Not all central nervous system lymphomas are created equal

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In this issue of *Haematologica*, Wight et al. present a comprehensive genomic analysis of patients with systemic diffuse large B-cell lymphoma (DLBCL) that has disseminated to the central nervous system (CNS).

Secondary CNS lymphoma (SCNSL) is an infrequent but devastating complication associated with poor outcomes and restricted long-term survival. SCNSL may occur at diagnosis or after frontline immunochemotherapy with isolated CNS involvement or concomitant CNS and systemic disease. It frequently occurs at first relapse within one year from the initial presentation, suggesting undetected CNS involvement might have been present from diagnosis. Clinical factors associated with a higher risk for CNS involvement have been extensively described, including nongerminal center phenotype, overexpression of MYC and BCL2 proteins, high-grade B-cell lymphoma with MYC and BCL2 rearrangements, cutaneous leg-type DLBCL, and specific extranodal sites such as bone marrow, testis, uterus, kidney, adrenal gland or breast. However, genomic drivers triggering CNS dissemination are poorly understood.

In 2018, two studies implemented multiplatform genomic analysis refining DLBCL into biologically different clusters. Genomic signatures assigned to clusters C5 and MCD (MYD88 and CD79b), both primarily associated with an activated B-cell-like DLBCL phenotype, appear to be associated with extranodal tropism, including CNS
In a subsequent study focusing on genomic signatures associated with CNS dissemination, *PIM1* (38%) was the most common mutated gene, followed by *MYD88* and *KMT2D* (31%). Similar to prior studies, SCNSL was associated with a higher prevalence of genes enriched in the MCD cluster.\(^8\)

In the present study,\(^1\) authors conducted targeted panel sequencing, copy number analysis, and gene expression profiling for cell of origin and immune gene signatures on 41 patients with EBV-negative SCNSL collected at three tertiary centers in Australia. The authors hypothesized that cases with CNS dissemination molecularly resemble primary CNS lymphoma when compared to a third cohort of systemic DLBCL NOS without CNS involvement. Among the 41 biopsies, 36 were obtained at diagnosis and five at relapse, with most from systemic (83%) rather than CNS (17%) sites. Gene expression profiling of the SCNSL samples demonstrated a predominance of germinal-center (48%) followed by activated B-cell (34%) signatures. Only one case of paired systemic (at diagnosis) and CNS (at relapse) biopsies was available, preventing a robust analysis of tumor spatial heterogeneity between compartments and clonal evolution after frontline immunochemotherapy. Upon genomic interrogation of cases with CNS dissemination, the authors observed common mutations in the B-cell receptor signaling (*MYD88*, mostly *L265P*, and *CD79b*) associated with functional loss in antigen presentation and immune surveillance (*CD58*, *B2M*, *CIITA*, and *MHC*), and tumor suppressor genes (*TP53* and *CDKN2A*) with uncommon gains in *PDL1/PDL-2* (Figure).

The current study provides relevant insight into the similarities to primary CNS lymphoma, including an underlying chronic active B-cell receptor and NF-kB signaling with enrichment aberrations in antigen presentation and immune surveillance, but
fundamental differences. These abnormal signatures were less frequent, underscoring the genomic heterogeneity in patients with SCNSL. A notorious finding was the higher frequency of germinal-center phenotype, which opposes prior observations of an activated B-cell phenotype predominance.\(^8,9\) The authors attribute the risk for CNS invasion to a higher incidence of \textit{MYC} rearrangement and antigen presentation/immune surveillance abnormalities in this population. These discrepancies are poorly understood and highlight the need for collaborative larger efforts to decode the genomic makeup of a rare disease such as SCNSL.

Overall, these findings support the rationale for testing similar therapies previously evaluated in primary CNS lymphoma, such as using BTK inhibitors-based approaches. One example is the TEDDI-R (ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, and rituximab) program, which achieved an impressive preliminary overall response rate of 96% with a complete response of 71% in ibrutinib-responder patients with SCNSL especially in those enriched with the MCD cluster.\(^10\) Contrary to studies in primary CNS lymphoma that demonstrated frequent structural variants located in 9p24.1 (PD-L1/PD-L2), the present study describes abnormalities in only 5% of the patients with SCNSL. This result correlates with the lack of efficacy of checkpoint inhibitors in systemic DLBCL with probable similar results in those with CNS invasion.\(^11\)

The best strategy to improve outcomes in patients with SCNSL is largely unknown. The international MARIETTA study represents the only large effort evaluating a treatment program focused on patients with SCNSL. Furthermore, CNS involvement represents a common exclusion criteria in most clinical trials testing novel agents such
as CD3xCD20 bispecific T-cell engaging antibodies and chimeric antigen receptor T-cell therapy. An important reason for lack of significant advances in drug development in this disease is the lack fundamental understanding of the underlying biological mechanisms associated with this event. The study conducted by Wight et al. represents a step forward in our understanding of SCNSL associated with an opportunity to develop therapeutical strategies toward overcoming present outcomes.
References

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Figure.

Mutational landscape of primary CNS lymphoma and secondary CNS lymphoma. Abnormalities observed in ≥50% (↑↑↑), ≥30% (↑↑), ≥10% (↑), and <10% (↔) of the cases.
Primary CNS lymphoma

- MYD88/CD79b
- CD58 loss
- CIITA loss
- B2M loss
- CN loss 6p
- 9p24 gain
- TP53 aberration
- CDKN2A loss

Secondary CNS lymphoma

- MYD88/CD79b
- CD58 loss
- CIITA loss
- B2M loss
- CN loss 6p
- 9p24 gain
- TP53 aberration
- CDKN2A loss