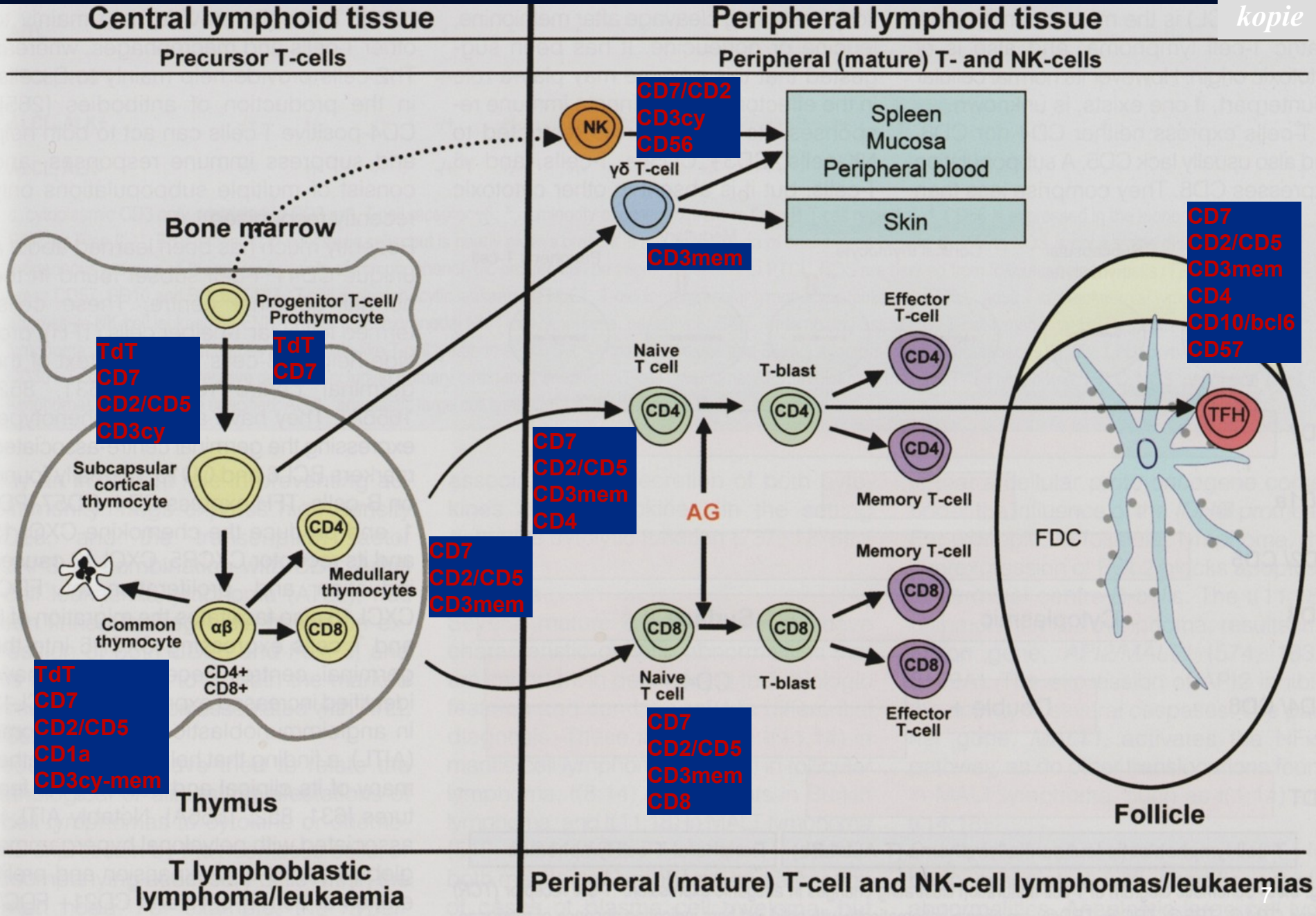
LYMPHOID NEOPLASMS (B-cell) — immunophenotype of cells of origin

kopie



T LYMPHOID NEOPLASMS – CELLS OF ORIGIN

kopie



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

Non-Hodgkin lymphomas/WHO classification

I. **Precursor B-Cell Neoplasms**

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

II. **Peripheral B-Cell Neoplasms**

- **B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)**
- B- prolymphocytic leukemia
- Lymphoplasmacytic lymphhoma
- **Follicular lymphoma (FL)**
- **Extranodal marginal zone lymphoma (MALT lymphoma)**
- **Mantle cell lymphoma (MCL)**
- Splenic and nodal marginal zone lymphoma
- Hairy cell leukemia
- **Plasmacytoma/plasma cell myeloma**
- **Diffuse large B-cell lymphoma (DLBCL)**
- **Burkitt lymphoma**

Non-Hodgkin lymphomas/WHO classification

III. **Precursor T-Cell neoplasms.**

- **T-cell acute lymphoblastic leukemia/lymphoma (T-ALL)**

IV. **Peripheral T-/NK-Cell Neoplasms**

- T- cell prolymphocytic leukemia
- **Mycosis fungoides/Sézary syndrome**
- **Peripheral T-cell lymphoma, NOS**
- Angioimmunoblastic T-cell lymphoma
- **Anaplastic large-cell lymphoma**
- **Enteropathy-type T-cell lymphoma**
- Panniculitis-like T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma
- NK/T-cell lymphoma, nasal type
- NK-cell leukemia
- **Adult T-cell leukamia/lymphoma (HTLV1)**

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

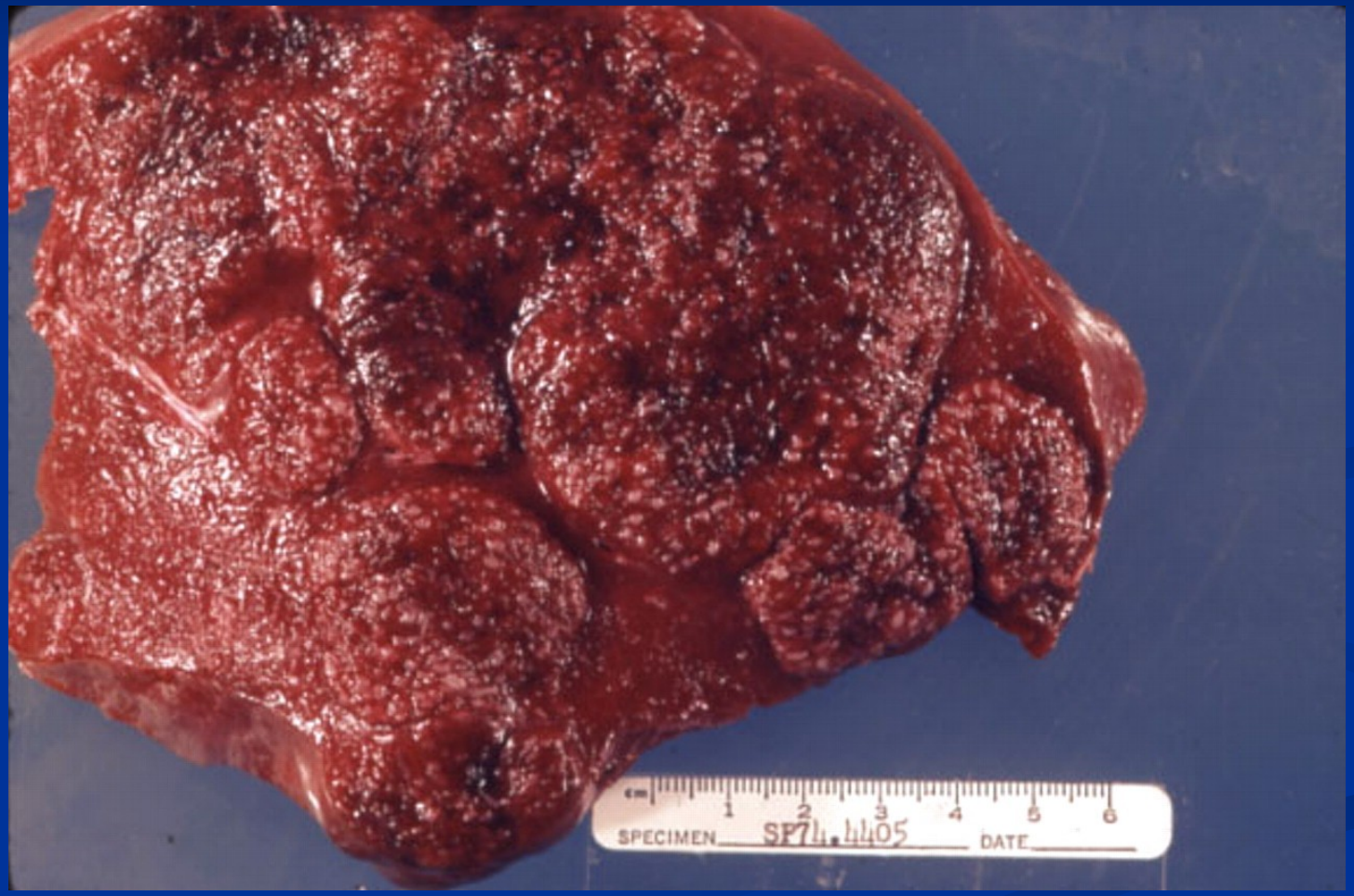
Neoplasms of mature B-cells (peripheral B cells neoplasms)

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

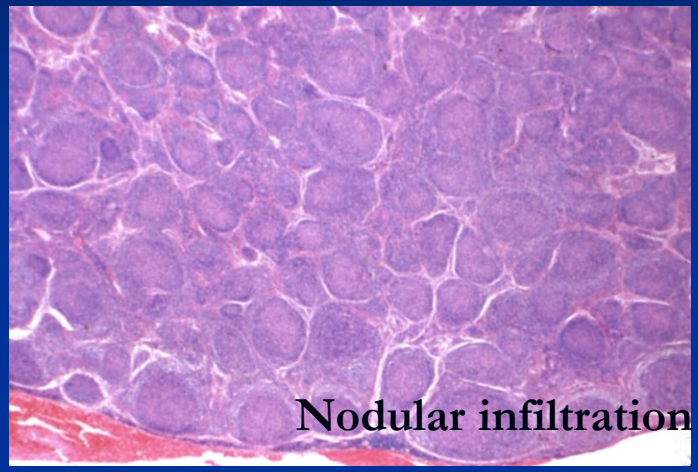
2. **Mantle cell lymphoma**
- naive B-cell of mantles (CD5+, cyclinD1+(promotesG1 to S phase progression)
- t(11;14); cyclinD1 locus/IgH locus
- older males, often extranodal (lymphomatous polyposis); moderately aggressive – resistent to therapy

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

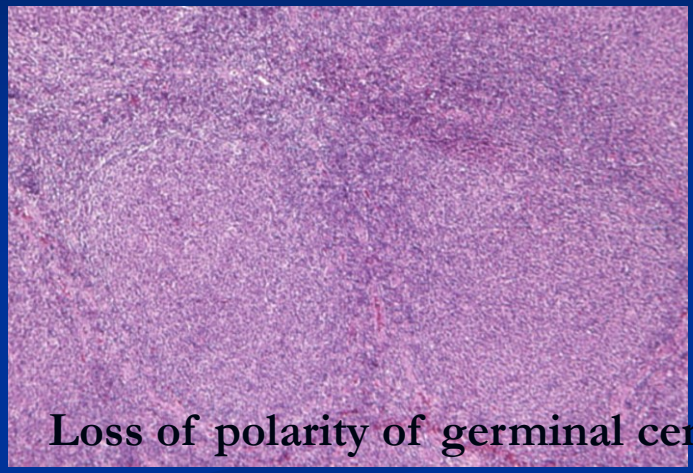
Spleen, follicular lymphoma



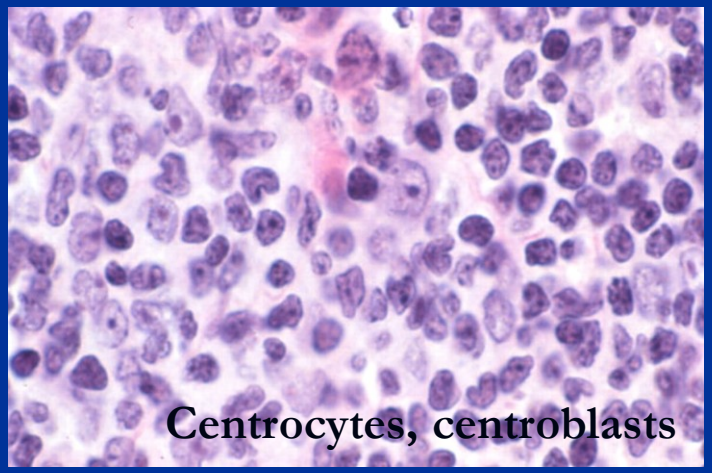
Follicular lymphoma



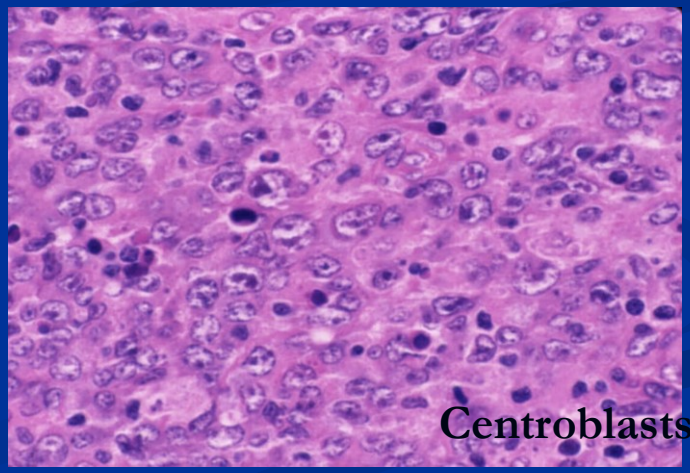
Nodular infiltration



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**

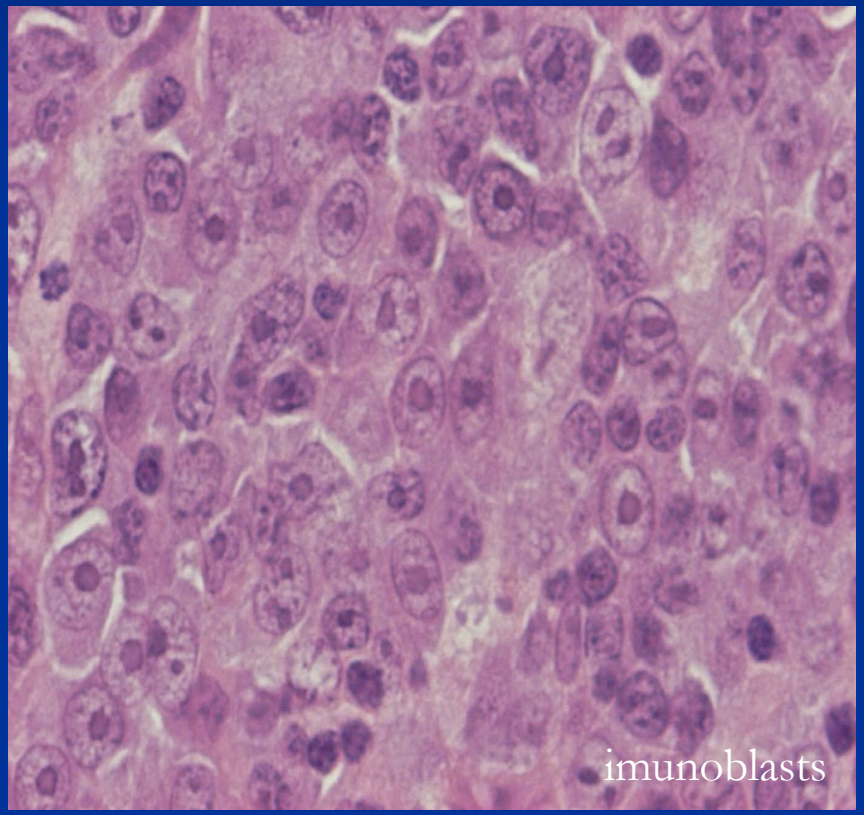
(African endemic (jaws); sporadic (intestinal); HIV+ related)

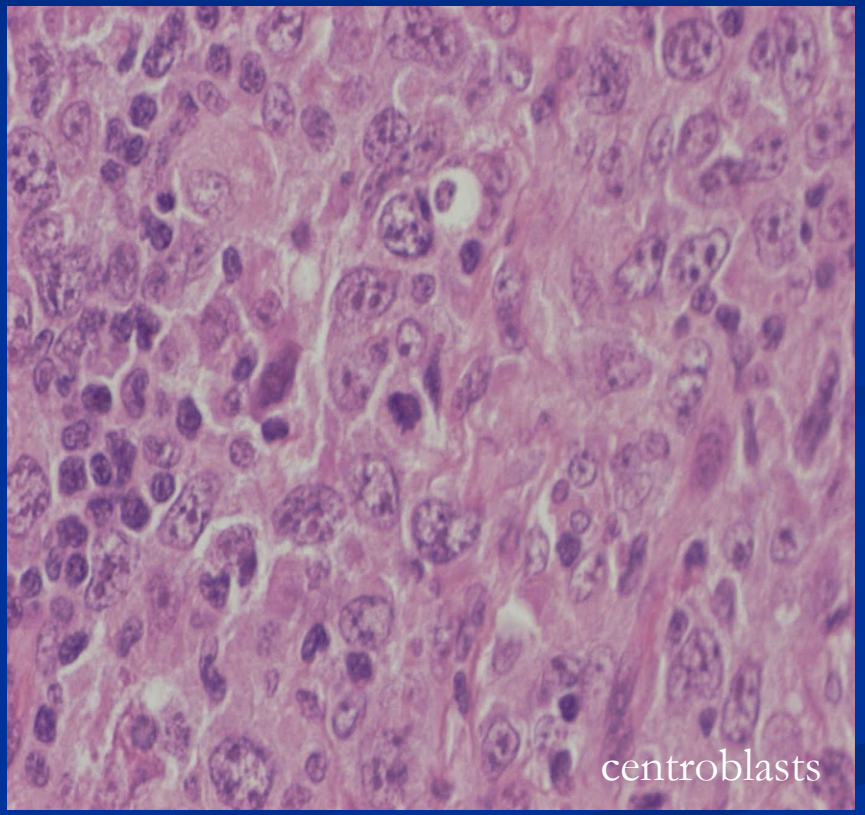
- germinal center B-cell (CD10+)?; „starry sky“ pattern; high mitotic rate, high apoptotic rate
- t(8;14) (c-myc/IgH), t(2;8) (c-myc/kappa light chains), t(8;22) (c-myc/lambda light chains)
- adolescents, young adults; aggressive, often association with EBV

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

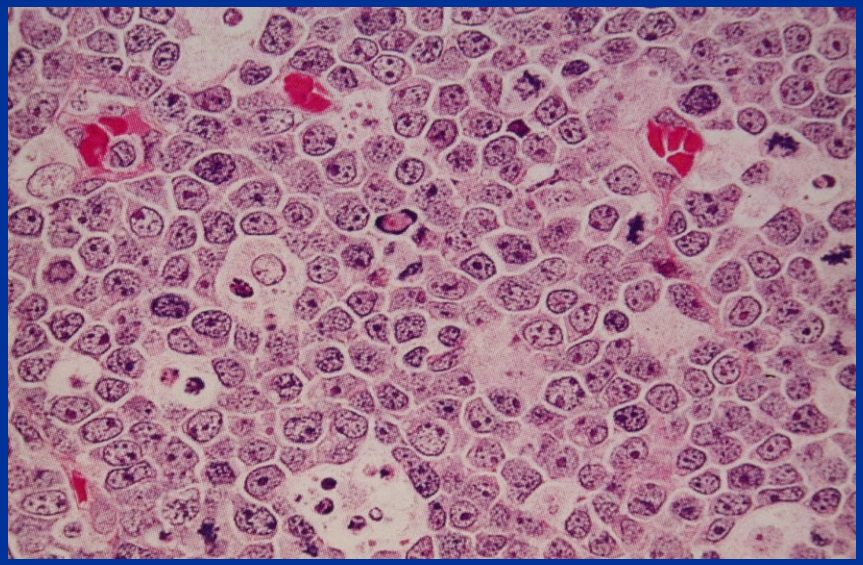
- postgerminal center memory B-cell
- extranodal in adults with chronic infalmmation (*Helicobacter pylori* gastritis, Sjogren´s syndrome, chronic lymphocytic autoimmune thyreoiditis,…); indolent, possible transformation into high grade lymphoma
- **+ nodal marginal zone B-cell lymphoma; + splenic marginal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

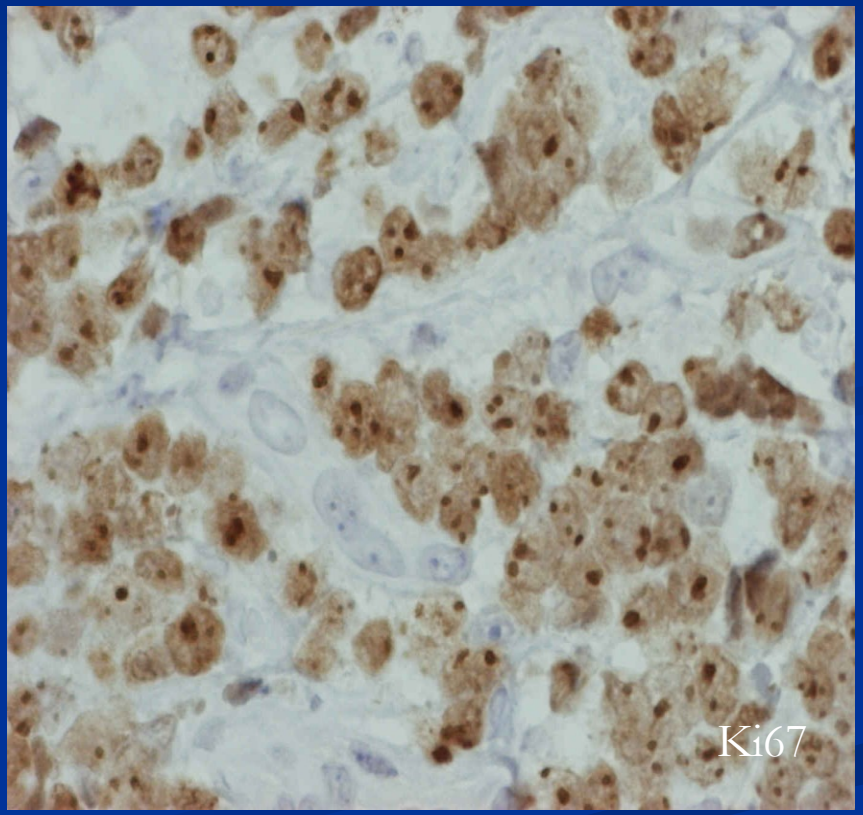
Diffuse large B cell lymphoma





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

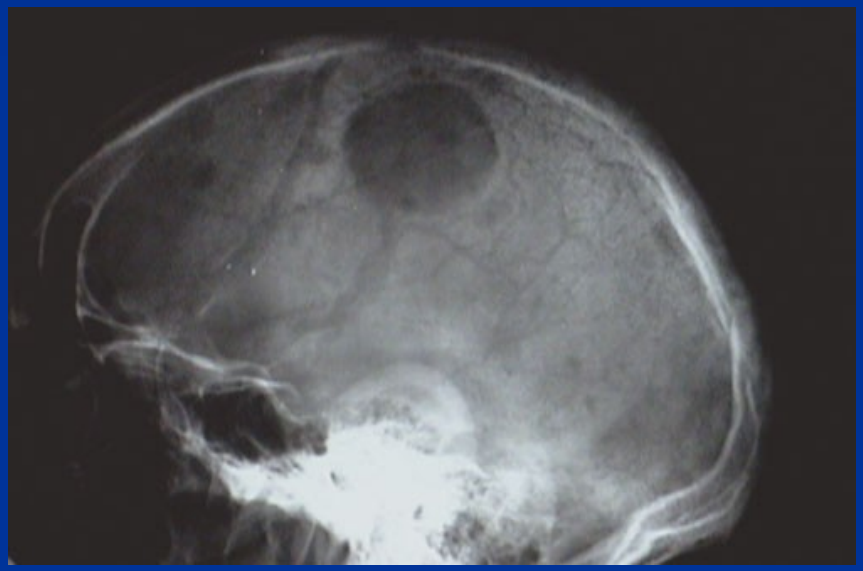
8. **Multiple (plasma cell) myeloma/plasmacytoma**

- 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**

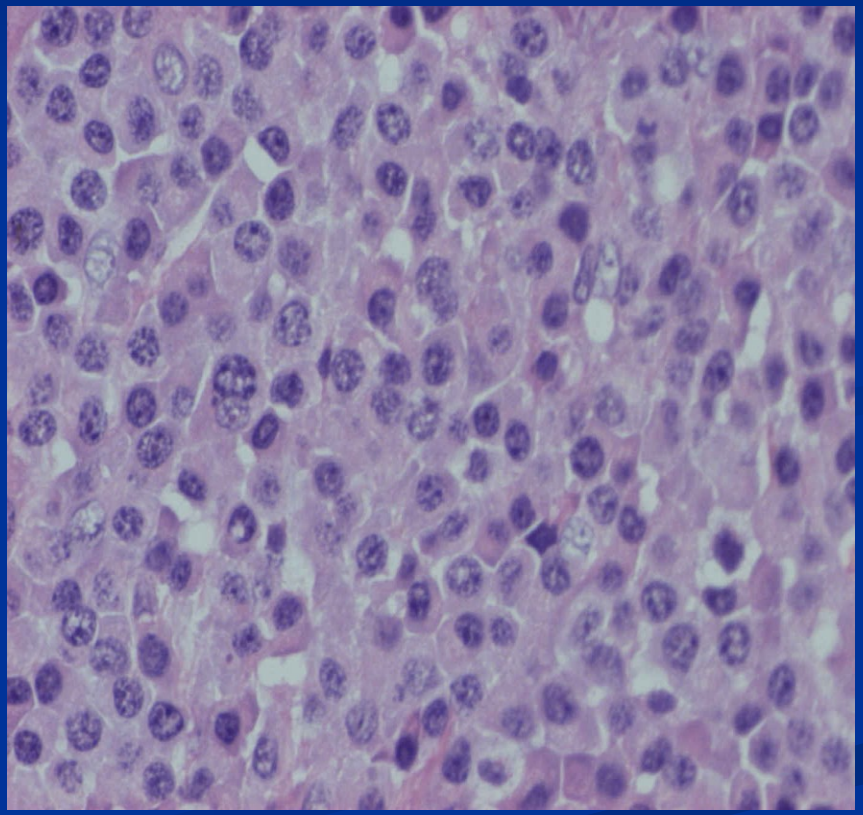
9. **Lymphoplasmacytic lymphoma**

- 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

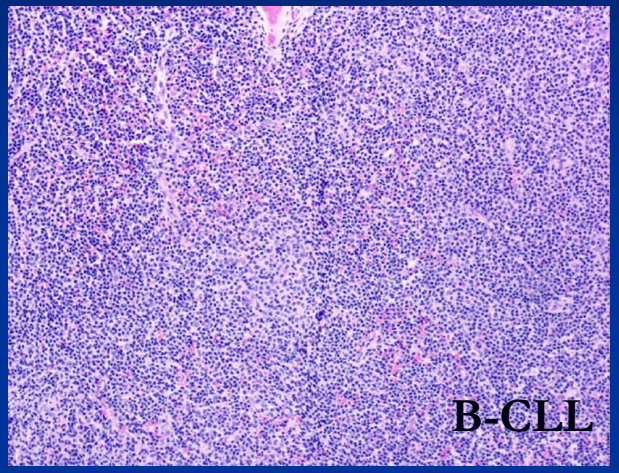


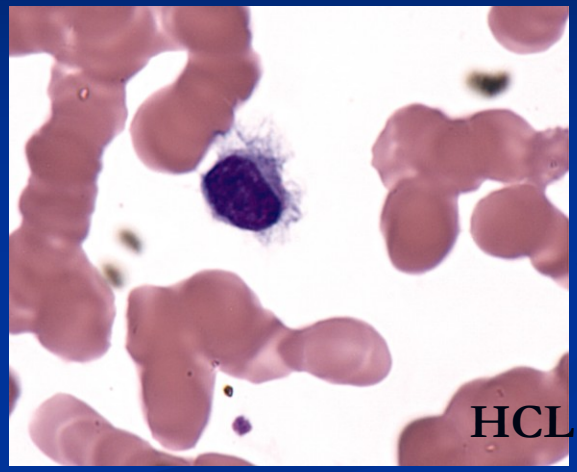
Osteolytic lesions

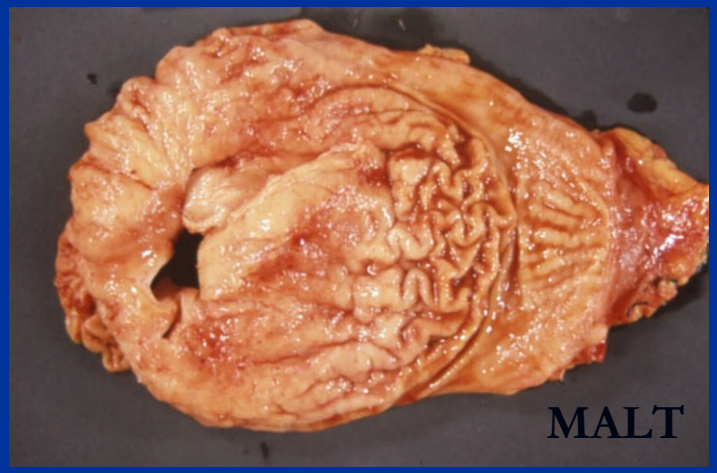


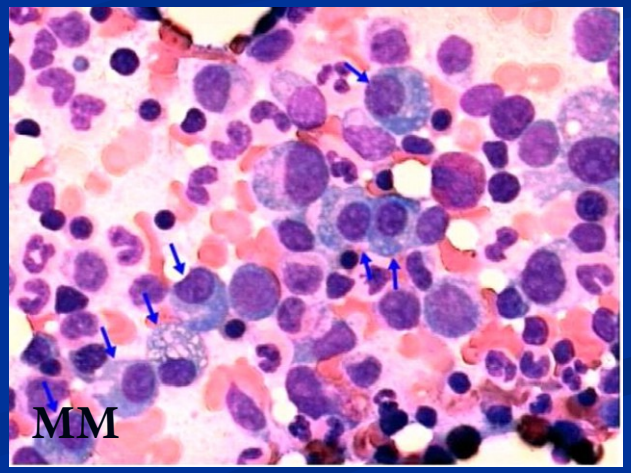
Infiltration by neoplastic plasma cells

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)

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

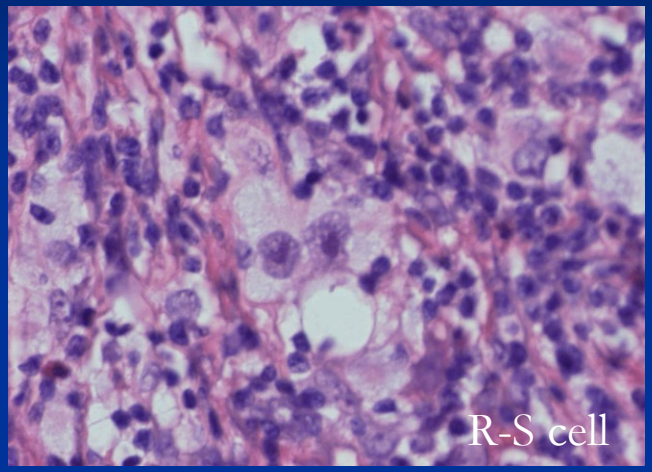
Clinical picture

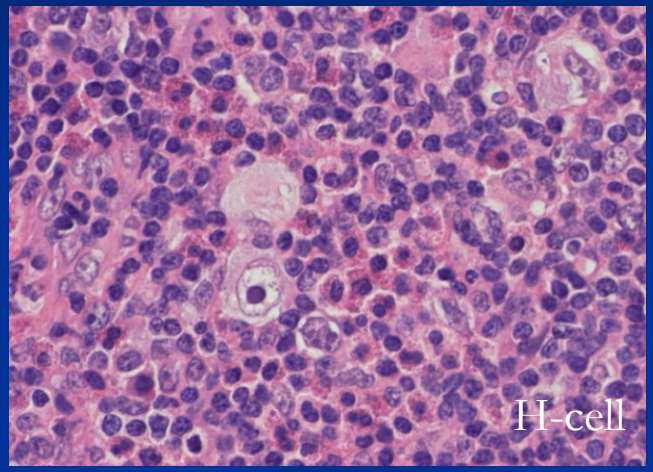
- Painless enlargement of lymph nodes (cervical, mediastinal, para-aortic: often localized to single axial group with spread by contiguity); mesenteric nodes and Waldeyer ring rarely involved, extranodal involvement uncommon
- Young patients
- Night sweats, weight loss

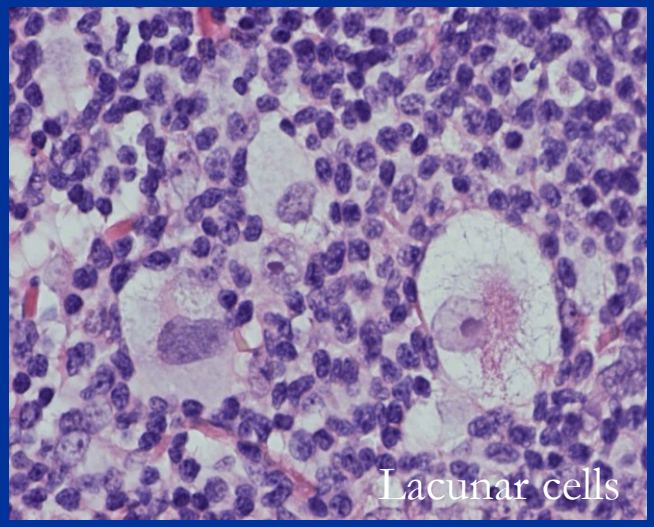
Neoplastic cells in classical HL

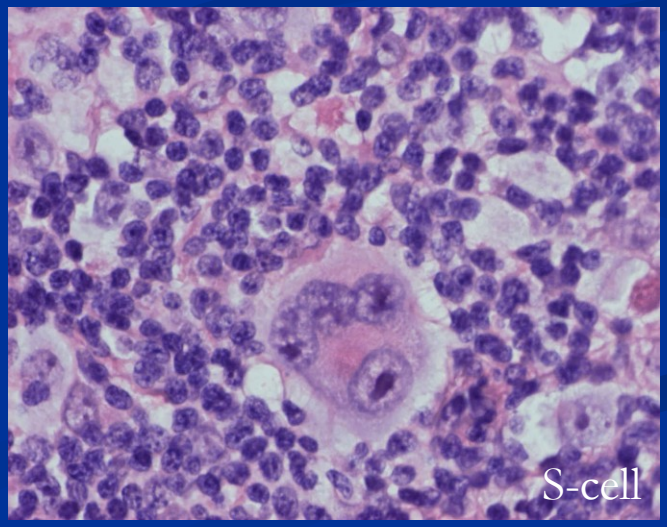
- Diagnostic Reed-Sternberg and Hodgkin cells (multiple or single nucleus)
- Lacunar cells

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

- multipotent myeloid stem cell
- increased marrow production of erythroid, granulocytic and megakaryocytic elements
- 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, increased risk of major bleeding and thrombosis
- transition into myelofibrosis
- development of AML (treatment related – alkylating drugs)

Thank you for your attention.