How I Diagnose Acute Leukemia of Ambiguous Lineage

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ABSTRACT

Objectives: Classification of acute leukemia involves assigning lineage by resemblance to normal progenitor cells. This approach provides descriptive information about the blast cells that is useful for disease monitoring, provides clues to pathogenesis, and can help clinicians select effective chemotherapeutic regimens. Acute leukemias of ambiguous lineage (ALALs) are those leukemias that either fail to show evidence of myeloid, B-, or T-lymphoid lineage commitment or show evidence of commitment to more than 1 lineage. The different treatment regimens for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) make ALAL a challenge both diagnostically and therapeutically.

Methods: Current classification criteria have reduced the reported incidence of mixed-lineage leukemias by emphasizing fewer markers and categorizing some biphenotypic leukemias with recurrent cytogenetic abnormalities as other entities. Several recent studies have explored the genomic and epigenetic landscape of mixed-phenotype acute leukemia (MPAL) and have suggested a further refinement of the World Health Organization classification to emphasize the genomic heterogeneity of MPAL.

Results: Genomic and expression profile data for MPAL reveal mutations commonly seen in both AML and ALL, with T-/myeloid MPAL showing overlapping features with early T-cell precursor lymphoblastic leukemia.

Conclusions: Our review aimed to discuss the diagnostic challenges, recent genomic studies, and therapeutic strategies in this poorly understood disease.

INTRODUCTION

Acute leukemias of ambiguous lineage (ALALs) include biologically diverse leukemias that fail to show commitment to either the myeloid, B-, or T-lymphoid lineages or show evidence of commitment to more than 1 lineage.[1] Cases in the former group are referred to as acute undifferentiated leukemias (AULs), while those in the latter group are identified as mixed-phenotype acute leukemias (MPALs). These MPAL cases can contain more than 1 lineage-defining marker on a single blast population (biphenotypic leukemia) or 2 or more identifiable single-lineage leukemia populations (bilineal leukemia).

Overall, MPAL is uncommon, accounting for 2% to 3% of acute leukemia cases and 0.35 cases per 1,000,000 person-years; it also has a male predominance (~1:1.6). Among cases of MPAL, the B/myeloid subtype accounts for 59% of cases, whereas the T/myeloid, B/T, and trilineage subtypes account for 35%, 4%, and 2% of cases, respectively. The different treatment regimens for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) make ALAL a challenge both diagnostically and therapeutically.

KEY POINTS

- Mixed-phenotype acute leukemia (MPAL) classification has changed; current criteria emphasize fewer markers and categorize some biphenotypic leukemias as other entities.
- Genomic and expression profile data for MPAL reveals mutations commonly seen in both acute myeloid leukemia and acute lymphoblastic leukemia (ALL).
- Optimal therapy is variable between adult and pediatric populations, and data suggest that regardless of age, most patients with MPAL benefit from ALL therapy.

KEY WORDS

Mixed-phenotype acute leukemia; Acute undifferentiated leukemia; Genetics

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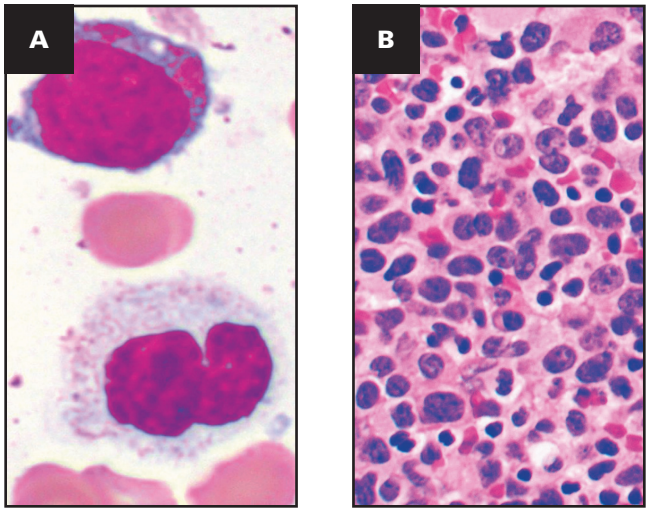

FIGURE 1 The aspirate and biopsy show dysplastic changes in myeloid cells (**A**; H&E, x40) and megakaryocytes (**B**; Wright-Giemsa, x100).

CASE 1

A 68-year-old woman with a remote history of stage IV recurrent high-grade serous ovarian carcinoma, treated with chemotherapy, presented with a new onset of fevers, chills, sore throat, and nausea. Bruising and bleeding gums were also noted on an exam. CBC revealed pancytopenia with circulating blasts. The bone marrow aspirate showed numerous blasts (69% by manual differential) in a background of trilineage hematopoiesis with dysplastic changes. The core biopsy showed a hypercellular marrow, with predominance of blasts and interspersed decreased trilineage hematopoiesis FIGURE 1. Flow cytometry identified a 50% population of medium-size to large cells with the following immunophenotype: CD2−, surface CD3−, cytoplasmic CD3+, CD4−, CD7 (partial +), CD11b−, CD13 (variably +), CD14−, CD15 (partial +), CD16−, CD22+, CD33 (variably +), CD34+, CD36−, CD38 (partial +), CD45+, CD56 (partial +), CD64−, CD117 (variably +), HLA-DR (partial dim +), MPO (small subset +), and TdT (few +). An immunohistochemical stain for CD3 also showed dim expression in a subset of the blasts. Cytogenetic analysis showed 48,XX,der(5;17)(p10;q10),+6,add(11)(q13),+21,+22[16]/96,idem,x2[4]. The ALL, AML, and myelodysplastic syndrome (MDS) fluorescence in situ hybridization (FISH) panel analyses showed evidence of deletion in the long arm of chromosome 5 in 95% of the cells examined, an extra copy of the *RUNX1* (21q22) gene in 84.5% to 86%, *KMT2A* (*MLL*) (11q23.3) gene amplification in 88.5%, and an extra copy of the *BCR* (22q11.2) gene in 93.5%.

CASE 2

A 22-year-old man presented with a 1-month history of worsening dyspnea on exertion and subsequent headaches, oral lesions, and gingival bleeding. Laboratory findings revealed pancytopenia, with 41% blasts in the peripheral blood. The aspirate and biopsy showed a diffuse infiltration by small to intermediate lymphoid cells, with scant and agranular cytoplasm FIGURE 2. Flow cytometry revealed a population of blasts that were positive for CD19, CD34, CD79a, CD22, CD20 (dim, minor), TdT, and MPO but lacked CD33, CD13, CD11c, CD14, CD56, CD117, and T-cell markers. MPO expression on blasts was confirmed with immunohistochemistry (IHC) and cytochemistry. Cytogenetic analysis showed a normal male karyotype, and FISH was negative for *BCR/ABL1* fusion and *KMT2A* rearrangement. Molecular genetics revealed *JAK1* and *CDKN2A* mutations.

DIAGNOSTIC APPROACH

In most patients with ALAL, both aspirate smears and the bone marrow trephine biopsy show a diffuse infiltration by morphologically diverse blasts. These MPAL blasts may resemble myeloblasts or monoblasts and occasionally lymphoblasts; there may be a dual/dimorphic population, or blasts may have an undifferentiated appearance.[2,3] Typically, AUL blasts lack standard myeloid features, such as granules in the cytoplasm or Auer rods.[4] The recognition of ALAL requires extensive multiparametric flow cytometry (FCM) immunophenotyping. International recommendations for performing immunophenotyping of leukemias suggest that markers of all hematopoietic lineages should be included in broad panels, even when morphology or other clinical features strongly suggest a specific type of leukemia.[5] Flow cytometry is the primary method for blast immunophenotyping in clinical practice, and IHC and cytochemistry also contribute in some cases.

Two primary approaches have been proposed to classify MPAL, and both are based on blast immunophenotype. The European Group for the Immunological Characterization of Leukemias (EGIL) strategy uses FCM to characterize blasts, with a broad panel of markers associated with B-cell, T-cell, and myeloid lineages; it assigns a weighted score to each marker depending on how strongly it is associated with a specific lineage TABLE 1.[6] Using this algorithm, biphenotypic leukemia is diagnosed when a score greater than 2 is calculated for more than 1 lineage. The EGIL authors defined positivity as expression on at least 20% of blasts for surface markers and at least 10% for cytoplasmic markers compared with an isotype control. Subsequently, the World Health Organization (WHO) classification streamlined this approach using a simplified set of lineage-specific markers TABLE 2.[7] Assigning T-cell lineage is the most straightforward method, relying exclusively on CD3 expression. Other T-cell markers, such as CD2, CD5, CD7, CD4, and CD8, are not used in T-cell lineage leukemia assignment in MPAL, as they are commonly expressed in other leukemias. B-cell lineage assignment requires multiple markers: CD19 plus an additional 1 or 2 (depending on intensity of CD19 expression) of CD79a, cytoplasmic CD22, or CD10. Myeloid lineage assignment requires identification of MPO expression or evidence of monocytic differentiation with 2 or more of CD11c, CD14, CD64, nonspecific esterase, or lysozyme. The WHO classification specifies no cutoffs for percentage of cells positive to assign lineage. Immunohistochemical stains, including MPO, PAX5, and CD3, although outside the formal definition, may provide helpful supplemental information for lineage specificity. The current criteria are fairly well accepted, but the omission of objective thresholds for antigen positivity has resulted in

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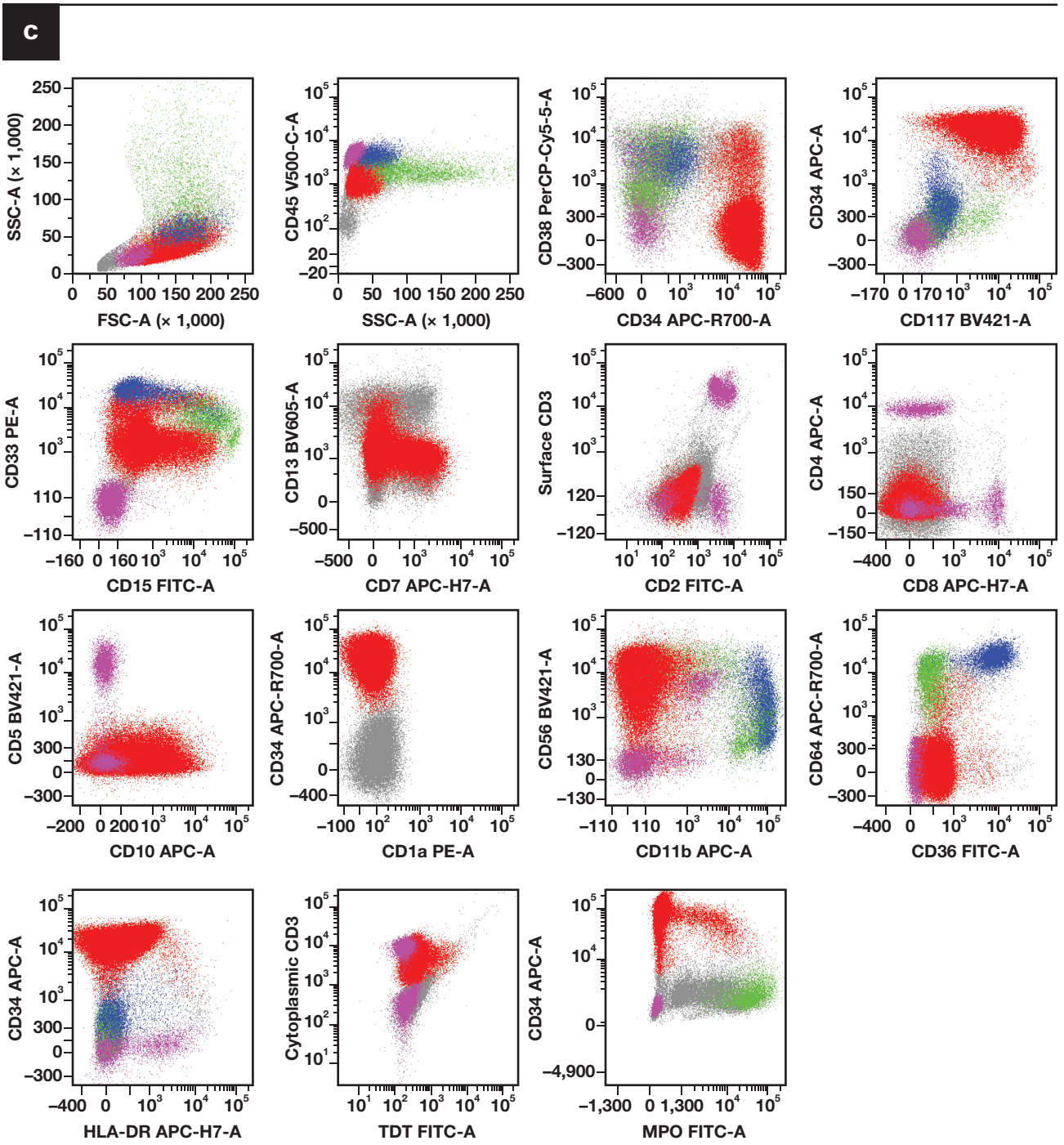

FIGURE 1 (cont) **C**, Flow cytometry plots identified a 50% population of medium-size blasts (in red) that were positive for CD34, CD117, CD33, CD13, cCD3, CD7, CD13, CD15, CD7, and CD56, with partial MPO, but lacked sCD3 and CD19. The population in blue is admixed monocytes, and green represents granulocytes.

continued subjective determinations of lineage assignment; therefore, diagnosing MPAL remains challenging.

GENETICS

The majority (64%-87%) of patients with MPAL have an abnormal karyotype.[8] The most common abnormalities include rearrangements of t(9;22) and t(v;11q23), which are recognized in the WHO classification as separate groups.[7] The t(9;22) rearrangement occurs in 15% to 20% of cases and is more common in adults.[9] The MPAL with KMT2A rearrangements account for approximately 10% of cases of ALAL and occur more frequently in infants. MPAL with *KMT2A* rearrangements accounts for approximately 10% of cases of ALAL and occurs more frequently in infants. In addition to these 2 widely recognized aberrancies, other cytogenetic abnormalities include del(1)(p32), trisomy 4, del(6q), 12p11.2 abnormalities, and

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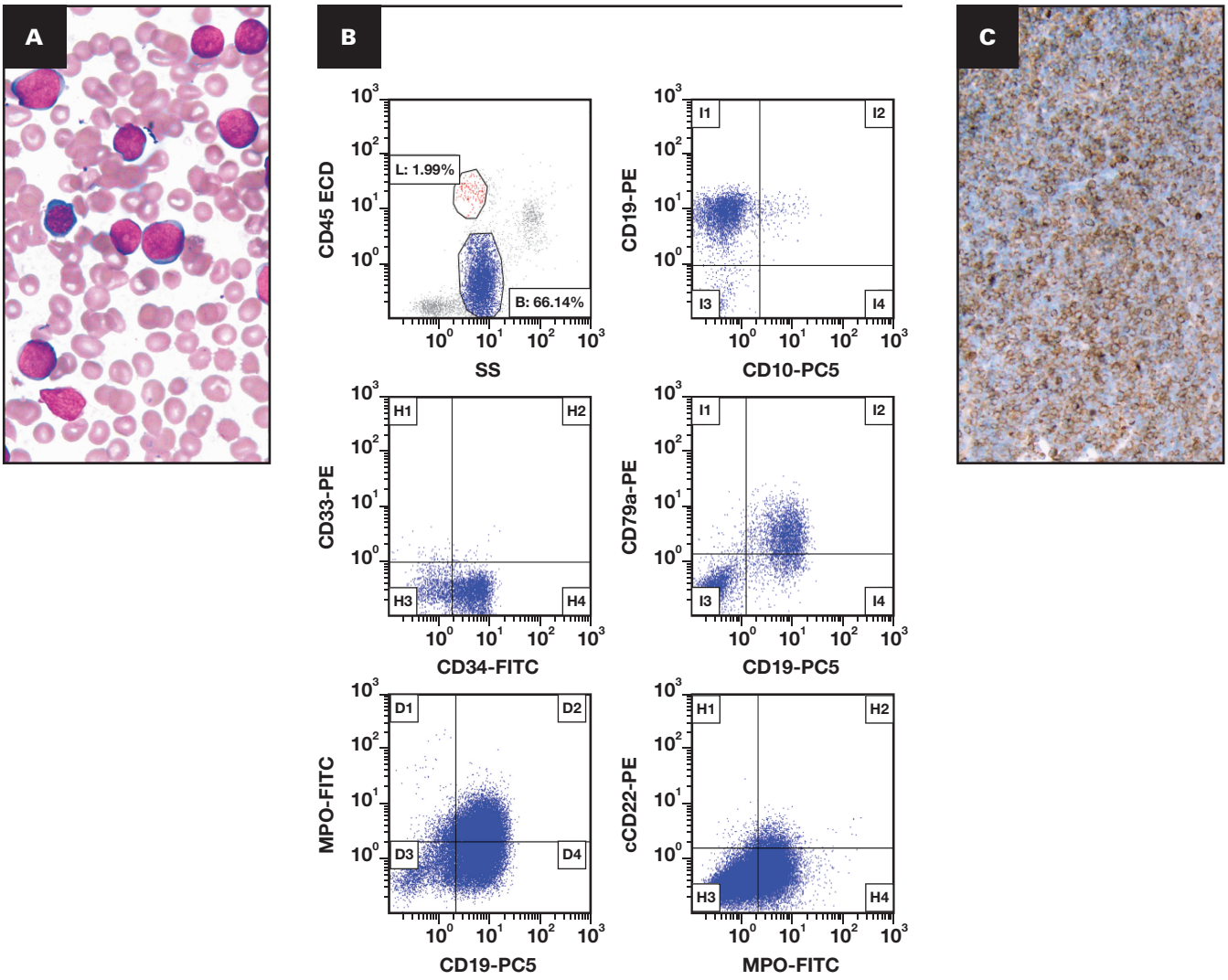

FIGURE 2 **A**, The aspirate smears showed a diffuse infiltration by small to intermediate immature lymphoid cells with scant and agranular cytoplasm. **B**, Flow cytometry revealed a population of blasts that were positive for CD19, CD34, CD79a, CD22, CD20 (dim, minor), TdT, and MPO but lacked CD33, CD13, CD11c, CD14, CD56, CD117, and T-cell markers. **C**, MPO immunohistochemical stain shows positivity in lesional B lymphoblasts.

TABLE 1 EGIL Scoring System for Biphenotypic Acute Leukemia

Points	B Lineage	T Lineage	Myeloid Lineage
2	CD79a, cIgM, cCD22	CD3, TCR-α/β, TCR-γδ	MPO, lysozyme
1	CD19, CD10, CD20	CD2, CD5, CD8, CD10	CD13, CD33, CDw65, CD117
0.5	TdT, CD24	TdT, CD7, CD1a	CD14, CD15, CD64

EGIL, European Group for the Immunological Characterization of Leukemias.

near tetraploidy.[10] Studies have also reported that about one-third of biphenotypic leukemias demonstrate a complex karyotype.[11]

Mutations in MPAL appear to be a mixture of those commonly seen in both AML and ALL TABLE 3. Deletions of the ALL-associated gene *IKZF1* as well as AML-associated epigenetic modifiers *TET2, EZH2,* and *ASXL1* have been reported in B/myeloid leukemias.[12] Whole-exome sequencing identified frequent mutations of epigenetic modifiers, including *DNMT3A,* in 33% of adult patients with

TABLE 2 World Health Organization Requirements for Lineage Assignment in Biphenotypic Acute Leukemia[a]

Myeloid: MPO; or evidence of monocytic differentiation: ≥2 of NSE, CD11c, CD14, and CD64
B lineage: Strong CD19 and ≥1 strongly expressed marker: CD79a, cCD22, or CD10; or weak CD19 and ≥2 strongly expressed marker: CD79a, cCD22, or CD10
T lineage: cCD3 (at level of expression of background T cells) or surface CD3

[a]Adapted from Swerdlow et al.[7]

TABLE 3 Comparative Mutational Analysis of Mixed-Phenotype Acute Leukemia[a]

Mutation	MPAL B-Myeloid		MPAL T-Myeloid		B/T MPAL	
	Takahashi et al[8] (n = 13)	Alexander et al[15] (n = 12)	Hirabayashi et al[16] (n = 35)	Alexander et al[15] (n = 11)	Hirabayashi et al[16] (n = 48)	Hrusak et al[20] (n = 9)
ASXL1	3 (23)	1 (8)	—	1 (9)	—	1 (11)
SRSF2	3 (23)	—	—	—	—	0 (0)
TET2	2 (15.4)	2 (16)	—	2 (18)	—	0 (0)
FLT3	3 (23)	0 (0)	6 (17)	2 (18)	21 (44)	0 (0)
CEBPA	0 (0)	1 (8)	0 (0)	1 (9)	5 (10.4)	0 (0)
RUNX1	6 (46)	1 (8)	8 (23)	1 (9)	3 (6)	1 (11)
PTNP11	1 (7.7)	0 (0)	6 (17)	0 (0)	4 (8.3)	2 (22)
ZNF384	0 (0)	0 (0)	15 (43)	0 (0)	0 (0)	—
NOTCH1	0 (0)	1 (8)	0 (0)	0 (0)	8 (17)	1 (11)
WT1	1 (7.7)	1 (8)	2 (6)	3 (27)	20 (41)	1 (11)
PHF6	0 (0)	1 (8)	1 (3)	2 (18) + 3 (27)	0 (0)	5 (55)
DNMT3a	1 (7.7)	0 (0)	—	4 (36)	—	1 (11)
ETV6	0 (0)	0 (0)	8 (23)	2 (18)	12 (25)	2 (22)
NRAS	3 (23)	1 (8)	11 (31)	2 (18)	4 (8.3)	0 (0)
KRAS	0 (0)	2 (16)	3 (8.5)	2 (16)	3 (6)	0 (0)
TP53	1 (7.7)	0 (0)	2 (6)	2 (18)	0 (0)	2 (22)

[a]Data given as No. (%) of patients.

MPAL.[13] Takahashi and colleagues[8] described a landscape of 38 recurrently mutated genes, including *NOTCH1, RUNX1, DNMT3A*, and *IDH2*, in adult patients with MPAL. Xiao and colleagues[14] reported similarly common gene mutations, including *PHF6, DNMT3A, TET2, WT1, RUNX1, KRAS, FLT3, ETV6, ASXL1*, and *NRAS*, in a study of 29 cases.

Alexander and colleagues[15] performed an extensive study of the genetics of childhood MPAL on 115 cases of ALAL and identified 158 recurrently mutated genes, including the common AML-associated genes *FLT3, RUNX1, CUX1*, and *CEBPA* as well as the ALL-associated genes *CDKN2, ETV6*, and *VPREB1*. Interestingly, most of the MPAL cases harbored mutually exclusive mutations of *WT1, ETV6, RUNX1*, or *CEBPA*. The authors also found that children with B/myeloid MPAL, not otherwise specified have a high frequency of rearrangements of *ZNF384* on chromosome 12.[15] B/myeloid MPAL with *ZNF384* rearrangement has a similar mutational, transcriptional, and epigenetic profile as B-ALL with *ZNF384* rearrangement, a recently well-characterized genomic subtype.[16,17] This striking biological similarity suggests that B-ALL and B/myeloid MPAL with *ZNF384* rearrangements could be classified together.

T/myeloid MPAL is reported to have a higher mutational burden than B/myeloid MPAL and commonly shows mutations in epigenetic regulators (*EZH2, PHF6*, and *DNMT3A*) and JAK-STAT signaling proteins.[15] T/myeloid MPAL shares many similarities in its molecular profile with ETP ALL. Both early T-cell precursor (ETP)-ALL and T/myeloid MPAL are frequently associated with biallelic WT1 alterations and show similar alterations in signaling pathways, including the RAS and JAK-STAT pathways, whereas PI3K signaling is more common in T-ALL.[15] Arguing, perhaps, for a difference between T/myeloid MPAL and ETP-ALL, T/myeloid MPAL frequently shows mutations of *CUX1* and *CEBPA*, whereas ETP- and T-ALL do not.[15] Although T-ALL–associated mutations in *NOTCH1* are present in T/myeloid MPAL, they are less common in T/myeloid MPAL and ETP-ALL.[18] B/T MPAL is rare, and few studies of its mutational landscape exist. A recent case series has revealed that the genomic landscape of B/T MPAL strongly resembles that of T-ALL subgroups, with prominence of *PHF6* mutations, and are associated with early developmental arrest, while genetic alterations that are common in B-ALL are rarely seen.[19]

DIAGNOSTIC CHALLENGES

The WHO definition of MPAL does not differentiate between biphenotypic and bilineal acute leukemias. The total sum of MPAL blasts must be greater than or equal to 20%, with the individual populations of bilineal MPAL classified according to standard AML and ALL criteria. In contrast, biphenotypic MPAL requires the use of lineage-assignment criteria. Some retrospective clinical reviews have suggested that patients with bilineal MPAL have a worse prognosis, although classification challenges in biphenotypic leukemia complicate this issue.[20] In practice, the accurate identification of minor blast populations of divergent lineage presents a challenge in diagnosing bilineal acute leukemia. Identification of immunophenotypic aberrancies can be essential to differentiating a small bilineal blast population from residual normal myeloid blasts or hematogones (physiologic B-cell precursors). In addition, it is important to consider the possibility of a monocytic blast population coexisting with ALL, which most often occurs in the context of *KMT2A* translocations, because monocytic blasts often resemble normal monocytes in FCM analysis.[21]

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What Is the Role of MPO in Defining Myeloid or Mixed-Lineage Assignment?

The role of MPO in defining myeloid lineage or mixed lineage remains a topic of active discussion. The WHO classification does not set a threshold for MPO positivity, and cases with an otherwise B-ALL immunophenotype with MPO as the sole aberrancy present a unique challenge, particularly as some reagents show nonspecific binding to MPO, and MPO mRNA can frequently be detected in B-ALL.[22] A few studies have investigated the prognostic importance of B/myeloid MPAL with low-level or isolated MPO expression. Oberley et al[23] examined a cohort of 293 patients with B-ALL, excluding leukemias with *BCR-ABL1* fusion or *KMT2A* rearrangement, and identified 29 cases that were positive for MPO and negative for other myeloid markers. Compared with the rest of the B-ALL cohort, MPO+ B-ALL cases were associated with shorter event-free survival and a higher rate of relapse. Raikar et al[24] compared B/myeloid MPAL with isolated MPO with other pediatric MPAL cases. Their findings demonstrated significant differences between B/myeloid MPAL with isolated MPO and other MPAL cases in terms of treatment approach and survival, with significantly better outcome for B/myeloid isolated MPO. This finding raises the question of whether this patient population should be considered within the spectrum of B-ALL rather than MPAL.[24]

The presence or absence of MPO is also a discriminating factor between the diagnosis of ETP-ALL and MPAL, T/myeloid subtype. ETP-ALL is defined by an immature hematopoietic phenotype with nonspecific myeloid features, such as CD13 or CD33.[25] The most prominent distinction between T/myeloid MPAL and ETP-ALL is the presence of MPO (or, rarely, monocytic markers) in T/myeloid MPAL. T/myeloid MPAL has a mutational and gene expression profile that overlaps with ETP-ALL, with frequent alterations in transcription factors *WT1, ETV6,* or *RUNX1.* A recent study of 43 ETP-ALL and 41 T/M-MPAL cases showed similar biological characteristics, immunophenotypes, genomic alterations, and outcomes.[26] The separate classifications of T/myeloid MPAL and ETP-ALL may be a distinction without a biological or therapeutic difference.

What Is the Role of Cytogenetic Analysis in Diagnosing ALALs?

The primary challenge in diagnosing MPAL is ruling out cytogenetically defined neoplasms that demonstrate an MPAL-like immunophenotype. Making these distinctions is often critical because of the different therapies involved. Currently, the most common clinical practice is to initially treat patients with MPAL by using ALL-directed chemotherapy.[27] The diagnostic error most likely to trigger inappropriate treatment is making a diagnosis of MPAL based on FCM when subsequent cytogenetic analysis changes the diagnosis to AML with t(8;21). AML with t(8;21)(q22;q22.1) is notorious for expressing B-lineage markers, including CD19, PAX5, and CD79a, and could potentially seem consistent with B/myeloid MPAL. Avoiding this pitfall requires careful correlation with the blood and bone marrow morphology. Most MPALs have numerous primitive blasts or partial monocytic differentiation, in contrast to AML with t(8;21), which usually has prominent granulocytic maturation in the bone marrow.

Overlapping features between MPAL and genetically defined AML with myelodysplasia-related changes (AML-MRC) creates a diagnostic challenge; however, the WHO classification specifies that AML with complex karyotype should be classified as AML-MRC. Recent case series of MPAL identified complex karyotype as the most common genetic abnormality.[28,29] A study of pediatric MPAL included several cases with complex karyotype, and most responded well to ALL-directed chemotherapy.[30] The use of complex karyotype and other myelodysplasia-related cytogenetic abnormalities to distinguish between MPAL and AML-MRC is problematic because these abnormalities also occur in ALL and therefore cannot be taken as definitive evidence of myeloid lineage. A study of 617 adult patients with Ph-negative B-ALL showed the presence of a complex karyotype in 5%, monosomal karyotype in 16%, and monosomy 7 in 10% of cases.[30]

How Should I Approach Cases of AML or ALL With a Small Aberrant Clone?

Other than requiring a total of 20% or more blasts among both clones, the WHO classification does not provide guidance on how to address very small aberrant clones in a case with otherwise straightforward AML or ALL. With sensitive FCM immunophenotypic methods, such second clones may be of a mixed phenotype, with overlap with the predominant leukemia, or may be a completely different immunophenotype that suggests bilineal disease. Such small populations should not be ignored and may actually represent the primary clone upon relapse, but it may not be clinically useful to label a case as MPAL based on a tiny clone. In such cases, the authors diagnose the case as AML or ALL based on the major leukemia population but add a modifier such as "with a small MPAL (or bilineal) leukemic clone detected," with more details provided in the body of the report. More studies are needed to determine the best approach to such cases.

How Many Myeloid Markers Are Allowed in the Diagnosis of Acute Undifferentiated Leukemia?

Because of its rarity, little is known about AUL, including the optimal number and types of myeloid markers allowed for this diagnosis. In a recent multi-institutional study of AUL cases, a significant number of cases were reclassified as AML-MRC based on cytogenetic findings, and only 24 cases were qualified as AUL.[31] Of these, only 6 AUL cases showed no myeloid marker expression (CD117, CD13, and CD33), while 15 showed partial or full expression of 1 myeloid marker and 3 cases showed 1 myeloid marker plus weak or partial expression of another myeloid marker.[31] Restricting the definition of AUL to cases with 1 or fewer myeloid marker expressions showed no difference in overall survival or relapse-free survival when comparing this group with AML with minimal differentiation. Compared with AML with minimal differentiation, AUL cases were characterized by significantly more frequent mutations in *PHF6,* and this difference was even more significant when reassigning AUL cases with partial expression of a second myeloid marker to the AML with minimal differentiation group (5/13 vs 0/21; $P = .0046$).[31]

CASES DIAGNOSIS AND DISCUSSION

Case 1 illustrates an example of therapy-related acute leukemia with complex karyotype. AML with complex karyotype, defined by 3 or

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more unrelated cytogenetic abnormalities, is present in 10% to 12% of all patients with AML and constitutes the second-largest cytogenetic subset of patients with AML (after those with normal karyotype).[32] Complex karyotype falls under MDS-related cytogenetics and is listed as an exclusion criterion for MPAL in the WHO classification. Both therapy-related AML and AML-MRC trump diagnosis of MPAL.[33] A recent study showed lymphoid antigen expression in cases of AML with complex karyotype and suggested that caution be exercised when making this diagnosis in clinical practice before completion of cytogenetic analysis.[32] The blasts in this case showed cytoplasmic CD3 expression, and studies suggested that cytoplasmic CD3 can rarely be detected in leukemias that are otherwise consistent with AML.[34] According to the WHO classification system, T-lineage assignment requires a fraction of blasts to show strong cCD3 expression, with the brightest expression comparable to background T cells.[34]

Case 2 illustrates a case of B-ALL with prominent expression of B-cell markers and partial expression of lineage-specific MPO with *BCR-ABL1*–like B-ALL genetics. The WHO classification has set no threshold for MPO positivity; however, care should be taken to discriminate small MPO populations from background myeloid blasts. *BCR-ABL1*–like B-ALL makes up 10% to 25% of B-ALL cases and is a genetically diverse group. It was initially described as a group of B-ALL with a gene expression profile similar to that of *BCR-ABL1*–positive B-ALL but without the *BCR-ABL1* rearrangement.[35] *BCR-ABL1*–like B-ALL shows activation of kinase or cytokine receptor signaling pathways using several different genetic alterations, including *CRLF2* rearrangements, ABL-class fusions, and alterations leading to activation of the JAK-STAT pathway. Because of the diversity of genetic changes that underly *BCR-ABL1*–like B-ALL, screening for this subtype is challenging. The interpretation of this case is complicated by the presence of MPO on FCM, cytochemistry, and IHC and suggests that this case could be inappropriately considered MPAL, B/myeloid subtype. The correct diagnosis in this case must reflect the underlying genetics and is therefore B-ALL with *BCR-ABL1*–like B-ALL genetics.

CONCLUSIONS

Patients with ALAL have inferior outcomes and a high risk of induction failure compared with patients who have ALL or AML, and they are often treated per high-risk leukemia protocols.[36] Poor prognostic factors include older age at diagnosis, higher WBC count at presentation, T-lymphoid/myeloid phenotype, adverse cytogenetics (such as a *KMT2A/AFF1* rearrangement), extramedullary disease at diagnosis, and MRD positivity.[37] There have been various chemotherapy approaches for the treatment of MPAL, including ALL protocols, AML protocols, and hybrid ALL-AML protocols (such as fludarabine, cytarabine, and granulocyte colony-stimulating factor plus idarubicin with vincristine and prednisone or hyper–cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens).[2,27] Optimal therapy remains a subject of debate, and differences between adult and pediatric treatment approaches are often striking. Advances in understanding the genetic landscape of MPAL may allow a more biologically driven classification of this heterogeneous group of leukemias in the future that will lead to optimized therapies for individual patients. Care must be taken to not overdiagnose ALAL when cases can be better classified in existing AML or ALL disease categories, for which better-defined therapies are known.

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