Case Report

Acute Lymphoblastic Leukemia With Surface Light Chain Expression

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DOI: 10.21276/APALM.3214

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Submitted: 31-May-2022
Final Revision: 22-Dec-2022
Acceptance: 06-Jul-2023
Publication: 02-Aug-2023

Abstract

Acute Lymphoblastic leukemias (ALL) are a heterogeneous group of neoplasms which can either be having precursor B cell immunophenotype or mature B cell immunophenotype. Surface immunoglobulin light chain restriction is usually a feature of mature B cell neoplasms. A precursor B cell lymphoblastic leukemia (pre-B-ALL) with surface immunoglobulin light chain expression is a rare immunophenotype . We report a case of a 4 year old female with L1 type of blast morphology yet showing surface light chain restriction. Recognizing this rare immunophenotype and arriving at a correct diagnosis has therapeutic implications as treatment regimens differ for precursor B ALL as compared to mature B cell neoplasms.

Keywords:

Acute Lymphoblastic leukemia, surface immunoglobulin light chain

Introduction

Neoplasms of B cell lineage can be classified according to the WHO classification either as precursor B lymphoblastic leukemia /lymphoma (pre-B-ALL) with an immature phenotype or as Burkitt leukemia/ lymphoma with a mature phenotype (1).This immunophenotypic classification derives its basis from the B cell ontogeny wherein B cell development proceeds through several stages distinguished on the basis of expression of various cell markers.(2). Thus at the more primitive end of spectrum, cells express CD34, TdT and lack CD20, while at the other end are cells that lack CD34 and express higher levels of CD20 and express cytoplasmic IgM (2). So a Pre B cell ALL is usually positive for Tdt , CD34 along with one or more pan B cell antigens, whereas surface light chain restriction is a feature of mature B cell neoplasms along with presence of c-myc translocation (3) . Cases of precursor B ALL described as transitional pre B ALL express cytoplasmic and surface IgM but they lack surface light chain immunoglobulins (4). Surface immunoglobulin expression is known to occur in some pre-B-ALL, wherein they show heavy chain

expression and are typically negative for surface light chain expression (5). Thus isolated expression of surface light chains in an otherwise precursor B ALL is a rare immunophenotype. Few cases with surface light chain restriction has been reported in pre-B-ALL cases but those were specifically seen to be associated with MLL gene rearrangement especially t (9:11). MLL gene rearrangement is more frequently seen in infantile leukemia rather than in other age groups (5, 6). Hence accurate diagnostic distinction between a precursor B ALL and mature B cell leukemia is critical for disease management as the treatment for Burkitt leukemia differs from that of pre B ALL (3,5).We report a case with this rare immunophenotype highlighting the importance of multiparametric approach in precise diagnosis of such hematolymphoid neoplasms.

Case Report

4 year old female presented with complaints of headache and vomiting since 4 days. On examination she had hepatosplenomegaly. Complete blood count (CBC) at presentation showed hemoglobin of 9.1 gm/dl, Total Leucocyte count (TLC) of 107 x 109/L and platelet count of 40 x 109/L. Peripheral smear showed 90% blasts with FAB L1 morphology. LDH was elevated (1090 U/L, normal range = 100-190 U/L) and uric acid level was 9mg/dl while other metabolic parameters were in normal range. Bone marrow flow cytometric immunophenotyping (FCM) done on BD FACS Canto II machine revealed a blast population constituting 86% with dim CD45 . These cells expressed CD19, CD10, CD38 , cytoplasmic CD79a and dim HLA-DR. A subset of these blasts showed CD34 positivity. Another small subset showed moderate CD20 expression with surface kappa light chain restriction. Both the subsets were negative for CD8, CD56, CD3, CD4, CD7, CD13, CD33, CD64, CD117, cytoplasmic MPO and cytoplasmic CD3. In view of this immunophenotype it was important to rule out possibility of Burkitt leukemia/lymphoma. However cytogenetic studies done revealed Philadelphia chromosome positivity in 93% of cells, while chromosomal translocations involving c-MYC, TEL/AML1 and MLL gene rearrangement were absent. In view of blasts which expressed dim to negative CD45 with CD34 positivity and a negative c-MYC it was best regarded as Pre-B ALL with surface kappa light chain restriction. CSF examination performed at the time of diagnosis showed TLC count of 26 cells/ul with presence of blasts.

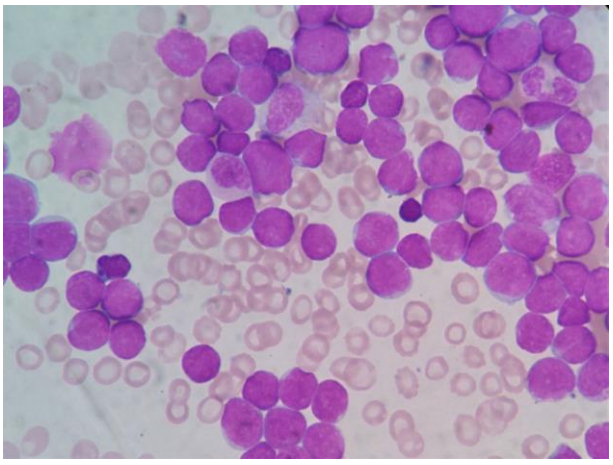

Figure 1 Peripheral smear showing 86 % blasts with high N/C ratio, scanty cytoplasm, open chromatin, inconspicous nucleoli (Leishman stain x1000, oil immersion)

The patient was started on BFM-95 protocol after receiving prophylactic rasburicase. Imatinib was added later after the cytogenetic confirmation of t(9:22). Day 8 CBC showed 1% blasts with an absolute count 39 cells/µm). Day 30 marrow was done for assessment of remission status which showed no morphological evidence of residual disease. Real time quantitative PCR (RQ-

PCR) for BCR-ABL done at this time point was 0.08% while post consolidation it was 0.001%. Presently she has completed maintenance therapy with latest RQ-PCR for BCR-ABL which was undetectable and now advised to follow up every three months.

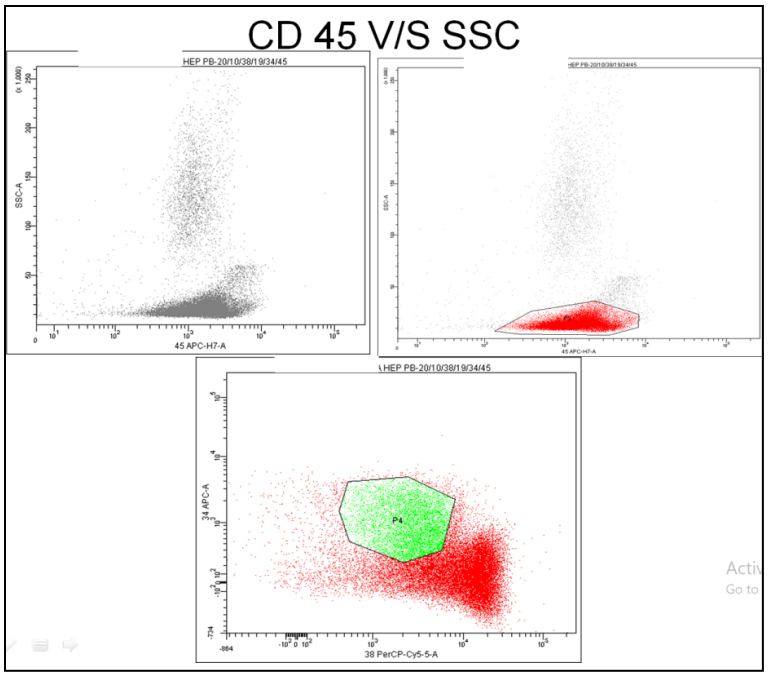

Figure 2 Flow cytometry images showing position of blasts on CD45 v/s SSC. The blasts (red) are dim CD45, positive for CD38 , with subset being CD34 positive

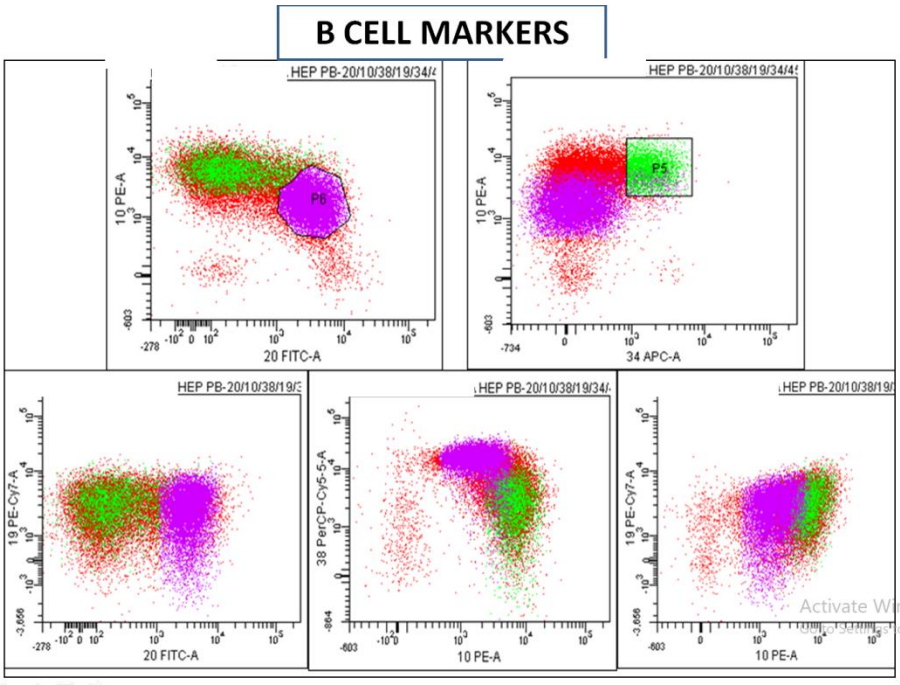

Figure 3 Flow cytometry images showing subset of blasts which are CD34 positive and CD20 negative (green) while other subset which is positive for CD20 and negative for CD34 (purple)

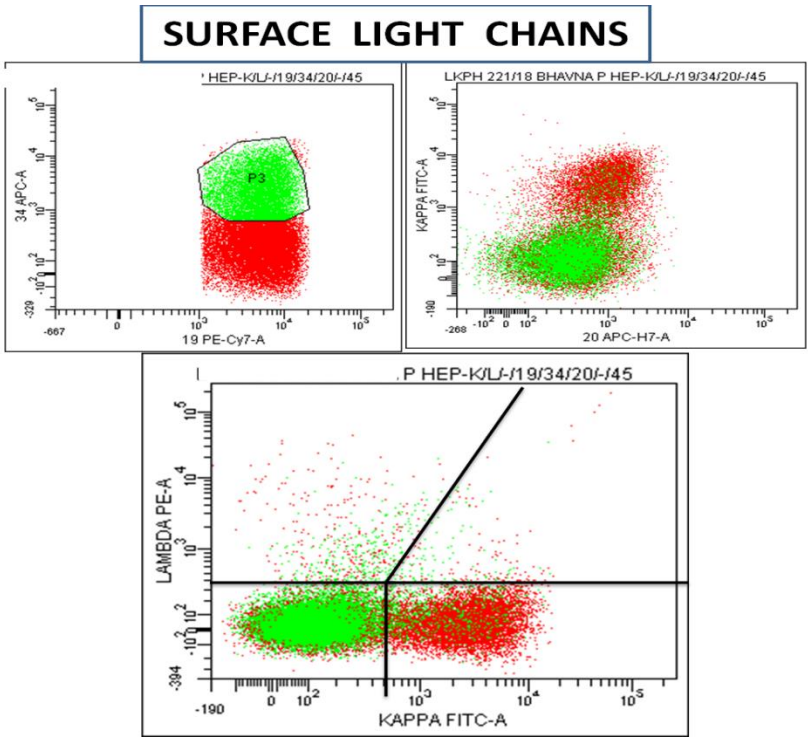

Figure 4 Flow cytometry images showing kappa surface light chain restriction on those subset of blasts which are CD34 negative and CD20 positive

Discussion

Surface immunoglobulin (sIg)light chain expression is characteristic of but not specific for Burkitt lymphoma/leukemia (6). Expression of (sIg) by L1 and L2 ALL of B lineage although unusual, has been reported in few pediatric patients diagnosed with ALL with blasts showing surface light chain expression overall representing less than 2 % of all cases. (2)The expression of surface light chain immunoglobulins in pre B ALL thus seems to be rare in the pediatric age group. We compared our case with one of the largest studies of pediatric ALL with this unusual immunophenotype (4). In this study, there were 9 pediatric cases with age ranging from 11 months to 13 years (median 5 years) and which included 6 males and 3 females. The WBC count ranged from lowest of 1.4 to 169.1 x 10 9/L (median = 4.2 x 10 9/ L). For all patients bone marrow examination was done at diagnosis which revealed blasts of either L1 or L2 morphology ranging from 59.6% to to 97.4% (median = 95.8%). In this study, FCM showed blasts with dim CD45 expression along with positivity for CD22, HLA-DR, CD19, CD10 bright similar to our case except in one case where CD10 showed dim expression. CD20 expression was dim positive in two cases similar to our case.CD34 positivity was present in all except in two cases. Tdt was demonstrated on clot sections by IHC for only two patients as bone marrow biopsy was not done for any patient.

All cases demonstrated kappa light chain restriction similar to our case except in one case which showed lambda light chain restriction with CD5 positivity along with CD 10, CD19, CD34 with dim CD20. This was the first case in literature of CD5 and surface lambda positive Pre B ALL Aberrant expression of CD13 and CD33 was demonstrated in four cases which was not there in our case. Surface heavy chain analysis done in 2 patients which revealed expression of IgD. FISH studies were performed in six out of nine cases which provided specific cytogenetic abnormalities like in one case which showed bcr-abl fusion similar to our case. However similar to our finding none out of these nine cases had c-MYC translocation. All the nine children were treated

according to the Pediatric Oncology Group chemotherapy protocols for Pre B ALL. In their study all except one achieved complete remission and were alive with no evidence of disease at 17 to 72 months (median, 26 months). The child who succumbed had t(9:22) .

Another study done by Liu Y et al and colleagues(3) had an eighteen month old female infant who presented with ecchymosis since one week and was found to have WBC count of 5.29x 10 9/L with 11% blasts. Bone marrow examination showed 85.2 % of blasts in marrow with FAB L2 morphology. The immunophenotyping showed positivity for CD34, CD19, CD10 CD20, CD9, CD22, HLA-DR, CD38, CD123, CD13 and lambda light chain restriction. Cytogenetic studies revealed normal karyotype and was treated with standard B ALL protocols. Follow up studies from 4 to 6 months showed complete remission. Li Shiyong et al (6) reported two pediatric cases (13 month old male and 12 month old female) with L1 type of blasts and were CD19, CD20 (dim and heterogenous) CD38, CD22, dim CD45 positive with surface lambda light chain expression in both cases however they were negative for CD10, CD34 and TdT.

Interphase FISH failed to demonstrate the presence of chromosomal translocations invovlving c-myc gene. Both the patients received treatment as per Children's Cancer Group(CCG) leukemia protocol. Both the patients achieved complete remission.

Four other studies done by Sullivan and colleagues (7,8) Van Eys et al (9) , Behm FG et al (10) and Finlay JL (11) have reported expression of surface IgM with a subset of blasts positive for Ig light chains with otherwise FAB L1 /L2 morphology. All the cases were of pediatric age group.

Probable hypothesis

These neoplasms probably arise from a B cell precursor at a stage of differentiation intermediate between that of transitional pre B cells (Tdt and cytoplasmic Ig positive but are surface Ig negative) and mature B cells which are TdT negative and express surface Ig Heavy and light chains (2) . Kansal R et al in their study proposed that surface light chain immunoglobulin restriction in precursor B lymphoblasts is not confined to any particular stage of B lymphoblast differentiation and instead may be seen in a heterogeneous group of pre B ALLs, showing different degrees of differentiation of B lymphoblasts (early, intermediate or late stages of precursor B cell) (4). Neoplastic cells are known to show deviation from the normal sequence of B cell maturation by showing unexpected surface light chain Ig expression which likely would not be present in normal hematogones. Thus it is not always possible to correlate leukemic B cells with normal B cell developmental stages.

One possible mechanism that would explain the occurrence of surface Ig in this heterogenous group of ALL cases is uncoupling of proliferation and maturation of B cells which has been reported to occur in these group of neoplasms (12). Other hypothesis is that surface Ig positive ALL cases can arise from a subset of leukemic cells within a typical surface Ig negative ALL whether early, intermediate or late pre-B cell stage and progress towards greater maturational status and eventually become the predominant clone as evidenced in two patients studied by Kansal R et al wherein only at relapse the blasts expressed sIg light chains which were absent at diagnosis (4).

Importance of multiparametric approach

This case highlights the importance of multidisciplinary approach in differential diagnosis of these B cell neoplasms that incorporates patient history, morphology, multiparametric flow cytometry and cytogenetic studies. Thus relying only on morphology or immunophenotype does not help in diagnosis rather its prudent to use a comprehensive approach to arrive at a correct diagnosis. Demonstration of chromosomal translocations involving the c-myc gene is necessary for correct diagnosis of

Burkitt leukemia /lymphoma (6).

Conclusion

Presently due to the limited number of case reports available till date there has not been sufficient evidence demonstrating the biological properties of this unusual immunophenotype and significance of this finding in the clinical course of pre B ALL yet remains to be determined. Also the prognostic significance of this rare immunophenotype is not known. In the available studies (4,5,6,7,8,9,10,11,13,14,15) both adult and pediatric patients with this immunophenotype were not treated differently and had survival and outcome similar to other B-ALL without this immunophenotype. Clinical aggressiveness might be related to other feature like co-existence of Philadelphia chromosome or age rather than the light chain expression (3). From a diagnostic standpoint, surface light restriction if detected in a neoplastic B cell population does not necessarily indicate a classification of a mature B cell neoplasm neither a precursor B cell neoplasm be solely ruled out by the presence of surface light chain immunoglobulin restriction. Identification of these rare phenotypes is imperative to avoid inadequate therapy or overtreatment as treatment regimens for precursor B cell ALL and mature B ALL differ significantly. From a laboratory point of view including surface light chains upfront in acute leukemia diagnostic panel can be of advantage especially in picking up these cases. Like in our case if this immunophenotype is demonstrated we can specifically look for c-MYC translocation in cytogenetic studies. Also this immunophenotype can serve as a diagnostic fingerprint which will also help at MRD evaluation at a later time point.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pilleri SA, et al. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. Lyon: IARC; 2017 Revised edition.
2. Vasef MA, Brynes RK, Murata-Collins JL, et al. Surface immunoglobulin light chain–positive acute lymphoblastic leukemia of FAB L1 or L2 type: a report of 6 cases in adults. Am J Clin Pathol. 1998;110:143-9.
3. Liu Y, et al. Precursor B cell Lymphoblastic Leukemia with surface immunoglobulin Light chain expression in two Chinese patients. Acta Hematol. 2013;130:188-91.
4. Kansal R, Deeb G, Barcos M, Wetzler M, Brecher ML, Block AW, et al. Precursor B lymphoblastic leukemia with surface light chain immunoglobulin restriction: A report of 15 patients. Am J Clin Pathol. 2004;121:512-25.
5. Rabade N, Bibi A, Ghodke K, Patkar N, Tembhare P, Amare P, et al. Lymphoblastic leukemia with surface light chain restriction: A diagnostic dilemma. Indian J Pathol Microbiol. 2016;59:410-2.
6. Li S. Is B linage Acute Lymphoblastic Leukemia with a Mature Phenotype and L1 morphology a Precursor B Lymphoblastic Leukemia/Lymphoma or Burkitt leukemia/ lymphoma. Arch Pathol Lab Med. 2003;127.
7. Sullivan MP, Pullen DJ, Crist WM, et al. Clinical and biological heterogeneity of childhood B cell acute lymphocytic leukemia: implications for clinical trials. Leukemia. 1990;4:6-11.
8. Sullivan MP, Crist W, Pullen J, et al. Childhood B cell ALL is unexpectedly clinically heterogeneous: A Pediatric Oncology Study (POG) study. Proc Soc Clin Oncol. 1987;6:148A.
9. Van Eys J, Pullen J, Head D, et al. The French –American-British (FAB) classification of leukemia: The Pediatric Oncology Group experience with lymphocytic leukemia. Cancer. 1986;57:1046-51.
10. Behm FG, Head DR, Pui CH, et al. B cell precursor ALL with unexpected expression of surface immunoglobulin (sIg) Mu and lambda. Lab Invest. 1995;72:106A.
11. Finlay JL, Borcherding W. Acute Lymphoblastic leukemia with L1 morphology: A report of two pediatric cases. Leukemia. 1988;2:60-2.
12. Hurwitz C, Loken MR, Graham ML, et al. Asynchronous antigen expression in B lineage acute lymphoblastic leukemia. Blood. 1998;72:299-307.
13. Michelis JJ, Adriaansen HJ, Hagemeijer A, et al. TdT positive B cell acute lymphoblastic leukemia(B-ALL) without

Burkitt characteristics. Br J Hematol. 1988;68:423-6.

14. Shende A, Festa RS, Wedgewood JF, Lanzkowsky P. A pediatric case of TdT positive B cell acute lymphoblastic leukemia (B-ALL) without Burkitt characteristics. Br J Hematol. 1988;70:129-30.
15. Navid F, Mosijczuk AD, Head DR, et al. Acute lymphoblastic leukemia with t(8:14) (q24:q23) translocation and FAB L3 morphology associated with precursor immunophenotype: The pediatric Oncology Group experience. Leukemia. 1999;13:135-41.