Encyclopedia of Pathology
Series Editor: J. H. J. M. van Krieken

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Thierry J. Molina *Editor*

Hematopathology

Springer

Encyclopedia of Pathology

Series Editor
J. H. J. M. van Krieken

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Thierry J. Molina
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Hematopathology

With 361 Figures and 48 Tables

Springer

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To my wife Sophie and my son Noah, for their love and acceptance of the evenings and nights dedicated to this project.
To my two mentors, Jacques Diebold and Tak W. Mak.

Series Preface

When Denis Diderot started the first encyclopedia in the eighteenth century, it was a groundbreaking and timely event. It was the time of the Enlightenment, and knowledge was seen as something which was to be spread to many and to build upon by creating new knowledge. His ambition was to bring all available knowledge together in one series of books so that every person who could read has access to all there is to know. Nowadays, in a time of easily accessible knowledge, the question is whether there is still need of an encyclopedia. It is obvious that the amount of knowledge is such that it is not possible to bring it all together in one encyclopedia. One may argue that the Internet is the encyclopedia of today, but that misses an important point of Diderot, a point that is probably even more valid today. He created a team that valued information and selected what was worth to be presented in the encyclopedia. He recognized that science is not a democratic process where the majority decides what is true and valuable, but rather a growing body of knowledge in which radical ideas from individuals may bring about huge changes, even though most would reject these new ideas in the beginning. Indeed, the Internet lacks such authority and it is not easy to select valuable information from nonsense, especially when one is not an expert in a certain field.

It is therefore that an encyclopedia is only as good as the team that creates it. It goes without saying the team that is responsible for the Encyclopedia of Pathology consists of recognized experts in the field. Pathology is a growing medical discipline in which the amount of information is probably already more than that the whole encyclopedia of Diderot contained. For experts in subspecialties within pathology, it is already almost impossible to keep an overview on new developments and to select relevant from less relevant new information. There are plenty of textbooks for every disease group, and scientific literature is available for most pathologists through PubMed or GoogleScholar. What is lacking is a systematic overview of what we know in an alphabetical order, easily accessible to all. The encyclopedia of pathology fills that gap. It is written by experts with the general pathologist in mind and also specialist from other disciplines. It will consist of a series of volumes on subspecialties, and when it is completed there will be an online version combining these. Yearly updates from the online version is foreseen and readers are welcome to provide suggestions for improvement. These will be judged by the editorial team in order to keep the encyclopedia authoritative yet using the expertise of many.

Finally, it is my hope that the encyclopedia will grow into a reliable body of knowledge in pathology, enabling communication though a common language, and that it will grow and adapt to new developments.

Nijmegen, the Netherlands
July 2019

J. H. J. M. van Krieken
Series Editor

Volume Preface

When Professor J. H. J. M. van Krieken (Han) came to me a few years ago with the proposal of being Editor of the Hematopathology section of the Encyclopedia, I was honored; although aware of the importance of the task, I rapidly accepted for four main reasons: first of all, the excellent previous collaboration with Han in a European collaborative project of molecular hematopathology underlining the importance of collaboration and links between pathologists throughout Europe; second, the importance of gathering in a single section blood, marrow, lymph node, extranodal hematopathology, which often, particularly in Europe, involves not only histopathologists but is crucial for a full understanding of hematological disorders; third, the close ties between the hematopathologists of European Association for Haematopathology and the US Society for Hematopathology facilitating the discussion and friendship between these pathologists, many of them being contributors to this section; fourth, the fact that this project concerns an Encyclopedia and that Denis Diderot is one of my favorite French writer and philosopher.

This project would have not been feasible without the expert contributions of numerous colleagues from the USA and Europe, thanks to the exchange during our regular annual meetings between our two societies. I thank them for dedicating part of their busy time to this project. I would also like to thank our Asian colleagues whose contributions have been instrumental particularly for some entities well known in this part of the world. The occurrence of a first joint workshop between Chinese Society for Hematopathology and US Society for Hematopathology in the end of 2019 underlines the emerging and important links we should all develop with all our Asian colleagues in the future as well as with pathologists of Africa, Middle East, and South America. This Hematopathology section is really a TEAM book, suggested by the acronym TEAM, "Together Everyone Achieves More," as large contributions have been made by pathologists, hematologists, scientists, and clinicians.

Hematopathology Encyclopedia contains majority of entries on reactive and neoplastic diseases of hematopoietic and lymphoid tissues as well as a review of normal blood, bone marrow, and lymph node. Of course, the entries took into account the new changes from the 2016 WHO classification of hematopoietic and lymphoid neoplasms. Besides cytopathology and histopathology, the input of phenotypical and molecular characteristics is detailed as well as differential diagnoses for each entity. Illustration with many typical figures of each entry is present to facilitate the understanding of the entry by the reader. Choosing a reasonable number of entries to cover all the aspects of

hematopathology has been a challenge and is not supposed to be the true or real list of entries for hematopathology as Diderot pointed out years ago (Citation below). In addition, as we know that name of entities, often given by pathologists, changed a lot with time, the pathologist should be familiar both with the updated nomenclature and also the previous ones (synonyms section present in each entry) sometimes to facilitate the understanding with their clinician. The crucial tie of the pathologist both with the clinician on one side and with the scientist on the other is strongly stimulating for the development of pathology. We hope that this section, which is the illustration of a nomenclature at one specific timeline, will be useful for students, pathologists, physicians, biologists, and scientists. With the future development of the online version, we thank in advance any reader for suggestion or comments to upgrade this section. The rapid development of molecular tools as well as artificial intelligence will surely strongly modify the work of the young pathologists, but it is skills as clinician of the tissue that will always be important to maintain the health of our patient.

On doit exiger de moi que je cherche la vérité, mais non que je la trouve.

One may demand of me that I should seek truth, but not that I should find it.

Pensées philosophiques (1746), Denis Diderot, éd. Thomas Crudeli, 1777, pensée 29, p. 53

Paris, France
July 2019

Thierry J. Molina
Volume Editor

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I would like to thank J. H. J. M. van Krieken for his support and trust. Thanks to Sunaina Dadhwal and Neha Thapa for their activity and support throughout the process.

Thanks to my collaborators of hematopathology in the Department of Hôtel-Dieu, Paris, particularly Dr. Agnès Le Tourneau and Josée Audouin as well as all my colleagues and the entire team of Pathology from Hôpital Necker-Enfants Malades. Thanks to all my colleagues from the LYSA (Lymphoma Study Association).

Thierry J. Molina
Volume Editor

Editor Biography

Thierry J. Molina, M.D., Ph.D., Department of Pathology, Paris Descartes University, University of Paris, Necker-Enfants Malades Hospital, AP-HP, Paris, France

Thierry Jo Molina, Professor of Pathology at the Paris Descartes University and, since 2019, University of Paris, is a pathologist with expertise in hematopathology, both pediatric and adult, as well as thymic pathology. He graduated in 1984 at the Faculty of Medicine Necker-Enfants Malades, Université René Descartes, and was board certified in pathology in 1988. He completed his Master of Science in 1989 and his Ph.D. in 1993 at the same University and after being in a postdoctoral position in Dr. Tak Mak's Laboratory in Toronto, Ontario Cancer Institute, Canada. Dr. Molina became Private Docent in Anatomic Pathology at the Faculty of Medicine Broussais Hôtel Dieu, Hospital Hôtel Dieu, Paris, in 1994, and Full Professor of Pathology in the same faculty in 2000. After being Head of the Department of Biology, Pharmacy, Pathology in Hôtel-Dieu from 2008 to 2010, and Head of the Department of Pathology in Hôtel-Dieu from 2010 to 2013, he was appointed since 2013 as the Chief of the Department of Pathology in Necker-Enfants Malades University Hospital.

Dr. Thierry Jo Molina has (co)authored more than 250 peer-reviewed publications mainly in hematopathology and immunopathology, and his research interest for more than 20 years has been B-cell lymphoma, mainly in diffuse large B-cell lymphomas (DLBCL). He has done numerous studies assessing the clinical and prognostical value of tissular protein and molecular

biomarkers in DLBCL. Dr. Molina is presently working in deciphering the role of the activation of alternative NF-kB pathway in DLBCL. He has written chapters in textbooks such as *Non-Hodgkin's Lymphoma in Childhood and Adolescence* (Springer, 2019; O Abla, A Attarbaschi, ed.) and edited textbook in French on hematopathology. Dr. Molina has been invited in numerous meetings of national societies of pathology and hematology, as well as international meetings in lymphoma or thymic pathology.

Professor Thierry Jo Molina is a member of European Association for Haematopathology (EAHP) since 1992 and was appointed as a member of the Executive Committee of EAHP from 2004 to 2008. He has been a member of the European Biomed-2 group linked to clonality study by PCR of lymphoproliferative disorders, now named EuroClonality. He was responsible of the organization of the French Annual Meeting of Pathology, organized by the French Society of Pathology from 2008 until 2012. He was appointed President of the French Society of Pathology from 2012 to 2014. He is presently coordinating the pathology group of the French clinical network dedicated to the management of patients with thymic epithelial tumors (named RYTHMIC) supported by the French National Cancer Institute (INCa). He is a member of the Executive Committee of the LYSA (Lymphoma Study Association) group, dedicated to all the academic clinical trials involving patients in France and Belgium with lymphoma and is co-responsible of the LYSA Pathology Platform.

Series Editor Biography

J. H. J. M. van Krieken is a pathologist with special expertise in the fields of hematopathology and the pathology of the gastrointestinal tract. He was Professor for tumor pathology since 1999 and kept from 2005 to 2015 the Chair of pathology at the Radboud University Nijmegen Medical Centre inNijmegen. He furthermore served as Chairman of the Board of the Oncology Institute of the Radboud University, Nijmegen, from 2008 to 2016. Since 2016, he is the Rector Magnificus (Vice Chancellor) of the Radboud University.

He was the Treasurer/Secretary of the European Association for Hematopathology from 2000 to 2008, from 2003 to 2011 the Treasurer, from 2013 to 2015 the President of the European Society for Pathology (ESP), and from 2015 to 2017 the past-President of the ESP. Furthermore, he coordinated the ESP quality assessment program from 2008–2018 and was the chair of IQN path from 2005–2008. He is (co) author of more than 600 papers in peer-reviewed journals (H-index 86), has written chapters in books on pathology and oncology, is editor of a Dutch textbook on oncology, and serves on the editorial board of the *American Journal of Surgical Pathology*, was managing editor of Virchows Archive from 2009–2015, and was the chief editor of the *Journal of Hematopathology* from 2008–2018. Since 2011, he is member of the German Academy of Sciences Leopoldina, and since 2014 of Academia Europea and Honorary Fellow of the Royal Society of Pathology of Great Britain and Ireland.

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A

Acute Leukemia, Ambiguous Lineage

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Synonyms

Bilineage acute leukemia; Biphenotypic acute leukemia; Mixed-lineage leukemia

Definition

According to the World Health Organization 2008 classification of tumors of hematopoietic and lymphatic tissues, the category "acute leukemia of ambiguous lineage" includes mixed phenotype acute leukemia (MPAL), acute undifferentiated leukemia (AUL), and a provisional entity of natural killer (NK) cell lymphoblastic leukemia/lymphoma (Borowitz et al. 2008) (Table 1).

MPALs are characterized by blasts that express antigens of more than one lineage to such a degree that it is not possible to assign the leukemia to any one lineage with certainty. MPALs can contain distinct blast populations, each of a different lineage, or one population with multiple antigens of different lineages on the same cells.

In extremely rare cases of AUL, although markers of all lineages have been investigated, no significant lineage-associated marker expression is detected on blast cells except for CD34 and/or HLA-DR. NK cell lymphoblastic leukemia/lymphomas appear morphologically and immunophenotypically to derive from immature NK cells.

Clinical Features

- **Incidence**
  The frequency of MPAL using the 2008 WHO criteria is low. Retrospective analysis of a pediatric acute leukemia cohort (633 patients) found that 1.7% of cases fulfilled MPAL WHO 2008 criteria (Al-Seraihy et al. 2009). A retrospective meta-analysis of major recent studies of biphenotypic acute leukemia using the 2008 WHO criteria (7,627 patients totally) found 119 patients (1.6%) who could be classified as MPAL (Weinberg and Arber 2010). Incidence of true AUL and NK cell lymphoblastic leukemia/lymphoma is extremely low and not well defined.

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Acute Leukemia, Ambiguous Lineage, Table 1 WHO 2008 classification of acute leukemias of ambiguous origin and expression of lineage assignment markers for mixed phenotype acute leukemia (MPAL) (Borowitz et al. 2008)

Category	B-lineage: CD19[a]	T-lineage: CD3[b]	Myeloid lineage: myeloperoxidase[c]	Monocytic lineage[d]: CD14, CD11c, CD14, CD64, lysozyme, nonspecific esterase
Acute undifferentiated leukemia	–	–	–	–
MPAL with t(9;22) (q34;q11.2) *BCR-ABL1*	+	±[e]	+	–
MPAL with t (v;11q23), MLL rearranged	+	–	±	±
MPAL, NOS B/myeloid	+	–	±	±
MPAL, NOS T/myeloid	–	+	±	±
MPAL, NOS other	+	+	+	±
Natural killer cell lymphoblastic leukemia/ lymphoma[f]	–	–	–	–

[a]Has to be corroborated by expression of one (if CD19 bright) or two (if CD19 dim) B-cell markers
[b]Cytoplasmic and/or membrane by flow cytometry. Due to cross-reactivity with CD3ε, cytoplasmic CD3 can also be detected by immunohistochemistry in NK cells
[c]Detected by cytochemistry and/or immunohistochemistry and/or flow cytometry
[d]Two of monocytic markers are needed to establish monocytic lineage
[e]Very rare
[f]Provisional entity

- **Age**
  Acute leukemia of ambiguous origin can occur at any age, including infants. There is no difference in incidence between children and adults.
- **Sex**
  There is a slight male predominance (M:F 1.6 (Matutes et al. 2011)).
- **Site**
  Most patients present as acute leukemia with symptoms of bone marrow failure (Weinberg and Arber 2010). There may also be extramedullary involvement at presentation.
- **Treatment**
  There is no standard therapy for MPAL. Retrospective analysis of 100 cases suggested that acute lymphoblastic leukemia (ALL)-directed treatment seems more effective with a higher response rate and better outcome compared with an acute myeloid leukemia (AML) or to an AML + ALL schedule. MPAL patients should be considered candidates for consolidation with intensive chemotherapy and stem cell transplantation at first remission, particularly in those who achieve CR but remain positive for minimal residual disease (Matutes et al. 2011).
- **Outcome**
  In several studies in adults, patients with MPAL had a worse prognosis in terms of achieving complete remission and overall survival when compared with AML or ALL patients (Weinberg and Arber 2010). Children have better prognosis

than adults, and children with MPAL seem to have similar prognosis as children with ALL (Weinberg and Arber 2010). The overall median survival in a retrospective series of 100 cases was 18 months, and survival at 5 years was 37%. Median survival for children was 139 months versus 11 months for adults. Age, *BCR-ABL1*, and type of induction therapy were significant strong predictors for survival (Matutes et al. 2011).

Microscopy

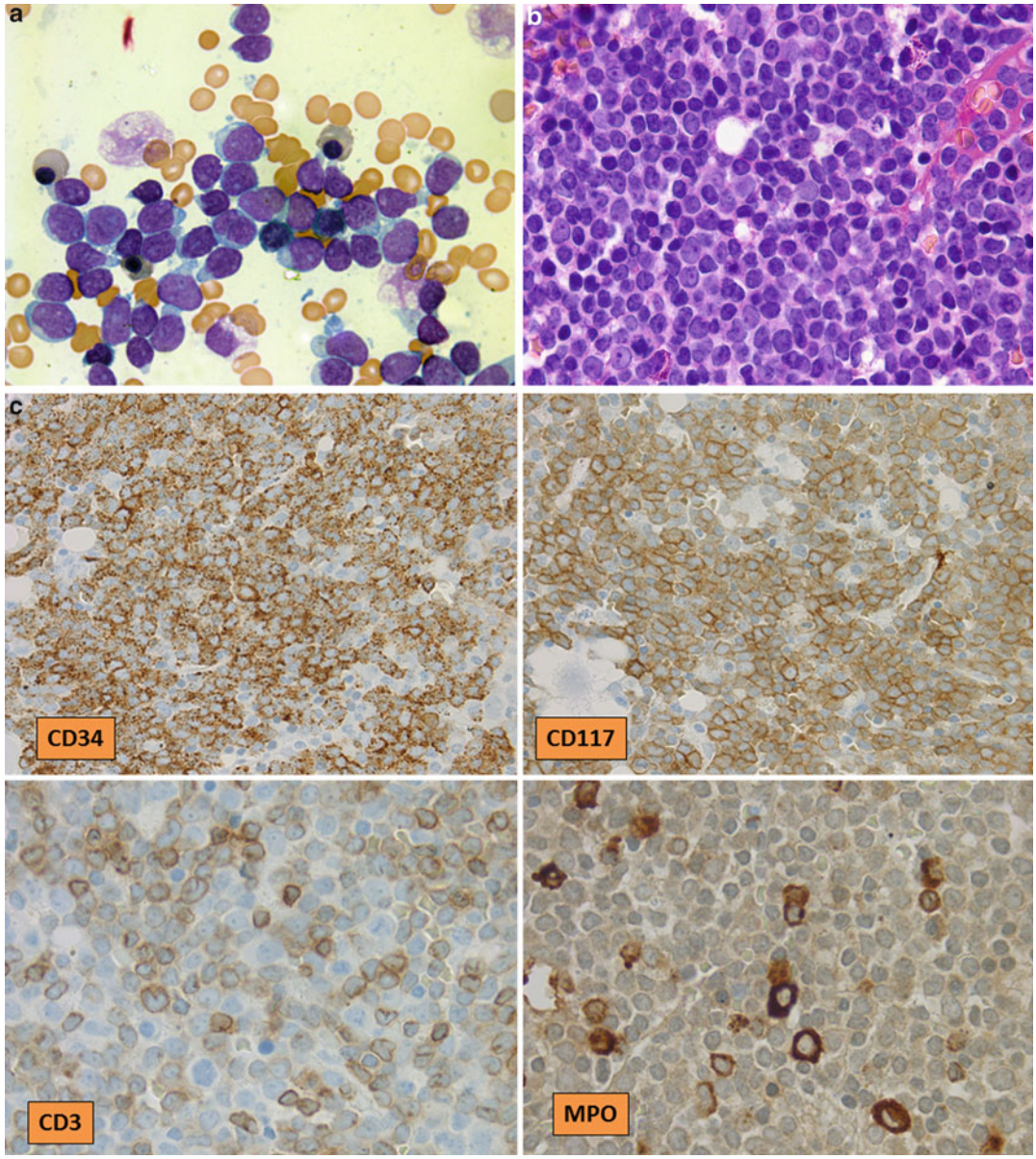
Most patients present with blastic morphology, which is mostly uninformative (Fig. 1). MPAL cells appear most often as morphologically undifferentiated agranular blasts but sometimes may differ in size and display more lymphoblastic or more myeloblastic cytology. In some cases, two types of blasts with a distinctive size and morphology point to the bilineal leukemia (Fig. 2).

Immunophenotype

The initial diagnosis of acute leukemia (AL) relies strongly on immunophenotyping. Cytoplasmic myeloperoxidase (MPO) detected by cytochemistry, immunohistochemistry (IHC), or flow cytometry (FCM) is considered as the most significant marker of myeloid lineage. In cases with monocytic differentiation, which may lack MPO, the presence of nonspecific esterase by cytochemistry, cytoplasmic lysozyme, or surface CD14, CD11c, CD36, or CD64 by FCM can be used. B-lineage assignment is based on CD19 expression. If the CD19 labeling is bright, the presence of another B-lymphocyte marker is considered enough to establish B-lineage. If CD19 expression is of low intensity, the presence of two other B-lineage-associated markers will be necessary. The markers corroborating B-cell lineage can be chosen between cytoplasmic CD79a, CD22, and CD24, intracytoplasmic μ-chains, and (less frequently expressed in MPAL) CD20 or CD21. The expression of CD10 can also be considered in this context as a B-lineage-related marker.

The strongest marker indicating T-lineage is the cytoplasmic expression of CD3, which must be investigated with a bright fluorochrome such as phycoerythrin or allophycocyanin and appears as a strong labeling. The presence of other T-cell-associated markers such as CD2, CD5, or CD7 is not lineage specific since some of these markers can be seen on myeloid cells in AML and therefore should only be considered when associated with cytoplasmic CD3 for MPAL diagnosis. In most cases, at least a subset of blasts shows coexpression of the markers on the same cells (Fig. 3). In rare cases of bilineal proliferations, two different blast populations can be detected, usually with different scatter characteristics suggesting different sizes. The diagnosis of MPAL without an access to fresh tissue and flow cytometry studies may be a challenge. However, a suspicion of MPAL can be raised using immunohistochemical staining of a bone marrow biopsy or extramedullary infiltrate in tissue sections if blastic populations express CD3 and/or MPO or MPO and/or more than one other B-cell-associated markers such as CD79a, PAX5, CD22, and CD10 (Fig. 4).

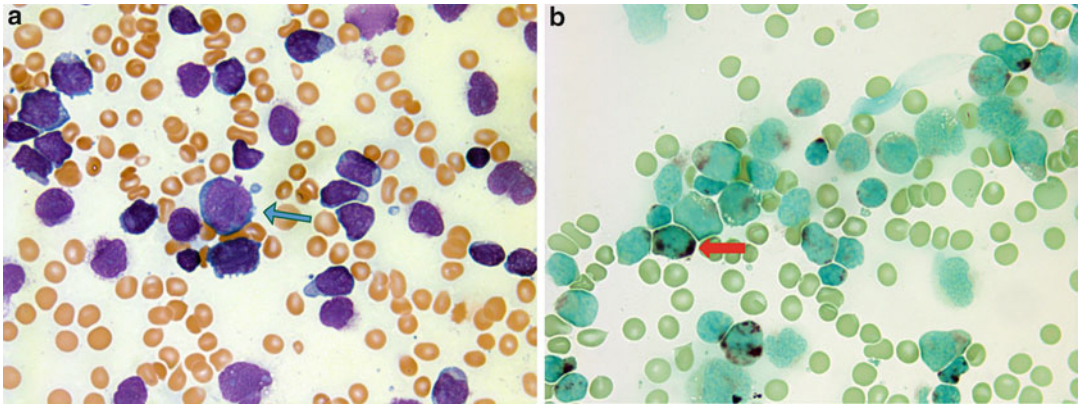
AUL can be identified only after an extensive immunophenotyping. The expression of classical myeloid and lymphoid markers and also markers associated with plasmacytoid dendritic cells (CD4/CD56), basophils, mast cells, and NK cells has to be excluded. Thus, cases of AUL may express only HLA-DR, CD34 and/or CD38, and/or TdT. NK cell lymphoblastic leukemia/lymphoma is still rather poorly defined; cases may share CD34, TdT, and some T-cell markers such as CD2 or CD7 and can express CD56, rarely CD16, and sometimes CD94 or CD161. Panels of anti-KIR antibodies may be required to better characterize these cells.



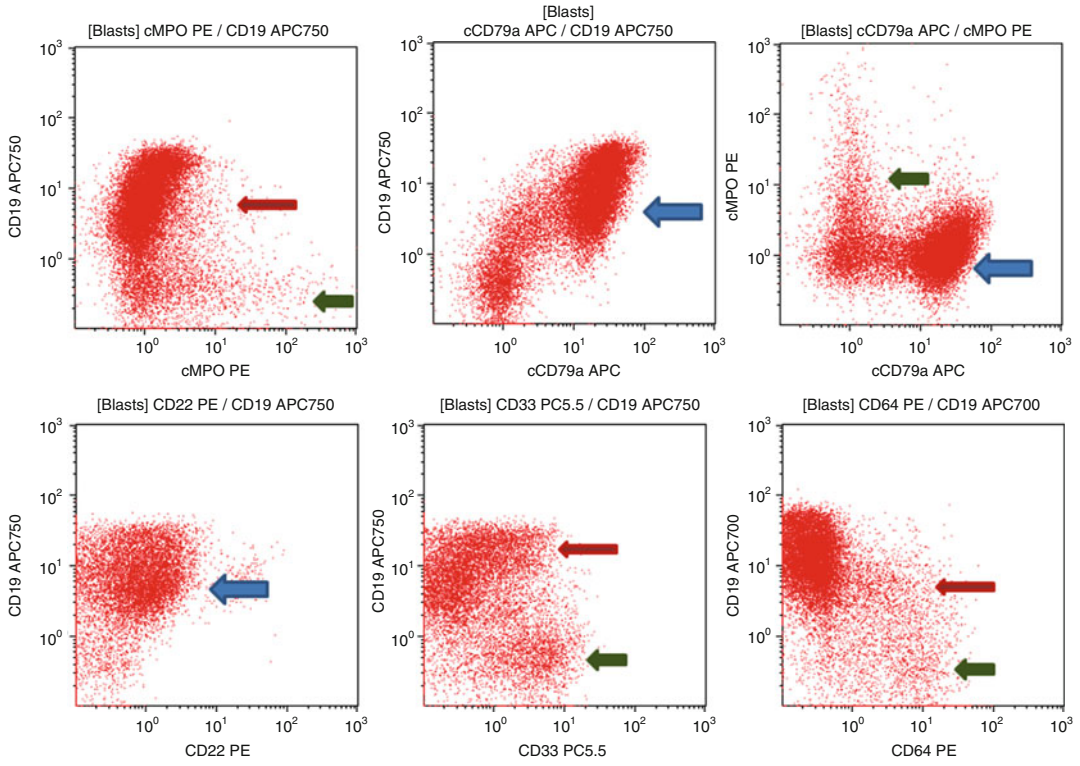
Acute Leukemia, Ambiguous Lineage, Fig. 1 (**a**) Bone marrow smear from a case of T/myeloid MPAL showing undifferentiated, agranular blast population. No maturation is seen in hematopoiesis. Obj.x63. (**b**) Bone marrow biopsy from the same case confirming dominance of blasts in the bone marrow. Obj.x40. (**c**) Immunohistochemical stains show positivity for CD34 and CD117 in the whole blast population. Large fraction is positive for CD3, and a minor population is positive for myeloperoxidase. Leukemic cells were also positive for CD33 (not shown)

Molecular Features

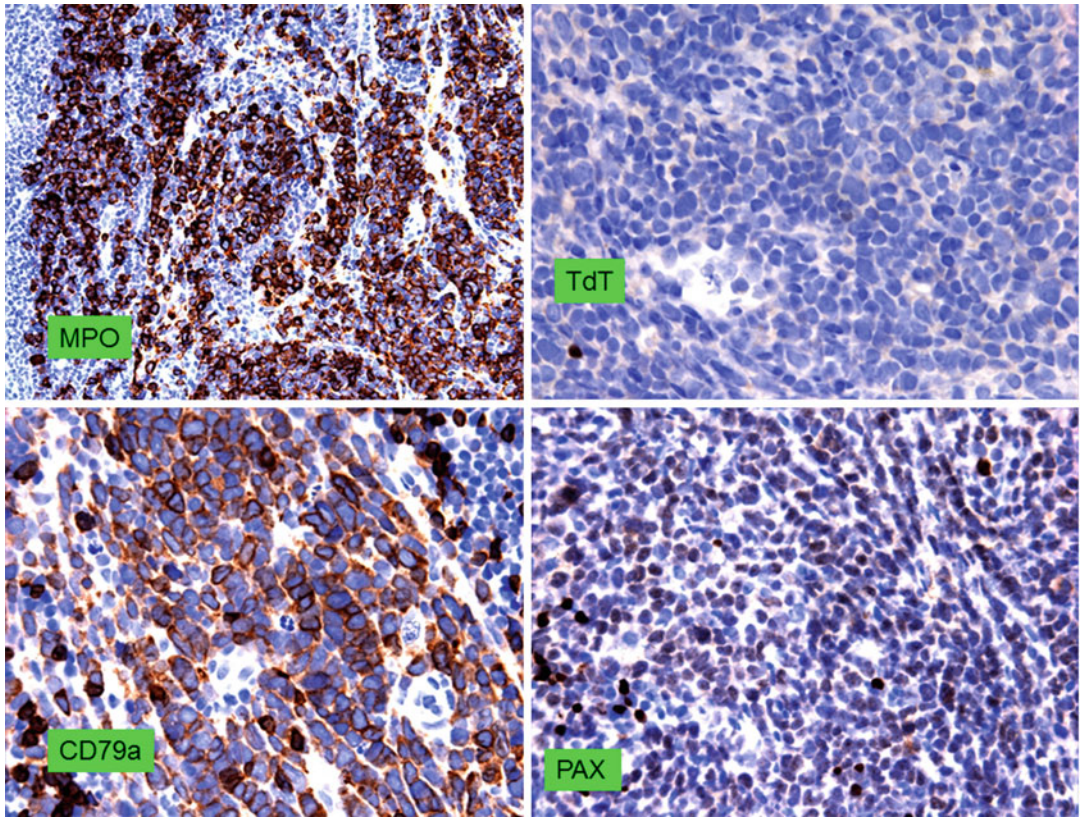
Two separate MPAL entities recognized by WHO 2008 are MPAL with *BCR-ABL1* and MPAL with the *MLL* gene rearranged (Borowitz et al. 2008). Different cytogenetic abnormalities were described in various case reports (Manola 2013). Approximately 30% of cases demonstrate complex karyotype, and several hyperdiploid/near-tetraploid cases were described (Matutes et al. 2011; Manola 2013). Molecular genetic studies are still very scarce.



Acute Leukemia, Ambiguous Lineage, Fig. 2 (**a**) Bone marrow smear from a case of MPAL B/myeloid with t(4;11)(q22;q23), *MLL-AF4*. Most blasts are small to medium sized with scant cytoplasm, but rare large blasts with abundant cytoplasm are also present (*Blue arrow*). Obj. x63. (**b**) Cytochemistry in the same case shows a fraction of cells positive for nonspecific esterase suggesting monocytic differentiation (*Red arrow*) Obj.x63



Acute Leukemia, Ambiguous Lineage, Fig. 3 Flow cytometry analysis of bone marrow in the same case as in Fig. 2 reveals major population of B lymphoblasts (CD19+, cyt.CD79a+, CD22dim, *blue arrows*) and minor population of myeloid blasts positive for MPO, CD64, and CD33 (*green arrows*). Rare cells are positive for both B-cell and myeloid markers (*brown arrows*)



Acute Leukemia, Ambiguous Lineage, Fig. 4 Case of MPAL B/myeloid UNS, where weak CD19 expression found by flow cytometry (not shown) was corroborated by CD79a and PAX5 detected by immunohistochemistry. Most leukemic blasts expressed MPO

Differential Diagnosis

It is important to identify MPAL and not misdiagnose them as ALL or AML by using immunophenotypic panels not comprehensive enough. It is of clinical importance, since some refractory cases of acute leukemia, with poor response to therapy, could well represent undetected MPALs by error assigned to a single lineage.

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Acute Myeloid Leukemia and Related Neoplasms

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Synonyms

Acute myelogenous leukemia; Acute non-lymphocytic leukemia; Agranular CD4+ CD56+ hematodermic neoplasm; Agranular CD4+ NK cell leukemia; Blastic NK cell lymphoma; Blastic NK leukemia/lymphoma

Definition

Acute Myeloid Leukemia (AML) is a bone marrow cancer, characterized by the clonal expansion and lack of differentiation of early myeloid cells. In the majority of cases, the diagnosis of AML requires a myeloid blast count $\geq$20% of nucleated cells in the blood or bone marrow. Blasts can also infiltrate other organs or tissues such as skin, gums, or lymph nodes. Rarely AML can present as an isolated myeloid sarcoma in any tissue. The definition of myeloid blasts includes abnormal promyelocytes in acute promyelocytic leukemia (APL), and promonocytes in monocytic/monoblastic AML. Almost any myeloid lineage can be affected; myeloid or monocytic are relatively common, but rare basophilic, pure erythroid and megakaryocytic forms of AML exist.

Classification

AML is an extremely heterogeneous disease, with many distinct subgroups defined by specific morphological, cytogenetic, molecular, and gene expression characteristics. The World Health Organisation (WHO) has classified AML according to some of the most significant clinical, morphological, cytogenetic, and molecular pathological factors (ref) (Table 1). Other subgroups include AML with myelodysplasia-related changes, therapy-related myeloid neoplasms, myeloid sarcoma, and myeloid proliferations related to Down Syndrome. The WHO classification has largely replaced the earlier French American British (FAB) classification, which was principally based on morphological characteristics. A morphological classification does remain, in the AML not otherwise specified (AML NOS) WHO subgroup, which is used if no other defining features are present.

Clinical Features

AML results in rapidly progressive bone marrow failure, hence the term "acute." The replacement of normal hematopoiesis by proliferating myeloid blasts causes clinically significant, and often rapidly progressive, anemia, thrombocytopenia, and neutropenia. The resulting symptoms include fatigue, shortness of breath, bleeding, bruising, petechiae, pyrexia, and symptoms of infection. Disseminated intravascular coagulation can also be a presenting feature, most commonly in APL, and untreated can cause rapidly fatal bleeding. Central nervous system involvement at presentation occurs in approximately 0.5% of cases and can cause headaches and neurological symptoms or signs.

The white cell count (WCC) is typically elevated, and if $>150 \times 10^9$/L, symptoms of leucostasis which include headache, respiratory distress, and visual disturbance may be present. This is more common if the high WCC is comprised of monoblasts. Up to 10% of cases of AML may have an "aleukemic" presentation, with cytopenias and possible dysplastic features, but no blasts present in the peripheral blood.

- **Predisposing Factors**
  The majority of cases of AML occur with no known predisposing factors. However, in 10–15% of cases, prior treatment with chemotherapy or radiotherapy is implicated, and as

Acute Myeloid Leukemia and Related Neoplasms, Table 1 WHO classification of AML and related neoplasms

WHO subtype	Morphology	Immunophenotype	Molecular/Other
AML with recurrent genetic abnormalities			
AML with t(8;21) (q22;q22); *RUNX1-RUNX1T1*	Blasts >5%. Large blasts with granulation and auer rods. Most commonly AML with maturation (see below), often with dysplastic features in maturing cells. Occasionally absence of maturation or rarely monocytic differentiation	CD34+, CD13+, CD33+, HLA-DR+, MPO+ Subpopulation with CD15+ (maturing granulocytes) Often aberrant CD19+, more rarely CD56+	Additional chromosomal abnormalities in 70%. *KRAS/NRAS* mutations in 30% pediatric cases *KIT* mutations in 20–25% 10 year survival 61%
AML with inv(16) (p13;q22) or t(16;16)(p13;q22); *CBFB-MYH11*	Blasts >5%. Morphological features of myelomonocytic leukemia (see below). Abnormal eosinophil component in the BM (large purple-red granules in immature forms). Rarely lack eosinophilia or show myeloid or monoctyic differentiation only	Multiple CD34+, CD117+ blast populations Granulocytic: CD13+, CD33+, CD15+, MPO+ Monocytic: CD14+, CD11b+, CD11c+, CD64+, CD36+ Often aberrant expression CD2	Inv(16) more common that t(16;16) Additional chromosomal abnormalities in 40%, trisomy 22 fairly specific *KIT* mutations in 30% 10 year survival 55%
APL with *PML-RARA*	Atypical promyelocytes >5%. Hypergranular variant with prominent red-purple granules (rare in PB). Some cells contain bundles of auer rods (faggot cells). Microgranular variant with more readily visible dumbbell or bilobed nucleus and high PB count	CD13+, CD33+, MPO+, HLA-DR−, CD34− Aberrant expression CD2 in microgranular variant	Additional chromosomal abnormalities in 40%, with trisomy 8 the most common Mutations in *FLT3 ITD* or *TKD* in 35–45% 10 year survival 73%
AML with t(9;11) (p21;q23); *MLLT3-KMT2A*	Blasts ≥20%. Morphological features most often monocytic or myelomonocytic (see below). Occasionally AML with or without maturation	In children: CD33+, CD65+, CD4+, HLA-DR+ CD13−/+, CD34−/+, CD14 −/+ In adults: markers of monocytic differentiation – CD14+, CD4+, CD11b+, CD11c+, CD64+, CD36+. Variable expression CD34, CD117, CD56	Secondary cytogenetic abnormalities are frequent, with trisomy 8 the most common 10 year survival 39%
AML with t(6;9) (p23;q34); *DEK-NUP214*	Blasts ≥20%. Most commonly AML with maturation or acute myelomonocytic leukemia (see below). Can have morphological features of any FAB subtype other than APL or acute megakaryoblastic leukemia. Marrow and PB basophilia in approximately 50% cases	MPO+, CD13+, CD33+, HLA-DR+ CD117±, CD34±, CD15± Tdt + in 50%	The t(6;9) translocation is the sole chromosomal abnormality in most cases. The fusion protein acts as an aberrant transcription factor *FLT3-ITD* very common 69%–78% cases 10 year survival 26%

(*continued*)

Acute Myeloid Leukemia and Related Neoplasms, Table 1 (continued)

WHO subtype	Morphology	Immunophenotype	Molecular/Other
AML with inv(3)(q21;q26) or t(3;3)(q21;q26); *GATA2*, *MECOM*	Blasts ≥20%. Most commonly AML without maturation, acute myelomonocytic leukemia or acute megakaryoblastic leukemia. Can have morphological features of any FAB subtype other than APL. PB may have dysplastic neutrophils, giant and hypogranular platelets. Multilineage dysplasia is common in the BM	CD13+, CD33+, HLA-DR+, CD34+, CD38 + Some aberrant CD7 expression. Some with megakaryocytic marker expression (CD41 and CD61)	Repositioning distal *GATA2* enhancer. *MECOM* activation and haploinsufficiency *GATA2* 10 year survival 3%.
AML (megakaryoblastic) with t(1;22)(p13;q13)	Blasts ≥20%. Morphologically acute megakaryoblastic leukemia. Fibrosis usually present. Occurs exclusively in infant and children <3 years	Megakaryocyte markers: CD41+ and/or CD61+. CD36 + Often CD34−, MPO− and HLA-DR−	The t(1;22) translocation is the sole chromosomal abnormality in most cases. The fusion gene may modulate chromatin organization
Provisional: AML with *BCR-ABL1*	Blasts ≥20%. May present as de novo disease or result from blast crisis of CML	CD13+, CD33+, MPO+	Preliminary data suggest deletion of *IGH*, *TCR*, *IKZF1* or *CDKN2A* may support a diagnosis of de novo disease vs. CML blast phase Unfavorable prognosis
AML with mutated *NPM1*	Blasts ≥20%. Most commonly myelomonocytic or monocytic (80–90% of acute monocytic leukemias have an NPM1 mutation). NPM1 mutations are also seen in AML with and without maturation. Some have multilineage dysplasia. WCC usually high	CD13+, CD33+, MPO+, CD34− Monocytic markers common: CD14+, CD11b+, CD68+	Abnormal karyotype in only 5–15%. *NPM1* mutations usually mutually exclusive of balanced translocations that define AML entities *FLT3-ITD* in 40%. Favorable prognosis when found in isolation
AML with biallelic mutations of *CEBPA*	Blasts ≥20%. No distinctive morphological features, but most commonly AML with or without maturation. Less commonly monocytic or myelomonocytic	CD13+, CD33+, CD65+, CD11b+, CD15+ HLA-DR ± and CD34± Aberrant CD7 in over 50%	Abnormal karyotype in 30% *FLT3-ITD* in 22–33% cases Favorable prognosis.
Provisional: AML with mutated *RUNX1*	Blasts ≥20%	CD13+, CD33+, MPO+	Cases with MDS-related cytogenetic abnormalities excluded from this category Unfavorable prognosis
AML with myelodysplasia-related changes			
AML with myelodysplasia-related changes	Blasts ≥20%. Most cases have morphological evidence multilineage dysplasia. Morphological classification requires dysplasia in ≥50% cells in ≥2 lineages Other defining criteria are MDS-related cytogenetic abnormalities or a preceding diagnosis of MDS	Variable findings CD34+, Tdt+, CD13+, CD33+ Aberrant CD7 and CD56 common	Chromosome abnormalities are similar to those in MDS (Table 6) 10 year survival 16%

(*continued*)

Acute Myeloid Leukemia and Related Neoplasms, Table 1 (continued)

WHO subtype	Morphology	Immunophenotype	Molecular/Other
Therapy-related myeloid neoplasms			
Therapy-related AML/MDS and AML/MDS/MPN	Blasts ≥20% to diagnose AML. Often preceded by myelodysplastic phase. Multilineage dysplasia present in the majority. Distinguishing therapy-related AML, MDS and MDS/MPN may not be clinically relevant. Best considered as one clinical syndrome	No specific immunophenotypic findings CD34+, CD33+, CD13+ Aberrant CD7 and CD56 common.	Abnormal karyotype in >90%. Unbalanced aberrations in 70%, mainly loss of material from chromosome 5 and 7, associated with myelodysplastic phase (longer latency) In 20–30% balanced translocations are found and most often present as de novo AML (shorter latency)
AML, not otherwise specified			
AML with minimal differentiation	≥20% blasts. No evidence of myeloid differentiation by light microscopy (absence of granulation and auer rods)	CD34+, HLA-DR+, CD38+, CD13+ MPO- CD117±, CD33± Aberrant CD7 in 40%	Complex karyotype most common abnormality. Unbalanced MDS-related abnormalities and *RUNX1* mutations result in assignment to alternative categories
AML without maturation	≥20% myeloid blasts. Blasts ≥90% of non-erythroid cells	MPO+, CD13+, CD33+, CD117+ CD34+, HLA-DR+ Aberrant CD7 in 30% Aberrant CD2, CD4, CD19 or CD56 in 10–20%	No association with specific recurrent chromosomal abnormalities
AML with maturation	≥20% myeloid blasts ± azurophilic granules; ≥10% maturing cells of neutrophil lineage. Cells of monocytic lineage ≤20% of BM cells	CD13+, CD33+, CD15+ CD34±, CD117±, HLA-DR± Aberrant CD7 in 20–30%	No association with specific recurrent chromosomal abnormalities
Acute myelomonocytic leukemia	≥20% myeloblasts, monoblasts, promonocytes; ≥20% monocytes and monocytic precursors; ≥20% neutrophils and granulocytic precursors	Multiple blast populations CD13+, CD33+ Immature: CD34+, CD117+ Granulocytic: CD15+ Monocytic: CD14+, CD4+, CD11b+, CD11c + CD64+, CD36+ Aberrant CD7+ 30%	Myeloid-associated, nonspecific cytogenetic abnormalities common e.g., trisomy 8
Acute monoblastic/ monoctyic leukemia	≥80% monocytic cells; monoblastic if ≥80% are monoblasts or monocytic if <80% are monoblasts	HLA-DR+, CD13+, CD33+, CD15+ ≥2 of CD14+, CD11b+, CD11c+, CD64+, CD36+ MPO−/+ more common in monocytic Aberrant CD7+/CD56+ 25–40%	Myeloid associated, nonspecific cytogenetic abnormalities are present in the majority of cases
Pure erythroid leukemia	>80% immature erythroid precursors with ≥30% proerythroblasts	CD117±, CD36+, CD235a (glycophorin A) −/+, MPO−, HLA-DR−, CD34−, CD41/61−	No specific chromosomal abnormality, complex karyotype most common Unfavorable prognosis

(*continued*)

Acute Myeloid Leukemia and Related Neoplasms, Table 1 (continued)

WHO subtype	Morphology	Immunophenotype	Molecular/Other
Acute megakaryoblastic leukemia	≥20% blasts with ≥50% shown to be of megakaryocyte lineage by immunophenotype	CD36+, CD61+, CD41+, CD42 −/+ HLA-DR±, CD34±, CD45−/+, MPO-	3q26 abnormalities and t(1;22) result in assignment to alternative category Unfavorable prognosis
Acute basophilic leukemia	≥20% blasts of basophilic lineage. Medium sized cells with oval to bilobed nucleus, nucleoli, basophilic cytoplasm and coarse basophilic granules	CD13+, CD33+, CD123+, CD203+,CD11b, CD34±, HLA-DR±, CD117− Aberrant CD9+ in most	No specific chromosomal abnormality
Acute panmyelosis with myelofibrosis	Pan myeloid proliferation with clusters of blasts. Dysplastic megakaryocytes. Marked reticulin fibrosis. Trephine diagnosis	Blasts MPO−, CD13+, CD117+ Multilineage involvement – erythroid, megakaryocytic, granulocytic markers present	Karyotype usually abnormal
Myeloid proliferations related to Down syndrome			
Transient abnormal myelopoiesis (TAM)	Unique disorder of Down syndrome newborns. Morphological features of acute megakaryoblastic leukemia. PB basophilia. Spontaneous remission in the majority. 20–30% develop nontransient AML 1–3 years later	CD34+, CD56+, CD117+, CD13+, CD33+, CD7+, CD41+, CD42+, CD36+, CD61+ MPO−, CD15−, CD14−	Trisomy 21 required and additionally acquired mutations in *GATA1* are present
Myeloid leukemia associated with Down syndrome	Most commonly acute megakaryoblastic leukemia. No biological difference between MDS and AML therefore the term myeloid leukemia includes both morphological cases of MDS and AML	CD34±, CD56±, CD117+, CD13+, CD33+, CD7+, CD41±, CD42+, CD36+, CD61+ MPO−, CD15−, CD14−	Trisomy 21 required and additionally acquired mutations in *GATA1* are present. Trisomy 8 common

increasing numbers of people survive their initial cancer, this is predicted to expand. AML can evolve from a prior acquired hematological condition, most often the myelodysplastic syndromes, but also myeloproliferative neoplasms. Rare environmental predisposing factors include exposure to benzene and ionizing radiation. Inherited conditions such as Down syndrome have long been known to greatly increase the risk of development of AML, particularly acute megakaryoblastic anemia. It was previously thought that the contribution of germline mutations to the development of AML was restricted to rare disorders such as Dyskeratosis Congenita and Fanconi anemia, or Bloom and Li-Fraumeni syndrome, which are characterized by defective DNA repair. However, it is increasingly recognized that up to 10% of people who develop AML have an inherited predisposition to hematological malignancies, and myeloid neoplasms with germline predisposition is a new entity in the most recent WHO classification (Table 2). The importance of a careful family history in patients with AML, and the involvement of geneticists to screen for potential germline alterations that may affect family members, is increasing.

- **Incidence**

  The overall incidence of AML in the general population is 3/100,000. AML accounts for 90% of cases of acute

Acute Myeloid Leukemia and Related Neoplasms, Table 2 Myeloid neoplasms with germline predisposition

Myeloid neoplasm with germline predisposition without a pre-existing disorder or organ dysfunction
Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid neoplasms with germline *DDX41* mutation
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
Myeloid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid neoplasms with germline *ETV6* mutation
Myeloid neoplasms with germline predisposition and other organ dysfunction
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Myeloid neoplasms associated with telomere biology disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome

leukemia in adults, but is rare in children, in whom acute lymphoblastic leukemia (ALL) predominates.

- **Age**
  The incidence of AML rises with age, from 1/100,000 at age 25 to over 15/100,000 by the age of 75. Due to the aging population, as well as increased survival post chemotherapy or radiotherapy for other cancers, the overall incidence of AML will rise over the coming decades.
- **Sex**
  The sex ratio is 1:1 in younger people presenting with AML but there is a slight male preponderance in the over 65 s (ratio 1.3:1). The reason for this remains unclear.
- **Treatment**
  The backbone of treatment for AML remains cytotoxic chemotherapy; however, as the molecular basis of this disease is becoming more understood, novel targeted therapies are starting to improve survival in this disease.
- **Treatment of Acute Myeloid Leukemia (Non-APL)**
  The mainstay of treatment for younger, fitter patients with AML is intensive induction chemotherapy consisting of an anthracycline (most often daunorubicin) and cytarabine (ELN guidelines 2017), followed by post-remission consolidation therapy. Molecularly targeted therapy, such as the FLT3 inhibitor midostaurin, or the anti-CD33 monoclonal antibody-drug conjugate gemtuzumab is now becoming increasingly used. Assessment of risk, based on genetic features, and the monitoring of minimal residual disease are critical to informing decisions regarding post remission treatment with additional cycles of intensive chemotherapy or high dose therapy followed by allogeneic transplant.
- **Treatment of Acute Promyelocytic Leukemia**
  The treatment of APL is significantly different to other forms of AML. Due to the coagulopathy that accompanies this form of AML, it used to be the subtype with the highest mortality. Since the 1980s, the PML-RARA fusion due to the t(15,17)(q22;q12) has been targetable directly with the vitamin A derivative all-trans retinoic acid (ATRA), which overcomes the differentiation block caused by this oncogene. ATRA may be used in combination with an anthracycline cytotoxic chemotherapy drug, resulting in complete remission rates of >90%. More recently, trials have demonstrated that an entirely chemotherapy-free treatment using ATRA with arsenic trioxide may be even more effective than the chemotherapy-containing regimes.
- **Outcome**
  Survival in AML is influenced primarily by age and the genetic abnormalities present. Overall, more than half of patients with AML will die from this disease. Increasing age adversely affects outcome for a number of reasons. These include inability to deliver intensive chemotherapy, higher treatment-related mortality, and higher rates of chemotherapy resistance. AML that is secondary to a prior hematological disorder such as MDS, or is therapy-related, have an adverse prognosis.

  The important role of genetics in risk stratification is highlighted by the European

Acute Myeloid Leukemia and Related Neoplasms, Table 3 ELN 2017 risk stratification of AML by genetics

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;22); *RUNX1-RUNX1T1* inv(16)(p13q22) or t(16;16)(p13;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*$^{low(}$ Bialleleic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3- ITD*^{high} Wild type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low} (w/o adverse risk lesions) t(9;11)(p21;q23); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34); *DEK-NUP214* t(v;11q23); *KMT2A* rearranged t(9;22)(q34;q11); *BCR-ABL1* inv(3)(q21;q26) or t(3;3)(q21;q26); *GATA2*,*MECOM*(EVI1) −5 or del(5q); −7; −17/abn(17p) Complex karyotype, monosomal karyotype Wild type *NPM1* and *FLT3- ITD*^{high} Mutated *RUNX1*, Mutated *ASXL1* Mutated *TP53*

LeukemiaNet (ELN) guidelines, which have categorized genetic abnormalities into favorable, intermediate, and adverse (Table 3).

Outcomes vary considerably between the groups: for example patients with APL, due to t(15,17) have a 73% 10-year survival, compared to a 3% 10 year survival in those with disruption of the gene MECOM due to alterations in chromosome 3. However, as these genetic alterations become therapeutic targets, their prognostic significance may change.

Diagnosis

The laboratory diagnosis of AML involves morphological and histological assessment of peripheral blood and bone marrow, in addition to molecular and cytogenetic analysis. Bone marrow is aspirated and biopsied most commonly from the posterior iliac crest. Liquid bone marrow can be spread immediately on slides to make a smear, which ideally contains particles at the end of trails. The slides are stained with Wright Giemsa or MGG (May-Grunwald Giemsa) stains.

While examination of the bone marrow trephine biopsy is not essential to establish the diagnosis of AML in most instances, and should be avoided in severely coagulopathic patients due to the increased bleeding risk, it may contribute valuable information. At diagnosis, where there is significant marrow fibrosis, hypocellular samples or other reasons for an inadequate aspirate, the trephine is needed for diagnosis. The diagnosis of acute panmyelosis with fibrosis can only be made from a trephine, or increased fibrosis in addition to other histological features may suggest a preceeding myeloproliferative neoplasm. For follow-up samples post-chemotherapy, histological examination of the bone marrow can often best inform the treatment response and hence remission status. Ideally the bone marrow core should be 1.5–2.0 cm in length. In the case of a dry or aparticulate aspirate, the trephine can be rolled on a slide to produce a trephine roll, which can give a more rapid indication of an elevated blast count. If a poor liquid sample is obtained, then a trephine biopsy may be taken into saline, and disaggregated for immunophenotyping by flow cytometry. The DNA obtained from trephine samples taken into saline is usually better preserved than when DNA is extracted from formalin-fixed trephine biopsies. This may be used for molecular analysis if no liquid bone marrow is available, and where there are low numbers of blasts in the peripheral blood.

Microscopy

The WHO classification has moved on from using morphology as the primary means for classification of AML. However, morphology is critical in identifying and enumerating blasts and in the identification of specific subgroups of AML. A myeloid blast count $\geq$20% in the peripheral blood or bone marrow is required for the diagnosis of AML, The exception to the requirement for >20% blasts is the presence of cytogenetic translocations t(8,21), inv(16), t(16,16), or t(15,17) which are categorized as AML provided >5% blasts are present.

Acute Myeloid Leukemia and Related Neoplasms, Table 4 Blast morphology

Myeloblasts	Medium to large sized cells (14–18 μm) with a single round or oval nucleus Fine chromatin with one to several distinct nucleoli Minimal to moderate amount of basophilic cytoplasm Myeloid blasts are usually granular (minimally differentiated AMLs being one exception) Some contain Auer rods (fused granules in a rod-like form), which are pathognomic of AML
Monoblasts	Larger than myeloblasts (15–20 μm) Single round nucleus and visible nucleoli Voluminous blue-grey cytoplasm Often vacuolated
Promonocytes	Blast equivalent Appearances similar to monoblasts Lobulated nucleus with less prominent nucleoli and more prominent vacuolation
Proerythroblasts	Medium to round large cells with nucleoli Minimal deeply basophilic cytoplasm Cases with ≥80% immature erythroid precursors and ≥ 30% proerythroblasts are classified as pure erythroid leukemia under AML, NOS.
Megakaryoblasts	Medium to large cells (12–18 μm) Usually lack granules Cytoplasmic blebbing

Blast morphology is best appreciated in the bone marrow aspirate sample and morphological features are detailed in Table 4 (Fig. 1a).

Immunocytochemistry is now rarely performed due to the universal use of flow cytometry. Historically, cytochemical stains such as Sudan black were used to confirm myeloid lineage. A toludine blue stain can be used to help confirm the diagnosis of the very rare acute basophilic leukemia, if this is suspected.

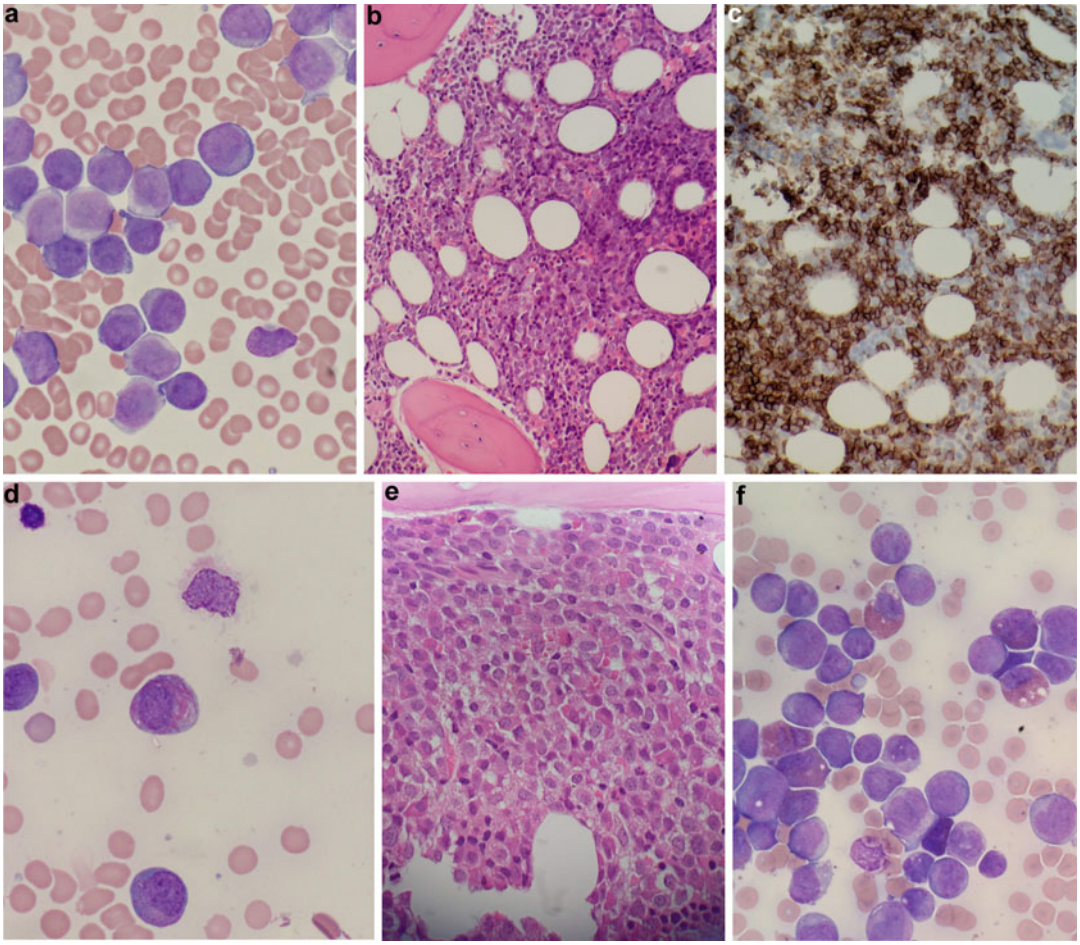
In most cases, the bone marrow trephine biopsy is hypercellular with expanded myelopoiesis and virtual maturation arrest (Fig. 1b). Most of the cellularity is accounted for by CD34+ immature hemopoietic precursors with a high nuclear to cytoplasmic ratio (Fig. 1c). The other two lineages might be difficult to appreciate in the routine hematoxylin and eosin (H&E) stained sections and necessitate the use of immunohistochemistry, particularly when there is a suspicion of AML with myelodysplasia-related changes. Careful examination of bone marrow trephine sample is particularly useful in cases of hypocellular AML and ones with significant fibrosis as bone marrow aspirate in both instances may be nondiagnostic.

AML with Recurrent Genetic Abnormalities

APL is the most important subtype of AML to identify morphologically, as appropriate supportive care and ATRA must be started as soon as possible to reduce early mortality. A careful examination of the peripheral blood is essential, as APL often presents as a pancytopenia, and hence there may be limited numbers of leukocytes to assess. The atypical promyelocytes in the more common hypergranular variant are often packed with large cherry-red granules, and the nucleus is often bilobed. These are often called "dumbell," "buttock," or "butterfly" cells. Auer rods can be a prominent feature, and the term "faggot cell" is used to describe the pathognomonic promyelocytes containing large numbers of Auer rods that resemble bundles of sticks (Fig. 1d). The microgranular variant can be less easy to identify morphologically as the granules are submicroscopic. The clue to the diagnosis lies in the typical nuclear morphology, as in the hypergranular variant. Auer rods and more typical granular forms are often present in small numbers.

The bone marrow trephine is hypercellular due to myeloid expansion (Fig. 1e). There is an accumulation of promyelocytes with abundant, often granular, cytoplasm and convoluted/bean shaped nucleli.

AML with t(8,21)(q22;q22) typically has the morphological appearances of AML with maturation. Auer rods are more often present than in other subtypes of non-APL AML, these are usually present singly within myeloid blasts. In AML with inv(16)(p13q22) or t(16,16)(p13;q22), the peripheral blood often contains increased numbers of monocytes and promonocytes, with an



Acute Myeloid Leukemia and Related Neoplasms, Fig. 1 Morphological features of AML (**a**) myeloblast in aspirate sample (**b**) the marrow is hypercellular with expansion of immature hemopoietic precursors expressing CD34 (**c**). (**d**) Faggot cell in a case of APL with an accumulation of Auer rods in its cytoplasm giving an appearance of a "bundle of sticks" (**e**) H&E appearances of APL in trephine biopsy. (**f**) Blast and dysplastic eosinophils in AML with inv(16)(p13q22)

often marked increase in eosinophils in the bone marrow (Fig. 1f).

AML with Myelodysplasia-Related Changes

Dysplastic features are often seen in AML; however, dysplasia must be present in >50% of cells in ≥2 lineages to be classified morphologically as AML with myelodysplasia related changes (Fig. 2). In the bone marrow trephine, dyserythropoiesis is characterized by maturation synchrony within and dys-synchrony between erythroid islands. Dispersal of immature erythroid precursors and paratrabecular translocation are also often seen. Dysmegakaryopoiesis often manifests as decreased cell size and simplification of nuclear features. Forms are often small/hypolobated or micromegakaryocytes (Fig. 2). They might display dispersal of nuclear lobes.

This diagnosis can also be made if AML develops from a prior myelodysplastic syndrome, or in the presence of MDS-related cytogenetic abnormalities (Table 5). AML with mutated *NPM1* or biallelic mutation of *CEPBA* are excluded from this category, even if significant dysplasia is present. They are categorized according to these mutations and the relatively