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First Report of Variant *BCL6* Gene Rearrangement; Inversion 3: Clinical Presentation in a Rare Entity of Splenic B-Cell Lymphoma/Leukemia with Prominent Nucleoli

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Abstract

Splenic B cell lymphoma/leukemia with prominent nucleoli (SBLPN), previously known as hairy cell leukemia variant (HCL-V), remains a rare and provisional entity within the spectrum of splenic B cell neoplasms. It demonstrates overlapping morphologic and immunophenotypic features with low-grade B cell lymphomas, posing diagnostic and therapeutic challenges. We report the first case of inversion 3q27 causing a variant *BCL6* gene rearrangement within a complex clonal karyotype, characterized by multiple copy number alterations, that is, duplication 1q, deletion 7p, partial trisomy 8q, deletion 9q, deletion 10p, isochromosome 14q, trisomy 18, and trisomy X, indicative of marked genomic instability in a rare entity of SBLPN. The aggressive clinical course observed further emphasizes the need for comprehensive diagnostic workups for prognostication. As exact defining genetic alterations are not yet established for this entity, expanding the cytogenetic and molecular landscape is crucial for refining classification, prognostication, and therapeutic strategies. The case illustrates how genetic complexity may drive disease aggressiveness and management challenges, underscoring the need for early multidisciplinary interventions and individualized treatment strategies.

Keywords
- HCLv
- SBLPN
- complex karyotype
- chromosome 3q27 inversion
- variant *BCL6* gene rearrangement
- fluorescence *in situ* hybridization

Introduction

Hairy cell leukemia variant (HCL-V) is classified under the provisional category of splenic B cell lymphoma/leukemia with prominent nucleoli (SBLPN) in WHO-HAEM5. SBLPN is composed of medium to large mature B lymphoid cells with prominent nucleoli and is biologically distinct from both classical hairy cell leukemia (HCL) and other well-defined B cell non-Hodgkin lymphomas. Although it shares some morphologic and immunophenotypic features with HCL, it typically lacks CD5 expression, the BRAF V600E mutation, an aggressive clinical course, and resistance to standard HCL-directed therapies.[1]

Unlike other B-cell lymphomas, which often have well-defined genetic profiles, SBLPN lacks consistent prognostic genetic markers, largely due to its extreme rarity, estimated at just 0.03 cases per 100,000 individuals per year. Comprehensive genetic characterization is therefore essential for

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improving diagnostic accuracy, understanding disease biology, and refining prognostic assessment.

In HCL-V, limited studies have identified chromosomal abnormalities, most frequently involving complex karyotypes, 17p deletions, and various copy number alterations.[2,3]

To our knowledge, this is the first documented case of a complex karyotype in SBLPN featuring a novel pericentric inversion of chromosome 3;inv(3)(p13q27), involving a variant *BCL6* rearrangement (5′deletion) with 3p13 as the novel partner region, a finding not previously reported in this disease entity, additionally marked with unique copy number alterations.

We identified two divergent clonal populations: one harboring inv(3)(p13q27) leading to variant *BCL6* rearrangement with 5′ deletion, and the other clone showing a 3q deletion, resulting in *BCL6* loss. These findings reveal the underlying genetic heterogeneity of SBLPN and offer novel insights into the potential pathogenic role of *BCL6* alterations in its evolution and aggressive clinical behavior.

Case Presentation

A 50-year-old female presented with fever, severe pancytopenia, large hematomas, low Glasgow Coma Scale, and intracranial hemorrhage, requiring ICU admission. CT brain showed acute subdural hematomas in bilateral frontal, left temporal, and left parietal regions, with the largest (11 mm) extending into the posterior interhemispheric fissure.

At presentation, complete blood count showed Hb 8.5 g/dL, TLC 2.28 $\times 10^9$/L, PLT 03 $\times 10^9$/L, and ANC 0.75 $\times 10^9$/L; liver function tests revealed TB 23.2 µmol/L, DB 13.9 µmol/L, and ALT 60 U/L; and coagulation profile demonstrated PT 19 seconds, APTT 35 seconds, and INR 1.7. Peripheral smear findings showed severe pancytopenia with atypical lymphocytes and no circulating blasts (►**Fig. 1A**).

Bone marrow aspirate was hypocellular and hemodiluted, with approximately 80% infiltration by atypical small to medium-sized lymphoid cells exhibiting prominent nucleoli, cytoplasmic blebs, and occasional vacuoles (►**Fig. 1A–D**). Trephine biopsy showed hypercellular marrow with similar diffuse atypical lymphoid infiltration and normal reticulin fibers (Grade 0–1 MF; ►**Fig. 1C, D**).

Bone marrow flow cytometry demonstrated 65.5% lymphocytes, predominantly (70.3%) clonal CD19+/CD20+/sIgM+/lambda-restricted B-cells, negative for CD5, CD10, CD23, CD25, CD103, and other markers (►**Fig. 1E**).

The immunophenotype was inconsistent with CLL or mantle cell lymphoma, and supported a diagnosis of a B-lymphoproliferative neoplasm, favoring a hairy cell leukaemia variant, that is, SBLPN.

Karyotype and FISH Analysis

Karyotype analysis from unstimulated culture revealed a complex clonal abnormal karyotype with structural alterations involving chromosomes 1, 3, 7, 8, 9, 10, and 15, resulting in copy number changes and numerical abnormalities with gains of chromosomes 3, 14, 18, and X. Composite karyotype as per ISCN nomenclature[4] was designated as:

47∼49,XXX,dup(1)(q25q42),+der(3)inv(3)(p13q27),del(3)(q12),del(7)(p15p13),iso(8)(q10),der(9;15)(p10;q10)del(9)(p11),del(10)(p13),+14,iso(14)(q10),+18,+18[cp20] (►**Fig. 2A**).

Fluorescence in situ hybridization (FISH) was performed using probes for *MYC, BCL2, IGH/CCND1*, and *BCL6* genes (Cytocell, VYSIS, Downers Grove, Illinois, United States) that confirmed the karyotype findings.

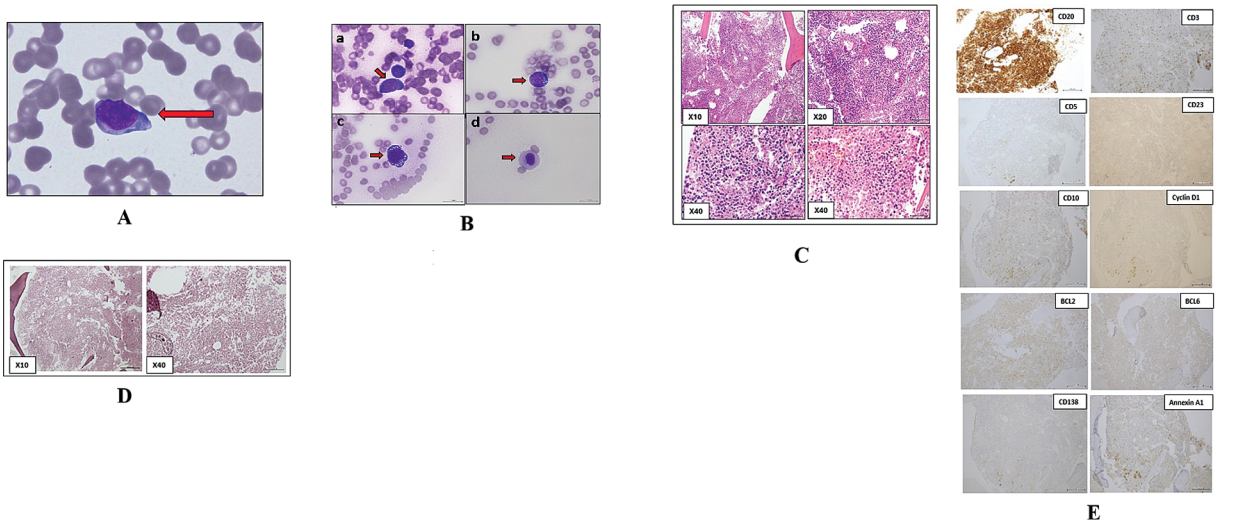

Fig. 1 (A) PB smear (×100). Lymphocytosis with many reactive and some atypical forms, the figure shows an atypical—spindle-shaped—lymphoid cell. (**B**) Bone marrow aspirate (Wright stain, ×100) BM with infiltrated approximately 80% atypical lymphoid cells; small to medium-sized with occasional nucleoli, cytoplasmic blebs/spindle shaped (a) and/or vacuolations (b, c), and some showed fried-egg like morphology (d). (**C**) Bone marrow trephine biopsy (H&E stain). (**D**) BM trephine biopsy reticulin special stained slides showing normal pattern of reticulin fibers (Grade 0–1 MF). (**E**) BM trephine biopsy immuno-stained slides showing strong diffuse positive CD20, partial positive BCL2 and annexin A1, with negative CD3, CD5, CD23, CD10, cyclin D1 and *BCL6*.

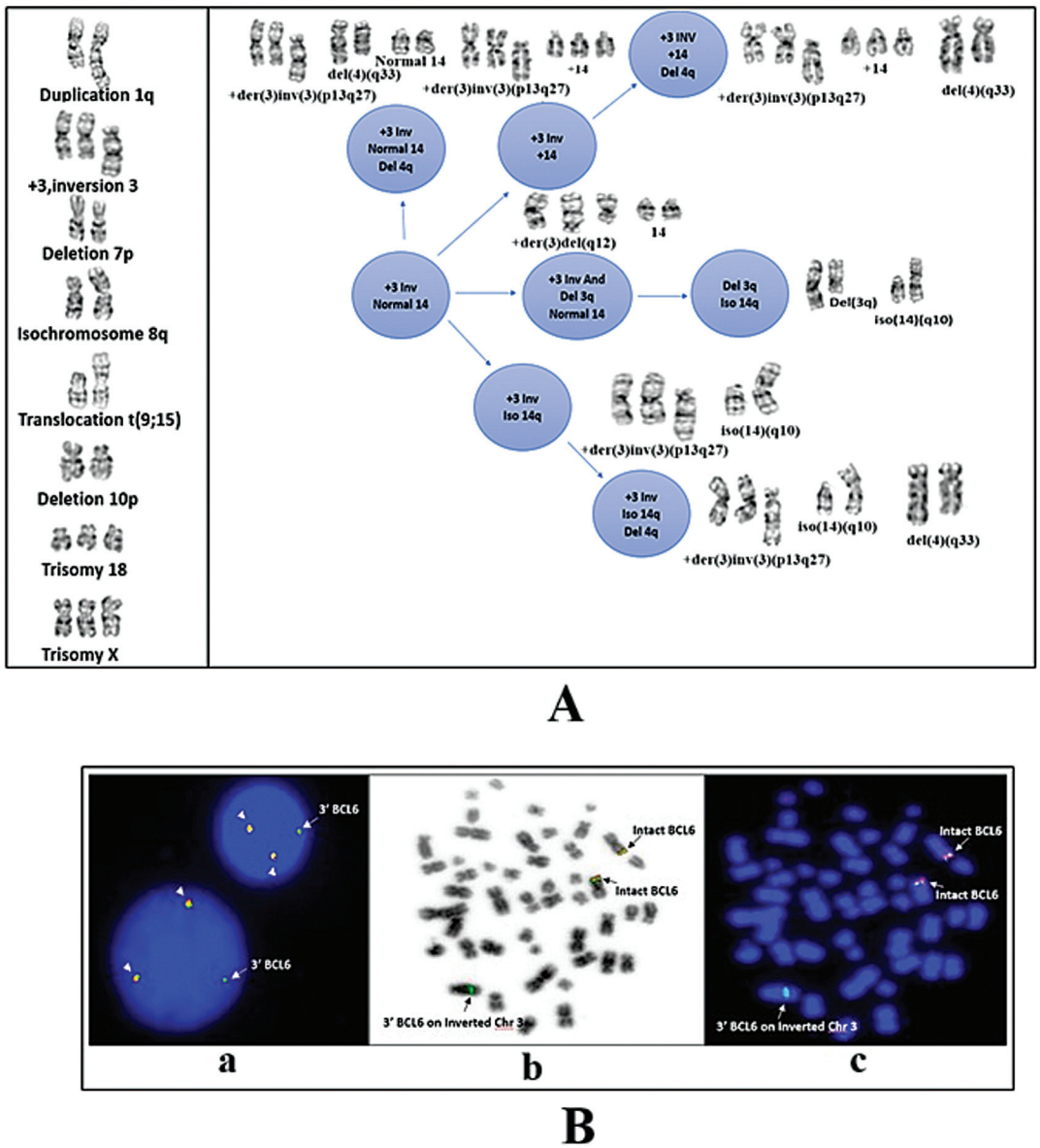

Fig. 2 (A) Representative karyotype image showing a complex karyotype with multiple clonal structural and numerical abnormalities. (B) FISH on interphase (a) and metaphase cells (b; inverted DAPI, d; DAPI) revealed a *BCL6* rearrangement, with intact yellow fusion signals on two normal chromosome 3 and an inverted chromosome 3 showing loss of the spectrum orange (5′) signal and retention of the spectrum green (3′) signal, consistent with an inversion of *BCL6* gene.

An atypical variant *BCL6* gene rearrangement was detected with three copies of the *BCL6* gene, on two normal chromosome 3 and one on derivative 3 as a result of 3q27 inversion, resulting in *BCL6* rearrangement with loss of the 5′ Spectrum orange signal (►**Fig. 2B**).

Molecular testing was negative for the BRAF mutation.

Based on the diagnosis, the patient was initiated on Rituximab and Bendamustine, planned for 6 monthly cycles. However, after the first cycle, she developed sepsis with disseminated intravascular coagulation, bilateral pleural effusion, persistent fever, and altered consciousness. CT brain showed progression of hemorrhages with new hemorrhagic foci due to severe thrombocytopenia at presentation and sepsis following chemotherapy. Advanced imaging could not be performed due to the patient's critical postchemotherapy condition and requirement for mechanical ventilation. Despite rituximab–bendamustine therapy and intensive supportive care, including ICU admission, oxygen support, transfusions, and antibiotics, the patient developed refractory cytopenias, recurrent sepsis, progression of intracranial bleed, and seizures requiring mechanical ventilation. Due to a complicated clinical course, she ultimately succumbed to sepsis with multiorgan failure, reflecting the aggressive nature of the disease that posed challenges in management.

Discussion

The diagnosis of SBLPN, newly classified as HCL-V, remains challenging due to overlapping features with other B-cell neoplasms.[5]

Considering the differential diagnosis of splenic marginal zone lymphoma versus SBLPN, the presence of large prolymphocytes, absence of BRAF V600E mutation, and lack of CD5 expression supported the diagnosis of SBLPN.

We identified a novel double-hit mechanism involving the *BCL6* gene, with the presence of two distinct divergent *BCL6*-abnormal clones within a complex karyotype. One clone harbored an extra copy of derivative chromosome 3 with inv(3)(p13q27), leading to an atypical *BCL6* rearrangement with 5′ deletion, while the other showed a 3q deletion encompassing the *BCL6* locus with a separate pathogenic tumor suppressor mechanism. The karyotype revealed clonal evolution from a complex stemline clone of extra copy of chromosome 3 with inversion, 1q duplication, isochromosome 8q, deletions of 7p and 10p, a derivative chromosome 9 resulting from t(9;15) and 9p deletion, trisomy 18, and trisomy X. As illustrated in the figure (►**Fig. 2A**), subclonal trajectories evolved from this stemline to acquire additional aberrations such as 3q deletion, trisomy 14, isochromosome 14q, trisomy 14 and 4q deletion reflecting genetic instability.

The copy number alterations in this case, that is, gain of 1q, trisomy 3, trisomy 18, partial trisomy 8q, and deletion of 7p that have been independently linked to disease progression and poor prognosis in aggressive lymphomas, such as diffuse large B cell lymphoma (DLBCL).[2]

Although complex karyotypes are frequently observed in SBLPN, the cytogenetic profile in the present case deviated from the classical alterations reported in HCLv, that is, abnormalities involving 5q, 14q32, 8q24, deletions of 17p and 7q, and trisomy 12.

We observed partial trisomies of 1q, and 8q and complete trisomies of chromosomes 3, 14, 18, and X, along with losses in 9p and 10p.

Chromosome 1 abnormalities are common in human cancers, with 1q gain (+1q) being the most frequent secondary aberration in Burkitt lymphoma, often associated with aggressive disease.

Notably, 1q gain has not been reported in classical or variant HCL, making its duplication in this case a novel finding with potential prognostic significance.[6]

Additionally, the presence of two distinct clones involving chromosome 14, one with trisomy 14 and the other with isochromosome 14q;i(14q), suggests parallel clonal evolution involving the same chromosomal region through different mechanisms, both resulting in increased gene dosage.

While 3q27 translocations are common in B-cell neoplasms, the present case represents the first reported SBLPN with a novel inversion, inv(3)(p13q27).

A similar inversion involving 3p24 and 3q27 has been described in only two cases according to the Mitelman database; one in follicular lymphoma and another in undifferentiated pleomorphic sarcoma. Thus, our finding expands the spectrum of 3q27 rearrangements in SLBPN and introduces 3p13 as a novel partner region.[7,8]

BCL6 (3q27) is an oncogene encoding a transcriptional repressor critical for germinal center B cell development and immune responses. Rearrangements occur in 19 to 30% of DLBCL, which deregulate *BCL6* and drive lymphomagenesis.

The involvement of 3p13 in our case expands the spectrum of *BCL6* partner loci, highlighting inversion 3 as a potential atypical mechanism of *BCL6* dysregulation. To date, over twenty *BCL6* translocation partners have been identified, typically involving immunoglobulin gene enhancers. Further investigation to define the unrecognized partner gene at 3p13 is warranted to elucidate its pathogenic role. Although this finding may have prognostic and therapeutic significance similar to *BCL6*'s role in DLBCL, long-term follow-up is essential to inform clinical management.

Meta-analyses link *BCL6* rearrangements to poor prognosis in DLBCL, particularly with rituximab-based therapy, underscoring the importance of reporting such findings in SBLPN for prognostic significance.[9,10]

Subclonal *BCL6* rearrangement with partial 5′ deletion is a novel disruption mechanism affecting *BCL6* expression and pathogenesis.

BCL6 translocations in follicular lymphoma and DLBCL involve the major translocation cluster at the 5′ end, a hotspot for somatic hypermutation, causing balanced promoter substitutions, deregulating expression, and promoting lymphomagenesis by blocking differentiation and apoptosis. In the present case, the telomeric (5′) region of *BCL6* was lost (absent orange FISH signal), while the centromeric (3′) region remained intact and rearranged. The intrachromosomal inversion, inv(3)(p13q27), represents an unusual unbalanced *BCL6* rearrangement that repositions the 5′ promoter and exon 1 under the regulatory influence of a novel partner at 3p13, likely causing promoter substitution and transcriptional deregulation. Despite loss of the classical 5′ coding region, the retained 3′ segment may allow aberrant or chimeric expression, contributing to lymphomagenesis.

Another notable finding was the absence of *BCL6* protein expression on immunohistochemistry (IHC). Such discordance, reported in rare DLBCL cases, may result from epigenetic silencing, nonfunctional fusion transcripts, or technical limitations of IHC.[11]

SBLPN typically follows an aggressive clinical course and shows resistance to Cladribine monotherapy, though improved responses have been reported with combination regimens such as Rituximab or Bendamustine.[12,13]

Hence, this clinically aggressive and genetically complex case necessitated a comprehensive evaluation to clarify diagnosis, define prognosis, and guide treatment.

Conclusion

Given the ongoing debate surrounding the classification of SBLPN and its overlap with entities such as HCL-V and B cell neoplasms, an integrated diagnostic approach, encompassing clinical, morphological, histological, immunophenotypic, and genetic data, is essential for accurate diagnosis and effective management. Early multidisciplinary involvement and considering individualized treatment plans with potential modifications in chemotherapy could possibly improve outcomes, but salvage is often difficult in such advanced cases.

Incorporating such insights into diagnostic frameworks will be pivotal in advancing these entities from provisional

status to well-defined categories in current guidelines with evidence-based, targeted treatment options.

Authors' Contributions

S.M.A.A.: Concept, design, experimental studies, data analysis, manuscript preparation, manuscript editing, and manuscript review.
A.P.: Concept, literature search, data analysis, manuscript preparation, manuscript editing, and manuscript review.
R.H.M.I.: Experimental studies, hematopathology study, data analysis, manuscript editing, and manuscript review.
U.Z. and N.M.B.: Clinical study, treatment, data analysis, manuscript editing, and manuscript review.

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Conflict of Interest

None declared.

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