# Non-*IgH::BCL2* rearranged Follicular Lymphoma progressing to Diffuse Large B Cell Lymphoma in a patient with Wiskott-Aldrich syndrome and EBV viremia: B-Cell Lymphoma arising in a background of immunodeficiency and dysregulation

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## Introduction

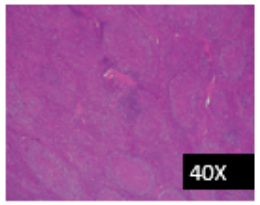
- Immune deficiency and dysregulation–associated lymphoproliferative disorders (IDD-LPDs) are a heterogeneous group classified based on immunodeficiency settings.
- The new framework for classifying IDD-LPDs integrates histological commonalities, variations in frequency, distinct causal associations, oncogenic virus involvement, and clinical or therapeutic implications. It employs a standardized, three-part nomenclature incorporating the histological lesion name, oncogenic virus presence or absence, and the clinical/immunodeficiency context.
- This approach facilitates comparative clinicopathological studies, clarifies shared and unique pathogenetic mechanisms, and recognizes that lymphoproliferation arises from immune deficiency, dysregulation, and hyperactivation, leading to the adoption of the term "immune deficiency and dysregulation–associated lymphoproliferative disorders.
- Lymphomas arising in patients with immune deficiency or immune dysregulation cover a spectrum of lymphoma types, and are frequently, but not exclusively, associated with EBV and/or KSHV/HHV8.
- Although IDD-associated B-cell lymphomas share some underlying pathogenesis, mechanisms specific to the immunodeficiency settings also play a role.

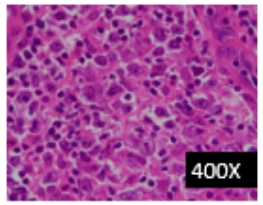
## Case Description

- 20-year-old male with an autosomal dominant variant of Wiskott-Aldrich Syndrome and EBV viremia, presenting with gradually progressive diffuse lymphadenopathy.
- An excisional biopsy of a left inguinal lymph node showed findings suspicious for lymphoid hyperplasia versus follicular lymphoma.
- Six months later, a subsequent excisional biopsy of an axillary lymph node showed extensive involvement by diffuse large B-cell lymphoma.

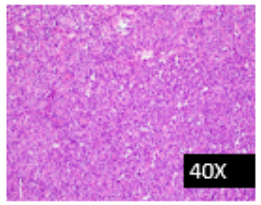
## Histology & Immunohistochemistry

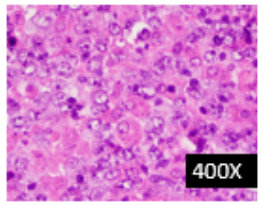
### Specimen 1

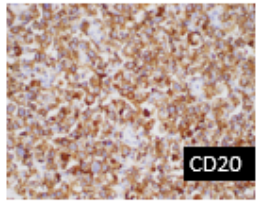


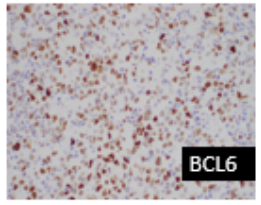



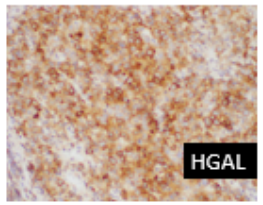

### Specimen 2

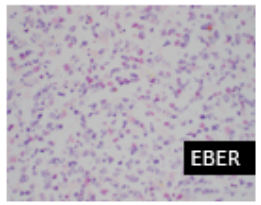



## Genomics

| Fluorescence in Situ Hybridization | t(14;18) | *BCL6* R | *MYC* R |
|---|---|---|---|
| **Specimen 1** | Negative | Positive | Not Performed |
| **Specimen 2** | Negative | Positive | Negative |

### Molecular Studies

**Specimen 1**

**NGS: *TNFRSF14* N116fs*117 (VAF: 8.7%)**
***CXCR4***
***NOTCH4***
***RAD54L***
***KMT2A***
***SPTA1***
***NKX2***
***TSHR***
**MGA**
**PTPRT**

**B-Cell Clonality: B CELL CLONE DETECTED IN A POLYCLONAL B CELL BACKGROUND (FR 3 (bp): 120.6; KA (bp): 145.35).**

**Specimen 2**

***NGS: TNFRSF14 N116fs*117 (VAF: 37.2%)***
***KRAS***
***TET2***
***BRAF***
***IGH-BCL7A rearrangement***
***IGH-BCL6 rearrangement***
***CD58***
***PIM1***

## Conclusions

- This is a challenging case of an unusual lymphoproliferative disorder initially interpreted to be an atypical IDD-associated hyperplastic lesion which rapidly progressed to diffuse large B cell lymphoma, EBV-negative.
- In the initial biopsy, NGS and FISH studies led to a revised interpretation of possible follicular lymphoma and a follow up biopsy showed clear DLBCL, likely clonally related.
- The initial and follow up biopsies showed some similarities (BCL6 / CD20+ B cell expansion with *BCL6* rearrangement and *TNFRSF14* mutation). The morphologic features and commutations were otherwise different between the two biopsies.
- The context of immunodeficiency and EBV viremia adds complexity, especially the negative EBER results in both lymphoma biopsies.
- It has been described that EBV+ DLBCLs arising in patients with IDD are most frequently of activated B-cell–like subtype, while EBV-negative DLBCLs presenting in patients with IDD are more often genetically similar to lymphomas in immunocompetent patients and also more often of germinal-center B-cell–like type.

## References

1. De Jong D, et al. Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation. In: WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2024 [cited 2025 01 06]. (WHO classification of tumours series, 5th ed.; vol. 11). Available from: https://tumourclassification.iarc.who.int/chapters/63.