Journal of Blood Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Clinical and Genomic Profile of Primary Cranial Neurolymphomatosis

Emily B Wolf[1], Robin Imperial[1], Liuyan Jiang[2], Amit K Agarwal[3], Han W Tun[1]

[1]Division of Hematology and Medical Oncology, Mayo Clinic Florida, Jacksonville, FL, USA; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic Florida, Jacksonville, FL, USA; [3]Department of Radiology, Mayo Clinic Florida, Jacksonville, FL, USA

Correspondence: Han W Tun, Division of Hematology and Medical Oncology, Mayo Clinic Florida, 4500 San Pablo Road S, Jacksonville, FL, 32224, USA, Email Tun.Han@mayo.edu

Abstract: Primary cranial neurolymphomatosis (PCNL) is a rare subtype of primary CNS lymphoma (PCNSL) in which infiltrative lymphomatous involvement is confined to cranial nerves. Here, we report a case of PCNL with successful genomic profiling. A 57-year-old male had a lengthy prediagnostic phase spanning approximately 30 months, characterized by multiple episodes of cranial neuropathies managed by steroids. At the time of diagnosis, the patient had right-sided cranial neuropathies involving cranial nerves (CN) V, VI, and VII. Pathological findings of the right cavernous lesion biopsy were consistent with large B-cell lymphoma-infiltrating nerve fibers. The clinical course was aggressive and refractory, characterized by relentless progression with the development of cervical spinal neurolymphomatosis, cerebrospinal fluid involvement, and ependymal and intraparenchymal cerebral involvement, despite multiple lines of therapy, including chemoimmunotherapy, Bruton's tyrosine kinase inhibitor, radiation, autologous stem cell transplant, chimeric antigen receptor T-cell therapy (CAR-T), and whole-brain radiation. The patient survived for 22 months from the time of the initial diagnosis and 52 months after the first episode of cranial neuropathy. Next-generation sequencing identified mutations (MYD88, CD79b, and PIM1) that are frequently observed in PCNSL. The unusual findings included a total of 22 mutations involving PIM1, indicating a highly active aberrant somatic hypermutation and two missense CXCR4 mutations. CXCR4 mutations have never been described in PCNSL and may have implications for disease biology and therapeutic interventions. We provide a literature review to further elucidate PCNL.

Keywords: DLBCL, cranial nerve, autologous stem cell transplant, CAR-T cell therapy, next generation sequencing

Introduction

Neurolymphomatosis (NL) refers to infiltrative lymphomatous involvement of the cranial, spinal, and peripheral nerves and nerve plexuses and is the least common neurological presentation of lymphoma.[1,2] Neuropathy resulting from compression or entrapment by adjacent large lymphomatous tumors is not considered NL. It is a rare lymphoma entity, as revealed by the largest retrospective studies from large institutions (Mayo Clinic and Massachusetts General Hospital) and the International Primary CNS Lymphoma Collaborative Group (IPCG) in which 40, 25, and 50 cases were gathered over 16, 28, and 15 years respectively.[1–3]

Based on these large studies, the median age at diagnosis of NL is approximately 55.5–63 years with a slight male preponderance of 54–60%. Most cases were B-cell non-Hodgkin lymphoma (NHL) (82–97%). Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma associated with NL (68–75.5%).[1–3] NL is divided into primary and secondary NL depending on the absence or presence of systemic lymphoma. Clinical manifestations depend on the type of nerve involved: cranial nerves, spinal nerves, cauda equina, peripheral nerves, or nerve plexuses. The neurological symptoms can be sensory, motor, or mixed.

Cranial nerve involvement in DLBCL has been regarded as central nervous system (CNS) involvement.[4] Thus, primary cranial nerve NL is a subtype of PCNSL in which lymphomatous involvement is confined to cranial nerves. However, this condition is extremely rare, and the biology, clinical course, and natural history have not been well studied.

Received: 11 February 2024
Accepted: 12 June 2024
Published: 24 June 2024

Here, we describe the clinical course of a 57-year-old patient with PCNL, the genomic profile of the tumor, and a literature review.

Case Presentation

A 57-year-old male patient presented to our institution for the evaluation of multiple cranial neuropathies, including bilateral cranial nerve (CN) VII and right CNs III, V, and VI, spanning the previous 30 months. The outside magnetic resonance imaging (MRI) brain showed some enhancement of the cranial nerves, but cerebrospinal fluid (CSF) analysis was negative. He was initially managed with steroids and azathioprine was subsequently administered. His neurological symptoms improved transiently with these treatments but recurred with a reduction in the steroid dose.

At the time of evaluation, he experienced right-sided facial weakness, diplopia, and pain. Positive findings on neurologic examination included ophthalmoplegia of the right eye with limited abduction and adduction, decreased sensation of soft touch in the right V1-V2 distribution, and right-sided facial droop with weakness of the right eye closure and inability to puff the right cheek. The neurological findings were consistent with palsies of the right CN V, VI, and VII. The patient underwent an extensive diagnostic evaluation.

Magnetic resonance imaging (MRI) of the brain revealed asymmetric prominent enhancement of the right seventh cranial nerve at the mastoid segment, extending into the right parotid space, and asymmetric thickening and enhancement of the right cavernous sinus and right foramen rotundum (Figure 1). No significant abnormalities were observed in the brain parenchyma or spinal cord. Positron emission tomography (PET) scan utilizing fludeoxyglucose (FDG) radiotracer showed a pancreatic lesion, and biopsy revealed a low-grade neuroendocrine tumor. The abnormalities found on MRI involving the brain were not seen on PET scan. The CSF analysis results were negative. He underwent a right craniotomy and biopsy of the enhancing right cavernous sinus lesion, which was consistent with a large B-cell lymphoma involving nerve fibers (Figure 2). Pathology revealed multiple

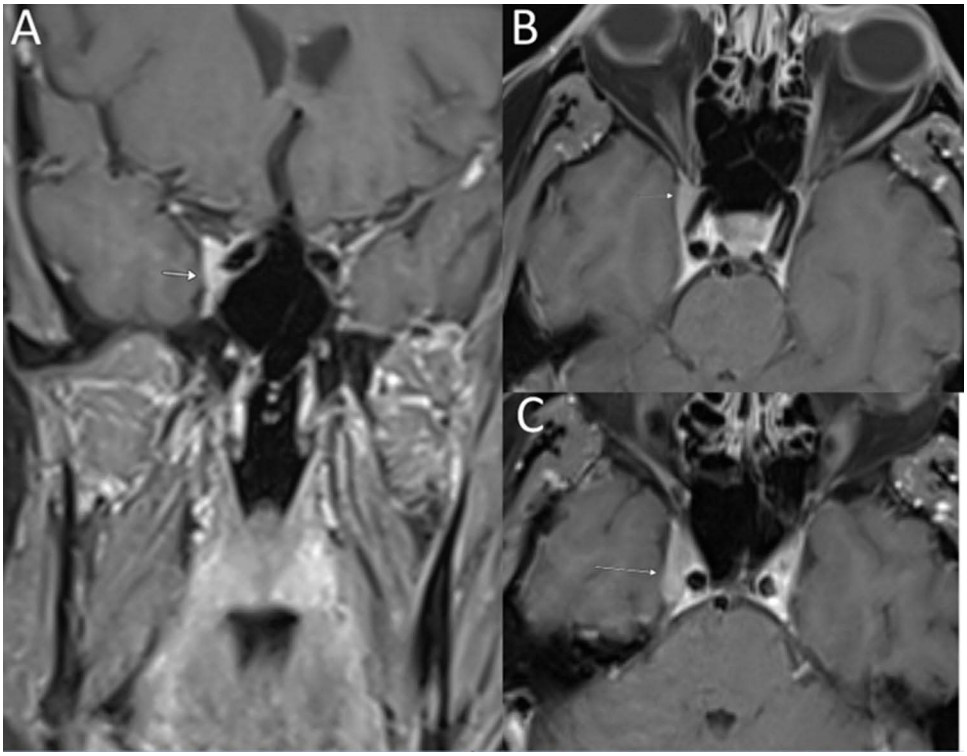

Figure 1 57-year-old man with multiple cranial neuropathies. Coronal (**A**) and axial (**B** and **C**) contrast-enhanced T1-weighted MR images showing a nodular enhancing lesion within the anterior right cavernous sinus (arrows) (B-cell lymphoma on biopsy).

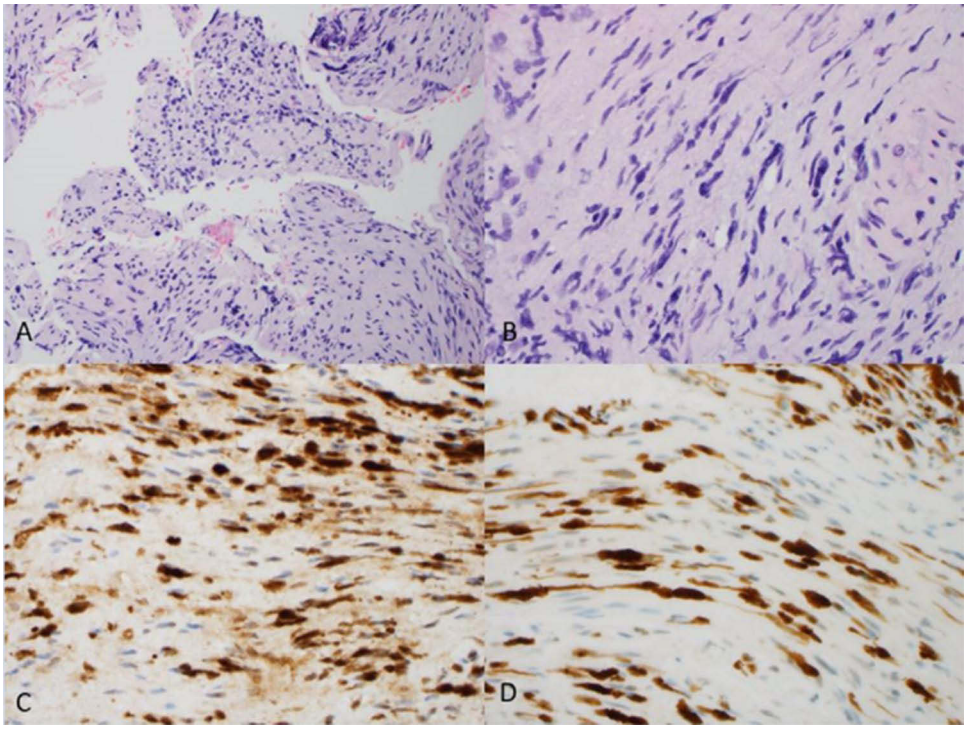

Figure 2 Biopsy of the right cavernous sinus lesion. The biopsy of the right cavernous sinus lesion comprises multiple fragments of nerve with the diffuse interstitial infiltrate of large, atypical cells (**A** and **B**, x 20 and x 40; respectively). The large, atypical cells are diffusely positive for PAX-5 (**C**, x 40) and CD20. The proliferative rate by Ki-67 is high (80%) (**D**, x 40). The findings confirmed a high-grade B cell lymphoma involving the cranial nerve.

fragments of nerves diffusely infiltrated by CD20+ and PAX5+ large atypical cells, with a Ki-67 proliferation index of 80%. A pathological diagnosis of cranial large B-cell neurolymphomatosis was made.

Formalin-fixed paraffin-embedded lymphoma tissue was sent for comprehensive genetic profiling using Hematology Profile Plus by the Genomic Testing Cooperative. Hematology Profile Plus uses next-generation sequencing, Sanger Sequencing, and fragment length analysis to identify molecular abnormalities in the DNA of 179 genes and RNA of 1408 genes associated with hematologic malignancies. The results are presented in Table 1. These findings are consistent with the activated B-cell (non-germinal center phenotype) signature with mutations in MYD88, CD79b, PIM1, CXCR4, and IKZF3.

Table 1 Genomic Profiling of the Tumor

Genomic Alterations				
Gene Name	Hgvsp	Consequence	Allele Frequency (%)	Predicted Effect
CD79B	NP_001035022.1:p.Tyr197Cys	Missense	24.03	Deleterious
CD79B	NP_001035022.1:p.Asp194Ala	Missense	23.27	Deleterious
CDC73	NP_078805.3:p.Ile252Met	Missense	20.61	Tolerated
CXCR4	NP_001008540.1:p.Arg152Gly	Missense	23.23	Deleterious
CXCR4	NP_001008540.1:p.Ile226Phe	Missense	16.24	Deleterious

(*Continued*)

Table 1 (Continued).

IKZF3	NP_036613.2:p.Phe146Leu	Missense	16.85	Deleterious
MITF	NP_937802.1:p.Glu419Lys	Missense	48.32	Deleterious
MYD88	NP_001166038.1:p.Leu265Pro	Missense	12.0	Deleterious
PIM1	NP_001230115.1:p.Gln128His	Missense	36.48	Deleterious
PIM1	NP_001230115.1:p.Glu226Lys	Missense	25.88	Deleterious
PIM1	NP_001230115.1:p.Gly119Asp	Missense, Splice region variant	22.06	Deleterious
PIM1	NP_001230115.1:p.Trp200Ter	Stop gain	20.58	Deleterious
PIM1	NP_001230115.1:p.Lys115Asn	Missense	16.67	Deleterious
PIM1	NP_001230115.1:p.Gln218Ter	Stop gain	16.23	Deleterious
PIM1	NP_001230115.1:p.Leu273Arg	Missense	16.17	Deleterious
PIM1	NP_001230115.1:p.Ser188Ile	Missense	16.15	Deleterious
PIM1	NP_001230115.1:p.Arg227Met	Missense	15.88	Deleterious
PIM1	NP_001230115.1:p.Gly136Asp	Missense	15.69	Deleterious
PIM1	NP_001230115.1:p.Glu121Asp	Missense	14.8	Deleterious
PIM1	NP_001230115.1:p.His159Asp	Missense	14.03	Deleterious
PIM1	NP_001230115.1:p.Leu268Val	Missense	13.41	Deleterious
PIM1	NP_001230115.1:p.Gly169Arg	Missense	12.86	Deleterious
PIM1	NP_001230115.1:p.Ser166Ala	Missense	12.72	Deleterious
PIM1	NP_001230115.1:p.Cys252Tyr	Missense	10.19	Deleterious
PIM1	NP_001230115.1:p.Ser65Arg	Missense	9.25	Deleterious

(*Continued*)

Table 1 (Continued).

PIM1	NP_001230115.1:p.Asn251Lys	Missense	8.97	Deleterious
PIM1	NP_001230115.1:p.Leu116Val	Missense	7.86	Deleterious
PIM1	NP_001230115.1:p.Gly73Asp	Missense	7.61	Deleterious
PIM1	NP_001230115.1:p.Met92Ile	Missense	6.61	Deleterious
PIM1	NP_001230115.1:p.Ser77Arg	Missense	6.42	Deleterious
Heterogeneity				
	There are abnormal clones with PIM1 (22 mutations), CD79B (2 mutations), CXCR4 (2 mutations), CDC73, IKZF3, and MYD88 mutations. The MITF mutation is detected at a high level, possible germline abnormality.			
Expression Profile				
	Increased B-cell markers. No significant increase in BCL1, BCL2, or MYC mRNA			
Chromosomal Structural Analysis				
	3p-, 6q-, 8p+, and +12.			
Cell of Origin				
	Expression profiling suggests ABC cell of origin, but less aggressive subtype (ABC1).			

The initial induction therapy used was the RMA regimen: rituximab, high-dose methotrexate (HD-MTX), and high-dose ara-c (HiDAC). The patient had an excellent clinical response, with resolution of the neurological symptoms after the first cycle. Unfortunately, he developed acute renal failure related to HD-MTX following the second cycle, which required hemodialysis. The patient's renal function eventually completely recovered. Repeat MRI after 2 cycles of chemotherapy showed persistent enhancement around the right trigeminal and facial nerves. He was then treated with skull-base radiation therapy, followed by the initiation of ibrutinib (560 mg daily). After radiation and four months of ibrutinib treatment, MRI showed improved enhancement around the cranial nerves, with no new lesions. He underwent high-dose chemotherapy with carmustine (BCNU) and thiotepa, followed by autologous stem cell transplantation (ASCT).

He was found to have relapse/progression four months after ASCT, with MRI showing new abnormal enhancement involving the cisternal segments of bilateral CN III and V with new enhancements within the left internal auditory canal along CN VII and VIII. Within a month, he experienced rapid neurological progression with severe bilateral shoulder pain, new left facial palsy, and difficulty with mastication. MRI of the cervical spine also showed multilevel cervical nerve root enhancement (Figure 3), whereas MRI of the lumbar spine showed enhancement of the cauda equina. The CSF cytology was positive for lymphoma. The patient underwent cervical spinal radiation with symptomatic relief. He received one cycle of rituximab, ibrutinib, and lenalidomide. Owing to rapid clinical deterioration, he was switched to two cycles of R-EPOCH (rituximab, etoposide, vincristine, cyclophosphamide, and doxorubicin) in combination with intrathecal triple chemotherapy with methotrexate, ara-c, and hydrocortisone. Due to relapsed and chemorefractory disease, the patient was referred for chimeric antigen receptor (CAR) T-cell therapy (CAR-T). He

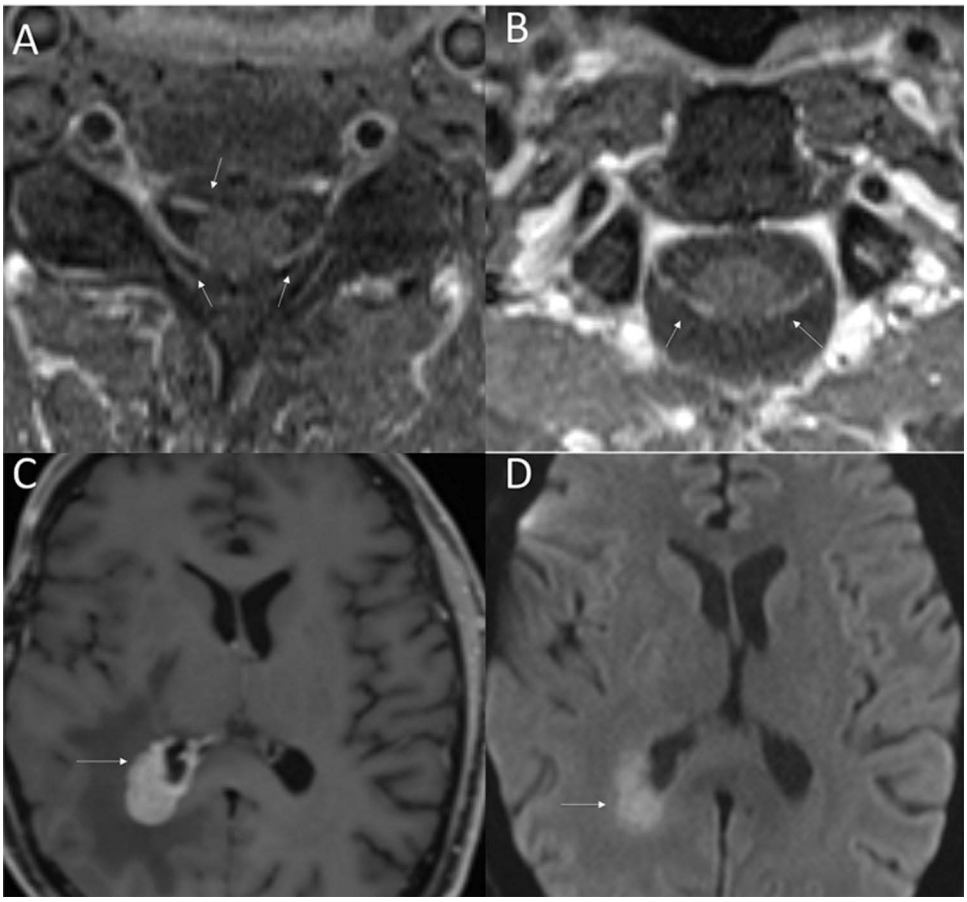

Figure 3 Follow up MRI of the cervical spine (**A** and **B**) and brain (**C** and **D**) after 1-year of initial presentation with progression of neurolymphomatosis. Axial (**A** and **B**) contrast-enhanced T1-weighted MR images of the cervical spine with thickening and enhancement of multiple dorsal and ventral nerve roots. Contrast-enhanced T1-weighted MRI of the brain reveals nodular enhancing lesion with ependymal involvement in the right peritrigonal region (**C**, arrow). Lesion shows restricted diffusion (**D**, arrow) suggesting high cellularity.

received low-dose fludarabine and cyclophosphamide lymphodepleting therapy followed by tisagenlecleucel infusion. CAR-T cell therapy was complicated by grade 1 cytokine release syndrome (CRS). MRIs performed 30 days post-CAR-T cell therapy showed interval improvement in the cranial nerve and cervical spine enhancement. However, MRI three months post-CAR-T showed disease progression with leptomeningeal and ependymal involvement (Figure 3). The patient returned home and underwent modified whole-brain radiation, excluding the skull base and upper cervical spine, based on prior treatments. Three months later, his disease progressed rapidly, with an outside MRI report indicating disseminated meningeal, ependymal, and brain parenchymal involvement, leading to his death 22 months after his initial diagnosis and 52 months after the initial episode of cranial neuropathy. The clinical timeline is shown in Figure 4. Throughout the disease course, he had periodic CT imaging that did not identify any lymphomatous involvement outside of the CNS. Additionally, monitoring of his pancreatic low-grade neuroendocrine tumor showed stability, and he never required treatment for this lesion.

Discussion

Our case illustrates many unique features that can be seen in PCNL. The patient had a rather long pre-diagnostic phase, spanning approximately 30 months, during which he had multiple relapsing episodes of cranial neuropathies. The patient was managed with steroids, which alleviated the symptoms; however, he was never in remission. Although there was no definitive evidence of PCNL during these months, it is quite likely that the patient already had PCNL. An analogous clinical scenario has been observed in PCNSL, in which some patients have control or even remission of the disease with steroid treatment only.[5] The PCNL in our patient shares this feature of steroid responsiveness, as described in PCNSL. As

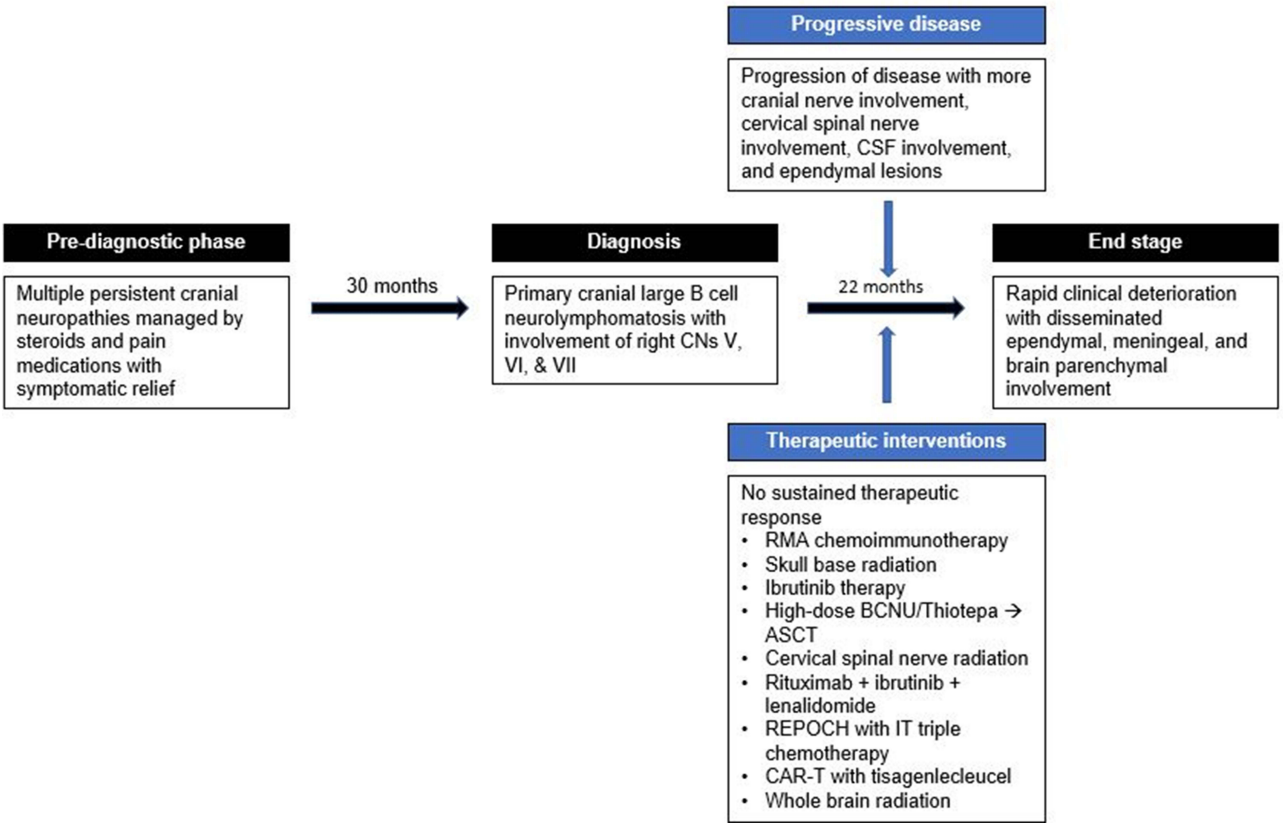

Figure 4 Diagram depicting the clinical timeline of our patient.

such, PCNL should be considered as a diagnostic possibility in patients with steroid-responsive but unexplained cranial neuropathies.

PCNL initially manifested in our patient with cranial neuropathies involving CN V, VI, VII, and VIII. He developed cervical spinal NL with CSF and brain involvement. Brain progression starts with ependymal tumors, followed by cerebral parenchymal tumors. A similar pattern of brain progression has been previously described.[1] In both cases, PCNL was initially observed in the brain as an ependymal tumor, followed by further dissemination in the brain parenchyma. This pattern of spread suggests that cerebral involvement occurs through the CSF pathway. Neither case showed evidence of PCNL via retrograde spread through the cranial nerves.

NL is difficult to diagnose in such cases. In the Massachusetts General Hospital (MGH) study covering the period 1972–2000, diagnosis was made by autopsy in 46% of the cases (33/72).[1] However, the IPCG study (1993–2008) showed a much lower incidence of diagnosis at autopsy at 8% (4/50), likely due to increased awareness and technology advancement.[2] In terms of diagnostic workup, MRI scans, PET scans, CSF analysis, and adequate biopsy of lesions on imaging are essential. PCNL appears as an enhancement along the tracts of cranial nerves. CSF cytology can be positive in approximately 40% of the cases.[1,2] PET can be used to rule out systemic lymphoma and peripheral nerve involvement. Collaboration with neurosurgical and radiology colleagues is essential to obtain adequate biopsies.

To the best of our knowledge, this is the first report of PCNL with genomic profiling. These findings include an activated B cell (non-germinal center phenotype) signature with MYD88 L265P, CD79b, and PIM1 mutations, which are similar to the typical genomic signature in PCNSL.[6] In terms of the mutation profile, this case can be classified as the MCD/C5 subtype.[7] Our patient had 22 mutations affecting PIM1, indicating highly active aberrant somatic hypermutation (Figure 5). PIM1 mutations have been associated with resistance to Bruton's tyrosine kinase inhibitors in ABC (non-germinal center phenotype)-DLBCL.[8] We identified four deleterious missense mutations

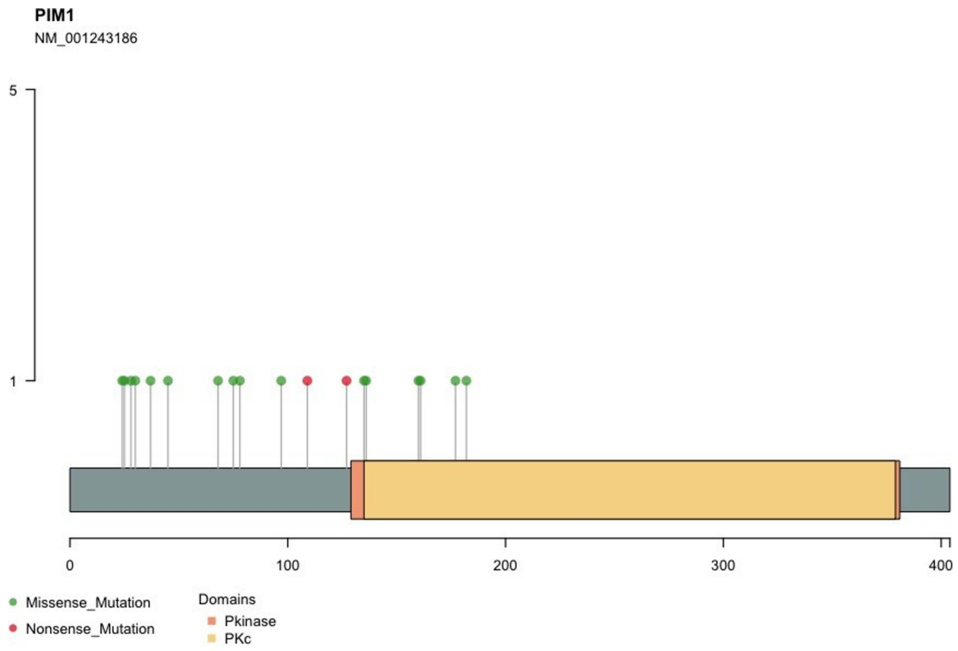

Figure 5 Lollipop plot of PIM1.

using SIFT and Polyphen prediction models (R136M, L182R, G45D, and G78R), two truncation mutations upstream of the functional kinase domain (W109* and Q127*), and four 5'UTR mutations.[9] 5'UTR mutations have been previously reported to result in overexpression of PIM1 and confer protection against autophagy.[10] Interestingly, the 5'UTR mutations were seen at lower allele frequencies than the non 5'UTR mutations (median 5'UTR Allele Frequency 7.11 (6.42–9.25) vs median non 5'UTR Allele Frequency 16.02 (7.86–36.48)). However, the significance of these findings remains unclear. Interestingly, our patient had two missense CXCR4 mutations that affected the carboxyl-terminus. This appears to be a unique feature of our case, as CXCR4 mutations have not been previously described in PCNSL.[11] The combination of MYD88, CD79, and CXCR4 mutations has been well-described in Waldenstrom macroglobulinemia (WM). Missense CXCR4 mutations in WM are associated with a more aggressive clinical course and resistance to ibrutinib.[12,13] Another unusual mutation found in our patient was IKZF3, which has not been previously described in PCNSL. Mutant IKZF3 in chronic lymphocytic leukemia has been associated with the hyperactive B-cell receptor signaling pathway and ibrutinib resistance.[14] Another novel finding was the TBL1XR1-ITPR1 fusion, which has not been described in the literature. TBL1XR1 mutations have been reported in 14–19% of PCNSL.[15,16] The profiling also revealed inversion 3, which has been previously described in myeloid leukemia and T-cell lymphoblastic leukemia/lymphoma.[17,18] The genomic profile in our case indicated highly upregulated signaling in B-cell receptors, Toll-like receptors, and NFKB signaling.

The patient did not respond to multiple lines of therapy in a sustained manner. Although there is no standardized approach for treating NL, it is reasonable to use the therapeutic approach adopted for PCNSL. HD-MTX based therapy appears to be associated with long-term survival in a subset of patients.[19–22] Survival has improved with the introduction of rituximab.[3] Radiation therapy was effective in terms of pain control, as observed in our patient. BTK inhibition was reasonable to consider for PCNSL, based on the MCD/C5 mutation profile. However, the ibrutinib therapy was ineffective. Thus, ASCT appears reasonable for eligible patients.[3] The blood-nerve barrier (BNB) appears to be structurally similar to the blood–brain barrier (BBB) and has been reported to be leakier.[23–25] BNB is also likely to be disrupted in the NL. In our case, R-EPOCH treatment had a disease-stabilizing effect, indicating its ability to permeate the BNB.

The findings of the literature review of the three largest NL studies are presented in Table 2. Cranial nerve involvement ranges 20–51% with CNS involvement 10–26%. 26–52% of the cases are primary NL. DLBCL

Table 2 Summary of the Three Largest NL Studies

	Mayo Study (2002–2018)	IPCG Study (1993–2008)	MGH Study (1972–2000)
Total number of cases (N)	40	50	72
Male	60%	60%	54%
Female	40%	40%	46%
Median age (Y)	60 Y	55.5 Y	63Y
B cell NHL	97%	82%	82%
DLBCL	68%	75.50%	NA
Cranial nerve involvement	20%	46%	51%
CNS involvement	10%	22%	26%
Primary NL	52%	26%	NA
Secondary NL	48%	74%	NA
HD-MTX therapy	62%	49%	12%
Rituximab	69%		
IT Chemotherapy	13%	49%	35%
Radiation therapy	13%	34%	72%
ASCT	40%	NA	NA
Median Overall Survival			
Whole Group	72.6 Months	10 Months (IY- 46%, 3Y- 24%)	NA
Primary NL	138 Months	20 Months	NA
Secondary NL	25.5 Months	8 Months	NA
Aggressive lymphoma	46.9 Months	NA	NA
Indolent lymphoma	Not reached	NA	NA

comprised 68–75.5% of the cases.[1–3] HD-MTX-based therapy was most frequently used in two recent studies.[1,3] The median overall survival for primary NL ranged from 20 (IPCG) to 138 months (Mayo). The Mayo series included patients with indolent B-cell lymphoma and peripheral nerve involvement. NL involvement in aggressive lymphoma was associated with a median OS of 46.9 months.[3]

We identified 12 cases of PCNL in the literature, with eight males and ages ranging from 33–74 (Table 3). All patients had B-cell lymphoma, with seven cases of DLBCL. The most common clinical manifestation was neurological facial symptoms seen in 8/12 patients with facial pain, numbness, or paralysis. The diagnosis was established by biopsy in 11/12 cases. CSF cytology was positive in 2/5 cases. HD-MTX-based therapy was used 7/12 cases. Complete response (CR) was reported in 8/12 patients. Long-term follow-up data was not available for all patients. Three patients died at 3, 14, and 18 months of follow-up. Two patients achieved CR at one-year follow up. One patient was in CR at 3-year follow up. One patient relapsed at eight months and was alive.

Table 3 Summary of Reported Cases of PCNL

Sex/Age	Histologic Subtype	Affected CN	Symptoms	Biopsy Proven Diagnosis	CSF cytology	Treatment	Response to Treatment	Outcome	Reference
47 M	DLBCL	(R) CN V	Facial pain	Yes	Negative	R-MPV, WBRT	CR	Remission at 1 year follow up.	[26]
40 F	B-cell lymphoma	(L) CN V, VI	Facial numbness Facial pain Headaches Diplopia	Yes	Negative	R-CHOP, RT	NR	NR	[27]
55 M	DLBCL	(L) CN V	Facial pain	Yes	Positive	MTX, WBRT, whole spine RT, and local RT	CR	Died 14 months later with MRI concerning for CSF relapse	[28]
52 F	B-cell lymphoma	(L) CN V	Facial pain	Yes	NR	NR	NR	NR	[29]
50 M	B-cell lymphoma	(R) CN V, VI, VII,	Facial pain Facial numbness Facial palsy Diplopia	Yes	NR	MTX, ARA-C	CR	Remission at 1 year follow up	[19]
60 M	DLBCL	(L) CN V	Facial pain	Yes	NR	Gamma knife radiosurgery initially MTX, WBRT at relapse.	CR	Relapsed 8 months following gamma knife radiosurgery. Remained in remission at 30 month following treatment for relapsed disease.	[20]
55 F	B-cell lymphoma	(R) CN V	Diplopia	Yes	NR	NR	NR	NR	[30]
74 M	DLBCL	(L) CN IX and X	Dysphagia Hoarseness	Yes	NR	Local RT	CR	Relapsed 1 month after RT. Died 3 months following diagnosis.	[31]
65 M	DLBCL	(L) CN V	Facial pain	Yes	NR	MTX, local RT, WBRT initially R-CHOP at relapse	CR	Relapsed at 3 months. Died 18 months after initial diagnosis from pneumonia.	[32]

https://doi.org/10.2147/JBM.S459123 DovePress

63 F	B-cell lymphoma	(L) CN V, VII	Diplopia Facial paralysis Facial pain Syncope Dysphagia Dysarthria	No	Positive	MTX-based chemotherapy	CR	Remission at 3 year follow up.	[21]
57 M	DLBCL	(L) CN V	Facial pain Hyperalgesia	Yes	Negative	MPV, Ferreri, aHSCT	CR	Remission at six month follow up.	[22]
33 M	DLBCL	Bilateral CN III and V	Hearing loss	Yes	NR	Chemotherapy (unspecified) and RT	NR	NR	[33]

Abbreviations: M, Male; F, Female; DLBCL, diffuse large B-cell lymphoma; L, left; R, right; CN, cranial nerve; NR, not reported; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; WBRT, whole-brain radiation therapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy; MTX, methotrexate; ARA-C, cytarabine; MPV, methotrexate, procarbazine, and vincristine; Ferreri, methotrexate, cytarabine, and rituximab; aHSCT, autologous hematopoietic stem cell transplant; CR, complete response.

https://doi.org/10.2147/JBM.S459123

Conclusion

Primary cranial NL is a rare subtype of PCNSL. Our patient shares a similar cell-of-origin signature (DLBCL-non-germinal center phenotype) and mutation profile with those of PCNSL (MYD88, CD79b, and PIM1 mutations). It is also associated with novel genomic alterations involving multiple mutations, such as PIM1, missense CXCR4 mutations, IKZF3 mutations, inversion 3, and TXL1XR1-ITPR1 fusion. The most common clinical symptoms are facial pain, numbness, and palsy, followed by diplopia. Therefore, PCNL should be considered in patients with unexplained steroid-responsive cranial neuropathies. Diagnostic evaluations should include MRIs, PET, CSF analysis, and biopsy. HD-MTX-based therapy has been frequently used in the management of NL in a subset of patients achieving long-term remission. Further research involving multiple institutions is needed to elucidate the biology and best therapeutic approach to PCNL.

Consent for Publication

The patient's next of kin has given written informed consent to publish the data, case details, and images. Institutional approval was not required to publish this case.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Baehring JM, Damek D, Martin EC, Betensky RA, Hochberg FH. Neurolymphomatosis. *J Neurooncl*. 2003;5(2):104–115.
2. Grisariu S, Avni B, Batchelor TT, et al. Neurolymphomatosis: an international primary CNS lymphoma collaborative group report. *Blood*. 2010;115(24):5005–5011. doi:10.1182/blood-2009-12-258210
3. Khurana A, Novo M, Nowakowski GS, et al. Clinical manifestations of, diagnostic approach to, and treatment of neurolymphomatosis in the rituximab era. *Blood Adv*. 2021;5(5):379–1387. doi:10.1182/bloodadvances.2020003666
4. Ferreri AJ. How I treat primary CNS lymphoma. *Blood*. 2011;118(3):510–522. doi:10.1182/blood-2011-03-321349
5. Weller M. Glucocorticoid treatment of primary CNS lymphoma. *J Neurooncol*. 1999;43(3):237–239. doi:10.1023/A:1006254518848
6. He X, Fan X, Shan Y, Ji X, Su L, Wang Y. Analysis of genomic alterations in primary central nervous system lymphoma. *Medicine*. 2023;102(35):e34931. doi:10.1097/MD.0000000000034931
7. Bertoni F, Montesinos-Rongen M. Primary diffuse large B-cell lymphoma of the central nervous system: molecular and biological features of neoplastic cells. *Ann Lymphoma*. 2022;6:1. doi:10.21037/aol-21-38
8. Kuo HP, Ezell SA, Hsieh S, et al. The role of PIM1 in the ibrutinib-resistant ABC subtype of diffuse large B-cell lymphoma. *Am J Cancer Res*. 2016;6(11):2489.
9. Flanagan SE, Patch AM, Ellard S. Using SIFT and PolyPhen to predict loss-of-function and gain-of-function mutations. *Genet Test Mol Biomarkers*. 2010;14(4):533–537. doi:10.1089/gtmb.2010.0036
10. Hoover DS, Wingett DG, Zhang J, Reeves R, Magnuson NS. Pim-1 protein expression is regulated by its 5'-untranslated region and translation initiation factor elF-4E. *Cell Growth Differ*. 1997;8(12):1371–1380.
11. Poulain S, Boyle EM, Tricot S, et al. Absence of CXCR4 mutations but high incidence of double mutant in CD79A/B and MYD88 in primary central nervous system lymphoma. *Br J Haematol*. 2015;170(2):285–287. doi:10.1111/bjh.13293
12. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Eng J Med*. 2015;372(15):1430–1440. doi:10.1056/NEJMoa1501548
13. Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. *N Eng J Med*. 2015;373(6):584–586. doi:10.1056/NEJMc1506192
14. Lazarian G, Yin S, Hacken ET, et al. A hotspot mutation in transcription factor IKZF3 drives B cell neoplasia via transcriptional dysregulation. *Cancer Cell*. 2021;39(3):380–393. doi:10.1016/j.ccell.2021.02.003
15. Gonzalez-Aguilar A, Ibdaih A, Boisselier B, et al. Recurrent mutations of MYD88 and TBL1XR1 in primary central nervous system lymphomas. *Clin Cancer Res*. 2012;18(19):5203–5211. doi:10.1158/1078-0432.CCR-12-0845
16. Bruno A, Boisselier B, Labreche K, et al. Mutational analysis of primary central nervous system lymphoma. *Oncotarget*. 2014;5(13):5065. doi:10.18632/oncotarget.2080
17. Jenkins RB, Tefferi A, Solberg LA, Dewald GW. Acute leukemia with abnormal thrombopoiesis and inversions of chromosome 3. *Cancer Genet Cytogenet*. 1989;39(2):167–179. doi:10.1016/0165-4608(89)90182-9
18. Rashidi A, McNeill S, Winters J, Alexander B, Roullet M. T-cell acute lymphoblastic leukemia/lymphoma with inversion (3)(q21q26). *Int J Lab Hematol*. 2013;35(5):e34–e36. doi:10.1111/ijlh.12064
19. Iplikcioglu AC, Dinc C, Bikmaz K, Ozcan D. Primary lymphoma of the trigeminal nerve. *Br J Neurosurg*. 2006;20(2):103–105. doi:10.1080/02688690600682630
20. Akaza M, Tsunemi T, Sanjo N, Wakimoto H, Kobayashi D, Mizusawa H. Malignant lymphoma presented as left trigeminal neuralgia. *Rinsho Shinkeigaku*. 2009;49(7):432–436. doi:10.5692/clinicalneurol.49.432
21. Sheng S, Sharma R, Samant R, Yuan J, Nalleballe K, Kapoor N. Isolated primary neurolymphomatosis with cranial multineuritis: a case presentation. *Neurol Sci*. 2021;42(3):1223–1226. doi:10.1007/s10072-020-04806-7

22. Jack AS, McDougall CM, Findlay JM. Primary lymphoma isolated to the trigeminal nerve. *Can J Neurol Sci*. 2014;41(1):103–105. doi:10.1017/S0317167100016371
23. Kanda T. Biology of the blood–nerve barrier and its alteration in immune mediated neuropathies. *J Neurol Neurosurg Psychiatry*. 2013;84(2):208–212. doi:10.1136/jnnp-2012-302312
24. Ubogu EE. The molecular and biophysical characterization of the human blood-nerve barrier: current concepts. *J Vasc Res*. 2013;50(4):289–303. doi:10.1159/000353293
25. Malong L, Napoli I, Casal G, et al. Characterization of the structure and control of the blood-nerve barrier identifies avenues for therapeutic delivery. *Dev Cell*. 2023;58(3):174191. doi:10.1016/j.devcel.2023.01.002
26. Ogiwara T, Horiuchi T, Sekiguchi N, et al. Primary malignant lymphoma of the trigeminal nerve: case report and literature review. *World Neurosurg*. 2015;84(2):592. e3–592. e7. doi:10.1016/j.wneu.2015.03.019
27. Abdel Aziz KM, van Loveren HR. Primary lymphoma of Meckel's cave mimicking trigeminal schwannoma: case report. *Neurosurgery*. 1999;44(4):859–862. doi:10.1097/00006123-199904000-00096
28. Kinoshita M, Izumoto S, Oshino S, et al. Primary malignant lymphoma of the trigeminal region treated with rapid infusion of high-dose MTX and radiation: case report and review of the literature. *Surg Neurol*. 2003;60(4):343–348. doi:10.1016/S0090-3019(02)01046-7
29. Bulsara KR, Kadri PA, Husain M, Al-Mefty O. Malignant lymphoma of the trigeminal region. Case illustration. *J Neurooncol*. 2005;73(3):279–280. doi:10.1007/s11060-004-5951-1
30. Perera C, Fitt G, Kalnins R, Lee S, Gonzalvo A. Lymphoma of the trigeminal nerve–the need for histological diagnosis. *Br J Neurosurg*. 2014;28(2):278–280. doi:10.3109/02688697.2013.835374
31. Sakai N, Ito-Yamashita T, Takahashi G, et al. Primary neurolymphomatosis of the lower cranial nerves presenting as dysphagia and hoarseness: a case report. *J Neurol Surg Rep*. 2014;75(01):e62–e66. doi:10.1055/s-0033-1363505
32. Sato H, Hiroshima S, Anei R, Kamada K. Primary neurolymphomatosis of the trigeminal nerve. *Br J Neurosurg*. 2023;37(4):697–700. doi:10.1080/02688697.2019.1568391
33. Koerbel A, Roser F, Psaras T, Beschorner R, Tatagiba M. Primary non-Hodgkin lymphoma of the cranial nerves mimicking neurofibromatosis Type 2: case illustration. *J Neurosurg*. 2005;102(6):1166. doi:10.3171/jns.2005.102.6.1166