American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2022; 23: e936401
DOI: 10.12659/AJCR.936401

Received: 2022.02.15
Accepted: 2022.05.05
Available online: 2022.05.16
Published: 2022.06.21

Primary Central Nervous System Burkitt Lymphoma, Presenting with Long-Term Fluctuating Level of Consciousness: A Case Report and Literature Review on Challenges in Diagnosis and Management

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Statistical Analysis C
Data Interpretation D
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Financial support: None declared
Conflict of interest: None declared

Patient: Male, 65-year-old
Final Diagnosis: Primary CNS Burkitt lymphoma
Symptoms: Flactuating level of consciousness
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Burkitt lymphoma (BL) is an aggressive subtype of B-cell non-Hodgkin lymphoma (NHL) rarely affecting the central nervous system (CNS) as a primary disease. Over the past years, only a few cases of primary CNS Burkitt lymphoma were reported. There is a challenge in early recognition and diagnosis of this type of brain lymphoma. Furthermore, there is no specific treatment protocols for primary CNS Burkitt lymphoma, which adds to the difficulty in managing those patients. We introduce a case of a 65-year-old who presented with fluctuating memory disturbance diagnosed as cerebral Burkitt lymphoma.

Case Report: A 65-year-old man developed a gradual decrease in his level of consciousness over a span of 4 days, associated with fluctuating memory disturbances. A CT scan showed a hyperdense mass in the region of the trigon of the left lateral ventricle and marked obstructive hydrocephalus involving the temporal, occipital horns, and the left lateral ventricle, with no evidence of other suspicious lesions. A brain biopsy of the lesion revealed features of encephalitis initially, but the patient presented later with worsening symptoms, and a repeated brain biopsy showed features of Burkett lymphoma, with normal pan-CT scan.

Conclusions: Primary CNS Burkitt lymphoma (PCNSBL) is a rare disease with no clear evidence in the literature of how to deal with it. Reporting such cases provides a better understanding of how to approach such unusual presentations. Treatment of PCNSBL is challenging and even with the currently adopted approaches, the disease still has a very poor outcome.

Keywords: Burkitt Lymphoma • Central Nervous System Neoplasms • Chemoradiotherapy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936401

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Background

Primary central nervous system lymphoma (PCNSL) is a rare form of aggressive extranodal non-Hodgkin lymphoma (NHL), representing only 2% to 3% of all cases [1]. PCNSL usually presents in elderly patients with an average age of 65 years [2]. It is usually of a diffuse large B-cell type that arises in the brain, leptomeninges, eyes, or spinal cord in the absence of systemic involvement [3]. PCNSLs subgroups include diffuse large B-cell lymphoma (DLBCL) (which is the more common subtype), Burkitt lymphoma, and T cell lymphomas [1,3-5].

Burkitt lymphoma is an aggressive subtype of B-cell NHL rarely affecting the central nervous system (CNS) as a primary disease [6-22], and can be distinguished from DLBCL by histopathology and immunohistochemistry, which is characterized by CD10+/bc-2-/bcl-6+ with a high Ki-67 proliferation index, and may show Epstein-Barr virus-encoded messenger RNA (EBER) and fluorescence in situ hybridization (FISH), and has the starry-sky appearance in some, but not all, cases, which is due to the presence of macrophages with relatively clear cytoplasm [23]. Over the past years, only a few cases of Burkitt lymphoma were reported as a primary disease affecting the CNS in both adults and children [6-33]. Unfortunately, there is a challenge in early recognition and diagnosis of such type of brain lymphoma, resulting in a delay in treatment and therefore, a poor prognosis [34]. Furthermore, there is no specific treatment protocol for primary CNS Burkitt lymphoma, which adds to the difficulty in managing those patients [35]. Here, we present a case of a 65-year-old man with primary CNS Burkitt lymphoma at the region of the trigone of the left lateral ventricle abutting the splenium of the corpus callosum. We also discuss the details of diagnosis and treatment approaches in this patient which included high-dose methotrexate and a ventriculoperitoneal (VP) shunt. In addition, a literature review is written to compare this case of PCNSBL to other similar case reports regarding treatment options and overall response to treatment in those patients.

Case Report

A 65-year-old-man, known to have diabetes mellitus and benign prostatic hyperplasia, developed a gradual decrease in his level of consciousness over a span of 4 days, associated with fluctuating memory disturbances that started 1 month prior to presentation. There was no associated headache, fever, abnormal movements, night sweating or weight loss. The patient was vitally stable on presentation with normal blood pressure, heart rate, temperature, and oxygen saturation; however, his Glasgow coma scale (GCS) was 13/15 due to eye opening only to verbal command and confusion; the other aspects of his neurological examination were normal.

He was started on 4 mg of dexamethasone every 4 hours empirically and showed significant improvement in term of level of consciousness, and he regained fully his neurological functions with GCS 15/15. Dexamethasone was then tapered and completely stopped after a course of 10 days.

A CT scan of the brain showed a hyperdense mass in the region of the trigon of the left lateral ventricle and marked obstructive hydrocephalus involving the temporal and occipital horns, and the left lateral ventricle.

CT scans of the cervical, abdominal, pelvic, and thoracic regions did not show any evidence of metastatic disease.

Cytologic examination of the cerebrospinal fluid (CSF) showed no abnormal cells, glucose level in CSF was 3.6 mmol/l (normal range 2.8-4.4 mmol/l), and protein level in CSF was 2.03 g/l (normal range 0.15-0.6 g/l).

A couple of months later, the patient presented again with similar signs and symptoms with fluctuating level of consciousness, and his GCS was 13/15.

A magnetic resonance imaging (MRI) of the brain showed an interval increase in the left lateral ventricle lesion with development of mild diffuse dural enhancement (**Figure 1A-1F**).

A mini-craniotomy and a biopsy of the previously descried brain lesion was done; the pathology report revealed features of encephalitis and no evidence of malignancy.

Dexamethasone was started then tapered slowly, this improved the patient's symptoms and confusion, and he was discharged and given an appointment to follow up as an out-patient while waiting for the biopsy results.

The patient presented again a few weeks later with decreased level of consciousness, GCS 13/15, with no constitutional or other neurological signs and symptoms.

A repeated CT scan of the brain showed left supratentorial hydrocephalus with an interval increase in size of the left intraventricular lesion which at this point measured 3.3×1.3 cm. A craniotomy and an excisional biopsy of the left ventricular lesion was done.

The histopathology report this time showed a diffuse infiltrate of lymphocytes with a starry-sky appearance at low power. The lymphocytes infiltrate was composed of sheets of monotonous, medium-sized lymphocytes with squares off borders, round nuclei, finely clumped chromatin, and several paracentral nucleoli. Numerous tangible macrophages, apoptotic bodies, and mitoses were also seen, all of which are features of

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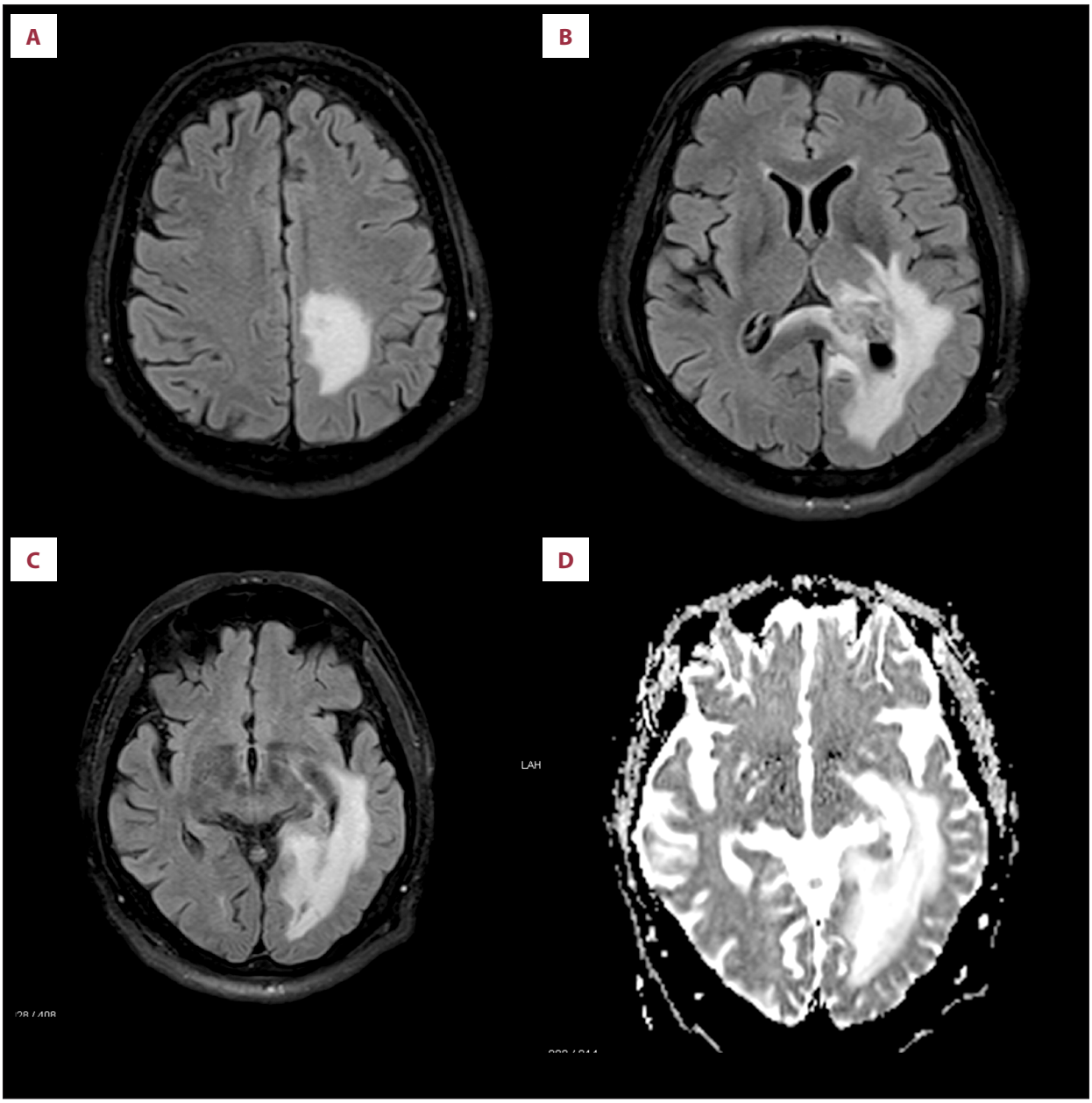
Burkitt lymphoma (**Figure 2A-2F**). A panel of immunohistochemical stains showed sheets of CD20-positive B-cells that coexpress CD10 and BCL6, and negative for BCL2. Proliferation index by Ki67 was approximately 100%. C-MYC rearrangement was detected by FISH studies. All of these histopathological, immunohistochemical, and molecular findings were indicative of a Burkitt lymphoma. A bone marrow biopsy showed no evidence of involvement by lymphoma, and pan-CT scans did not show any other lesions.

A ventriculoperitoneal (VP) shunt was inserted, and corticosteroids were started immediately after surgery, which improved the patient's level of consciousness.

A repeat lumbar puncture (LP) showed a glucose level of 2.8 mmol/l (2.8-4.4 mmol/l), protein level of 6.65 g/l (0.15-0.6 g/l), and no abnormal cells. Viral and bacterial cultures were negative.

A bone marrow biopsy showed no evidence of involvement by lymphoma, and pan-CT scans did not show any other lesions.

At this point, chemoimmunotherapy (rituximab, vincristine, and high-dose methotrexate) was started. On day 1, the patient received rituximab (375 mg/m^2) followed by high-dose methotrexate (3.5 g/m^2) and vincristine (total dose of 2 g) on day 2.



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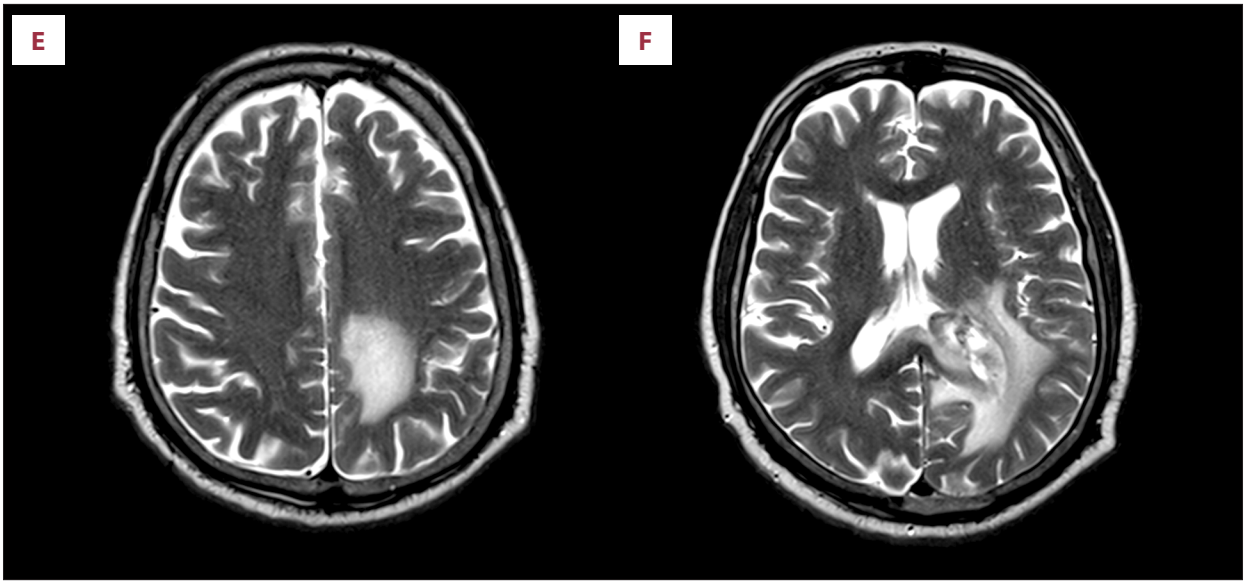

Figure 1. Multiple axial views of the magnetic resonance imaging (MRI) showing left lateral ventricle lesion with mild diffuse dural enhancement, with multiple series. (**A-C**) Represent series of T2 TIRM (turbo inversion recovery magnitude) dark fluid. (**D**) Represents series of DWI (diffusion weighted imaging). (**E, F**) Represent series of T2 TSE (turbo spin-echo).

The patient showed excellent tolerance to treatment and complete clinical neurological response was noted at day 3 where the GCS was 15/15.

A Brain CT scan on day 10 of treatment showed improvement of the left cerebral hemispheric edema, the midline shift, and no interval development of new lesions.

The laboratory investigations on day 12 of treatment showed that patient started to have neutropenia, and his CBC revealed white blood cells count (WBC) of 1.12 K/uL (4-10 K/uL), neutrophil count of 0.45 K/uL (2.5-7 K/uL), hemoglobin of 8.5 g/dl (13-16.5 g/dl), and platelets count of 157 K/uL (150-450 K/uL).

On day 18 of treatment, the patient developed febrile neutropenia with a temperature of 38.9°C and a neutrophil count of 0.4 g/l. Empirical antibiotic treatment was started initially using Piperacillin/Tazobactam (Tazocin) followed by Meropenem and Vancomycin; however, the patient was transferred to the intensive care unit due to septic shock. Blood cultures later came back positive for a multi-resistant *Acinetobacter baumannii*. Despite adding Colistin (polymyxin E) to target this bacterium, the patient died due to septic shock.

Discussion

Burkett lymphoma is a very aggressive subtype of NHL which rarely presents as a primary central nervous system disease and is usually associated with a poor outcome [34]. Initial symptoms and clinical signs of PCNSBL are sometimes difficult to recognize, and can be associated with long-term and fluctuating symptoms as seen in this case, hindering early diagnosis and treatment [34]. And since only a limited number of cases are reported in the literature, not enough information is available regarding different clinical presentations, diagnosis, and treatment modalities.

The sensitivity of CSF cytology is variable but is generally low (2-32%) [36]. This can be a result of low fluid volume, delays in processing, or the patient's exposure to corticosteroids prior to obtaining the specimen [36]. The yield of cytology specimens can be improved when serial samples are sent to the pathology lab and with the aid of immunohistochemistry and flow cytometry studies are performed if there is enough fluid volume [36].

Due to the above-mentioned reasons, a tissue biopsy for diagnosis is often needed. Central nervous system biopsies present a diagnostic challenge, especially when it comes to diagnosing lymphoma, because many times, the tissue is scant; therefore, preventing the use of an elaborate panel of immunohistochemical stain. Furthermore, many times, primary CNS Burkitt lymphomas are extensively necrotic, making biopsy interpretation even more challenging. Repeated tissue biopsy is sometimes needed to get a definitive diagnosis, as shown in our case, and other factors like steroid therapy can affect the quality of the biopsy. Lastly, biopsies may not be representative of the disease process if only the edges of the lesion are sampled, especially in deeper-seated lesions that are difficult to reach.

Multiple approaches have been used to treat PCNSBL in the literature (**Table 1**). Taking into consideration the rarity of this

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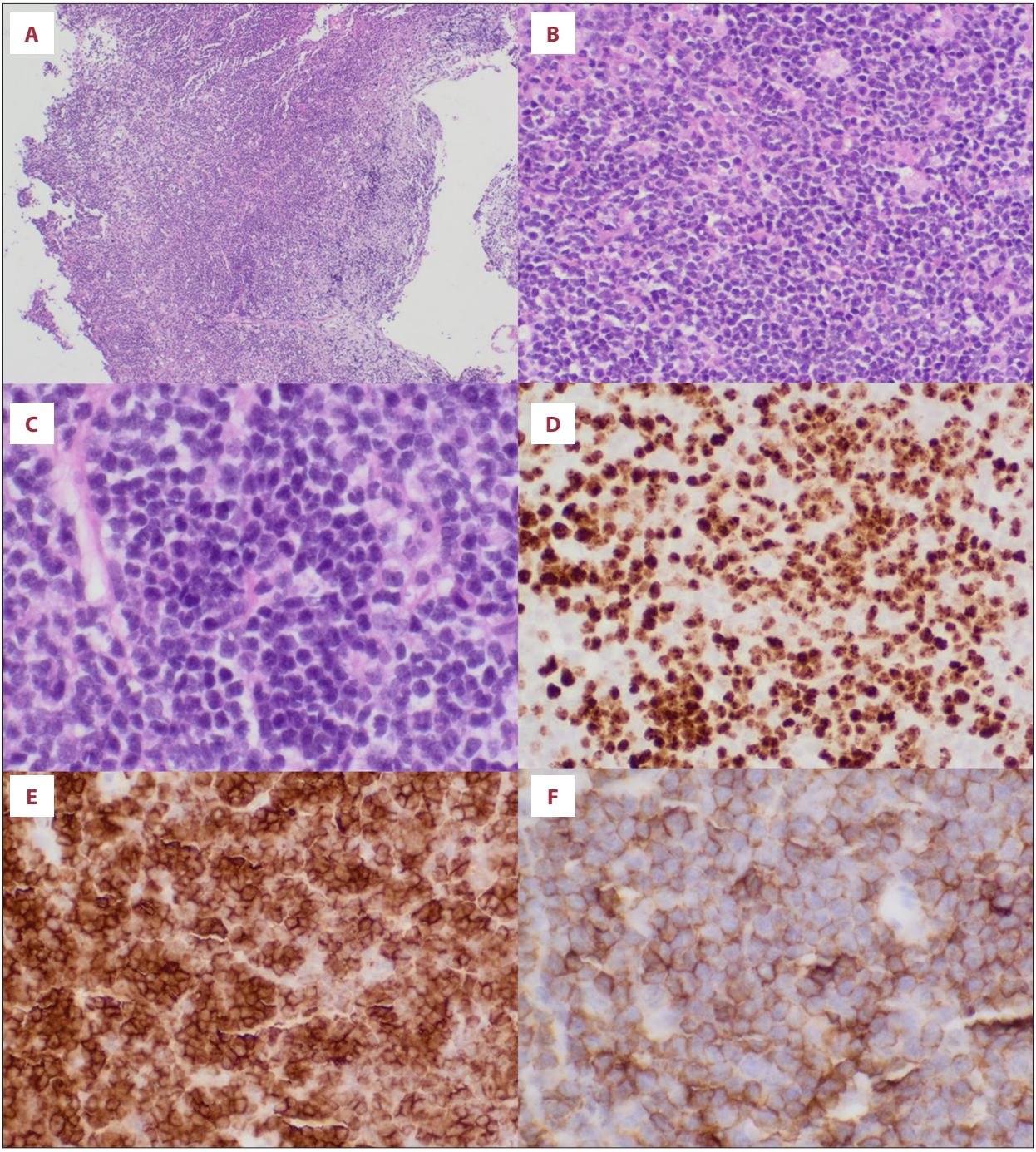

Figure 2. (**A**) Diffuse infiltrate of lymphocytes with a starry-sky appearance at low power. (**B**) Diffuse infiltrate of lymphocytes with a starry-sky appearance at high power. (**C**) Diffuse infiltrate of lymphocytes with a starry-sky appearance at intermediate power (×60). (**D**) Diffuse infiltrate of lymphocytes with immunohistochemical stains showing proliferation index by Ki67 was approximately 100%. (**E**) Diffuse infiltrate of lymphocytes with immunohistochemical stains showing CD10-positive. (**F**) Diffuse infiltrate of lymphocytes with immunohistochemical stains showing CD20-positive.

subtype and the lack of treatment guidelines [35], the treatment recommendations of PCNSL were followed in most of the reported cases, but even with these adopted modalities, the overall outcome was still unfavorable.

In the literature, patients with PCNSBL were mainly treated with high-dose methotrexate-based regimens (HD-MTX), either alone or in combination with surgery, radiotherapy, systemic and/or intrathecal (IT) chemotherapy.

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Table 1. Reported cases of primary central nervous system lymphoma in the literature, the multiple approaches used for treatment, and the outcomes.

Author	Year	Age	Gender	Presenting symptoms	Modality of diagnosis	Location
Valsamis et al [6]	1976	6 month	M	Fever, vomiting, seizure	Tissue biopsy	Left parietal,bilateral temporal with abdominal and peeriaortic lymph node involvement
Gawish et al [7]	1976	8 year	M	Left frontal fungating mass without neurological symptoms	Tissue biopsy	Left frontal lobe
Gigormini et al [18]	1981	11 year	M	Headache and confusion	Tissue biopsy	Left temporo-occepital
Kobayashi et al [27]	1984	55 year	F	Headache	Tissue biopsy	Right temporo-parietal
Hegedus [28]	1984	50 year	F	Seizures, vomiting	Post mortum autopsy	Right lower parietal
Pui et al [29]	1985	6 year	M	Paraplasia, loss of sensation below T8	Tissue biopsy	Epidural mass T2-T5
Pui et al [29]	1985	14 year	F	Paresis and parasthesia of right lower extremity	Tissue biopsy	Epidural mass L5-S1, left axillary lymph nodes, pleura, and abdomen.
Pui et al [29]	1985	7 year	M	Paraplasia	Tissue biopsy	Epidural mass C7-T4
Pui et al [29]	1985	12 year	M	Paraplasia, loss of sensation below T11	Tissue biopsy	Epidural mass T7-T10
Mizugami et al [30]	1987	6 year	M	Back pain, paraplasia	Tissue biopsy	Epidural mass T10
Mizugami et al [30]	1987	5 year	M	Parasthesia in lower limb, difficulty in walking	Tissue biopsy	Epidural mass L2-L3
Mizugami et al [30]	1987	7 year	F	Sensory and motor disturbances	Tissue biopsy	Epidural mass T11
Shigemori et al [31]	1991	49 year	M	Headache, memory disturbance and weakness in right lower extremities	CT, MRI and carotid angiogram and tissue biopsy	Left frontal lobe
Tekkok et al [32]	1991	5 year	M	Headache and loss of vision in left eye	CT and tissue biopsy	Parasellar mass extended to bilateral sphenoid bone and sella turcica
Toren et al [33]	1994	6 year	F	Ataxia, external ophthalmoplegia, facial diplegia, chewing and swallowing difficulties and irritability	CSF analysis	Brain CSF?
Spath-Schwalbe et al [8]	1999	40 year	M	Positional vertigo, nausea and vomiting	MRI and tissue biopsy	Cerebellum and pons
Mora et al [9]	1999	9 year	M	Low back pain then unable to walk	Myelogram and histopathology	Epidural T9-11 mass
Mora et al [9]	1999	18 year	M	Low back pain, then unable to walk, sever constipation and bladder incontinence	Myelogram and histopathology	T11

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Table 1 continued. Reported cases of primary central nervous system lymphoma in the literature, the multiple approaches used for treatment, and the outcomes.

Author	Year	Age	Gender	Presenting symptoms	Modality of diagnosis	Location
Wilkerning et al [10]	2001	43 year	F	Lumboischialgia, hypaesthesia of the right leg and radicular pain	Spine MRI and histopathology	L2-3 epidural tumor involving the dura and cauda equina
Monabati et al [11]	2002	49 year	F	Emotional disorder, left-sided weakness	MRI and histopathology	Right parietal mass
Daley et al [12]	2003	13 year	F	Low back pain, a burning sensation in the vaginal area, and difficulty voiding then unable to walk	Spine MRI and histopathology	L1-2 epidural mass
Shehu et al [13]	2003	8 year	M	Headache, lower right limb weakness and protrusion of the right eye. Later on blurred vision in the right eye and diplopia	CT brain and tissue biopsy	Left temporal and right orbit masses
Huisman et al[14]	2003	12 year	M	Right ophthalmoplegia, exophthalmos, headache, nausea and vomiting	Brain CT, MRI, tissue biopsy and BM aspiration	Right cavernous sinus mass extending into the orbital apex
Gobbato et al [15]	2006	38 year	M	Headache	CT, craniotomy, excisional biopsy	Subdural, fronto-temporo-parietal
Takasu et al [16]	2010	71 year	M	Generalized fatigue, disorientation	CSF, CT, MRI, biopsy	Hypothalamus, 3rd ventricle
Gu et al [17]	2010	75 year	F	Headache, speech disturbance	MRI, excisional biopsy	3rd and left ventricles
Lim et al [19]	2011	43 year	F	Headache	CSF, MRI, biopsy	Medulla-leptomeningeal seading
Jiang et al [20]	2011	14 year	M	Headache	MRI, excisional biopsy	Right lateral ventricle
Akhaddar et al [21]	2012	13 year	F	Right facial pain	MRI, biopsy	Temporal dura of the skull base, maxillary sinus
Yoon et al [22]	2012	10 year	M	Headache	CSF, MRI, biopsy	Suprasellar, cerebellum, 3rd ventricle
Yoon et al [22]	2012	32 month	M	Lethargic features	CSF, MRI, biopsy	Sellar area extend to orbit
Jiang et al [23]	2012	69 year	M	Bilateral lower limb weakness and pain	CSF, MRI, biopsy	Right temporal and occepital lobe
Alabdulsalam et al [24]	2014	18 year	M	Ataxia, double vision, dysphagia, facial asymetry	CT, MRI, biopsy	Posterior fossa, 3rd ventricle
Bower et al [25]	2018	55 year	M	Bilateral lower limb weakness	MRI, biopsy	Suprasellar, hypothalamus, right ventricle
Patel et al [26]	2019	7 year	M	Headache, decreased vision in left eye	MRI, excisional biopsy	Middle cranial fossa

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Table 1 continued. Reported cases of primary central nervous system lymphoma in the literature, the multiple approaches used for treatment, and the outcomes.

Author	Treatment	initial response	EFS	OS
Valsamis et al [6]	Steroid, whole brain and spinal radiation with relapse, IT MTX	Partial response	3 months	20 months
Gawish et al [7]	Total resection of tumor, chemotherapy (cyclophosphamide)	Complete response	>3 years	>3 years
Gigormini et al [18]	Total resection of tumor	Complete response	>1 year	>1 year
Kobayashi et al [27]	Total resection of tumor	Complete response	1 month	2 months
Hegedus [28]	None			3 months
Pui et al [29]	Laminectmy T2 to T5, chemotherapy CHOP without prednisone	Comlete response		>2 years
Pui et al [29]	Raditherapy L3-S2, chemotherapy CHOP	Comlete response		22 months
Pui et al [29]	Laminectomy C7 to T4, radiotherapy C7-T12, dexamethasone, cyclophosphamide	Comlete response		5 months
Pui et al [29]	Laminectomy T7 to T10, chemotherapy CHOP	Comlete response		4 months
Mizugami et al [30]	Laminectomy T7 to T11, surgical resection, spinal irradiation, systemic chemotherapy, then leukemic transformation and CSF recurrence, IT MTX and cranial irradiation	Complete response		20 months
Mizugami et al [30]	Laminectomy T12 to T4, spinal irradiation, chemotherapy with systemic recurrence	Complete response		7 months
Mizugami et al [30]	Laminectomy T9 to L2, surgical resection, spinal irradiation, systemic chemotherapy	Refractory		3 months
Shigemori et al [31]	Resection, radiation, Chemotherapy, CHOP, MTX.	Good response		>6 months
Tekkok et al [32]	Resection, chemotherapy, CHOP and MTX, craniospinal radiation.	Good response		>18 months
Toren et al [33]	Steroids, IVIG, doxorubicin, vincristine, HD MTX, with IT MTX, cytarabine, and hydrocortisone. Changed to CHOP with MTX and IT MTX, cytarabine, hydrocortisone	Complete remission		> 2 years
Spath-Schwalbe et al [8]	Chemotherapy combined with MTX then subsequent radiotherapy	Partial response initially then full remission after radiotherapy		>1 year
Mora et al [9]	Laminectomy, chemotherapy via LSA3 protocol. Then received palliative radiation in second recurrence	Relapse		>1 year
Mora et al [9]	Laminectomy, CHOP substitute daunorubicin for doxorubicin and radiation.	Relapse and refuse treatment		>8 months

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Table 1 continued. Reported cases of primary central nervous system lymphoma in the literature, the multiple approaches used for treatment, and the outcomes.

Author	Treatment	initial response	EFS	OS
Wilkerning et al [10]	Surgical resection, radiation and IT MTX, cyclophosphamide, vincristin, methotrexate, ifosfamid, adriamycin, and dexamethasone	Good response		>2 years
Monabati et al [11]	Complete resection, CHOP, and craniospinal radiation. Refused further treatment.	Good response		>6 months
Daley et al [12]	Laminotomy, CHOP with MTX, and IT MTX and cytarabine and steroids.	Good response		>5 years
Shehu et al [13]	Cy, vincristine, and MTX with IT cytosine arabinoside	Deteriorated progressively due to viral hepatitis then died		11 months
Huisman et al[14]	IV and intrathecal chemotherapy according to the NHL-BFM-1995 protocol. Then anti-CD20 antibodies (rituximab) after relapse	Relapse, and died due to liver failure		3 months
Gobbato et al [15]	Total resection of tumor	Refractory		11 days
Takasu et al [16]	Partial resection, WBRT	Good partial response		
Gu et al [17]	Total resection of tumor, WBRT	Complete response	>9 months	>9 months
Lim et al [19]	Chemotherapy (HD-MTX based protocole)	Refractory		6.7 months
Jiang et al [20]	Total resection, gamma-knife therapy, chemotherapy (MPV)	Complete response	>18 months	>18 months
Akhaddar et al [21]	Chemotherapy	Partial response		3 months
Yoon et al [22]	Systemic chemotherapy (HD-MTX and HD cytarabine), IT	Complete response	>86 months	>86 months
Yoon et al [22]	Systemic chemotherapy (HD-MTX and HD cytarabine), IT	Complete response	6 months	9 months
Jiang et al [23]	WBRT, chemotherapy (HD-MTX, cytarabine,rituximab)	Partial response		
Alabdulsalam et al [24]	Total resection, chemotherapy(CHOP-R and HD-MTX), IT	Complete response	>18 months	>18 months
Bower et al [25]	WBRT, chemotherapy (HD-MTX, cytarabine)	Complete response	>30 months	>30 months
Patel et al [26]	Total resection, WBRT, chemotherapy(HD-MTX, cytarabine), IT	Complete response	>12 months	>12 months

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Except for high-dose methotrexate therapy, most other therapeutic modalities are controversial, especially intrathecal chemotherapy and whole-brain radiotherapy (WBRT) [16].

Although most of the international guidelines and review articles discourage total surgical resection of PCNSL due to the infiltrative behavior, multifocality of the tumor, and the elevated risk of post-operative complications [37-39], some studies recommend and adopt such an approach and state that aggressive resection of PCNSL correlated with better progression-free survival (PFS) and overall survival (OS) compared to biopsy without total resection of the tumor [37,40].

Based on these data, total resection of tumor in PCNSBL could be beneficial in selected cases, in addition to the other treatment modalities, especially when the tumor is solitary and not deeply infiltrating the brain.

As there is no specific guideline in treating PCNSBL, and most of the reported cases of PCNSBL were treated according to the guidelines of PCNSL, the current recommendations in treatment of PCNSL put chemotherapy as the first line of treatment, either alone or in combination with radiotherapy [41]. HD-MTX remains the best single agent effective in treating these tumors as it effectively penetrates the blood brain barrier [42]. Another effective single agent is HD-Cytarabine; the combination of this agent with HD-MTX and WBRT has shown better complete remission rate and overall response rate compared to HD-MTX and WBRT alone (46% and 69% vs 18% and 40%, respectively [43].

WBRT alone does not produce remission; however, it is considered an additional approach to other modalities [44]. Most of the studies do not recommend WBRT due to the risk of neurotoxicity, especially in the elderly population [44-46]. In a phase III randomized trial, the addition of WBRT to those patients who were in complete remission (CR) after methotrexate-based chemotherapy showed no statistically significant improvement in OS [47]. In those who achieved partial response after methotrexate-based chemotherapy, the addition of WBRT revealed a benefit in term of PFS (P=0.002) but not OS (P=0.119) [47].

IT chemotherapy is usually not recommended in the treatment of PCNSL, as it only increases toxicity, with minimal to no survival benefits when added to i.v. chemotherapy [47,48].

Conclusions

PCNSBL is a rare entity of brain lymphomas that affects elderly individuals, which makes its diagnosis and treatment challenging, and most of the cases of PCNSBL reported in the literature were following the treatment recommendations of PCNSL. Reporting these cases enriches the literature and provides a better understanding on how to approach and treat those patients with PCNSBL. Treatment of PCNSBL is challenging and even with the available options and current adopted approaches, the disease still has a very poor outcome.

Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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