

CASE REPORT

Primary large B-cell lymphoma of the central nervous system with cyclin D1 expression and t(11;14) (*IGH-CCND1*): Diffuse large B-cell lymphoma with *CCND1* rearrangement or mantle cell lymphoma?

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Abstract

Mantle cell lymphomas (MCLs) are the prototypic B-cell non-Hodgkin lymphomas defined by cyclin D1 gene (*CCND1*; or other cyclin D family gene) rearrangements. However, extremely rare cases of diffuse large B-cell lymphomas (DLBCLs) harboring *CCND1* rearrangements, resulting in cyclin D1 protein expression, have also been reported. In this report, we describe an unusual primary large B-cell lymphoma of non-germinal center immunophenotype of the central nervous system (CNS) in an elderly male patient, which was negative for CD5 and SOX11, and exhibited cyclin D1 expression. Fluorescence in situ hybridization analysis detected *IGH-CCND1* and *BCL6* rearrangements. This case may represent the first report of a primary CNS DLBCL with *IGH-CCND1* rearrangement. The clinico-pathologic features that can help differentiate primary CNS MCL from primary DLBCL of the CNS with *IGH-CCND1* rearrangement are discussed.

KEYWORDS

cyclin D1, diffuse large B-cell lymphoma, mantle cell lymphoma, pleomorphic/blastoid, primary CNS, t(11;14)

1 | INTRODUCTION

The cell cycle regulator cyclin D1 plays a critical role in the G1-S cell cycle transition, and its aberrant expression is implicated in the pathogenesis of a number of hematologic neoplasms, including the vast majority (>95%) of mantle cell lymphomas (MCLs), a large proportion (40%) of plasma cell neoplasms, and in nearly all hairy cell leukemias. Since cyclin D1 expression is uncommon in other B-cell neoplasms, its detection is a valuable tool in discriminating MCL from other B-cell neoplasms, which can display similar cytomorphologic or immunophenotypic features. Importantly, near uniform cyclin D1 expression allows distinction of large cell variants of MCL (pleomorphic and blastoid), which are aggressive forms of MCL, from diffuse large B-cell lymphomas (DLBCLs), a fraction

of which may exhibit variable degrees of cyclin D1 expression.^{1,2} The chromosome rearrangement t(11;14)(q13;32), which juxtaposes the *CCND1* region on 11q13 with the immunoglobulin (Ig) heavy-chain joining region on chromosome 14q32, is a critical oncogenic driver of MCLs and a subset of plasma cell neoplasms and the basis of aberrant cyclin D1 expression in these neoplasms.^{3,4} On the other hand, an increase in *CCND1* copy number is considered responsible for cyclin D1 expression in HCL and certain DLBCLs.^{1,5} Over the past decade, only rare systemic DLBCLs with *CCND1* rearrangement have been reported, challenging the specificity of this genomic alteration for MCL.^{6,7} Here we describe an unusual case of primary large B-cell central nervous system (CNS) lymphoma with cyclin D1 expression and t(11;14) (*IGH-CCND1*) and review the relevant literature.

2 | METHODS

2.1 | Morphologic and immunophenotypic analyses

Formalin-fixed, paraffin embedded (FFPE) sections of core biopsies were stained with Hematoxylin and Eosin for morphologic assessment. Immunohistochemical (IHC) staining with a comprehensive panel of antibodies and in situ hybridization staining was performed as previously described.⁸

2.2 | Flow cytometry

Multi-color FC analysis was performed on fresh biopsy suspensions as previously described.⁹ Multi-color FC antibody panels included B-cell (CD19, CD20, CD45, surface κ , surface λ , CD10, CD5, CD43, CD103, CD23, CD38, FMC7, CD11c, CD30, CD34, CD52, IgM, IgD, cytoplasmic IgM, cytoplasmic CD79a, and TdT) and plasma cell (CD138, CD38, CD117, CD56, CD27, CD28, CD45, CD19, CD20, cytoplasmic κ , and cytoplasmic λ). All antibodies were obtained from BD Biosciences (San Jose, CA). Data was analyzed using FCS Express Version 7 software (De Novo Software, Los Angeles, CA).

2.3 | Fluorescence in situ hybridization analysis

Fluorescence in situ hybridization (FISH) analysis was performed on FFPE sections according to standard methods using the following probes: dual fusion probes targeting *14q32/11q13* (*IGH/CCND1*) and *14q32.2/18q21* (*IGH/BCL2*) and break apart probes targeting *3q27* (*BCL6*) and *8q24* (*MYC*) (Vysis; Abbott Molecular, Des Plaines, IL).

3 | CASE SUMMARY

The patient is an 81-year-old immunocompetent man who presented with 2 months of cognitive decline and gait instability. An outpatient evaluation with brain magnetic resonance imaging (MRI) revealed T2/fluid-attenuated inversion recovery hyperintense focally enhancing lesions in the right cingulate gyrus and along the right posterior periventricular white matter (Figure 1). His symptoms progressively worsened, and he developed left-sided weakness prompting an admission to a local hospital, where work-up including contrast-enhanced MRI of the spine and computerized tomography imaging of the chest and abdomen were unremarkable. He was transferred to our institution for further management. His exam was notable for left hemiparesis and inability to walk independently. A repeat MRI showed marked increase in size of now homogeneously enhancing right cingulate gyrus mass, measuring 3 x 4 cm with associated vasogenic edema and diffusion restriction (Figure 1). Cerebrospinal fluid analysis was significant for elevated protein, white blood cells (WBCs) count of 6 (55% lymphocytes), negative cytology, however, limited flow cytometry

(FC) analysis due to low cellularity. Complete blood count, lactate dehydrogenase, and beta-2 microglobulin were normal. The patient underwent stereotactic biopsy of the enlarging mass. Pathology revealed a large B-cell lymphoma with activated B-cell phenotype and aberrant cyclin D1 expression, and cytogenetic analysis detected evidence of t(11;14) translocation with *CCND1* rearrangement.

In the post-surgical period, staging, including a repeat MRI of the spine, ophthalmologic evaluation, positron emission tomography scan of the body, testicular ultrasound, peripheral blood FC, and bone marrow biopsy, did not reveal organomegaly, lymphadenopathy, or any additional sites of disease. Viral studies for human immunodeficiency virus and Epstein-Barr virus were negative. The patient received high-dose methotrexate (HD-MTX)-based induction therapy with MT-R (HD-MTX, temozolomide, rituximab) per Cancer and Leukemia Group B (CALGB) 50202 protocol.¹⁰ He achieved complete clinical and radiographic response (CR) with a total of seven HD-MTX cycles. MRI at end of treatment showed a minimal residual patchy enhancement most consistent with post-operative changes (Figure 1). He then received consolidation therapy with two cycles of high-dose cytarabine (3 g/m²) given every 4 weeks. The patient remains in remission almost a year after CR.

4 | RESULTS AND DISCUSSION

The biopsy sections showed brain parenchyma with infiltrates of atypical pleomorphic lymphocytes in a perivascular/angiocentric distribution (Figure 2). The cells are medium to large in size with coarsely clumped chromatin, variably distinct small nucleoli, and little eosinophilic cytoplasm. Apoptotic debris was noted and a few scattered small lymphocytes were present. The atypical cells were positive for PAX5, BCL6, MUM1, Cyclin D1 (strong and diffuse), and BCL2 and negative for CD5, CD10, and SOX11 (Figure 2). The Ki-67 proliferation index was 70%. Approximately 5% of lymphocytes expressed C-MYC. Stains for CD3 and CD5 highlighted small T-cells in the background. In situ hybridization for EBER was negative. FC detected a population of lambda light chain-restricted B-cells (85% of gated lymphocytes), which expressed CD20, CD19, CD79a, HLA-DR, FMC7 (bright), CD25, and IgM and were negative for CD10, CD5, CD38, CD11c, CD103, CD30, CD43, and IgD.

FISH analysis demonstrated *IGH/CCND1* and *BCL6* (3q27) rearrangements in 96% of cells (Figure 3). *IGH/BCL2* translocation and *MYC* break-apart probes were negative for rearrangement, but detected multiple copies of *IGH*, *BCL2*, and *MYC*, consistent with near tetraploidy (polyploidy). The bone marrow aspirate showed a normal karyotype with no evidence of *CCND1* rearrangement by FISH analysis.

Thus, the patient's large B-cell lymphoma exhibited a non-germinal center (GC) phenotype, with strong and diffuse cyclin D1 expression and an absence of extra-CNS disease. This lymphoma raises the challenging differential diagnosis of an unusual aggressive variant of MCL with a primary CNS presentation vs a primary CNS

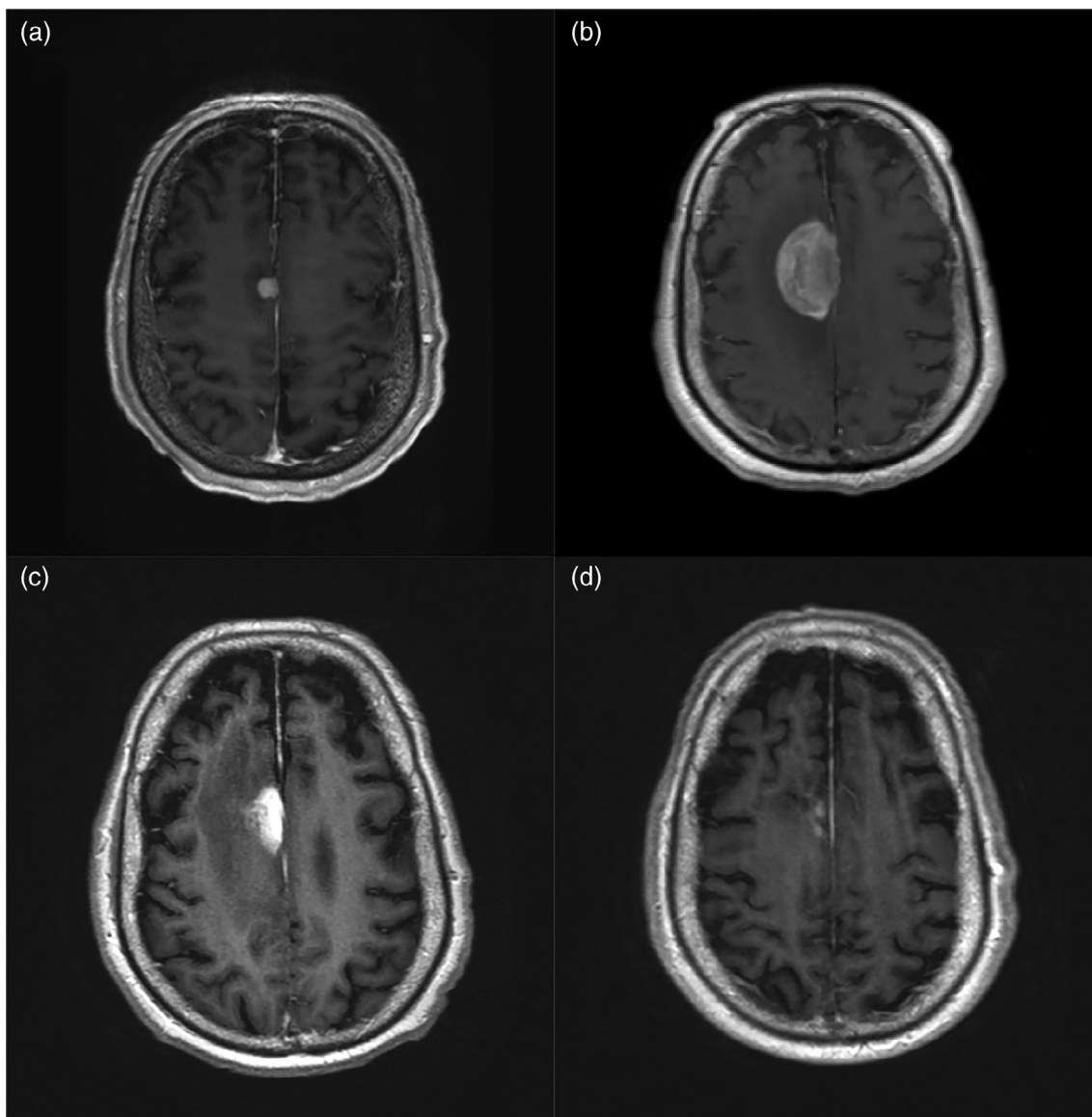


FIGURE 1 MRI images. Post-contrast T1-weighted MRI images demonstrating (a) small enhancing mass in the right cingulate gyrus at time of presentation. (b) Significant increase in size of the lesion 4 weeks later. (c) Partial response after first cycle of methotrexate, rituximab, temozolomide. (d) Complete response following treatment completion

DLBCL with cyclin D1 expression associated with *IGH-CCND1* rearrangement.

Primary central nervous system lymphomas (PCNSLs) account for approximately 4% of all brain tumors and less than 1% of all non-Hodgkin lymphomas.^{11,12} They are most commonly represented by DLBCL of non-GC or activated B-cell phenotype (express *BCL6* and *MUM1*), whereas *CD10* expression is rare, and the vast majority (>80%) are double expressors of *BCL2* and *MYC*.¹³ The frequency of *BCL6* rearrangements (17%) is considerably less common than in DLBCL arising outside the CNS, while rearrangements of *MYC* and *BCL2* are essentially not seen.^{13,14} Most CNS DLBCLs demonstrate evidence of genomic instability and numerous copy-number alterations. This is likely the result of frequent deletion of *CDKN2A* and/or *FHIT*, which occur far more often in CNS DLBCL than in ABC-type DLBCL elsewhere.¹³ Additional events include amplification of

NFKB1Z on 3q12.3, gain of 18q (leading to *BCL2* overexpression), and amplification of 9p24, including *CD274* and *PDCD1LG2*.¹³ Deletions of HLA class II genes on 6p21 are also seen in approximately 75% of CNS DLBCLs, further contributing to escape of immune surveillance.¹³

Secondary CNS involvement by MCL is uncommon, reported rates vary widely from 4% to 26%, and typically occurs late in the course of the disease.¹⁵ Rare cases of PCNSLs with Cyclin D1 expression and/or rearrangement have been reported in the literature. In one case, both *IGH-CCND1* and *IGH-MYC* rearrangements were detected by FISH analysis.¹⁶ The lymphoma was composed of medium- to large-sized B-cells that expressed *CD20*, *CD5*(weak), *CD10*, Cyclin D1, and *BCL2* and had a high Ki-67 proliferation index.¹⁶ The authors considered it to be an example of “double-hit” lymphoma with Burkitt and MCL characteristics. Two other cases of

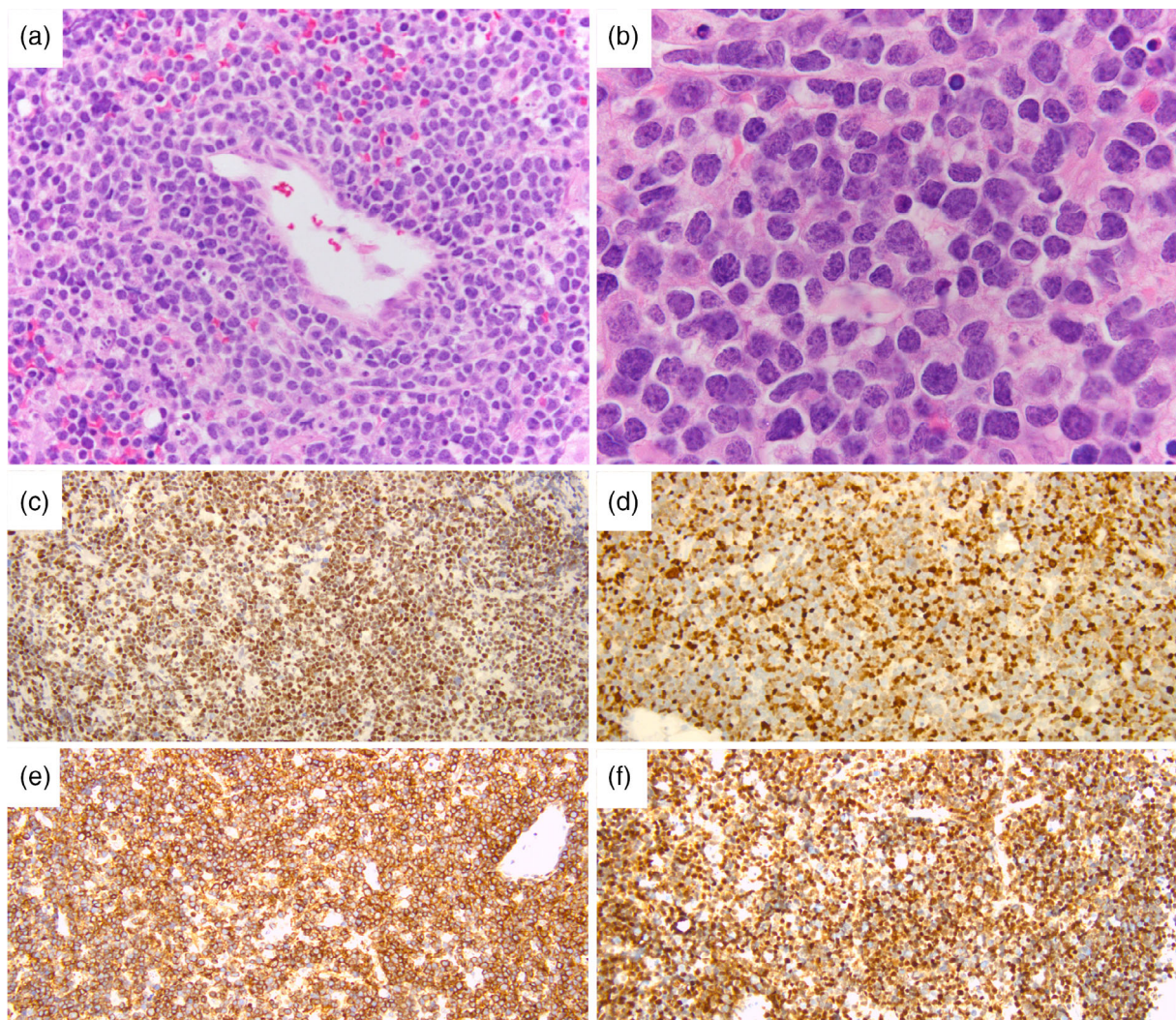


FIGURE 2 Morphology and immunohistochemical stains. (a) 20x and (b) 40x H&E staining showing diffuse, medium to large-sized pleomorphic lymphoid cells with a perivascular/angiocentric distribution. Lymphoma cells are positive for BCL6 (c), MUM1 (d), BCL2 (e) and Cyclin D1 (f) (images are 10x)

primary CNS MCLs did not document cytogenetic analysis.^{17,18} However, the immunophenotype of one case (CD19+, CD20+, CD79a+, CD5+, and Cyclin D1+ and an absence of CD10, CD11c, and CD23 expression) was consistent with classic MCL, but the immunophenotype of the other lymphoma diagnosed as “MCL” was only partially provided. Classic MCL is usually positive for CD20, CD5, IgM, IgD, CD38, CD43, and Cyclin D1. Expression of CD10 (2.4-6.6%) and BCL6 (10-12%) is typically absent in MCL, while lack of CD5 (2-11%) or Cyclin D1 (6%) expression is uncommon.¹⁹⁻²² SOX11 nuclear expression has been shown to be a highly specific marker for MCL (>93%), since it is not expressed in other B-lymphoid neoplasms, with the exception of lymphoblastic lymphoma, and some Burkitt's lymphomas.^{23,24} The current B-cell lymphoma was negative for CD5, CD10, CD38, CD43, and SOX11 (Figure 2). This immunophenotype and absence of systemic disease argue against the diagnosis of MCL, though the possibility of an unusual pleomorphic variant of MCL presenting as PCNSL cannot be ruled out entirely.

Aberrant expression of Cyclin D1 in systemic DLBCL is uncommon, but has a frequency of up to 15% in some case series.¹ Cyclin D1+ DLBCL can exhibit either GC or non-GC B-cell phenotype, but invariably lack CD5 and SOX11 expression.^{1,25} Chromosome rearrangement of the *CCND1* gene is not typically detected in such lymphomas, but an increase in *CCND1* copy number has been described.^{1,25} To date, only four examples of systemic DLBCL with *CCND1* rearrangement have been reported in the literature.^{6,7} Juskevicius et al. reported two systemic DLBCLs, one harboring t(11;14)(q13;q32) and the other with a complex t(4;11;14)(q22;q13;q32) translocation with features intermediate between MCL and DLBCL.⁷ FISH analyses for *MYC* and *BCL2* rearrangements were negative, while *BCL6* abnormalities were not reported.⁷ The cases reported by Al-Kawaaz et al. comprised two systemic DLBCLs harboring t(11;14) in patients with diffuse lymphadenopathy.⁶ The authors found concurrent *BCL6* rearrangements in both cases, and since *BCL6* rearrangement is a frequent genetic aberration in non-GCB subtype

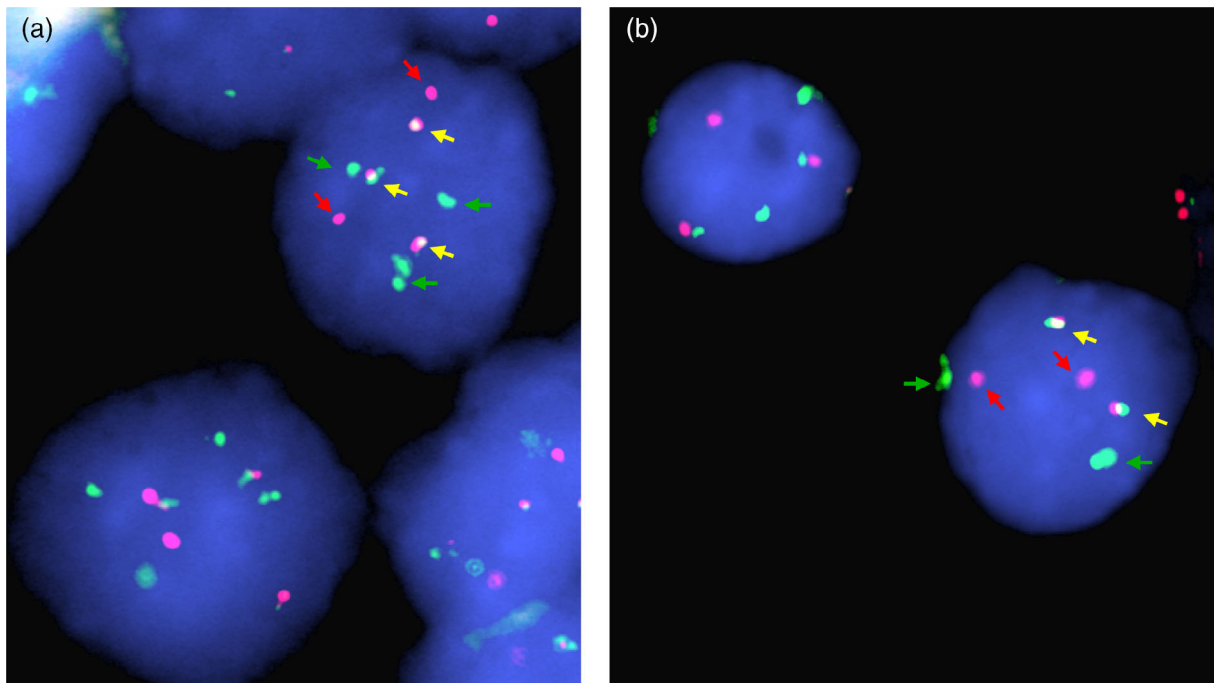


FIGURE 3 FISH studies. Identification of cytogenetic abnormalities by FISH on FFPE tissue sections. (a) Dual-color dual-fusion IGH-CCND1 translocation probe showing t(11;14)(q13;q32). Yellow arrows indicate fusion copies. Orange and green arrows indicate unrearranged copies of CCND1 and IGH, respectively. (b) BCL6 break apart probe showing rearrangement of the BCL6 gene. Yellow arrows indicate normal copies of BCL6. Orange and green arrows indicate rearranged copies of BCL6

DLBCL (detected in 72.7% of this study's non-GCB cohort), this feature was considered supportive of DLBCL in their cases.⁶ As mentioned above, BCL6 rearrangements are less frequent events in primary CNS DLBCL, but are rarely seen in MCL (4/315 cases of MCL in one study²⁶). The CNS large B-cell lymphoma in our patient has immunophenotypic and cytogenetic similarities to these rare systemic DLBCLs, as well as near tetraploidy genotype (multiple copies of IGH (Figure 3), BCL2 and MYC detected by FISH analysis), therefore may represent the first documentation of a primary DLBCL of the CNS with CCND1 rearrangement.

Primary CNS DLBCL typically shows activating mutations in MYD88 and CD79B and inactivating mutations in CARD11 and TNFAIP3.¹³ This somatic mutation profile is different from the somatic mutation landscape of MCL in general, which includes most frequently mutations of ATM, CCND1, TP53, genes encoding the anti-apoptotic protein BIRC3 and Toll-like receptor 2 (TLR2) and the chromatin modifiers WHSC1, MLL2, and MEF2B.²⁷ Given the differences in the somatic mutation profiles between primary CNS DLBCL and MCL, targeted molecular studies could have contributed to further resolve the differential diagnosis in our case; however, molecular studies could not be performed due to exhaustion of biopsy material.

Regardless of the pathologic classification of this primary CNS large B-cell lymphoma and despite the aberrant Cyclin D1 expression and underlying t(11;14), the patient was treated with a regimen typically used for primary CNS DLBCL and achieved CR. While HD-MTX and rituximab-based therapy can be used in MCL, the rapidity, extent, and duration of treatment response seen in our patient further

support the diagnosis of primary CNS DLBCL rather than MCL involving the CNS.²⁸

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/hon.2779>.

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How to cite this article: Parrott AM, Haggiagi AM, Murty VV, Bhagat G, Alobeid B. Primary large B-cell lymphoma of the central nervous system with cyclin D1 expression and t(11;14) (IGH-CCND1): Diffuse large B-cell lymphoma with CCND1 rearrangement or mantle cell lymphoma? *Hematological Oncology*. 2020;38:815-820. <https://doi.org/10.1002/hon.2779>