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SHORT COMMUNICATION

Neurological presentation of lymphoma: Report of six cases

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ABSTRACT

Primary or secondary lymphomas of the central nervous system may present with various focal or nonfocal neurologic signs and symptoms depending on the location and size of the lesions in the brain and the amount of surrounding edema and mass effect. The most common of these symptoms are cranial nerve deficits, but mental status changes, focal weakness, sensory loss, epileptic seizures, increased intracranial pressure, headache, and radicular pain may also be observed. However, neurological presentations of lymphomas are rare. The diagnosis may be challenging due to the various involvement patterns both clinically and radiologically. Although biopsy is the gold standard method in diagnosis, cerebrospinal fluid cytopathology and flow cytometry are useful in detecting hematological malignancy in the cerebrospinal fluid. Herein, we reported six cases of lymphoma with neurologic presentation.

Keywords: Central nervous system, neurologic presentation, primary lymphoma, secondary lymphoma.

Central nervous system lymphomas (CNSL), which constitute 2% of all brain tumors, are divided into two groups as primary or secondary (the most common) according to their origin.[1] Lymphomas originating from the brain, medulla spinalis, meninges, and vitreoretinal area are called primary CNSLs.[1] Central nervous system (CNS) involvement of a systemic lymphoma is called secondary CNSL. The diagnosis of lymphoma may be challenging both clinically and radiologically, since it may involve various parts of the nervous system, which leads to diagnostic difficulties.[2] In this case report, we aimed to discuss patients with CNSL who presented with neurological symptoms with their diagnostic stages to raise awareness about this rare and often late-diagnosed disease (Table 1).

CASE REPORTS

Case 1- A 26-year-old female patient with a normal medical history presented with complaints of weakness and numbness in the legs and urinary incontinence. The patient was in her postpartum second month and stated that the complaints increased after delivery. Neurologic examination revealed paresis at lower extremities, increased deep tendon reflexes, and decreased vibration. Cranial magnetic resonance imaging (MRI) revealed a contrast-enhancing hyperintense (T2 and FLAIR [fluid-attenuated inversion recovery]) area around the fourth ventricle. Diffusion-weighted imaging (DWI) was normal (Figure 1a). Additionally, leptomeningeal contrast enhancement at the level of the lesion, in the infratentorial structures, and at the level of the lower spinal segment were detected. Vasculitis and tumor markers and the positron emission tomography examination were normal. Cell-based neuromyelitis optica (NMO) and myelin oligodendrocyte glycoprotein (MOG) antibodies were negative. Lumbar puncture revealed elevated protein and lactate dehydrogenase; immunoglobulin (Ig) G index was increased, oligoclonal band (OCB)

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TABLE 1
Summary of clinical and laboratory features of the patients

Case	Age/Sex	Presentation	MRI	CSF	Cytopathology
1	26/F	- Weakness and numbness in the legs - Urinary incontinence	Infiltrative lesion around the fourth ventricle, C*+	- Protein ↑ (251 mg/dL) - Cell count ↑ (189/mm³; 188 MNL**, 1 PML***)	Burkitt lymphoma
2	40/F	- Blurred vision - Numbness in the left half of the face, left arm and leg - Seizure	Diffusion restricted infiltrative lesion in the right parietal lobe, C+	- Normal	Diffuse large B-cell lymphoma
3	39/F	- Pain in the legs	Lumbosacral roots enlargement and hyperintensity on T2, C–	- Protein ↑ (709 mg/dL) Cell count ↑ (238/mm³ (237 MNL, 1 PML) - Glucose ↓ (10 mg/dL)	HIV-associated primary effusion lymphoma
4	22/M	- Numbness in the left half of the face, - Difficulty in speaking and chewing	Normal	- Protein ↑ (179 mg/dL) Cell count ↑ (7303/mm³ (7249 MNL, 61 PML)	Burkitt lymphoma
5	58/M	- Weakness in both legs - Drooping eyelids	Normal	- Protein ↑ (690 mg/dL) Cell count ↑ (211/mm³ (164 MNL, 47 PML)	Diffuse large B cell lymphoma
6	54/M	- Weakness in both legs - Facial asymmetry	Normal	- Protein ↑ (400 mg/dL) - Cell count ↑ (795/mm³ (785 MNL, 10 PML) - Glucose ↓ (13 mg/dL)	Non-Hodgkin malignant lymphoma

MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; MNL: Mononuclear leukocytes; PML: Polymorphonuclear leukocytes; HIV: Human immunodeficiency virus; * Contrast; ** Mononuclear cells; *** Polymorphonuclear cells

was positive with type 4, and monocytic white blood cells (WBCs) were detected. Cerebrospinal fluid (CSF) examination revealed atypical cells, and a cytopathological diagnosis of Burkitt lymphoma was established. A written informed consent was obtained from patient.

Case 2- A 40-year-old female patient on tenofovir treatment for chronic hepatitis B was admitted with the complaint of left-sided numbness and focal clonic seizures in the left arm, leg, and half of the face. In her history, it was learned that she had unilateral painless blurred vision, which lasted for a

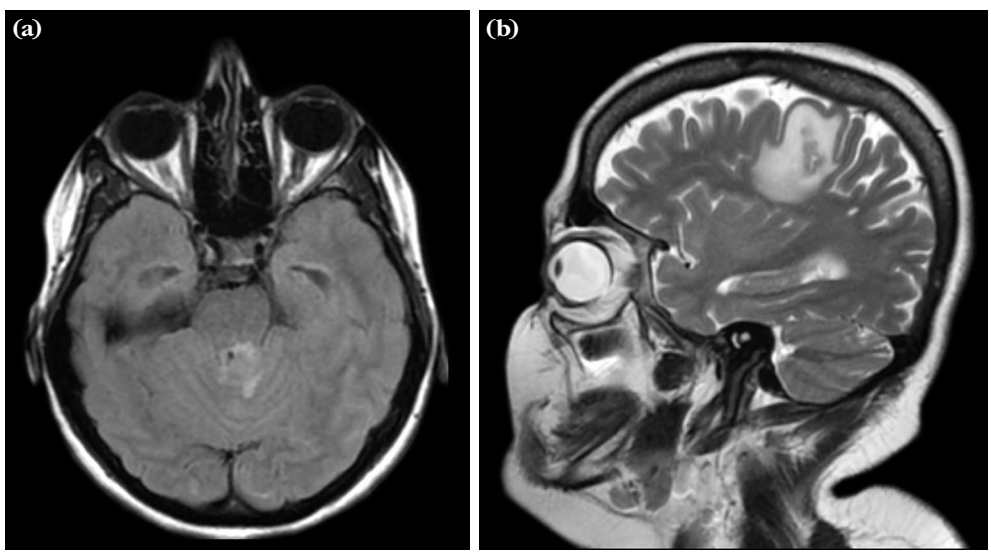

Figure 1. (a) Hyperintensity in the left lateral neighborhood of the fourth ventricle in the axial FLAIR sequence (Case 1). **(b)** Right parietal infiltrative lesion detected on cranial MRI (Case 2).
FLAIR: Fluid-attenuated inversion recovery; MRI: Magnetic resonance imaging.

couple of days six months ago, with no pathologic findings on neurologic examination and cranial MRI at that time. Neurologic examination revealed left hemihypoesthesia, including the left half of the face. Additionally, the patient had epilepsia partialis continua in her left arm. A right parietal diffusion-restricting, contrast-enhancing infiltrative lesion was detected on cranial MRI (Figure 1b). Vasculitis panel and cell-based NMO and MOG antibodies were negative. Biochemical and microbiologic examination of the CSF was normal, and 1 g/day intravenous methylprednisolone and levetiracetam 1000 mg/day were started. Regression in the lesion and clinical improvement were found on follow-up imaging after a month. In the follow-up of the patient, the same complaints developed again one year later, and the infiltrative lesion was detected again in the same localization. Magnetic resonance spectroscopy was performed; there were nonspecific findings. A biopsy from the lesion established the diagnosis of diffuse large B-cell lymphoma. A written informed consent was obtained from patient.

Case 3- A 39-year-old female patient with a diagnosis of human immunodeficiency virus (HIV) infection and under antiretroviral treatment presented with pain radiating from her lower back to both legs for two months. It was learned that the patient was diagnosed with primary effusion lymphoma in the fluid sampling performed upon development of pleural effusion during HIV follow-up. After four months and six cycles of R-EPOCH (rituximab, etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin), the patient started to complain of subacute onset of back pain radiating to the legs, which gradually worsened and became permanent. Lumbar MRI revealed enlargement of the lumbosacral roots without contrast enhancement on T2-weighted sequences (Figure 2). No parenchymal or leptomeningeal involvement was observed on cranial MRI. Nerve conduction study showed decreased combined muscle action potentials in the lower extremities and absence of tibial F-waves. Needle electromyography revealed neurogenic motor unit potentials. In the CSF, glucose was low, protein was high, and cell count revealed increased WBC with mononuclear predominance. Intravenous Ig was administered (0.4 g/kg/day for five days). Cerebrospinal fluid cytopathology and flow cytometry revealed CD79a-positive large, atypical B cells. The patient was transferred to the oncology unit to receive treatment for lymphoma. A written informed consent was obtained from patient.

Case 4- A 22-year-old male patient was admitted to our clinic with numbness starting from the left lip and spreading to the whole face, difficulty in speaking, and swallowing. One month before admission to our clinic, the patient was investigated due to a persistent cough, and a mediastinal mass was detected. Examination revealed weak right-sided peripheral facial paresis. The left half of the tongue was mildly atrophic, and the tongue deviated to the left with tongue protrusion, suggesting left 12th nerve palsy (Figure 3). No pathology was detected on cranial MRI. Lumbar puncture revealed elevated protein and increased WBCs with monocytic predominance. Cytopathologic examination of the CSF was compatible with Burkitt lymphoma. A written informed consent was obtained from patient.

Case 5- A 58-year-old male patient with an unremarkable medical history presented with weakness in both legs and drooping eyelids. He had peripheral fascial paralysis six weeks ago and recovered completely. On examination, there was no movement in the right eye, except for minimal upward gaze. There was inward and downward gaze limitation in the left eye. Bilateral ptosis (right eye fully closed), bilateral weakness in the frontalis muscle, lower extremity paresis, absence of deep tendon reflexes, and decreased vibration were detected. No significant findings were found on cranial MRI. Repetitive nerve stimulation was normal. The CSF examination revealed high level of protein, increased monocytic WBC, decreased level of glucose, increased level of albumin, and increased IgG index. Cytopathological evaluation of the CSF revealed abundant atypical lymphoid cells, and flow cytometry revealed findings in favor of CD5- and CD10-negative diffuse large B-cell lymphoma. The patient was transferred to the intensive care unit due to respiratory distress in the follow-up and he died within a few days. A written informed consent was obtained from patient.

Case 6- A 54-year-old male patient was admitted to our clinic with complaints of pain and numbness starting from the left groin area, radiating to the left leg for about one year, and spreading to the right leg for the last three months, with the development of facial asymmetry for a week. On examination, outward gaze limitation in both eyes, lower extremity paresis, and absence of deep tendon reflexes were detected. No pathology was found in cranial and spinal imaging. Electromyography

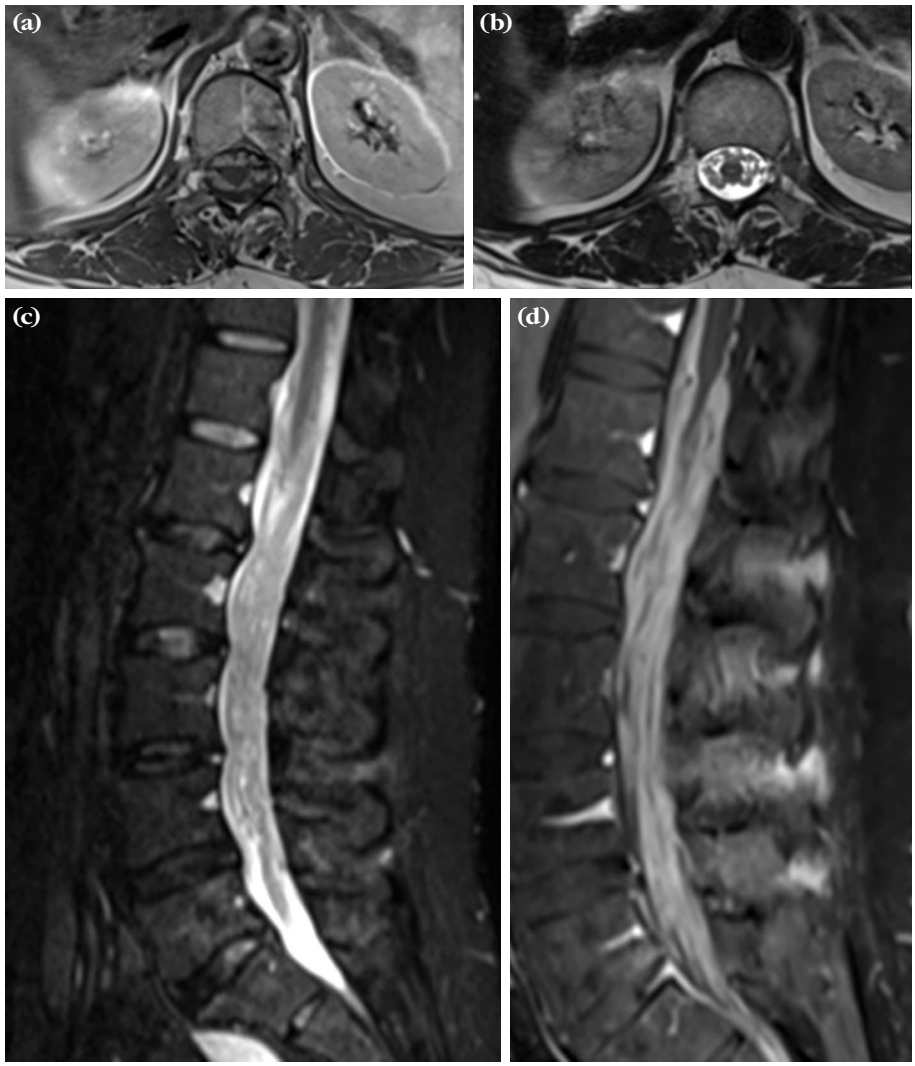

Figure 2. T1- and T2-weighted images of **(a, b)** axial and **(c, d)** sagittal magnetic resonance imaging showing thickening of the lumbosacral roots without contrast enhancement.

examination revealed axonal dominant sensorimotor type polyneuropathy. The CSF examination revealed high protein level, low glucose level, and increased monocytic WBC count. Intravenous Ig 0.4 g/kg/day was administered for five days. Cytopathologic examination revealed diffuse mature lymphocytes and lymphoid cells with atypical nuclei, and the patient was diagnosed with non-Hodgkin malignant lymphoma. A written informed consent was obtained from patient.

DISCUSSION

Primary lymphomas can be encountered in the CNS, as there can be central involvement of systemic lymphomas. Although most lymphoma subtypes can involve the CNS, diffuse large B-cell lymphoma is the most common.[3] The incidence of CNS lymphoma increases with age, particularly in patients older than 70 years.[4] However, our patients were younger than the expected age group for lymphoma, with a mean age of 40 (range, 22 to 58) years.

Primary or secondary CNSL may present with various neurologic symptoms. The symptoms develop subacutely and vary according to the localization of the involvement. Focal neurological deficits may be detected in 70% of patients, while 40% may develop nonspecific cognitive impairment and behavioral changes.[5] Headache, nausea, and vomiting secondary to increased

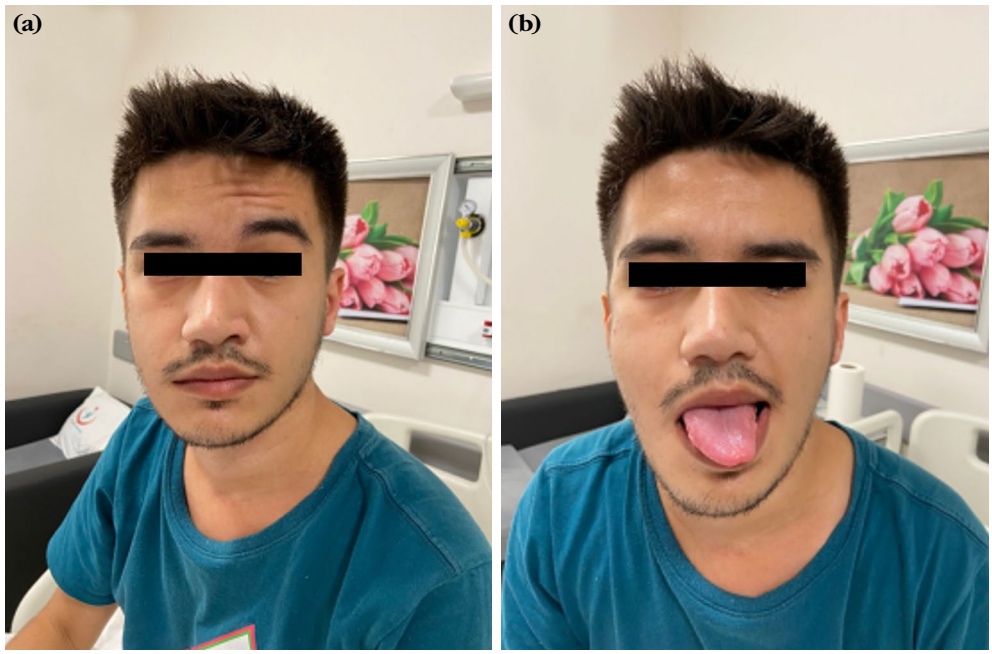

Figure 3. **(a)** Seventh and **(b)** 12th cranial nerve palsy in Case 4.

intracranial pressure are common symptoms. Despite frequent ocular involvement (20-25%), visual symptoms are rare (4%).[6] In secondary CNSL, leptomeningeal involvement and secondary peripheral or cranial nerve involvement are more common compared to primary lymphomas.[7] Painful radiculopathy, saddle-like anesthesia, and urinary retention are also common symptoms. The most common presentation in our six cases was lower extremity paresis and hypoesthesia. Cranial nerve involvement (cranial nerves III, IV, VI, VII, and XII), neuropathic pain, and seizures were other symptoms. Involvement of systemic non-Hodgkin lymphoma can occur either at the time of initial diagnosis or, more commonly, in the setting of disease relapse.[2] The true incidence of CNS involvement may vary based on the histologic subtype of systemic non-Hodgkin lymphoma, with more aggressive subtypes more likely to experience CNS involvement at some point in their disease course.[2] Approximately two-thirds of the patients present with leptomeningeal spread and one-third with parenchymal disease. The incidence of CNS involvement in patients with Burkitt lymphoma and lymphoblastic lymphoma may be as high as 50%.[8] There has also been consideration given to the primary site of disease as a factor in CNS relapse. The testes, nasal/paranasal sinuses, and bulky retroperitoneal involvement were associated with increased risk of CNS disease.[9] Immunodeficiency is an important risk factor.[7] We had one patient who was positive for HIV and under antiretroviral therapy. There was no immunosuppressive condition in our other patients. Central nervous system involvement was observed in two of our patients with secondary CNSLs, which were Burkitt lymphoma and HIV-associated primary effusion lymphoma. Since we had two secondary CNSL cases, it is difficult to state a relationship between aggressiveness and CNS involvement.

Patient with symptoms concerning lymphoma should immediately undergo imaging. In lymphoma, contrast-enhanced cranial MRI shows lesions that are isointense to hypointense on T1- and T2-weighted sequences, hyperintense on FLAIR sequences, homogeneously contrast-enhancing, and predominantly diffusion-restricting on DWI.[2,5] The lesions are often periventricular (%60), within the deep white matter, the corpus callosum, or the basal ganglia.[7] In immunosuppressive patients, multifocal, ring-shaped lesions with contrast enhancement and central necrosis are more common. This pattern may mimic demyelinating disorders. Therefore, initially, demyelinating diseases such as multiple sclerosis, NMO, and MOG antibody disease are included in the differential diagnosis. That is why CSF OCB and NMO and MOG antibodies should be checked in suspected

patients. In the cranial imaging studies of our patients, no abnormal findings were observed in two patients, while cranial and thoracolumbar infiltrative lesions were encountered in the others. We found contrast enhancement to be more heterogeneous. The thoracolumbar MRI finding in our immunosuppressed patient was root enlargement without contrast enhancement.

In two of our lymphoma cases, one with Burkitt lymphoma and another with malignant non-Hodgkin lymphoma, MRI findings were absent. Other cases demonstrated various MRI abnormalities in cranial and lumbosacral imaging. In a patient with HIV-associated primary effusion lymphoma, we identified enlargements in the lumbosacral roots without any contrast enhancement. In the other, there was an infiltrative lesion in the right parietal lobe that exhibited diffusion restriction on DWI and appeared hyperintense on the FLAIR/T2 sequence, with heterogeneous contrast enhancement in contrast-enhanced sequences. Our patient with Burkitt lymphoma in Case 1 had a hyperintense lesion on FLAIR sequences with a heterogeneous contrast enhancement pattern adjacent to the fourth ventricle, which did not restrict diffusion. We also observed leptomeningeal enhancement in this case. Although diffusion restriction in DWI of lymphoma is an expected finding, there was diffusion restriction in one of our two cases with cranial involvement. In addition, in these cases, contrary to expectations, instead of a homogeneous contrast enhancement pattern, there was a heterogeneous contrast enhancement pattern, which is more frequently encountered in immunosuppressive lymphoma patients. Imaging findings in lymphoma can vary, as in our patients. Therefore, it should be considered in the differential diagnosis in patients with atypical MRI findings.

Cerebrospinal fluid analysis may aid in the diagnosis of CNSL since malignant cells may be present in up to 40% of patients with primary CNSL.[2] Evaluation of the CSF should include cell count, protein, glucose, cytology, flow cytometry, and OCB for differential diagnosis of demyelinating disorders. The typical CSF profile demonstrates elevated protein, normal glucose, and lymphocytic predominant pleocytosis.[2] Five of our six patients had pathological findings in the CSF examination performed at the diagnostic stage, while the diagnosis of the patient with normal CSF was made by biopsy. The most common abnormal CSF finding was protein elevation accompanied by an increase in mononuclear-dominant CSF cell count in accordance with the literature. The CSF glucose levels were lower than two-thirds of the simultaneously measured fingerstick blood glucose values in two of six patients (<25 mg/dL). Although biopsy is the gold standard method in diagnosis, there are studies showing that flow cytometry has a high specificity in diagnosing lymphoma.[10,11] It is also faster than immunohistochemistry, which allows for rapid initiation of treatment in aggressive tumors.[10] In our case series, pathological CSF findings, including the presence of atypical cells in five of our six cases, along with subsequent flow cytometry and cytopathological examination of these atypical cells, led to the diagnoses. We used biopsy to diagnose only one patient who had no CSF findings. A positive cytology finding consistent with clinical and radiologic findings is advantageous over CNS biopsy, which is more difficult and has a higher probability of complications.

In conclusion, central nervous system lymphomas can affect various parts of the nervous system and can subsequently cause various clinical and radiological findings depending on the localization and size of the lesion. Therefore, they can initially mimic many neurological diseases, which can present a diagnostic challenge. In addition to clinical and radiological findings, CSF cytology contributes to early diagnosis.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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