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CASE REPORT

Clonally unrelated primary large B-cell lymphomas separated by over a decade involving the central nervous system and testicle: Possible predisposition to lymphomas of immune-privileged sites?

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Abstract

Primary large B-cell lymphomas of immune-privileged sites (IP-LBCLs) comprise LBCLs arising within "immune sanctuaries," including the central nervous system (CNS), vitreoretina, and testes. Although patients present with localized disease, the prognosis remains poor with high relapse rates, either at the originating site or within another immune-privileged site. Generally, in the presence of an antecedent IP-LBCL, subsequent LBCLs are expected to be clonally related. However, we present a primary CNS LBCL and later primary testicular LBCL in a middle-aged man, diagnosed over a decade apart, which proved to be clonally unrelated by targeted ultra-deep next-generation sequencing of the *IgH* locus.

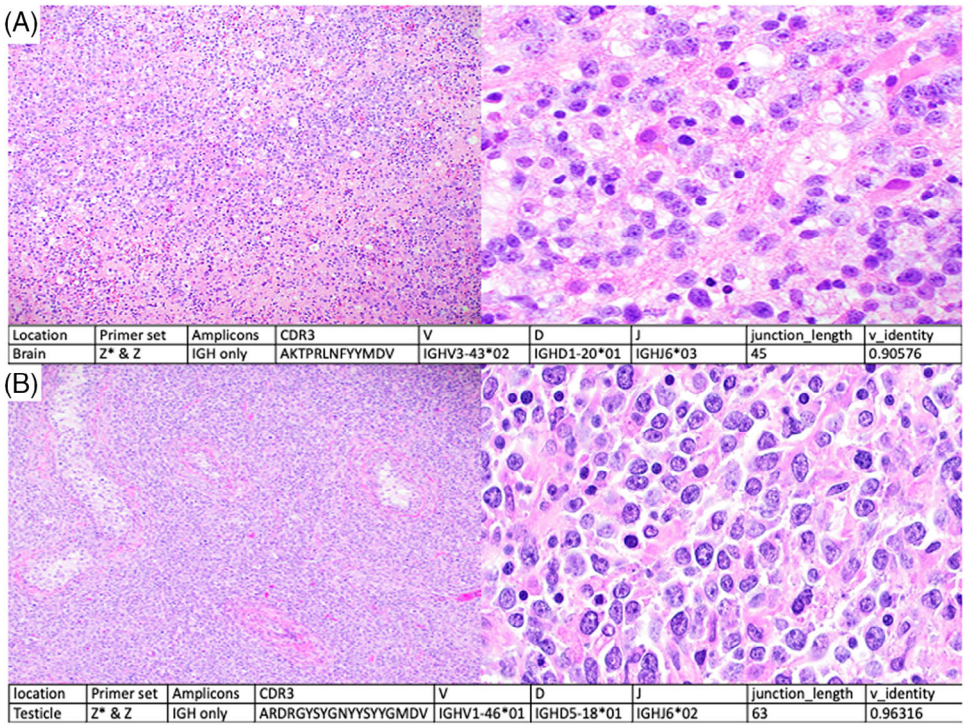
KEYWORDS
clonality, primary large B-cell lymphomas of immune-privileged sites

1 | INTRODUCTION

Primary large B-cell lymphomas of immune-privileged sites (IP-LBCLs) comprise LBCLs that arise within the central nervous system (PCNS-LBCL), vitreoretina (PVR-LBCL), and testes (PT-LBCL) [1]. PCNS-LBCL accounts for 2%–3% of all primary brain malignancies, whereas PVR-LBCL represents approximately 1% of all ocular tumors and PT-LBCL are responsible for 3%–9% of all testicular cancers in men older than 50 years [1, 2]. Although IP-LBCLs share common morphologic, immunophenotypic, and molecular features, the origin of the post-germinal center B-cell progenitor remains uncertain given that these immune-privileged sites lack normal lymphoid tissue [1]. Generally, however, it is assumed that IP-LBCLs arise due to decreased immune surveillance [3]. Although patients may present with localized disease, the overall prognosis remains poor, with high rates of relapse typically at the site of origin or within another immune-privileged site [1, 2, 4–6]. Previous studies suggest that IP-LBCL relapses are generally clonally related to the primary tumor by means of linear or parallel evolution [2, 4, 7–10].

Here, we describe the occurrence of PCNS-LBCL, followed by PT-LBCL in a middle-aged man, diagnosed over a decade apart. Clonality assessment performed by targeted ultra-deep next-generation sequencing (NGS) of the immunoglobulin (*IgH*) locus revealed that the two cases were not, in fact, clonally related. To our knowledge, this phenomenon has not yet been fully evaluated in literature.

Giby V. George and Diana G. Aldowitz contributed equally to this work.



Location	Primer set	Amplicons	CDR3	V	D	J	junction_length	v_identity
Brain	Z* & Z	IGH only	AKTPRLNFYYMDV	IGHV3-43*02	IGHD1-20*01	IGHJ6*03	45	0.90576

location	Primer set	Amplicons	CDR3	V	D	J	junction_length	v_identity
Testicle	Z* & Z	IGH only	ARDRGYSYGNYYSYYGMDV	IGHV1-46*01	IGHD5-18*01	IGHJ6*02	63	0.96316

FIGURE 1 Primary large B-cell lymphomas of immune-privileged sites involving the central nervous system and testicle. (A) Brain tissue showing a diffuse, dense infiltrate composed of large neoplastic cells with immunoblastic features. (B) Testicular tissue demonstrating a diffuse, dense infiltrate composed of large neoplastic cells with immunoblastic features. *IGH* clonality assessment (framework 2 through J) performed on both specimens (A and B) showed two distinct CDR3 sequences and VDJ products.

2 | CASE PRESENTATION AND DISCUSSION

A 47-year-old male with no significant medical or family history presented in 2008 with intermittent confusion and falls. Brain magnetic resonance imaging (MRI) revealed a deep, right-sided enhancing lesion involving the corpus callosum splenium, right corona radiata, and centrum semiovale with no evidence of systemic disease. Pathology evaluation was consistent with a primary central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL) of non-germinal center subtype (non-GCB) (Figure 1A). He was treated with five cycles of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) prior to undergoing to autologous stem cell transplantation (ASCT).

He remained asymptomatic until 2022, at which time he presented with diffuse enlargement of the right testicle. Scrotal ultrasound and Doppler revealed significant right testicular enlargement ($5.1 \times 3.2 \times 4.6$ cm) with diffuse, heterogenous, and coarse echotexture and markedly increased blood flow. Testicular tumor markers, including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH), were within normal limits. He subsequently underwent a right radical orchiectomy.

Pathology evaluation revealed serial sections of testicular tissue involved by DLBCL (non-GCB) (Figure 1B). Interphase fluorescence in situ hybridization (FISH) demonstrated copy number gain of the *BCL2* (18q21) locus in 29.5% of nuclei, with no evidence of *BCL6* (3q27), *IgH/MYC*, or *IgH/BCL2* rearrangements. To further understand the clonal relationship between the patient's PCNS-LBCL and subsequent PT-LBCL, *IgH* clonality assessment (framework 2 through J) was performed on both specimens using NGS based on Burack et al. [11]. Sequencing demonstrated unique CDR3 segments of different amino acid sequence and length, supportive of clonal unrelatedness of the two lymphomas (Figure 1A,B). NGS analysis to evaluate for the presence of *MYD88* and *CD79B* mutations on the two specimens was precluded by tissue exhaustion.

Although the patient achieved complete response following six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), intrathecal methotrexate/hydrocortisone, and scrotal radiation consolidative therapy (3060 cGy), he presented again in 2023 with chest and back pain. Computed tomography (CT) chest showed multiple, bilateral enlarged tracheal, sub-carinal, hilar, and mediastinal lymph nodes (largest 3.7 cm), and bilateral parenchymal lesions within the left lower lobe (10.6 cm in the greatest diameter) and right lower lobe (5.4 cm in the greatest diameter). Microscopic evaluation of a cell block of a subsequent bronchoalveolar lavage/fine-needle aspiration specimen was consistent with a diagnosis of DLBCL, non-GCB subtype. A concurrent punch biopsy of an abdominal plaque also demonstrated cutaneous involvement by DLBCL. Study of clonal relatedness of these two lymphomas to the brain and testicular lymphomas was not feasible. Given the patient's clinical progression and extensive disease, he was admitted for salvage treatment with rituximab, dexamethasone, cytarabine, and oxaliplatin, followed by CD19-targeted CAR

T-cell therapy with axicabtagene ciloleucel. He later experienced disease progression, and is presently being managed with a CD20×CD3 bispecific antibody (glofitamab).

Here, we describe the occurrence of two clonally unrelated IP-LBCLs in a middle-aged man, diagnosed over a decade apart. PCNS-LBCLs and PT-LBCLs are known to harbor frequent *MYD88* mutations, often with concomitant *CD79B* variants. Chapuy et al. previously reported 9p24.1/programmed cell death ligand (PD-L1/2) copy number alterations and translocations with associated protein overexpression in IP-LBCLs [12]. PD-1 and the PD-L1 and PD-L2 ligands are known to play a pivotal role in T-cell repression in the tumor microenvironment, both in solid tumors and hematologic malignancies. However, Minderman et al. recently demonstrated infrequent PD-L1 expression in PCNS-LBCL, but confirmed loss of HLA class I and II expression, which may partly explain their capability for immune evasion [13].

We posit whether our case might represent an exceedingly rare instance in which the patient may possess a predisposition to developing IP-LBCLs [2, 8]. Alternatively, his ASCT and associated immunosuppression may have placed him at an increased risk for developing another IP-DLBCL and subsequent recurrences. As standard DLBCL treatment regimens are largely ineffective in PCNS-LBCL given the poor blood–brain barrier penetrance, induction with high-dose chemotherapy (HDC) followed by consolidation therapy and ASCT is presently standard-of-care [14]. However, this treatment strategy is associated with a greater degree of myeloablation [14], which may perhaps enhance susceptibility to secondary malignancies.

3 | CONCLUSION

Whether the association between these two clonally unrelated IP-LBCL diagnoses in our case is coincidental or suggests an underlying predisposition remains unknown. Regardless, given that patients with IP-LBCLs are living longer, further evaluation of similar cases may prove valuable in understanding the biology and clonal evolution of IP-LBCLs.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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The study was not supported by a sponsor or funding agency.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

The authors have confirmed that an ethical approval statement is not required for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed that a patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed that clinical trial registration is not required for this submission.

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