Have we truly uncovered the key to primary vitreoretinal lymphoma's pathway to the central nervous system?

The article by Kota Yoshifuji and colleagues[1] presents a significant contribution to the field of primary vitreoretinal lymphoma (PVRL), a rare and aggressive subtype of diffuse large B-cell lymphoma (DLBCL). This study's focus on the impact of genetic alterations on the central nervous system (CNS) progression of PVRL is particularly noteworthy, given the high rate of CNS progression in these patients and the consequent need for improved prognostic markers and therapeutic targets. This study identified *ETV6* loss and *PRDM1* alteration as candidate risk factors associated with CNS progression in PVRL, and introduced a genetics-based CNS progression model that categorizes patients into slow-, intermediate-, and rapid-progression groups based on the presence of *ETV6* loss and *PRDM1* alteration, which may guide future clinical practice in choosing optimal strategies for PVRL patients with different risks. It seems that we have uncovered the key to PVRL's pathway to the CNS, but we are far from there. Detailed information concerning the treatments for each patient and laboratory tests of cerebrospinal fluid (CSF) were not provided in this study, which may hinder our correct interpretation of the findings from this study.

No standard treatment strategies have been defined for PVRL due to the rarity, and CNS prophylaxis is generally recommended, although the best prophylactic treatment and optimal time point are not yet known. Lam *et al.*[2] demonstrated that intravenous high-dose methotrexate (IV HD-MTX)-based systemic therapy was efficient to prevent brain relapse with the median brain-free survival being 73 months. Thus, IV HD-MTX is often provided to patients with PVRL. In the current study reported by Kota Yoshifuji and colleagues,[1] 16 of 36 patients did not receive systemic HD-MTX, and subsequently 19 of 36 patients developed CNS progression. Since no detailed information concerning individualized treatment was provided, we cannot help but consider that it may be the patients who did not receive HD-MTX that experienced more CNS progression, which may obviously affect the identification of candidate genetic alterations, unless patients treated with or without HD-MTX were balanced in those with CNS progression. Similar with the role of IL-10/IL-6 in diagnosing PVRL, this ratio in CSF could be helpful in early detection of CNS progression when no obvious lesions are found in brain through magnetic resonanace imaging scan.[3] However, no detailed laboratory tests of CSF were provided in the current study, which may biased the basic status of CNS progression in those 36 PVRL patients.

In this study, the authors conducted a comprehensive genetic analysis using whole-exome sequencing and amplicon sequencing on vitreous humor samples from 36 PVRL patients. This approach is commendable as it leverages next-generation sequencing technologies to uncover the genetic landscape of the disease, which is crucial for understanding its pathogenesis and identifying potential therapeutic vulnerabilities. Consistent with previous studies,[4,5] *MYD88* L265P and/or *CD79B* mutations, *PIM1*, and *CDKN2A/B* alterations were most found in PVRL patients. As the MCD subtype of DLBCL, PVRL may be sensitive to BTK inhibitors. Guan *et al.*[6] found that monotherapy with BTK inhibitors could induce quick local response in the eyes, but this strategy did not reduce the risk of CNS progression and improve PVRL prognosis.[7] Thus, future prospective trials are urgently needed to explore more efficient CNS prophylaxis strategies. As hinted in this study, BTK inhibitors or immunotherapy targeting PD-1/PD-L1 may be added to systemic HD-MTX to further reduce the risk of CNS progression for PVRL patients.

In conclusion, Yoshifuji *et al.*'s study[1] represents an important step forward in the molecular characterization of PVRL. The identification of genetic risk factors and the development of a prognostic model are promising advancements that could lead to more personalized and effective treatment strategies for patients with PVRL. While the study's limitations suggest the need for further research, its findings provide a solid foundation for future investigations and highlight the importance of integrating genetic information into clinical decision-making in PVRL management.

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Disclosures

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