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Review Article

Immunophenotypic Characterisation of Mixed Phenotype Acute Leukemia: A Review of Published Series

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Summary

Mixed phenotype acute leukaemia is defined by antigen expression thresholds expressed relative to normal cells, and the resulting label determines whether a patient receives lymphoblastic-directed or myeloid-directed therapy. Since lymphoblastic-directed treatment produces better outcomes, a relative flow cytometric measurement is doing more clinical work than its reproducibility comfortably supports.

Objectives: To review the published evidence on immunophenotypic characterisation of mixed phenotype acute leukaemia: which markers define each lineage and at what thresholds, how the lineage combinations distribute, how immunophenotype relates to morphology and cytogenetics, and how the assignment influences treatment and outcome.

Material and Methods: Narrative review of clinicopathological series, classification documents, diagnostic reviews and case reports indexed in PubMed and the major haematology and pathology journals. Studies were eligible if they reported immunophenotypic features, diagnostic criteria or outcomes in a defined mixed phenotype acute leukaemia population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Across 100 cases meeting consensus criteria, immunophenotyping showed B and myeloid combinations in 59 per cent, T and myeloid in 35, B and T in 4 and trilineage in 2 per cent. Morphology was consistent with lymphoblastic leukaemia in 43 per cent, myeloid in 42 and inconclusive in 15, and there was no correlation between age, morphology, immunophenotype or cytogenetics. Cytogenetic findings were complex in 32 per cent, otherwise aberrant in 27, t(9;22) in 20, normal in 13 and 11q23 rearranged in 8 per cent. In a separate series of 52 patients, 69.2 per cent received lymphoblastic-directed and 30.8 per cent myeloid-directed regimens, complete remission was achieved in 76.9 per cent, and lymphoblastic-directed treatment, paediatric age and biphenotypic blast type were each associated with higher remission rates and better overall survival.

Conclusion: Morphology contributes almost nothing to the diagnosis and the immunophenotype carries it entirely. Because the thresholds are relative rather than absolute and because lineage can switch under treatment pressure, the assignment is less stable than the treatment decision resting on it.

Abbreviations: MPAL – Mixed Phenotype Acute Leukaemia, ALAL – Acute Leukaemia of Ambiguous Lineage, BAL – Biphenotypic Acute Leukaemia, ALL – Acute Lymphoblastic Leukaemia, AML – Acute Myeloid Leukaemia, MPO – Myeloperoxidase, cCD3 – Cytoplasmic CD3, sCD3 – Surface CD3, EGIL – European Group for the Immunological Characterization of Leukemias, WHO – World Health Organization, ICC – International Consensus Classification, NSE – Nonspecific Esterase, My+ ALL – Myeloid Antigen-Positive ALL, CR – Complete Remission.

Keywords: Mixed Phenotype Acute Leukaemia; Immunophenotyping; Myeloperoxidase; Lineage Assignment; Flow Cytometry

Introduction

Acute leukaemia is categorised as myeloid, lymphoid, or of ambiguous lineage, and the third category exists because a minority of cases express antigens of more than one lineage on the same blasts or on separate blast populations [2]. Mixed phenotype acute leukaemia is the principal entity within it, and the designation replaced the earlier term biphenotypic acute leukaemia when consensus criteria were revised [1,2].

The revision was substantive rather than cosmetic. Earlier scoring systems assigned weighted points to a range of markers, which allowed cases with aberrant expression of one or two antigens to qualify [1]. The current criteria narrow the definition sharply, requiring myeloperoxidase for myeloid assignment and cytoplasmic or surface CD3 for T assignment, and explicitly excluding genuine lymphoblastic or myeloid leukaemia with aberrant markers, leukaemias with defining recurrent abnormalities, and chronic myeloid leukaemia in blast crisis [1,2].

That matters because aberrant myeloid antigen expression is common. Up to a third of B-lineage lymphoblastic leukaemias express CD13 or CD33 when a limited panel is applied, and none of those is mixed phenotype disease [7]. The tightening was designed to separate the two, and it also removed a group of patients from a diagnosis that carries different treatment implications [7,5].

This review sets out what the criteria require, how the phenotypes distribute across published series, what relation immunophenotype bears to morphology and genetics, and how the resulting assignment influences treatment.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and pathology journals were searched for studies of mixed phenotype acute leukaemia. Search terms combined mixed phenotype acute leukaemia, biphenotypic acute leukaemia and acute leukaemia of ambiguous lineage with immunophenotype, myeloperoxidase, lineage assignment, flow cytometry, diagnostic criteria and lineage switch. Reference lists of retrieved series and classification documents were screened by hand.

Eligibility: Studies were included if they reported immunophenotypic characteristics, diagnostic criteria, cytogenetic findings or outcomes in a defined mixed phenotype acute leukaemia population. Case reports are cited only where they illustrate a diagnostic pitfall documented in larger series, and are identified as such.

Data extraction and handling: Design, cohort size, classification edition applied, marker panel, lineage distribution and reported outcomes were extracted as published. The classification edition is stated alongside every proportion, because criteria have been revised repeatedly and a case meeting one edition may not meet another. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What the criteria require: Under current classification, myeloid lineage is assigned when myeloperoxidase intensity in at least part of

the blast population exceeds 50 per cent of the level in mature neutrophils, or when at least two monocytic antigens are expressed from nonspecific esterase, CD11c, CD14, CD64 and lysozyme [9,5]. B lineage requires strong CD19 with weak expression of CD10, CD22 or CD79a, or weak CD19 with strong expression of two of those markers [9]. T lineage requires strong cytoplasmic or surface CD3 with intensity in part exceeding 50 per cent of that in mature T cells [9,3].

Two features of that definition deserve attention. The thresholds are relative, expressed as a proportion of the signal from a normal cell population in the same sample, rather than as an absolute value [9,3]. And cytoplasmic CD3 detected by immunohistochemistry may not be entirely T-specific, since polyclonal antibodies can react with the CD3 zeta chain that natural killer cells also carry [3].

How the phenotypes distribute: In the largest series assembled under consensus criteria, 100 cases showed B and myeloid combinations in 59 per cent, T and myeloid in 35, B and T in 4 and trilineage in 2 per cent (Figure 1) [12]. Sixty-eight per cent were adults, and there were 62 men and 38 women [12]. A later series of 52 cases classified under the fifth edition and the consensus classification reported a similar predominance of B and myeloid disease [9].

Cytogenetics were abnormal in most cases: complex in 32 per cent, otherwise aberrant in 27, t(9;22) in 20, normal in 13 and 11q23 rearranged in 8 per cent (Figure 4) [12]. Both t(9;22) and 11q23 rearrangement now define separate diagnostic categories within the classification rather than being merely associated findings [1,2].

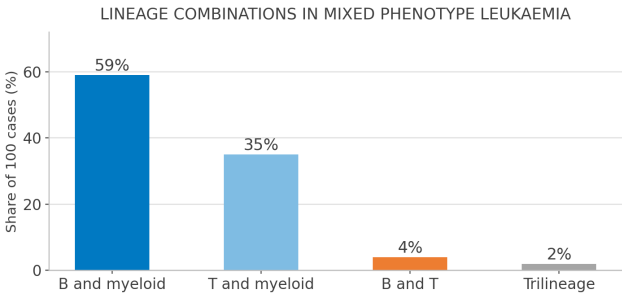


Figure 1: Lineage combinations in 100 cases meeting consensus criteria [12]

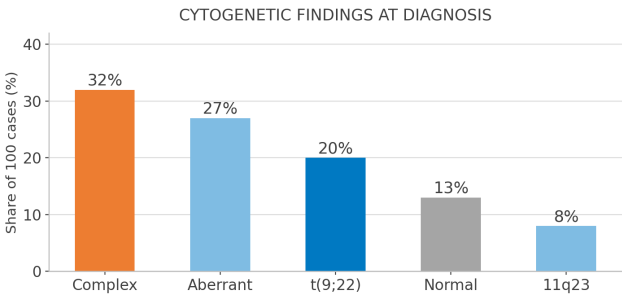


Figure 4: Cytogenetic findings in the same series [12]

Study	n	Criteria	Principal reported finding
Matutes et al. 2011 [12]	100	WHO 2008	B/myeloid 59%; no correlation between features
Weinberg et al. 2017 [5]	Review	WHO 4th ed	Diagnostic criteria and pitfalls set out
Wolach et al. [3]	Review	Current	Ambiguous lineage categories and induction outcomes
Zhang et al. 2026 [9]	52	WHO 5th ed and ICC	ALL-directed therapy linked to better remission and survival

Table 1: Principal studies reviewed, with the criteria applied and the finding as reported by the original investigators

Morphology contributes almost nothing: Blast appearance under the microscope was consistent with lymphoblastic leukaemia in 43 per cent of cases, with myeloid leukaemia in 42 and was inconclusive in 15 (Figure 2) [12]. That distribution is close to what random assignment between the two possibilities would produce.

More striking is the absence of relationship between any of the diagnostic dimensions. The investigators found no correlation between age, morphology, immunophenotype and cytogenetics [12]. A case that looks lymphoblastic is no more likely to be B and myeloid than T and myeloid, and neither predicts the karyotype. The immunophenotype therefore carries the diagnosis entirely, and nothing else corroborates it.

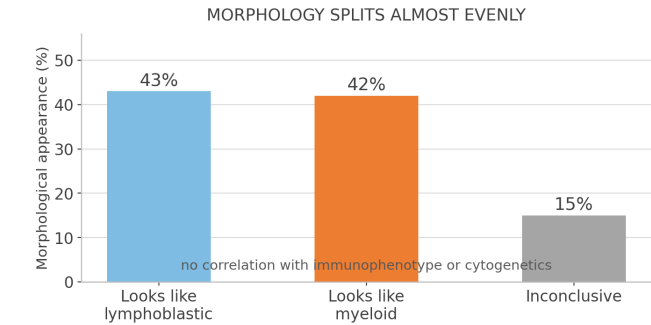


Figure 2: Morphological appearance across the same 100 cases [12]

The assignment determines the treatment: There is no established regimen for this disease, so patients receive either a lymphoblastic-directed or a myeloid-directed protocol, and the choice follows from how the case is characterised [3,4]. In the 100-case series, 27 received lymphoblastic therapy, 34 myeloid therapy, 5 a combination and 1 imatinib alone [12]. In the later 52-case series, 36 patients (69.2 per cent) received lymphoblastic-directed and 16 (30.8 per cent) myeloid-directed regimens (Figure 3) [9].

Outcome differed by that choice. Complete remission after initial induction was achieved in 40 of 52 patients (76.9 per cent), and lymphoblastic-directed regimen, paediatric age and biphenotypic blast type were each significantly associated with higher remission rates ($p = 0.007$, $p < 0.001$ and $p = 0.021$ respectively). The same three factors correlated with significantly better overall survival ($p < 0.001$, $p < 0.001$ and $p = 0.006$) [9].

Relapse remained substantial among those who responded, occurring in 10 of 32 B and myeloid patients and 2 of 4 T and myeloid patients who had initially achieved remission [9]. Outcome in ambiguous lineage leukaemia has been compared across induction approaches in review, with broadly concordant conclusions [3].

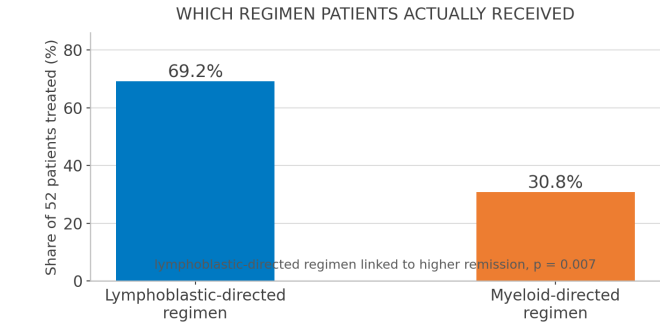


Figure 3: Treatment allocation in a series of 52 patients [9]

Lineage is not fixed: Two patients in the 52-case series, one B and myeloid and one T and myeloid, both with biphenotypic blasts, underwent phenotypic switch to myeloid leukaemia under treatment pressure [9]. Lineage switch is documented more widely, including from myeloid antigen-positive lymphoblastic leukaemia to a myeloid phenotype during lymphoblastic-directed therapy, with an underlying genetic lesion persisting throughout [7].

This complicates the diagnostic framework in a specific way. If the blast population can change lineage under selective pressure, then a phenotype recorded at diagnosis describes the state of the disease at one moment rather than a fixed property of it, and a treatment chosen on that phenotype may select for the population it does not target [7,9,20].

Lineage	Required for assignment	Nature of the threshold
Myeloid	MPO above 50% of mature neutrophil intensity, or two monocytic antigens	Relative to normal cells in the same sample [9,5]
B lymphoid	Strong CD19 with one weak marker, or weak CD19 with two strong	Graded by expression strength [9]
T lymphoid	cCD3 or sCD3 above 50% of mature T cell intensity	Relative; antibody may cross-react with zeta chain [9,3]

Table 2: Lineage assignment criteria and the nature of the thresholds each depends on

Genetics gives the category a basis that phenotype alone lacks:

Large-scale genomic analysis has provided what the immunophenotype cannot, showing that the cell of origin and the founding mutation determine the subtype and drive expression of multiple lineage-defining antigens [16]. On that account the mixed phenotype is a consequence of where in haematopoiesis the transformation occurred rather than an artefact of measurement.

Integrative genomic analysis in adults has delineated lineage-associated molecular subtypes [17], and specific mutation patterns concentrate in particular groups, with PHF6 and DNMT3A enriched in mixed phenotype disease showing T-lineage differentiation [18]. Genetically defined categories of this kind are reproducible in a way that antigen intensity thresholds are not, and current classifications already carve out t(9;22) and 11q23-rearranged disease on that principle [2,12].

The practical consequence is that genetic subtyping may eventually replace phenotype as the basis for treatment allocation, which would resolve the reproducibility problem rather than mitigate it. That has not happened yet, and the series reviewed here still allocate treatment on immunophenotype [9,12].

Series	n	Population n	Reported emphasis
Killick et al. 1999 [15]	—	Adults	Outcome of biphenotypic disease
Rubnitz et al. 2009 [10]	—	Children	Single-institution experience
Al-Seraihy et al. 2009 [14]	—	Children	Clinical characteristics and outcome
Gerr et al. 2010 [8]	—	Children	Therapy recommendations proposed
Yan et al. 2012 [11]	117	Adults	Immunophenotype with molecular features
Weinberg et al. 2014 [6]	61	Mixed	WHO against EGIL criteria compared
Hrusak et al. 2018 [13]	International	Children	Treatment strategy identified
Duong et al. 2020 [19]	Multicentre	Adults	Favourable outcomes with hyperCVAD

Table 3: Published series contributing to current understanding, with the emphasis of each

Which regimen, and the evidence behind the answer: An international cooperative study in childhood ambiguous lineage leukaemia identified a treatment strategy on the basis of pooled outcomes, favouring lymphoblastic-directed therapy [13], and paediatric series had pointed the same way earlier [8,10,14]. In adults, a multicentre retrospective study reported favourable

outcomes with an intensive lymphoblastic regimen [19].

Comparison of the two classification systems on the same cases found meaningful discordance between criteria [6], which is the measurement problem restated: a case may be mixed phenotype under one system and not under another, and the treatment implication differs accordingly. Adult series combining immunophenotype with molecular characterisation have described the resulting heterogeneity in detail [11].

Discussion

Three observations combine into a single difficulty. The immunophenotype carries the diagnosis alone, since morphology splits almost evenly and correlates with nothing [12]. The thresholds defining that immunophenotype are relative measurements against normal cells in the same sample rather than absolute values [9,3]. And the resulting label determines whether the patient receives lymphoblastic-directed or myeloid-directed therapy, a choice that predicts remission and survival [9].

A great deal therefore rests on where a flow cytometrist draws a line against a reference population. That is not an argument against the criteria, which were tightened for good reasons and do exclude the aberrant-antigen cases that previously inflated the category [1,7]. It is an argument for reporting the measurement rather than only the conclusion.

Why the treatment finding should be read cautiously

Lymphoblastic-directed therapy was associated with better remission and survival, and that association has been reported often enough to shape practice [9,3,4]. But treatment was not randomly assigned. Clinicians choose a lymphoblastic regimen for cases that look more lymphoblastic, in patients who are younger and fitter, and paediatric age was independently associated with better outcome in the same analysis [9].

Disentangling the regimen from the patient would require randomisation, which the rarity of the disease makes unlikely. What can be said is that the association is consistent across series and that no series reports the opposite, which is weaker evidence than a trial but not nothing [9,3,12].

The cases the tightened criteria excluded

Narrowing the definition removed from the category a group of patients with genuine lymphoblastic leukaemia expressing myeloid antigens, and that was the intended effect [1,7]. The concern raised in response is that minimising the weight given to myeloid markers other than myeloperoxidase could lead to a patient with an aggressive myeloid component being treated as having favourable lymphoid disease, potentially without consolidative transplantation [7].

The documented case of lineage switch from myeloid antigen-positive lymphoblastic leukaemia to refractory myeloid disease during lymphoblastic-directed therapy illustrates the concern concretely [7]. Whether it represents a systematic problem or an unusual event is not established by a single report, and larger series applying the current criteria prospectively would be needed to settle it [9,5].

Study limitations

The limitations belong to the underlying literature. Mixed phenotype acute leukaemia accounts for a small minority of acute leukaemias, so even the largest series contain around 100 cases and subgroup comparisons rest on very small numbers [9,12]. Diagnostic criteria have been revised repeatedly, and cases classified under one edition would not all qualify under another, which makes cross-series comparison unreliable [1,2,9]. Antibody clones, fluorochrome panels and gating strategies differ between laboratories, and the thresholds are relative, so the same sample may be classified differently in different centres [9,3,5]. Treatment was allocated by clinician choice in every series reviewed, with no randomised comparison available [9,12]. And outcome data are frequently incomplete, with response and outcome available for only 67 and 70 of 100 patients in the largest series [12].

Two gaps deserve naming. No study reviewed here reports interobserver agreement on lineage assignment between laboratories applying the current criteria to the same samples, which is the measurement most in question [9,5]. And no prospective series reports how often lineage switch occurs under each type of directed therapy, although the phenomenon is documented in both directions [7,9,20].

Conclusion

Mixed phenotype acute leukaemia is diagnosed on immunophenotype alone. Morphology suggests lymphoblastic disease in 43 per cent of cases and myeloid disease in 42, and correlates with neither the immunophenotype nor the karyotype. B and myeloid combinations account for 59 per cent of cases, T and myeloid for 35, and cytogenetics are abnormal in most. The criteria defining lineage rest on antigen intensity expressed relative to normal cells in the same sample, and that relative measurement determines whether a patient receives lymphoblastic-directed or myeloid-directed therapy, a choice associated with a difference in both remission rate and survival. Lineage can also switch under treatment pressure. Reporting the underlying measurements alongside the diagnostic conclusion, and establishing interobserver agreement between laboratories, would do more for this disease than another revision of the criteria.

The longer-term direction is clearer than the immediate one. Cytogenetic and molecular characterisation is already how the leukaemias generally are classified [21,24], targeted agents are selected on genetic rather than phenotypic grounds [25], and mixed phenotype disease has been shown to have a genetic basis that phenotype merely reflects [16,17]. Classification here will most likely follow the same route.

Until it does, the practical position is modest. Report the marker intensities alongside the lineage call so a reader can see how close the case sat to the threshold. Recognise that a phenotype recorded at diagnosis may not describe the disease at relapse. And treat the association between lymphoblastic-directed therapy and better outcome as the consistent but non-randomised finding it is [9,13,22,23].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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