Not all central nervous system lymphomas are created equal

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In this issue of *Haematologica*, Wight *et al.*[1] 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.[2,3] SCNSL may occur at diagnosis or after front-line 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.[4] Clinical factors associated with a higher risk for CNS involvement have been extensively described, including non-germinal 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.[5] 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 dissemination.[6,7] 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] the authors conducted targeted panel sequencing, copy number analysis, and gene expression profiling for cell of origin and immune gene signatures on 41 patients with Epstein-Barr virus-negative SCNSL collected at 3 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 not otherwise specified (NOS) without CNS involvement. Among the 41 biopsies, 36 were obtained at diagnosis and 5 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 front-line 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 1).

The current study provides an important insight into the similarities to primary CNS lymphoma, including an underlying chronic active B-cell receptor and NF-κB signaling with enrichment aberrations in antigen presentation and immune surveillance, but also some fundamental differences. These abnormal signatures were less frequent, underscoring the genomic heterogeneity in patients with SCNSL. A striking finding was the higher frequency of germinal-center phenotype, which is in contrast to prior observations of an activated B-cell phenotype predominance.[8,9] The authors attribute the risk for CNS invasion to a higher incidence of *MYC* rearrangement and antigen presentation / immune surveillance abnormalities in this population. These discrepancies are poorly understood and highlight the need for larger, collaborative efforts to decode the genomic makeup of rare diseases, such as SCNSL.

Overall, these findings support the rationale for testing similar therapies previously evaluated in primary CNS lymphoma, such as using Bruton's tyrosine kinase inhibitor-based ap-

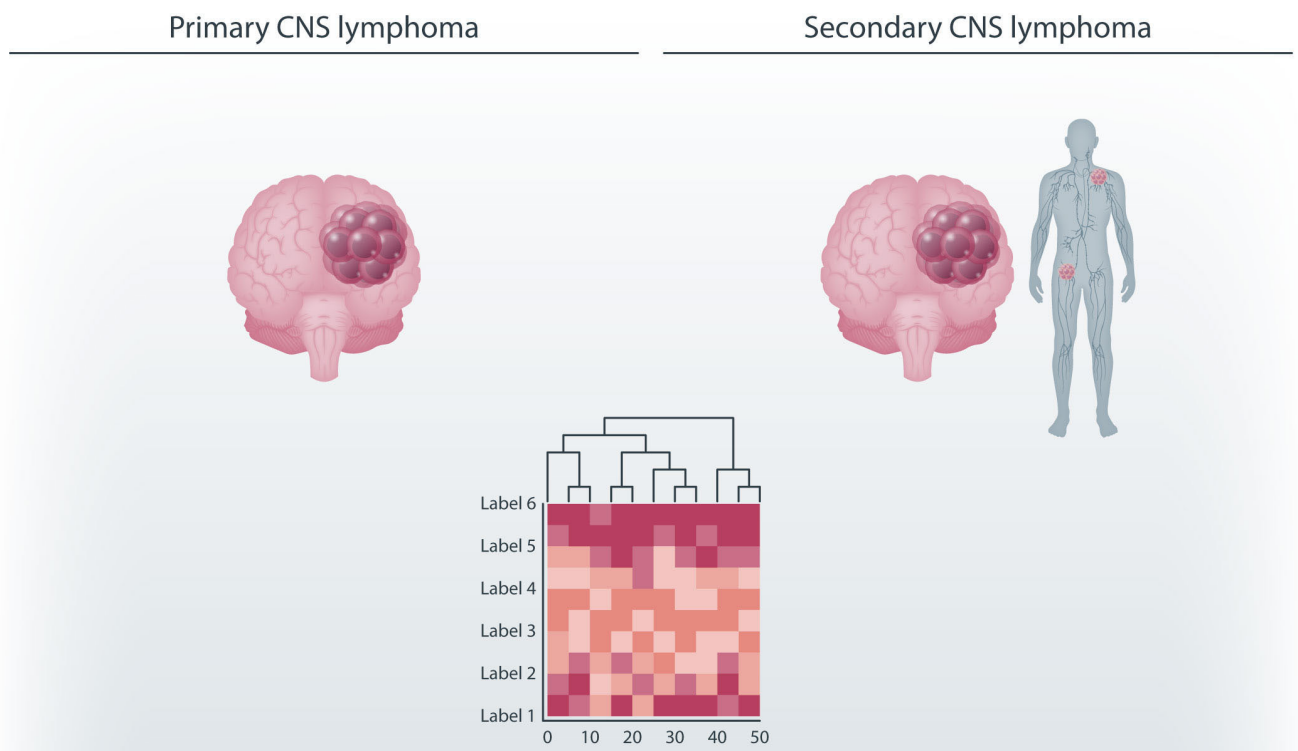

Figure 1. Mutational landscape of primary and secondary central nervous system lymphoma. Abnormalities observed in ≥50% (↑↑↑), ≥30% (↑↑), ≥10% (↑), and <10% (↔) of the cases.

proaches. One example is the TEDDI-R program (ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, and rituximab), which achieved an impressive preliminary overall response rate of 96%, with a complete response of 71% in ibrutinib-responder patients with SCNSL 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 possibly similar results to those with CNS invasion.[11]

The best strategy to improve outcomes in patients with SCNSL remains 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 the fact that there have been no significant advances in drug development in this disease is the lack of a fundamental understanding of the underlying biological mechanisms associated with it. The study conducted by Wight *et al*. represents a step forward in our understanding of SCNSL, which can help promote the development of therapeutic strategies aimed at improving the current poor outcomes.

Disclosures

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Contributions

Both authors wrote the manuscript.

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