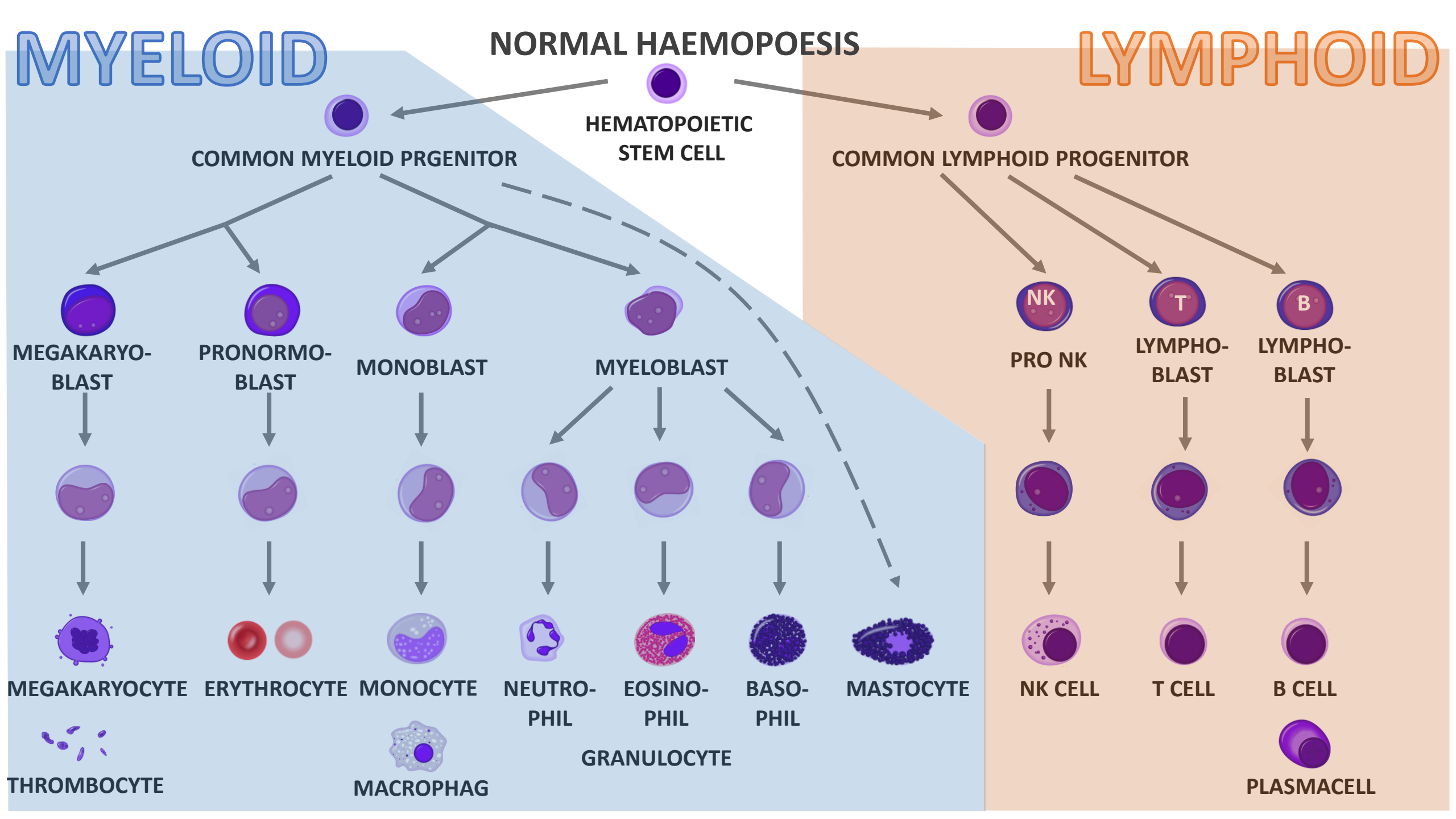
HEMATOPATHOLOGY

2017/2018

2nd semester


MYELOID
NORMAL HAEMOPOESIS
LYMPHOID
HEMATOPOIETIC STEM CELL
COMMON MYELOID PRGENITOR
COMMON LYMPHOID PROGENITOR
MEGAKARYO-BLAST
PRONORMO-BLAST
MONOBLAST
MYELOBLAST
NK
T
B
PRO NK
LYMPHO-BLAST
LYMPHO-BLAST
MEGAKARYOCYTE
ERYTHROCYTE
MONOCYTE
NEUTRO-PHIL
EOSINO-PHIL
BASO-PHIL
MASTOCYTE
NK CELL
T CELL
B CELL
THROMBOCYTE
MACROPHAG
GRANULOCYTE
PLASMACELL

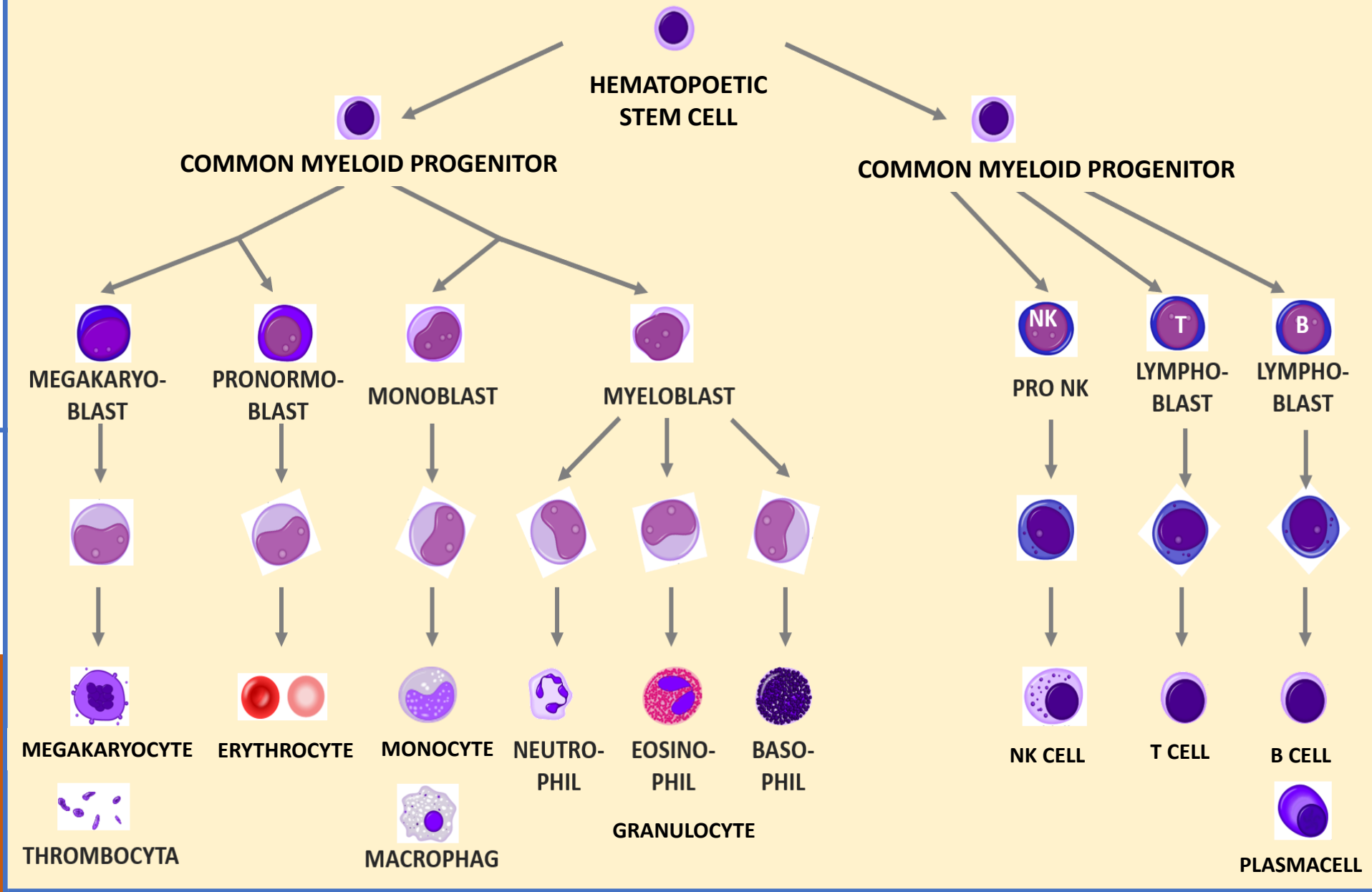
ACUTE

Immature cells - blasts

CHRONIC

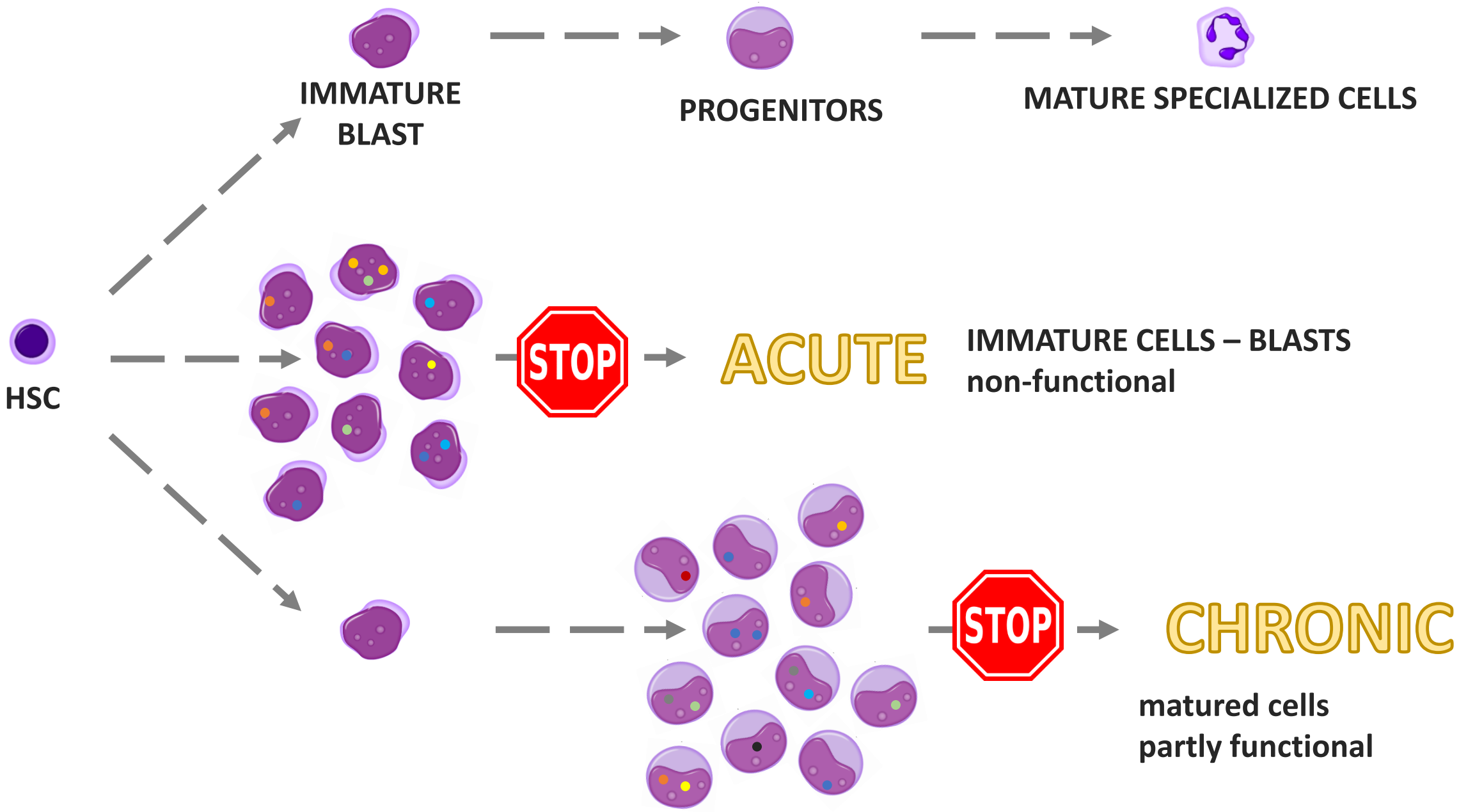
mature cells

Classification of bone marrow neoplasms

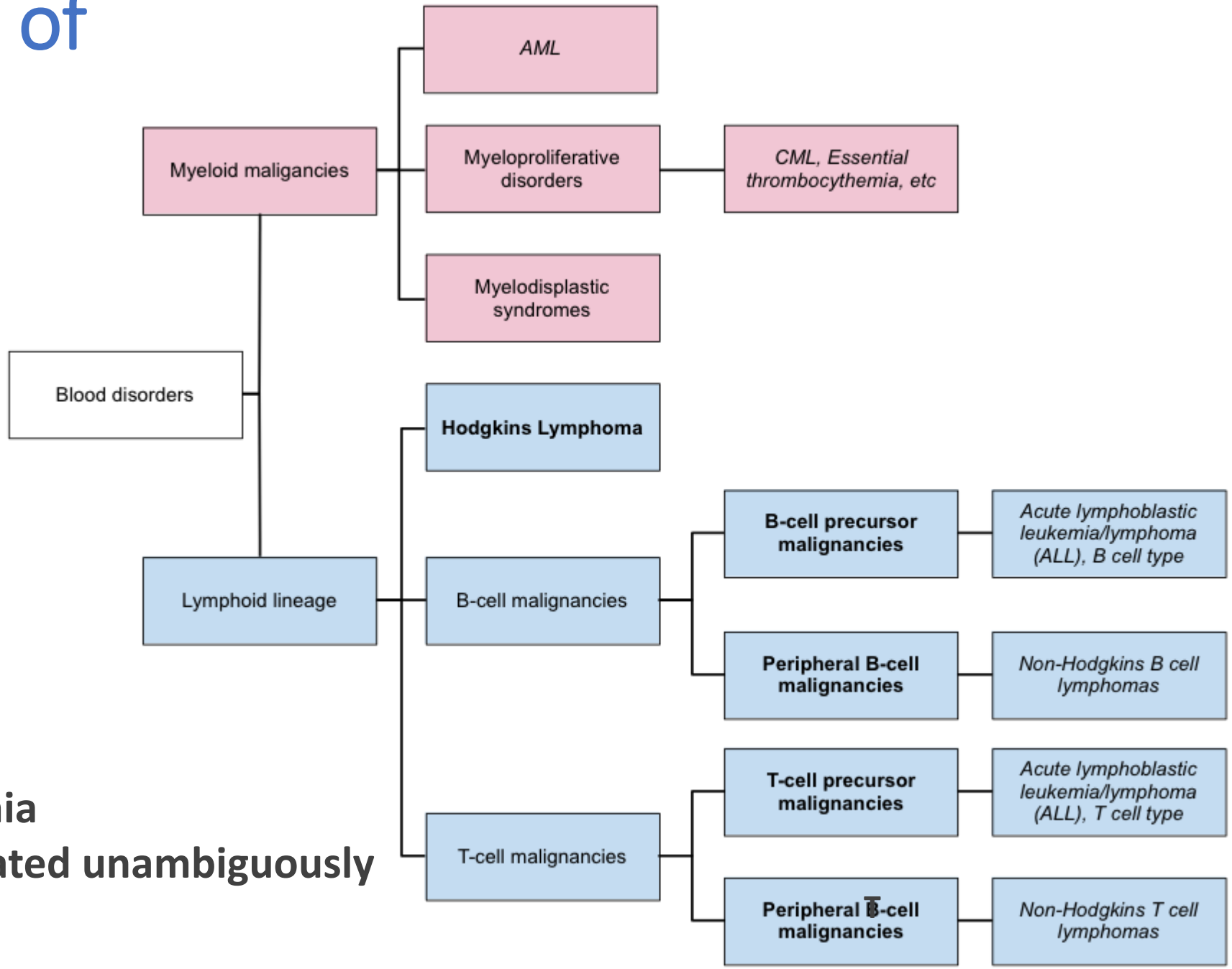


MYELOID

LYMPHOID


IMMATURE
BLAST
PROGENITORS
MATURE SPECIALIZED CELLS
HSC
STOP
ACUTE
IMMATURE CELLS – BLASTS
non-functional
STOP
CHRONIC
matured cells
partly functional

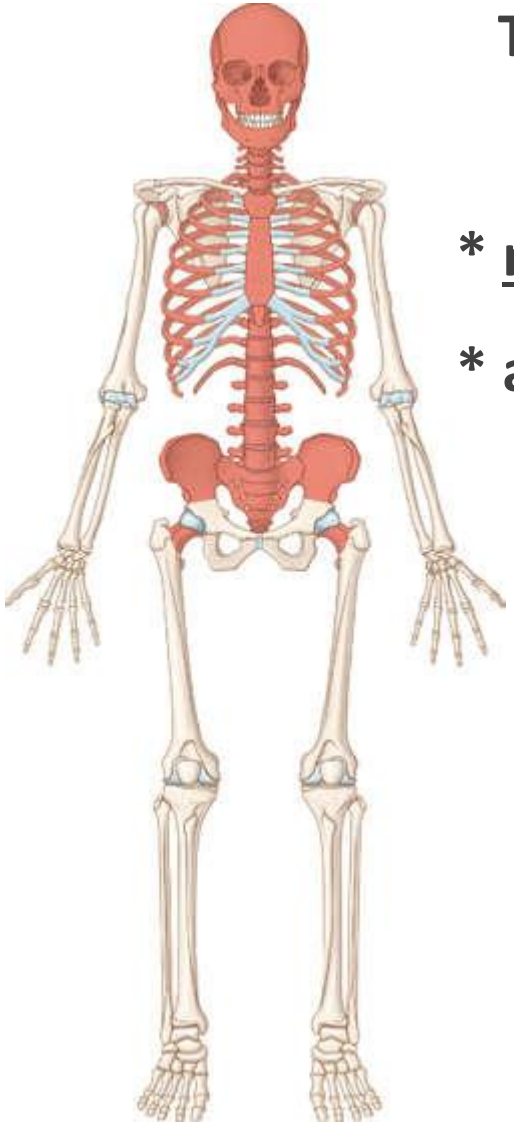
Classification of hematologic diseases (WHO)



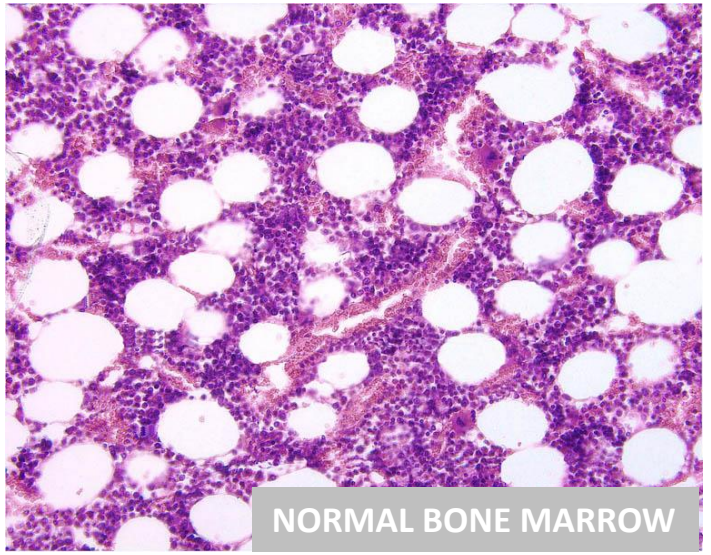
Lymphoma – Leukemia
cannot be separated unambiguously

http://iatreum.com/what-are-lymphomas-and-malt-lymphomas.html

Leukemia → derives from the bone marrow



RED BONE MARROW IN ADULTS



NORMAL BONE MARROW

Totally immature blast cells (acute) or more matured progenitors (chronic)

* <u>replace</u> normal haematopoiesis

* after a while they get into circulation

Bone marrow

- Blast < 5% → normal
- Blast > 20% → acute leukemia

SYMPTOMS: Rapid development ⇒ see: ACUTE leukemia

In children days / 1-2 weeks

Slow development ⇒ see: CHRONIC leukemia

https://img.tfd.com/medical/Davis/Tabers/th/m03.jpg
http://www.histology-world.com/photoalbum/displayimage.php?album=65&pid=2283

Leukemia

GENERAL SYMPTOMS:

BONE MARROW FAILURE

: Tumor cells replace normal hematopoiesis

Red blood cell ↓	Thrombocyte ↓	Neutrophil ↓	Blast ↑	Metabolism ↑
ANAEMIA	THROMBOCYTOPENIA	NEUTROPENIA	LEUKOCYTOSIS	SWEATS FATIGUE
Fatigue	Hemorrhage; DIC	Infections; Fever	Leukostasis	

ORGAN INFILTRATION

: Tumor cell infiltration of different organs

Spleen	Liver	Lymph node (rarely affected)	Gingiva	Bone marrow
SPLENOMEGALY	HEPATOMEGALY	LYMPHADENOMEGALY	GINGIVAHYPERPLASIA	BONE PAIN

Acute leukemia – Separation

LYMPHOID

TdT :DNA polymerase

- ☑ lymphoblast
- ☒ lymphocyte
- ☒ myeloblast

Nuclear staining

MYELOID / MONOCYTAER

MPO :myeloperoxidase

Auer rod (HE) – crystallized MPO

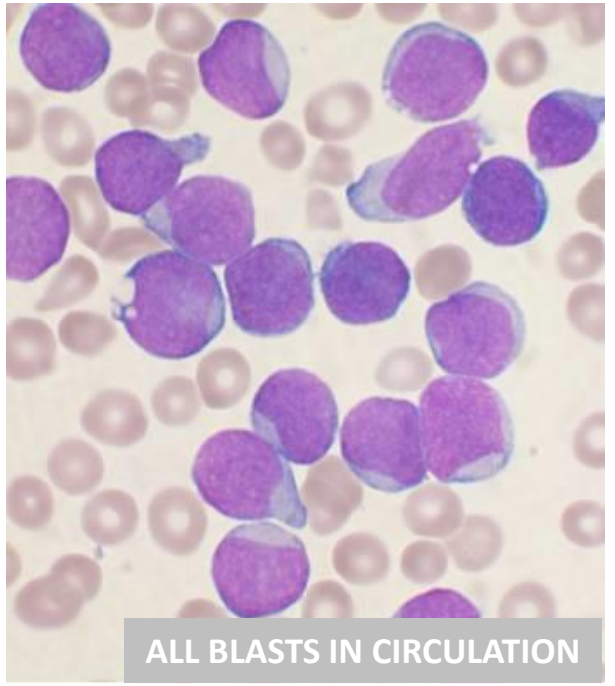
NSE :non-specific esterase

Cytoplasmic staining

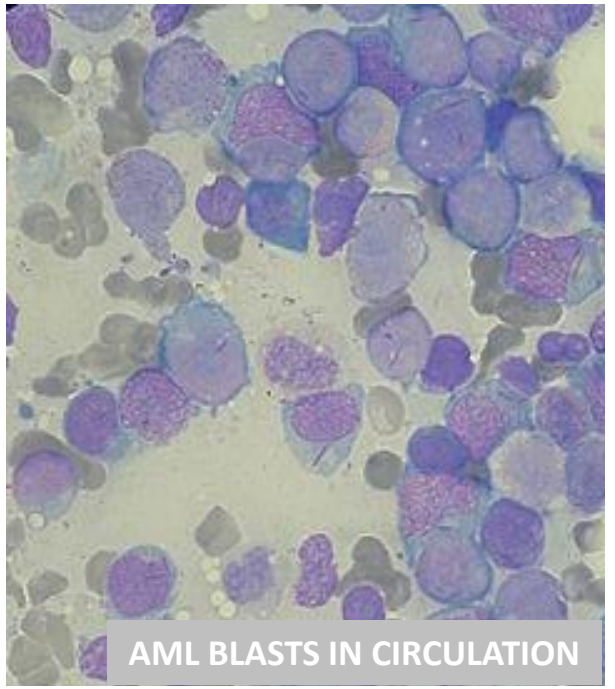
N.B.: Not 100% specificity

TdT can be expressed by any blast cell, but it is more characteristic in lymphoid cells

MPO do not present in all AML forms



ALL BLASTS IN CIRCULATION



AML BLASTS IN CIRCULATION

TdT = Terminal deoxynucleotidyl Transferase

https://commons.wikimedia.org/wiki/File:akut_leukaemia-ALL.jpg
https://commons.wikimedia.org/wiki/File:Myeloblast_with_Auer_rod_smear_2010-01-27.jpg

Acute lymphoid leukemia

80% of childhood leukemias are ALL

Useful information:
30% of acute leukemias are ALL, 70% are AML
75% of ALL present under the age of 6
80% of childhood leukemias are ALL
85% of ALLs are B-ALL, 15% are T-ALL
Recovery rate in children is 80%
in adults is 50%

B-ALL (85%) : markers: Ig, CD10, CD19, CD20

Currently used WHO classification depends on genetic alterations

pl.: t(12;21) – ETV6-RUNX1; good prognosis; usually in children
t(9;22) = Ph^+ – BCR-ABL1; poor prognosis; usually in adults

T-ALL (15%) : markers: CD3, CD4, CD8

T-Lymphoblastic Leukemia/Lymphoma
Teenagers; Thymus/mediastinal widening

Formerly: FAB classification
based on cytomorphology
no prognostic or therapeutic consequence
not used anymore

Acute myeloid leukemia

Median age at the time of diagnosis: 68 y.o.

Useful information:

- 30% of acute leukemias are ALL, 70% are AML
- AML most commonly: between the age of 50 and 70
- Cytomorphologic classification is also changed by **cytogenetic classification (FAB vs WHO)**
- Genetic aberrations predict prognosis:
  good – intermediate – poor prognosis

Poor prognostic factors:

Older age
FLT3 mutation (tyrosine kinase); del chr 5/7
Association with MDS or therapy (chemo/radio)

WHO classification (not obligatory to learn)

- ***AML with recurrent genetic abnormalities***
  - AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16); CBEB-MYH11
  - Acute promyelocytic leukemia (APL) with t(15;17); PML-RARA
  - AML with t(9;11); MLLT3-MLL
  - AML with t(6;9); DEK-NUP214
  - AML with inv(3) or t(3;3); RPN1-EVI1
  - AML (megakaryoblastic) with t(1;22); RBM15-MKL1
  - Provisional entity: AML with mutated NPM1
  - Provisional entity: AML with mutated CEBPA
- ***AML with myelodysplasia-related change***
- ***Therapy-related myeloid neoplasms***
- ***AML NOS (not otherwise specified):***
- ***Myeloid sarcoma***
- ***Myeloid proliferations related to Down syndrome***
- ***Blastic plasmacytoid dendritic cell neoplasm***

FAB classification (see. slide 2-3) (not obligatory to learn)

FAB	Name		Adult patients (%)
M0	Min. differentiated acute myeloblastsic leukemia		5%
M1	Acute myeloblastic leukemia without maturation		15%
M2	Acute myeloblastic leukemia with maturation	25%	
M3	Acute promyelocytic leukemia		10%
M4	Acute myelomonocytic leukemia		20%
M4eos	Acute myelomonocytic leukemia with bm. eosinophilia		5%
M5	Acute monocytic leukemia		10%
M6	Acute erythroid leukemia		5%
M7	Acute megakaryocytic leukemia		5%

Acute myeloid leukemia

Acute promyelocytic leukemia (APL) tumor cells with Auer rods!

Success story of leukemia therapy
Worst prognosis until the `70s

→ rapid progression, fatal hemorrhages (DIC)

1977 – discovery of **t(15;17)** → PML-RARA fusion protein blocks differentiation

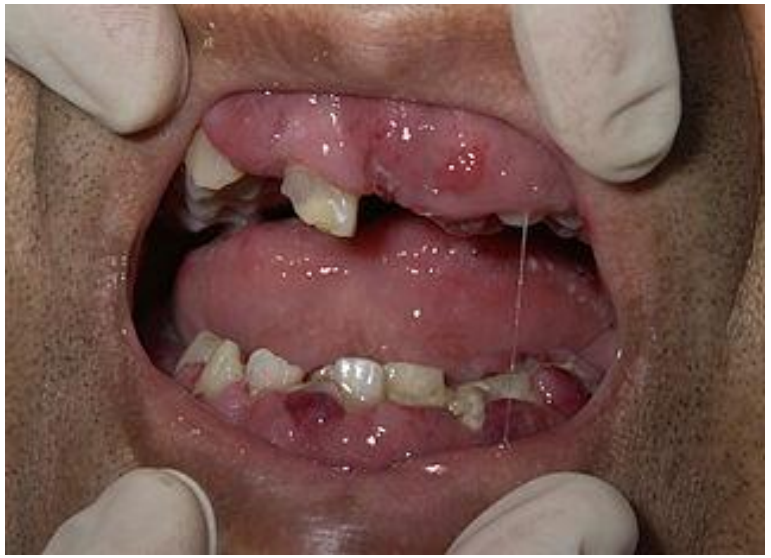
Th.: **ATRA** + chemo – induce the differentiation of promyelocytes, complete remission in 95%

Acute monocytitic leukemia

Increased number of monoblasts
Gingival hyperplasia!

Acute megakaryoblastic leukemia

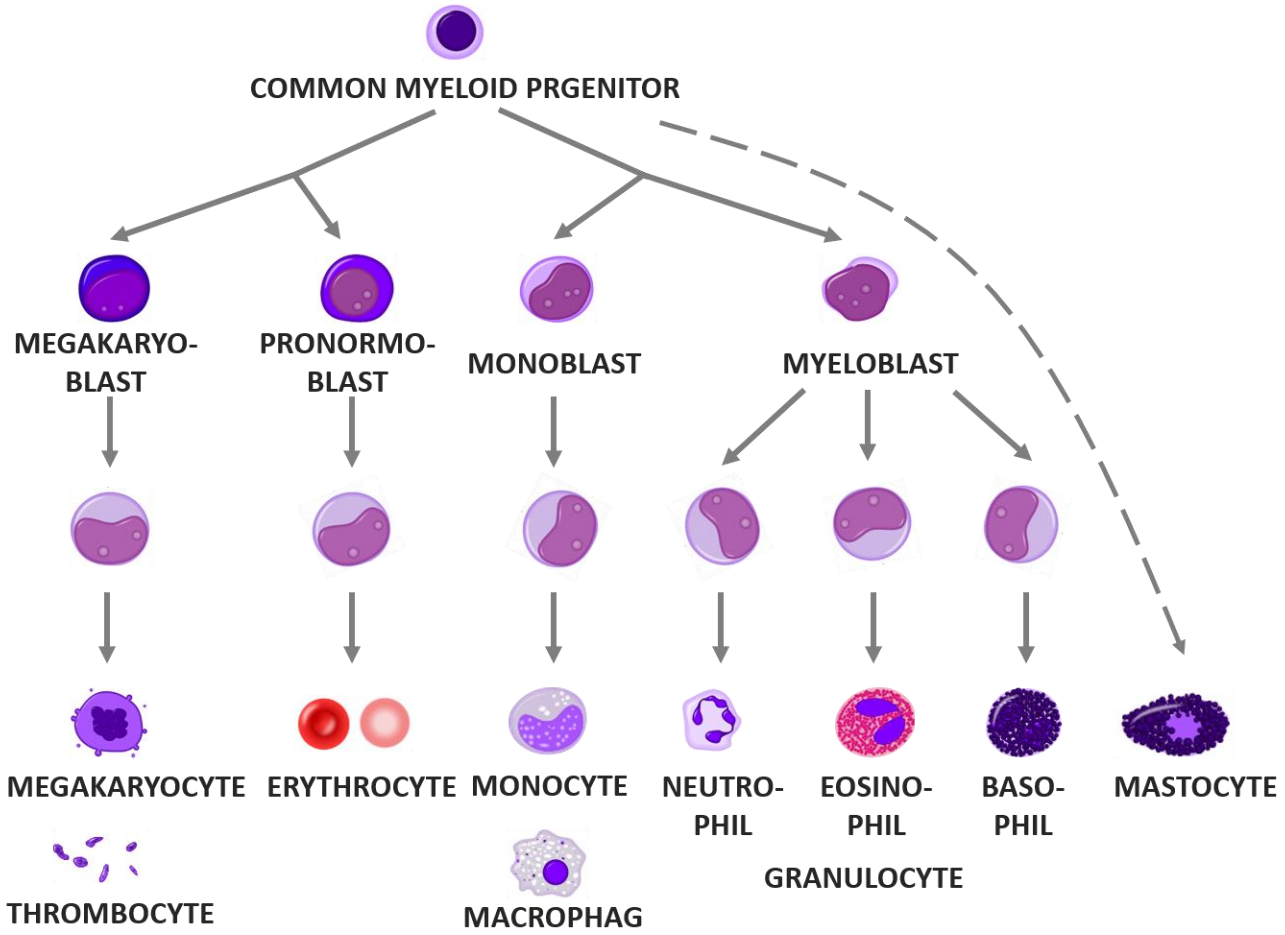
Associated with **Down syndrome** under the age of 5



https://commons.wikimedia.org/wiki/File:AMLCase-66.jpg

RARA = retinoid receptor α
ATRA = all-trans retinoic acid
PML = promyelocytic leukemia gene

Chronic myeloproliferative diseases



Chronic megakaryocytic leukemia
= idiopathic myelofibrosis (MF)

Essential thrombocytaemia (ET)

Polycythemia vera (PV)

Chronic neutrophil leukemia
Chronic eosinophil leukemia
Chronic basophil leukemia

CML

Myelodysplasia

Ineffective hemopoesis; pancytopenia

Chronic myeloid leukemia (CML)

Useful information:
- 20% of leukemia in adulthood are CML
- **Median age at the time of diagnosis: 66 y.o.**

Median age at the time of diagnosis: 66 y.o.

Low prevalence in younger age group, usually presents in a more aggressive form

Specific genetic alteration

t(9;22) = Philadelphia chromosome → BCR-ABL fusion gene→ BCR-ABL fusion protein

presents in >90% of CML

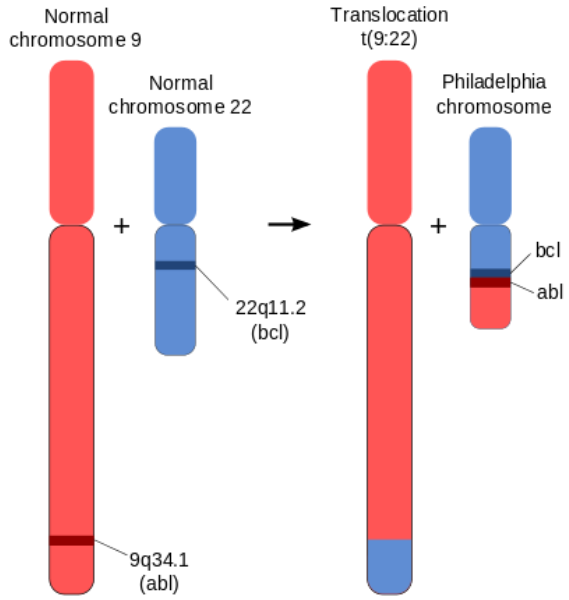
- Intensive tyrosine-kinase activity
- The exact pathomechanism is unclear

3 phases:

1. Chronic (proliferation of more mature cells; 90% in asymptomatic)
2. Accelerated (further cytogenetic alterations)
3. Blast crisis (totally immature blast cells)

Therapy (much better prognosis)

1. Imatinib (TKI)
2. Allogenic stem cell transplantation



https://commons.wikimedia.org/wiki/File:Schematic_of_the_Philadelphia_Chromosome.svg

Chronic lymphoid leukemia (CLL)

Useful information:
- Most common leukemia in adulthood
- Median age at the time of diagnosis: 72 y.o.

Clonal proliferation of nearly mature **B cells**

No or impaired Ig production

hypogammaglobulinaemia → autoimmune hemolytic anemia
immune thrombocytopenia

In the case of multiple lymph node involvement leukocytosis do not present:

CLL = SLL (small lymphocytic lymphoma)

+ It can transform to large B cell lymphoma (Richter transformation)

Cells are „fragile" → they crush when smear is made = **smudge cells**

Markers: CD19+, CD20+, CD5+, CD23+, CD38+, Zap70+, γ or δ Ig chains; CD10-, cyclinD-

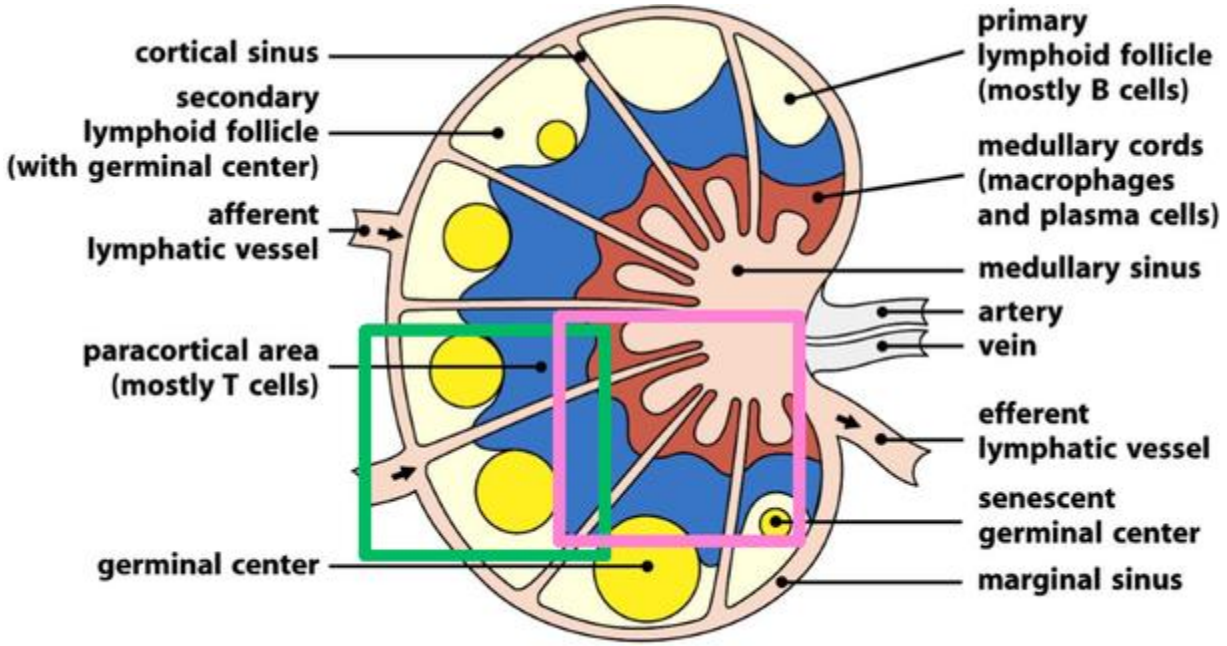
Pathogenesis: 13q14 del. → miR-15, miR-16 del. → **bcl2 overexpression** → anti-apoptosis

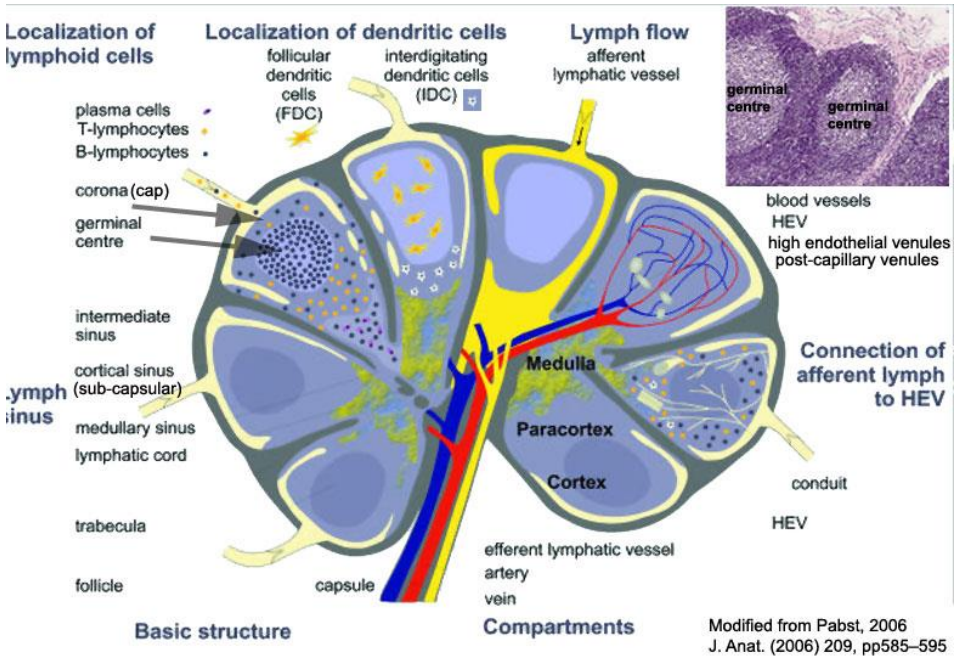
Therapy

1. **Incurable** (elderly patients, bone marrow transplantation have high mortality rate)
2. **The therapeutic goal is the asymptomatic condition, ex. biological therapies - rituximab (anti-CD20)**
3. **Indolent cases do not need any therapy**

https://commons.wikimedia.org/wiki/File:Schematic_of_the_Philadelphia_Chromosome.svg

Structure of normal lymph node



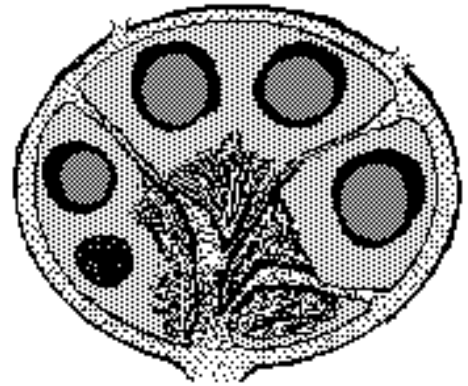


https://upload.wikimedia.org/wikipedia/commons/thumb/d/d2/Lymph_node.png/640px-Lymph_node.png
https://embryology.med.unsw.edu.au/embryology/index.php/Lymph_Node_Development

Reactive lymphadenopathy

Benign, reversible, secondary enlargement of lymph nodes - hyperplasia

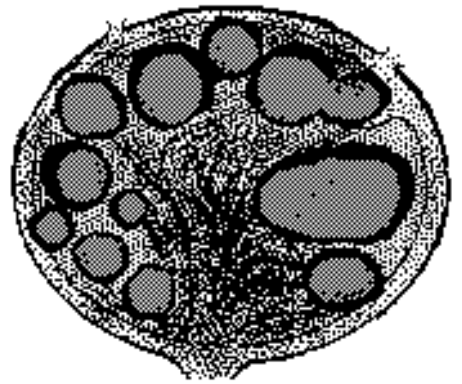
Morphological patterns (can refer to etiology)



Normal Lymph Node

1. Follicular hyperplasia

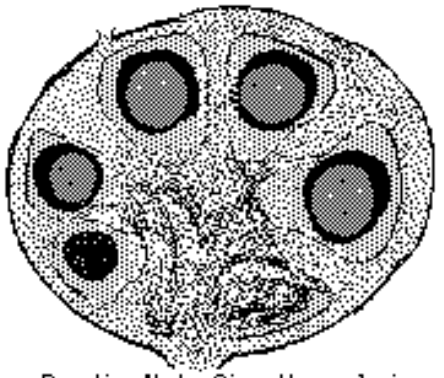
B cell response
Follicles with various size and shape
Enlarged germinal centers with prominent mantle zone
Small and large B-lymphocytes in the germinal center→ centrocytes, centroblasts
Mitotic figures
Tingible body macrophages
No dominance of any cells type
Preserved subcapsular sinus



Reactive Follicular Hyperplasia

2. Sinus histiocytosis

Dilated sinuses with groups of **histiocytes/macrophages**



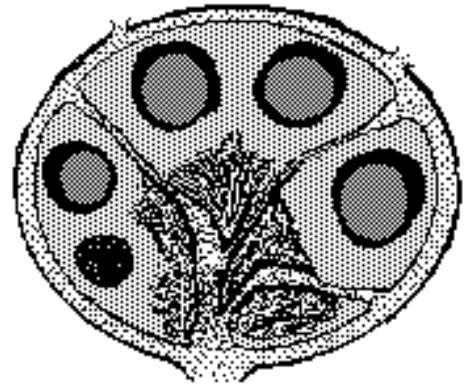
Reactive Node : Sinus Hyperplasia

https://www.med-ed.virginia.edu/courses/path/innes/wcd/reactive.cfm

Reactive lymphadenopathy

Benign, reversible, secondary enlargement of lymph nodes - hyperplasia

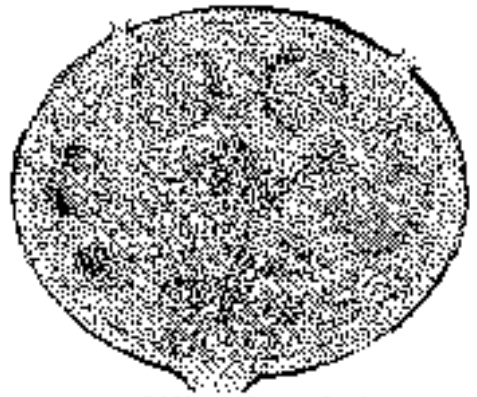
Morphological patterns (can refer to etiology)



Normal Lymph Node

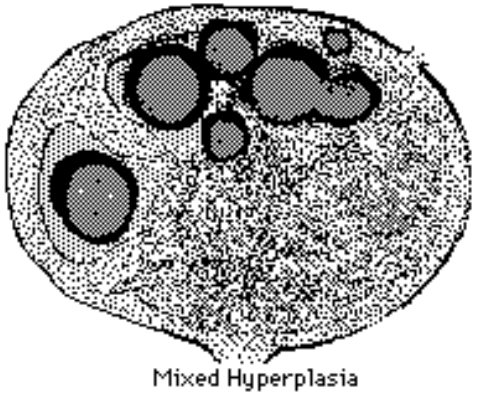
3. Diffuse paracortical hyperplasia

T cell response
Expansion of paracortical and interfollicular zones
Heterogenic cell population, no dominance of any cell type
Proliferation of HEV venules



Diffuse Hyperplasia

4. Mixed



Mixed Hyperplasia

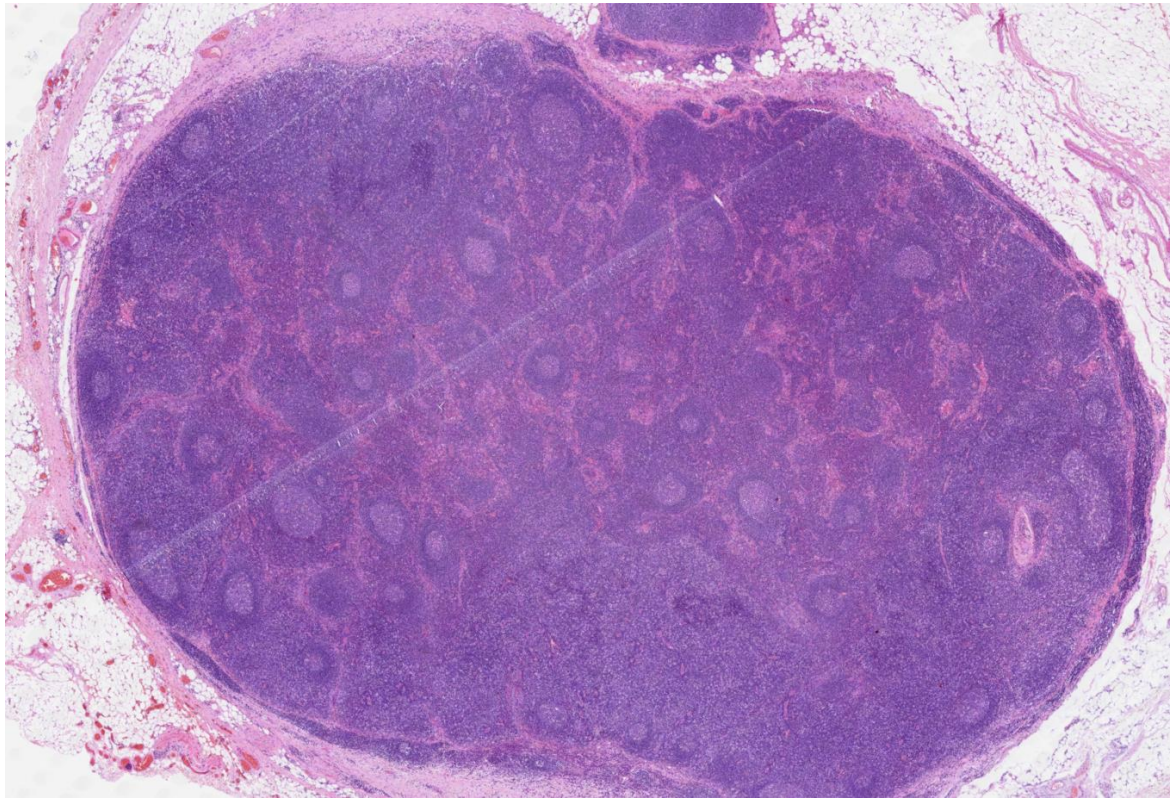
5. Acute lymphadenitis

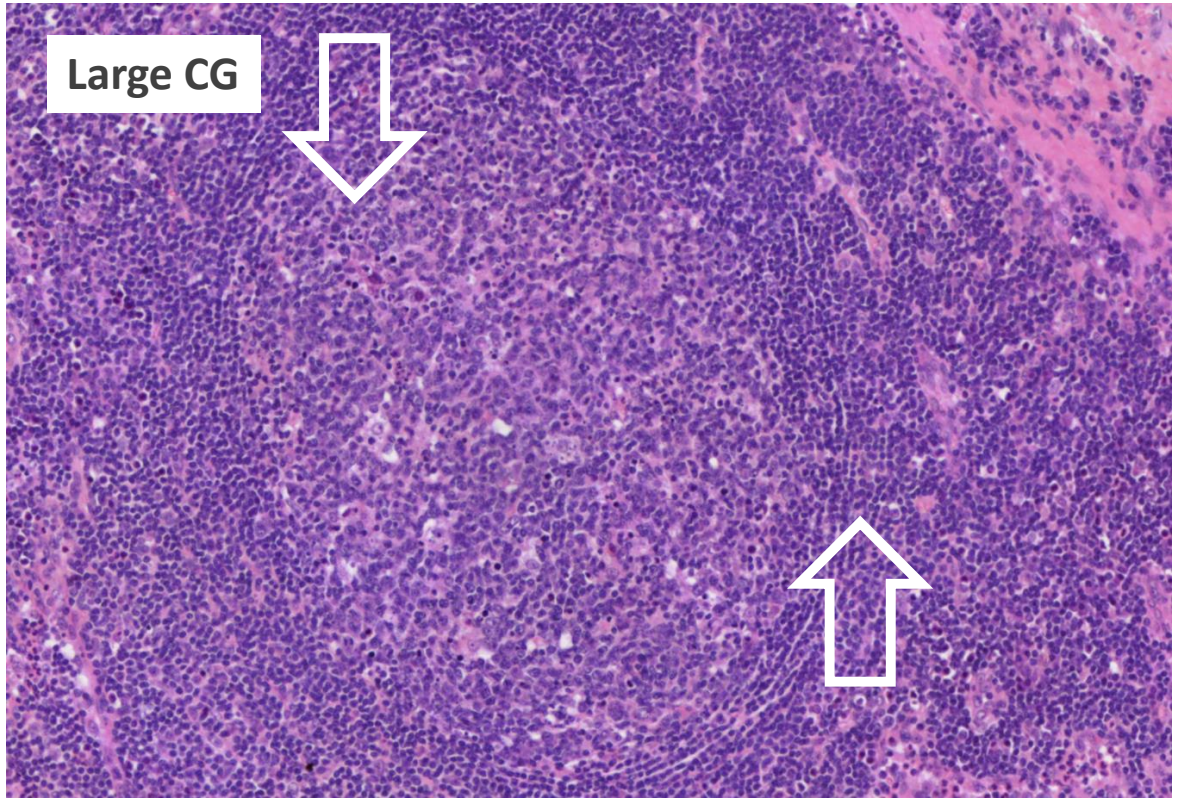
The lymph node is infiltrated by **neutrophil granulocytes**
They present in the sinuses, in severe cases the whole lymph node is necrotic

https://www.med-ed.virginia.edu/courses/path/innes/wcd/reactive.cfm

Morphology of reactive lymphadenopathy – slide

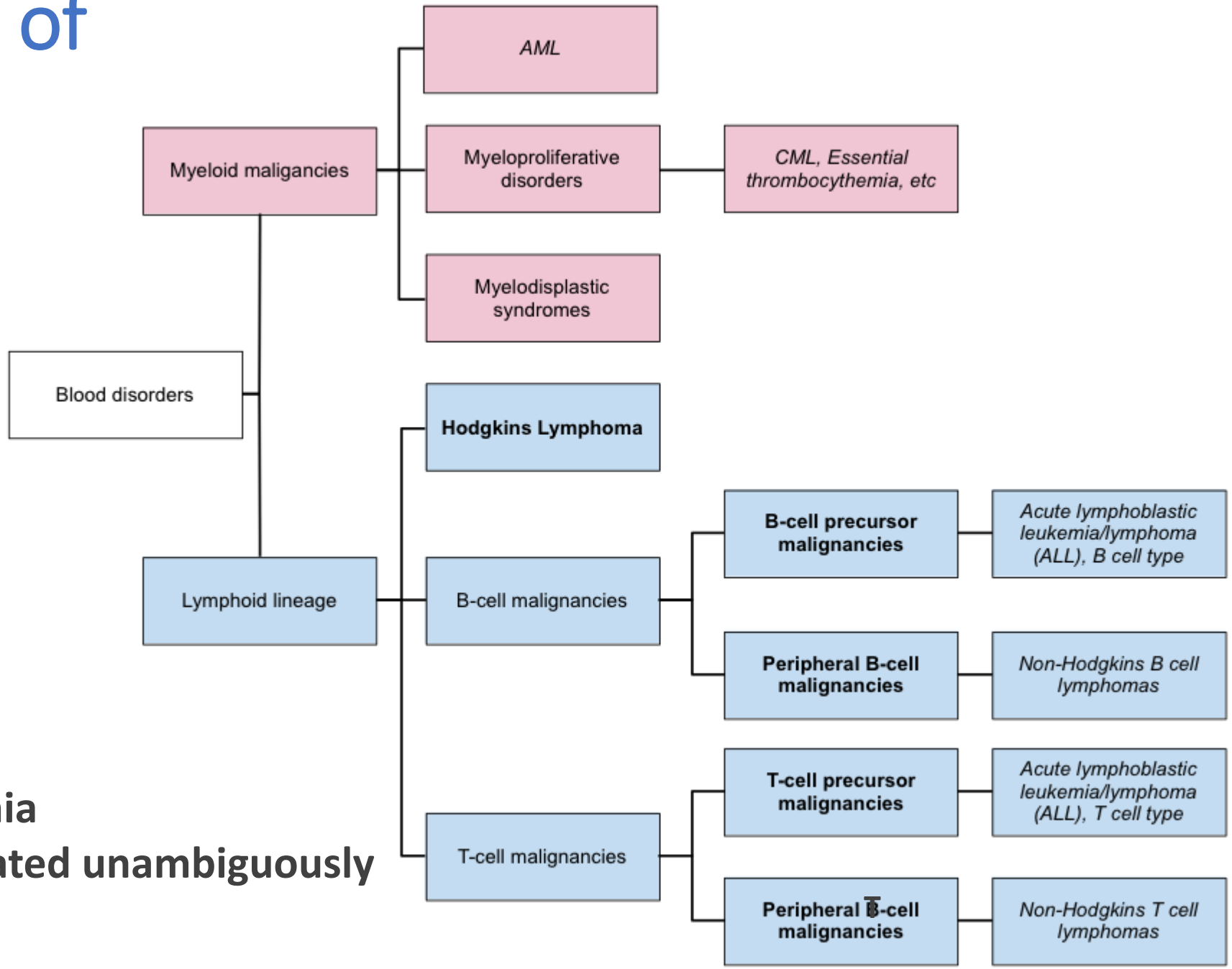
- Enlarged lymph node, but it has normal shape (not roundish)
- Lots of transformed follicles = follicular hyperplasia





Normally stratified MZ

Classification of hematologic diseases (WHO)



Lymphoma – Leukemia
cannot be separated unambiguously

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Hodgkin lymphoma

Lymphomas
85% – NHL
15% – HL

Malignant, clonal, derives from B cells

Bimodal age distribution: Most common types:
- 1st peak: age of 25-30 → nodular sclerosis
- 2nd peak: age of 50-70 → mixed cellularity

Etiology: Male > Female
- EBV
- immunodeficiency (pl. HIV, chemo, transpl.)
- autoimmune diseases (pl. RA, sarcoidosis)

Staging: I – IV
- one ore more lymphn. / extralymph organ below and/or above the diaphragm
- B symptoms +/-

5 year survival: 80-90%

Clinical presentation:
Painless enlargement of lymph nodes
- cervical lymphn. 60-70%
- axillary lymphn. 20-30%
- inguinal lymphn. 10-20%

mediastinal involvement
hepatosplenomegaly
B symptoms:
- night sweats
- weight loss
- fever

Pel-Ebstein fever
Alcohol induced pain of lymph nodes

Laboratory:
- WBC count ↑/↓
- eosinophilia, anemia, LDH↑, vitD & Ca^{2+}↑

Therapy:
- chemoradiotherapy
- the first successfully treated neoplasia

Hodgkin lymphoma – Histology

Histological classification (WHO)

Morphology

CLASSIC Hodgkin lymphoma (CHL) → = Reed-Sternberg cell (multinucleate)
= Hodgkin cell (uninucleate)

Nodular sclerosis (NSHL)
most common subtype (> 60%); good prognosis
Localization: mostly mediastinal and cervical

Mixed cellularity (MCHL)
<30%; slightly poorer prognosis
Localization: mostly abdominal lyphn. and spleen

Lymphocyte-rich (LRHL)
rare; good prognosis
Localization: mostly cervical and axillary

Lymphocyte-depleted (LDHL)
very rare (< 1%); worst prognosis
Localization: mostly below the diaphragm

CD15+, CD30+, CD25+
CD45-, CD20-

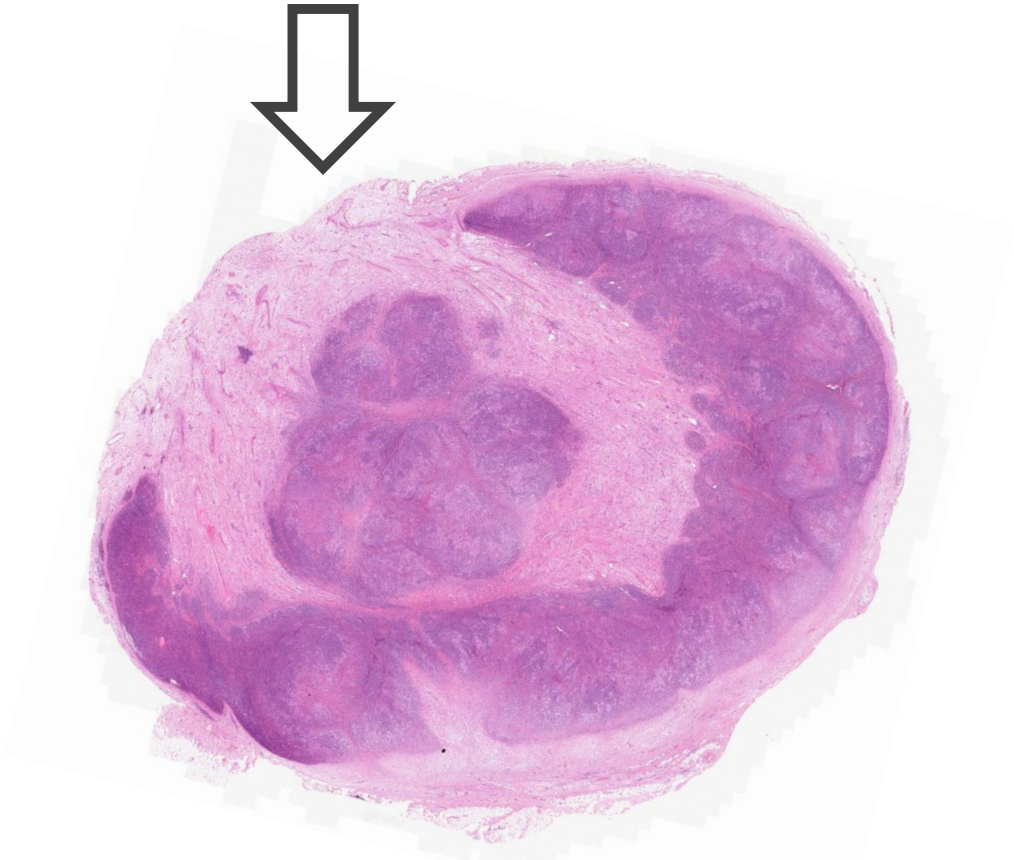
Inflammatory background:
eosinophils, neutrophils, macrophages, lymphocytes, plasma cells, fibroblasts

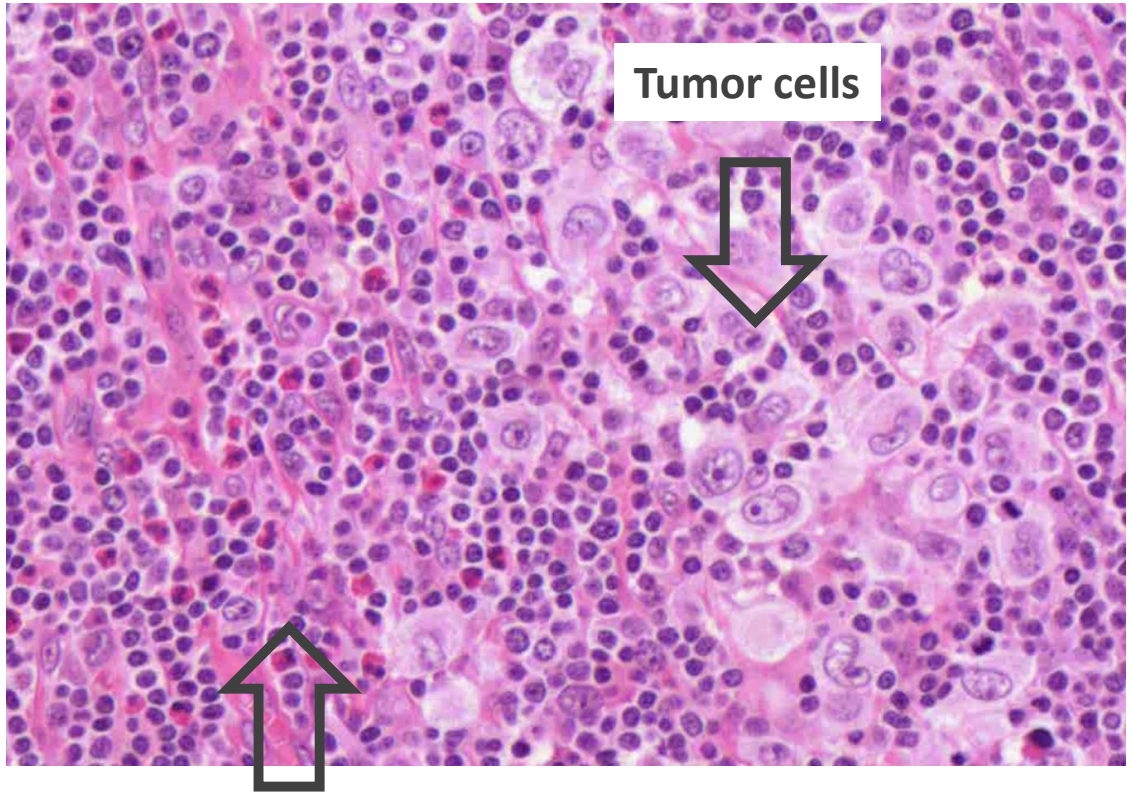
Granuloma formation can occur

NODULAR LYMPHOCYTE-PREDOMINANT (NLPHL) → = popcorn cell (multilobulated nucleus)
Rare (5%); best prognosis
CD15-, CD30-, CD20+ Ø RS cell

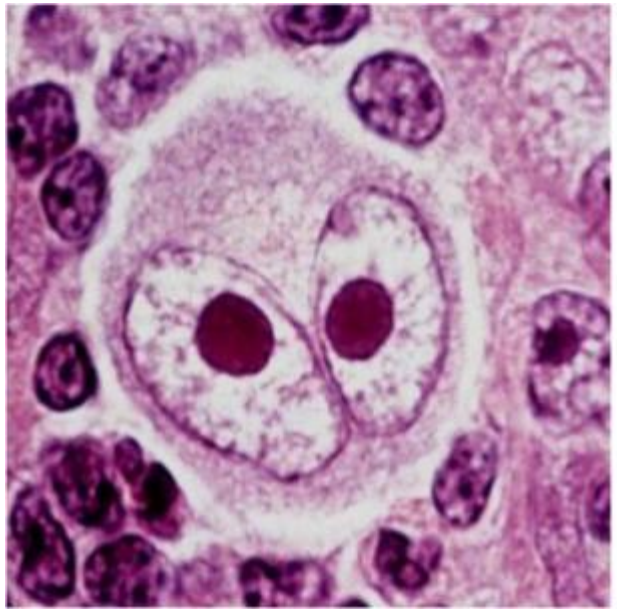
Morphology of HL (nodular sclerosis) – slide

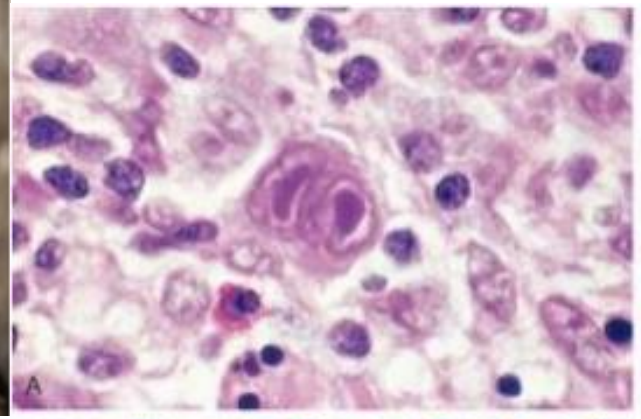
- Partial or complete involvement of lymph nodes
- Tumor cells with characteristic morphology! (ratio of tumor cells <10%)
- Accompanying sclerosis

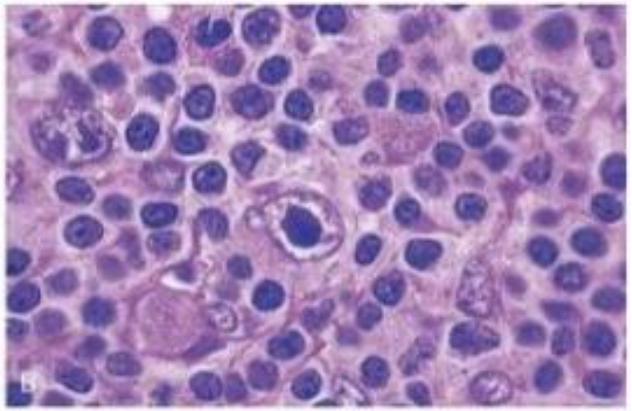


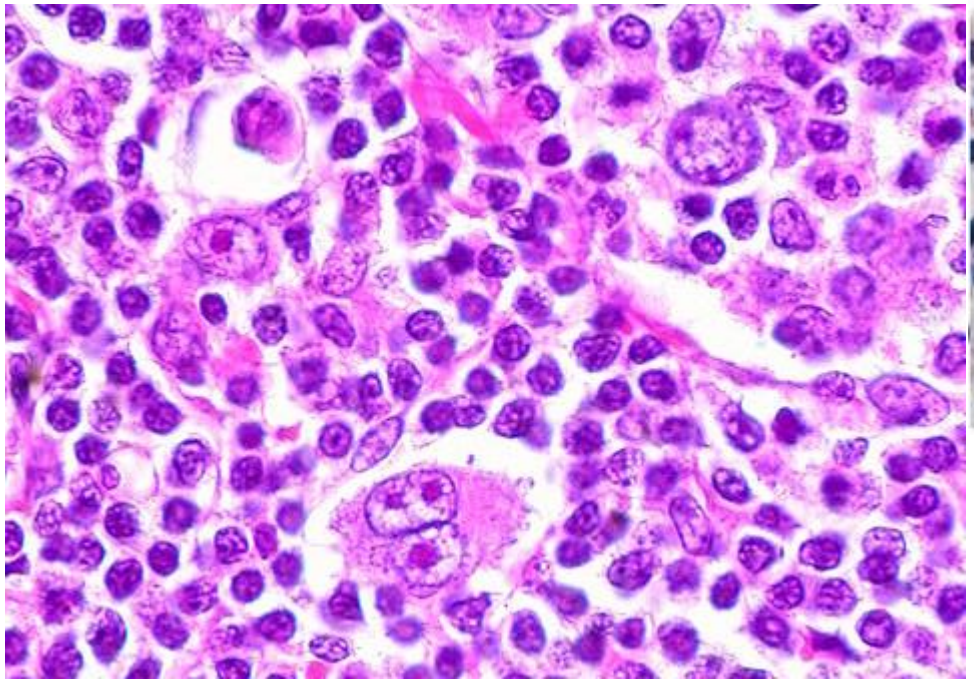


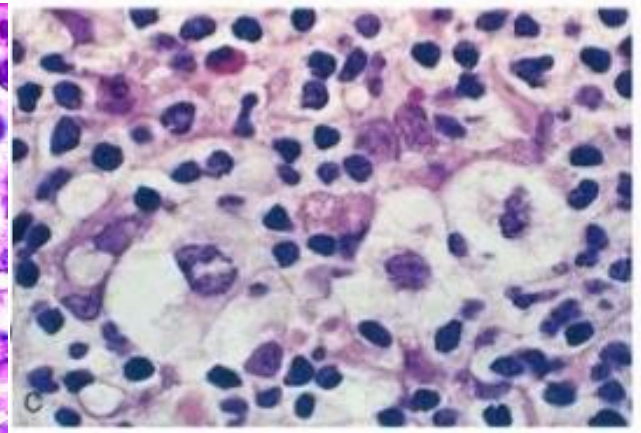
Hodgkin lymphoma – Reed-Sternberg cells

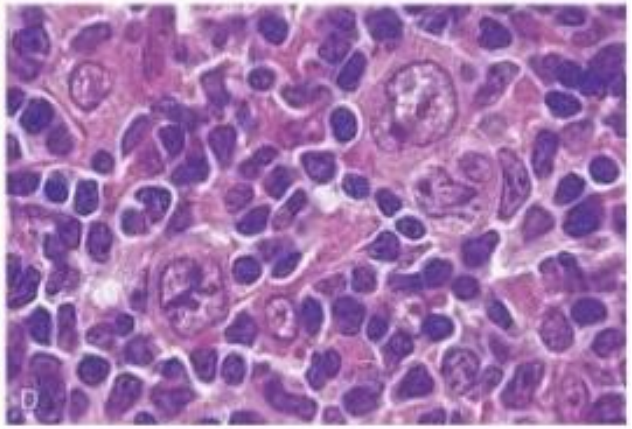












https://www.slideshare.net/Siddz0312/hodgkins-lymphoma-72629944

https://commons.wikimedia.org/wiki/File:Hodgkin_Disease,_Reed-Sternberg_Cell.jpg

Non-Hodgkin lymphoma

6th most common neoplasm (85% of all lymphomas)

Increasing incidence worldwide

Incidence grows by age → peak: **>50 y.o.**

Risk factors:

- Immunological (pl. autoimmune (pl. Hashimoto, Sjögren))
- Infectious (pl. HTLV, EBV, HIV, HCV, H. pylori)
- Genetic (pl. Klinefelter's sy, SCID)
- Environmental (pl. smoking, pesticide, herbicide)

Malignant, **monoclonal** B or T cell proliferation

N.B.: reactive, non-tumorous lymphoid proliferation is polyclonal!

Presentation: **Nodal** and/or **Extranodal**

→ **lymph node** → **skin, GI system, CNS, testicle, …**

Growth patterns: **Follicular** or **Diffuse**

Survival (if not treated):

- Low grade → 6-10 years
- High grade → months

Poor prognostic markers:

- Older age
- Involved regions↑
- LDH ↑
- β2-microglobulin ↑

B cell NHL (85%)

☺ indolent
☹ aggressive

Precursor B cell lymphoblastic leukemia/lymphoma

N.B.: acute lymphoblastic leukemia (ALL) = lymphoblastic lymphoma (LBL), same biological entities, different presentation

Mature B cell lymphoma

- Follicular lymphoma ☺
- Diffuse large B cell lymphoma ☹
- Burkitt lymphoma ☹
- MALT lymphoma ☺ / extranod. marg. zone lymphoma
- Hairy cell leukemia ☺
- Mantle cell lymphoma ☹
- Lymphoplasmocytic lymphoma / Waldenström
- B-CLL/SLL (small lymphocytic) lymphoma ☺

T cell NHL (15%)

Precursor t cell lymphoblastic leukemia/lymphoma

Mature T cell lymphoma

- Peripheral T cell lymphoma ☹
- Adult T cell leukemia/lymphoma ☹
- Mycosis fungoides ☺ / Sezary-sy ☹

Follicular lymphoma

2nd most common NHL

Most common indolent NHL

Centrocyte origin

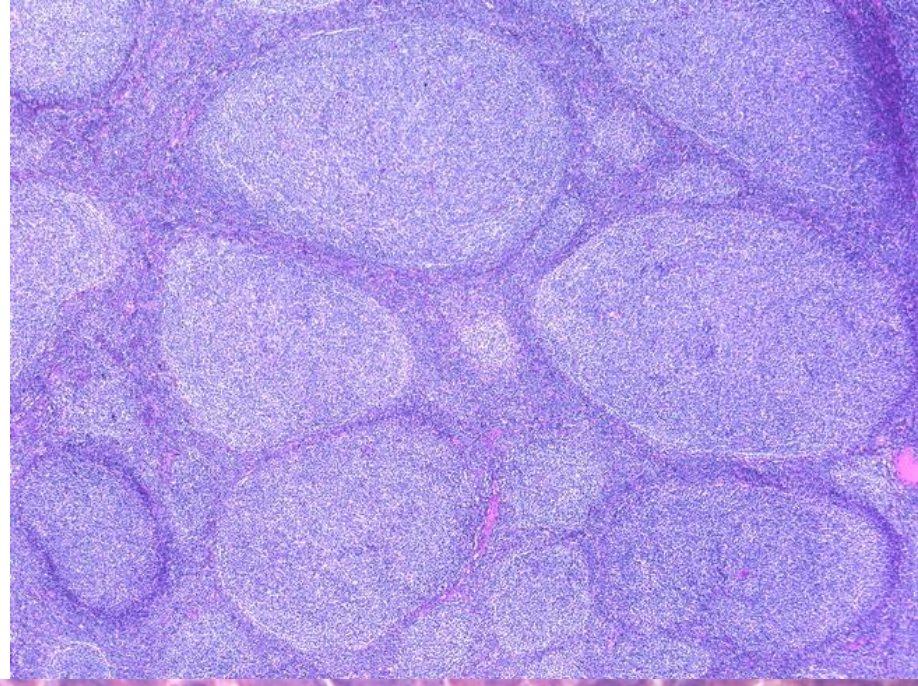
t(14;18) **bcl-2** gene translocation behind the Ig-promoter

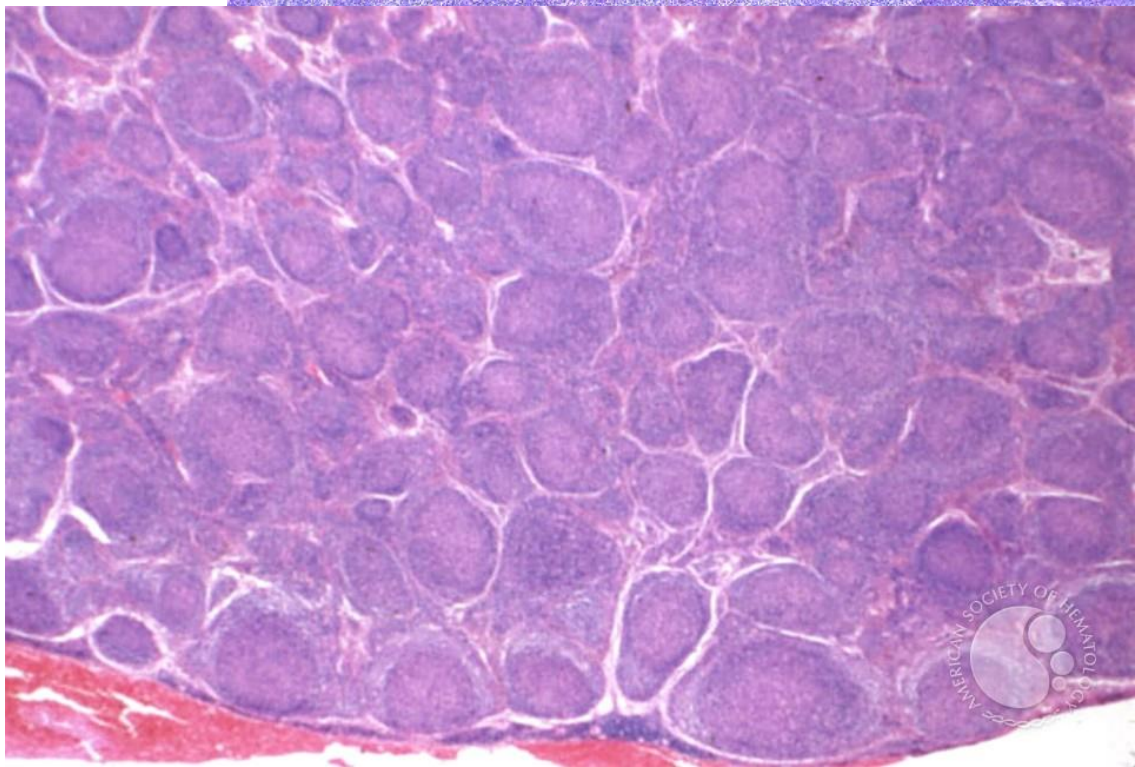
inhibition of apoptosis

Malignant follicles loose their polarity

(no light-dark zones)

Absent or thin mantle zone





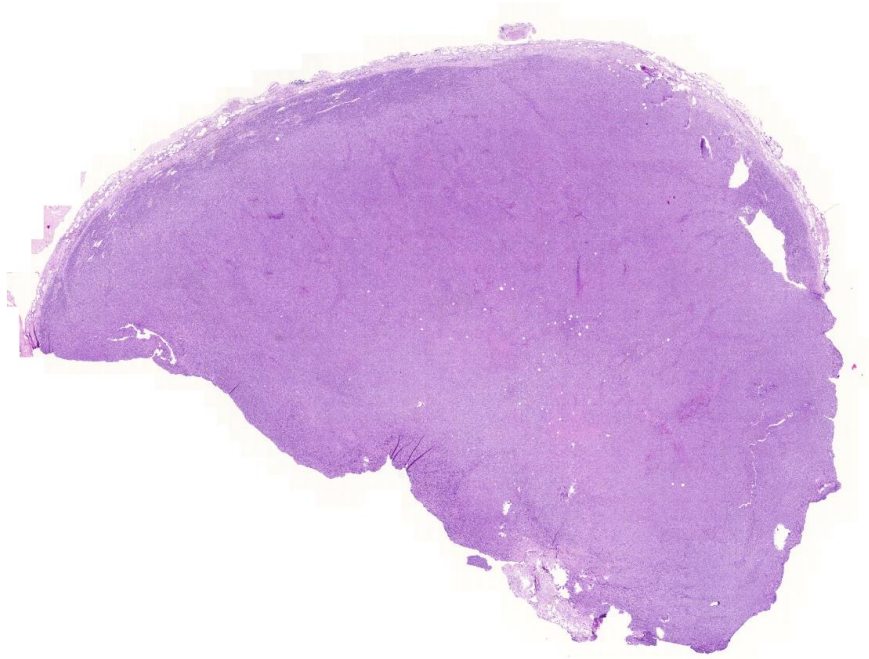
http://www.wikicell.org/index.php/Follicular_Lymphoma
https://imagebank.hematology.org/image/2050/follicular-lymphoma--1?type=upload

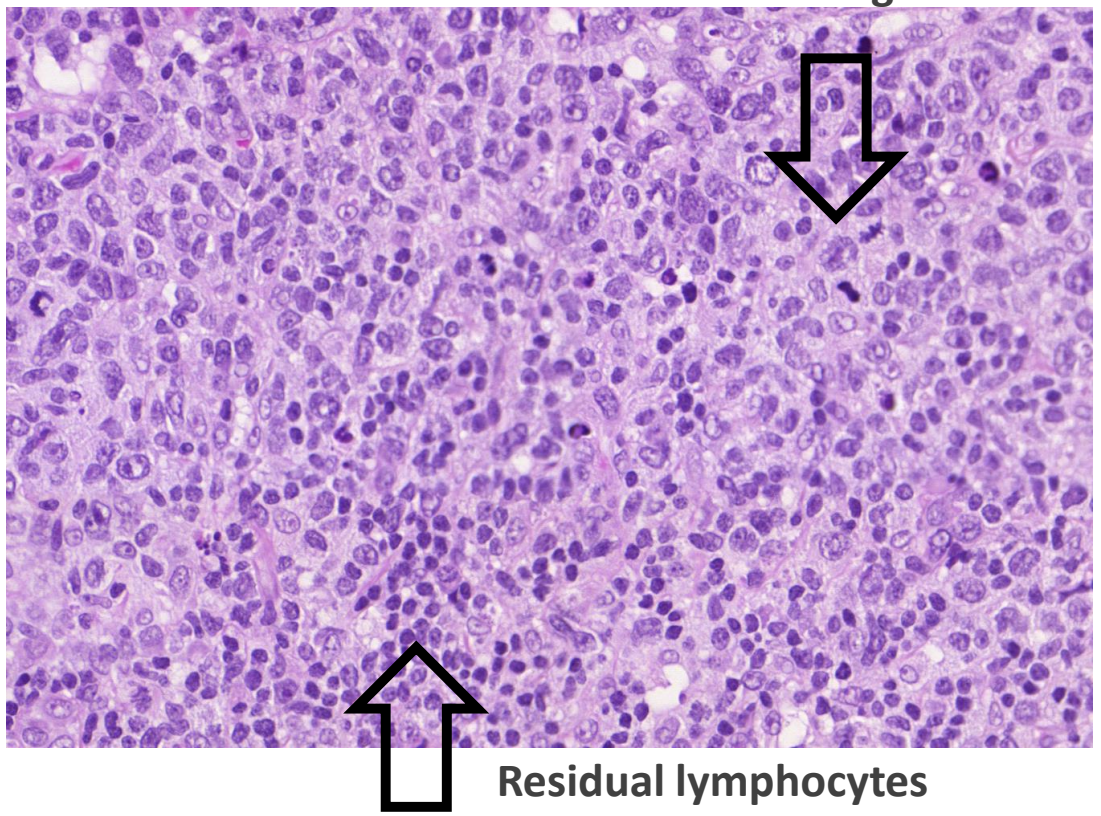
Diffuse large B cell lymphoma (DLBCL)

- **Most common** NHL (20% OF NHLs)
- Most common **aggressive** NHL
- Development: de novo
  from other type of lymphomas by transformation (Richter transformation)
- Clinical presentation:
  painless enlargement of lymph nodes in one or more regions
  or extranodal mass
  → stomach, Waldeyer ring, skin, soft tissue, brain, later bone marrow
- Rapid progression and fatal outcomes without therapy;
  60-80% complete remission with therapy

Morphology of DLBCL - slide

- Diffuse growth pattern – the basic structure of the lymph node disappears
- centroblast, immunoblast-like tumor cells (ratio of tumor cells>90%)
- Many mitotic figures - apoptoses (not in germinal centers but diffusely)



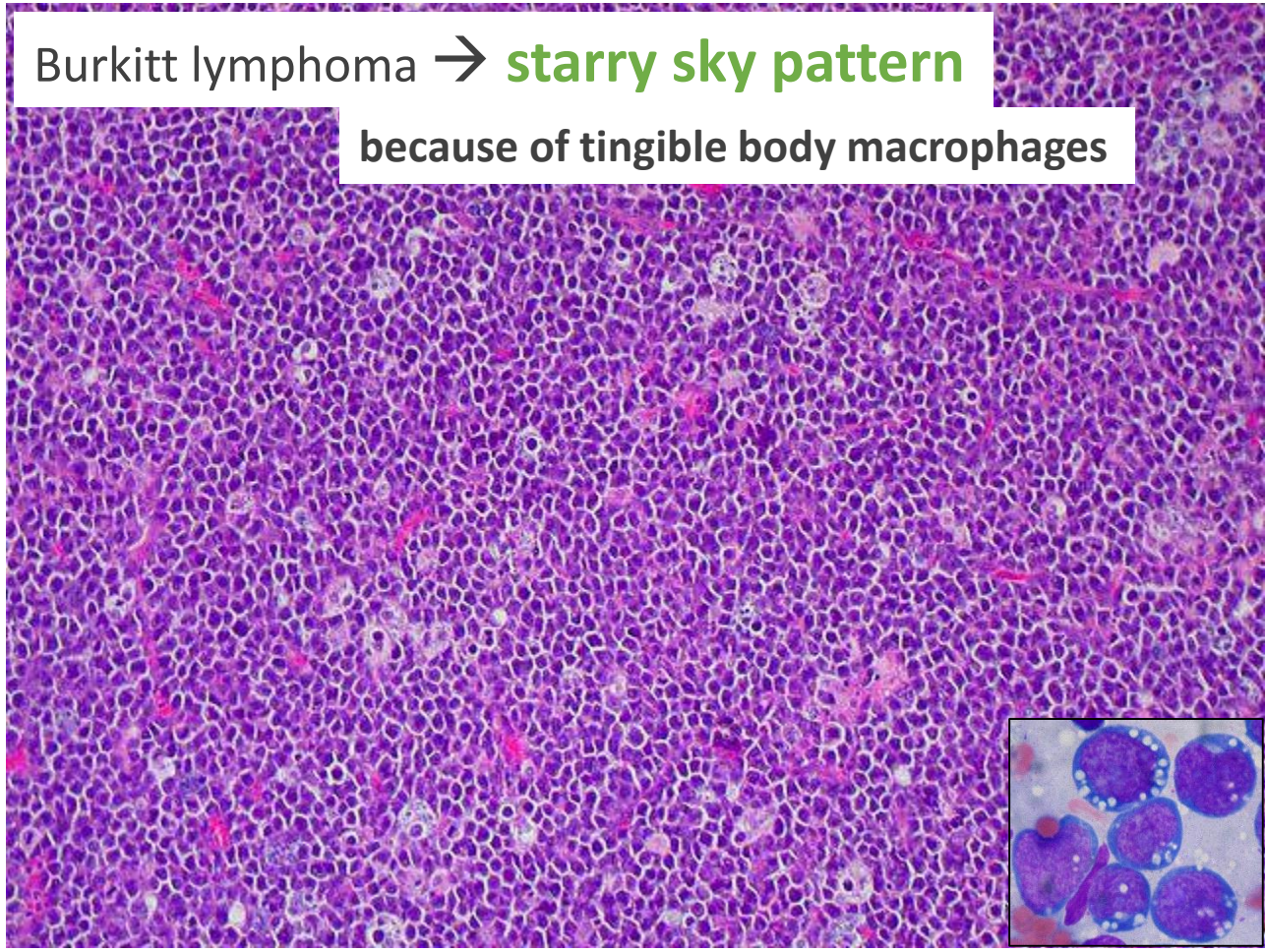


Mantle cell lymphoma

Aggressive NHL
Mantle zone origin
t(11;14) translocation of **bcl-1/cyclinD1** gene behind the Ig-promoter
stimulation of cell proliferation

Burkitt lymphoma

highly aggressive NHL
Centroblast origin
t(8;14) translocation of **myc** gene behind
the Ig-promoter
stimulation of cell proliferation
Presentation:
endemic: extranodal → **jaw**
Africa; **EBV** association
sporadic: nodal → abdominal
less association with EBV
Characteristic histology: „ **starry sky pattern**”



https://commons.wikimedia.org/wiki/File:Burkitt_lymphoma,_H%26E_(144136196).jpg

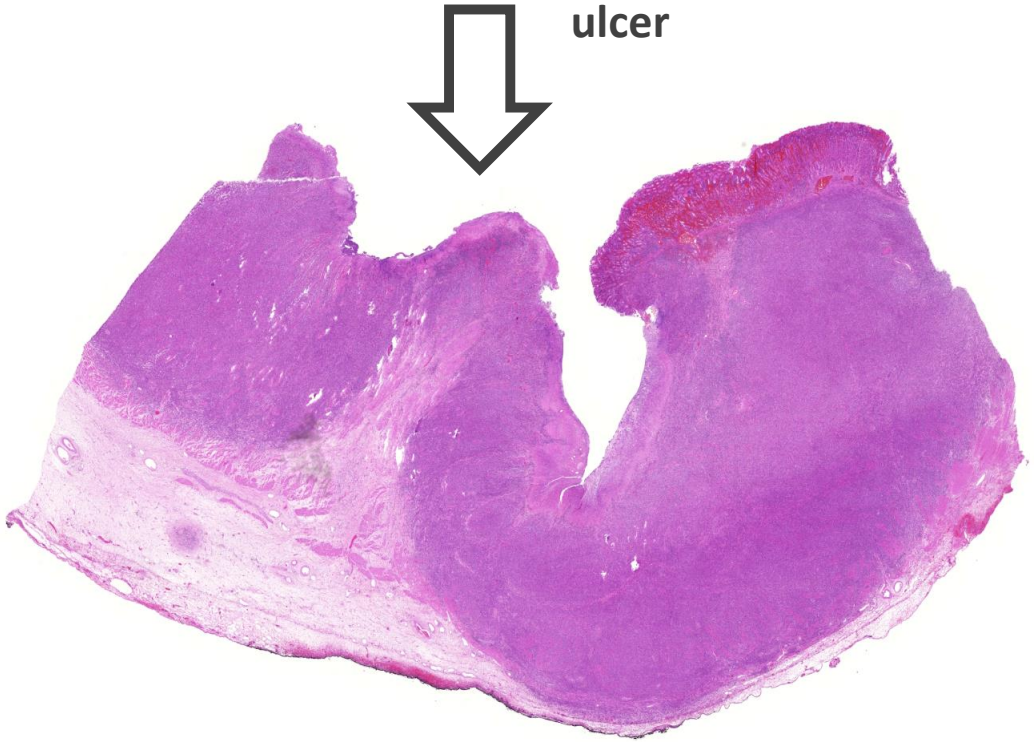
Marginal zone lymphoma

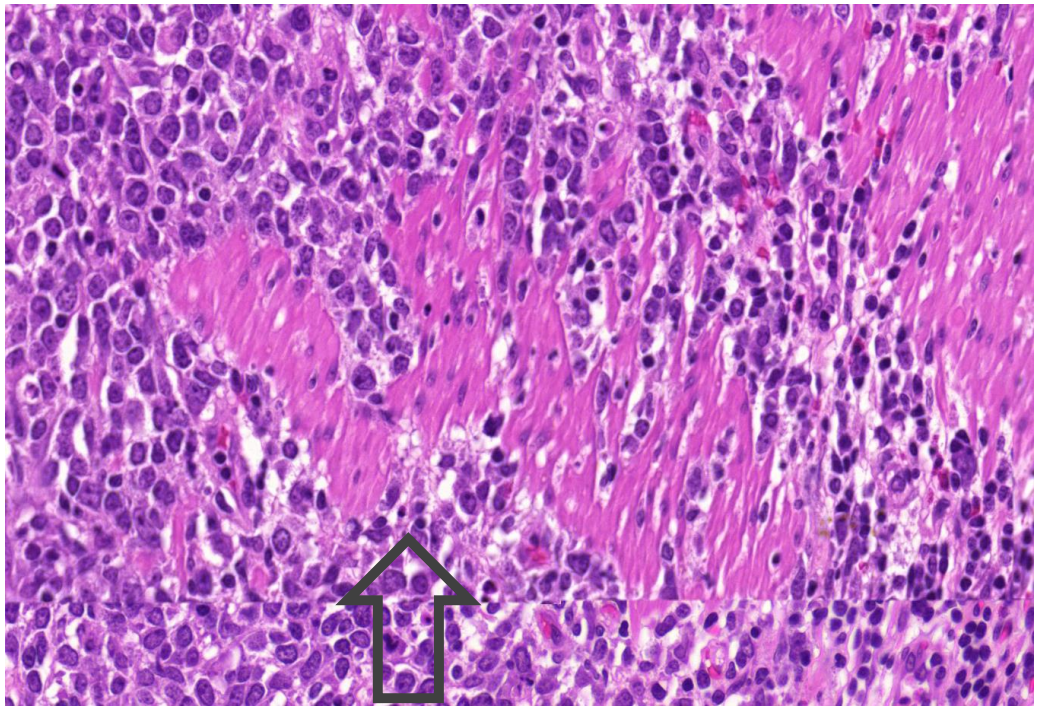
Indolent NHL
Marginal zone origin
Subtypes:

- Nodal
- Splenic
- **MALT-lymphoma (most common extranodal lymphoma)**
  - **M**ucosa **A**ssociated **L**ymphoid **T**issue
  - Most common localization: **stomach**
    cause: chronic gastritis caused by **H. pylori**
    remission after eradication of H. pylori (in 55-75%)!
  - Transformation: **DLBCL**

Stomach lymphoma morphology -slide

- Diffuse growth pattern in the stomach wall (ddg: diffuse type gastric cancer)
- Predominance of blasts, many mitotic figures = DLBCL





Infiltration of tumor cells in gastric wall

T cell lymphomas

Peripheral T cell lymphoma

Heterogenous group of diseases
Mostly disseminated

Adult T cell leukemia/lymphoma

Japan, Caribbean, Middle-Africa- endemic
Associated with **HTLV-1**

Mycosis fungoides

CD4 helper T cell origin
Involvement of dermis and epidermis → Pautrier microabscesses
Most common lymphoma of the skin
Indolent
Progression = **Sezary syndrome**

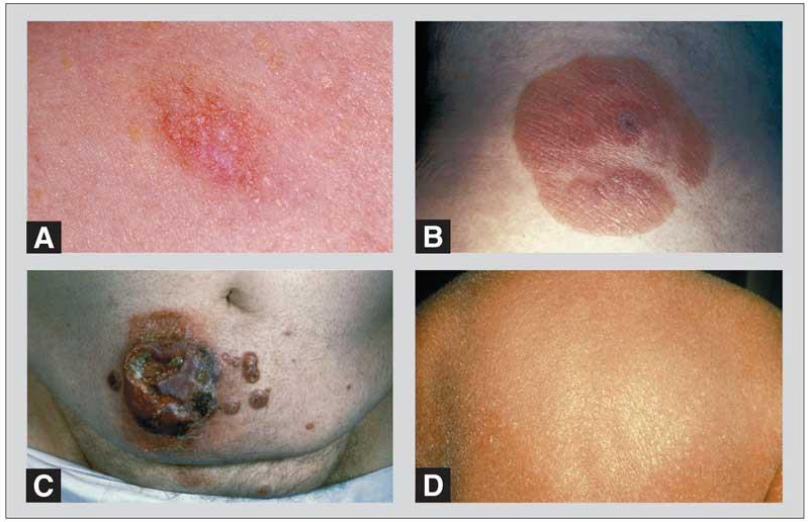


Figure 1: Clinical manifestations of mycosis fungoides—Image **(A)** shows typical early patch with erythema and mild scale; **(B)** shows a typical plaque, with raised, palpable borders, central clearing, and overlying scale; **(C)** shows a large tumor with necrosis and ulceration; and **(D)** shows generalized erythroderma. Reprinted with permission from Figure 1 in Smith B, Wilson L: *Oncology (Williston Park)* 17:1281-1288, 2003.[63]