Molecular Cytogenetic Features of Primary Central Nervous System Lymphomas

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Introduction

Primary central nervous system lymphomas (PCNSL) are rare and account for 1% of non-Hodgkin lymphomas and 5% of primary brain tumors. The clinical course is often aggressive with a poorly understood biology. Due to clinical heterogeneity and lack of prognostic biomarkers, effective and less toxic therapies are yet to be discovered.

Array-comparative genomic hybridization (a-CGH) is a powerful technique to explore copy number changes in tumor DNA that can reveal more regional copy numbers to use for cancer prediction. We aim to study chromosomal changes in PCNSL using a-CGH.

Methods

Cases with diagnosis of PCNSL diagnosed between 2004 and 2014 at our institution were reviewed. Cases with secondary involvement of CNS by diffuse large B-cell lymphoma (DLBCL) were excluded as well as HIV+ PCNSL. Clinicopathological parameters retrieved from electronic medical charts included age, sex, medical history, location of lymphoma, phenotype and when available molecular testing results. a-CGH was performed at Cancer Genetics on each case using formalin-fixed-paraffin-embedded Tissue following DNA qualification and quantification.

Results

42 cases of PCNSL without HIV infection were included in the study. The diagnosis was confirmed for each case according to the WHO diagnostic criteria (figure 1).

Results (cont)

The median age was 68 years (ranging 29 to 86) with a male:female ratio of 1.75 (M=21, F=12). Tumor DNA was extracted from microdissection of unstained slides cut from FFPE blocks. The DNA yield was sufficient in 30 samples to perform a-CGH using Agilent 8x60K array. The analysis revealed presence of gain in chromosomes 12 and 18 in 30% and 23% of the cases and loss of 6q in 40% of the cases, similar to the literature. Interestingly, there was a focal gain in 2q22.3 that contains the gene *ZEB2* in 27% of cases (n=8) as well as gain in 4q24 that contains *BANK1* and *UBE2D3* genes in 20% (n=6) cases (figure 2).

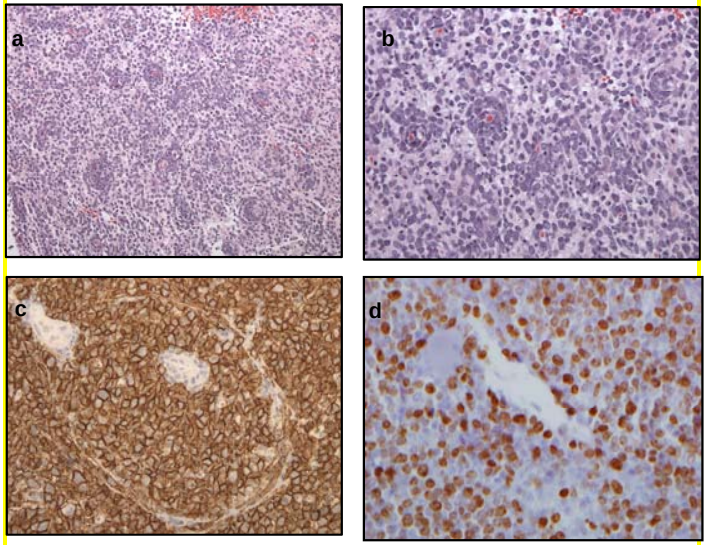

Figure 1. PCNSL involving brain parenchyma in a diffuse pattern (a) with typical perivascular concentration (b). Lymphoma cells are diffusely positive for CD20 (c) with a high Ki-67 proliferation rate (d)

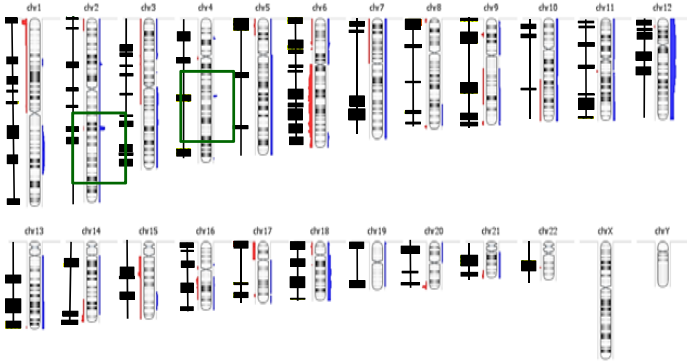

Figure 2. Gain in chromosome 2q22.3 (n=8, 27%) and 4q24 (n=6, 20%) Each found in 2/240 (0.8%) cases of DLBCL.

Discussion

The common cytogenetic abnormalities defined in PCNSL include *BCL6* translocation, del 6q and gains of 12q, 22q and 18q (1-3). *ZEB2* is a Zfh1 family of 2-handed zinc finger/homeodomain proteins that controls cell proliferation in forebrain, hippocampus development, nervous system development, neural crest cell migration, neural tube closure, positive regulation of JUN kinase activity and WNT signaling pathway (4). This might suggest that PCNSL has a characteristic signature that is specific to neural origin cells. *BANK1* is a B-cell scaffold protein with ankyrin repeats that is known to be involved in B-cell activation and *UBE2D3* is a ubiquitin-conjugating enzyme that is known to function in the ubiquitination of *TP53* which is rarely seen in DLBCL. Our study results suggest that PCNSL has a unique signature that differs from DLBCL. *ZEB2, BANK1* and *UBE2D3* genes function in important pathways for cell proliferation and apoptosis and are potential targets for targeted therapies in this aggressive disease.

References

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