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Ocular involvement in neurolymphomatosis

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ABSTRACT

Purpose: To describe the ophthalmic symptoms and histopathological findings in a case of primary neurolymphomatosis (NL).

Observations: A man in his 60s with a prior diagnosis of chronic inflammatory demyelinating polyneuropathy developed facial numbness, diplopia, drooling, and difficulty swallowing. Over a 3-month period, he developed total ptosis and ophthalmoplegia of the right eye with a dilated, non-reactive pupil considered secondary to cranial nerve III and VI palsies. His left pupil subsequently became non-reactive to light and accommodation, and extraocular motility of the left eye was partially limited in all directions of gaze without ptosis. Autopsy findings included primary NL, diffuse large B-cell lymphoma of activated B-cell subtype, involving right and left cranial nerves V, VI, IX, and X; spinal nerve roots; both femoral nerves; and extrascleral, intrascleral, and intraocular short and long posterior ciliary nerves with extension into the adjacent choroid of both eyes. No evidence of lymphoma was identified elsewhere in the body.

Conclusions and importance: Our patient is only the second histological demonstration of ciliary nerve involvement by NL, and the first, to our knowledge, of primary NL spreading secondarily from the ciliary nerves into the choroid. Our patient demonstrates that NL, though rare, should be included in the differential diagnosis of ocular cranial nerve palsies and ophthalmoplegia.

1. Introduction

Neurolymphomatosis (NL) is defined as invasion of cranial nerves, peripheral nerve roots, plexuses, or peripheral nerves by non-Hodgkin lymphoma or lymphoblastic leukemia. This may be the primary manifestation of malignancy or secondary to dissemination from a systemic site or the central nervous system.[1,2] We report a fatal case of primary NL by a diffuse large B-cell lymphoma of activated B-cell subtype involving extrascleral, intrascleral, and intraocular short and long posterior ciliary nerves with extension into the adjacent choroid. To our knowledge, this is the first histological documentation of intraocular involvement by primary NL.

2. Case report

Our patient developed right foot numbness approximately 14 years prior to death. His symptoms worsened, and three years later nerve conduction studies suggested chronic inflammatory demyelinating polyneuropathy (CIDP), though a peripheral nerve biopsy disclosed only mild axonal degeneration and regeneration without inflammation. Treatment with intravenous immunoglobulin (IVIG) and mycophenolate mofetil were discontinued nine years later when symptoms stabilized. After two years off therapy, when in his 60s, he developed facial numbness, diplopia, drooling, and difficulty swallowing. He was restarted on IVIG, prednisone, and then plasmapheresis for presumed CIDP flare. Over three months, he developed complete ptosis and ophthalmoplegia of the right eye (Fig. 1) with a 5-mm diameter dilated, non-reactive pupil, considered secondary to cranial nerve (CN) III (oculomotor) and VI (abducens) palsies. At this time, the left pupil was 2 mm in diameter and reactive to light and accommodation. He subsequently experienced an acute onset of blurry vision in the left eye, with a corrected visual acuity of 20/400. The left pupil became non-reactive to light and accommodation and fixed at 4.5 mm. Extraocular motility of the left eye was partially limited in all directions of gaze without ptosis. Slit lamp exam revealed severe superficial punctate keratopathy of the left eye. Dilated fundus exam was unremarkable. Left eye visual acuity improved to 20/100 after aggressive corneal lubrication.

Magnetic resonance imaging (MRI) two weeks prior to his death revealed abnormal enhancement and enlargement of CN V bilaterally (trigeminal; Fig. 2), bilateral abnormal enhancement of CN VI, IX (glossopharyngeal), and X (vagus), abnormal enhancement in the right

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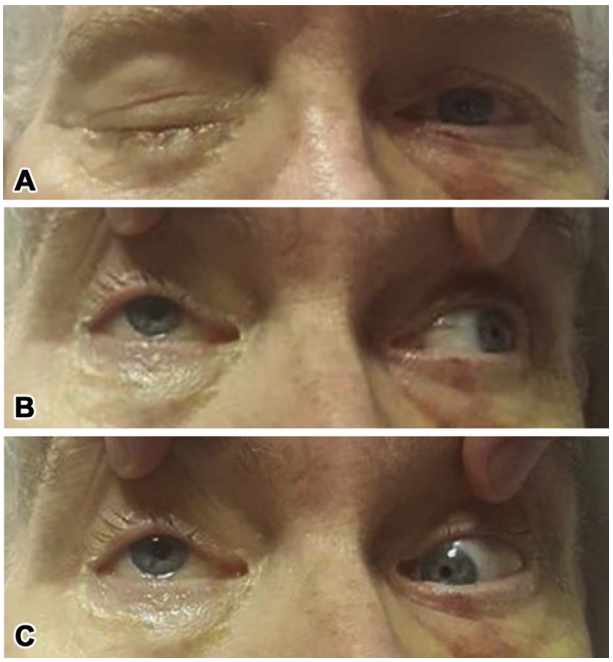

Fig. 1. Clinical examination six weeks prior to death.
Ptosis (A) with complete ophthalmoplegia of the right eye (B, C) six weeks prior to death.

anterior inferior cerebellar artery involving the right CN VII (facial)/VIII (vestibulocochlear) complex, and abnormal enhancement of nerve roots in the cervical and visualized upper thoracic spine. Flow cytometry of cerebrospinal fluid (CSF) had an increased number of small, mature lymphocytes, no abnormal T-cell population, and no definitive monoclonal B-cell population. The patient developed aspiration pneumonia resulting in his death.

Autopsy disclosed primary NL, diffuse large B-cell lymphoma of activated B-cell subtype (CD20+, CD10-, BCL6-, MUM1+),[3] involving right and left cranial nerves V, VI, IX, and X; spinal nerve roots; both femoral nerves; and extrascleral, intrascleral, and intraocular short and long posterior ciliary nerves with extension into the adjacent choroid of both eyes (Fig. 3). Lymphoma formed periosteal masses adjacent to the foramen rotundum, foramen ovale, and trigeminal nerves bilaterally, with the mass in the right middle cranial fossa (Fig. 4A) being thicker than in the left (Fig. 4B). Lymphoma did not grossly involve either right or left CN III in the skull base, but no sections of the nerves near the midbrain were available for microscopic examination. No lymphadenopathy or lymphoma was identified in the bone marrow, spleen, brain and spinal cord parenchyma, or elsewhere.

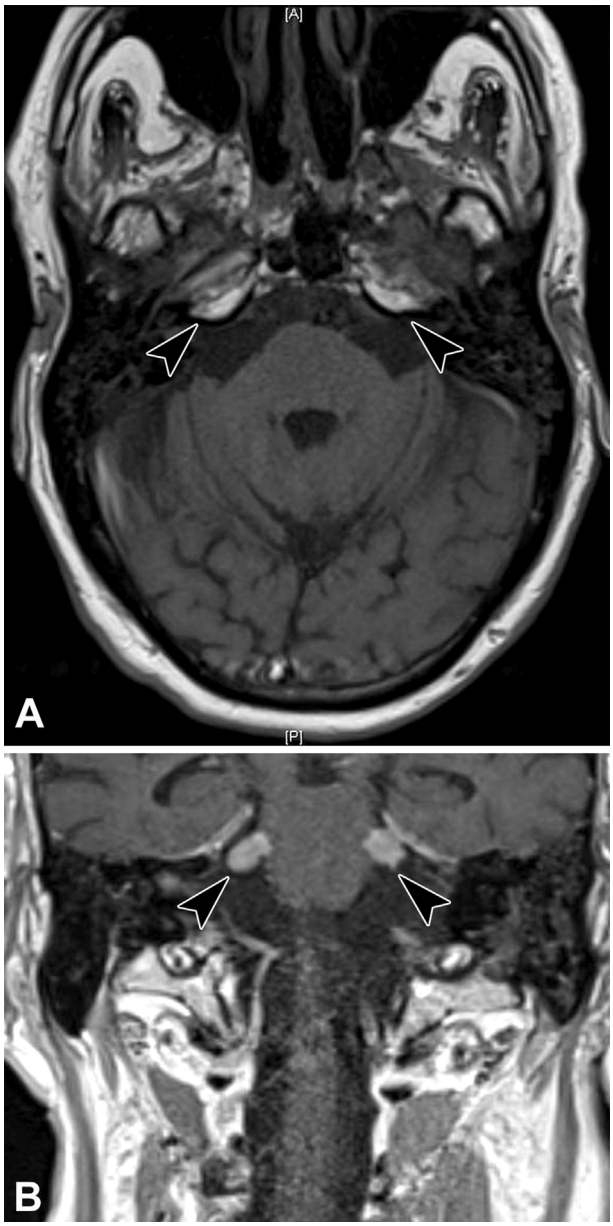

Fig. 2. Magnetic resonance images two weeks prior to death.
Two weeks prior to death, axial (A) and coronal (B) T1 weighted magnetic resonance images following gadobenate dimeglumine administration revealed abnormal enhancement and enlargement of cranial nerves V (arrowheads).

3. Discussion

NL is a rare manifestation of non-Hodgkin lymphoma and leukemia, with lymphoma accounting for 90% of cases.[2] NL is slightly more common in men than women with a peak incidence in the 6th to 7th decades.[2] It can present as painful involvement of nerves or roots (31% of patients), cranial neuropathy with or without pain (21%), painless involvement of peripheral nerves (28%), or painful or painless involvement of a single peripheral nerve (15%).[4] NL is an extranodal site of systemic lymphoma in 40%–66% of patients and the initial presentation of malignancy in about 25%–30% of patients.[2,5] Ocular manifestations are uncommon: a study of 72 patients noted abducens nerve palsy (n = 4), oculomotor neuropathy (n = 4), and trigeminal neuropathy (n = 2).[4] There are single case reports of oculomotor nerve (CN III) palsy,[6] abducens nerve palsy (CN VI),[7] orbital apex syndrome,[8] and of systemic lymphoma infiltrating extrascleral ciliary nerves, ciliary ganglia, and optic nerves in a patient with Argyll Robertson pupils.[9] Our patient is only the second histological demonstration of ciliary nerve involvement by NL, and the first, to our knowledge, with primary NL having documented intraocular spread.

NL diagnosis is often elusive and is ultimately confirmed by biopsy of involved peripheral nerves.[1,2,10] 20%–40% of patients have malignant cells identified in CSF.[1] MRI is considered the best non-invasive diagnostic tool.[1,2] No standard treatment for NL exists, but most employ systemic chemotherapy.[1,2] In a recent study, median survival from diagnosis of NL was 10 months with a 12- and 36-month survival of 46% and 24%, respectively.[2] Combination high-dose methotrexate and alkylating agents may prolong survival by increasing drug penetration across the blood-nerve barrier.[10]

4. Conclusion

Our patient demonstrates that NL, though rare, should be included in the differential diagnosis of ocular cranial nerve palsies and ophthalmoplegia. This case also demonstrates that NL may spread