



Primary central nervous system lymphoma: epidemiology and clinical presentation

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Abstract: Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin lymphoma that can affect any component of the central nervous system: brain, eyes and/or spinal cord. While it is a rare entity, the incidence has been rising since the 1960s with an increase in incidence in the 1990s that coincided with the human immunodeficiency virus (HIV) pandemic. More recently in the last two decades, incidence has been rising in the elderly population. PCNSL can have a wide range of presentations given possible involvement of any part of the nervous system, which can often lead to a delay in the diagnosis and treatment. Depending on the location involved, PCNSL can present with a variety of symptoms. Intracranial lesions are the most common manifestation of PCNSL and the majority present with focal neurologic symptoms, but nonspecific non-specific neuropsychiatric symptoms are also common. Primary leptomeningeal involvement is rare and can manifest with cranial neuropathies. Primary vitreoretinal lymphoma can present with blurred vision and symptoms mimicking uveitis. Spinal cord involvement can present with subacute myelopathy and peripheral nerve involvement or neurolymphomatosis can present with focal sensory and motor involvement. Given the wide range of clinical presentation, an understanding of the variable clinical manifestations of PCNSL is important for prompt diagnosis and treatment.

Keywords: Primary central nervous system lymphoma (PCNSL); epidemiology; clinical presentation

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Introduction

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin lymphoma that manifests in the nervous system. It is a rare, but highly aggressive neoplasm associated with high morbidity and mortality. However, it is potentially curable, which warrants rapid diagnosis and prompt treatment. Since it can present in any part of the central nervous system (CNS) and may commonly manifest with non-specific symptoms, diagnosis is often delayed. Additionally, the incidence of PCNSL has been increasing among the elderly population and thus a high

degree of clinical suspicion is important. We will review the epidemiology of the PCNSL as well as provide an overview of the highly variable clinical presentations of PCNSL.

Epidemiology

PCNSL affects both immunocompromised and immunocompetent patient populations. In immunocompetent patients, it is a rare tumor comprising 2–4% of newly diagnosed intracranial tumors (1,2). Histologically, most PCNSL are of diffuse large B-cell lymphoma (DLBCL-NOS) subtype, but a minority is comprised of T-cell lymphomas,

low-grade lymphomas, and very rarely Hodgkin lymphoma (3). In immunocompromised patients, such as in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), CNS lymphoma is postulated to be a separate clinical entity and on imaging often appears as ring-enhancing and multifocal lesions compared with immunocompetent patients (4). Organ transplant recipients are another immunocompromised population in which CNS lymphoma can be among the most common secondary malignancies, which fall the spectrum of primary central nervous system post-transplant lymphoproliferative disorder (PCNS-PTLD). Higher risk of developing CNS lymphoma may be associated with more intensive immunosuppressive regimens (5,6). There might also be an increase of PCNSL risk in diseases that lead to immunosuppression such as systemic lupus erythematosus and vasculitis and possibly, to a lesser extent, in patients with autoimmune disease that requires immunosuppression such as multiple sclerosis (5).

In general, PCNSL is more prevalent in men compared to women (7), there is a higher incidence in white versus the black population (2) and in the elderly population (7). The median age of diagnosis is 66 years in immunocompetent adults (2). PCNSL is rare in childhood, but the median age is approximately 14 years in the pediatric population (8).

Temporal trends

PCNSL incidence has undergone fluctuations over the past six decades with a general increase in incidence from the 1960s to 1990s, followed by a period of stabilization and increased incidence in the elderly in the last two decades. In the 1960s to 1990s, an increase in incidence was noted in immunocompetent populations based on improved diagnostic capabilities (9) as well as overall increased incidence (5). Given improved imaging techniques through computed tomography (CT) and magnetic resonance imaging (MRI) scans at the time, the incidence was initially thought to be increasing due to better diagnostic tools. However, despite global improvements in imaging techniques in the 1973–1977 period, the incidence of CNS lymphoma appeared to be increasing compared to systemic lymphomas and is not completely attributable to improved diagnostic methods and availability (10).

In the 1990s, PCNSL did experience a spike in incidence largely attributed to the HIV pandemic (1). Patients with AIDS had a 3,600-fold higher rate of developing CNS lymphoma compared with the general population (11). Thus, CNS lymphoma peaked in the mid-1990s, but

then decreased in the late 1990s corresponding with a decreasing incidence of AIDS, and better treatment with of highly active anti-retroviral therapy (HAART) (1,12). The prevalence of PCNSL cases occurring in HIV positive individuals declined from 64.1% in 1992 to 12.7% in 2011 (13). Afterwards, the incidence of PCNSL stabilized after the late 1990s in the general population (7,13). However, the rates continued to increase in women as well as in the elderly (13,14). In the past two decades, there is again some evidence of increasing incidence (15,16). However, a study in an Irish population found stabilization of incidence from 2007 to 2017 (17). Despite possible stabilization in the general population (13), the rates in the elderly continue to increase (18).

Survival

Survival in PCNSL has significantly improved since the 1960s but continues to lag behind systemic lymphoma. The median survival is estimated to be 14 months with relative 5-year survival estimated at 31.2% (7). For those younger than 49 years of age, survival is improved in whites versus blacks. However, in those older than 50 years of age, blacks have a trend of improved survival versus whites, but this difference is not statistically significant (7). In the younger population, white females have improved survival, whereas in older populations, black females have improved survival.

HIV positive individuals and immunocompromised individuals have worse survival rates compared to immunocompetent patients (4). The 5-year survival in HIV positive patients was 9% compared to 26% in non-HIV positive patients. However, 5-year survival did mildly improve to 15.8% in HIV positive individuals with the advent HAART therapy (13). In immunocompetent individuals, the 5-year survival also mildly improved from 19% to 30% from the 1990s to the 2000s (13). However, survival is worse in the elderly with median survival of 6–7 months (18). Survival is especially poor in the over 85 years old population with women generally living longer than men (19).

Clinical presentation

PCNSL has a variable clinical presentation depending on which part of the CNS is initially involved such as brain, meninges, spinal cord, eyes or peripheral nerves. As a result, initial symptoms can be wide-ranging and requires a high degree of suspicion and prompt investigation.

Given the heterogeneity of clinical presentations in

Table 1 Clinical features of intracranial PCNSL

Clinical characteristics
Focal neurologic deficit (weakness, sensory changes, loss of reflexes, cranial nerve deficit, ataxia)
Neuropsychiatric / Behavior changes
Increased intracranial pressure
Seizures
Vitreous involvement (most commonly blurred vision, floaters) (26)
Rarely, B-symptoms (fever, night sweats, weight loss are uncommon as presenting symptoms)

PCNSL, primary central nervous system lymphoma.

PCNSL, there are five clinical entities based on the initial CNS compartment involved: (I) intracranial lesions; (II) leptomeningeal lesions; (III) ocular/vitreoretinal lesions; (IV) spinal cord lesions; (V) peripheral nerve lymphoma [also called neurolymphomatosis (NL)] (20,21). While primary CNS lymphoma is predominantly of B-cell origin, primary CNS lymphoma can also be of T-cells subtype. Clinical presentation of T-cell PCNSL lymphoma is similar to B-cell PCNSL with possible increase in B-symptoms and a decrease in ocular involvement (22). Rarely, intravascular lymphoma can present with isolated CNS manifestations (23,24).

Intracranial lesions

Intracranial lesions in the brain parenchyma are the most common manifestation of PCNSL (25). The most common presentation of intracranial PCNSL is a focal neurologic deficit in 70% of patients, followed by neuropsychiatric or behavior changes in 43% of patients (25) (*Table 1*). Focal neurologic symptoms were most commonly motor or sensory, with headache as the most common non-focal symptom, and hemiparesis and papilledema as the most common signs (27). Focal neurologic symptoms at presentation can prompt neurologic investigation and imaging leading to a faster diagnosis. Psychiatric manifestations include depression, personality change, apathy, slowness of thought, impulsive behavior, psychosis, or hallucinations (20,28). While a focal neurologic manifestation was the most common manifestation, followed by neuropsychiatric symptoms (25), personality change was the most common symptom noted to subsequently affect approximately 60% of patients (20). Personality changes were thought to be due to infiltration of the brain parenchyma and visual hallucinations and

symptoms were due to involvement of the occipital lobe or direct eye involvement (20). With psychiatric or nonspecific presentations, diagnosis is often delayed with a mean of 80 days from symptom onset to admission in one study (25). Intracranial meningeal involvement can later develop leading to cranial neuropathies or new onset of headache (20). Primary CNS lymphoma can also present with increased intracranial pressure (ICP) (33% of patients), seizures (14%) and vitreous involvement leading to impaired vision and symptoms of floaters (4%). Rarely, in approximately 7% of patients, systemic symptoms such as fever, gastrointestinal, or respiratory symptoms will occur prior to neurologic symptoms. B symptoms such as fever, night sweats and weight loss, that are observed in systemic lymphoma, are rare in PCNSL (29).

PCNSL can present as either single or multiple intracranial masses. Approximately 45–50% of intracranial lesions are multifocal (20,27,30) [*Figure 1* (20)]. In PCNSL, most lesions are supratentorial rather than infratentorial in approximately a 3:1 ratio (20,27). In terms of the supratentorial lesions, the most common location was in the frontal lobe, while the cerebellum was the most common location among the infratentorial lesions (27). MRI with or without contrast is the preferred diagnostic modality to evaluate for PCNSL. On brain MRI, PCNSL lesions are generally homogeneously enhancing with areas of diffusion restriction and edema (31). Solitary lesions in immunocompetent patients compared to immunocompromised patients were found to be larger in size and occurred most commonly in the frontal lobes, corpus callosum or basal ganglia (32). One imaging study examining immunocompetent patients with CNS lymphoma found that 96% had diffusion restriction and 98.5% had enhancement, of which 51.5% was homogenous, 42.6% was heterogeneous and 4.4% was ring. The majority

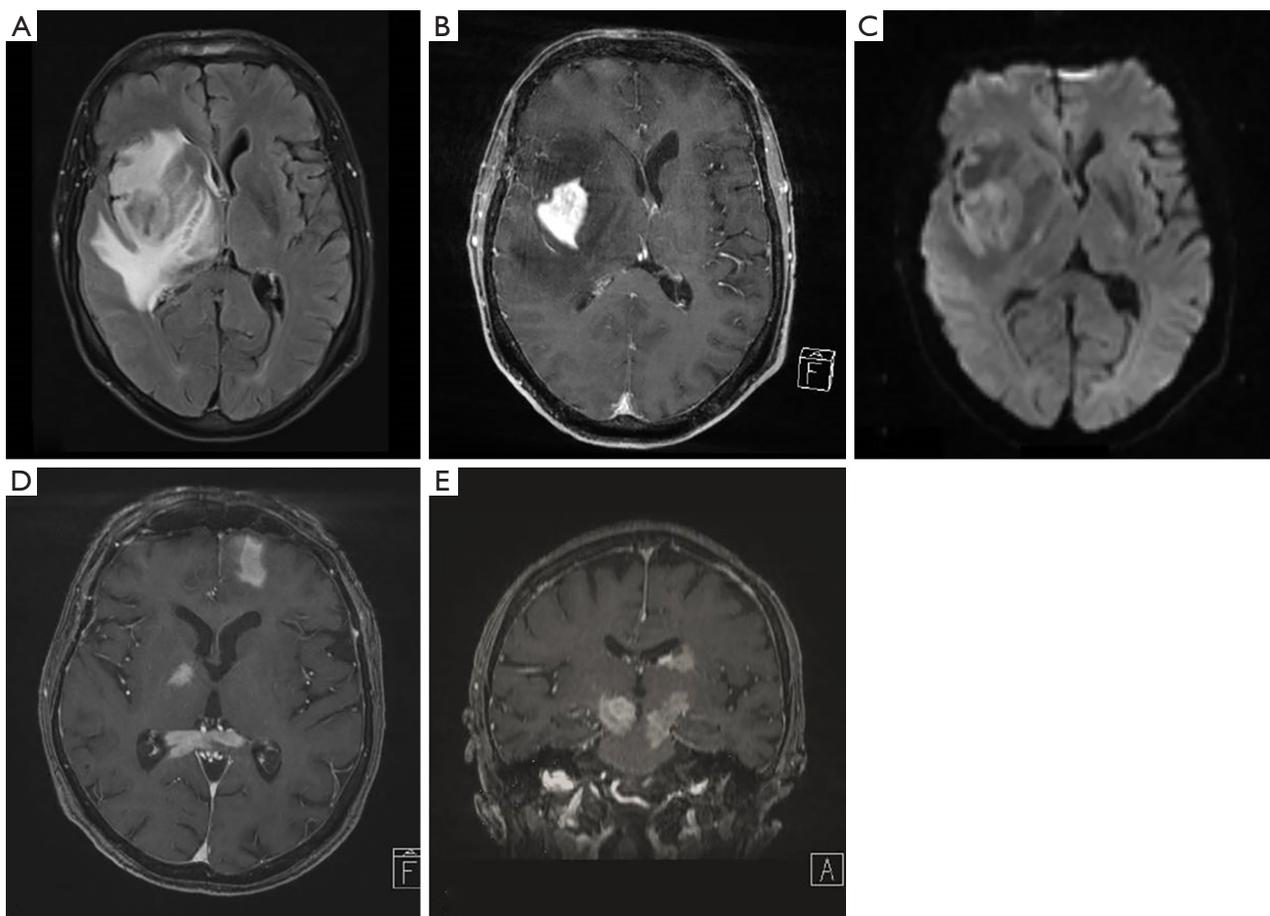


Figure 1 Brain magnetic resonance imaging (MRI) of two patients (A,B,C,D,E) with primary central nervous system lymphoma (PCNSL): (A) axial fluid-attenuated inversion recovery (FLAIR) sequence demonstrating a hypointense lesion surrounded by hyperintense edema; (B) axial, T1-weighted, contrast-enhanced sequence with homogeneous enhancement; (C) diffusion-weighted axial sequence showing bright signal in the lesion, indicating restricted diffusion; (D,E) axial and coronal T1-weighted, contrast-enhanced sequences revealing multifocal contrast-enhanced PCNSL lesions. (courtesy of Martin Bendszus, M.D., Division of Neuroradiology, University of Heidelberg). Figure from Löw S, Han CH, Batchelor TT. Primary central nervous system lymphoma. *Ther Adv Neurol Disord* 2018;11:1756286418793562.

(98.6%) also had a degree of edema with 43.4% showing mild edema and 55.2% with marked edema. Necrosis was seen in a small minority (~7%) of lesions. Approximately 97% of lesions were in contact with a cerebrospinal fluid (CSF) surface (33).

Leptomeningeal

Primary leptomeningeal lymphoma is rare and accounts for 7% of all PCNSL (34). In contrast, leptomeningeal dissemination is more commonly encountered in parenchymal primary CNS lymphoma with a range of 7–42% (35). As a result, diagnosis of leptomeningeal

lymphoma should commonly prompt work-up for intracranial or systemic involvement (3). Given the rarity, descriptions of clinical presentations are limited. Patients are generally diagnosed in the 6th decade of life (34,36) with large B-cell lymphoma as the most common entity and a minority (19%) of cases with T-cell (34). Primary CNS T-cell lymphoma is rare, but in one report, it was thought that 23% of primary CNS T-cell lymphoma cases presented with primary leptomeningeal involvement and suggests that isolated leptomeningeal disease may be a more common presentation in T-cell PCNSL (37).

A majority (68%) of patients present with multifocal symptoms (34). The most common symptoms and signs are

Table 2 Clinical features of primary leptomeningeal lymphoma

Clinical characteristics	
Cranial neuropathy (VI, VII)	
Encephalopathy	
Seizures	
Headache	
Ataxia	
Bowel/bladder dysfunction	
Peripheral neuropathy	
Back pain	
CSF characteristics	
Low glucose (median 47 mg/dL)	
Elevated protein (median 235 mg/dL)	
Elevated white count (median 96/mm ³)	
Lymphocytic predominance	
Positive cytology (67%)	
Positive flow cytometry (80%)	
Positive IgH or TCR gene rearrangement (71%)	

IgH, immunoglobulin heavy chain; TCR, T cell receptor.

cranial neuropathies (58%), particularly cranial nerves VI (abducens) and VII (facial), followed by spinal involvement (48%), headache (44%), ataxia (25%) and encephalopathy (25%) (34). A minority of patients present with isolated bowel or bladder symptoms (21%) (34). In another study 33% of patients presented with lumbosacral spinal signs and symptoms such as painful cauda equina syndrome, leg weakness and areflexia without cervical or cranial nerve involvement (36). Rarely (8%), patients present with seizures (34). CSF analysis shows low glucose (median of 47 mg/dL) in 54% of patients, elevated protein (median 235 mg/dL) in 92% of patients and elevated white blood cell count in 92% of patients (median 96/mm³ with lymphocytic predominance). A median of 2 lumbar punctures were required in one report to make the diagnosis (34). Cytology is positive in approximately two-thirds of patients (34,36). Flow cytometry was positive in 80% of patients and molecular rearrangements in immunoglobulin heavy chain (IgH) or T cell receptor (TCR) were positive in 71% of patients (34) (Table 2). A meningeal biopsy may be required if CSF is non-diagnostic. Most patients (81%) had abnormal neuroimaging including 79% with abnormal leptomeningeal enhancement [Figure 2 (38)]. A case report

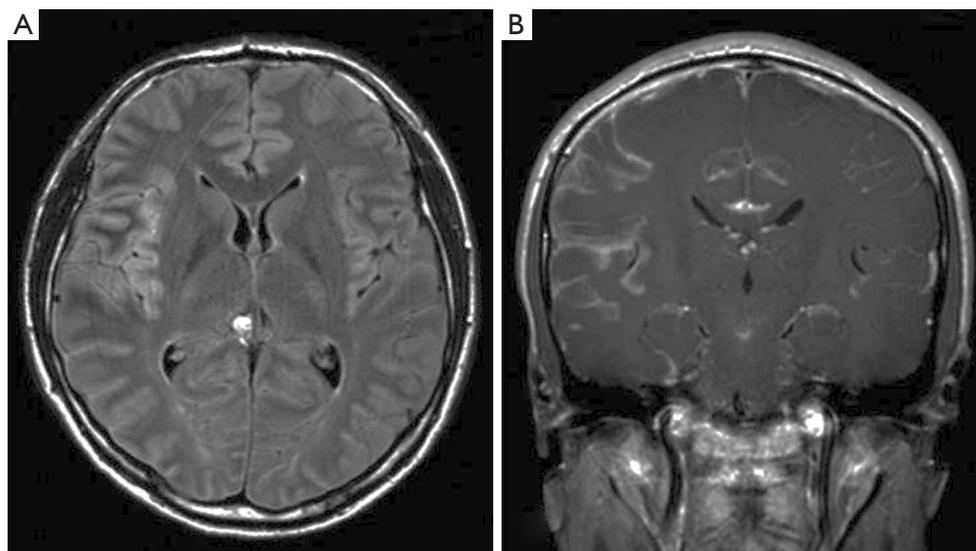


Figure 2 Brain MRI with (A) axial T2/fluid-attenuated inversion recovery (FLAIR) sequence shows hyperintense signal in right temporal lobe sulci and (B) coronal T1-post-contrast sequence showing leptomeningeal enhancement in the right temporal lobe and insula. Figure adapted from Park JS, Park H, Park S, *et al.* Primary central nervous system ALK positive anaplastic large cell lymphoma with predominantly leptomeningeal involvement in an adult. *Yonsei Med J* 2013;54:791-6.

showed meningeal calcification with low-grade marginal zone lymphoma (39).

A minority of PCNSL can present with dural-based lesions including DLBCL, marginal zone lymphoma (40-42), small lymphocytic B-cell lymphoma (43) and T-cell lymphoma (40). The radiographic appearance may mimic a meningioma. There is a greater incidence in women (40,41) with the calvarial dura as the most common site of involvement followed by the dura of the skull base (40). Patients commonly present with headaches, cranial nerve deficits, weakness, sensory changes, gait instability or vertigo that are related to mass effect of the tumor (40). CSF studies are reported positive for lymphoma in 46% of cases in one study (40).

Ocular/vitreoretinal

Primary vitreoretinal lymphoma (PVRL) is a subset of PCNSL with initial presentation of ocular involvement that may or may not be followed by brain or CNS involvement. PVRL mainly consists of B-cell lymphoma, with a minority consisting of T-cell lymphomas (44). An estimated 15–25% of patients with PCNSL will have ocular involvement at some point (20,45). Patients with PVRL have a high rate of progression to involvement of other CNS compartments. Approximately half of patients develop other sites of CNS involvement (45,46) and one study demonstrated up to 69% prevalence of non-ocular involvement (45). In one study, 31% of patients had ocular symptoms that preceded the cerebral involvement (47). Additionally, intraocular involvement may be the presenting sign of relapse in PCNSL (48) as well as systemic lymphoma, but less commonly (49).

PVRL affects women slightly more than men (44,50). Monocular or binocular involvement can be the initial presentation. While monocular symptoms may be more common initially (51), binocular involvement eventually develops in 64–83% of patients despite initial monocular symptoms (26,46). The most common presentations of PVRL are blurred vision (52%), decreased visual acuity (37%) and floaters (30%) (48). A minority of patients (17–38%) are asymptomatic (46,48).

Given nonspecific symptoms, patients can be misdiagnosed with corticosteroid refractory chronic uveitis (52). However, the posterior segment of the eye is preferentially involved in PVRL (53), which rarely involves the anterior segment of the eye. Additionally, PVRL does not demonstrate the anterior inflammation encountered

in uveitis (54). Diagnosis is often made with vitreal biopsy, vitrectomy, or vitreal fluid examination by cytology, cell markers studies, PCR or other molecular testing (50,55). CSF cytology is positive in 35% of patients (50). Recently, IL-10 and IL-10/IL-6 level in the vitreal fluid has been used to screen for PVRL (55). Given the high rate of concomitant CNS involvement, patients with PVRL should have a contrast-enhanced brain MRI to screen for brain involvement.

Spinal cord

Primary spinal cord lymphoma is rare and presents initially as a myelopathy. While patients with systemic lymphoma can develop leptomeningeal disease or cord compression from epidural lesions, intramedullary spinal lesions may also occur (56). Pathologically, most patients have B-cell morphology, but a minority are T-cell lymphomas (57).

In a retrospective review of 14 patients with primary spinal cord lymphoma most were male and presented in the 7th decade of life. All patients presented with a progressive myelopathy, that was predominantly subacute (56). Sixty-four percent of patients were found to have associated constitutional symptoms. Back pain was the presenting symptom in a minority of patients (29%), but was an associated symptom in 64% of patients. Forty-three percent of patients had lower motor neuron signs with areflexia or flaccid paralysis.

Neuroimaging demonstrates abnormal spinal MRI (*Figure 3*) in all patients with 64% showing multifocal involvement. Concomitant brain MRI lesions are also observed in 64% of patients. CSF cytology is positive in 27% of patients after 3 lumbar punctures, but non-diagnostic in a majority of patients. CSF demonstrates elevated protein, lymphocytic pleocytosis, but low glucose in a minority of patients (25%). Given the diagnostic limitations of spinal cord biopsy, brain biopsy of CNS lesions when present is preferred. However, spinal cord biopsy may be necessary in these rare primary spinal lymphoma cases to make an accurate diagnosis.

Peripheral nerves

NL is a descriptive term that identifies lymphoma patients with predominant involvement of peripheral nerves, nerve roots, plexuses or cranial nerves and is another rare presentation of PCNSL (58). In a retrospective review of leukemia and lymphoma patients who were diagnosed



Figure 3 Lumbar spinal magnetic resonance imaging (MRI) shows (A) sagittal T1-post contrast sequence with heterogeneously enhancing conus lesion (arrow) and (B) axial T1-post contrast sequence demonstrating intramedullary location of enhancing lesion (arrow). Images courtesy of Dr. Lakshmi Nayak, Department of Neurology, Brigham and Women's Hospital.

with NL, 26% of patients had NL as the initial presenting symptom (21). Primary NL typically presents with a painful neuropathy without CNS or systemic lesions. Initial presentation involves multiple peripheral nervous system components in 58% of patients most commonly in the peripheral nerves (60%), spinal nerve roots (48%), cranial nerves (46%) and nerve plexuses (40%). A painful neuropathy occurs in 76% of patients with sensorimotor neuropathy as the most common, but patients can also present with pure motor and, less commonly, pure sensory neuropathy (21). In one study, NL commonly presented in 1 of 4 patterns: (I) painful involvement of the nerves or nerve roots in 31% of patients; (II) cranial neuropathy with or without pain in 21% of patients; (III) painless peripheral polyneuropathy in 28% of patients; (IV) mononeuropathy with or without pain in 15% of patients (58). Approximately 5% of patients had mixed syndromes. Of the cranial nerves involved, the most common are oculomotor (III), abducens (VI), and facial (VII) (58).

CSF analysis demonstrates elevated protein (61% of patients), low glucose (11% of patients) and elevated cell count (44% of patients). Malignant cells are detected in the CSF in 40% of patients and 33% of CSF specimens

were positive for monoclonal gene rearrangements (21). MRI scans are abnormal in 77% of patients and fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans are usually positive in 87% of patients (21) (Figure 4). MRI images demonstrate abnormal enhancement (76%), enlarged nerves (53%) with a minority showing nodular (30%) or diffuse (17%) involvement of the nerve. Imaging is not definitive in approximately 50% of patients, who then required a nerve biopsy, reported to be positive in 88% of patients. Histologically, most cases are B-cell lymphoma with a minority showing T-cell lymphoma.

Conclusions

PCNSL is a rare lymphoma that can mimic multiple different neurologic diseases. The incidence of PCNSL continues to increase in the elderly population. Given the wide variety of possible clinical presentations of PCNSL, it is important to have a high degree of clinical suspicion. Primary CNS lymphoma can often mimic a variety of other CNS pathologies, especially demyelinating diseases given their steroid responsive nature. While intracranial PCNSL remains the most common manifestation, PCNSL can also

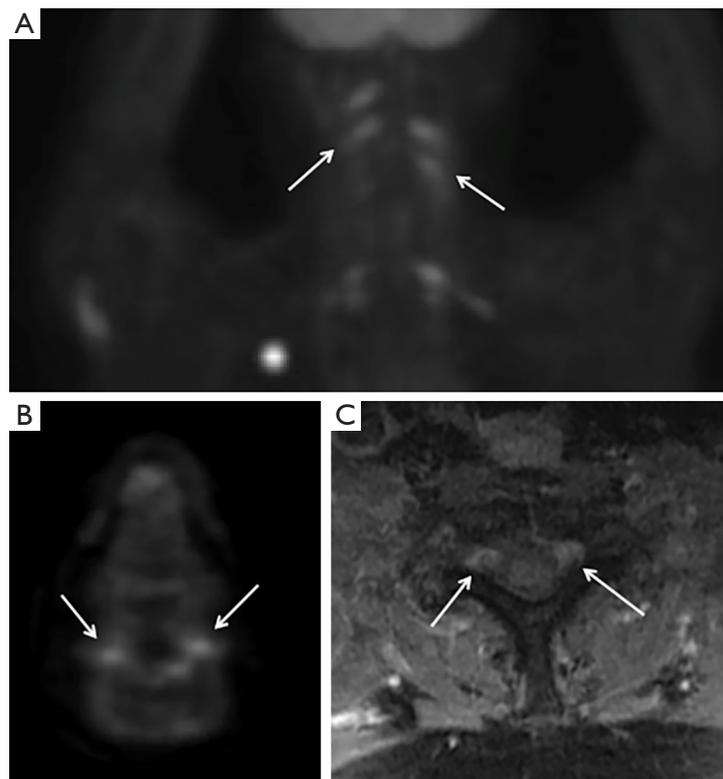


Figure 4 Neck positron emission tomography (PET) scan (A,B) and cervical spine magnetic resonance imaging (MRI) (C) in primary central nervous system lymphoma (PCNSL) patient with neurolymphomatosis. PET scan demonstrates linear fluorodeoxyglucose (FDG) activity (arrows) along bilateral cervical and thoracic spinal nerve roots in coronal sequence (A) and axial sequence (B). Cervical spine MRI shows increased prominence of bilateral C8 nerve roots (C).

present initially in the leptomeninges, eyes, spinal cord, or in the peripheral nervous system. Additionally, psychiatric manifestations are a common symptom in PCNSL leading to delay in diagnosis. Consequently, it is important to understand the different manifestations of PCNSL for prompt evaluation and treatment of a potentially curable, CNS malignancy.

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