BIFOCAL OPTIC AND FACIAL NERVE T-CELL LYMPHOMA

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ABSTRACT

Purpose: Optic nerve and optic nerve sheath infiltration by a systemic lymphoma is uncommon, but is exceedingly rare when caused by a T-cell lymphoma. This then generally occurs in association with central nervous system (CNS) involvement. We report on a rare case of optic and facial nerve T-cell lymphoma infiltration, without CNS involvement.

Methods: A 63-year old female with systemic T-cell lymphoma in clinical remission presented with painful loss of vision in the left eye. She was initially treated for presumed recurrent optic neuritis. A thorough clinical work-up was performed, followed by an optic nerve biopsy with histopathology.

Results: There was no perception of light in the left eye, with a marked relative afferent pupillary defect. Fundoscopy showed significant optic disc oedema and a large peripapillary subretinal infiltration. Subsequently, she developed a 7th cranial nerve paresis. Cranial MRI showed thickening and contrast enhancement of the left optic nerve and right facial nerve. Optic nerve biopsy showed infiltration of CD3- and CD5- positive lymphocytes. A complete systemic workup revealed no evidence of disease elsewhere. The patient was thus considered to have bifocal cranial recurrence of T-cell lymphoma, for which radiotherapy was started.

Conclusions: Optic nerve infiltration from systemic lymphoma is rare and generally occurs with CNS involvement. A bifocal pattern of recurrence from systemic T-cell lymphoma involving the right facial nerve and left optic nerve was seen in this patient.
A review of the literature highlights the highly atypical nature of this presentation.

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Submitted: Aug 31, 2012
Accepted: Nov 21, 2012

KEY WORDS

infiltration, facial nerve, intraocular, optic nerve, T-cell lymphoma

INTRODUCTION

Ocular or adnexal lymphoma of the T-cell type is exceedingly rare and only represents approximately 1% to 3 % of all lymphoproliferative lesions in these sites (1). Indeed, it is apparently unusual for these tumours to primarily originate from these sites, with most involving the eye only as a secondary site (1). Optic nerve infiltration from systemic lymphoma is rare (2). We report on an unusual case of biopsy-proven lymphomatous infiltration of the optic nerve by a systemic T-cell non- Hodgkin lymphoma (NHL) with intraocular spread and facial nerve involvement and discuss the appropriate literature.

CASE REPORT

A 63-year-old female was referred to our university outpatient clinic by her own ophthalmologist with loss of vision in the left eye since 10 days. She had initially been treated twice with high-dose systemic steroids for two earlier episodes of presumed optic neuritis by the referring ophthalmologist, with complete visual recovery two and three months respectively, prior to her referral. Eight months before her first episode of supposed optic neuritis, she had been diagnosed with a peripheral T-cell lymphoma around the uterus, for which she had received eight cycles of chemotherapy with a cyclophosphamide-doxorubicin-vincristine cocktail and prednisolone, and subsequently had achieved complete remission of the disease. She had been considered completely cured for at least one month prior to the development of the first bout of presumed optic neuritis.
On ocular examination, her best-corrected visual acuity with a spherical correction of +0.50 diopters was 20/20 in the right eye, and no perception of light in the left eye. Inspection revealed a relative afferent pupillary defect in the left eye. Slit-lamp examination was unremarkable in both eyes. Fundus examination showed only minimal disc oedema in the left eye and a normal right optic disc. Magnetic resonance imaging (MRI) revealed a slightly thickened appearance, with a discrete hyperintensity around the left optic nerve on T1-weighted images (*Fig. 1*). A diagnosis of a third episode of optic neuritis was entertained. Although vincristine

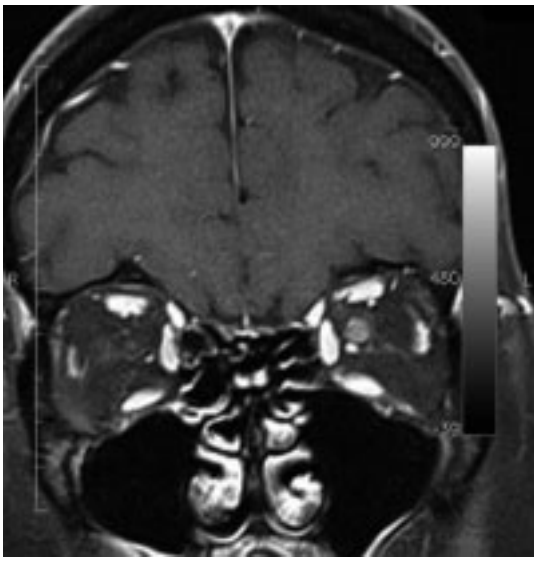

Fig. 1: Magnetic resonance imaging (MRI) of brain and orbit, T1-weighted images depicting slightly thickened appearance with discrete hyperintensity around left optic nerve

is a known cause of reversible peripheral neuropathy, it only very rarely involves cranial nerves, and generally recovers fairly rapidly after cessation of treatment (10-14). In addition, a third bout of optic neuropathy occurred in our patient without concurrent vincristine treatment. Hence, a diagnosis of toxic optic neuropathy due to vincristine treatment was considered extremely unlikely. The patient was again started on high dose of steroids followed by rapid tapering (intravenous methylprednisolone 4 x 250 mg daily during 3 days followed by oral methylprednisolone 1mg/kg body weight for 11 days). However this time, the patient did not experience any subsequent visual improvement. Thereafter the patient was kept on methylprednisolone 8 mg daily.

Three months later, the patient presented in emergency with severe pain in and around the left eye. On examination her visual acuity was 20/20 without correction in the right eye and no light perception in the left eye. Clinical and anterior segment examination revealed swelling of the upper eyelid, marked conjunctival congestion, chemosis and a relative afferent pupillary defect in the left eye (*Fig. 2*). Intraocu-

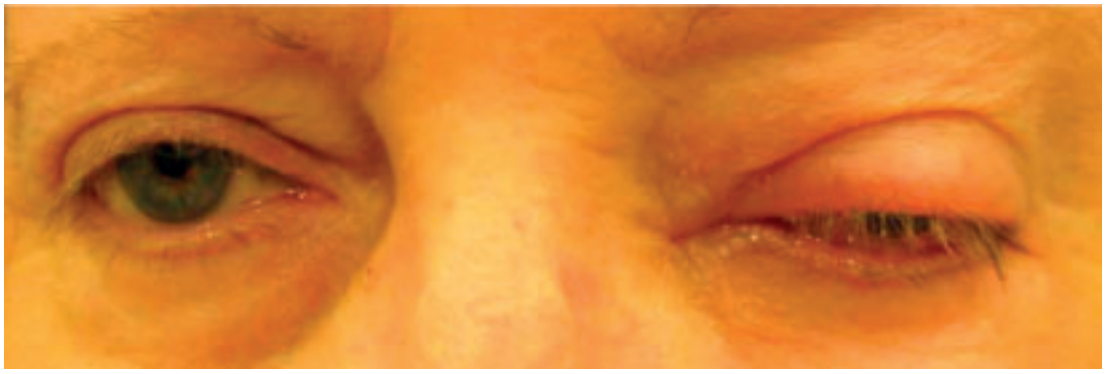

Fig. 2: Clinical picture showing swelling of left upper eyelid

lar pressure by applanation tonometry was 14 mmHg in right and 17 mmHg in left eye. Fundus examination of the left eye showed significant optic disc oedema with a subretinal white infiltrative zone with an aspect of pseudohypopion about 4-5 disc diameters (DD) around the disc. Associated exudation and flame-shaped haemorrhages were present in the macula and peripheral retina. In addition, inner retinal oedema consequent upon multiple retinal arterial and venous occlusions was seen in the whole posterior pole (*Fig. 3*). The dome-shaped bullous retinal detachment and the inner retinal oedema in the macula were visible on OCT (*Fig. 4*). On day ten of her subsequent admission, she developed paresis of the right facial muscles due to a right peripheral seventh nerve paresis. An MRI-scan of the brain and orbit showed increased thickening of the left optic nerve compared to the previous scan, with contrast enhancement of the nerve sheath and of retrobulbar fat (*Fig. 5*). Furthermore, contrast enhancement was seen in the temporal part of the right facial nerve (*Fig. 6*). Hence, infiltration was seen in a right (facial) and left (optic) cranial nerve.

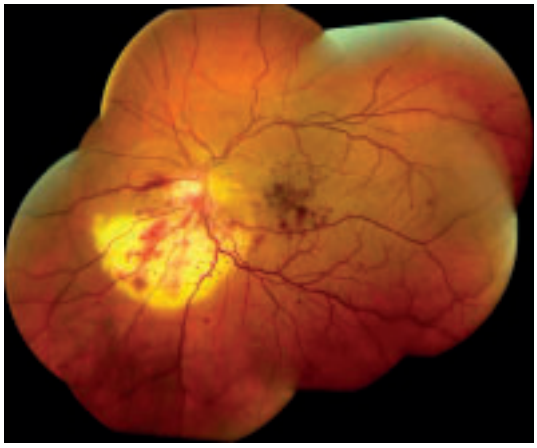

Fig. 3: Fundus of left eye: significant optic disc oedema with subretinal white infiltrative zone with aspect of pseudohypopion about 4-5 DD around optic disc; associated exudation and flame-shaped haemorrhages in macula and peripheral retina; additional inner retinal oedema due to multiple retinal arterial and venous occlusions in posterior pole

A lymphomatous infiltration was suspected and a biopsy of the intra-orbital part of the left optic nerve was performed through a medial orbitotomy approach. Histopathological examination showed a marked necrotic process with infiltration of CD3- and CD5-positive T- lymphocytes into the nerve and its sheath (*Fig. 7*).
A systemic work-up, including a complete blood count, liver and kidney function tests, a bone marrow biopsy and a lumbar puncture, was entirely normal. Additional screening for human immunodeficiency virus and Epstein-Barr virus was negative. A whole body PET-CT scan was also normal. Consequently, the patient was diagnosed with bifocal T-cell lymphoma, with an infiltration of the left optic nerve with intraocular spread, along with right facial nerve involvement. Although independent involvement of two cranial nerves suggests lymphomatous meningitis, because of the normal elaborate systemic work-up, as well as the age of the patient, localized radiotherapy to the cranial nerves was deemed preferable initially. The patient was started on local radiotherapy (46 Gy, 23 fractions of 2 Gy) to the two involved nerves,

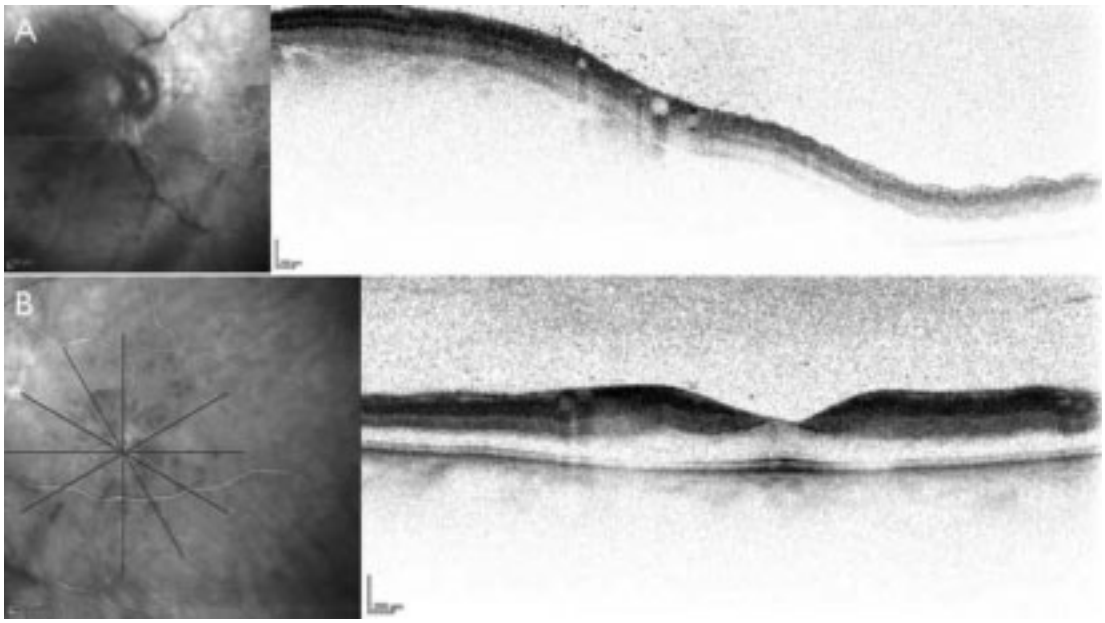

Fig. 4: OCT-scan showing dome-shaped bullous retinal detachment (Panel A) and inner retinal oedema in macula (Panel B)

i.e. the left optic nerve and the temporal part of the right facial nerve. Fundoscopy after radiotherapy revealed several areas of intraretinal lipoid exudation nasal and inferior to the optic disc resulting from the bullous lesion with lipoid pseudohypopion seen at the previous visit, with multiple intraretinal haemorrhages. Superficial intraretinal haemorrhages in a star-

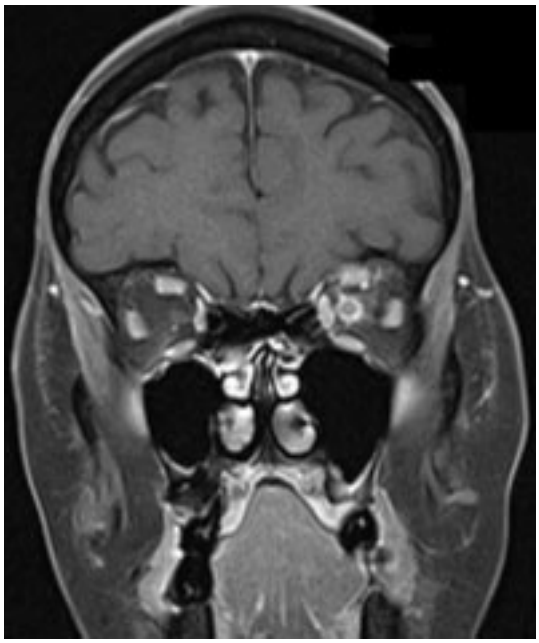

Fig. 5: MRI-scan of brain and orbit showing increased thickening of left optic nerve as compared to previous scan (see Fig. 1), also with contrast enhancement of optic nerve sheath and retrobulbar fat

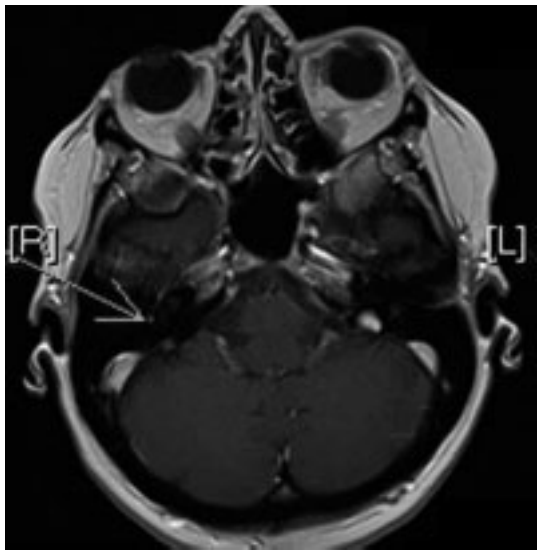

Fig. 6: MRI-scan of brain and orbit illustrating contrast enhancement in temporal part of right facial nerve (arrow)

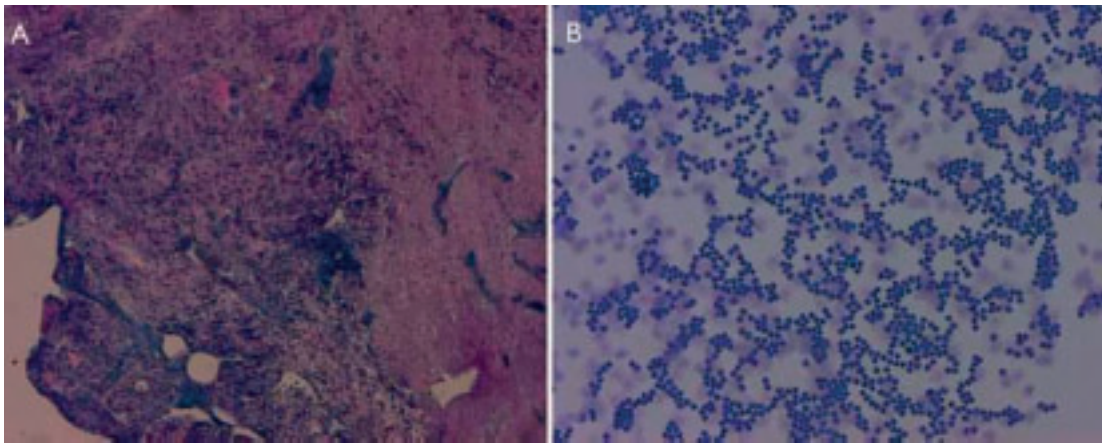

Fig. 7: Histopathological examination: marked necrotic process with infiltration of CD3+/CD5+ T-lymphocytes into optic nerve and its sheath (Panel A); detail of CD3+/CD5+ T-lymphocytes (Panel B)

shaped pattern surrounded the fovea in the area of inner retinal oedema, consequent upon mixed arterial and venous occlusive disease (*Fig. 8*). One week after completion of the radiotherapy, the patient was admitted with lymphomatous meningitis, proven by a lumbar puncture positive for T-cells. Both the MRI of the brain and bone marrow biopsy were entirely normal.

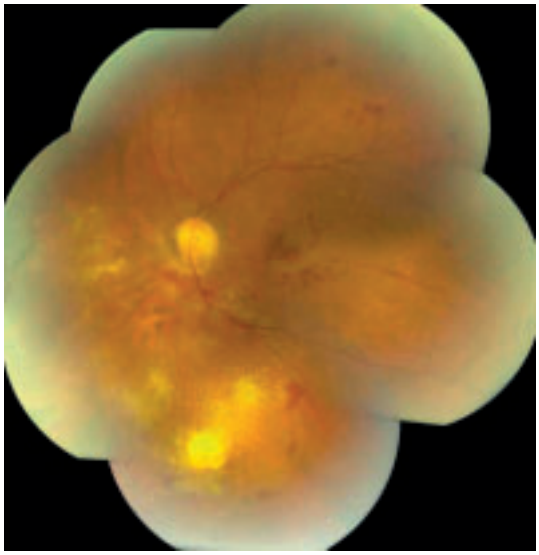

Fig. 8: Fundus of left eye after radiotherapy: several areas of lipoid exudation nasal and inferior to optic disc resulting from bullous lesion with lipoid pseudohypopion seen at previous visit (Fig. 3), with multiple intraretinal haemorrhages; superficial retinal haemorrhages surrounding fovea in area of inner retinal oedema due to vascular occlusive disease

Intrathecal chemotherapy produced a remission after 6 sessions proven by two subsequent lumbar punctures. However, two weeks later a PET-scan revealed a mass posterior of the inferior pole of the right kidney, which was responsive to corticosteroids.

Treatment with systemic MPV (methotrexate-procarbazine-vincristine)-chemotherapy was commenced. After only two sessions the treatment was halted because it was considered too dangerous on the basis of raised inflammatory parameters (CRP 20,5 mg/dl; normal range 0-0,5 mg/dl) and pneumonia. MRI of the brain revealed multiple deep white matter lesions suspicious for small perivascular infiltrates of Tcell lymphoma. A lumbar puncture then showed lymphoid infiltration. The patient died shortly thereafter.

DISCUSSION

Optic nerve infiltration secondary to systemic lymphoma is uncommon and generally occurs in a setting of CNS involvement (2). There are very few case reports of optic nerve infiltration from a systemic B-cell lymphoma (2-6) but it is even much more rarely reported due to T-cell lymphoma (7, 8). In such cases, the central nervous system is then also involved. Indeed, Kitzmann et al. reported a case of 39-year old male with bilateral optic nerve infiltration confirmed on biopsy along with CNS involvement in a patient with peripheral T-cell

lymphoma (7). Yamamoto et al. reported optic nerve infiltration in a 45-year old female patient with T-cell leukemia with CNS involvement (8).

Optic nerve infiltration without concurrent CNS involvement is extremely rare with only two cases reported to date. The first case was dealing with an isolated optic nerve infiltration in a two-year old female with systemic B-cell lymphoma in clinical remission (2). In the second reported case, an optic nerve in filtration was described in a 55-year-old female patient with undifferentiated histiocytic lymphoma and additional malignant cells in the CSF, indicating more diffuse lymphomatous meningitis (6).
To the best of our knowledge, this is the first reported case of biopsy-proven optic nerve infiltration from a T-cell lymphoma without simultaneous CNS involvement after a period of complete remission from a systemic lymphoma. In vivo studies in mice have shown that lymphoma cells preferentially enter the brain through the choroid plexus and cranial nerves, and migrate along the optic nerve sheath into the eye infiltrating the choroid and further into the ciliary body, iris and anterior chamber (9). This is interesting because the initial involvement of the optic nerve, with subsequent choroidal and subretinal spread in our patient, was entirely in keeping with this route of propagation of lymphoma cells. The pattern of ocular involvement in our patient including an initial presumed recurrent optic neuritis which finally became unresponsive to steroids, and then progressive optic nerve thickening in consecutive MRI scans followed by intraocular involvement, was highly suggestive of a lymphomatous spread in a patient who was in clinical remission of a T-cell lymphoma of the uterus.

A subsequent optic nerve biopsy confirmed this hypothesis and proper treatment was initiated. This pattern of ocular involvement in a systemic T-cell lymphoma has also never been reported previously. A further delay in diagnosis would potentially have led to further spread of lymphoma cells into the iris and anterior chamber, presenting as iris nodules and pseudohypopyon.
Toxic optic neuropathy caused by vincristine was considered highly unlikely, albeit not impossible. The patient had received 8 cycles of chemotherapy for a T-cell lymphoma of the uterus, which included vincristine, prior to the onset of ocular symptoms. Vincristine can cause reversible peripheral neuropathy and only very rarely involves the cranial nerves, including the optic nerve (10-14). In addition, such toxic neuropathy is generally reversible (10-14). In the case of our patient, ocular symptoms occurred more than one month after finishing the treatment with vincristine. Furthermore, she had several relapses of the optic neuropathy without concurrent vincristine treatment and without visual recovery after the third episode. This makes a toxic neuropathy related to vincristine very unlikely.

Involvement of cranial nerves other than the optic nerve is also an uncommon feature of NHL, and usually occurs in the setting of CNS or meningeal involvement 7 by systemic lymphoma (15). Direct involvement of a solitary cranial nerve by lymphoma cells is rare with only very few case reports (16, 17). In our patient, a brain MRI scan showed thickening and contrast enhancement of the temporal part of the right facial nerve without detectable meningeal or CNS involvement, suggestive of a direct infiltration by malignant lymphoma cells. However, involvement of two cranial nerves can in fact be considered as proof of CNS involvement, even in the absence of a positive lumbar puncture. As such, bifocal involvement could have been a reason to commence intrathecal chemotherapy, rather than bifocal localized radiotherapy.

After treatment of the foci in the two cranial nerves, the patient developed a lymphomatous meningitis as proven by a positive lumbar puncture. Further indication of a subsequent systemic spread was a mass detected near the right kidney on PET scan.

Though optic nerve infiltration is rare in systemic lymphoma, it must be considered in the differential diagnosis of patients presenting with what is thought to represent a recurrent optic neuritis, which eventually becomes resistant to steroids.
An optic nerve biopsy may be required to prove the exact underlying nature of the disease. How-

ever, in cases with still some remaining vision, this approach may be more difficult to defend. The multicentric nature of recurrence from a systemic lymphoma should be kept in mind and a thorough evaluation must be performed before initiating any treatment.

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