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ORIGINAL REPORT

Del(6)(q22) and *BCL6* Rearrangements in Primary CNS Lymphoma Are Indicators of an Aggressive Clinical Course

Francois M. Cady, Brian Patrick O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Alyx B. Porter, Paul J. Kurtin, Patrick B. Johnston, Ahmet Dogan, and Ellen D. Remstein

From the Department of Pathology, CellNetix Pathology, Olympia, WA; and Departments of Laboratory Medicine and Pathology, Neurology, Internal Medicine, and Biostatistics, Mayo Clinic, Rochester, MN.

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Corresponding author: Ellen D. Remstein, MD, Mayo Clinic, 200 1st St SW, Rochester, MN 55905; e-mail: remstein.ellen@mayo.edu.

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ABSTRACT

Purpose
Primary CNS lymphoma (PCNSL) is an aggressive lymphoma but clinically validated biologic markers that can predict natural history to tailor treatment according to risk are lacking. Several genetic changes including *BCL6* rearrangements and deletion of 6q22, containing the putative tumor suppressor gene *PTPRK*, are potential risk predictors. Herein we determined the prevalence and survival impact of del(6)(q22) and *BCL6*, immunoglobulin heavy chain (*IGH*), and *MYC* gene rearrangements in a large PCNSL cohort treated in a single center.

Patients and Methods
Interphase fluorescence in situ hybridization was performed using two-color probes for *BCL6*, *MYC*, *IGH-BCL6*, and del(6)(q22) on thin sections of 75 paraffin-embedded samples from 75 HIV-negative, immunocompetent patients newly diagnosed with PCNSL. Survival data were analyzed using Kaplan-Meier survival curves, log-rank tests, and proportional hazards regression adjusting for age, deep structure involvement, and high-dose methotrexate (HDMTX) treatment.

Results
The prevalence of del(6)(q22) and *BCL6*, *IGH*, and *MYC* translocations was 45%,17%, 13%, and 3%, respectively. The presence of del(6)(q22) and/or a *BCL6* translocation was associated with inferior overall survival (OS; $P = .0097$). The presence of either del(6)(q22) alone or a *BCL6* translocation alone was also associated with inferior OS ($P = .0087$). Univariable results held after adjusting for age, deep structure involvement, and HDMTX.

Conclusion
Del (6)(q22) and *BCL6* rearrangements are common in PCNSL and predict for decreased OS independent of deep structure involvement and HDMTX. Unlike systemic diffuse large B-cell lymphoma, del(6)(q22) is common and *IGH* translocations are infrequent and usually involve *BCL6* rather than *BCL2*, suggesting a distinct pathogenesis.

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INTRODUCTION

Primary CNS lymphoma (PCNSL) is an aggressive non-Hodgkin's lymphoma (NHL) that is confined to the CNS. In immunocompetent patients PCNSL is an uncommon tumor, accounting for approximately 1% of NHL and 5% of primary brain tumors.[1,2] PCNSL typically shows the morphologic and immunophenotypic features of diffuse large B-cell lymphoma (DLBCL); however, extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) lymphoma, peripheral T-cell lymphoma, and Hodgkin's lymphoma may rarely show isolated CNS involvement.[2-7] Because PCNSL has heterogeneous clinical behavior despite its relative morphologic homogeneity, investigators have tried to identify clinically relevant prognostic biomarkers in order to individually tailor treatment and minimize toxicity. So far these attempts have met with limited success and clinical parameters, such as age and performance status, are the only consistently identified independent prognostic variables.[8-11] Therefore, identification of new prognostic biomarkers and treatment targets remains a high clinical priority.

Only a limited number of genetic studies have been performed in PCNSL, partly due to lack of available tissue specimens. The few karyotypes obtained from PCNSL have shown no recurrent abnormalities. The frequency of chromosomal translocations common to systemic DLBCL has recently been assessed by interphase fluorescence in situ hybridization (FISH) in two small series of PCNSL.[12,13] These studies suggested that chromosomal translocations that involve the *BCL6* gene are relatively common (23% to 37%) but

other abnormalities characteristic of systemic DLBCL, such as *IGH-BCL2*, appear to be rare. Interestingly, most of the *BCL6* translocations in PCNSL involve nonimmunoglobulin partners unlike systemic DLBCL, in which *BCL6* is frequently juxtaposed to immunoglobulin genes. Translocations involving *MYC* at 8q24, which have been associated with poorer survival in systemic DLBCL, are thought to be rare in PCNSL but very few cases have been studied.[12]

Another abnormality reported to be common in PCNSL is deletion of the long arm of chromosome 6, primarily involving 6q21-23.[14-18] The genes involved in this region are not known. Loss of heterozygosity studies in PCNSL have demonstrated loss of one or more loci at 6q22-23 in 66% of cases in a small series.[16] More precise mapping has implicated the putative tumor suppressor gene *PTPRK* within the 140 kb common minimally deleted region in these cases. Deletion of this region was often associated with loss of expression of PTPRK, and both loss of heterozygosity at the *PTPRK* locus as well as lack of PTPRK protein expression was associated with a poorer prognosis.

BCL6 translocations and 6q22-23/*PTPRK* deletions may be important in the pathogenesis of PCNSL and may have prognostic significance, but the prevalence and survival impact of these markers have not been well studied. The aim of this study is to determine the prevalence and survival impact of del(6)(q22), *BCL6*, *MYC*, and *IGH* gene rearrangements as well as prevalence of Epstein-Barr virus (EBV) infection in PCNSL in immunocompetent patients.

PATIENTS AND METHODS

Patient Characteristics

The cohort comprised 75 formalin-fixed, paraffin-embedded (FFPE) specimens from 75 HIV-negative, immunocompetent patients with PCNSL newly diagnosed and treated at Mayo Clinic between 1985 and 2006. Clinical information including age, sex, and therapy and imaging records (in order to determine unifocal *v* multifocal involvement and presence or absence of deep structure involvement) were available on all 75 patients. Performance score (PS) was available for only four patients. All cases were classified as DLBCL according to the WHO classification.[19] All patients consented to research use of their tissue. The study was approved by Mayo Foundation institutional review board.

FISH Probes

Interphase FISH was performed on thin sections of the FFPE tumor samples as described previously.[20] All cases were screened using a homebrew two-color probe for del(6)(q22), consisting of a SpectrumGreen labeled control probe at 6p24 and an Alexa-594-labeled probe at 6q22-23 (RP11-151E20 and CTD-2378A7). All cases were also screened for *BCL6* and *MYC* translocations. For *BCL6*, a two-color breakapart probe (BAP; Vysis Inc, Downers Grove, IL) and a homebrew two-color dual fusion (D-FISH) IGH-BCL6 probe consisting of a SpectrumGreen labeled probe and a SpectrumOrange-labeled probe labeled at 3q27.3 (BACS RP11-88P6, RP11-211G3, and CTD2522K3) were used. Two-color IGH BAP (Vysis Inc) probes were also used in cases showing extra FISH signals without fusion using the IGH-BCL6 probe. For *MYC*, a two-color BAP probe (Vysis Inc) was used.

A minimum of 50 tumor cells were scored in each sample. For BAP and D-FISH probes, a minimum of 20 cells with a recognized abnormal signal pattern were required to deem the cytogenetic abnormality present.[21] For the del(6)(q22) probe, a cohesive group of at least 20 cells, of which at least 80% were abnormal was required for that sample to be considered abnormal.[22]

In Situ Hybridization

In situ hybridization was performed using probes that recognize EBV-encoded RNA on FFPE tumor sections in 75 cases. Any nuclear staining in tumor cells was considered positive.

Statistical Analysis

Survival data were analyzed for all patients, with overall survival (OS) being calculated from the date of tissue diagnosis to date of death or last contact. Survival curves were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival across groups. Proportional hazards regression was used to evaluate the association of genetic abnormalities with survival adjusting for age, deep structure involvement, and high-dose methotrexate (HDMTX). Two-tailed *P* values less than .05 were considered statistically significant.

RESULTS

The cohort comprised 43 men and 32 women. Mean and median age at diagnosis were 63.5 and 67.0 years, respectively, with a range of 26 to 87 years. There were four patients with a recorded PS; two stuporous patients had a PS of 4 and two intact patients who presented only with seizures had a PS of 0. Sixteen patients (21%) had unifocal disease. Fifty-four patients (72%) had involvement of deep structures (periventricular areas, corpus callosum, basal ganglia, brainstem, and cerebellum). Twenty-eight patients (37%) received HDMTX as initial therapy.

BCL6 translocations were identified in 13 (17%) of 75 PCNSL cases. Eight cases showed *IGH-BCL6* fusion and in the remaining five cases the *BCL6* translocation partner was unknown. Del(6)(q22) was present in 34 cases (45%), with a spectrum of homozygous (n = 9), heterozygous (n = 4), and mixed homozygous/heterozygous (n = 21) del(6)(q22) patterns. Four cases (5%) possessed both a *BCL6* translocation and del(6)(q22). Translocations involving *MYC* were present in two cases; one also had *IGH-BCL6* fusion while the other lacked a *BCL6* translocation or del(6)(q22) (Fig 1).

Using the IGH-BCL6 D-FISH probe, in addition to the eight cases showing *IGH-BCL6* fusion described earlier, 65 cases lacked an abnormality involving *IGH* and three cases had an extra *IGH* signal in the absence of *IGH-BCL6*. An IGH BAP FISH probe used on the latter three cases showed that two had a 1R1G1F pattern indicating *IGH* translocation to an unknown gene partner (one also had del(6)(q22) while the other also had a *BCL6* translocation to an unknown gene partner) while the third showed three intact fusion signals indicating trisomy 14. All cases were negative for EBV-encoded RNA.

There were 51 deaths and the median follow-up time for surviving patients was 399 days (range, 0 to 2,520 days). Patients who had a *BCL6* translocation and/or del(6)(q22) had a median OS of 316 days, compared with those who lacked a *BCL6* translocation or del(6)(q22), whose median OS was 713 days ($P = .0097$; Fig 2). Differences in OS were also statistically significant between patients with a *BCL6* translocation only (median OS, 129 days), patients with del(6)(q22) only (median OS, 412 days) and patients who lacked a *BCL6* rearrangement or del(6)(q22) (median OS, 713 days, $P = .0087$; Fig 3). Proportional hazards regression was used to adjust for age, HDMTX, and deep structure involvement. Similar results were observed after adjusting for the above variables (Table 1). We were unable to adjust for performance score, lactate dehydrogenase, or CSF protein due to limited data for these variables.

Only four patients had both a *BCL6* translocation and del(6)(q22); these abnormalities did not appear to have an additive deleterious

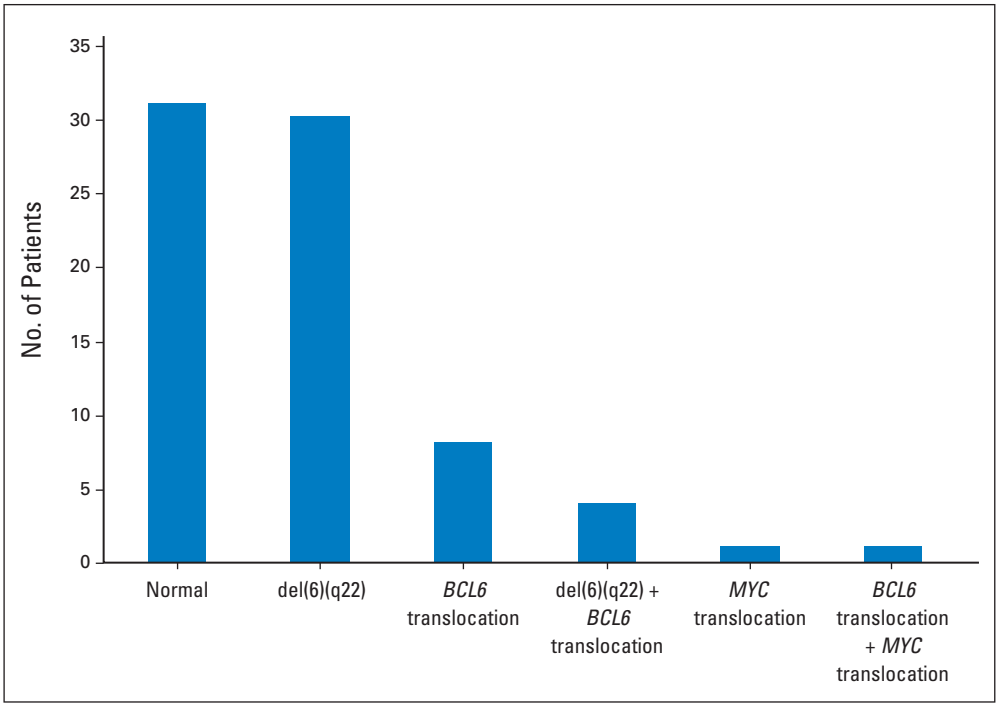

Fig 1. Prevalence of del(6)(q22), *BCL6* translocations, and *MYC* translocations in primary CNS lymphoma.

effect on survival. Younger patients (age < 60 years) showed a trend toward a more favorable OS than older patients (age > 60 years; OS 713 days *v* 412 days), but this did not reach statistical significance ($P = .113$).

DISCUSSION

PCNSL is a rare extranodal lymphoma with aggressive clinical behavior. Although there are effective treatment modalities none are reliably curative and treatment-associated neuro-toxicity is common. Patient-specific therapy is difficult to achieve as there are no good biologic markers that predict the natural history of the disease because little is known regarding the molecular pathogenesis of PCNSL. In this study, we have demonstrated that the prevalence of *BCL6* translocations and del(6)(q22) in PCNSL is 17% and 45%, respectively, and both are associated with diminished OS.

The prevalence of several specific cytogenetic abnormalities in our PCNSL cohort is different than that previously reported in systemic DLBCL. Specifically, although the prevalence of *BCL6* rearrangements in PCNSL (17%) is comparable with that of systemic DLBCL (19% to 36%),[23-27] del(6)(q22) is more common in PCNSL (45%) than in systemic DLBCL (25%)[28] and *IGH* translocations are less common in PCNSL (13%) than in systemic DLBCL (45% to 51%).[29,30] Furthermore, the most common *IGH* translocation partner in PCNSL is *BCL6* (80%) while in systemic DLBCL *IGH* is more frequently juxtaposed to *BCL2* (12% to 20%)[29-32] than to *BCL6* (6.5% to 8%).[29,30]

In our study, the prevalence of both *BCL6* rearrangements (17%) and del(6)(q22) (45%) is comparable to that previously reported in

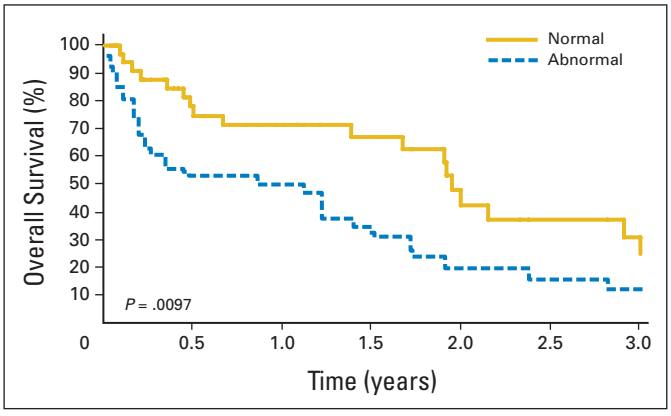

Fig 2. Kaplan-Meier estimate of overall survival (OS) for all patients. OS according to the presence or absence of del(6)(q22) and/or a *BCL6* translocation.

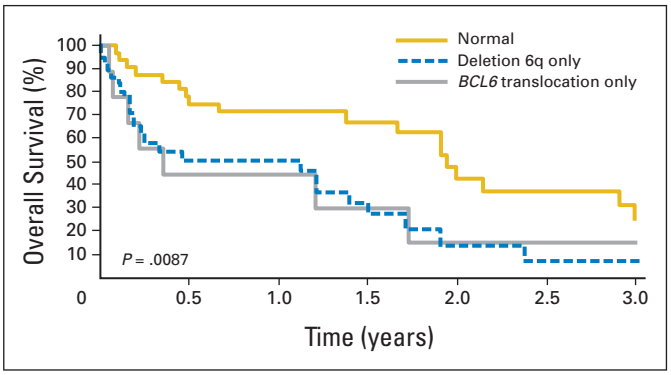

Fig 3. Kaplan-Meier estimate of overall survival (OS) for all patients. OS according to the presence of del(6)(q22) only, a *BCL6* translocation only, or neither of these abnormalities.

Table 1. Association of Genetic Abnormalities With Survival

Parameter	Univariable			Adjusted*		
	Hazard Ratio	95% CI	P†	Hazard Ratio	95% CI	P†
BCL6 translocation and/or del (6)(q22)	2.08	1.18 to 3.70	.012	2.40	1.30 to 4.42	.005
Normal	1.0	—		1.0	—	
Del (6)(q22)	2.55	1.36 to 4.77	.012	2.62	1.36 to 5.05	.011
BCL6 translocation	2.08	0.86 to 4.99		2.62	1.0 to 6.88	
Normal	1.0	—		1.0	—	
Del (6)(q22)	1.83	1.04 to 3.20	.035	1.87	1.05 to 3.33	.034
Normal	1.0	—		1.0	—	

*Adjusted for age, high-dose methotrexate use, and deep structure involvement.
†Proportional hazards regression.

PCNSL (23% to 37%[12,13] and 47% to 75%,[14-18] respectively), although in the prior PCNSL studies smaller cohorts were evaluated. The prevalence of *MYC* translocations in our study was 3%, which is similar to that of systemic DLBCL.[33] Interestingly, recent gene expression profiling studies have demonstrated that PCNSL shows higher expression of *MYC* than nodal DLBCL.[34] Our data suggest that a mechanism other than a *MYC* translocation may be responsible for the *MYC* overexpression in PCNSL. In addition, all cases lacked EBV-encoded RNA. These data are in contrast to post-transplant lymphoproliferative disorders arising in immunosuppressed patients, in which both *MYC* translocations and EBV positivity are common, and suggest that both *MYC* translocation and EBV status are less critical in the routine diagnostic evaluation of lymphoproliferative lesions involving the CNS of immunocompetent patients.

The discrepancies in translocation frequency between our PCNSL data and the accumulated systemic DLBCL data suggest distinct pathogeneses for these two disorders. Although PCNSL tumor cells are morphologically and immunohistochemically identical to malignant lymphocytes of systemic DLBCL, PCNSL differs from systemic DLBCL in several important ways. First, PCNSL by definition arises only in the CNS and relapses locally/regionally; systemic relapse is rare. Second, although PCNSL is highly responsive to HDMTX, it is rarely curable. Third, although gene expression profiling studies have demonstrated that both PCNSL and systemic DLBCL can be subcategorized into activated B cell (ABC), germinal center B-cell (GBC), and non-ABC, non-GBC forms,[34,35] unlike systemic DLBCL, a subset of PCNSL cases show concurrent expression of both activation genes, such as cyclin D2, and germinal center genes, such as *BCL6*,[34] suggesting a unique molecular origin. It is interesting to note that a subset of PCNSL of both the ABC and GBC subtypes show high expression of *BCL6*, raising the question of whether this may be associated with a *BCL6* translocation regardless of subtype.

When analyzed separately or grouped together, both del(6)(q22) and *BCL6* rearrangements showed a negative survival impact in our immunocompetent PCNSL cohort. Deletion of 6q has been previously associated with diminished survival in immunocompetent PCNSL patients.[16,17] Because R-PTP-κ (*PTPRK*) is within a common minimally deleted region at 6q22 and its loss has been associated with loss of *PTPRK* expression in PCNSL,[16] *PTPRK* is a candidate tumor suppressor gene in PCNSL. *PTPRK* has also been shown to be a functional tumor suppressor in Hodgkin's lymphoma.[36] It is thought to be a regulator of growth factor receptor mediated phosphorylation and thus may be a key mechanism for inhibition/control of cell proliferation. PTPRK belongs to the protein tyrosine phosphatase superfamily of enzymes.[37-39] In the context of antigen receptor-mediated signaling in lymphocytes protein tyrosine phosphatases tend to have a primarily inhibitory role,[38] and by controlling proliferation and survival signals generated by protein tyrosine kinases, such as SRC or SYK, have emerged as a new generation of candidate tumor suppressor genes and potential therapy targets.

The International Prognostic Index (IPI) was recently adapted to include PCNSL. Based on five measures—lactate dehydrogenase, CSF total protein, involvement of deep structures (periventricular areas, corpus callosum, basal ganglia, brainstem, and cerebellum), age, and PS—three prognostic tiers were proposed.[10] These results have been validated and the IPI-PCNSL is now widely used. In our study, too few patients had elevated lactate dehydrogenase (n = 7), elevated CSF protein (n = 20), and a PS (n = 4) in their initial episode of care and thus an IPI-PCNSL score could not be determined. Although there have been attempts to retrospectively assess stroke score,[40,41] these focused on neurologic examination findings and did not assess performance as defined by Karnofsky or Zubrod/Eastern Cooperative Oncology Group systems. We could find no report supporting the retrospective assignment of PS.

There were sufficient cases to assess the influence of involvement of deep structures on survival. In this analysis the significance of both del(6)(q22) and a *BCL6* rearrangement was maintained. Similarly, in our series, the use of HDMTX in newly diagnosed patients did not seem to correct for the presumed loss of the tumor suppressor effect of del(6)(q22). This is not surprising. Although HDMTX is considered the standard regimen for newly diagnosed PCNSL patients,[42] the improved survival may be as much a function of salvage therapies as of the HDMTX.[43] A population-based analysis did not confirm that OS improved consistently over the past three decades despite the introduction of HDMTX and the impressive clinical trials results.[44]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Alyx B. Porter, Paul J. Kurtin, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein
Financial support: Brian P. O'Neill, Ellen D. Remstein
Provision of study materials or patients: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Alyx B. Porter, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein
Collection and assembly of data: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Alyx B. Porter, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein
Data analysis and interpretation: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Paul J. Kurtin, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein
Manuscript writing: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Alyx B. Porter, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein
Final approval of manuscript: Francois M. Cady, Brian P. O'Neill, Mark E. Law, Paul A. Decker, David M. Kurtz, Caterina Giannini, Alyx B. Porter, Paul J. Kurtin, Patrick B. Johnston, Ahmet Dogan, Ellen D. Remstein

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