

Original Article

Diagnosis of biphenotypic acute leukemia: a paradigmatic approach

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Abstract: Biphenotypic acute leukemia (BAL), or acute leukemia with a single population of blasts coexpressing markers of two different lineages, is a rare clinical entity. To define BAL, a scoring system was proposed by the European Group of Immunological Markers for Leukemias (EGIL) in 1995. However, increasing evidence suggests that this system has limitations, as acknowledged by the 2008 World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues. Although substantially improved in relation to the EGIL, the new WHO Classification is still not optimal for guiding the clinical management of patients with BAL. We propose a new paradigmatic approach to defining BAL based on recent clinical studies of BAL and advances in immunologic marker definition and cytogenetics, and applied our new approach to 8 cases of “BAL” among a cohort of 742 new acute leukemias in our Cancer Center. By our new criteria, 6 cases were reclassified as acute lymphoblastic leukemia (ALL), while only 2 were still classified as BAL. Our approach is also supported by analyses of the BAL cases previously reported by other institutions.

Key words: Biphenotypic acute leukemia, AML, ALL, EGIL, classification

Introduction

Often confused with acute bilineal leukemia (BLL) that is composed of a mixed population of leukemia cells of two different lineages [1], biphenotypic acute leukemia (BAL) refers to acute leukemia with a single population of blasts coexpressing markers of two different lineages [2]. Smith et al. initially used the term “lineage infidelity” to explain several examples of leukemic blasts with a cytoplasmic marker of one lineage and a surface marker of a different lineage [3]. Consensus criteria for the diagnosis of BAL were established in 1995, when the European Group for the Immunological Characterization of Leukemias (EGIL) proposed a scoring system for the immunological classification of acute leukemias [4]. This scoring system assigned different scores to several immunological markers based on their lineage specificity. Cytoplasmic markers, including CD3, CD22, CD79a, IgM, myeloperoxidase (MPO) and T-cell receptor (TCR), were given a score of 2, which was the highest score. Less lineage-specific markers (CD2, CD5, CD8,

CD10, CD13, CD19, CD20, CD33, CD65 and CD117) were assigned a score of 1. The least specific markers (CD1a, CD7, CD14, CD15, CD24, CD64 and TdT) were assigned a score of 0.5. This scoring system was adopted in the 2001 World Health Organization (WHO) Classification of Tumors of the Hematopoietic and Lymphoid Tissues, with minor modifications [2], and guided us for over a decade. Although the EGIL scoring system (hereafter referred to as EGIL) defined the lineage determination scores as >2, a modified EGIL (scores of ≥ 2) has been frequently used to define BAL [5, 6], resulting in confusion and overdiagnosis of BAL. With increasing numbers of such BAL cases being reported, and more information accumulating on the nature of immunological markers and on cytogenetic abnormalities seen in “BAL”, the 2008 WHO Classification [7] acknowledged the limitations of the EGIL and proposed to define BAL as “a single population of blasts that would meet criteria for B-ALL or T-ALL but that also express MPO” or have “unequivocal evidence of monoblastic differentiation” based on specific

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Table 1. Requirements for defining BAL proposed by the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (modified from reference 7)

Myeloid lineage	MPO (by flow cytometry, immunohistochemistry or cytochemistry) <i>or</i> Monocytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, lysozyme)
T-lymphoid lineage	Cytoplasmic CD3 (flow cytometry with antibodies to CD3 epsilon chain; immunohistochemistry using polyclonal anti-CD3 antibody may detect CD3 zeta chain, which is not T-cell specific) <i>or</i> Surface CD3 (rare in mixed phenotype acute leukemias)
B-lymphoid lineage (multiple antigens required)	Strong CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10 <i>or</i> Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10

requirements (**Table 1**). However, the new WHO Classification did not address the clinical significance of the proposed new definition of BAL, nor the implications for treatment.

Based on recent advances in immunology, genetics and clinical studies, here we discuss the limitations of the EGIL scoring system and propose a paradigmatic approach for defining BAL. We analyzed cases of BAL diagnosed at our Cancer Center from 2000 to 2007 and reclassified them according to our new approach, and discuss the potential implications for clinical decision-making.

Materials and methods

With Institutional Review Board approval, we retrospectively reviewed consecutive acute leukemias newly diagnosed at our Cancer Center from 2000 to 2007. Cases that were previously diagnosed as “BAL” were identified. The morphology, immunophenotype, cytogenetic findings, treatment and clinical outcome of these cases were analyzed.

Results

Among 742 consecutive acute leukemias, 8 cases were previously diagnosed as “BAL”. Four cases (cases 4, 6, 7, 8) fulfilled the EGIL criteria for BAL, but the other 4 cases only met the modified EGIL criteria (score ≥ 2) [5] and were also included in this study. These cases, representing an incidence of 1.1%, are summarized in **Table 2**. The BAL patients include 7 males and 1 female

(M:F = 7:1), ages 11, 17, 19, 20, 30, 40, 48 and 81 years (median 25 years). Leukemia cells in most of the cases had scant basophilic cytoplasm, high nuclear/cytoplasmic ratio, fine or slightly clumped chromatin and inconspicuous nucleoli, and resembled lymphoblasts. These blasts often show substantial variation in size (**Figure 1**). Two cases expressed both myeloid and B-cell (B/M) markers and harbored t(9;22)(q34;q11.2). One of these two cases had an additional t(3;15)(p21;q22). Two cases expressed both myeloid and T-cell (T/M) markers and had t(6;14)(q25;q32) [8]. An additional T/M leukemia had t(6;11)(q27;q23). One case expressed both B- and T-cell markers and had a complex karyotype including -5, +6, -10 and del(11q23); molecular studies revealed a clonal TCR rearrangement and polyclonal VDJ recombination. The last two cases were additional T/M cases with +19, i(22)(q10) and with del(20)(q11.2).

Treatment and clinical outcome of these “BAL” cases are also summarized in **Table 2**. Five patients were treated with acute lymphoblastic leukemia (ALL) regimens and three with acute myeloid leukemia (AML) regimens. Six patients underwent allogeneic hematopoietic stem cell transplantation (alloSCT). In our small series, several patients had favorable outcomes with ALL regimens, which is consistent with the findings of two recent large series [5, 6].

Discussion

BAL is a rare clinical and pathological entity that is listed as a “rare disease” by the Office of Rare

Table 2. Summary of 8 cases of biphenotypic acute leukemia

Case	Age/Sex	Previous Diagnosis	Immunophenotype	Karyotype	Initial therapy & response	Additional treatment	Clinical outcome survival
1	81/F	BAL(B/M)	CD10/CD13/CD19/CD33/CD34/CD38/TdT	46,XY,t(9;22)(q34;q11.2) [8]/46,XX[12]	Imatinib; CR	Relapsed (+9mos), dasatinib	Died of progressive disease (13+mos)
2	30/M	BAL(B/M)	dimCD10/CD13/CD19/ dimCD33/CD34/HLA-DR/TdT	46,XY,t(9;22)(q34;q11.2), t(3;15)(p21;q22)[3]/46,XY[9]	ALL induction + imatinib; CR	MUD alloSCT	Alive in CR (16+mos); lost for follow up
3	17/M	BAL(T/M)	CD2/cCD3/CD7/CD13/ CD38/CD117/HLA-DR	47,XY,t(6;14)(q25;q32) [20]	ALL regimen; CR	MUD alloSCT	Alive in CR (68+mos)
4	11/M	BAL(T/M)	CD2/cCD3/CD7/CD13/ dimCD33/CD34/CD58/ CD117	46,XY,t(6;14)(q25;q32), +9,der(16)t(16;18)(p13.3; q21)del(16)(q22), der(18) t(16;18)(p13.3;q21),-20[2]/ 46,XY,t(6;14)(q25;q32)[18]	AML regimen; persistent leukemia at 21d	ALL regimen; CR MRD alloSCT	Alive in CR (13+mos)
5	20/M	BAL(T/M)	cCD3/CD11c/CD13/CD33/ subsetCD34/CD38/HLA-DR	46,XY,t(6;11)(q27;q23) [20]	AML regimen; CR	Relapsed; x3 sal- vage regimens	Died of refractory disease (13.4+mos)
6	48/M	BAL(B/T)	CD2/cCD3/CD5/CD19/ CD20/CD38/cCD79a/ CD117/HLA-DR	47,XY,-5,+6,-10, del(11) (q23),+2mar[6]	ALL regimen; CR	MUD alloSCT	Alive in CR (23+mos)
7	19/M	BAL(T/M)	CD3/CD13/CD56/CD68/ CD99/MPO/lysozyme/TdT	47,XY,+19[6]/46,XY,+19,i(22) (q10)[3]/46,XY[11]	ALL regimen; CR	AML regimen, Relapsed (12+mos); Relapsed (3+mos), MUD alloSCT	Died of recurrent disease (35+mos)
8	40/M	BAL(T/M)	subsetCD2/cCD3/CD7/ dimCD13/CD15/dimCD34/ CD38/CD117/subsetHLA-DR/ subsetMPO/subsetTdT	46,XY,de(20)(q11.2)[20]	AML regimen; refractory leukemia	MRD alloSCT	Died of refractory disease (16.6+mos)

CR: complete remission; MRD: matched related donor; MUD: matched unrelated donor.

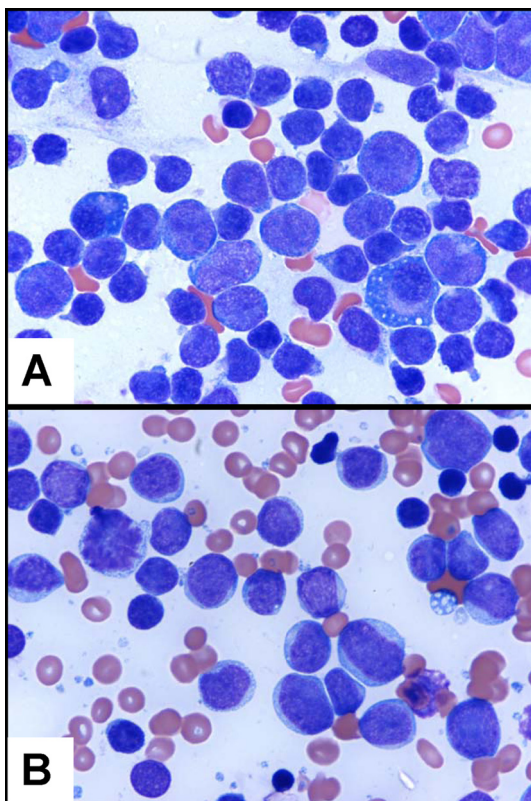


Figure 1. Morphology of some BAL blasts. The T/M leukemia cells (A) and B/T leukemia cells (B) show more variation in size and morphology than typical lymphoblasts (original magnification x1000).

Diseases (ORD) of the National Institutes of Health (NIH) [9]. An accurate definition of BAL has significance in guiding treatment decisions. The 2008 WHO Classification uses more restrictive criteria than the EGIL to define BAL [7]. However, ambiguity still exists and a guideline for clinicians is still lacking. We propose a paradigmatic approach to defining BAL based on recent data on the nature of the immunological markers that are the basis of defining BAL, the cytogenetic data, and clinical studies.

Nature of immunological markers

B-lymphoid markers

In the EGIL, the highest scoring markers for B-lymphoid lineage are cytoplasmic CD79a, cytoplasmic CD22 and cytoplasmic IgM. CD79a, also known as immunoglobulin-associated α (Ig α), is encoded by the *mb-1* gene [10]. With a similar structure to the CD3 γ chain, CD79a is

non-covalently associated with surface immunoglobulin, thus forming the B-cell antigen receptor complex, which initiates the B-cell antigen receptor signal transduction pathway [11]. Although CD79a was previously considered to be specific for B-cell lineage [12], there have been increasing numbers of reports of its aberrant expression in both acute myeloid and acute T-cell leukemias [13-15].

CD19 is the most commonly used marker to define B cells. The new WHO Classification uses CD19, together with at least one antigen among CD10, cytoplasmic CD22, and CD79a, to define B-cell lineage. However, CD19 expression is seen in approximately one third of AML with t(8;21)(q22;q22), and serves to predict the presence of this cytogenetic abnormality in AML [16]. Those leukemias also express CD79a [17]. Thus, if CD19 and CD79a are employed as B-cell lineage-specific markers, some AML cases will be diagnosed as BAL [17].

The human B-lymphocyte-restricted antigen CD22, also known as sialic acid binding immunoglobulin-like lectin 2 (SIGLEC-2) [18], is expressed early in pro-B cells as a cytoplasmic protein and later in pre-B cells as a surface protein. Therefore, the presence of CD22 is a specific marker for precursor B-cells. Compared to CD79a, CD22 is considered more reliable in acute leukemia lineage determination [19, 20]. Although CD22 has also been detected in basophils [21], due to the distinct morphology of acute basophilic leukemia, it is less a problem to differentiate B lymphoblasts from basophilic blasts. Furthermore, certain clones of CD22 monoclonal antibody (B3 and 4KB128) can detect B lymphoblasts, but not basophilic blasts [21].

Among the three high-scoring markers, cytoplasmic IgM may be the most specific, though less sensitive, for B cells. To our knowledge, IgM has never been detected in myeloid or T-cells.

In contrast, the other B-cell markers are less specific. Although known as common acute lymphoblastic leukemia antigen (CALLA) [22], CD10 is also expressed on the surface of granulocytes [23] as well as on several malignant lymphomas [24]. CD20 expression is variable in B-ALL. CD24 is expressed in B cells as well as in myeloid cells [25]. Terminal deoxynucleotidyl transferase (TdT) is an early lymphoid marker that is shared by precursor T and precursor B cells.

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T-lymphoid markers

CD3 and T-cell receptor (TCR) are both parts of the TCR complex [26]. CD3 itself is a protein complex composed of four distinct chains (CD3 γ , CD3 δ and two CD3 ϵ), that associate with TCR and the ζ -chain to generate an activation signal in T cells [27]. Many studies have shown that CD3 and TCR are the most specific markers for T cells [28, 29]. To date, aberrant expression of CD3 has been extremely rare in other lineages.

Conversely, expression of CD1a, CD2, CD5, CD7 and CD8 has been identified in various other lineages. CD1a is expressed in a subset of precursor T cells as well as in Langerhans cells [30]. CD2, CD5 and CD7 are frequently expressed in myeloid leukemias [31-33]. CD8 is often co-expressed with CD4 in precursor T cells. CD10 and TdT expression is shared with precursor B cells (see above) and these two markers can also be expressed in AML.

Myeloid/monocytic markers

Thirty-three years after the French-American-British (FAB) classification was published [34], myeloperoxidase (MPO) remains the most specific marker of myeloid differentiation [7, 35]. In AML, MPO is usually associated with expression of other myeloid markers, such as CD13, CD33 and CD117. Even in AML-M0, there is evidence of MPO expression in the blasts by either flow cytometry or electron microscopy [35, 36]. However, aberrant MPO expression has been detected in ALL and even lymphomas by flow cytometry, immunohistochemistry and electron microscopy [37-41]. MPO expression is most commonly detected in B-ALL with t(9;22) (q34;q11) [40]. Fortunately, MPO activity is not detectable by cytochemical stain in cases of ALL [39, 40], suggesting that cytochemistry is still the most discriminating assay for differentiating AML from ALL.

In contrast, co-expression of CD13 and CD33 is particularly associated with B-ALL with cytogenetic abnormalities [42-44]. CD14, CD15 and CD64 are very rarely expressed in the absence of CD13 and CD33. CD65 is less well studied. CD117 expression has been identified in T-cells, B-cells and mast cells [44-47].

In summary, the reliable lineage-specific immunologic markers include: 1) IgM and CD22 for B

cells; 2) CD3 and TCR for T cells; and 3) MPO for myeloid/monocytic cells.

Limitations of EGIL

Since the publication of the EGIL in 1995 [4], approximately 250 reports of BAL have been published in the English literature and EGIL criteria have been used for the diagnosis of BAL in up to 20 papers. Based on those studies, we have identified the following limitations of the EGIL:

- (1) *The EGIL did not define lineage-specific markers:* Although the EGIL gave the highest score to some lineage-specific markers (such as CD3, CD22 and MPO), these markers score only slightly higher than the lineage-associated markers (such as CD7, CD13, CD19, CD20, and CD33), thus leading to overdiagnosis of BAL.
- (2) *The high score given to CD79a needs to be changed:* The EGIL recognized the specificity of CD79a for B cells, but ignored its frequent aberrant expression in myeloid and T cells, leading to more frequent diagnosis of B/myeloid and B/T BAL.
- (3) *The EGIL ignored cytogenetic data:* The EGIL is based on immunological markers, and omitted cytogenetic data. Because of this, even well-defined AML may be misdiagnosed as BAL.
- (4) *The EGIL does not optimally guide treatment decisions:* Overdiagnosis of BAL creates uncertainty for clinicians. Due to the lack of standard regimens for BAL, hematologists/oncologists may choose to treat their patients with regimens for either AML [48] or ALL [5], or both [17]. Better lineage definition will provide clinicians better guidelines for choosing therapeutic regimens for patients, since the treatment of AML is quite different from that of ALL.

Proposed redefinition of BAL

The above limitations of the EGIL result in overdiagnosis of BAL. Therefore, it is necessary to better define acute leukemias with expression of multi-lineage markers. We propose that cytogenetic abnormalities should be considered the most important factors in classifying acute

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leukemias because of their importance for choosing therapy, and that immunological markers be used for lineage determination only when the blasts do not have well defined cytogenetic abnormalities (**Figure 2, Table 3**). For lineage determination of an acute leukemia, we propose to divide the immunological markers into lineage-specific and lineage-associated markers. Lineage-specific markers will determine the lineage of an acute leukemia, whereas lineage-associated markers will help in lineage determination when lineage-specific markers are not present. A paradigmatic approach can be used in differentiating B-ALL, T-ALL, AML and true BAL (**Figure 2**). The new paradigm has the following rules:

(1) *Recurrent cytogenetic abnormalities rule:* Unless new research data prove otherwise, acute leukemia with well-defined recurrent cytogenetic abnormalities associated with AML or ALL should not be diagnosed as BAL,

even if immunological markers of other lineages are present. For example, even with CD79a expression, acute leukemia with t(8;21)(q22;q22) should still be classified as AML with t(8;21)(q22;q22) [7]. Therefore, the immunological markers only apply when the well-defined recurrent cytogenetic abnormalities are not present.

(2) *Lineage-specific markers rule:* BAL will be diagnosed only when two or more lineage-specific markers are coexpressed on the same population of blasts. CD79a is a provisional B-cell marker only if myeloid and T-cell lineage-specific markers are absent (**Table 3**).

(3) *Myeloid lineage assignment requires MPO/NSE positivity in $\geq 3\%$ of the blasts:* In a case otherwise defined as ALL, MPO expression must be present in $\geq 3\%$ of the blasts by cytochemical staining to warrant a diagnosis of

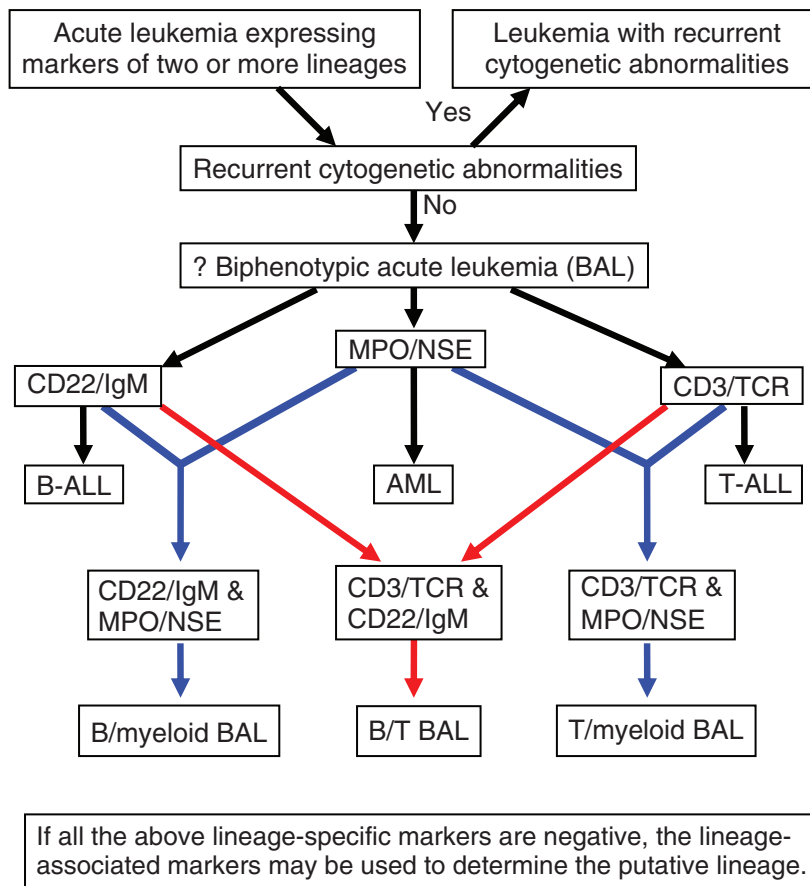


Figure 2. Paradigmatic approach in diagnosing BAL. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MPO, myeloperoxidase; NSE, nonspecific esterase; TCR, T-cell receptor.

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Table 3. Proposed classification of the immunological markers

Markers	B-lymphoid	T-lymphoid	Myeloid
Lineage-specific markers ¹	IgM (cyt) CD22 (m/cyt)	CD3 (m/cyt) anti-TCR	MPO/NSE ($\geq 3\%$)
Lineage-associated markers	TdT CytCD79a ² CD19 CD20 CD10	TdT CD1a CD2 CD5 CD7 CD4/CD8 CD10	CD117 CD13 CD14 CD15 CD16 CD33 CD64

¹Lineage specific markers rule. MPO/NSE should be positive in $\geq 3\%$ blasts by cytochemical stains.

²CD79a is a provisional B-cell marker only if myeloid and T-cell lineage-specific markers are absent.

BAL. If MPO is detected in $< 3\%$ of the blasts, the leukemia is not considered as myeloid lineage unless no other lineage-specific markers are identified (as in AML-M0). Flow cytometry is not reliable in estimating the percentage of MPO+ cells, which is often overestimated due to artifacts during specimen preparation. Furthermore, we also found MPO positivity in some lymphoblasts by flow cytometry, but not by cytochemical stain or immunohistochemistry. Whenever MPO is found to be positive in cells that are otherwise lymphoblasts by flow cytometry, the positivity should be confirmed by either cytochemical stain and/or immunohistochemistry. BAL with monocytic lineage differentiation is extremely rare, and should only be defined by $\geq 3\%$ NSE+ blasts using α -naphthyl butyrate as the substrate.

- (4) *Scoring in the absence of lineage-specific markers:* The putative lineage of an acute leukemia may be determined by the lineage-associated markers only if no lineage-specific markers are detectable by current technology. Expression of more than two (> 2) lineage-associated markers may serve to assign the putative lineage. Additionally, CD79a is a provisional B-cell marker that can be used to assign B-cell lineage if MPO and T-lineage-specific markers are absent.

Reclassification of our cases using the new paradigmatic approach

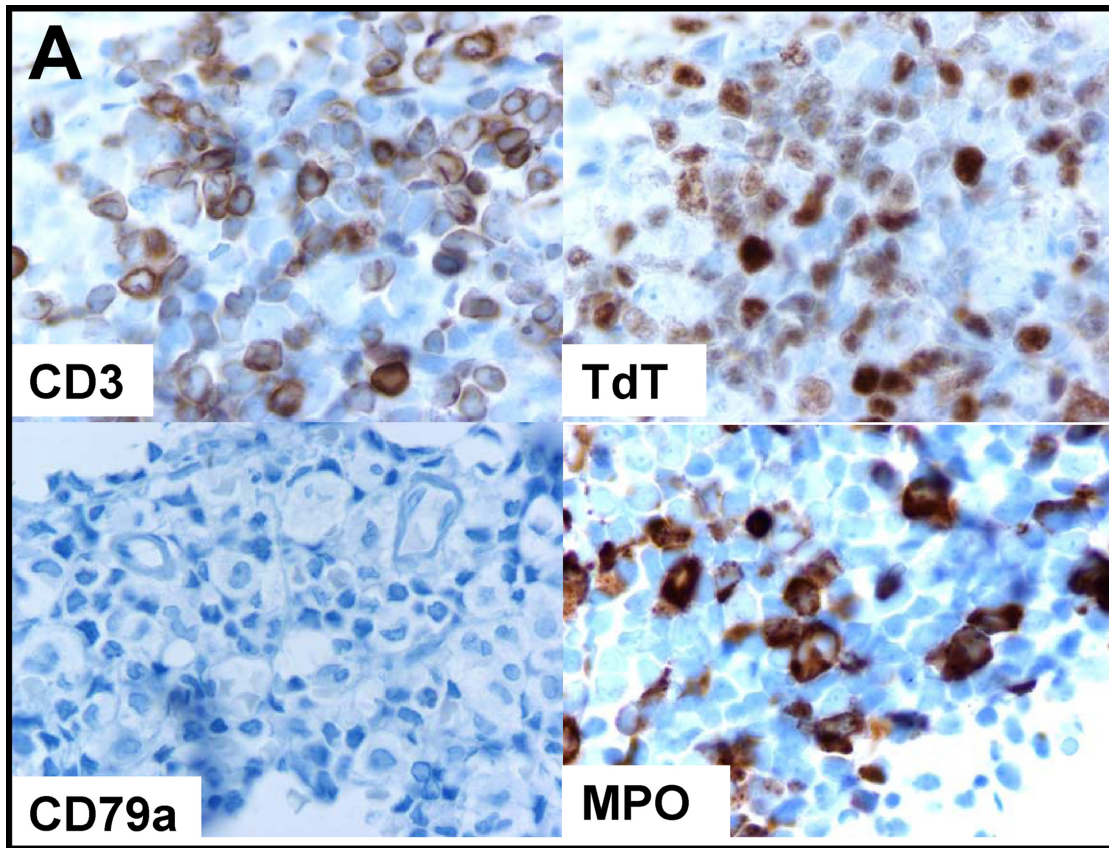
Eight cases of acute leukemia initially diagnosed as "BAL" were reclassified using our

new approach. When we use CD3, CD22 and MPO as lineage specific markers, the first 6 cases are reclassified as B-cell acute lymphoblastic leukemia (B-ALL) with aberrant expression of myeloid markers, T-cell acute lymphoblastic leukemia (T-ALL) with aberrant expression of myeloid markers, and B/T-ALL. In contrast, two of these 6 cases were diagnosed BAL using the EGIL score > 2 . The last two BAL cases remained classified as BAL because of their coexpression of T-cell- and myeloid lineage-specific markers.

Clinical implications of the proposed new approach

Since the publication of the EGIL thirteen years ago, many retrospective clinical studies have been performed to evaluate the efficacy of different chemotherapy regimens in patients diagnosed with BAL [5, 6, 17, 48-52]. Earlier studies indicated that BAL was a heterogeneous entity with a poor prognosis [49-51], due to the presence of prognostically unfavorable karyotypes and the difficulty of choosing appropriate therapy. Our series and others showed that some BAL cases can be redefined as AML with aberrant expression of lymphoid markers and ALL with aberrant expression of myeloid markers, which will help in choosing treatment regimens. For example, the first 6 cases of our series were redefined as ALL.

One recent large series demonstrated that BAL (defined by a modified EGIL score ≥ 2) patients treated with hyper-CVAD (hyperfrac-



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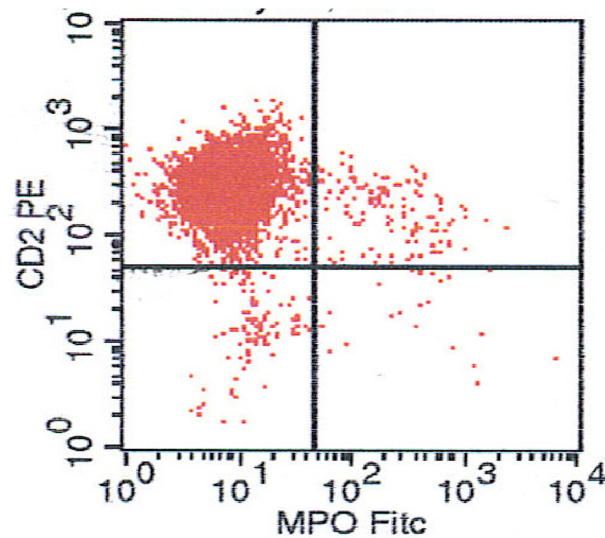


Figure 3. Precursor T lymphoblastic leukemia with aberrant expression of myeloid markers (in an 11-year-old boy). (A) Paraffin immunoperoxidase stains performed on a crushed small marrow biopsy showed focal blasts that were CD3+ and TdT+. These cells were negative for CD79a. Scattered MPO+ cells were also detected (Original magnification x400). (B) Flow cytometry identified a predominant population of precursor T-cells and a separate small population of myeloid precursors (<3% of the total events). The patient was treated with hyper-CVAD and is currently in CR.

tionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) had a higher CR rate (78%) than patients treated with AML regimens (57%) [5]. Although data on some cytoplasmic lineage-specific markers such as CD3, CD79a, IgM or TCR were not given in the paper, based on low MPO (MPO=0 in 10 cases, MPO < 3 in 15 cases), high CD22 (CD22 \geq 50 in 9 cases, not available in 12 cases) and TdT (TdT > 50 in 21 cases) expression in most of the 31 cases of BAL [5], those cases were actually ALL rather than BAL when using the new approach. Thus it is not surprising that most of those patients responded favorably to hyper-CVAD therapy for ALL [53]. We also analyzed a recently reported large series of pediatric BAL [6]. Based on the new definition, cases 5, 6, and 24 should be reclassified as ALL with aberrant expression of myeloid markers. Two of the 3 redefined ALL cases responded favorably to ALL therapy and gained CR, whereas one died of toxicity [6]. One recent multicenter study indicated that T/myeloid BAL had a much worse prognosis than other BAL [48]. However some of those T/myeloid BAL might be reclassified as T-ALL with aberrant expression of myeloid markers by using the new approach, and this group of patients was treated with AML regimens and did not respond [48]. A single-institution study defined a group of "biphenotypic AML" in mostly young patients with better outcome than other AML, without mentioning their treatment regimen (52). Using the new approach, most of those patients would be reclassified as ALL with aberrant expression of myeloid markers. Another study reported a series of BAL with recurrent t(8;21)(q22;q22) and CD79a expression [17]. Since expression of CD79a is usually driven by the aberrant expression of PAX5 in myeloblasts [54, 55], based on this new approach, these cases should be diagnosed as AML with t(8;21)(q22;q22), rather than BAL. The patients in that series responded favorably to concurrent AML and ALL chemotherapy [17], but they might have responded equally well to AML therapy alone. One earlier study showed that the use of combined lymphoid and myeloid regimens for induction in BAL patients resulted in a high incidence of early death [50], suggesting that accurate lineage determination might decrease patient mortality.

Possible diagnostic pitfalls

Even with the new approach, BAL could still be overdiagnosed due to inappropriate interpretation of immunological studies. For example, misinterpretation of MPO staining could lead to diagnosis of "BAL." In one of the cases presented (Case 4), small numbers of MPO+ cells mixed together with CD3+/TdT+ cells might have suggested that the leukemia was also of myeloid lineage (**Figure 3A**), even though the marrow was packed with lymphoblasts and flow cytometry indicated a separate population of MPO+ cells (**Figure 3B**). However, if these myeloid precursors morphologically resembled myeloblasts, the leukemia might be misdiagnosed as BAL or BLL.

Conclusion

BAL is a rare clinical entity. With our proposed paradigmatic approach, BAL will be even rarer (~0.3%). The evolving definition of BAL reflects our increasing knowledge and understanding of this rare type of leukemia. With our proposed paradigmatic approach, acute leukemia will be better defined and better managed by the clinicians. Future larger series may be required to further validate this approach.

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