Isolated Third Cranial Nerve Palsy Leading to the Diagnosis of Disseminated Burkitt Lymphoma

A Case Report and Literature Review

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Introduction: Dysfunction of the third cranial nerve can result from lesions anywhere along its course between the midbrain and the orbit. Lymphoma is a rare cause of isolated oculomotor nerve palsy (OMP), with only 19 cases reported in the literature. We describe a case of an isolated OMP leading to the diagnosis of disseminated Burkitt lymphoma (BL).

Case Report: A 37-year-old man presented with acute onset diplopia and right ptosis and was found to have a right pupillary sparing OMP. The diagnostic workout was unremarkable, including contrast-enhanced brain and orbital magnetic resonance imaging, MR angiography, exhaustive laboratory tests, and cerebrospinal fluid analysis. After a course of high-dose intravenous steroid therapy, the patient recovered almost completely. Three weeks after the discharge, he developed lumbar radicular pain and lower limbs weakness followed by the relapse of the right OMP. A second lumbar puncture revealed the presence of "small monomorphic lymphocytes," consistent with leptomeningeal lymphomatosis. A whole-body positron emission tomography scan disclosed a mediastinal mass, whose histopathologic "starry sky" appearance was pathognomonic for BL.

Conclusions: Reviewing the literature, we were able to find only 3 cases of OMP as the presenting manifestation of BL, all occurring in patients with predisposing HIV infection. Our case of isolated OMP highlights some "red flags" for a lymphomatous etiology, including young age, a progressive course, a response to high-dose steroid therapy, and relapse upon steroid discontinuation; these cases require a comprehensive evaluation, including repeated cytological cerebrospinal fluid analysis and sensitive imaging techniques to detect a possible primary lesion.

Key Words: cranial neuropathy, Burkitt lymphoma, neurolymphomatosis

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Dysfunction of the third cranial nerve may result from lesions anywhere along its course between the midbrain and the orbit.[1,2] Lymphoma is a rare cause of oculomotor nerve palsy (OMP) through direct invasion of the nerve, infiltration of the cavernous sinus, or dissemination to the surrounding leptomeninges.[2] Only few cases of disseminated lymphoma presenting with an isolated OMP have been reported in the literature[3–20] (Table 1), mainly non-Hodgkin lymphoma and only 3 reports of Burkitt lymphoma (BL).[8,14,18]

We report a case of an otherwise healthy man who developed an isolated OMP as the presentation of a disseminated BL.

CASE REPORT

A 37-year-old man with unremarkable past medical history presented with acute onset diagonal diplopia and right palpebral ptosis. Neurological examination showed complete extrinsic OMP with pupil sparing; general and neurological examination was otherwise normal.

The initial work-up included routine blood tests with thyroid function testing, contrast-enhanced brain and orbital magnetic resonance imaging (MRI) and MR angiography, and was unremarkable. A panel of second level diagnostic tests was unremarkable, too, including blood screening for rheumatic and infective diseases (ie, borreliosis, HIV, and syphilis), thrombophilia tests, chest radiography to exclude sarcoidosis, repetitive nerve stimulation, and anti-GQ1b antibody testing.

The cerebrospinal fluid (CSF) examination revealed normal proteins (32 mg/dL, normal range, 15 to 45 mg/dL) and cells (none, normal range <5/mm^3); CSF polymerase chain reactions for neurotropic viruses and mycobacterial culture were negative.

High-dose intravenous corticosteroid therapy (methylprednisolone, 1 g once daily for 5 days) was administered for a presumptive diagnosis of inflammatory cranial neuritis and was followed by subsequent OMP improvement excepting mild residual ptosis.

Three weeks after the discharge, the patient developed lower back pain and proximal legs weakness, which were followed by the relapse of diplopia and the appearance of pin and needles involving the feet. Neurological examination revealed the relapse of right OMP with pupil sparing, proximal legs weakness, and patellar areflexia.

Neurophysiological studies (including sensory and motor conduction studies, needle electromyography, motor, and somatosensory-evoked potentials), showed delayed peroneal and tibial nerves F waves latencies suggestive of a radicular or proximal nerve disorder. Nevertheless, lumbar spine MR imaging was unrevealing.

A second lumbar puncture revealed an increase in proteins (95 mg/dL) and cells (6/mm^3); CSF cytology disclosed "small monomorphic lymphocytes," consistent with leptomeningeal lymphomatosis. A whole-body nuclear medicine positron emission tomography (PET) scan showed a mediastinal mass, which was subsequently biopsied. Its histopathologic "starry sky" appearance and immunohistochemistry findings were pathognomonic for BL.

Disease progression was noted in the ensuing couple weeks, with left Vth and XIIth cranial nerves involvement.

The patient received 2 courses of chemotherapy, followed by autologous stem cell transplantation. The cranial multineuropathy and the lower limb symptoms resolved within 2 months after the last cycle of chemotherapy.

At our last follow-up examination, 3 years after the presentation, he did not have any residual neurological deficit and was disease-free.

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TABLE 1. Case Reports of Patients Manifesting Isolated Oculomotor Nerve Palsy Due to Lymphoma

References	Age (y)/ Sex	Diagnosis	Pupil	MRI Findings	CSF Cytology	Postmortem Examination
Braverman[3]	59/F	Reticulum cell sarcoma	Involved	Not performed	Not performed	Thickening of the leptomeninges in the basal area, septum pellucidum involvement
Miller[4]	14 mo/ M	Reticulum cell sarcoma	Involved	Not performed	Not reported	Infiltration of the OcN and leptomeninges
Wilkins and Samhouri[5]	62/M	Histiocytic lymphoma	Spared	Not performed	Negative	Leptomeningeal infiltration and infiltration of the OcN within the midbrain
Mitsumoto and Sweeney[6]	43/F	Histiocytic lymphoma	Not reported	Not performed	Negative	Infiltration of the OcN and the cavernous sinus
Teoh et al[7]	23/M	Reticulum cell sarcoma	Involved	Not performed	Negative	Infiltration of the OcN roots and leptomeninges
Jack et al[8]	37/M	Burkitt Lymphoma, AIDS	Not reported	Not performed	Malignant cells	Not performed
Galetta et al[9]	72/M	Large B-cell lymphoma	Involved	Bilateral enhancement and enlargement of the OcN	Malignant cells	Not performed
Berger et al[10]	25/M	Non-Hodgkin Lymphoma, AIDS	Spared	Normal	Negative	Not performed
Kajiya et al[11]	60/F	Non-Hodgkin Lymphoma	Not reported	Enhancement and enlargement of the OcN	Malignant cells	Not performed
Manabe et al[12]	69/M	Large B-cell lymphoma	Spared	Enhancement of the cavernous sinus and posterior clinoid process	Malignant cells	Not performed
Bhatti et al[13]	45/M	Large B-cell lymphoma, AIDS	Involved	Enhancement and enlargement of the OcN	Malignant cells	Leptomeningeal infiltration and extensive invasion of the OcN
Levy et al[14]	34/M	Burkitt lymphoma, AIDS	Involved	Normal	Not reported	Not performed
Park et al[15]	53/F	Large B-cell lymphoma	Involved	Invasion of the sphenoid sinus and cavernous sinus	Not performed	Not performed
Chen et al[16]	53/M	Natural killer-cell lymphoma	Involved	Enhancement and enlargement of the OcN	Negative	Not performed
Sato et al[17]	71/M	Large B-cell lymphoma, AIDS	Spared	Enlargement of the cavernous sinus and invasion of the clivus	Malignant cells	Not performed
Sato et al[17]	89/F	Large B-cell lymphoma	Spared	Enlargement of the cavernous sinus	Malignant cells	Not performed
Verma et al[18]	45/M	Burkitt lymphoma, AIDS	Involved	Enlargement of the cavernous sinus	Negative	Not performed
Tsai et al[19]	51/F	Large B-cell lymphoma	Involved	Enhancement and enlargement of the OcN	Not reported	Not performed
Meireles et al[20]	69/F	Hodgkin lymphoma	Involved	Enhancement of the OcN	Negative	Not performed

CSF indicates cerebrospinal fluid; F, female; M, male; mo, month; MRI, magnetic resonance imaging; OcN, oculomotor nerve.

Nowadays, the patient is under regular follow-up at the medical oncology clinic.

DISCUSSION

Lymphomatosis infiltration of the peripheral nerves, nerve roots, and cranial nerves has been termed neurolymphomatosis (NL). Cranial nerves and nerve roots involvement is often associated with lymphomatous meningitis.[21,22]

Most cases are due to non-Hodgkin lymphoma, including Burkitt type, whereas Hodgkin lymphoma rarely infiltrates nerves.[21,22] An estimated 10% of lymphomas metastasize to the peripheral nervous system.[2,3]

Four clinical patterns have been recognized[21,22]: a painful polyneuropathy or polyradiculopathy, a painless polyneuropathy, a cranial neuropathy with or without pain, and a painful or painless peripheral mononeuropathy.

Other clinical features suggestive of lymphoma usually accompany nerve infiltration, namely B-symptoms, central nervous system abnormalities, lymphadenopathy, or cutaneous manifestations.[23]

An isolated cranial neuropathy as the sole presentation of NL is rare.[21,22] In the largest case series of NL (n = 72), Baehring et al[23] identified 15 NL cases with involvement of a single cranial nerve at presentation, whereas 37 cases showed cranial nerves involvement during the course of the disease. The facial nerve was the most commonly affected cranial nerve.[24]

Isolated OMP as the initial manifestation of lymphoma is extremely rare. We identified 19 cases after thorough review of the English-language published literature (Table 1).

The cell types were specified in 17 cases. Large B-cell lymphoma was the most common phenotype (n = 7); only 3 patients had BL,[8,14,18] whereas there was a single case report of Hodgkin lymphoma.[20]

Postmortem examination was performed in 6 cases; only 1 case report[13] correlated the MR imaging findings with the gross anatomy and histopathologic observations.

The main histopathologic findings were cell infiltration of third cranial nerve (affected side or bilaterally), its root or fascicle within the midbrain, leptomeningeal infiltration, cavernous sinus invasion, and septum pellucidum involvement in a single case report of reticulum cell sarcoma.[3]

Brain MR imaging was abnormal in 11 of 13 cases. The main abnormalities were third cranial nerve enhancement and/or enlargement, enhancement of the cavernous sinus, and invasion of the sphenoid bone (clivus or posterior clinoid process).

Blake et al[25] investigated by MRI scan 50 patients affected with OMP; they found 9 cases of cranial nerve III enhancement, including 3 cases due to lymphoma (the remaining diagnoses were viral meningitis, coccidioidomycosis, syphilis, Miller-Fisher syndrome, and ophtalmoplegic migraine). Mark et al[26] retrospectively studied 30 patients with enhancement of the cisternal portion of the third cranial nerve, concluding that this finding is always suggestive of an underlying inflammatory or neoplastic process; however, without being constantly associated with clinically apparent oculomotor nerve dysfunction.

The sensitivity of brain MR imaging in diagnosing leptomeningeal disease had been investigated in a few studies.[27–29] T1-weighted imaging seems to be the most sensitive technique,[27] with a reported sensitivity varying between 59% and 76%.[28,29]

MRI abnormalities suggestive of leptomeningeal metastasis include leptomeningeal, subependymal, dural, or cranial nerve enhancement, superficial cerebral lesions and communicating hydrocephalus.[27–29]

Recent literature reports support the use of fluorine-18 fluorodeoxyglucose PET (F-FDG PET) in diagnosis of NL by providing evidence of the primary malignancy or showing abnormal uptake in the affected nervous sites.[30]

CSF cytology was positive in 7 of 14 examined patients. In a large series of patients with disseminated lymphoma and central nervous system involvement, CSF cytology was positive in 77% of cases, but >2 examinations were necessary in 72% of positive cases.[31] In another case series[28] of cancer patients suspected of having leptomeningeal metastasis, CSF cytology had a sensitivity of 75%.

Eleven of 16 cases reported in the literature had OMP with pupillary involvement.

Pupillary parasympathetic fibers are located superficially within the nerve and receive a greater blood supply from the vasa nervorum than from the central trunk. As a result, they are usually spared from ischemic injuries, whereas they are usually affected by compressive lesions.[2]

Surprisingly, in our review, 9 of 11 cases with pupil involvement showed infiltration of the oculomotor nerve on histologic or MRI examination. In contrast, Jacobson[32] reported mass compressing lesions in 42% of patients with pupil-sparing oculomotor palsy.

On the basis of such evidence, the involvement or sparing of the pupil is not clearly predictive of the underlying pathology (ie, infiltrative or compressive mechanism).

Compared with the other 3 prior reports of isolated OMP secondary to BL, our case report is unique due to absence of underlying HIV infection or immunosuppression. In addition, it highlights "red flags" suggestive of underlying NL, such as: (a) young age, (b) a progressive course, and (c) improvement with high-dose steroid therapy and relapse upon steroid discontinuation. Comprehensive evaluation is indicated in these cases even in the absence of signs of malignancy, HIV infection, or immunosuppression. Investigations must include repeated cytological CSF analysis and sensitive imaging techniques (T1-weighted brain MRI and whole-body PET scan) to increase the diagnostic yield for underlying disseminated lymphoma. The dramatic response to chemotherapy in our subject further underscores the importance of early diagnosis.

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