ACUTE LEUKEMIAS

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PREFACE

Acute leukemias are a heterogeneous group of hematologic malignancies characterized by the clonal proliferation of immature hematopoietic cells and a rapidly progressive clinical course. Despite significant advances in the understanding of their molecular pathogenesis, classification systems, and therapeutic approaches, they remain a major clinical challenge in both pediatric and adult populations.

This book, *Acute Leukemias*, aims to provide a comprehensive and systematic overview of acute leukemias within a clinicopathological correlation framework. The content is structured to cover fundamental topics such as definition, epidemiology, etiology, and classification, followed by detailed discussions of acute lymphoblastic leukemia and acute myeloid leukemia.

The primary objective of this work is to serve as a practical reference for pathologists, hematologists, oncologists, and medical trainees, and to contribute to a better understanding of disease mechanisms and diagnostic approaches. Contemporary classification systems and up-to-date literature have been integrated to ensure scientific relevance.

It is hoped that this book will contribute to both academic education and clinical practice by bridging morphological findings with molecular-level insights in acute leukemias.

CHAPTER 1

ACUTE LEUKEMIAS: DEFINITION AND HISTORY

Acute leukemias are malignant hematologic disorders arising from the uncontrolled proliferation of hematopoietic cells. In these patients, leukemic cells that fail to differentiate into mature forms and retain self-renewal capacity accumulate in the bone marrow, leading to suppression of normal hematopoiesis. Consequently, clinical manifestations such as anemia, infections, and bleeding occur (Tebbi, 2021).

The identification and understanding of this disease group began in the 19th century with the widespread use of the microscope. In 1811, Peter Cullen diagnosed a 35-year-old male patient presenting with abdominal pain and fever as having “acute splenitis” and noted that the blood had an unusual milky appearance. Sixteen years later, Alfred Velpeau followed this observation; during the autopsy of a 63-year-old patient, he identified hepatosplenomegaly and observed that the blood had a thick, porridge-like white consistency, suggesting a possible association between the disease and the circulatory system. In 1844, Alfred Donné examined blood samples from leukemia patients under the microscope, identifying an abnormal increase in white blood cells and demonstrating that leukocytes, previously confused with purulent cells, were in fact disease-specific elements. In the following year, John Hughes Bennett examined the blood of a patient with hepatosplenomegaly and identified marked leukocyte accumulation along with fibrin filament formation. He was the first to emphasize that leukocytosis was not secondary to infection but rather a primary disorder of the blood. Finally, in 1847, Rudolf Virchow explained the increase in white blood cells as an imbalance between red and white blood cells, distinguished these cells from pus, and introduced the term “leukemia” for the disease (Kampen, 2012) (Figure 1).

Figure 1. Rudolf Virchow (1821–1902), the German pathologist who coined the term leukemia.
Source: Wikimedia Commons

CHAPTER 2

ACUTE LEUKEMIAS: EPIDEMIOLOGY

Acute leukemia represents a significant public health problem in modern society due to its relatively high incidence and frequently poor prognosis (Kampen, 2012). According to data from the International Agency for Research on Cancer (IARC) of the World Health Organization, leukemias ranked 13th among newly diagnosed cancer cases worldwide in 2020 and 10th among cancer-related deaths (Leukaemia, 2020) (Figure 2). In the same year, the incidence of leukemia was reported as 6.3 per 100,000 in males and 4.5 per 100,000 in females, with the highest incidence observed in North America (Leukaemia, 2020).

Acute lymphoblastic leukemia (ALL) is the most common type of acute leukemia in childhood and adolescence. ALL accounts for approximately one-quarter of all pediatric cancers and nearly 75% of all leukemia cases in individuals under 20 years of age. The peak incidence is observed between 2 and 5 years of age (Tebbi, 2021).

In the general population, acute myeloid leukemia (AML) is more common, with an incidence of approximately 3–5 cases per 100,000 individuals. In the 0–14 age group, the incidence of AML is reported as 7.7 per 100,000. The median age at diagnosis is 66 years; 54% of patients are diagnosed after the age of 65, and 33% after the age of 75 (Tebbi, 2021).

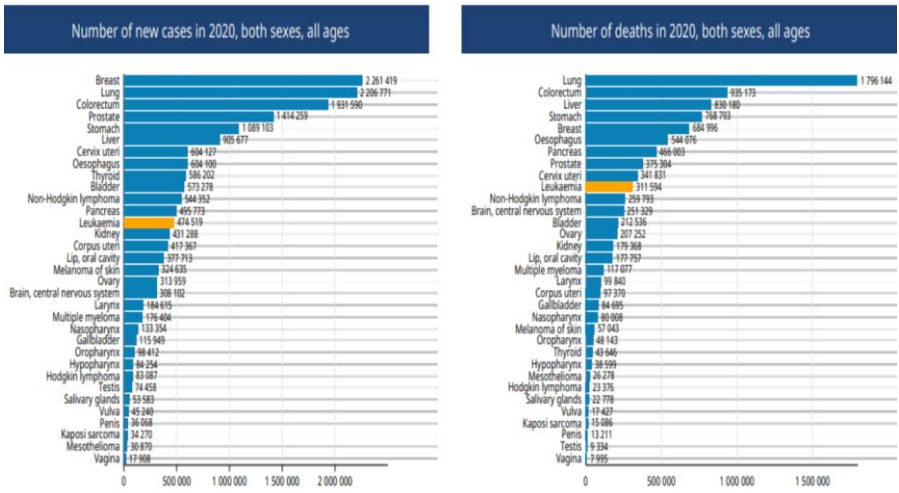

Figure 2. Global cancer incidence and mortality in 2020 (Leukaemia, 2020).

CHAPTER 3 –

ACUTE LEUKEMIAS: ETIOLOGY

1. Genetic Factors

Genetic predisposition plays an important role in the development of acute leukemias. In monozygotic twins, if one individual develops the disease before the age of 7, the risk for the co-twin increases approximately twofold (Tebbi, 2021).

Autosomal dominant inherited genes may increase susceptibility to leukemia, including CEBPA, RUNX1, and GATA2. CEBPA regulates granulocytic differentiation; RUNX1 is a critical transcription factor involved in hematopoiesis; and GATA2 maintains hematopoietic stem cell integrity and regulates phagocytosis. Mutations in GATA2 may lead to congenital neutropenia and are frequently associated with myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or chronic myelomonocytic leukemia.

In addition, genetic disorders such as Li-Fraumeni syndrome, Down syndrome, Fanconi anemia, and other hereditary conditions increase the risk of leukemia. Notably, approximately one-third of patients with Fanconi anemia develop a hematologic malignancy before the age of 40 (Stieglitz & Loh, 2013).

Primary inherited immunodeficiency syndromes, such as Wiskott-Aldrich syndrome and Bruton agammaglobulinemia, also confer a high risk for malignant diseases, including leukemia (Tebbi, 2021).

2. Environmental and Occupational Factors

Environmental exposures, occupational risks, and individual habits are important etiological factors in the development of leukemia (Zeeb & Blettner, 1998). It has been demonstrated that the risk of disease increases particularly in individuals working in occupations involving exposure to chemical agents and radiation. Recent systematic reviews have identified ionizing radiation and benzene exposure as the most strongly established environmental risk factors for leukemia (Smith, 2010; Vlaanderen et al., 2010).

Hydrocarbons, especially benzene, are among the best-characterized chemical agents in leukemia pathogenesis. Benzene, which is found in many industrial and household products such as paints, solvents, and fuels, is metabolized into toxic intermediates in the body and subsequently in the bone marrow, leading to DNA damage in hematopoietic cells and impairment of repair mechanisms (Lichtman, 2007; Belson et al., 2006). Experimental and epidemiological data have shown a strong association between benzene exposure above certain levels (approximately 20–40 ppm/year) and the development of acute myeloid leukemia (AML) (Lichtman, 2007). In addition, meta-analyses support a dose-dependent

increase in leukemia risk with occupational benzene exposure (Vlaanderen et al., 2010).

Smoking is also an important environmental risk factor. The genotoxic effects of tobacco smoke are associated with chromatin alterations and micronucleus formation. The relationship between smoking and leukemia is thought to be largely mediated by benzene present in cigarette smoke. It has been shown that most benzene exposure in smokers is directly derived from smoking and is significantly higher compared to non-smokers (Lichtman, 2007). Epidemiological studies report that smoking increases the risk of AML by approximately 1.4-fold, reaching nearly a twofold increase in heavy smokers (Thomas & Chelghoum, 2004). The International Agency for Research on Cancer (IARC) has also recognized smoking as a causal factor for AML (Smoke & Smoking, 2004).

Pesticides represent another important group of environmental exposures associated with leukemia. These chemicals, widely used in agriculture, may enter the body through both occupational and environmental routes (Bacanlı & Erdem, 2021). Prenatal and childhood exposure, in particular, has been associated with an increased risk of leukemia (Belson et al., 2006). Recent reviews emphasize that pesticides are potential risk factors, especially for childhood ALL (Onyije et al., 2022). Exposure may occur via inhalation or dermal contact during production, application, and storage processes, as well as through contaminated food and household products (Belson et al., 2006; SECERLİ et al., 2021).

From an occupational perspective, leukemia risk is increased in professions with significant exposure to chemical agents, radiation, and certain biological agents. Elevated risk has been reported in agriculture and forestry, oil and gas industries, petrochemical and refining sectors, automotive repair, construction, and nuclear energy fields. Increased risk has also been described in healthcare workers (due to infectious agent exposure), hairdressers, painters, dry-cleaning and textile workers (chemical exposure), and transportation sector workers (Tebbi, 2021). Certain chemicals such as formaldehyde have also been reported to exert adverse effects on the hematopoietic system (Kang et al., 2021). In contrast, evidence for some occupational exposures such as silica remains limited, and further research is needed (Shao et al., 2025).

3. Radiation Exposure

Ionizing radiation is one of the environmental risk factors most strongly associated with the development of leukemia. Exposure to radiation at different stages of life, including prenatal, postnatal, and adult periods, has been shown to induce DNA damage and chromosomal breaks in hematopoietic cells, thereby triggering malignant transformation. In this process, particularly double-strand DNA breaks and the resulting genomic instability play a central role in leukemogenesis (Tebbi, 2021).

A positive correlation between radiation dose and leukemia incidence has been demonstrated in numerous epidemiological studies. One of the most striking examples of this relationship is the data obtained from survivors of the atomic bombings of Hiroshima and Nagasaki. Individuals exposed within approximately 1000 meters of the blast center showed a markedly increased incidence of leukemia compared with the general population, with some studies reporting up to a 20-fold increase (Tebbi, 2021). These findings strongly support the role of high-dose ionizing radiation in leukemogenesis.

The effects of low-dose radiation exposure are more controversial. Some studies have reported an increased risk of leukemia following exposure to diagnostic X-rays, particularly computed tomography (CT) scans in childhood. However, other studies have failed to demonstrate a statistically significant association between diagnostic radiation and leukemia development. This suggests that the effect of low-dose radiation may vary depending on individual susceptibility, duration of exposure, and coexisting risk factors (Tebbi, 2021).

Exposure to high-dose ionizing radiation for therapeutic purposes also represents an important risk factor. Secondary leukemias developing in patients receiving radiotherapy are well documented, and this risk is known to be related to the total dose received and the irradiated field. Radiation-induced leukemias typically arise after a latent period, and accumulated genetic damage during this period is thought to play a key role in pathogenesis (Tebbi et al., 2007).

The role of non-ionizing radiation, such as electromagnetic fields, in leukemia development remains unclear, and current evidence is insufficient to support a definitive causal relationship (Tebbi, 2021).

4. Infections

Infections are among the environmental factors that may play a role in leukemogenesis, either independently or through interactions with genetic predisposition and mutations. The effects of bacterial, viral, and fungal agents on leukemia development have been investigated in various studies, and infectious agents are generally considered to be potentially associated particularly with acute leukemias; however, no single causative and consistent agent has yet been identified (Tebbi, 2021).

Some viruses have been directly linked to leukemia. Human T-cell leukemia virus type 1 (HTLV-1) induces T-cell leukemia/lymphoma through integration of viral DNA or RNA into the host genome. After a latent period, approximately 5% of carriers develop T-cell leukemia (Matsuoka, 2003). Other viral agents, including Epstein–Barr virus, herpesviruses, HIV, and SARS-CoV/COVID-19, may also have the potential to trigger malignant transformation of hematopoietic cells, particularly in immunocompromised individuals (Tebbi, 2021).

Experimental animal models have demonstrated that mice with loss of the B-cell transcription factor PAX5 develop increased susceptibility to B-cell acute lymphoblastic leukemia (B-ALL) following exposure to HTLV-1. This finding suggests that infectious agents may contribute to leukemogenesis when combined with genetic susceptibility (Martín-Lorenzo et al., 2015).

Fungal agents and mycotoxins such as aflatoxin are known carcinogens; however, their mechanisms in relation to leukemia have not been fully elucidated. In small studies investigating fungal isolation from the homes of leukemia patients, particularly those with ALL, these agents have been suggested to exert indirect effects through immunosuppression (Tebbi, 2021).

Overall, infectious agents are considered risk factors in leukemogenesis not as sole causative agents but through interactions with genetic susceptibility and environmental exposures. Current evidence suggests that they may play an important role in leukemogenesis through immune modulation and the induction of genomic instability.

CHAPTER 4

ACUTE LEUKEMIAS: CLASSIFICATION

Acute leukemias are classified according to cell of origin, degree of maturation, and morphological characteristics. Myeloid neoplasms include granulocytic lineages (neutrophils, eosinophils, basophils), monocytes, erythroid cells, megakaryocytes/platelets, and mast cells, and are designated as acute myeloid leukemia (AML) (Beham-Schmid & Schmitt-Graeff, 2020; Fujita et al., 2021). Lymphoid neoplasms consist of B- and T-lymphocytes as well as natural killer (NK) cells and are defined as acute lymphoblastic leukemia (ALL) (Beham-Schmid & Schmitt-Graeff, 2020; Fujita et al., 2021). Rarely, mixed acute leukemias with no clear lineage or with both lymphoid and myeloid features may also be observed (Beham-Schmid & Schmitt-Graeff, 2020).

The French–American–British (FAB) classification system, developed in the late 1970s, categorized neoplastic cells based on morphology and cytochemical reactions and was widely used until 1999 (Beham-Schmid & Schmitt-Graeff, 2020). However, with the introduction of immunophenotyping, cytogenetic, and molecular genetic techniques, the World Health Organization (WHO) and the International Society of Hematology proposed a more comprehensive classification system. Today, the WHO classification is considered the standard system for the diagnosis and classification of acute leukemias (Bennett et al., 1985; McKenzie et al., 2020; World Health Organization, 2022).

CHAPTER 5

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by the uncontrolled proliferation of early lymphoid precursor cells (Gavralidis & Brunner, 2020; Paul et al., 2016; Pui et al., 2008). The disease may originate from B, T, or NK cell lineages; however, it most commonly arises from B-cell precursors, and rarely from NK cells.

In ALL, lymphoblasts lose their ability to mature and differentiate, while their proliferative capacity is increased. As in acute myeloid leukemia, this leads to suppression of normal hematopoiesis in the bone marrow, resulting in impaired production of erythrocytes, platelets, and leukocytes. Leukemic blasts accumulate not only in the bone marrow but also in peripheral blood and extramedullary tissues such as lymph nodes, spleen, liver, and the central nervous system (Heim & Mitelman, 2015).

ALL demonstrates a bimodal age distribution, with peaks in childhood and around 55 years of age. It accounts for approximately 20% of adult leukemias. Treatment response and cure rates are high in childhood, reaching up to 98%, whereas in adults—particularly those over 55 years of age—treatment outcomes and survival rates are significantly lower (Gavralidis & Brunner, 2020).

Table 1: WHO 2022 Classification of Acute Lymphoblastic Leukemia(Arber et al., 2022)

B-ALL (B-cell Acute Lymphoblastic Leukemia)
• B-ALL with recurrent genetic abnormalities
• B-ALL, t(9;22)(q34.1;q11.2)/BCR:ABL1
○ Lymphoid lineage only
○ Involving multiple cell lineages
• B-ALL with t(v;11q23.3)/KMT2A rearrangement
• B-ALL with t(12;21)(p13.2;q22.1)/ETV6:RUNX1
• B-ALL, hyperdiploid
• B-ALL, low hypodiploid
• B-ALL, near haploid
• B-ALL with t(5;14)(q31.1;q32.3)/IL3:IGH
• B-ALL with t(1;19)(q23.3;p13.3)/TCF3:PBX1
• B-ALL, BCR::ABL1-like, ABL1-class rearrangement

- B-ALL, BCR::ABL1-like, JAK-STAT activated
- B-ALL, BCR::ABL1-like, NOS
- B-ALL, iAMP21
- B-ALL with MYC rearrangement
- B-ALL with DUX4 rearrangement
- B-ALL with MEF2D rearrangement
- B-ALL with ZNF384(362) rearrangement
- B-ALL with NUTM1 rearrangement
- B-ALL with HLF rearrangement
- B-ALL, UBTF:ATXN7L3/PAN3, CDX2 (“CDX2/UBTF”)
- B-ALL with IKZF1 N159Y mutation
- B-ALL with PAX5 P80R mutation
- B-ALL, ETV6::RUNX1-like transient entity
- B-ALL, PAX5-altered transient entity
- B-ALL, ZEB2 (p.H1038R)/IGH:CEBPE mutated transient entity
- B-ALL, ZNF384 rearrangement-like transient entity
- B-ALL, KMT2A rearrangement-like transient entity
- B-ALL, NOS

T-ALL (T-cell Acute Lymphoblastic Leukemia)

- Early T-cell precursor ALL with BCL11B rearrangement
- Early T-cell precursor ALL, NOS
- T-ALL, NOS

B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

B-cell acute lymphoblastic leukemia (B-ALL) is a hematologic malignancy characterized by the uncontrolled proliferation of B-lymphocyte precursors. In this disease, immature blast cells accumulate and proliferate in the bone marrow and peripheral blood. Diagnosis is established using immunophenotypic and molecular tests, which confirm the B-cell lineage of the blasts (World Health Organization, 2022).

B-ALL accounts for approximately 80–85% of childhood ALL cases and about 70% of adult cases. In children aged 2–10 years, long-term disease-free survival exceeds 80%, whereas in adults this rate is approximately 30–50% (McKenzie et al., 2020). These data demonstrate that B-ALL shows significant prognostic variation across age groups and that treatment strategies should be tailored accordingly.

In B-ALL, blast cells accumulate densely in the bone marrow and may also be observed in peripheral blood. These cells are immature and may vary from case to case in terms of size, nuclear shape, chromatin density, and amount of cytoplasm. Morphological evaluation constitutes the first step in the diagnostic process today and allows recognition of blasts, thereby guiding further immunophenotypic and genetic testing.

Historically, the French–American–British (FAB) classification was developed based on the morphological characteristics of B-ALL blasts. This system subdivides cases according to criteria such as cell size, amount of cytoplasm, nuclear contours, and the presence of nucleoli (Lilleyman et al., 1986):

- L1: Small, homogeneous blasts with scant cytoplasm; nucleoli are generally inconspicuous. This subtype is more commonly seen in pediatric B-ALL cases.

- L2: Large and heterogeneous blasts with irregular nuclei and prominent nucleoli; cytoplasm is more abundant compared to L1. It is more frequently observed in adults.

- L3 (Burkitt type): Blasts with homogeneous chromatin, large round-to-oval nuclei, and one or more nucleoli; the cytoplasm is deeply basophilic and vacuolated. The L3 subtype shows histological features resembling Burkitt leukemia (Katzilakis et al., 2004).

Although the FAB classification is of historical importance in demonstrating morphological heterogeneity, current prognostic and therapeutic decisions are

primarily based on immunophenotypic and genetic profiles. Nevertheless, morphological identification of blasts remains a critical step in the diagnostic process and is routinely evaluated by hematologists and pathologists. B-ALL is a hematologic malignancy defined by the presence of markers of B-cell differentiation. Under normal conditions, precursor B cells in the bone marrow exhibit a regulated and predictable pattern of antigen expression throughout their developmental stages. In contrast, blasts in B-ALL typically display an immunophenotype that is inconsistent with normal B-cell differentiation. This abnormal antigen expression profile enables distinction between malignant precursor B cells and reactive (benign) precursor B cells. B-ALL is characterized by malignant proliferation of precursor B cells, and immunophenotypic analysis plays a central role in its diagnosis. Multiparameter flow cytometry allows evaluation of antigen expression patterns, enabling both identification of cell lineage and differentiation from normal hematopoietic cells (Jaffe et al., 2017).

B-ALL blasts typically express markers of the B-cell lineage. In this context, CD19 is positive in almost all cases and represents one of the most reliable surface antigens for demonstrating B-cell origin. CD79a is another important marker that can be expressed in cytoplasmic or membranous form and is present from early stages of B-cell development. In addition, terminal deoxynucleotidyl transferase (TdT) and HLA-DR expression are among the findings supporting the immature nature of blast cells (Jaffe et al., 2017).

Other markers reflecting different stages of B-cell differentiation are also detected at varying frequencies. CD10 is positive in the majority of cases and suggests a pre-B-cell stage, although it may be negative in some cases. CD22 is generally expressed at low surface density but in a consistent manner; its cytoplasmic form is considered a highly sensitive marker. In contrast, CD20 is associated with more advanced stages of differentiation, and its expression varies significantly between cases; it may be completely negative in some patients, while showing moderate or strong positivity in others (Jaffe et al., 2017).

Another notable aspect of immunophenotypic evaluation is the presence of aberrant antigen expression in some cases. In this context, low-level expression of myeloid-associated antigens such as CD13, CD33, and CD15 may be observed. However, this finding alone does not suggest myeloid lineage and does not exclude the diagnosis of B-ALL. On the other hand, CD117 expression is quite rare, and when present, the possibility of mixed-phenotype acute leukemia should be considered (Jaffe et al., 2017).

PAX5 is one of the B-cell lineage–specific markers and is a nuclear transcription factor. Although it is considered more specific compared to CD79a, it may rarely show positivity in some cases of acute myeloid leukemia (Jaffe et al., 2017).

At the molecular level, rearrangements of immunoglobulin heavy chain genes occur early in B-cell development and can be demonstrated clonally in B-ALL cases. However, despite these genetic rearrangements, surface immunoglobulin expression is absent in most cases (Jaffe et al., 2017).

In conclusion, the immunophenotypic profile of B-ALL is characterized by the presence of B-cell markers, the co-expression of immaturity-associated markers, and occasionally aberrant antigen expression. These features are of major importance for diagnosis, subclassification, and differential diagnosis of the disease.

B-ALL is further divided into different clinical subgroups, each with a distinct antigen expression pattern. Some subgroups are associated with specific molecular or cytogenetic abnormalities and exhibit characteristic clinical features.

Pre–B-cell ALL is distinguished from other B-cell ALL types by the expression of cytoplasmic immunoglobulin μ heavy chain without surface immunoglobulin. Approximately 25% of cases of this subtype show a characteristic t(1;19) translocation (Jaffe et al., 2017).

Transitional pre–B-cell ALL represents a subgroup with maturation features intermediate between pre–B-cell ALL and Burkitt leukemia/lymphoma. In this subtype, surface immunoglobulin μ heavy chain is present, whereas immunoglobulin light chains are not expressed. In addition, these tumors lack the typical L3 morphology of Burkitt leukemia/lymphoma and do not carry MYC oncogene-associated translocations. Immaturity markers such as CD34 and TdT are present in this subgroup, whereas they are generally absent in more mature B-cell leukemias. These tumors must be distinguished from Burkitt leukemia/lymphoma, as they respond well to ALL-specific chemotherapy protocols. However, in rare B-ALL cases with non-L3 morphology, both heavy and light immunoglobulin chains may be expressed in the absence of MYC translocations. Although systematic data are limited, these rare cases are treated in clinical practice similarly to other B-cell ALL patients.

B-cell acute lymphoblastic leukemia (B-ALL) is commonly associated with specific genetic alterations and chromosomal abnormalities. These include

translocations, hypodiploidy, and hyperdiploidy (Tyner et al., 2012). Clinically significant and prognostically relevant translocations include t(12;21)(p13.2;q22.1)/ETV6-RUNX1, t(v;11q23.3) / KMT2A, t(9;22)(q34;q11)/BCR-ABL1, t(5;14)(q31;q32.3)/IL3-IGH2, t(1;19)(q23.3;p13.3)/E2A-PBX1 (TCF3-PBX1), BCR-ABL1-like mutations, and intrachromosomal amplification of chromosome 21 (iAMP21) (Ney-Garcia et al., 2012).

In pediatric B-ALL cases, the most common genetic alteration, occurring in approximately 25% of cases, is the t(12;21)(p13;q22.3) translocation, which results in the ETV6(TEL)–RUNX1 fusion gene (Fuka et al., 2011). The ETV6 and RUNX1 genes may also be involved in different translocations in other types of leukemia. The ETV6–RUNX1 fusion protein contributes to leukemogenesis by disrupting cellular differentiation, apoptosis, adhesion, and DNA damage response pathways, and its presence is associated with an overall survival rate of approximately 90% (Ney-Garcia et al., 2012).

In infant B-ALL, the t(v;11q23.3)/KMT2A rearrangement is frequently observed. The KMT2A protein plays a role in chromatin remodeling and epigenetic regulation of cell cycle–related proteins, and its prognostic significance varies according to patient age; in younger patients, prognosis may be improved with stem cell transplantation.

In adults, the BCR-ABL1 translocation t(9;22)(q34.1;q11.2) is observed at a higher frequency of approximately 10–15% (Xing et al., 2012). The t(5;14)(q31.1;q32.3) translocation involves the IL3 and IGH genes and is associated with reactive, non-clonal variable eosinophilia. Blasts in these cases typically exhibit a CD19(+) and CD10(+) immunophenotype, and diagnosis is established based on immunophenotypic and genetic findings, independent of blast percentage.

Hyperdiploid B-ALL is common in children and is observed in approximately 20–26% of cases; FLT3 mutations are present in most cases and lead to constitutive activation of receptor signaling (Markovic et al., 2005; McKenzie et al., 2020). Hypodiploid clones may exhibit structural abnormalities; however, they are not specific for diagnosis.

Poor prognostic factors include t(4;11)(q21;q23)/MLL-AFF1 (9%), t(1;19)(q23.3;p13.3)/PBX1-E2A (5%), t(9;22)(q34;q11.2)/BCR-ABL1 (4%), and hypodiploidy (5%) (McKenzie et al., 2020). Intrachromosomal amplification of chromosome 21, which is frequently observed in children, involves five or more copies of RUNX1 and requires aggressive treatment. BCR-ABL1–like mutations

are also associated with poor prognosis in childhood leukemia and may respond to tyrosine kinase inhibitors (Arber et al., 2016).

T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

T-cell acute lymphoblastic leukemia (T-ALL) is an acute lymphoblastic leukemia arising from precursor T cells. Immature T cells (blasts) proliferate rapidly and infiltrate the bone marrow. T-ALL accounts for approximately 10–15% of childhood ALL cases and 10–25% of adult ALL cases. While B-ALL typically occurs in younger children, T-ALL is more commonly seen in older children, adolescents, and young adults. In addition, T-ALL is more frequent in males, with approximately 70% of cases occurring in male patients. This sex difference is partly attributed to recurrent alterations in X-chromosome–located genes such as PHF6, MED12, STAG2, USP9X, RPL10, KDM6A, DDX3X, and BCOR in T-ALL (Liu et al., 2017; Pölönen et al., 2024; Van Vlierberghe et al., 2010).

T-ALL typically presents with a high peripheral leukocyte count and a mediastinal mass, the latter resulting from leukemic infiltration of the thymus. T-lymphoblasts share several morphological features with B-ALL lymphoblasts; they are variable in size and may contain cytoplasmic vacuoles. Cytochemically, although they share similarities with B-ALL, acid phosphatase staining shows strong positivity in T-ALL (McKenzie et al., 2020).

Risk stratification in T-ALL has historically been based on clinical features such as mediastinal mass, central nervous system (CNS) involvement, peripheral blood leukocyte count, hemoglobin and platelet levels, age, and splenomegaly at diagnosis. However, in modern risk assessment, minimal residual disease (MRD) response has become a key determinant, and among traditional factors, only age and CNS involvement have retained consistent prognostic value. T-ALL is rare in infants; therefore, available data are limited, and the impact of age on prognosis is less pronounced than in B-ALL. A high white blood cell (WBC) count at diagnosis, particularly >200,000/μL, has been associated with poorer survival in non–early T-cell precursor T-ALL cases. Overall, however, WBC count is a less robust prognostic factor in T-ALL compared with B-ALL, and many cooperative groups no longer use it as a primary criterion for risk stratification (Pölönen et al., 2025).

According to the WHO 2022 classification, T-cell acute lymphoblastic leukemia (T-ALL) is subdivided based on immunophenotypic and genetic characteristics. Classical T-ALL (NOS) includes blasts that do not exhibit an early T-cell precursor phenotype and typically show positivity for TdT, CD7, and

cytoplasmic CD3, with variable expression of membrane CD3, CD1a, CD4, and CD8.

Early T-cell precursor (ETP) T-ALL (NOS) is characterized by an early thymic precursor phenotype with low or absent CD5 expression, negativity for CD1a and CD8, and positivity for at least one myeloid or stem cell marker (such as CD34, CD117, CD13, or CD33). This subtype generally shows a slower response to therapy and may demonstrate high minimal residual disease (MRD) levels at the end of induction.

A further entity, ETP T-ALL with BCL11B rearrangement, shares the same ETP immunophenotype but is defined by BCL11B genetic alteration and may require specific therapeutic considerations in certain treatment protocols. Overall, the WHO 2022 classification defines T-ALL based on immunophenotypic and genetic features of blasts, providing important guidance for both prognostic assessment and therapeutic planning (World Health Organization, 2022).

Table 2: WHO 2022 Classification of T-cell Acute Lymphoblastic Leukemia Subtype (Arber et al., 2022)

T-ALL Subtype	Immunophenotype	Genetic Feature	Clinical / Prognostic Notes
T-ALL, NOS	TdT+, CD7+, cCD3+, sCD3 variable, CD1a/CD4/CD8 variable	None specific	Classic T-ALL; ETP phenotype negative
Early T-cell Precursor (ETP) T-ALL, NOS	CD5 low/negative, CD1a−, CD8−, at least one myeloid/stem cell marker positive (CD34, CD117, CD13, CD33)	None specific	Early T-cell precursor phenotype; slower induction response, high MRD at end of induction
ETP T-ALL with BCL11B rearrangement	Same as ETP T-ALL	BCL11B rearrangement	ETP phenotype + BCL11B genetic change; may require special treatment consideration

Notes:

- cCD3 = cytoplasmic CD3; sCD3 = surface CD3
- MRD = minimal residual disease
- TdT = terminal deoxynucleotidyl transferase

T-ALL originates from immature T-cell precursors, and its pathogenesis involves chromosomal translocations, transcription factor dysregulation, and signaling pathway mutations. In approximately one-third of cases, the alpha and delta T-cell receptor loci (14q11.2), the beta locus (7q35), or the gamma locus (7p14–15) are affected, leading to aberrant expression of genes such as MYC, TAL1, RBTN1/2, HOX11, and HOX11L2.

In the ETP T-ALL subtype, NOTCH1 mutations are rare; instead, alterations in genes associated with myeloid malignancies, such as FLT3, IDH1, and GATA2, are observed. In contrast, most non-ETP T-ALL cases frequently show NOTCH1 activation, which promotes cellular proliferation, while genes such as FBXW7, PTEN, PHF6, and RUNX1 are also commonly affected.

These molecular and genetic differences, together with immunophenotypic features, are critical for defining T-ALL subtypes and for evaluating treatment response and prognosis in patients (Alaggio et al., 2022; Arber et al., 2016; Coustan-Smith et al., 2009; McKenzie et al., 2020).

CHAPTER 6

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by uncontrolled proliferation and differentiation arrest of myeloid precursor cells (blasts) in the bone marrow. This process leads to suppression of normal hematopoiesis, resulting in clinical findings such as anemia, thrombocytopenia, and neutropenia. Although diagnosis is generally established by the presence of ≥20% blasts in the bone marrow or peripheral blood, this threshold may not be required in the presence of specific recurrent genetic abnormalities (Khoury et al., 2022).

AML is the most common acute leukemia in adults, and its incidence increases significantly with age. The median age at diagnosis is approximately 65–70 years, and the disease is less common in childhood. A slight male predominance has been reported. Epidemiologically, advanced age, pre-existing myelodysplastic syndromes or myeloproliferative neoplasms, exposure to cytotoxic chemotherapy and radiotherapy, and environmental toxins such as benzene are among the major risk factors for AML development (Döhner et al., 2022; Khoury et al., 2022).

Clinical manifestations are primarily related to bone marrow failure. Patients commonly present with fatigue and weakness due to anemia, increased susceptibility to infections due to neutropenia, and bleeding tendency due to thrombocytopenia. In some cases, hepatosplenomegaly, gingival hypertrophy, and skin infiltration (leukemic infiltration) may also be observed. In the acute promyelocytic leukemia (APL) subtype, the development of disseminated intravascular coagulation (DIC) is a particularly notable feature (Khoury et al., 2022).

At the molecular level, AML arises from the accumulation of genetic and epigenetic alterations. According to the WHO 2022 classification, AML is largely categorized based on genetic features, including AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, and therapy-related AML. These genetic alterations not only play a central role in leukemogenesis but are also critical for prognostic assessment and the development of targeted therapeutic strategies (Döhner et al., 2022; Khoury et al., 2022).

Table 3. WHO 2022 Classification of Acute Myeloid Leukemia(Khoury et al., 2022)

Category	Entity
AML with defining genetic abnormalities	AML with RUNX1::RUNX1T1 AML with CBFB::MYH11 Acute promyelocytic leukemia with PML::RARA AML with KMT2A rearrangement AML with DEK::NUP214 AML with MECOM rearrangement (e.g., inv(3)/t(3;3)) AML with RBM15::MRTFA AML with BCR::ABL1 AML with NUP98 rearrangement AML with NPM1 mutation AML with CEBPA mutation AML with other defined genetic alterations
AML, myelodysplasia-related	AML, myelodysplasia-related (AML-MR)
Therapy-related myeloid neoplasms	Therapy-related myeloid neoplasms
AML, defined by differentiation	AML with minimal differentiation AML without maturation AML with maturation

	Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia
Myeloid sarcoma	Myeloid sarcoma

The World Health Organization (WHO) 2022 classification of acute myeloid leukemia (AML) is based primarily on genetic and molecular abnormalities rather than solely on morphological features. This approach reflects the critical importance of recurrent genetic alterations in AML in terms of both prognosis and therapeutic implications.

Distinct genetic abnormalities such as RUNX1::RUNX1T1, CBFB::MYH11, PML::RARA, and NPM1 mutations define AML subtypes with specific biological and clinical behaviors. In addition, AML is classified as myelodysplasia-related AML and therapy-related myeloid neoplasms, which are generally associated with a poorer prognosis. Cases lacking specific genetic abnormalities are categorized as AML, not otherwise specified (NOS), and are primarily defined based on morphological and cytochemical features. Furthermore, myeloid sarcoma is recognized as a distinct category representing an extramedullary form of AML.

This integrated classification system emphasizes the central role of molecular genetics in the diagnosis, risk stratification, and therapeutic decision-making in AML (Döhner et al., 2022; Khoury et al., 2022).

1-AML WITH DEFINING GENETIC ABNORMALITIES

This group includes AML subtypes characterized by specific chromosomal translocations or gene mutations and represents one of the most important components of the WHO 2022 classification. Fusion genes such as RUNX1::RUNX1T1, CBFB::MYH11, and PML::RARA directly affect cellular proliferation and differentiation, thereby determining the biological behavior of the disease.

In particular, acute promyelocytic leukemia (APL) defined by the PML::RARA fusion is of special clinical importance due to its high risk of disseminated intravascular coagulation (DIC). In addition, molecular alterations such as NPM1 and CEBPA mutations are also included in this group and play a critical role in prognosis and treatment response (Döhner et al., 2022; Khoury et al., 2022).

***AML WITH RUNX1::RUNX1T1**

The RUNX1::RUNX1T1 fusion gene resulting from t(8;21)(q22;q22.1) is one of the core-binding factor (CBF) AML subtypes. This fusion protein inhibits the DNA-binding function of RUNX1, acting as a transcriptional repressor and suppressing differentiation in hematopoietic cells. As a result, proliferation of leukemic clones increases and blast transformation develops (McKenzie et al.,

2020). In the WHO 2022 classification, this entity is included in the “AML with defining genetic abnormalities” group, where the presence of the genetic lesion is the primary diagnostic determinant, and in some cases the blast percentage criterion is not mandatory for diagnosis (World Health Organization, 2022).

This AML subtype accounts for approximately 5–10% of all AML cases and is typically seen in young adults. Morphologically, blasts show abundant granulated cytoplasm, may contain Auer rods, and can demonstrate pseudo–Chédiak-Higashi–like granulation. Immunophenotypically, CD13, CD33, and MPO positivity are typical, and CD34 is frequently positive. In addition, aberrant CD19 expression may be observed, which is considered highly characteristic of CBF-AML (Aster et al., 2013).

The clinical course is generally favorable, with high response rates to standard intensive chemotherapy regimens. However, the presence of KIT mutations is associated with increased relapse risk and worse prognosis. Similarly, CD56 expression has been linked to higher relapse rates and a more aggressive clinical course. Therefore, current approaches emphasize that not only the presence of the fusion gene but also accompanying molecular alterations are important for risk stratification (Arber et al., 2022; Swerdlow, 2017).

***AML WITH CBFB::MYH11**

AML with CBFB::MYH11 is characterized by the CBFB–MYH11 fusion gene resulting from inv(16)(p13.1q22) or, more rarely, t(16;16)(p13.1;q22). This entity belongs to the core-binding factor (CBF) AML group and is classified under “AML with defining genetic abnormalities” in the WHO 2022 classification. The presence of this genetic lesion is the key diagnostic determinant, and in some cases the blast percentage criterion is not required for diagnosis (World Health Organization, 2022).

CBFB normally forms part of the core-binding factor complex together with RUNX1, playing a central role in regulating hematopoietic differentiation. The CBFB::MYH11 fusion protein disrupts this complex, leading to transcriptional repression and a differentiation block in myeloid cells. As a result, impaired maturation occurs in both granulocytic and monocytic lineages (World Health Organization, 2022).

Morphologically, the most characteristic feature is the presence of abnormal eosinophils. These cells are immature eosinophil precursors with large, dark basophilic granules. They are typically accompanied by myeloblasts and a monocytic component, resulting in a heterogeneous cellular population.

Immunophenotypically, MPO, CD13, and CD33 positivity are typical, while the monocytic component may express CD14 and CD64. CD34 expression is variable (Aster et al., 2013; World Health Organization, 2022).

Clinically, this subtype is more commonly seen in young adults, and leukocytosis may be variable. Extramedullary involvement, particularly gingival and cutaneous infiltration, may occur. Prognostically, it is generally considered part of the favorable-risk AML group; however, the presence of KIT mutations is associated with an increased risk of relapse and is regarded as an adverse prognostic factor. According to WHO 2022, CBF-AML, including both t(8;21) and inv(16), is placed within the favorable-risk spectrum, but accompanying molecular alterations play a decisive role in risk stratification (World Health Organization, 2022).

***ACUTE PROMYELOCYTIC LEUKEMIA WITH PML::RARA**

Acute promyelocytic leukemia (APL) with PML::RARA fusion gene is a distinct subtype of acute myeloid leukemia characterized by the t(15;17)(q24.1;q21.2) translocation. It is classified under the "AML with defining genetic abnormalities" group in the WHO 2022 classification and represents a biologically and clinically unique entity that requires urgent treatment. The fusion of the PML gene on chromosome 15 with the RARA (retinoic acid receptor alpha) gene leads to repression of RARA-mediated transcription, resulting in a differentiation arrest at the promyelocyte stage. This block causes accumulation of leukemic promyelocytes and malignant proliferation (Döhner et al., 2022).

Morphologically, the bone marrow and peripheral blood show heavily granulated promyelocytes with irregular nuclei. Cells may contain numerous Auer rods, sometimes forming bundles known as "faggot cells," which are highly characteristic of this entity. In the hypogranular (microgranular) variant, blasts are smaller, less granulated, and often exhibit bilobed or kidney-shaped nuclei; this variant may be associated with more prominent leukocytosis (Jaffe et al., 2017).

Immunophenotypically, classic APL shows strong CD33 positivity, MPO positivity, and CD13 positivity, while CD34 and HLA-DR are typically negative. This immunophenotypic profile is highly useful in distinguishing APL from other AML subtypes.

Clinically, APL is defined by a severe coagulopathy and a strong tendency toward disseminated intravascular coagulation (DIC), which remains the leading cause of early mortality. Therefore, APL is considered a true hematologic

emergency in clinical practice (McKenzie et al., 2020). Treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) directly targets the PML::RARA-driven differentiation block and achieves high cure rates.

Prognostically, with prompt recognition and immediate initiation of therapy, APL is one of the most curable AML subtypes. Early diagnosis and effective management of coagulopathy are critical determinants of survival (Arber et al., 2022; Döhner et al., 2022).

***AML WITH KMT2A REARRANGEMENT**

AML with KMT2A (lysine methyltransferase 2A, formerly MLL) rearrangement is an acute myeloid leukemia subtype included in the "AML with defining genetic abnormalities" category of the WHO 2022 classification, characterized by heterogeneous clinical and morphological features (World Health Organization, 2022). This group is defined by chromosomal translocations involving the KMT2A gene and various partner genes, resulting in fusion proteins that increase HOX gene expression in hematopoietic cells and lead to differentiation arrest at an early progenitor stage (Arber et al., 2022).

KMT2A rearrangements are most commonly observed in infant leukemias and pediatric AML cases, although they may also occur in adults. The most frequent translocation is t(9;11)(p21.3;q23.3), resulting in KMT2A::MLLT3 fusion; however, numerous alternative fusion partners have been identified, contributing to marked biological heterogeneity (World Health Organization, 2022).

Morphologically, AML with KMT2A rearrangement typically shows monocytic or myelomonocytic differentiation (Döhner et al., 2022). The bone marrow is characterized by increased blasts along with monoblasts and promonocytes. When the monocytic component is prominent, the morphology may resemble AML without maturation or acute monocytic leukemia. In some cases, there is a strong tendency for tissue infiltration and extramedullary disease.

Immunophenotypically, CD33 and CD13 are frequently positive, while markers associated with monocytic differentiation such as CD64, CD14, and CD11b may also be expressed. CD34 expression is variable and may be low or negative in some cases (World Health Organization, 2022).

Clinically, KMT2A-rearranged AML is generally aggressive, particularly in infants and children, and is associated with high leukocytosis, hepatosplenomegaly, and extramedullary involvement, especially in the skin and central nervous system. In adults, it is typically classified within the intermediate to adverse risk group (Döhner et al., 2022).

Prognostically, overall outcomes are poorer compared with many other AML subtypes, and infant cases carry a particularly high risk of relapse. Treatment response varies depending on the specific fusion partner and accompanying genetic alterations (Döhner et al., 2022).

***AML WITH DEK::NUP214**

AML with DEK::NUP214 is a rare subtype of acute myeloid leukemia classified under the "AML with defining genetic abnormalities" group in the WHO 2022 classification and is characterized by the t(6;9)(p23;q34.1) translocation (World Health Organization, 2022). The resulting DEK::NUP214 fusion gene disrupts nuclear transport and transcriptional regulation associated with the nuclear pore complex, leading to differentiation arrest and leukemic transformation in hematopoietic progenitor cells (Arber et al., 2022).

This subtype is most commonly seen in young adults and is often characterized by prominent basophilia and dysplastic changes. In the bone marrow, increased blasts are accompanied by dysplastic features affecting both granulocytic and monocytic lineages. The presence of basophilia is an important morphological clue that helps distinguish this entity from other AML subtypes (World Health Organization, 2022).

Immunophenotypically, CD13, CD33, and MPO positivity are typical. CD34 and HLA-DR are frequently positive, consistent with an immature myeloid phenotype.

Clinically, DEK::NUP214 AML typically presents with marked leukocytosis and follows an aggressive disease course. FLT3-ITD mutations are also frequently associated and contribute to increased biological aggressiveness, representing an adverse prognostic factor (Döhner et al., 2022).

Prognostically, outcomes are generally poorer compared with most non–CBF AML genetic subtypes, and intensive chemotherapy and, in selected cases, allogeneic stem cell transplantation may be required (Döhner et al., 2022; World Health Organization, 2022).

***AML WITH MECOM REARRANGEMENT**

AML with MECOM rearrangement is a subtype of acute myeloid leukemia characterized by inv(3)(q21.3q26.2) or t(3;3)(q21;q26.2) and is classified under the "AML with defining genetic abnormalities" group in the WHO 2022 classification (World Health Organization, 2022). These genetic rearrangements result in overexpression of the MECOM (EVI1) gene, leading to transcriptional dysregulation, differentiation arrest, and proliferation of leukemic clones in

hematopoietic progenitor cells (Arber et al., 2022). In particular, 3q rearrangements promote the maintenance of a stem cell–like phenotype and suppression of myeloid differentiation.

Morphologically, the bone marrow often shows marked dysplasia, increased blasts, and, in some cases, features of micromegakaryocytic or megakaryocytic differentiation. Multilineage dysplasia may also be present, and the blast percentage does not always correlate with clinical aggressiveness.

Immunophenotypically, CD34 and CD117 are frequently expressed, while myeloid markers such as CD13, CD33, and MPO show variable positivity. In cases with megakaryocytic differentiation, CD41 and CD61 positivity may be detected.

Clinically, MECOM-rearranged AML is typically seen in adults and is classified as a high-risk AML subtype. The disease is often associated with poor response to chemotherapy, high relapse rates, and an adverse prognosis (Döhner et al., 2022). Therefore, treatment strategies frequently include allogeneic stem cell transplantation.

***AML WITH RBM15::MRTFA**

AML with RBM15::MRTFA is a rare subtype of acute myeloid leukemia included in the "AML with defining genetic abnormalities" group in the WHO 2022 classification and is most commonly associated with the t(1;22)(p13.3;q13.1) translocation (World Health Organization, 2022). This translocation results in fusion of the RBM15 and MRTFA (formerly MKL1) genes, leading to disruption of the megakaryocytic differentiation program and causing abnormal megakaryoblastic proliferation in hematopoietic progenitor cells (Arber et al., 2022).

This AML subtype is most frequently seen in infants and early childhood, forming a distinct biological group within pediatric AML. The disease commonly presents with hepatosplenomegaly, marked leukocytosis, and megakaryoblastic infiltration of the bone marrow. Morphologically, the bone marrow shows small- to medium-sized blasts, megakaryoblast-like cells with cytoplasmic blebbing, and variable degrees of dysplasia.

Immunophenotypically, megakaryocytic markers such as CD41, CD61, and CD42b are typically positive. CD34 and CD117 expression may be variable, while MPO is usually negative or weakly expressed. This immunophenotypic profile supports the megakaryoblastic origin of the disease.

Clinically, RBM15::MRTFA AML is aggressive, particularly in infants, and may show rapid progression. Although treatment response is variable, it is generally considered a high-risk AML subtype, and allogeneic stem cell transplantation may be required in selected cases (Döhner et al., 2022).

***AML WITH BCR::ABL1**

AML with BCR::ABL1 is a subtype of acute myeloid leukemia included in the "AML with defining genetic abnormalities" group in the WHO 2022 classification and is characterized by the presence of the Philadelphia chromosome t(9;22)(q34.1;q11.2), resulting in the BCR::ABL1 fusion gene (World Health Organization, 2022). This fusion protein exhibits constitutive tyrosine kinase activity, leading to continuous activation of proliferative signaling pathways such as JAK/STAT, RAS/MAPK, and PI3K/AKT, which ultimately causes uncontrolled proliferation and differentiation arrest in hematopoietic progenitor cells (Arber et al., 2022).

This AML subtype must be distinguished from blast phase chronic myeloid leukemia (CML blast crisis) with BCR::ABL1 positivity. The distinction is mainly based on clinical history (previous diagnosis of CML), the presence of basophilia, splenomegaly, and background hematopoietic features. In AML with BCR::ABL1, there is usually no prior history of CML, and the disease presents as de novo AML (World Health Organization, 2022).

Morphologically, the bone marrow shows myeloblastic proliferation with blasts often exhibiting granular cytoplasm, variable maturation, and sometimes an associated monocytic component. Immunophenotypically, blasts are typically positive for CD13, CD33, and MPO, while CD34 and CD117 expression may be variable.

Clinically, this disease is more common in adults and often presents with marked leukocytosis. It is considered an aggressive subtype with poor prognosis; however, targeted therapy with tyrosine kinase inhibitors (TKIs) forms the backbone of treatment and is usually combined with intensive chemotherapy (Döhner et al., 2022).

***AML WITH NUP98 REARRANGEMENT**

AML with NUP98 rearrangement is a subtype of acute myeloid leukemia included in the "AML with defining genetic abnormalities" group in the WHO 2022 classification and is characterized by chromosomal rearrangements involving the NUP98 gene with various partner genes, resulting in a biologically heterogeneous disease entity (World Health Organization, 2022). NUP98 fusion

proteins disrupt transcriptional regulation associated with the nuclear pore complex, leading to increased HOX gene expression and differentiation arrest in hematopoietic progenitor cells (Arber et al., 2022).

NUP98-rearranged AML can be seen in both pediatric and adult patients; however, it represents a more prominent subgroup within childhood AML. Because multiple fusion partners may be involved, the clinical and morphologic spectrum is highly variable. Among the most common fusions, NUP98::NSD1 is frequently observed and is typically associated with marked leukocytosis and an aggressive clinical course.

Morphologically, the bone marrow shows predominant blast proliferation with immature myeloid cells and variable patterns of differentiation. In some cases, dysplastic features or a monocytic component may be present; however, morphologic findings are not specific, and genetic analysis is essential for diagnosis.

Immunophenotypically, blasts commonly express CD34, CD33, and CD117, while MPO expression is variable. This profile is consistent with an immature myeloid phenotype but is not specific for NUP98-rearranged AML.

Clinically, NUP98-rearranged AML is generally classified within the high-risk AML group. Particularly in NUP98::NSD1-positive cases, poor prognosis, high relapse rates, and suboptimal treatment response have been reported (Döhner et al., 2022). Therefore, intensive treatment strategies and, in selected cases, allogeneic stem cell transplantation are often considered.

***AML WITH NPM1 MUTATION**

AML with NPM1 mutation is a subtype of acute myeloid leukemia included in the “AML with defining genetic abnormalities” group in the WHO 2022 classification and is characterized by somatic mutations in the NPM1 gene (World Health Organization, 2022). NPM1 mutations typically lead to abnormal cytoplasmic localization of nucleophosmin protein, disrupting transcriptional and epigenetic regulation in hematopoietic cells and resulting in myeloid differentiation arrest (Arber et al., 2022).

NPM1-mutated AML most commonly occurs as de novo AML and is frequently associated with a normal karyotype. This subtype constitutes a significant proportion of adult AML cases and is often accompanied by co-occurring mutations such as FLT3-ITD, which has a major impact on prognostic stratification (Döhner et al., 2022).

Morphologically, the bone marrow often shows blasts with monoblastic or myelomonocytic features. Cells may demonstrate abundant granular cytoplasm, irregular nuclear contours, and variable maturation patterns. A characteristic feature of NPM1-mutated AML is the frequent absence or low expression of CD34, which serves as an important diagnostic clue in distinguishing it from other immature AML subtypes.

Immunophenotypically, blasts are typically positive for CD13, CD33, and MPO. CD117 expression is variable, while CD34 negativity is common. Aberrant CD56 expression may also be observed in some cases.

Clinically, NPM1-mutated AML is generally associated with a favorable prognosis in the absence of high-risk co-mutations. In particular, cases with isolated NPM1 mutation are classified within the favorable-risk group; however, the presence of FLT3-ITD can significantly modify this prognostic advantage (Döhner et al., 2022).

***AML WITH CEBPA MUTATION**

AML with CEBPA mutation is a subtype of acute myeloid leukemia included in the "AML with defining genetic abnormalities" group in the WHO 2022 classification and is characterized by pathogenic mutations in the CEBPA gene (World Health Organization, 2022). CEBPA is a key transcription factor involved in the regulation of granulocytic differentiation, and mutations in this gene lead to differentiation arrest and leukemic transformation in myeloid progenitor cells (Arber et al., 2022).

In the WHO 2022 classification, the presence of bZIP domain biallelic CEBPA mutations is particularly important and defines a distinct biological and prognostic subgroup. Since single-allele and biallelic mutations may have different prognostic implications, accurate determination of mutational type and allelic status is essential in current diagnostic approaches (Döhner et al., 2022).

Morphologically, the bone marrow shows blast proliferation, typically with a myeloblastic appearance. Blasts may contain Auer rods, but there is no highly specific morphologic feature unique to this subtype.

Immunophenotypically, blasts are typically positive for CD13, CD33, and MPO. CD34 expression is variable and may be positive, consistent with an immature myeloid phenotype in some cases.

Clinically, CEBPA-mutated AML, particularly in the presence of biallelic mutations, is generally considered within the favorable-risk AML group and is associated with good response to chemotherapy. However, additional cytogenetic

and molecular abnormalities may modify the overall prognostic assessment (Arber et al., 2022; World Health Organization, 2022).

2-AML, MYELODYSPLASIA-RELATED

AML, myelodysplasia-related (AML-MR) is a subtype of acute myeloid leukemia that, in the WHO 2022 classification, is not included within the "AML with defining genetic abnormalities" group but is instead classified under "myeloid neoplasms related to myelodysplasia" (World Health Organization, 2022). It is defined either by a prior history of myelodysplastic neoplasm (MDS) or by the presence of MDS-related genetic or cytogenetic abnormalities. This category represents a revised and more strictly defined replacement of the former AML-MRC (AML with myelodysplasia-related changes) classification.

The diagnosis of AML-MR is established through two main pathways: (1) a documented previous history of MDS or MDS/MPN, or (2) identification of MDS-related cytogenetic and/or molecular abnormalities. These include cytogenetic changes such as monosomy 7, del(7q), del(5q), and complex karyotype, as well as gene mutations such as ASXL1, RUNX1, SRSF2, SF3B1, U2AF1, ZRSR2, BCOR, and EZH2 (Arber et al., 2022).

Morphologically, AML-MR is typically characterized by prominent dysplasia involving one or more hematopoietic lineages. Dysplastic changes may be observed in erythroid, granulocytic, and megakaryocytic series. Although blast counts are increased, diagnosis is not based solely on blast percentage but also on the presence of associated MDS-defining features.

Immunophenotypically, there is no specific diagnostic profile. Blasts generally express myeloid markers such as CD13, CD33, and MPO. CD34 is frequently positive but may show variability.

Clinically, AML-MR is most commonly seen in older adults and is associated with an adverse prognosis, largely due to its relationship with antecedent MDS and high-risk genetic features. Treatment response is generally poorer compared to other AML subtypes, and allogeneic stem cell transplantation is an important therapeutic option in eligible patients. In the ELN 2022 risk classification, AML-MR is predominantly categorized within the adverse-risk group (Döhner et al., 2022).

3-THERAPY-RELATED MYELOID NEOPLASMS

Therapy-related myeloid neoplasms (t-MN) are a group of diseases included in the WHO 2022 classification under “myeloid neoplasms related to therapy or germline predisposition” and encompass acute myeloid leukemia (AML), myelodysplastic neoplasms (MDS), and MDS/MPN overlap syndromes that arise in patients previously exposed to chemotherapy and/or radiotherapy (World Health Organization, 2022). This category represents therapy-induced clonal hematopoietic disorders and is biologically strongly associated with marked genomic instability.

t-MN typically develops after exposure to alkylating agents, topoisomerase II inhibitors, or ionizing radiation. In cases related to alkylating agents, the latency period is generally longer and progression through an MDS phase is common before AML develops. In contrast, topoisomerase II inhibitor–related cases usually have a shorter latency period and more frequently present as de novo AML (Arber et al., 2022).

Genetically, t-MN is frequently associated with complex karyotypes and chromosomal abnormalities such as -5/del(5q) and -7/del(7q), as well as TP53 mutations. Among these, TP53 mutation plays a central role in therapy-related hematologic neoplasms and is strongly associated with genomic instability and adverse clinical outcomes.

Morphologically, AML in this category may show MDS-like dysplastic features with variable degrees of blast increase. However, a key diagnostic point is the patient’s history of prior cytotoxic therapy; in WHO 2022, blast percentage alone is not sufficient for diagnosis in this group (World Health Organization, 2022).

Immunophenotypically, there is no specific diagnostic profile, and blasts typically express myeloid markers such as CD13, CD33, and MPO. CD34 expression is often positive, reflecting a predominance of immature cells.

Clinically, t-MN represents one of the AML subtypes with the worst prognosis overall. Treatment response is generally poor, and allogeneic stem cell transplantation is often considered the only potentially curative option in eligible patients (Döhner et al., 2022).

4-AML, DEFINED BY DIFFERENTIATION

AML, defined by differentiation refers to a group of acute myeloid leukemia cases that cannot be classified by defining genetic abnormalities and are primarily characterized based on the morphologic and immunophenotypic features of blasts (WHO Classification of Haematolymphoid Tumours, 5th ed., 2022). This category represents the restructured counterpart of the former "AML, not otherwise specified (NOS)" group and includes AML cases that remain after the expansion of genetically defined AML entities. Diagnosis is based on the degree of blast differentiation and lineage assignment (World Health Organization, 2022).

AML with minimal differentiation is characterized by a lack of clear myeloid differentiation, with weak or absent MPO expression and a predominance of immature markers such as CD34 and CD117. AML without maturation shows a predominance of myeloblasts with minimal evidence of maturation, typically with more evident MPO positivity. AML with maturation is defined by the presence of both blasts and maturing granulocytic elements, reflecting a spectrum of myeloid differentiation (World Health Organization, 2022).

Acute myelomonocytic leukemia shows dual granulocytic and monocytic differentiation, with MPO positivity accompanied by expression of monocytic markers such as CD14 and CD64. Acute monoblastic/monocytic leukemia is characterized by a predominance of monoblasts and promonocytes, with strong expression of CD14, CD64, and lysozyme, reflecting monocytic differentiation.

Acute erythroid leukemia is defined by a marked expansion of the erythroid lineage, with predominance of erythroid precursors expressing markers such as glycophorin A and CD71. Acute megakaryoblastic leukemia is characterized by proliferation of megakaryoblasts with expression of CD41, CD61, and CD42b. Acute basophilic leukemia is a rare subtype characterized by blasts with basophilic granules and variable expression of markers such as CD123 and CD203c (World Health Organization, 2022).

Table 4: AML, Defined by Differentiation (WHO 2022)

Subtype	Morphologic Features	Immunophenotype	Notes
AML with minimal differentiation	No clear myeloid maturation; blasts are agranular	MPO negative/weak, CD34+, CD117+, variable CD13/CD33	Diagnosis relies on immunophenotyping
AML without maturation	Predominance of myeloblasts with minimal maturation	MPO+, CD13+, CD33+, often CD34+	Corresponds to FAB M1
AML with maturation	Blasts with evidence of granulocytic maturation	MPO+, CD13+, CD33+, CD15+	Corresponds to FAB M2
Acute myelomonocytic leukemia	Both granulocytic and monocytic differentiation	MPO+, CD13+, CD33+, CD14/CD64+	Corresponds to FAB M4
Acute monoblastic/monocytic leukemia	Predominance of monoblasts/promonocytes	CD14+, CD64+, CD11b+, MPO variable	Corresponds to FAB M5
Acute erythroid leukemia	Predominant erythroid precursors (>80%), proerythroblasts ≥30%	Glycophorin A+, CD71+, MPO negative	Re-defined in WHO 2022
Acute megakaryoblastic leukemia	Proliferation of megakaryoblasts with cytoplasmic blebbing	CD41+, CD61+, CD42b+	Corresponds to FAB M7
Acute basophilic leukemia	Basophilic blasts with dense granules	CD123+, CD203c+, variable MPO	Very rare entity

*WHO 2022 classification defines “AML, defined by differentiation” as a group of acute myeloid leukemias that are not characterized by defining genetic abnormalities. This category includes AML cases that lack specific genetic defining lesions and is subdivided into eight morphologic subtypes based on lineage differentiation and immunophenotypic features (World Health Organization, 2022).

5-MYELOID SARCOMA

Myeloid sarcoma is a myeloid neoplasm characterized by the formation of a tumoral mass composed of myeloid blasts in extramedullary tissues, and it is considered within the same biological spectrum as acute myeloid leukemia (AML) (World Health Organization, 2022). It may present as an isolated lesion (isolated myeloid sarcoma), may occur concurrently with AML, may appear at relapse, or, less commonly, may precede the development of systemic AML. The most frequently involved sites include the skin, lymph nodes, bone, soft tissue, and the gastrointestinal tract (Jaffe et al., 2017; World Health Organization, 2022).

Immunohistochemically, markers such as MPO, CD117, CD34, and CD68 (KP1) are used to confirm myeloid lineage. In cases showing monocytic differentiation, additional markers including CD163 and CD14 may also be positive (Swerdlow, 2017; World Health Organization, 2022).

At the molecular level, myeloid sarcoma often shares the same genetic abnormalities as the underlying AML. Reported associations include RUNX1::RUNX1T1, CBFB::MYH11, KMT2A rearrangements, and NPM1 mutations (World Health Organization, 2022). Therefore, myeloid sarcoma is not considered a separate disease entity but rather an extramedullary manifestation of systemic myeloid neoplasia (Arber et al., 2016; World Health Organization, 2022).

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