Diseases of bone marrow, BM

- anemias
- bone marrow failure / aplastic „anemia“

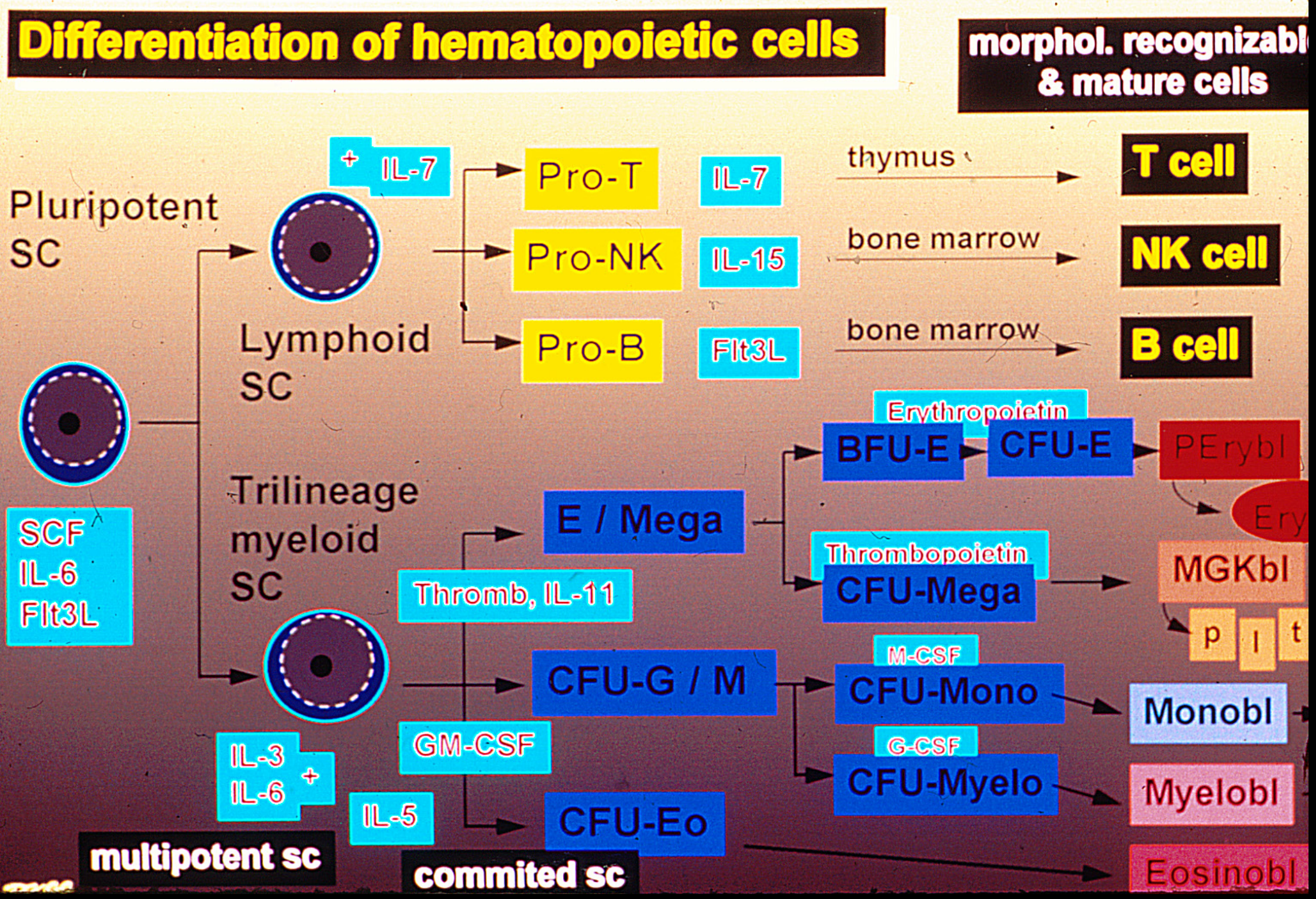
- myelodysplastic syndrome, MDS
- myeloid leukemias
- myeloproliferative syndrome / diseases, MPS

- lymphoblastic leukemia / lymphoma
- lymphocytic leukemia / lymphoma
- hairy cell leukemia

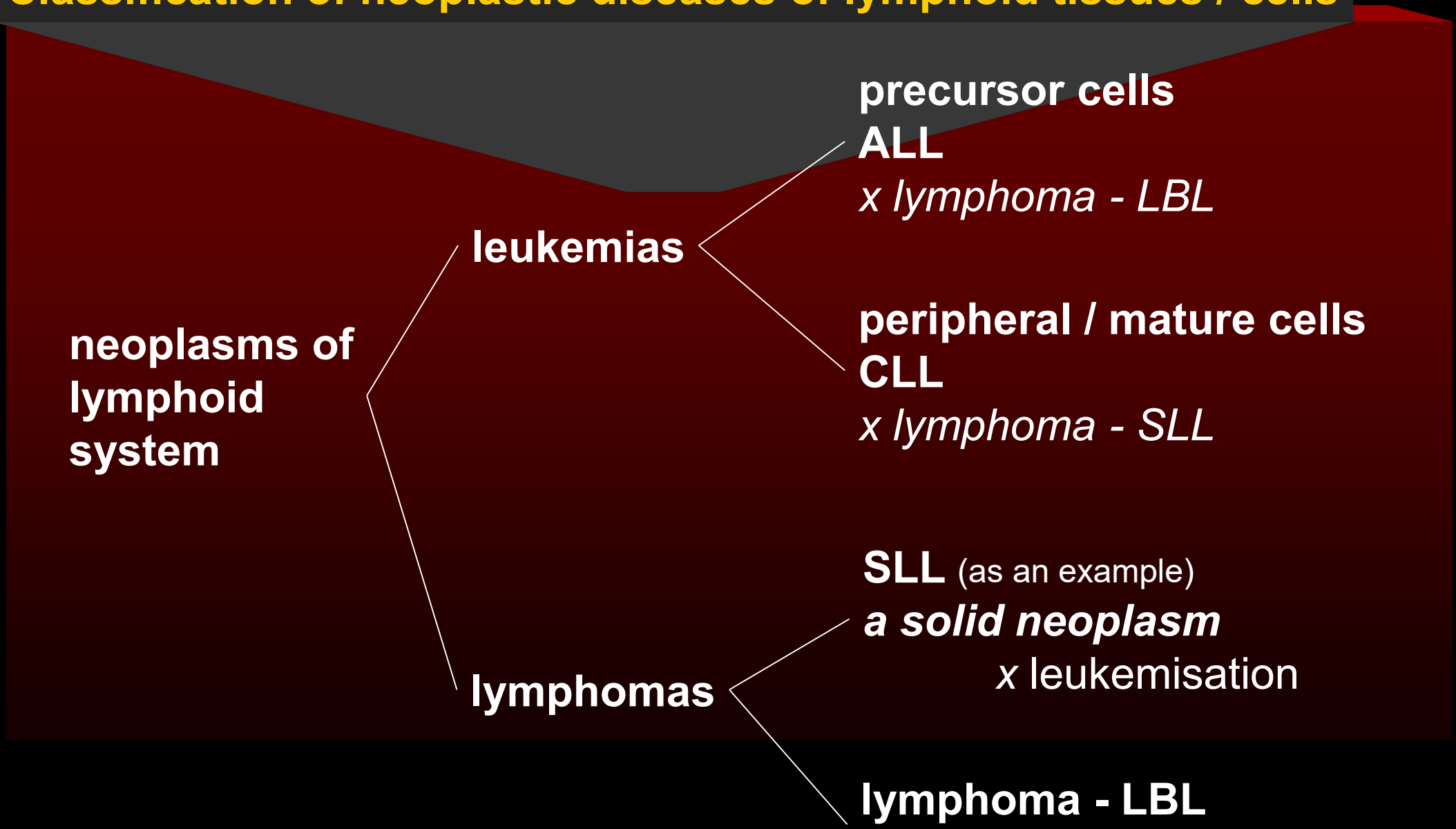
- dissemination of other diseases to BM
  - tuberculosis
  - metastatic neoplasms
    - lymphomas
    - solid neoplasms, e.g. breast carcinoma

Differentiation of hematopoietic cells

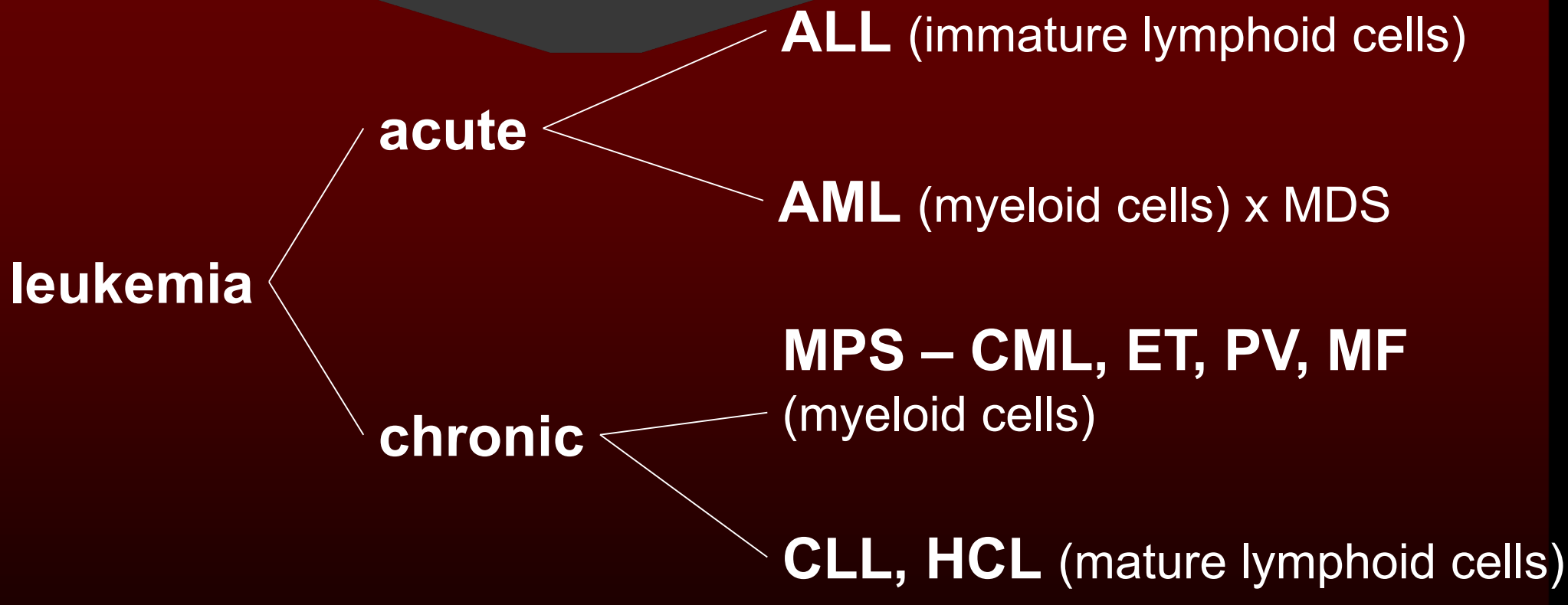
morphol. recognizabl
& mature cells



Classification of neoplastic diseases of lymphoid tissues / cells



Leukemia(s) – traditional conception and classification



Classification of neoplastic diseases of myeloid cells

neoplasms of BM progenitor cells capable of terminal differentiation in myeloid cell lines

AML

MDSs → **AML**

chronic myeloproliferative syndromes MPS - leukemias

CML, PV, ET, PMF

chronic myeloid leukemia
polycytemia vera
essential thrombocytosis
primary myelofibrosis

ALL vs AML principal cytochemical features

	MPO	ChAE	NSE	PAS	ACP
ALL	-	-	± fokální	+ 75%	± fokálně T-ly
AML	+	+	+ M4, M5	±	+

myeloperoxidase
apha-naphtyl chloroacetate esterase
non-specific esterase

Leukemia - incidence

all types of leukemias	**9,5 / 100 tis**
acute leukemias	**3,7 / 100 tis**
ALL	1,6 / 100 tis
AML	2,1 / 100 tis
chronic leukemias	**5,8 / 100 tis**

Leukemia – semantic and traditionnal conception – historical myths

leukos = white

other lineages are affected, not only white cells

.. emia = circulating neoplastic cells in peripheral blood

a disease of BM, LN, organs

*- **PB** represents a mirror of the disease arizing elsewhere (BM)*
- the leukemia means a capacity of leukemic cells to enter the circulating blood and survive in it

leukemia *vs* **aleukemic leukemia**

many non-hematologic neoplasms have circulating cells in PB

Myelodysplastic syndrome

MDS

Myelodysplastic syndrome – MDS

mutation of a stem BM cell → clonal expansion
PB pancytopenia
BM normo – hyper cellular with dysplastic features (10% hypocellular)

ČR
15 / 100 000 over 60 y

clinically
- anemia
- leukocytopenia
- thrombocytopenia

classification

Myelodysplastic syndrome – MDS

mutation of a stem BM cell → clonal expansion
PB pancytopenia
BM normo – hyper cellular with dysplastic features (10% hypocellular)

idïopathic – primary MDS
> 60y

therapy related, tMDS

genetically / molecular defined

bone marrow
dyserythropoesis
- megaloblastoid
- nuclear irregularities - budding
- ring sideroblasts

dysgranulopoesis
- pseudo Pelger-Huët cells
- hypogranulation
- myeloblasts

megakaryocytes
- multinucleated

Myelodysplastic syndrome – MDS

classification

refractery cytopenia with dysplasia of one cell line
- refractery anemia RA
- refractery neutropenia RN
- refractery thrombocytopenia RT

refractery anemia with ring sideroblasts - RARS
refractery cytopenia with multilineage dysplasia - RCMD
refractery anemia with excess of blasts 1, 2, - RAEB1,2
unclassified MDS MDS-U
MDS with isolated deletion of 5q

Myelodysplastic syndrome – MDS

mutation of a stem BM cell → clonal expansion

PB pancytopenia

BM normo – hyper cellular with **dysplastic features** (10% hypocellular)

dyserythropoesis

- megaloblastoid
- nuclear irregularities – budding, internuclear bridging, karyorhexis
- multinucleated cells
- cytoplasm - ring sideroblasts, vacuolisation

dysgranulopoesis

- pseudo Pelger-Huët cells = hyposegmented
- hypersegmentation
- hypogranulation - agranulation
- myeloblasts

megakaryocytes

- micromegakaryocytes, nuclear hypolobation, multinucleated

Myelodysplastic syndrome – MDS

most common mutations and related gene mutations:

- **Adverse** -
  ASXL1, SRSF2, DNMT3A, RUNX1,
  U2AF1, TP53, EZH2, STAG2, CBL, NRAS, BCOR

- **Favorable** –
  SF3B1

- **Neutral or uncertain** –
  TET2, ZRSR2, IDH1, IDH2

Myelodysplastic syndrome – MDS

Risk categories

four-year risk for transformation to AML (AML-t):

- **Very low – OS 10.6 years / AML-t 2.8 %**
- Low – OS 6.0 years / AML-t 5.1 %
- Moderate-low – OS 4.6 years / AML-t 11.4 %
- Moderate-high – OS 2.8 years / AML-t 18.9 %
- High – OS 1.7 years / AML-t 29.2 %
- **Very high – OS 1.0 years / AML-t 42.8 %**

Akutní myeloidní leukémie - AML

Acute myeloid leukemia - AML

BM > 20% blasts ↓ hemopoesis

PB ~ 10 000 / 100 000 x aleukemic form

organs ±

tumoriform myelosarcoma, chloroma

clinical features:

bleeding

infections

fatigue ...

organs ± skin, gingiva

CSF + CNS

AML - FAB morphological classificatkon / WHO „not otherwise specified“

M0	minimally differentiated	2-3%
M1	AML without differentiation	20%
M2	AML with maturation	30-40%
M3	acute promyelocytic	5-10%
M4	acute myelomonocytic	15-20%
M5	acute monocytic	10%
	M5A nízce diferencovaná M5B diferencovaná	
M6	acute erytroleukemia	5%
M7	acute megakaryocytic	1%

AML / WHO classification

		prognosis
I. AML with stable chromosomal rearrangements		
t(8;21)(q22;q22)	CBFα / ETO	favourable
inv(16)(p13;q22)	CBFβ / MYH11	favourable
t(15;17)(q22;q11)	RARα / PML	intermediate
t(11q23;v)	MLL / various genes	unfavourable
II. AML with multilinear dysplasia		
with preceeding MDS		very unfavourable
without preceeding MDS		unfavourable
III. AML after previous chemotherapy		
alkylating drugs		very unfavourable
inhibitors of topoizomerase II	*(epipodofylotoxin)*	very unfavourable
IV. AML not otherwise specified		
AML defined by a lineage differentiation		intermediate
V. AML of uncertain lineage		
undifferentiated, bifenotypical, bilinear		

Chronic myeloproliferative syndromes

Myeloproliferative diseases

Philadelphia chromosome + (ABL-BRC)
- chronic myeloid leukemia (CML) – Philadelphia chromosome +

Philadelphia chromosome –
frequently JAK2 gene + (Janus kinase 2), and other genes
- essential thrombocytemia (ET)
- polycytemia vera (PV)
- primary myelofibrosis (PMF)

- chronic eosinophilic leukemia
- chronic neutrophilic leukemia
- systemic mastocytosis (SM)

lymphoid leukemias / lymphomas

lymphoblastic / lymphocytic leukemias

Neoplasms of B & T precursor cells - acute lymphoblastic leukemia

Morphological classification of ALL – FAB, now only orientative

Cytological features	L1	L2	L3
size of cells	small	heterogenous	intermediate
cytoplasma	chudá	různorodá	střední
basofilie	mírná	různá	výrazná
vakuolizace	různá	různá	prominentní
nukleoly	nenápadné	1-x, velké	1-x, výrazné
tvar jádra	pravidelný	nepravidelný	kulatý
rozštěpení	±	+	-
chromatin	homogenní	heterogenní	jemně hrudkovitý

Immunological classification of ALL

	TdT	CD34	CD10	CD19	clg μ	slg μ // κ / λ	
EPB	++	+	++	+++	-	-	-
PB	++	+	++	+++	+++	-	-
TPB	+	+	++	+++	+++	+++	-
B	-	-	+	+++	+++	+++	+++

	TdT	CD34	CD10	CD19	CD7	CD5	CD3
T	++	+	+	-	+++	+++	+

TdT - terminal deoxynucleotidyl transferase

Acute **B** lymphoblastic leukemia / lymphoma

aberration	frequency	prognosis	special features
t(12;21)(p13;q22) **ETV6-RUNX1**	**25%**	**very favourable** **relaps late**	**not in infants, rarely adults**
hyperdiploidy **> 50 až < 66 ch**	**25%**	**favourable, esp.** **trisomy 4,10,17**	**not in infants, rarely adults**
t(9;22)(q34;q11.2) **BCR-ABL1**	**2-4% children** 25% adults	**very unfavourable**	
t(v;11q23) **MLL rearrang.** most 4q21 AF4	**infants mostly** **esp. by** 6m	**unfavourable**	**may appear in utero** **PB high load of blasts** **CNS+**
hypodiploidy **< 46 ch**	**children** **adults**	**unfavourable** **esp. by 44 chr.**	**sine**
t(1;19)(q23;p13.3 **TCF3-PBX1**	**6%** less in adults	**average** on intensive th	**pre-B frequenty**
t(5;14)()q31;q32 **IL3-IGH**	**< 1%**	**average**	typical - eosinofilia

Neoplasms of B & T precursor cells - acute lymphoblastic leukemia

clinical manifestation

ALL-B as leukemia

ALL-T as Ílymphoma

symptoms

bone marrow failure

bone pain

- generalised lymphadenopathy
- hepatosplenomegaly

expansion of thymus in ALL T

infiltration of non-hemopoetic organs

- testicles
- CNS – meninges / cerebrospinal fluid

Acute lymphoblastic leukemia, ALL

prognosis

less favourable

age < 2 years
adolescents and adults
blasts v PB > 100tis
„unfavourable“ chromosomal translocations
and a molecular profile
e.g. t(9;22)

favourable

age 2 – 10 years
early-pre B fenotype
low number of blasts in PB
hyperdiploidy of neoplastic cells
„favourable“ chromosomal translocations
and a molecular profile
t(12;21)

Chronic lymfocytic leukemia (CLL) / small cell B lymphoma (SLL)

6,7% NHL

90 % chronic lymfocytic leukemia

CLL 9823/3
SLL 9670/3

Chronic lymfocytic leukemia (CLL) / small cell B lymphoma (SLL)

CLL > 4x10^9/l v PK (fragile cells, „crushed“ cells in smears)
„B“ line

BM **interstitial infiltration / non-paratrabecular / diffuse**

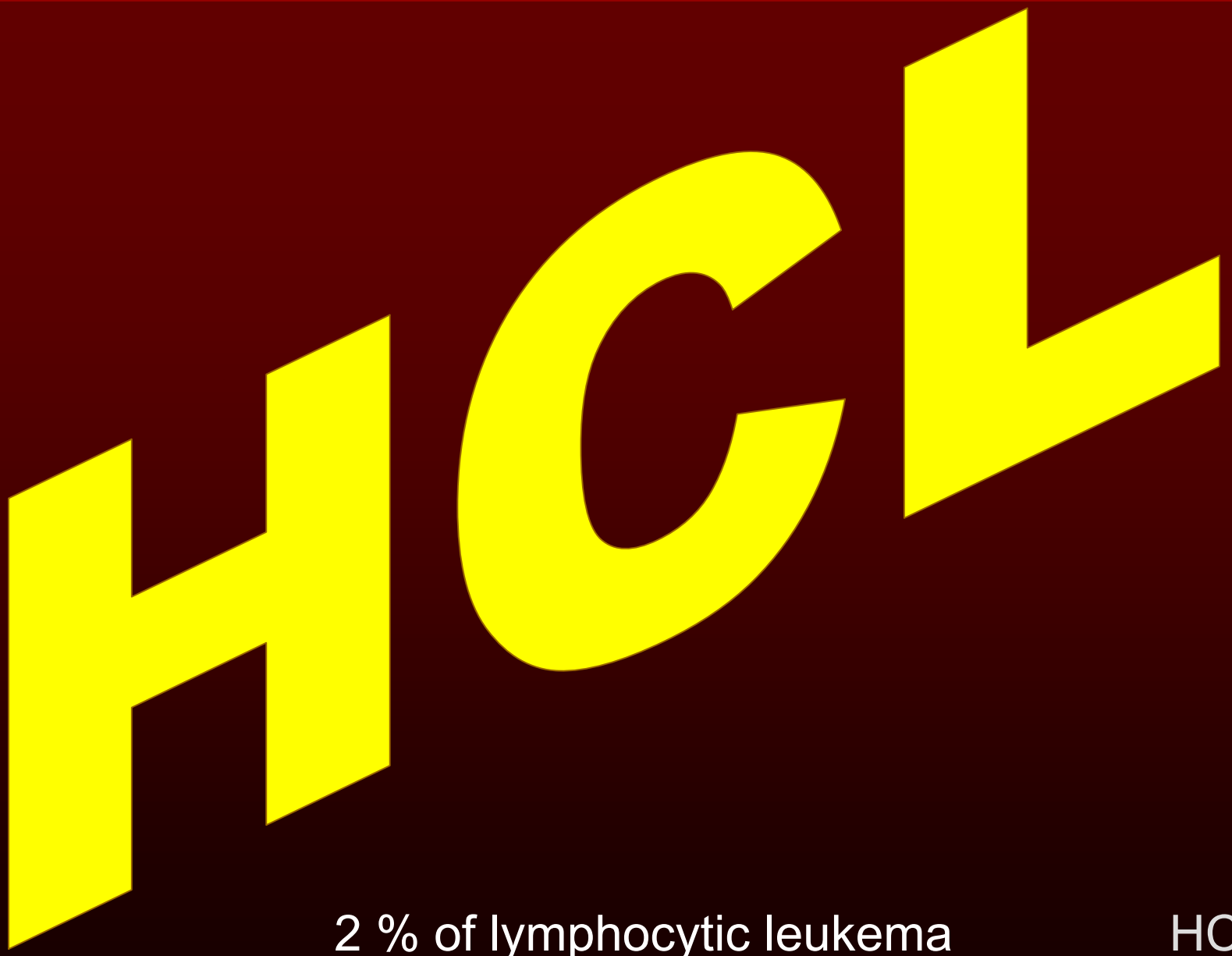
LN **diffuse** **small lymphocytes**
proliferative centers **prolymfocytes & paraimunoblasts**

PB **variable**
SLL without circulating mass of neoplastic cells
CLL sometimes even 200 000

CLL / SLL – immunohistochemical profile

immunohistochemistry		flow cytometry	
CD79α	+	CD19	+
CD20	±	CD23	+
CD23	±	CD5	+
CD5	+	Sm Ig IgM	+
		IgD	±
CD10	-	CD10	-
cyklín D1	-	FMC7	-

Hairy cell leukemia



2 % of lymphocytic leukema

HCL 9940/3

Hairy cell leukemia, HCL

age median 55 let
gender 5 : 1

BM
splenomegaly ↑ up to 3 000 g
PB low numbers of HCs/ cytopenia, typical monocytopenia
játra, LU, kůže ±

neoplastic cells
nucleus „bean like“
chromatin ground glass like *vs* lymfocyte
nucleolus inconspicuous *or* missing
cytoplasm abundant, mild basophilia, hairy projections, DBA44+
genetics – cyclin D1 ↑, without t(11;14)

Hairy cell leukemia

BM interstitial infiltration / spotty like

Spleen white pulp infiltration
block of blood flow → lakes of erythrocytes
+ neoplastic cells in around

prognosis favourable

reactive to a common chemotherapy
esp. interferon alfa 2b
+ purinová analogs

splenectomy