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BTK INHIBITORS: A DOUBLE-EDGED SWORD IN RICHTER'S TRANSFORMATION TO PLASMABLASTIC LYMPHOMA? A CASE REPORT

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INTRODUCTION

- Richter's Transformation (RT) from Chronic Lymphocytic Leukemia (CLL) to Plasmablastic Lymphoma (PBL) is extremely rare and aggressive.
- We report a case of CLL with prior Bruton's Tyrosine Kinase inhibitor (BTKi) use, which evolved into PBL.
- This case highlights the potential association between BTKi therapy and transformation to plasmablastic morphology.

CASE CAPSULE

- A 57-year-old male with lymphocytosis, splenomegaly, and lymphadenopathy, leading to a diagnosis of CLL.
- LN Bx & FC: c/w CLL/SLL +CD 19/CD 20, CD 5, CD 23, CD 38 in 17% of cells and CT CAP- pathologic adenopathy in supraclavicular, lower neck and axilla and mediastinum, massive splenomegaly.
- (FCR) chemotherapy resulted in improvement in lymphadenopathy and had minimal residual disease.
- Recurrence (worsening lymphadenopathy). FC: 42% cells with monoclonal B cells- ZAP 70+/ IGVH unmutated (more aggressive features) CD 38 76% +Trisomy 12. CLL prognostic panel ZAP 70+, CD 38 +, B2 microglobulin 3.28 FISH + trisomy 12 TP 53 neg.
- Started (I) therapy but intolerable due to arthralgias. Started (A) therapy was introduced leading to a temporary decrease in adenopathy.
- CT Splenomegaly, S/p (BR) 6 cycles - leading to interval improvement
- Progression by worsening lymphadenopathy and peritoneal carcinomatosis.
- IR omental biopsy-diffuse aggressive NHL morphologically; Ki 67 100%, plasmacytoid immunoblastic and both CD 20 and PAX 5 are negative - suggestive of plasmablastic lymphoma
- Despite various treatments, including FCR (Fludarabine, Cyclophosphamide, and Rituximab), Bendamustine, Rituximab, and eventually Acalabrutinib, the disease progressed to PBL after years of remission.
- Treatment with Daratumumab and EPOCH x 5 cycles with a favorable response, followed by Teclistamab for BCMA-positive disease in March 2024, but the disease progressed rapidly.
- The patient experienced a rapid relapse and did not survive to undergo allogeneic stem cell transplantation (ASCT) and ultimately leading to death.

Abbreviations: Fludarabine (F), Cyclophosphamide (C), Rituximab (R), Ibrutinib (I), Acalabrutinib (A), Bendamustine (B), Daratumumab (D), Etoposide (E), Prednisone (P), Vincristine (O), Doxorubicin (H)

DISCUSSION

Richter's transformation

RT from CLL typically involves the development of aggressive lymphomas, with diffuse large B-cell lymphoma (DLBCL) being the most common type. Rarely, CLL may transform into other types like: [1]

- Hodgkin's lymphoma
- T-cell lymphoma
- Plasmablastic lymphoma
- B- cell prolymphocytic leukemia (B-PLL)
- Dendritic Cell Sarcoma
- Histiocytic Sarcoma

Literature review:

Case Reference	Gend	Age at diag.	BTKi/ duration (m)	Time to RT (m)	Site of RT	Clonally related (CLL/ PBL)	RT diagnosis	EBV	Clinical outcome
Current case	M	57	Y, 33	33	Lymph node	NS	PBL	NS	D, 6 m
Ramsey M et al.	M	71	Y,12	14	Lymph node	Y	PBL	Neg (EBER-ISH)	D, 19 m
Gángó A et al.	M	75	Y,18	52	Gingiva	NS	PBL	NS	D, 53 m
Marvyin K et al.	M	53	Y,24	93	Lymph node	Y	PBL	Neg (EBER-ISH)	D, 94 m
Chan KL et al.	M	63	Y, 96	102	GI	Y	PBL	Neg (EBER-ISH)	D, 102 m
Chan KL et al.	M	67	Y, 84	89	Lymph node	Y	PBL	Neg (EBER-ISH)	D, 92 m

- Most cases received Ibrutinib BTKi therapy and had an unfavorable outcome.[1-3]
- TP53abnormalities were the most common genetic change in RT–PBL.[1-3]

Genetic Mutations Contributing to Transformation

- **TP53 mutations**: One of the most common genetic alteration that is linked to aggressive disease progression and resistance to standard treatments.
- **NOTCH1 mutations**: Occurs in approximately 10-15% of CLL cases. Enhances the self-renewal capacity of CLL cells and may cooperate with other genetic abnormalities to drive transformation. (Rossi et al., 2012).
- **MYC amplification**: BTK inhibition may inadvertently promote MYC-driven transformation in subclones that have escaped BCR dependency (Swerdlow et al., 2016).

Our case underscores the potential for CLL to evolve into PBL, particularly in the context of prior BTKi therapy. Literature suggests that BTKi treatment might contribute to the selection and expansion of minor plasmablastic subclones through B-cell receptor (BCR) inhibition. Additionally, NOTCH1 mutations in CLL could further promote this transformation. This case emphasizes the necessity for close monitoring of CLL patients, especially those on BTK inhibitors, for early signs of transformation.

CONCLUSIONS

- Despite the rarity of PBL in CLL patients, this case underscores the importance of considering the potential for transformation, especially with the widespread use of BTK tyrosine kinase inhibitors.
- Further investigations, including cohort NGS analysis of PBL as RT cases, are warranted to identify unique genetic factors contributing to the development of PBL as RT over DLBCL.

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