

Hematopathology

Diseases of bone marrow - part 2

Acute myeloid leukaemia

Acute myeloid leukaemia (AML)

= clonal neoplastic disorder of hematopoietic stem cell characterized by **proliferation and accumulation** of **immature myeloid cells** and by **presence** of these **neoplastic cells in peripheral blood** (**$\geq 20\%$ of blasts** in PB or BM)

= group of distinct but related diseases

Acute myeloid leukaemia (AML)

- **30%** of all adult leukaemias, 80% of acute leukaemias
- Incidence 2-4: 100 000 (increases with age; median 69 years)

Acute myeloid leukaemia (AML)

Etiopathogenesis

- Exogenic factors: radiation, carcinogens (benzen, pesticides, cytostatic drugs etc.) etc.
! post cytotoxic AML with very poor prognosis !
- Endogenic factors: genetic predisposition syndromes
(Down sy., Fanconi anaemia, ataxia teleangiectatica, Wiskott-Aldrich sy., Bloom sy. etc.)
- multiple genetic alterations in hematopoietic stem cells
 - dysregulated **proliferation** and **maturation arrest** of HSCs
 - clonal expansion of neoplastic immature cells (blasts)
 - blockage of normal hematopoiesis → **pancytopenia**
 - release of tumor cells to PB → **leukocytosis** consisting mostly of neoplastic blasts
 - infiltration of extramedullary organs by neoplastic cells (not that common)

Acute myeloid leukaemia (AML)

Manifestation

- Typically **sudden onset**
- Peripheral blood:
 - **leukocytosis** with so called „**hiatus leukemicus**“
(consisting mainly of **myeloid blasts** vs. just **minimal differentiated white blood cells**)
 - **anaemia and thrombocytopenia**
- **Hyperviscosity syndrome, fatigue, malaise, weight loss, night sweats**
- Usually no organomegaly
- Infiltration of extramedullary sites can be present, but not much common

Acute myeloid leukaemia (AML)

Classification

- **AML with defining genetic abnormalities**
- **AML defined by morphology**
- **Myeloid sarcoma**
- **Secondary AML**

Acute myeloid leukaemia (AML)

with defining genetic abnormalities

- Most cases of all AML
- **Acute promyelocytic leukaemia with *PML::RARA* fusion**
 - **excellent prognosis** (long-term survival rate >90%)
 - common complications = **DIC**
- **AML, myelodysplasia related**
 - either history of MDS (without cytotoxic therapy)
or genetic alterations associated with MDS
 - **poor prognosis** (long-term survival 10-20%)

Acute myeloid leukaemia (AML)

defined by morphology

- No specific genetic alteration
- Pathogenesis still not completely understood

Acute myeloid leukaemia (AML)

Myeloid sarcoma

- **Solid mass** in extramedullary site composed of myeloid blasts
- Most often during relapse of AML, only rarely as primary manifestation of AML
- Reported in approximately 5% of patients with AML

Acute myeloid leukaemia (AML)

Secondary AML

- **AML, post cytotoxic**
 - history of chemotherapy or radiotherapy
 - usually complex genetic changes
 - **very poor prognosis** (median survival time < 1 year)
- **AML associated with germline predisposition**
 - prognosis depends on type of germline predisposition syndrome

Acute myeloid leukaemia (AML)

Classification

- **AML with defining genetic abnormalities**
- **AML defined by morphology**
- **Myeloid sarcoma**
- **Secondary AML**

Acute myeloid leukaemia (AML)

Diagnostic approach

- **Peripheral blood count:** leukocytosis ($\geq 20\%$ blasts), cytopenia
- **Cytology:** morphology of blasts
- **Flow cytometry:** aberrant immunophenotype
- **Molecular examination:** detection of defining genetic alterations
- **Bone marrow biopsy:** in most cases not needed for the diagnosis

Acute myeloid leukaemia (AML)

Treatment

- Different based on type of AML, clinical performance of the patient etc.
- Mostly chemotherapy followed by allogenic transplantation of HSCs
- Complications:
 - tumor lysis syndrome
 - GvHD

LYMPHOID NEOPLASMS

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL)

= clonal neoplastic disorder of **precursor lymphoid cells** (B or T) characterized by **proliferation of immature lymphoid cells (lymphoblasts)** with massive involvement of **bone marrow** and usually also **peripheral blood**

vs.

Lymphoblastic lymphoma (LBL)

= same neoplastic cells but primary forming **extramedullary mass** with absent or mild involvement of bone marrow and peripheral blood (< 25% of blasts in blood and bone marrow)

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

- **Most common** type of malignant tumor **in childhood**
- Incidence (in first 4 years of life) 7 : 100 000 (decreases with age)
vs. incidence in adults 1-1,5 : 100 000

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Etiopathogenesis

- Similar to AML
- Exogenic factors: radiation, carcinogens, infections (EBV, HIV etc.) etc.
- Endogenic factors: genetic predisposition syndromes

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Classification

- **B-ALL/LBL** (**85%** of all ALL/LBL)
 - typically young children (75% of patients are < 6 years)
- **B-ALL** (90%)
- **B-LBL** (10%)
- **T-ALL/LBL** (15% of all ALL/LBL)
 - more common in **adolescents, male** predilection
- **T-ALL** (25%)
- **T-LBL** (75%)

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Manifestation

- **Common features:**
 - **Sudden onset**
 - Fatigue, malaise, weight loss, night sweats...
 - **Hepatosplenomegaly**
 - **Infiltration of extramedullary tissues**

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Manifestation

- **B-ALL**

- Massive infiltration of bone marrow → **bone marrow failure**
- Usually also **leukocytosis** consisting mainly of **lymphoblasts**
- **Infiltration of extramedullary tissues:**
 - CNS, intrabdominal organs, testes, pleura, pericardium...
 - **bone pain** (from massive infiltration of bone marrow and periosteum)
 - **joints pain** (from infiltration of synovial cavity)

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Manifestation

- **B-LBL**
 - **Lymphadenopathy**
 - Tumour masses in **skin** or **soft tissues**
 - **Osteolytic masses in bones**

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Manifestation

- **T-ALL**

- Infiltration of bone marrow but usually not massive (bone marrow failure less common than in B-ALL)
- **Leukocytosis** consisting mainly of **lymphoblasts**
- **Hepatosplenomegaly**
- **Lymphadenopathy**
- **Tumour mass** typically in **mediastinum** (→ same complications as in T-LBL)

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Manifestation

- **T-LBL**
 - **Rapidly growing mass in anterior mediastinum**
 - compression of intrathoracic organs
 - dyspnea or even **respiratory failure**
 - **superior vena cava syndrome**
 - Pleural and pericardial effusions are common

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Diagnostic approach

- **Peripheral blood count:** leukocytosis +/- cytopenia
- **Cytology:** morphology of blasts
- **Flow cytometry:** immunophenotype (differentiating between B- and T-)
- **Molecular examination:** detection of some typical genetic alterations
- **Bone marrow biopsy:** in most cases not needed for the diagnosis
- **Biopsy of extramedullary mass:** in LBL cases

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL)

Prognosis

- Overall 5-years survival rate 70-75%
- Young children having the **best prognosis**
(98% attain remission on therapy, with 5-years survival rate >90% and risk of relapse < 1%)
- Prognosis declines with age
 - adolescents and young adults still have good prognosis (5-years survival rate 75-85%)
vs. adults with 5-years survival rate 30-40%

Chronic lymphocytic leukaemias

Chronic lymphocytic leukaemias

= group of clonal neoplastic disorder
characterised by **proliferation of mature lymphoid cells**
with massive involvement of **bone marrow**
and usually also **peripheral blood**

Chronic lymphocytic leukaemias

from B cells

- **Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL)**
- **Hairy cell leukaemia (HCL)**
- Leukemic phase of some lymphomas (FL, MCL, SMZL, less common LBCCL or BL)

from T/NK cells

- **Sezary syndrome**
- **Adult T-cell leukaemia/lymphoma (ATLL)**
- **Large granular lymphocytic leukaemia (LGL)**
- T-prolymphocytic leukaemia (T-PLL)

Chronic lymphocytic leukaemia /
small lymphocytic lymphoma

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL)

= clonal neoplastic proliferation of **monomorphic small mature B cells**
with typical **coexpression of CD5 and CD23**
infiltrating **bone marrow, peripheral blood, lymph nodes** or even some
other extramedullary tissues

CLL = with massive involvement of peripheral blood (lymphocytosis $\geq 5 \times 10^9/l$)

SLL = without major involvement of peripheral blood (lymphocytosis $< 5 \times 10^9/l$)

CLL/SLL

- **Most common** leukaemia **in adults**
- **25-30%** of all leukaemias
- Incidence 3 : 100 000 (increases with age, **median 65 years**, male predominance)
- Etiopathogenesis:
 - unknown
 - no specific gene translocation

CLL/SLL

Manifestation

- Typical leukemic presentation (**CLL**) vs. presentation as SLL is not common
- Very often **asymptomatic** (→ incidental diagnosis)
- Peripheral blood:
 - **lymphocytosis** (if massive → hyperviscosity syndrome)
 - +/- anaemia and thrombocytosis (autoimmune, moderate infiltration of bone marrow)
- **Lymphadenopathy**
- **Hepatosplenomegaly**
- B-symptoms

CLL/SLL

Diagnostic approach

- **Peripheral blood count:** lymphocytosis
- **Cytology:** morphology of neoplastic cells
- **Flow cytometry:** immunophenotype (typical coexpression of CD5 and CD23)
- **Molecular examination:** detection of some prognostic genetic alterations
- **Bone marrow biopsy:** in most cases not needed for the diagnosis
- **Biopsy of lymph node:** especially in SLL cases

CLL/SLL

Diagnostic approach

- **Peripheral blood count:** lymphocytosis
- **Cytology:** morphology of neoplastic cells
- **Flow cytometry:** immunophenotype (typical coexpression of CD5 and CD23)
- **Molecular examination:** detection of some prognostic genetic alterations
- **Bone marrow biopsy:** in most cases not needed for the diagnosis
- **Biopsy of lymph node:** especially in SLL cases

CLL/SLL

Bone marrow

- Typical **nodular** infiltration

CLL/SLL

Diagnostic approach

- **Peripheral blood count:** lymphocytosis
- **Cytology:** morphology of neoplastic cells
- **Flow cytometry:** immunophenotype (typical coexpression of CD5 and CD23)
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- **Biopsy of lymph node:** especially in SLL cases

CLL/SLL

Lymph node

- **Diffuse** infiltration of lymph node by **small mature lymphocytes**
- Proliferation centers
= paler areas with admixture of
prolymphocytes and immunoblasts
- Low mitotic activity

CLL/SLL

Complications

- **Richter syndrome (3-5%)**
= transformation to aggressive lymphoma (usually DLBCL)
- **Immunosuppression**
→ risk of infections
- **Synchronic or metachronic malignancies**

CLL/SLL

Prognosis

- **Generally quite good, but remains largely incurable**
- 1/3 of cases have **indolent** behaviour (for a long time surviving even without treatment)
vs. 1/3 of cases with slow **progression** and recurrent relapses even on therapy
vs. 1/3 of cases with **aggressive** behaviour from the beginning of the disease

Hairy cell leukaemia

Hairy cell leukaemia (HCL)

= clonal neoplastic proliferation of **mature B cells** with **abundant cytoplasm** and characteristic **hairy projections** (called „**hairy cells**“) infiltrating **bone marrow, peripheral blood and spleen**

- **Rare** type of leukaemia (2% of all leukaemias)
- Incidence 0,3 : 100 000 (**median 55 years**, male predominance)
- Most cases have **mutation of gene *BRAF*** (p.V600E)
- Manifestation:
 - **pancytopenia**
 - **immunosuppression** → recurrent infections (even opportunistic)
 - low levels of neoplastic cells in peripheral blood
 - **splenomegaly**
 - usually no hepatomegaly or lymphadenopathy
- **Indolent** course (10-year survival rate 85%)

Sezary syndrome

Sezary syndrome

= clonal neoplastic proliferation of **mature T cells** defined by triad of **erythroderma**, **generalized lymphadenopathy** and presence of neoplastic cells with cerebriform nuclei (**Sezary cells**) in peripheral blood

- **Rare**, incidence 0,3 : 100 000, typically **older males** (>60 years)
- Incidence 0,3 : 100 000 (**median 55 years**, male predominance)
- Manifestation:
 - **erythroderma**, pruritus, alopecia, hyperkeratosis, onychodystrophy
 - **generalized lymphadenopathy**
 - **Sezary cells** in peripheral blood
- **Aggressive** disease (5-year survival rate 10-30%)

Adult T-cell leukaemia/ lymphoma

Adult T-cell leukaemia/lymphoma

= clonal neoplastic proliferation of **mature T cells** associated with **HTLV-1**

- **Endemic** (Japan, Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea), mainly middle aged and older adults
- Etiopathogenesis:
 - infection of HTLV-1 (especially early in life by breastfeeding)
 - risk of developing of ATLL after long latency period
- Manifestation:
 - **generalized lymphadenopathy**
 - **hepatosplenomegaly**
 - infiltration of extramedullary tissues (especially skin)
 - **immunodeficiency**
- Prognosis **generally poor** (median survival 1-2 years)

Large granular lymphocytic
leukaemia

Large granular lymphocytic leukaemia (LGL)

= clonal neoplastic disorder characterised by **persistent increase** of **cytotoxic large granular T cells** (or **NK cells**) in peripheral blood

- **Rare** (< 5% of all lymphoproliferative disorders, incidence 0,02 : 100 000), usually middle aged or older patients (median 60 years)
- Etiopathogenesis:
 - unknown, but frequently associated with autoimmune diseases and other haematological malignancies
- Manifestation:
 - **1/3** of cases **asymptomatic**
 - disease-associated **cytopenias** (mainly neutropenia and anaemia)
- **Indolent course**

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