Leukaemias. Lymphomas. (WHO classification)

MARKÉTA HERMANOVÁ

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***

Tumour groups of haematopoeietic and lymphoid tissue

Lymphoid neoplasms/lymphomas

→ **non-Hodgkin lymphomas**

(including lymphocytic leukaemias and plasma cell dyskrasias)

→ **Hodgkin lymphomas**

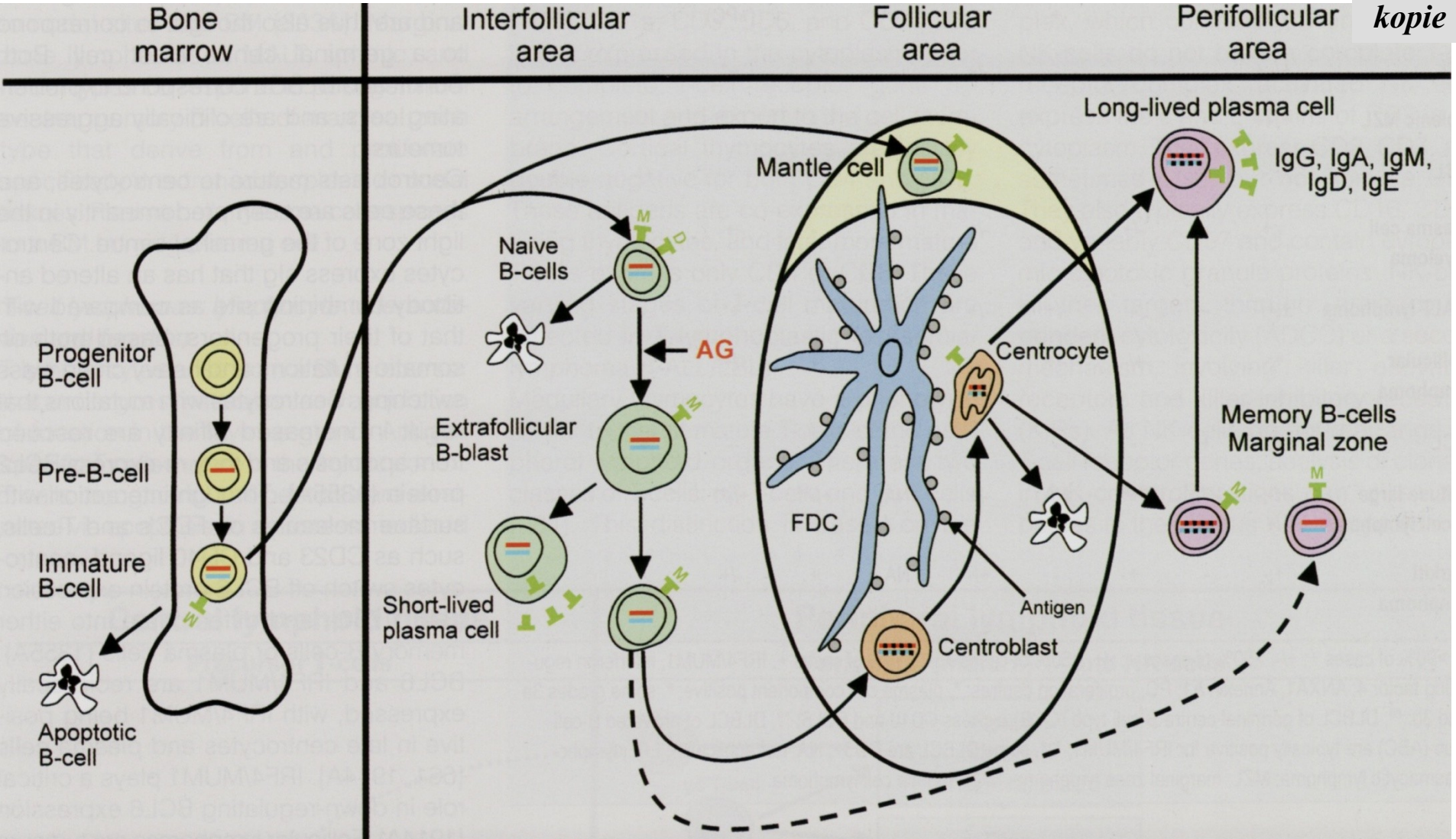
Myeloid neoplasms

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

Histiocytic neoplasms

Lymphoid neoplasms/lymphomas

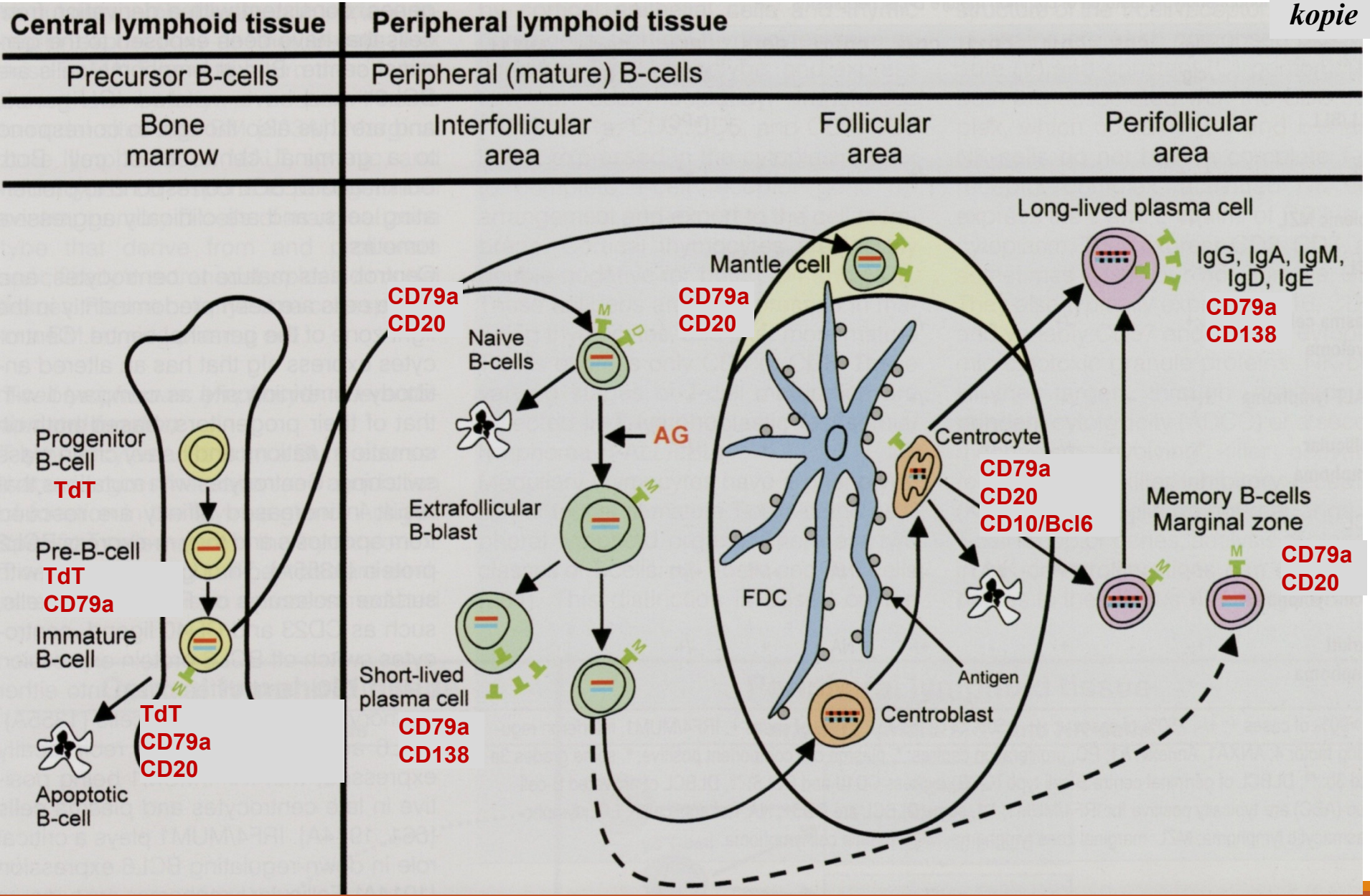
LYMPHOID NEOPLASMS (B-cell) – cells of origin



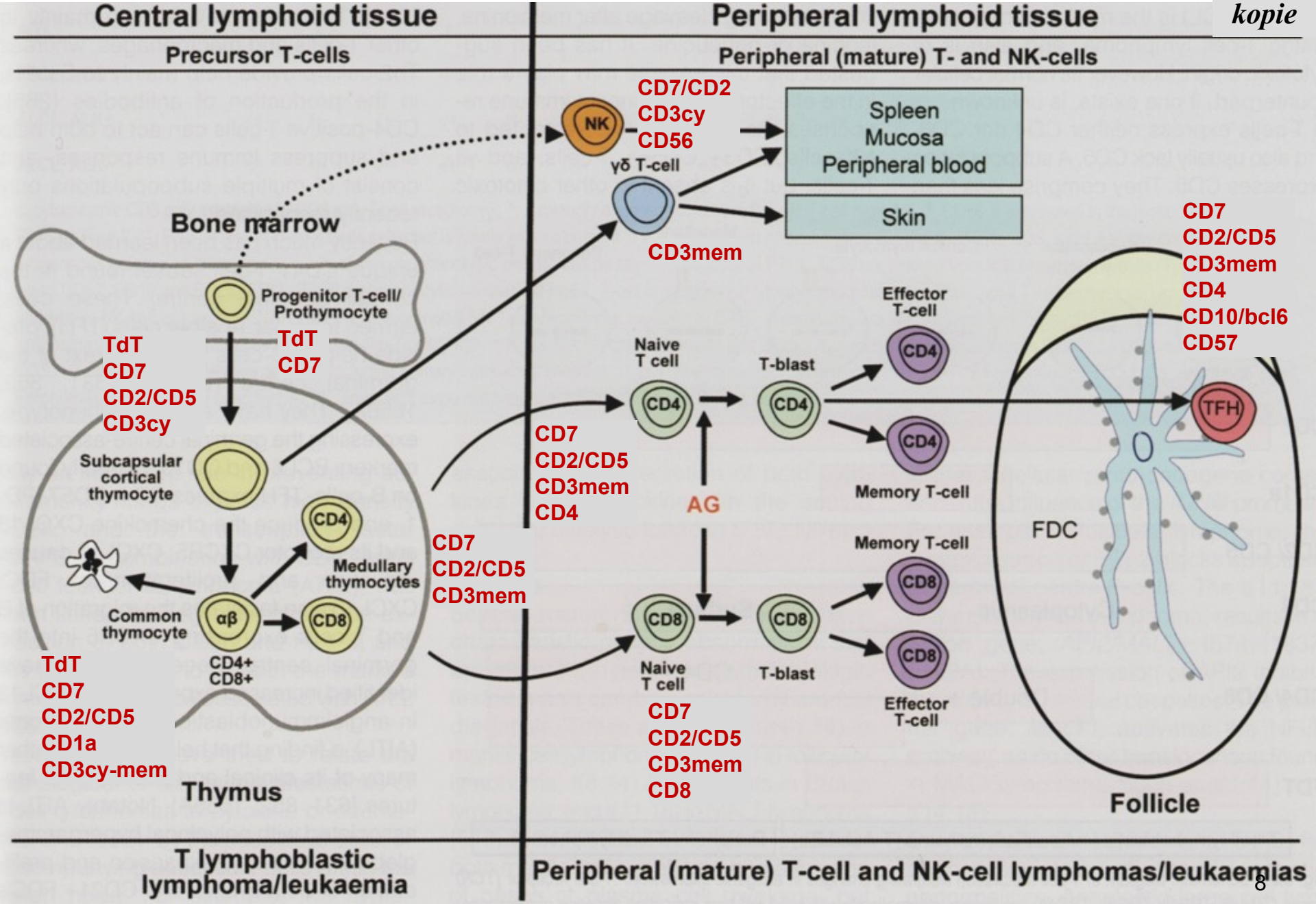
Precursor B-cell neoplasms	Pre-GC neoplasm	GC neoplasms	Post-GC neoplasms
B lymphoblastic leukaemia/lymphoma	Mantle cell lymphoma	Follicular lymphoma Burkitt lymphoma DLBCL (some) Hodgkin lymphoma	Marginal zone & MALT lymphoma Lymphoplasmacytic lymphoma CLL/SLL, DLBCL(some) Plasma cell myeloma

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

kopie



T LYMPHOID NEOPLASMS – CELLS OF ORIGIN



WHO classification of lymphomas

Non-Hodgkin lymphomas (NHL)

B-cell neoplasms

precursor B-cell lymphoid neoplasms

mature B-cell neoplasms

T-cell neoplasms

precursor T-cell lymphoid neoplasms

mature T-cell neoplasms

Hodgkin lymphomas (HL)

Classic HL

- nodular sclerosis
- lymphocyte rich
- mixed cellularity
- lymphocyte depleted

Nodular lymphocyte predominant HL

Non-Hodgkin lymphomas/WHO classification

I. Precursor B-Cell Lymphoid Neoplasms

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

II. Mature B-Cell Neoplasms

- **B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)**
- B- prolymphocytic leukemia
- Lymphoplasmacytic lymphhoma
- **Follicular lymphoma (FL)**
- **Extranodal (MALT lymphoma)/nodal/splenic marginal zone lymphoma**
- **Mantle cell lymphoma (MCL)**
- Splenic and nodal marginal zone lymphoma
- Hairy cell leukaemia
- **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 leukaemia/lymphoma (T-ALL)**

IV. Peripheral T-/NK-Cell Neoplasms

Mainly leukaemic:

- T- cell prolymphocytic leukemia
- **Adult T-cell leukamia/lymphoma (HTLV1)**
- T-cell granular lymphocytic leukemia

Mainly nodal:

- **Peripheral T-cell lymphoma, NOS**
- Angioimmunoblastic T-cell lymphoma
- **Anaplastic large-cell lymphoma**

Mainly extranodal:

- NK/T-cell lymphoma, nasal type
- **Mycosis fungoides/Sézary syndrome**
- **Enteropathy-type T-cell lymphoma**
- Panniculitis-like T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma
- Primary cutaneous T-cell lymphomas

……..

Precursor B and T cell lymphoid neoplasms
Acute lymphoblastic leukaemias

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, leukaemic presentation (80 %)
- infiltration of bone marrow, LN, liver, spleen,…

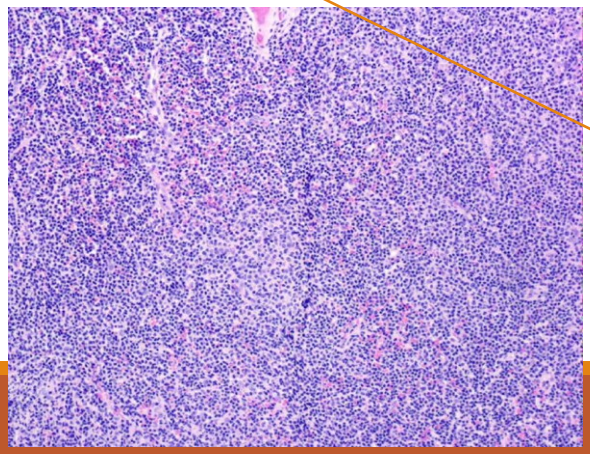
2. **Precursor-T-cell acute lymphoblastic leukemia/lymphoma**

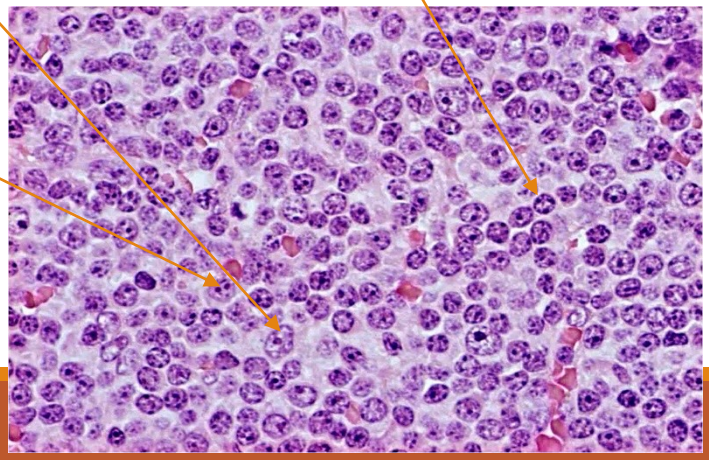
- precursor T-cell (often of thymic origin) expressing TdT
- Adolescent males, thymic mass/mediastinal tumour, variable splenic, hepatic, and bone marrow involvement; aggressive
- B-ALL>>>T-ALL

Mature B-cells neoplasms

1. **B-chronic lymphocytic leukemia/small lymphocytic lymphoma (B-CLL/SLL)**

- cell of origin: naive B-cell or postgerminal center memory B-cell (CD5+)
- most frequent leukaemia in adults
- infiltration of bone marrow, lymph nodes, spleen, liver
- clinically indolent; transformation into high grade lymphoma – Richter´s syndrome
- in lymph nodes: diffuse infiltrate of monomorphic small lymphocytes prolymphocytes and paraimmunoblasts with proliferation centres/pseudofollicles

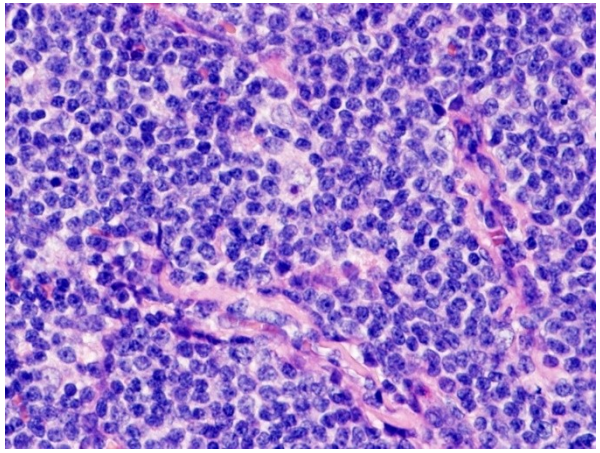


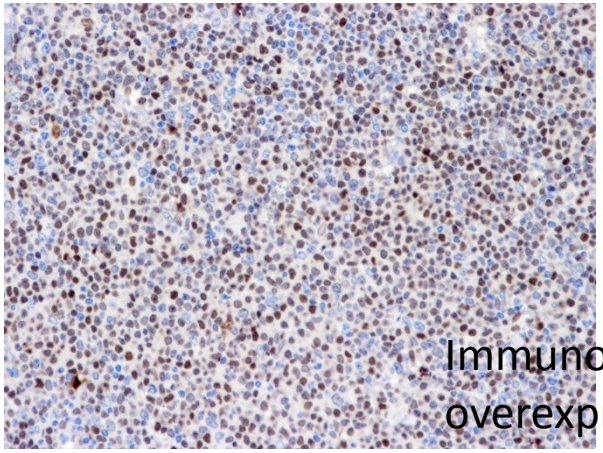


Mature B-cells neoplasms

2. Mantle cell lymphoma

- t(11;14); cyclinD1 locus/IgH locus
- naive B-cell of mantles (CD5+, cyclinD1+(promotes G1 to S phase progression)
- older males, often extranodal (lymphomatous polyposis); moderately aggressive – resistent to therapy





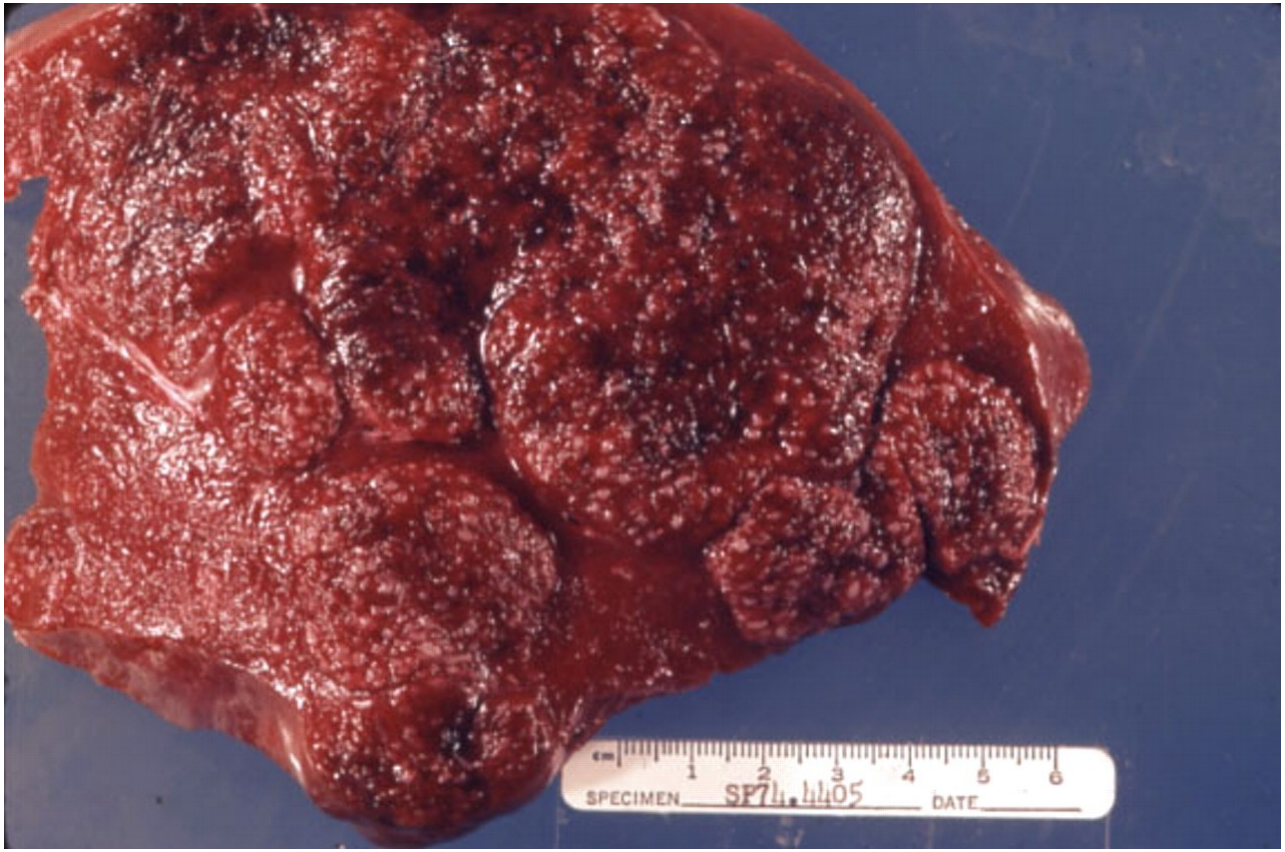
Immunohistochemistry: overexpression of cyclinD1

Mature B-cells neoplasms

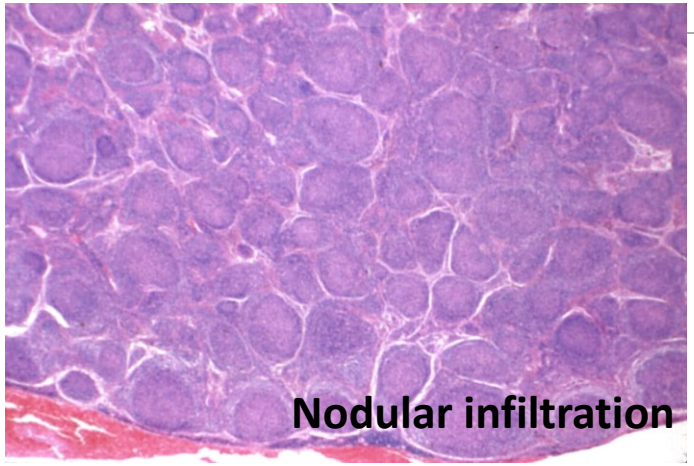
3. Follicular lymphoma

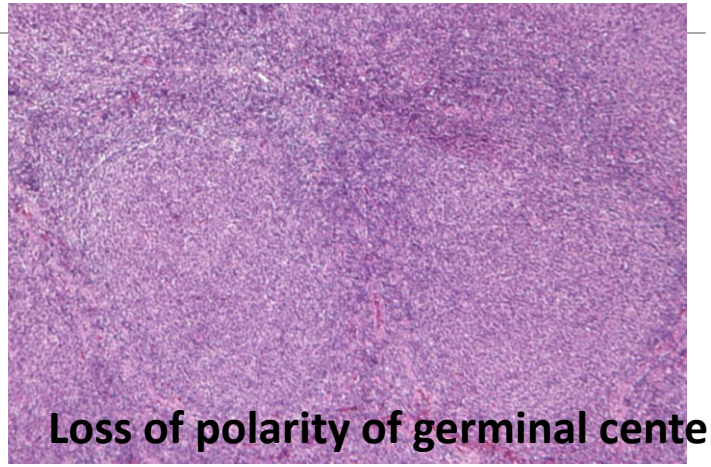
- 2nd most common NHL
- germinal center B-cell (CD10+, bcl-2+, bcl-6+): centrocytes; centroblasts and immunoblasts
- t(14;18); bcl-2/IgH (bcl-2 (inhibitor of apoptosis) overexpression – promotion of the survival of follicular lymphoma cells)
- adults; primary nodal, later disseminated; indolent with possible transformation into high grade lymphoma (DLBCL)

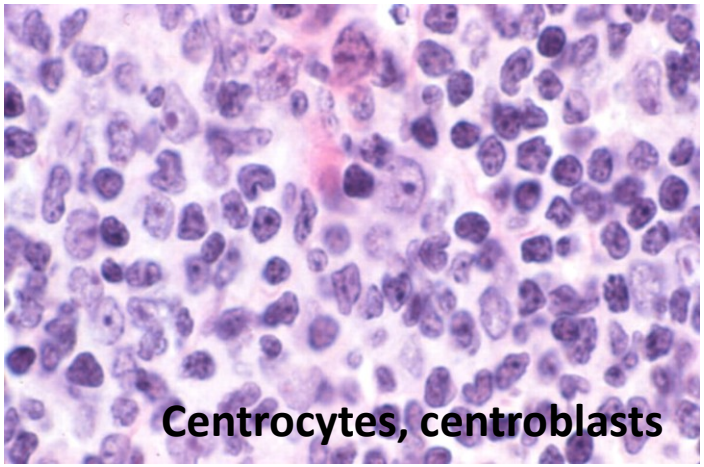
Spleen, follicular lymphoma

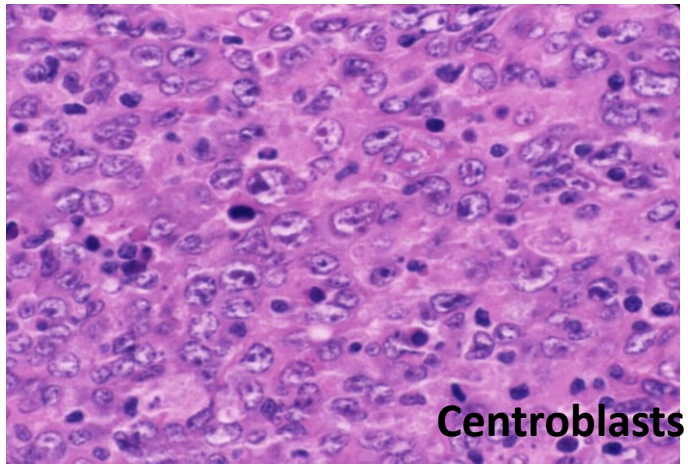


Follicular lymphoma


Nodular infiltration

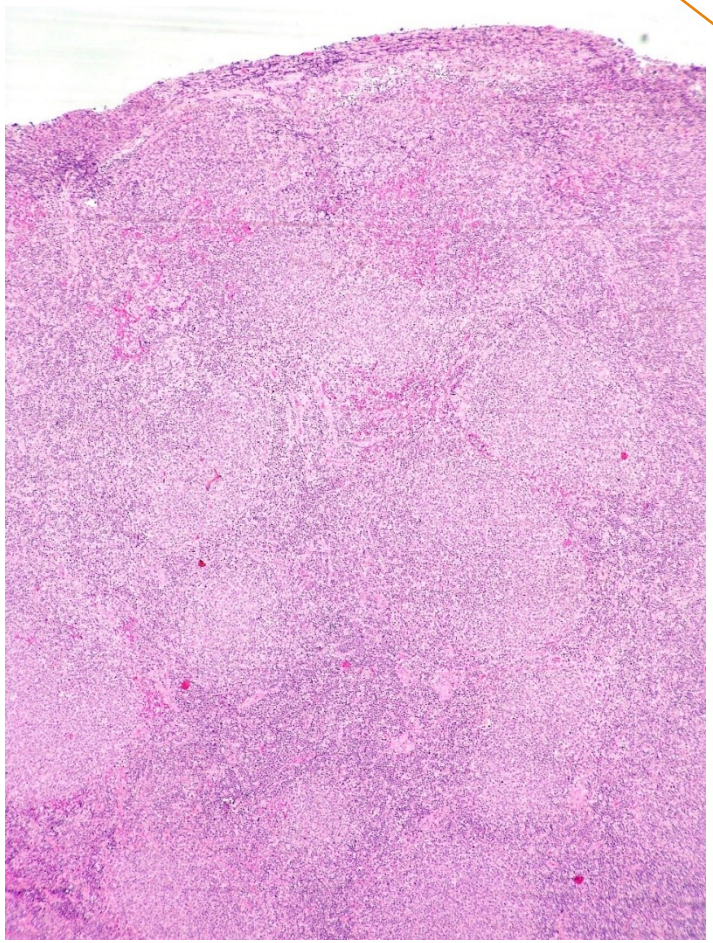

Loss of polarity of germinal centers

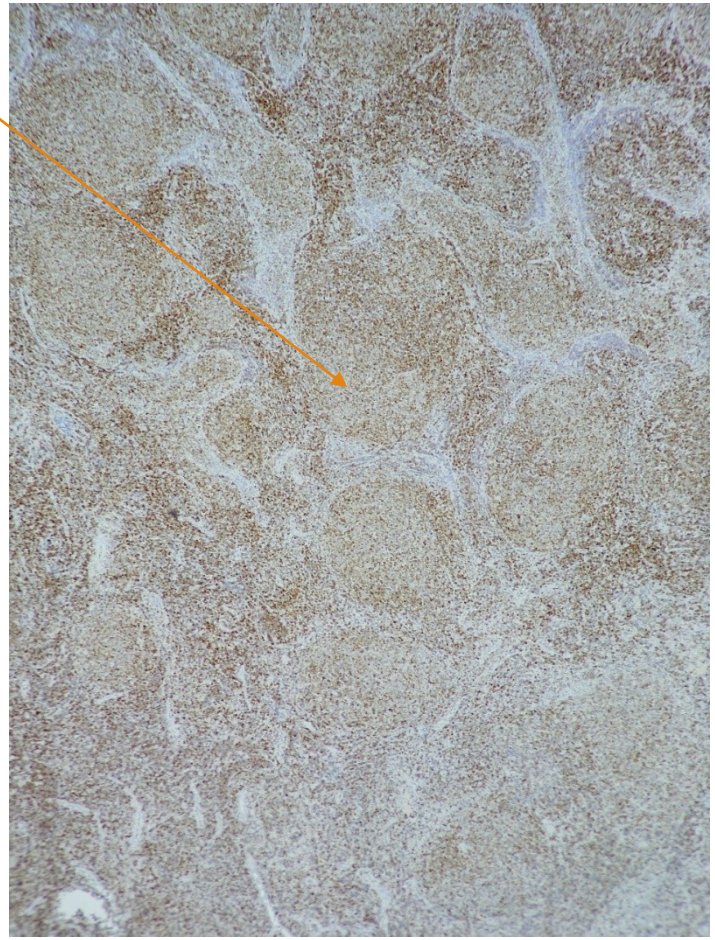

Centrocytes, centroblasts


Centroblasts

Follicular lymphoma

Immunohistochemistry: overexpression of bcl-2



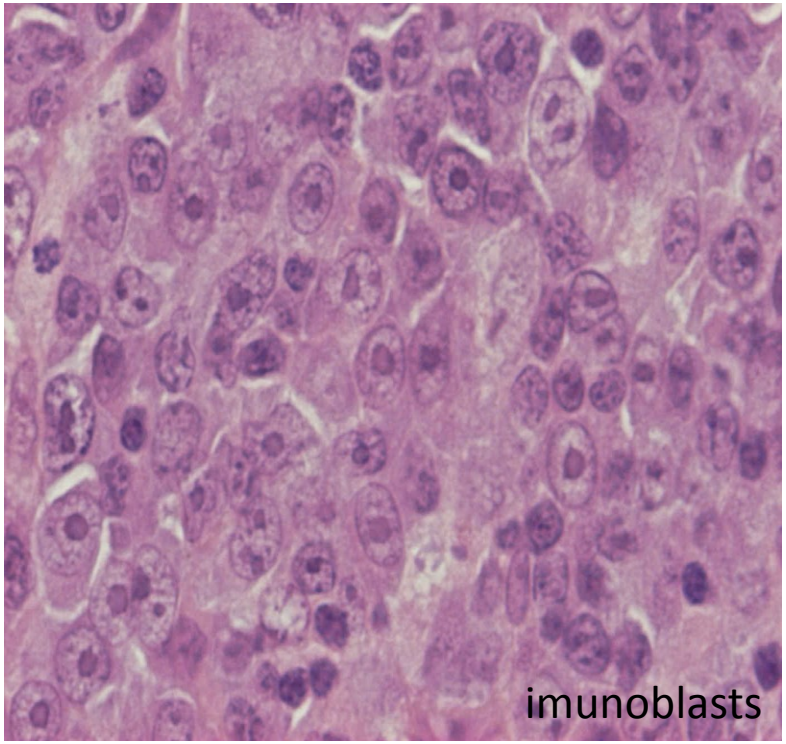


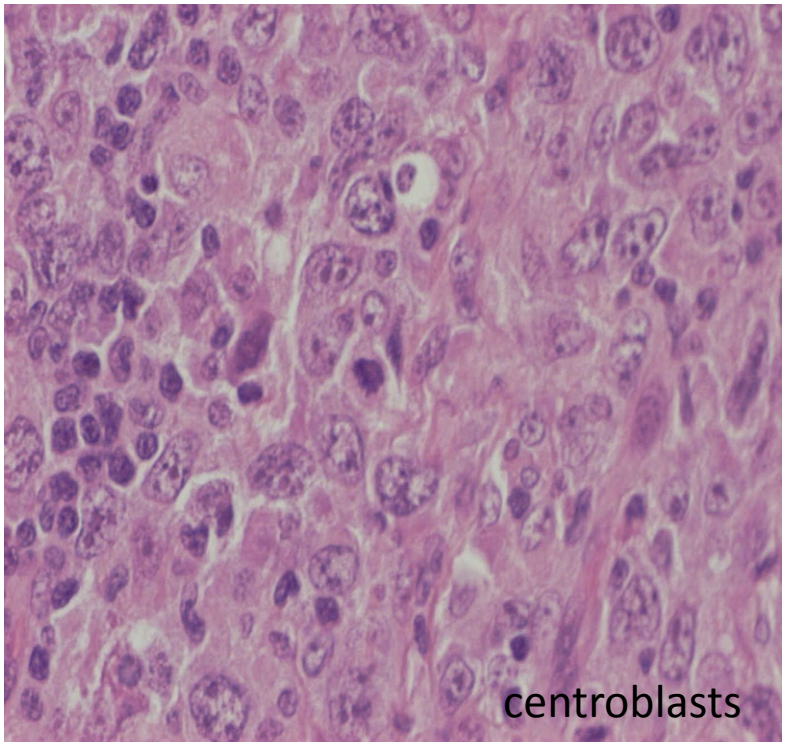
Mature B-cells neoplasms

4. Diffuse large B-cell lymphoma

- most frequent lymphoma, 45 % of all NHL
- cell of origin: germinal center or postgerminal center B-cell (centroblasts and immunoblasts)
- de novo or progression from low grade lymphoma (CLL, FL, MZL)
- variable cytogenetic alterations (bcl-6, bcl-2, MYC,…)
- all ages, usually adults; 40 % extranodal; aggressive

Diffuse large B cell lymphoma





Mature B-cells neoplasms

5. **Burkitt lymphoma**

   African endemic (jaws)

   sporadic (intestinal)

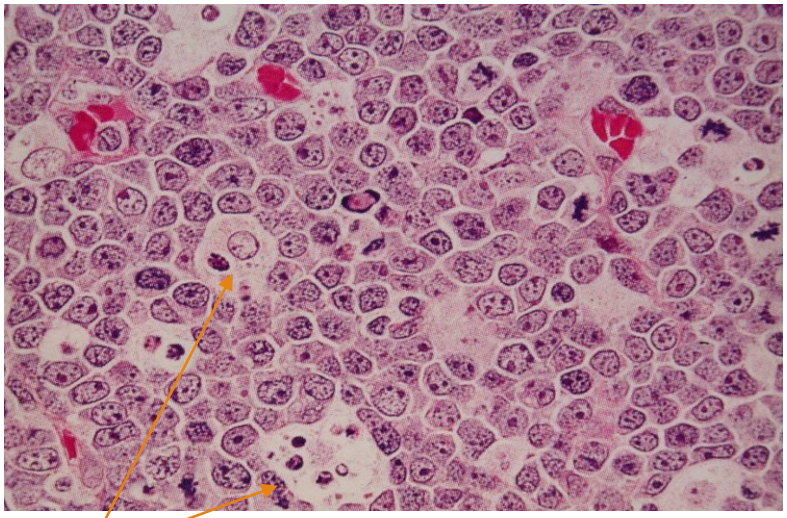
   immunodeficiency-associated

   germinal center B-cell (CD10+)?; „starry sky“ pattern; high mitotic rate, high apoptotic rate

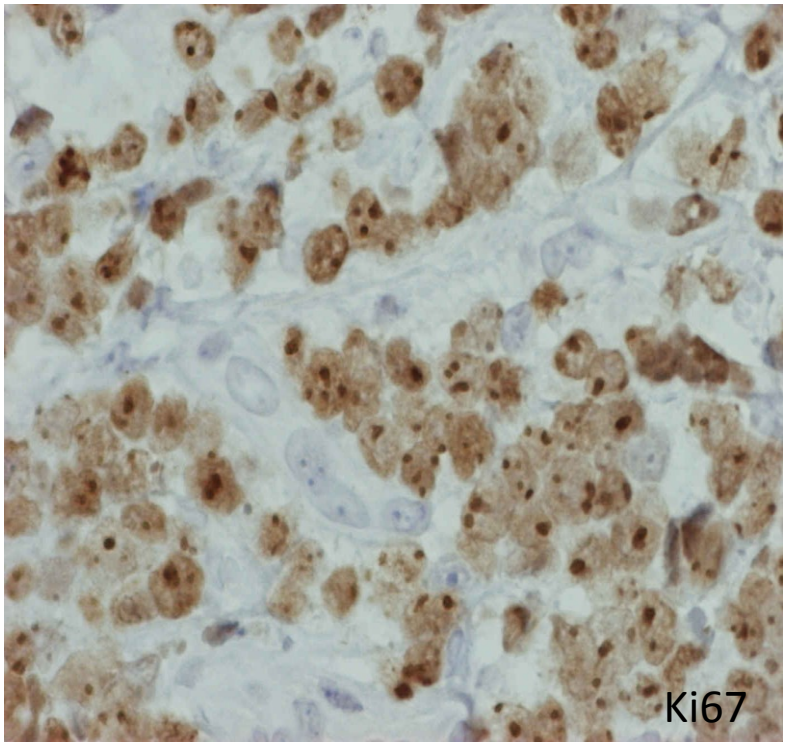
- t(8;14) (c-myc/IgH), t(2;8) (c-myc/kappa light chains), t(8;22) (c-myc/lambda light chains) → high proliferative activity
- adolescents, young adults; aggressive, often association with EBV

Burkitt lymphoma

HE: „starry sky“ pattern



Macrophages with apoptotic bodies

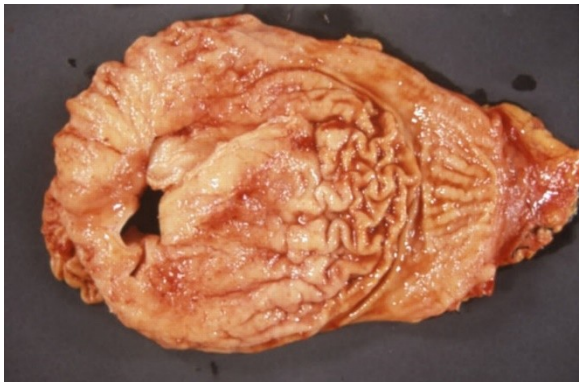


Immunohistochemistry: High expression of Ki67 – marker of proliferation.

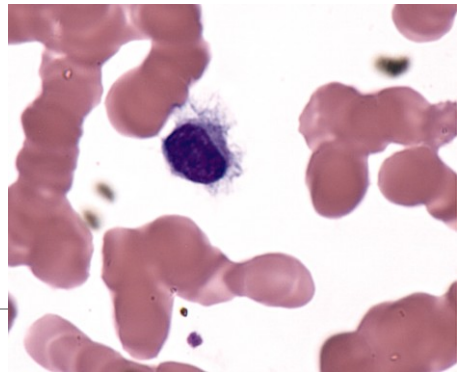
Mature B-cells neoplasms

6. Extranodal marginal zone lymphoma (MALT lymphomas)

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



Mature B-cells neoplasms



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. 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
- Waldenström macroglobulinemia (excess of IgM, hyperviscosity syndrome)
- Indolent

Mature B-cells neoplasms/ plasma cell dyskrasias/neoplasms

9. **Plasma cell myeloma/multiple myeloma**

   Plasmacytoma (solitary plasmocytoma of bone, extraosseous plasmocytoma)

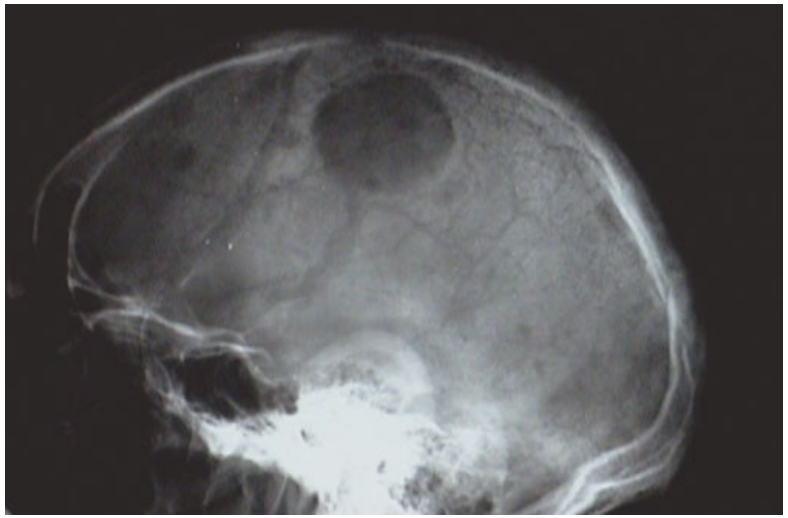
   Monoclonal gammapathy of undetermined signifikance

   Light and heavy chain disease

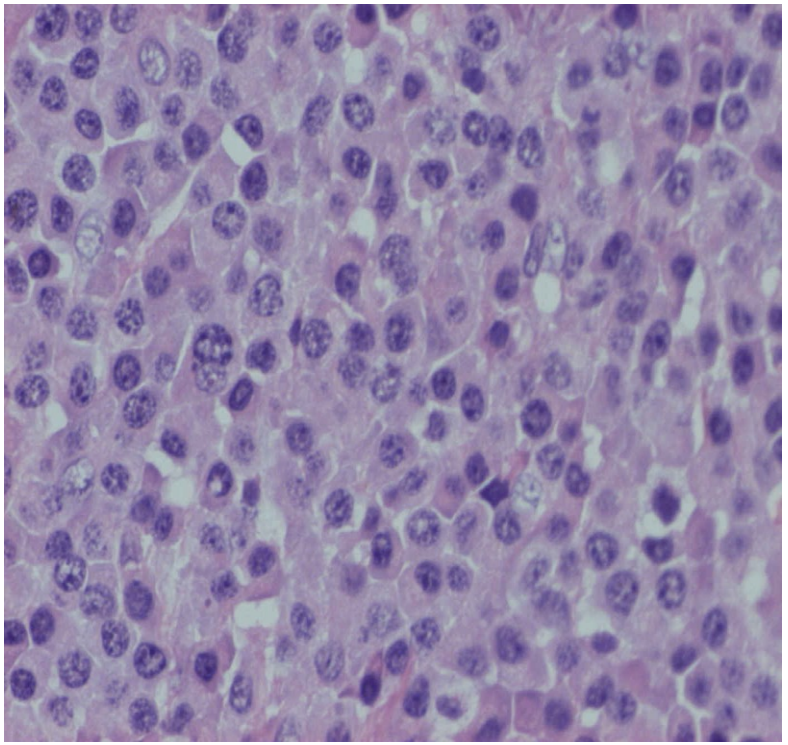
   Primary amyloidosis

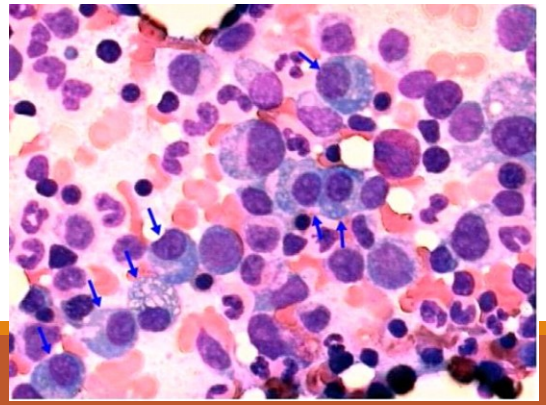
- cell of origin: plasma cell derived from a postgerminal center B-cell
- neoplastic cell synthesizes and secretes a single homogeneous immunoglobulin or its fragments (monoclonal neoplastic proliferation of plasma cells)
- Myeloma: older adults; lytic lesions of bones, primary amyloidosis, renal failure (myeloma kidney due to excretion of Bence Jones proteins).
- Plasmacytoma: neoplastic plasma cell masses in bone or soft tissues

Multiple myeloma



Osteolytic lesions





Infiltration by neoplastic plasma cells

Mature T-cells neoplasms/ peripheral T- and NK-Cell Neoplasms

Peripheral T-Cell Lymphoma, unspecified

- wastebasket“ diagnosis

- derived from mature T-cells

- most patients with generalized lymphadenopathy, accompanied by eosinophilia, pruritus, fever, weight loss

- worse prognosis compared with DLBCL

Anaplastic Large-cell lymphoma; ALCL (ALK positive and ALK negative)

- rearangements in the ALK gene (2p23) → ALK fusion proteins = tyrosinkinase activita that trigger the RAS and JAK/STAT signaling pathways

- ALK+ ALCL, children and young adults, soft tissues, good prognosis

- ALK- ALCL, in older adults, worse prognosis

Mature T-cells neoplasms/ peripheral T- and NK-Cell Neoplasms

Mycosis fungoides/Sezary syndrome (leukaemic)

- different manifestation of a tumour of CD4+ helper T cells that home to the skin
- cutaneous lesions of MF: premycotic phase, plaques phase and tumour phase
- SS: skin involvement manifested as generalized exfoliative erythroderma

Enteropathy-type T-cell lymphoma

- develops in some patients with coeliac disease
- derived from intramucosal cytotoxic CD8+ T cells
- abdominal pain, often intestinal perforation, sometimes prodrome of refractory celiac disease accompanied by ulceration (ulcerative jejunitis)
- aggressive with very poor prognosis

Mature T-cells neoplasms/ peripheral T- and NK-Cell Neoplasms

Adult T-cell leukemia/lymphoma

- aggressive tumour of CD4+ T cells
- uniformly associated with HTLV-1 infection
- Skin lesion, generalized lymphadenopathy, hepatosplenomegaly, peripheral blood lymphocytosis, hypercalcemia, osteolysus; aggressive

Extranodal NK/T cell lymphoma, nasal and nasal typ

- Aggressive tumour, usually derived from NK cells
- Strongly associated with EBV infection
- Most frequently presentation as a destructive nasopharyngeal mass („lethal midline granuloma“)

Large granular lymphocytic leukemia

- Tumour of cytotoxic T cells or NK cells
- Associated with mutations in the transcription factor STAT3 and with autoimmune phenomena and cytopenias
- T-cell origin – indokent clinical course, NK-cell tumours more aggressive

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

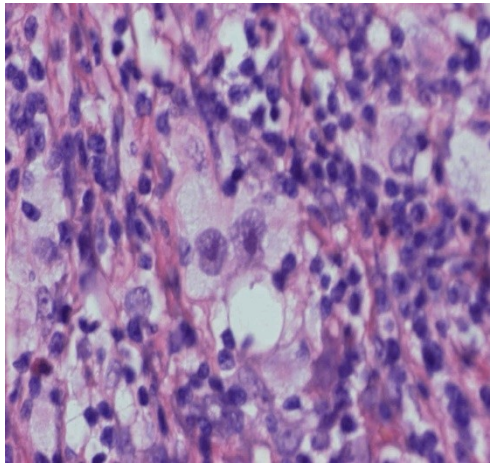
Neoplastic cells in classical HL

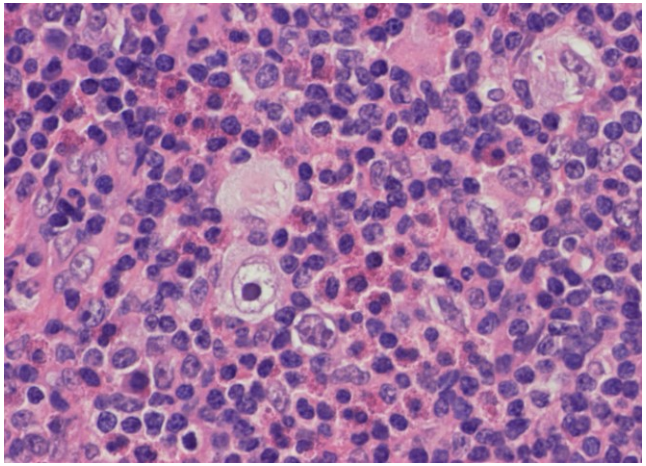
Diagnostic Reed-Sternberg and Hodgkin cells (multiple or single nucleus)

Lacunar cells

Diagnostic cells – HL, classical

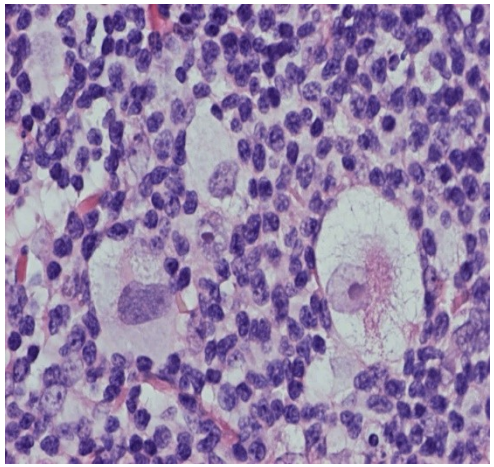
R-S cell

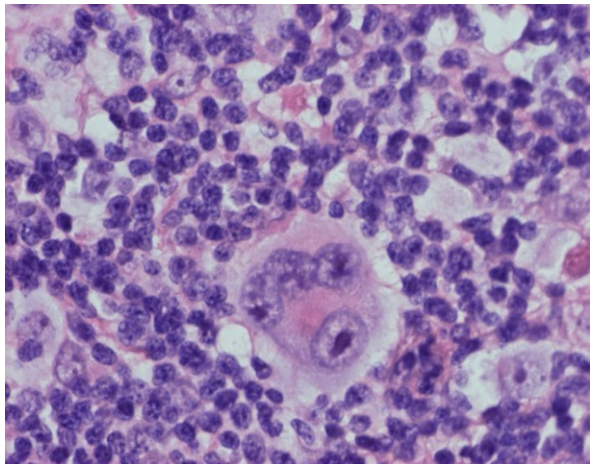




H-cell

Lacunar cells





S-cell

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 myeloid leukaemias**
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)

Acute myeloid leukaemie (AML)

- WHO classification*

- ***I. AML WITH RECURRENT GENETIC ABNORMALITIES***
  - ***AML WITH BALANCED TRANSLOCATIONS/INVERSIONS***
    - AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
    - AML with inv(16)(p13;1q22) or t(16<16)(P13.1;q23); CBFB-MYH11
    - Acute promyelocytic leukaemia with PML-RARA
    - AML with t(9;11)(p21.3.;q23.3); KMT2A-MLLT3
    - AML with t(6;9)(p23;q34.1); DEK-NUP214
    - AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
    - AML (megakaryoblastic) with t(1;22)(q13.3;q13.1); RB?15-MKL1
    - AML with BCR-ABL1
  - ***AML WITH GENE MUTATIONS***
    - AML with mutated NPM1
    - AML with biallelic mutation of CEBPA
    - AML with mutated RUNX1

- ***II. AML WITH MDS-RELATED CHANGES***

*just informative, no active knowledge requidred

Acute myeloid leukaemia (AML)

- ***III. THERAPY-RELATED MYELOID NEOPLASMS***
- ***IV. AML, NOT OTHERWISE SPECIFIED*****
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation;
  - Acute myelomonocytic leukaemia
  - Acute monoblastic and monocytic leukaemia
  - Pure erythroid leukaemia
  - Acute megakaryoblastic leukaemia
  - Acute basophilic leukaemia
  - Acute panmyelosis with myelofibrosis
- ***V. MYELOID SARCOMA***
- ***VI. MYELOID PROLIFERATIONS ASSOCIATED WITH DOWN SYNDROME***
  - Transient abnormal myelopoiesis associated with Down syndrome
  - Myeloid leukaemia associated with Down syndrome

**corresponding with previous FAB classification (M0-M7)

French-American-British (FAB) AML classification*

1. **M0 AML with minimal differentiation**
2. **M1 AML without maturation**
3. **M2 AML with maturation**
4. **M3 acute promyelocytic leukemia**
5. **M4 acute myelomonocytic leukemia**
6. **M5 acute monoblastic and monocytic leukemia**
7. **M6 pure erythroid leukaemia**
8. **M7 acute megakaryoblastic leukaemia**

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

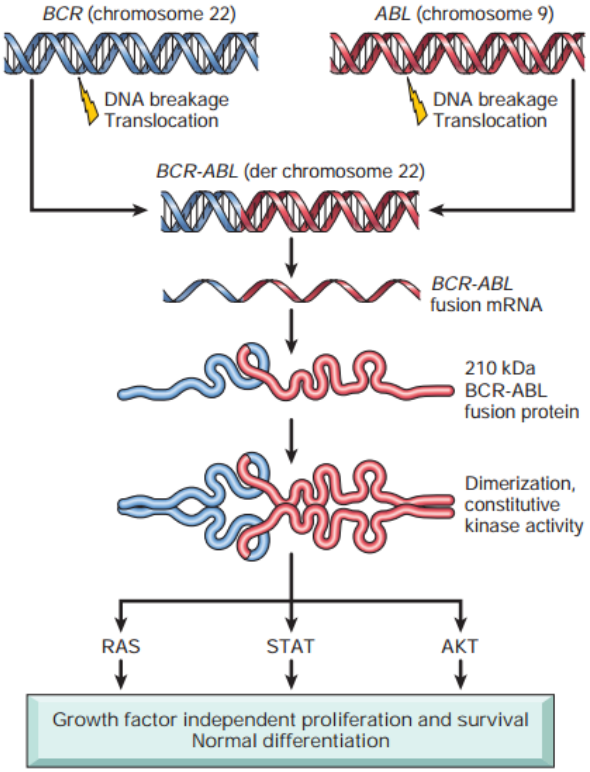
Essential thrombocythaemia

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

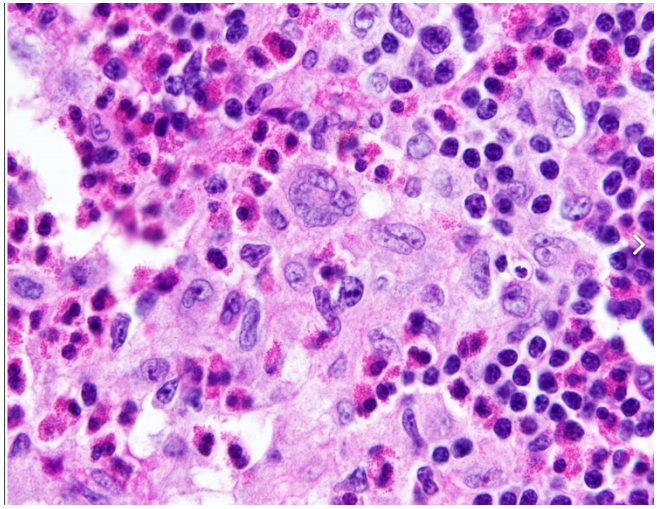
Polycythemia vera

- 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)

Histiocytic and dendritic cell neoplasms

Langerhans cell sarcoma

(high grade malignancy, skin and soft tissue involvement, multisystem)

Histiocytic sarcoma

Dendritic cell sarcomas

(follicular DCS, interdigitating DCS, other rare forms….)

Erdheim Chester disease

- rare clonal systemic proliferation of histiocytes, with foamy component and containg giant Touton cells

- involvement of different organs (bones, retroperitoneum, CNS,……), multisystem disease and CNS involvement with worse prognosis

Thank you for your attent