Spotlight on hematology

AML - Acute Myeloid Leukemia

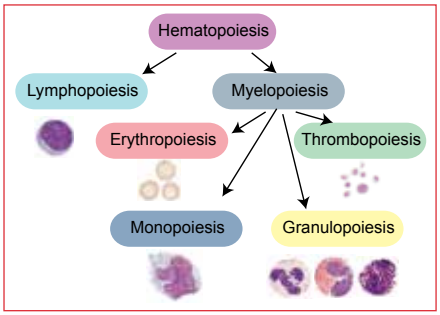
MQZH 2014-01

Introduction

In acute myeloid leukemia (AML), malignant proliferation of myeloid progenitor cells in the bone marrow occurs. AML appears mostly in adults; approx. half of the patients are over 60 years old. Men are affected slightly more often than women.
The bone marrow of patients is usually clearly hypercellular, whereas the white blood cell count in peripheral blood is increased in only approx. half of the patients. By definition, the myeloblast proportion in the peripheral blood or bone marrow must be above 20%. In addition, neutrophil granulocytes are greatly reduced in the blood and bone marrow, and anemia and thrombocytopenia also appear. The classification of AML subtypes is based on the WHO classification of 2008, and in accordance with FAB.
Our current survey specimen is derived from a 40-year-old patient with acute promyelocytic leukemia (APL), FAB AML M3. This type of AML exhibits the typical cytogenetic translocation t(15;17)(q22;q12). APL assumes a special position among AMLs in terms of diagnostics, prognosis, and treatment since very high remission rates (> 90%) are achieved with current treatments. The major risk for APL patients are disease-associated coagulation disorders.

Pathogenesis and aberrations of bone marrow and peripheral blood smear

Acute myeloid leukemia (AML) is characterized by the malignant clonal expansion of precursor cells in bone marrow myelopoiesis. This results in formation of significantly hypercellular marrow. Myeloblasts are predominantly found (>20%) which, depending on stage of maturation, may also contain granulation or Auer rods.



In the majority of AML, blast migration does not occur. Pancytopenia is commonly found in APL (FAB M3); in approx. 80% of cases the course is aleukeamic. In absence of blast or promyelocyte migration into peripheral blood, morphological diagnosis can be made only in bone marrow. Therefore, with unclear pancytopenia, there is always an urgent indication for bone marrow aspiration.

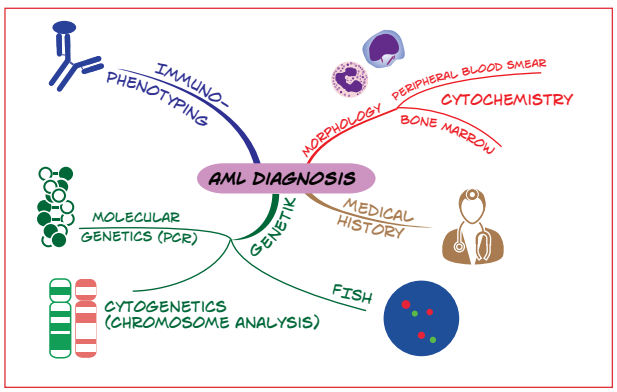
If left untreated, acute myeloid leukemia quickly leads to death. Because of the absence of mature, functional neutrophils and monocytes, patients do not have functioning immune protection

Classification of acute myeloid leukemia per WHO 2008

Compared to the FAB classification (French-American-British) the WHO classification applies additional criteria. These are genetic characteristics of the leukemia cells, the presence of multilineage dysplasia, and the medical history of the patient regarding pre-existing conditions and previous cytostatic treatments.

To simplify, 4 types of AML are distinguished:
1. Genetically defined AML with specific chromosomal aberrations or mutations
2. AML with dysplasia in at least two lineages
3. Treatment-related AML/MDS
4. AML not otherwise classified

Diagnostics:



Morphology of acute myeloid leukemia per FAB

AML M0	without maturation, myeloblasts without granulation
AML M1	minimum maturation, myeloblasts ± granules or Auer rods
AML M2	with maturation, myeloblasts with granules, possibly Auer rods, occasional myelocytes
AML M3	promyelocytic heavily granulated, partly saddle-shaped nuclei, multiple Auer rods, «Faggot Cells»
AML M4	mixed myelo-monocytic differentiated blasts
AML M5a	monoblasts
AML M5b	monoblasts, promonocytes and monocytes
AML M6	erythroleukemia
AML M7	megakaryoblastic leukemia

Glossary of laboratory methods

Morphology
Appearance of cells in light microscopy after staining (blood or bone marrow). For the classification in accordance with FAB, in addition to the usual May Grünwald-Giemsa staining, special cytochemical stains such as peroxidase and esterase are used.

Immune phenotype
Detection of surface antigen patterns of cells by antibody labeling and subsequent flow cytometric measurement.

Cytogenetic (chromosome analysis)
General light microscopic examination of chromosomes (karyotype) for numerical or structural abberations.

FISH
Based on a presumptive diagnosis, specific chromosomal aberrations can be detected with fluorescence in situ hybridization (FISH) using specific probes.

Molecular genetics
Gene mutations or genes for disease-specific fusion proteins are looked for with the help of highly sensitive PCR-based methods.

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Minimal residual disease

Minimally existing leukemia cells that cannot be recognized by light microscopy examination. Highly sensitive testing methods such as PCR or FISH can still «find» these cells.

Allogeneic bone marrow or stem cell transplants

For this treatment hematopoietic stem cells are obtained from a healthy donor. They are obtained either by isolation from harvested bone marrow, or from stem cells mobilized directly into blood from where they are isolated. These are intravenously administered to the recipients after their own bone marrow was removed by chemotherapy, potentially in combination with whole body irradiation. The stem cells migrate independently into patient's bone marrow where they give rise to new, healthy hematopoiesis.

About
Autor *Annette Steiger*
Photos *Dr. Roman Fried*

Advisory
K.Schreiber, Dr. J. Goede, Klinik für Hämatologie, Universitätsspital Zürich

Course of AML therapy

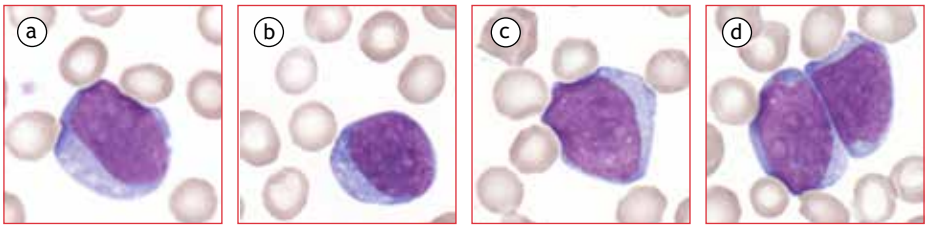
1. Induction therapy
→ with cytostatic combinations
Goal: achieving a complete remission (blast content <5% in bone marrow)

2. Consolidation and potential maintenance therapy
→ cytostatic therapy
Objective: stabilization, elimination of last remaining leukemia cells - minimal residual disease (MRD)
→ Potential allogeneic bone marrow or stem cell transplantation.

Examples of cell morphology in acute myeloid leukemia

AML FAB M0

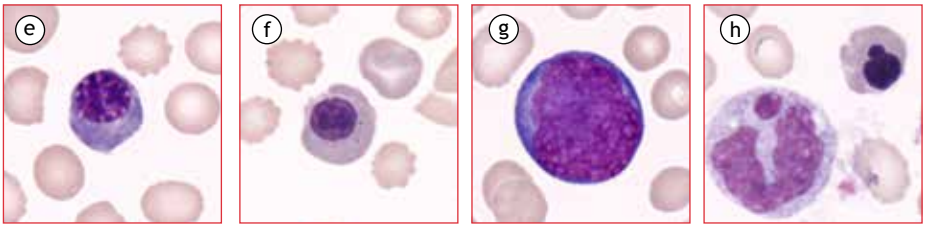
Survey specimen MQZH 2011-04 H3B



a - d) myeloblasts without maturation characters (no granules)

WHO: AML with multilineage dysplasia with prior hematologic neoplasia (CMML)

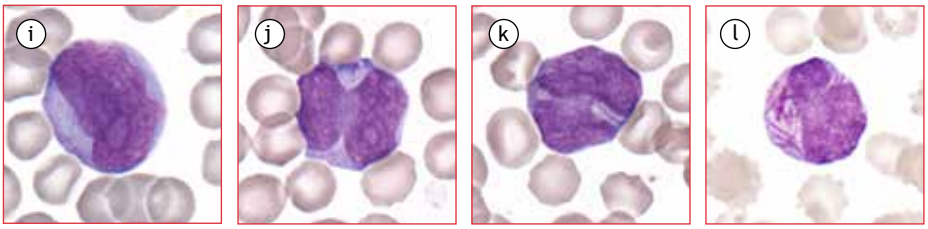
Survey specimen MQZH 2010-03 H3B



e - f) polychromatic erythroblasts
g) myeloblast
h) atypical monocyte with nucleus loss and erythroblast with karyorrhexis (nucleus fragmentation)

WHO: AML - APL Akute Promyelozytenleukämie Translokation t(15;17), AML FAB M3

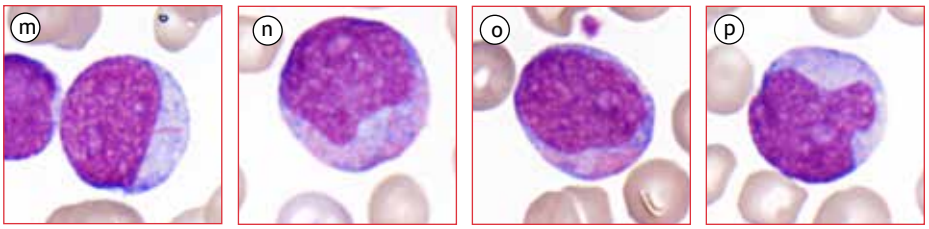
Survey specimen MQZH 2014-01 H3B und 2007-04 H3B



i - k) atypical promyelocytes with Auer rods
j - k) saddle-shaped nucleus
l) atypical promyelocyte from MQ 2007-4 H3B with bundles of Auer rods («Faggot Cell»)

AML FAB M1

Survey specimen MQZH 2006-04 H3B



m) myeloblast with single Auer rod
n) myeloblast with weak azur granulation
o) myeloblast with zonally compressed azur granulation
p) ungranulated myeloblast with irregular nuclear contours and 1 nucleolus