

Successful CNS-Centric Therapeutic Management and Genomic Profiling of Primary Cranial Vault Diffuse Large B-Cell Lymphoma

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Abstract: Primary cranial vault lymphoma (PCVL) is a rare lymphoma involving the skull with or without extra- and intracranial extension. Most cases of PCVL are diffuse large B-cell lymphoma (DLBCL). We report a case of primary cranial vault diffuse large B-cell lymphoma (PCV-DLBCL) that was successfully treated with anthracycline-based chemoimmunotherapy (CIT) alternating with central nervous system (CNS)-directed CIT with high-dose methotrexate and high-dose cytarabine. CNS-centric therapy was given for suspected cerebral cortical involvement and presumed elevated risk of CNS recurrence. The patient has remained in complete remission for 4.25 years following treatment. We suggest that PCV-DLBCL is potentially curable with CNS-directed therapy. Additionally, we provide genomic profiling results indicating an indeterminate cell of origin and multiple genetic mutations which are not frequently seen in DLBCL.

Keywords: diffuse large B-cell lymphoma, central nervous system, calvarium, chemotherapy, scalp lesions

Introduction

The World Health Organization (WHO) recognizes diffuse large B-cell lymphomas (DLBCL) localized to specific extranodal sites.¹ These extranodal lymphomas include primary central nervous system (CNS) lymphoma, primary vitreo-retinal lymphoma, primary testicular lymphoma, primary cutaneous large B-cell lymphoma, and primary effusion lymphoma.¹

Primary cranial vault lymphoma (PCVL), or calvarial lymphomas, are extranodal non-Hodgkin lymphomas characterized by localized involvement of the cranial vault with tri-compartment (extracranial, calvarial, and intracranial) involvement.⁴ PCVL is rare and has been sparsely reported in the medical literature.²⁻⁴ Patients often present with painless scalp lesions with normal overlying skin. Neurologic symptoms vary by location and extent of disease.^{3,4,9} The diagnosis is established with a combination of imaging and tissue biopsy of the identified mass.^{3,9} PCVL is managed with surgical resection of the tumor, radiation therapy, systemic chemotherapy, or a combination of these therapies.^{4,6,9,12} The optimal treatment approach remains uncertain, however, given the rarity of this entity and limited reports of long-term follow-up.⁴ We present a case of PCVL successfully treated with CNS-centric systemic chemoimmunotherapy (CIT).

Case Presentation

A 69-year-old Caucasian male with a history of chronic headaches presented with rapidly enlarging scalp masses involving the left periauricular and temporal areas that varied in size and shape and were sensitive to touch. He also noted worsening frontal headaches, dizziness, and cramping of the jaw. Seven months prior, these scalp lesions were presumed to be shingles, and he was treated with valacyclovir without improvement in his symptoms. Initial magnetic

resonance imaging (MRI) and computed tomography (CT) scans of the head revealed an incidental pituitary microadenoma but did not explain his scalp lesions.

Given the worsening symptoms, repeat imaging was obtained. MRI and positron emission tomography–computed tomography (PET-CT) demonstrated a 1.8×3.5 cm subgaleal hypermetabolic tumor of the scalp in the parietal area with permeative erosion of the adjacent calvarial bone and intracranial extension with extensive pachymeningeal involvement (Figure 1A–C). In addition, hypermetabolic changes were seen in three regional lymph nodes in the left preauricular region (Figure 2A). The tumor was resected, and pathology revealed a diffuse proliferation of large, atypical lymphocytes in a fibrotic background adjacent to periosteal soft tissue and attached to the dura (Figure 3A and inset). The neoplastic lymphocytes were diffusely positive for CD20, CD10, BCL2, and BCL6 by immunohistochemistry, and 90% of cells stained positive for Ki-67 (Figure 3B–3F). The lymphocytes were negative for MUM1, MYC, CD30, and CD23. Myeloperoxidase, CD1a, S100, and epithelial membrane antigen (EMA) were also negative. Epstein-Barr encoded RNA (EBER) in situ hybridization (ISH) was negative. Fluorescence in situ hybridization (FISH) studies were negative for MYC/IGH translocation. The tissue was also sent for comprehensive genomic analysis with GTC-Hematology Profile Plus by Genomic Testing Cooperative which combines expression and fusion with mutation analysis in DNA and RNA. The test covers 179 DNA genes and 1408 RNA genes which are known to be associated with hematologic malignancies. The genomic analysis supported the diagnosis of DLBCL. These results are summarized in Table 1. Based on Han's criteria, the cell of origin (COO) was initially classified as germinal center B-cell (GCB) subtype of DLBCL; however, the genomic findings including gene expression signature indicated mixed COO.

He was diagnosed with stage IV primary cranial vault diffuse large B-cell lymphoma (PCV-DLBCL) with an International Prognostic Index score of 3 based on age >60, stage IV disease, and involvement of 2 extranodal sites. Initial laboratory investigations including complete blood count, comprehensive metabolic profile, and lactate dehydrogenase were all within normal limits. Lumbar puncture was deferred given the concern for CNS involvement and plan for CNS-directed therapy. He was treated with rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 2 mg on day 1, and prednisone 100 mg daily on days 1–5 (R-CHOP), alternating with rituximab (R) 375 mg/m², high-dose (HD)-methotrexate (MTX) 3.5 g/m² on day 1, and high-dose cytarabine (HiDAC) 1000 mg/m² q12H on days 2–3 (R-MA regimen) for a total of eight cycles. HiDAC was reduced by 20% with cycle six due to pancytopenia requiring hospitalization. It was further reduced by 20% for the final cycle due to cytopenias. He achieved a complete remission (CR) after four cycles of CIT and has remained in CR for 4.25 years with no adverse sequelae from his lymphoma or lymphoma treatment (Figure 2A–H).

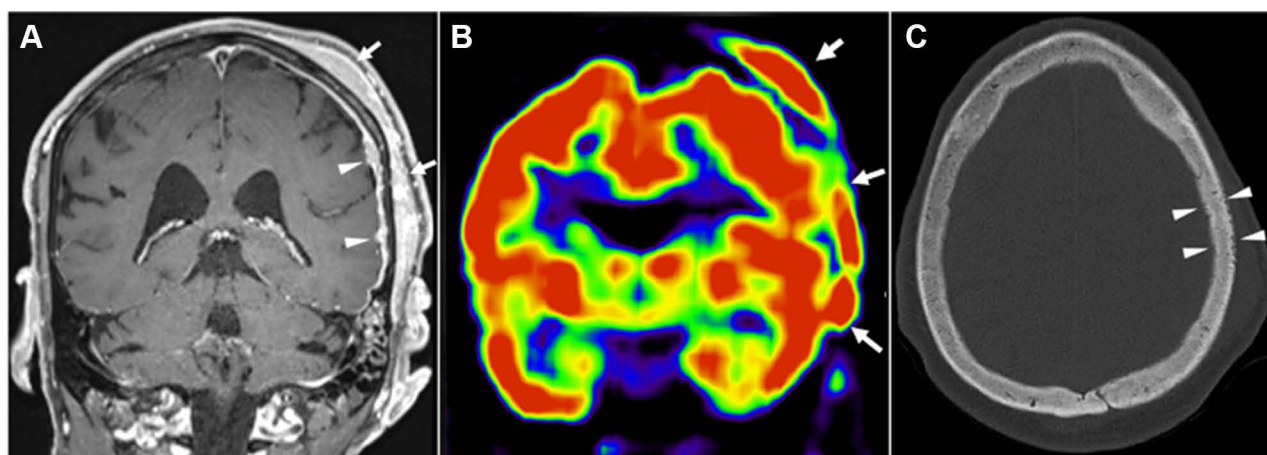


Figure 1 Initial FDG PET-MRI Images. (A) Coronal contrast enhanced T1 weighted MRI shows infiltrating subgaleal mass (arrows) with abnormal enhancement of the underlying calvarial marrow and nodular thickening of the dura (arrowheads). (B) The infiltrating mass is hypermetabolic on FDG-PET (arrows). (C) High-resolution CT of the skull reveals permeative erosions and slightly increased density of the involved parietal bone.

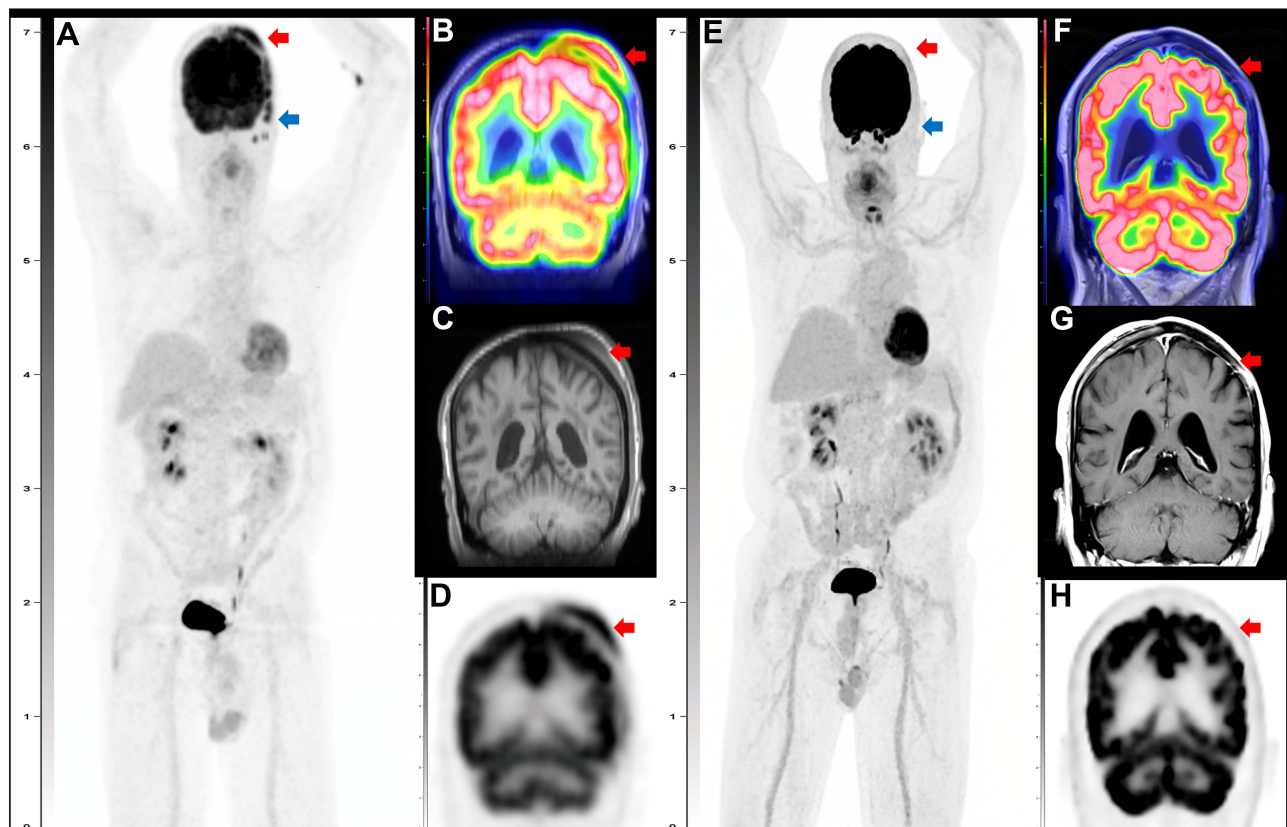


Figure 2 Initial and Post-Treatment FDG PET-MRI. Composite fused FDG PET-MRI images at initial diagnosis and after treatment with R-CHOP alternating with R-MA. Coronal view of FDG PET maximum intensity projection (MIP) at initial diagnosis (**A**) demonstrates moderately hypermetabolic soft tissue in the scalp subcutaneous tissues with SUV max of 7.8 (red arrow). The subcutaneous tissue has transcalvarial extension and involvement of the underlying pachymeninges as seen on fused coronal FDG PET-MRI (**B**), T1 MRI (**C**), and FDG PET (**D**) (red arrows). Initial FDG PET MIP (**A**) also demonstrates hypermetabolic left preauricular lymph nodes and temporalis muscle involvement (blue arrow). Post-treatment fused FDG PET-MRI MIP (**E**) demonstrates complete resolution of the scalp subcutaneous tissues (red arrows) and lymphadenopathy (blue arrow) and is confirmed on coronal fused PET-MRI (**F**), T1 + contrast (**G**) and FDG PET (**H**) (red arrows).

Discussion

PCVL is a rare extranodal lymphoma that involves the skull with or without extra- and intracranial extension (ie, the scalp, calvarium, and intracranial space).^{3,4} It accounts for 0.2% of all lymphomas, and PCV-DLBCL represents 0.3–0.5% of extranodal non-Hodgkin lymphomas.^{2,14} PCVL appears to be quite distinct from primary dural lymphoma, which is predominantly an extranodal marginal zone B-cell lymphoma.¹¹ PCVL is more common among Caucasian individuals in their 7th decade of life.³ Patients present with painless scalp lesions with normal overlying skin and often endorse regional headache.^{3,4,9} Neurologic symptoms including seizures, mental status changes, apraxia, and hemiparesis may be present as a result of intracranial extension or mass effect.⁴ PCVL should be considered in a patient presenting with a scalp mass with or without headache or other neurologic symptoms.^{3,9}

A diagnosis of PCVL can be made after evaluation with imaging (MRI, CT, or PET-CT) and biopsy of the affected area.^{3,9} On imaging, PCVL may involve all three compartments of the cranial vault (scalp, calvarium, and dura). Tri-compartment involvement was reported in 87% of patients with PCVL in one meta-analysis.^{3,9} Bone destruction and parenchymal brain involvement may also be seen on imaging but are more common in advanced disease.¹⁰ Early in the disease course, these cancers cause little to no bone destruction despite transcalvarial involvement. In later stages of disease, however, there is often extensive infiltrative destruction of the skull.^{2–7} The lymphoma cells infiltrate the diploic spaces and extend along emissary veins to involve the soft tissue on both sides of the skull, resulting in enlargement of the subcutaneous scalp mass without initial damage to the intervening bone.^{3–5,8} This infiltrative pattern of bone destruction is unique to PCVL.⁵ Patients with complete bone destruction without brain parenchymal disease, as well as those with parenchymal involvement without bone destruction have been reported.^{2,4,10} Involvement of the brain parenchyma should be suspected if

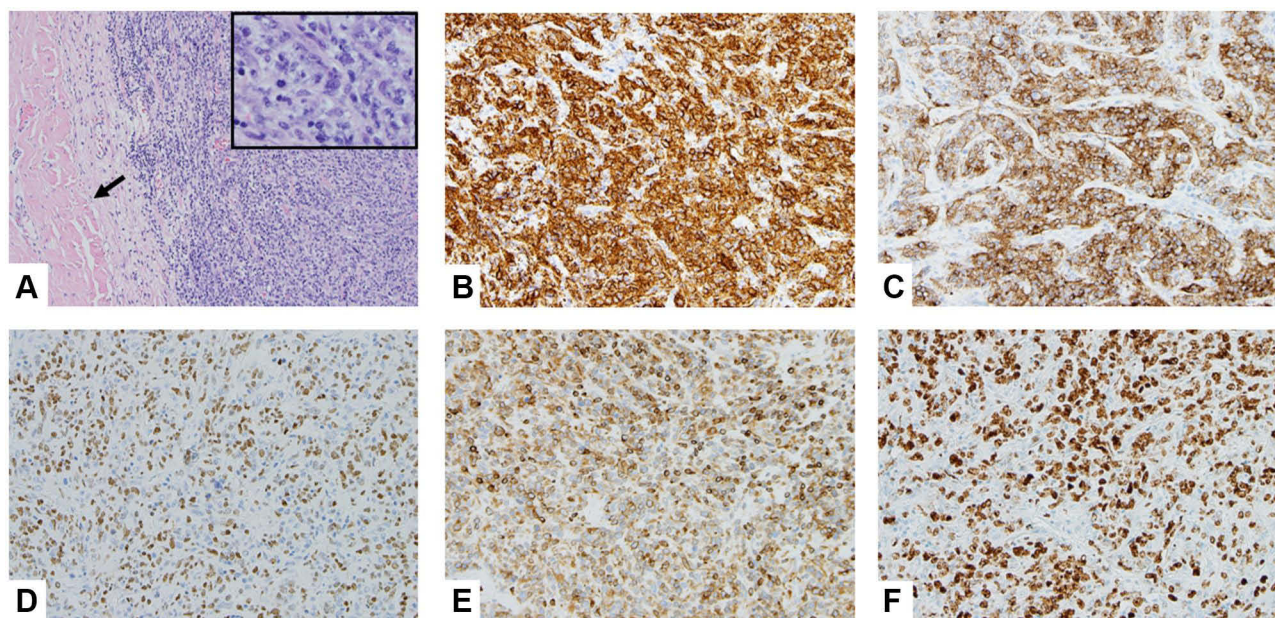


Figure 3 Pathologic Evaluation of Resected Tumor. The H&E sections (**A**, x 10) show the proliferation of neoplastic lymphocytes adjacent to the periosteal soft tissue (arrow); and neoplastic lymphocytes are large with open chromatin and prominent nucleoli; mitosis is brisk (inset, x 40). They are positive for CD20, CD10, BCL6, BCL2, with a high proliferative rate by Ki-67, 90% (**B–F**, x 20).

the MRI demonstrates an indistinguishable border between the meninges and cortex in the presence of subcortical edema.³ In our patient, the tumor exhibited involvement of the three compartments with the parietal bone showing minimal osteolytic changes, extracranial extension into the scalp with sub-galeal tumor, and intracranial extension with extensive hemispheric pachymeningeal involvement in association with three regional lymph nodes without evidence of distant disease. Patients with PCVL may also develop distant disease due to hematogenous spread, and PET-CT can help identify metastasis.⁹

Table I Pathologic and Genomic Findings in a Patient with PCV-DLBCL

Pathology Findings	
Immunohistochemistry	Positive - CD20, CD10, BCL2, BCL6
	Negative - MUM1, MYC, CD30, CD23
EBER ISH	Negative
Cell of origin (Han's criteria)	Germinal center B cell subtype
Genomic Profile ^a	
Mutation Profile	KRAS 183A>C, EZH2 1936T>A, MYD88 814C>T, XPO1 1654C>T, STAT3 2147C>T, ATRX 2975–2982del, TNFAIP3 617C>T and 547C>T, KMT2B 6137delG, HGF 1505G>A, POT1 1632G>A, CD22 381A>T, EBF1 416T>G, CD58 168G>A, NIPBL 5044C>T
Chromosomal Analysis	6p+, 10p+, +19 No translocation involving BCL2, BCL6, and MYC
Cell of Origin (Gene Expression Profiling)	Indeterminate Cell of origin

Note: ^aBased on GTC Hematology Profile Plus by Genomic Testing Cooperative.

Abbreviations: ABC, activated B-cell; CIT, chemoimmunotherapy; CNS, central nervous system; COO, cell of origin; CR, complete remission; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein-Barr encoded RNA; EMA, epithelial membrane antigen; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; HD, high-dose; HiDAC, high-dose cytarabine; ISH, in situ hybridization; MRI, magnetic resonance imaging; MTX, methotrexate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PCV-DLBCL, primary cranial vault-diffuse large B-cell lymphoma; PCVL, primary cranial vault lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; WHO, world health organization.

A recently published meta-analysis evaluating 62 patients with PCVL revealed that the majority of cases result from B-cell lymphomas (58/62 cases) with only 1 reported case of T-cell lymphoma.⁹ The majority were aggressive B-cell lymphomas [DLBCL (61%), Burkitt lymphoma (5%), and high-grade B-cell lymphoma (3%)], however, low-grade B-cell lymphomas were also reported (follicular lymphoma, extranodal marginal zone B-cell lymphoma, small lymphocytic lymphoma, and unspecified low-grade B-cell lymphomas).⁹ Genomic data of PCVL are lacking.

Our report appears to be the first one to provide comprehensive genomic profiling results on PCV-DLBCL. The genetic profile of the case is quite interesting in that the cell of origin (COO) and molecular subtype cannot be definitively classified. The algorithm used by GTC Hematology Plus indicates that the COO is unclassifiable/mixed based on the gene expression profile. Out of fifteen mutations detected, EZH2 mutation is frequently associated with GCB COO whereas TNFAIP3 and MYD88 mutations are frequently seen in non-GCB COO.^{17,18} The remaining mutations are not frequently found in DLBCL. The MYD88 814C>T mutation found in our patient is a truncating mutation and has been associated with innate immune deficiency.¹⁹ It is distinct from MYD88 L265P which is frequently associated with non-GCB DLBCL¹⁷ and is the most common mutation in primary CNS lymphoma.²⁰ As for molecular subtype, EZH2 mutation suggests EZB subtype.^{25,26} However, TNFAIP3 and STAT3 mutations are not typically seen in EZB subtype. TNFAIP3 mutation is associated with BN2 whereas STAT3 mutation is associated with ST2.^{25,26} Based on mutation profile, multiple signaling pathways are affected: epigenetic regulation (EZH2, ATRX, and KMT2B), JAK-STAT signaling (STAT3), NFκB signaling (TNFAIP3 and MYD88), B cell related pathways (CD22, EBF1, and CD58), chromosome regulation (POT1 and NIPBL), cell proliferation (KRAS and HGF), and regulation of nuclear export (XPO1).^{27,28}

The optimal therapeutic approach for PCVL is not well characterized given its rarity.⁴ Historically, surgical resection of the tumor, radiation therapy, and systemic chemotherapy with CHOP have been used.^{4,6,9,12} Treatment with surgical excision alone is likely insufficient and may not improve remission rates when compared to systemic therapy.^{9,12} There are several reports of patients with PCV-DLBCL without CNS involvement achieving CR with radiotherapy alone, or in combination with systemic chemotherapy without CNS-penetrating agents.^{5,9,21–23} The longest reported follow-up was 4.8 years.²¹ Two other patients achieved CR with surgery and radiotherapy alone, but these patients had mucosa-associated lymphoid tissue (MALT) lymphoma, a subtype of non-Hodgkin lymphoma known to be particularly sensitive to radiotherapy that is distinct from DLBCL.^{4,10} CNS-penetrating chemotherapeutics have been used previously to treat PCV-DLBCL.^{5,13} One patient received rituximab in combination with cytarabine following surgical resection, while the other received methotrexate alone, followed by rituximab, cyclophosphamide, cytarabine, etoposide, and dexamethasone.^{5,13} Both patients achieved a CR.

R-CHOP is the standard treatment for systemic DLBCL, but it is ineffective for treatment of CNS lymphoma due to its poor CNS penetration.¹⁶ We utilized a CNS-centric therapeutic approach for our patient given the concern for cerebral involvement. Our patient received a combination of R-CHOP alternating with Rituximab, HiDAC, and HD-MTX. He achieved CR after four cycles of CIT and has remained in CR for 4.25 years.

There are limited overall survival (OS) data for PCVL given the scarcity of reported cases in the literature and lack of long-term follow up. In one small case series, the median OS was reported to be 17.8 months in patients without cerebral cortical involvement and 10.5 months for those with PCVL involving the brain parenchyma.¹³ Ultimately, given the risk of cerebral involvement in patients with PCVL, we believe CNS-directed therapies should be considered in its management, particularly PCV-DLBCL and other high-grade B-cell lymphoma subtypes.^{9,15}

Extensive genomic profiling of lymphomas is becoming more common; however, it is still not widely employed and the utility of genomic testing to predict response to therapy is limited.²⁴ With further genomic characterization of these tumors, we may be better equipped to individualize treatment to improve outcomes.

Conclusion

PCV-DLBCL is a rare primary extranodal lymphoma of the calvarium with or without extracranial and intracranial extension. The genomic profiling of our case revealed an indeterminate COO and multiple genetic mutations which are not commonly seen in DLBCL. While there is no standard treatment for PCV-DLBCL, we suggest that a CNS-centric therapeutic approach is warranted due to high CNS risk and is potentially curative. More research is needed to have a better understanding of the biology of PCV-DLBCL and identify an optimal therapeutic approach.

Consent for Publication

The study participant has given written informed consent to participate as well as consent to publish their data and images. IRB approval was not required to publish the case details.

Disclosure

The authors report no conflicts of interest in this work.

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