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Optic Nerve Lymphoma. Report of Two Cases and Review of the Literature

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Abstract

Lymphoma may involve the optic nerve as isolated optic nerve lymphoma or in association with CNS or systemic lymphoma. We present two biopsy-proven non-Hodgkin lymphomas of the optic nerve and compare our findings with previously reported cases. We discuss the mechanism of metastasis, classification of optic nerve involvement, clinical features, radiologic findings, optic nerve biopsy indications and techniques, histologic features, and treatments. We propose a classification system of optic nerve lymphoma: isolated optic nerve involvement, optic nerve involvement with CNS disease, optic nerve involvement with systemic disease, and optic nerve involvement with primary intraocular lymphoma. Although it is an uncommon cause of infiltrative optic neuropathy, optic nerve metastasis should be considered in patients with a history of lymphoma. The recommended approach to a patient with presumed optic nerve lymphoma includes neuroimaging, and cerebrospinal fluid evaluation as part of the initial work-up, then judicious use of optic nerve biopsy, depending on the clinical situation.

Keywords

Optic Nerve; Metastasis; Lymphoma; Optic Nerve Lymphoma

I. Introduction

In 2013, roughly 70,000 new cases of non-Hodgkin lymphoma (NHL) were diagnosed in the United States, which comprised approximately 3-4% of all malignancies.^{24,47,53}

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Method of Literature Search: Search of Pubmed database was performed using the following key words: lymphoma, lymphomatous, optic nerve, optic neuropathy, and metastatic. Articles cited in the reference lists of the retrieved articles were also reviewed. Articles in languages other than English or French were not included. Non-English articles excluded from this study were excluded on review of the abstract in English.

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Epidemiologic data suggests that the incidence of NHL has been increasing at 0.5% annually over the last 10 years.²⁴ However, mortality due to all types of cancer has been declining, and in the last 10 years, NHL has had a 3% annual decrease in mortality.⁴⁷

Approximately 10% of patients with NHL have central nervous system (CNS) involvement, and of these patients about 5% may develop optic nerve infiltration.^{39,55} The frequency of CNS involvement of NHL varies according to histologic type I as well as the aggressiveness of the NHL subtype. The incidence of CNS involvement may be increasing as effective treatments result in longer survival and decreased mortality. Thus, ophthalmologists may encounter patients with ophthalmic sequelae of NHL.⁵⁵

Metastatic disease to the eye and orbit most frequently involves the choroid, presumably because of its blood supply. In an Armed Forces Institute of Pathology clinicopathologic review, isolated optic nerve metastasis occurred in ~1.3-12% of cases of all metastasis to the eye and orbit.^{9,14} Metastases to the optic nerve originate most frequently from breast (25-33%) or lung (11-15%) carcinomas, which is consistent with the most common primary tumor metastatic to the eye and orbit.^{1,14}

Systemic NHL with isolated metastasis to optic nerve is rare. A study of nearly six thousand cases of all types of lymphoma found that there was only one case with optic nerve involvement.³⁴ Biopsy confirmed cases of metastatic lymphoma to the optic nerve are even more uncommon, as many are empirically treated when there is a high index of suspicion.³⁹ We report two cases of systemic NHL with optic nerve metastasis in which optic nerve biopsies were performed to confirm the diagnosis and review the literature on optic nerve lymphoma.

II. Case Reports

Case 1

A 65-year-old woman presented with abdominal pain in June, 2011, that led to the diagnosis of abdominal follicular B-cell NHL by retroperitoneal lymph node biopsy. At that time a bone marrow biopsy showed normal cellular marrow with several lymphoid aggregates, but the sample was not diagnostic for lymphoma. Additionally, flow cytometry did not show any abnormal lymphoid population. She was in clinical remission after receiving six cycles of cyclophosphamide, vincristine, prednisone and rituximab ending in June of 2012.

One month after completing chemotherapy, she developed symptoms of a sinus infection, including right-sided injection, pain, and irritation, as well as blurry vision in her right eye. She was being treated with a second course of antibiotics for presumed sinus infection on referral to ophthalmology. She had no previous ophthalmic history. On initial examination, she had a visual acuity of count fingers at two feet in the right eye and a right relative afferent pupillary defect (RAPD). Slit lamp examination of the anterior segment was normal with the exception of swelling of her right upper and lower eyelids. Dilated fundus examination of the right eye showed optic disk edema, vascular engorgement, an ischemic macula, and scattered intra-retinal hemorrhages (Figure 1A). Magnetic resonance imaging (MRI) with and without gadolinium of the orbits showed findings consistent with a right

optic neuritis including moderately intense enhancement of the right optic nerve sheath, and right optic nerve and sheath swelling to approximately seven millimeters while for comparison the left optic nerve measured approximately three millimeters (Figure 1B). A lumbar puncture yielded cerebrospinal fluid (CSF) negative for malignant cells, bacteria and fungi. A systemic infectious disease evaluation was negative. A bone marrow biopsy and did not show any evidence of lymphoma.

She subsequently progressed to no light perception right eye, and an optic nerve biopsy was recommended as the patient had no evidence of lymphomatous involvement elsewhere. She underwent a medial anterior orbitotomy with incisional biopsy of the optic nerve sheath. Examination of the biopsy specimen showed that the nerve fiber bundles were largely necrotic, and only myelin remained. The fibrovascular pial septa were distended with mononuclear cells, including primarily small, round lymphocytes and occasional larger lymphocytes. Tumor cells were present in both the nerve tissue as well as the nerve sheath and pial septa, and there was no apparent follicular architecture (Figures 1C-E). Immunohistochemical stains were positive for CD45 and CD20 in many lymphocytes (Figure 1F), CD10 in scattered lymphocytes with no discernible follicular architecture, and negative for CD3. Flow cytometry was precluded due to a low cell count. Polymerase chain reaction (PCR) showed a clonal IgH Kappa gene rearrangement and was negative for T cell receptor gene rearrangement. After biopsy confirmation of lymphoma, the patient underwent re-staging of her NHL, which included computer tomography (CT) of her chest, abdomen and pelvis as well as an MRI brain that did not show any other areas of metastasis. One month post-biopsy, the patient was undergoing radiation therapy to the right optic nerve, remained NLP in the right eye, and intrathecal chemotherapy was being considered.

Case 2

A 25-year-old Hispanic woman initially presented in February 2012 with weight loss, fatigue, night sweats, and increasing abdominal girth. MRI showed an ovarian mass with mild hydronephrosis and a thickened and dilated small bowel. She underwent an exploratory laparotomy with total abdominal hysterectomy and bilateral salpingoophorectomy in March 2012 and pathologic evaluation was consistent with Burkitt lymphoma. A positron emission tomography (PET) scan revealed hypermetabolic activity in multiple organs including the thyroid gland, breasts, right atrium, left ventricle, kidneys, small bowel, periportal and aortocaval lymph nodes, and multiple bones, suggesting widespread involvement of the lymphoma. She promptly began R-HCVAD (rituximab-cyclophosphamide, vincristine, dexamethasone, doxorubicin) combination systemic and intrathecal chemotherapy for Stage 4 Burkitt lymphoma. A follow-up PET scan in June, 2012, showed near resolution of hypermetabolic activity, and a repeat PET scan indicated complete response to therapy.

She was admitted to the oncology service in August, 2012, for her scheduled seventh of eight rounds of chemotherapy and reported decreasing vision in her left eye. Initial ophthalmic evaluation showed 20/200 acuity left eye, no RAPD, and 1/14 color plates in her left eye, while her right eye examination was normal. A dilated fundus examination showed no disc edema and retinal pigmentary changes in both eyes. Follow-up examination three weeks days later showed in her left eye no light perception vision, a RAPD, a possible

ophthalmic artery occlusion, and the optic nerve appeared edematous and infiltrated (Figure 2A). She underwent a lumbar puncture and bone marrow biopsy, both of which were negative for malignant cells. An MRI of the brain and orbits with and without gadolinium showed an abnormal T2 signal and enhancement of the left optic nerve with a soft tissue infiltrate most prominent along the intraorbital left optic nerve and filling the left retrobulbar space (Figure 2B).

A left frontal orbitotomy with biopsy of the lacrimal gland was attempted, as the tissue was more accessible; however, pathologic examination was negative for malignancy. Since the patient was otherwise considered to be in clinical remission and the biopsy was negative, she underwent a left anterior medial orbitotomy with biopsy of the left optic nerve and optic nerve sheath. The biopsy specimen showed that the fibrovascular septa of the optic nerve were infiltrated with lymphocytes and occasional histiocytes (Figure 2C). There was no clear evidence of a starry sky pattern as there was a significant amount of crush artifact (Figures 2C-E). Immunohistochemical stains demonstrated diffuse positivity for CD20 (Figure 2F), scattered positivity for histiocytic marker CD68, and were negative for CD3 and CD5. Flow cytometry was precluded due to a low cell count. PCR showed a clonal IgH Kappa gene rearrangement and was negative for T cell receptor gene rearrangement.

On re-staging PET scan and MRI imaging, she was found to have trigeminal nerve involvement and progression along the left optic nerve extending to the optic tracts representing perineural spread of the tumor. The patient began whole brain radiation for multifocal CNS involvement of Burkitt lymphoma. Approximately two months after presentation with visual symptoms, she was admitted for neutropenic fever, slowly declined, and transitioned to hospice care.

III. Mechanisms of Optic Nerve Lymphoma Spread

Primary CNS lymphoma is more common than secondary involvement of the CNS by a systemic lymphoma; however, secondary disease can more often involve the meningeal, perivascular, and spinal epidural areas. Optic nerve involvement more commonly occurs from secondary infiltration than by a primary optic nerve tumor.⁹ Routes of metastatic spread to the optic nerve and leptomeninges are not well established, although theories include direct extension of tumor cells, hematogenous dissemination, dissemination through the CSF, or perineural spread.^{8,9,54}

Direct invasion from dural involvement to the pia-arachnoid has been postulated; however, in many cases the dura appears to function as an effective barrier to leptomeningeal invasion as evidenced by histologic examination.²⁰ Spread via the bloodstream to the pia-arachnoid is possible and could be the result of direct extension from adjacent involved bone via perforating dural vessels.²⁸ A case reported by Griffin and colleagues raises the possibility of CNS spread of lymphoma via dissection within peripheral nerve sheath.²⁰ One previous report found a consistent correlation between bone marrow involvement and CNS disease.⁵ This relationship raises the possibility of lymphomatous spread directly from the medullary cavity of bone via perforating vessels and nerves through the dura into the arachnoid space.^{5,29}

While primary central nervous system lymphoma (PCNSL) and NHL may be indistinguishable on histologic examination, clinical features may help to differentiate these two entities. PCNSL often involves brain parenchyma typically near the ventricles, while NHL metastatic to the CNS is often found in the leptomeninges or dura.⁵⁶

IV. Clinical Categories of Lymphomatous Optic Nerve Involvement

We propose a classification of optic nerve lymphoma: primary optic nerve involvement, optic nerve involvement with CNS disease, optic nerve involvement with systemic disease, and optic nerve involvement with primary intraocular lymphoma (PIOL). This classification system may allow for better understanding of pathophysiology of spread and course of the disease, as well as provide insight into optimal treatment options. Anatomically, the optic nerve is composed of nerve fiber bundles invested by fibrovascular pial septa. The septa consist of blood vessels, fibroblasts, and pia mater meningotheelial cells. We also further classify optic nerve involvement depending on the location of the malignant lymphoma cells: intrinsic (within the nerve fiber bundles), leptomeningeal (within the fibrovascular pial septa), or both.

There were several cases reported prior to 1975 in which optic neuropathy was the presenting sign of a widespread lymphoma. Given that imaging modalities of that era were limited to plain x-rays and angiograms, these cases are not included in the following classification and discussion. Many of these patients had rapid CNS and neurologic decline and expired between three and nine months after presentation, and most of these patients had widespread lymphomas at the time of optic nerve involvement.^{15,23,35,38,42,52}

A. Primary Optic Nerve Involvement

Cases in the literature supporting isolated lymphomatous optic nerve involvement that were confirmed by tissue diagnosis are included in this category (Table 1).^{15,22-24} Two of the three cases were bilateral as they had involvement of the chiasm. Most cases presented with decreased acuity, and all had a visual field defect. In each of these cases, CSF analysis was negative for malignant cells. In one case, tumor cells were intrinsic to the nerve. In another case, malignant cells were both intrinsic and leptomeningeal. For the third case, there was no optic nerve biopsy done, but an MRI suggested optic nerve infiltration. It was not possible to localize the involvement for this case. Most patients had improvement or stabilization of visual acuity and field defects with treatment, which included a combination of radiation therapy, corticosteroids, and chemotherapy. These patients had varied overall outcomes, ranging from rapid onset of meningeal lymphomatosis leading to death in six weeks⁴⁹ to stable and no recurrence at last follow up.

This type of presentation has caused confusion regarding classification of the lymphoma in that one author used the diagnosis of primary intraocular lymphoma³, the ocular manifestation was a harbinger of meningeal lymphomatosis in another case⁴⁹ and in other cases the lymphoma seemed to be isolated to the optic nerve.^{3,13} It is unknown whether malignant cells in this type of lymphoma arise *de novo* or are actually metastases from a clinically undetected primary tumor.

B. Optic Nerve Involvement with CNS Disease

Cases categorized as optic nerve involvement with CNS disease (Table 2) include those that had previously known CNS disease^{21,33,55}, presented with decreased vision with simultaneous CNS symptoms^{4,30,37}, or presented with decreased vision and simultaneous CNS findings on neuroimaging.^{11,40,45,56}

Patients with established CNS involvement of lymphoma who subsequently developed optic nerve involvement complained of decreased vision^{33,55}, diplopia²¹, or both.^{4,30,37} One prior case⁴⁵ and our Case 2 seemingly presented as isolated optic nerve metastasis until neuroimaging discovered evidence of additional CNS involvement. Four previously reported patients initially appeared as having isolated optic nerve involvement based on presenting symptoms; however, neuroimaging revealed optic chiasm and tract enhancement⁵⁶, suprasellar involvement⁴⁰, optic chiasm involvement⁴⁰, and optic tract, chiasm and frontal lobe edema¹¹. The patients with periventricular involvement and optic chiasm involvement had the longest survival of the cases classified as optic nerve with CNS involvement as they ultimately expired 24 and 39 months after onset of visual symptoms.^{40,45}

Time of onset of visual symptoms in those patients already diagnosed with lymphoma ranged from as short as one month after chemotherapy initiation or after two rounds of chemotherapy to as late as eight years after the initial diagnosis of lymphoma. One patient had a completely normal fundus examination, although the majority presented with optic nerve edema or evidence of vascular compromise. Neuroimaging by CT was normal in 2 cases, and the remaining patients had optic nerve enhancement or other CNS lesions. Of the seven patients with CSF analysis, two had malignant lymphocytes, two had normal CSF constituents, and the other two had nonspecific abnormalities. A biopsy was performed in six cases, and histopathologic confirmation was obtained at autopsy in three. Out of the 9 cases with histologic results, 2 had intrinsic involvement of the nerve, 3 had leptomeningeal, and 1 had both. The findings in the remaining 3 cases were not specified.

Most patients were treated with a combination of intravenous chemotherapy, intrathecal chemotherapy, and radiation therapy. Outcomes of these patients ranged from death within three weeks of onset of visual symptoms to as long as two years after onset of visual symptoms.

Of note, two patients in this series expired from infectious causes. One had gram-positive cocci in the lung tissue found on autopsy.²¹ Another was a diabetic male with diplopia and orbital x-ray findings suspicious for mucormycosis. On autopsy, he was found to have pneumococcal pneumonia of the left lung.⁴

C. Optic Nerve Involvement with Systemic Disease

Cases supporting optic nerve involvement with systemic disease include those in which optic nerve involvement is evident in the absence of CNS lymphoma (Table 3). This category includes cases^{16,28,29,50} where, after visual symptoms occurred, CSF analysis was positive for malignant cells. However these CSF positive patients did not have any further evidence of CNS disease as manifested by other cranial neuropathies or lesions on neuroimaging.

Timing of symptoms ranged from as early as onset of the fourth cycle of chemotherapy to as late as three years after initial diagnosis of lymphoma. Almost all cases presented with unilateral decreased acuity, and many also presented with a visual field defect. One case in which visual acuity was not reported was a 2-year-old child with diffuse large B-cell lymphoma who presented with redness and pain of the right eye, eyelid edema, conjunctival congestion, and axial proptosis.³² Findings in most patients in this category included optic disk edema with or without peripapillary hemorrhages, although there was one patient with a relative afferent pupillary defect and a normal fundus exam, and one patient presented with a combined central retinal artery and vein occlusion. Most patient had positive neuroimaging with optic nerve enhancement. All but one patient in this category underwent lumbar puncture. Of the eight cases where CSF analysis was available, two had completely normal CSF constituents. Four had atypical lymphocytes present in the CSF analysis, and the other two had elevated intracranial pressure. Our Case 1 fits into this category and had an optic nerve biopsy to confirm histologically that lymphoma infiltrated the optic nerve. Out of the 9 cases, only our case had an optic nerve biopsy, and tumor cells were both intrinsic and leptomeningeal.

Treatment for patients in this category included a combination of radiation, intrathecal chemotherapy and corticosteroids, intravenous chemotherapy, intravenous steroids, and oral corticosteroids. Five of the nine patients had improvement in visual acuity, visual field, or neuroimaging findings. One patient initially had improvement in visual acuity, but then subsequently lost vision in both eyes prior to death 6 weeks later.¹⁶ Three patients had no change in visual acuity with treatment and the patient who presented with a combined central retinal artery and vein occlusion developed neovascular glaucoma. Two patients in this category expired 6 weeks and 7 months after onset of visual symptoms, respectively.

D. Optic Nerve Involvement with Primary Intraocular Lymphoma

PIOL may involve the retina, vitreous, or optic nerve and has been extensively reviewed.¹⁸ In short, the optic nerve may be involved in PIOL, and the mechanism of spread is likely by direct extension of tumor.

E. Other Forms of Optic Nerve Involvement by Lymphoma

There are several other mechanisms by which the optic nerve may become involved in a patients with NHL. Case reports highlight compressive optic neuropathy by orbital lymphoma³⁴, paraneoplastic optic neuritis¹², and central retinal artery occlusion secondary to hyperviscosity.¹⁰ Optic neuropathy may also develop secondary to radiation-related necrosis, vincristine toxicity, or infection.

Although our two cases presented with presumed isolated optic nerve involvement, Case 1 represents optic nerve lymphoma with a systemic lymphoma and Case 2 represents optic nerve lymphoma with concurrent CNS lymphoma in which the optic nerve involvement was a harbinger of widespread CNS disease. We conclude from our two cases and our literature review that isolated optic nerve lymphoma metastasis from CNS spreads from extension via the meninges in the fibrovascular pial septa and from systemic lymphoma spreads hematogenously via the fibrovascular pial septa. This is supported by histologic examination

displaying infiltration of the fibrovascular pial septa without surrounding dural involvement and sparing of the nerve fiber bundles by the lymphomatous infiltrate.

V. Radiographic Features

Current standards for evaluation of optic neuropathy include neuroimaging to evaluate for compressive, demyelinating, inflammatory, and infiltrative etiologies. MRI is the imaging modality that best distinguishes the meningeal, cerebrospinal fluid, and axonal portions of the optic nerve. CT imaging is less frequently used to evaluate the optic nerve given exposure to ionizing radiation, side effects related to contrast dye administration, and decreased resolution of optic nerve components; however it may be the neuroimaging modality of choice in patients unable to undergo MRI.^{2,54}

MRI imaging findings of lymphomatous infiltration of the optic nerve include enlargement of the optic nerve, enhancement of the nerve sheath, or tram-tracking.^{2,27} Findings on MRI are non-specific; thus, the history and clinical findings are indispensable.⁴³

The differential diagnosis of neuroimaging findings include primary optic nerve tumors such as optic nerve sheath meningioma and optic glioma, secondary optic nerve tumors such as metastatic carcinoma or other primary brain tumors, inflammatory disorders such as multiple sclerosis or sarcoidosis, and infectious etiologies such as syphilis or tuberculosis.^{17,25,54} Specific radiologic, clinical and pathologic findings of optic nerve disorders have been previously described.⁵⁴

VI. Lumbar Puncture and Cerebrospinal Fluid Analysis

CSF analysis aids in the diagnosis of lymphomatous involvement of the optic nerve and when diagnostic, precludes the need for an optic nerve biopsy to confirm the diagnosis. Some recommend 3-4 lumbar punctures in patients who have signs or symptoms suggestive of lymphomatous CNS involvement.^{3, 36} Glantz et al performed a literature review to determine how many CSF samplings are necessary to exclude a false-negative result. They noted a high yield of positive CSF results on a second lumbar puncture and little additional benefit from a third lumbar puncture.¹⁹

CSF samples should be greater than 10.5mL and immediately hand carried to the laboratory for processing the same day.⁴⁶ Routine CSF indices including cell count, protein, and glucose may be normal or abnormal in cases of leptomeningeal lymphoma. At the time of diagnosis, at least one of the aforementioned indices are abnormal in greater than 80% of CNS lymphomas. Several studies have proven that cell counts and CSF protein are normal in 33-60% and 33-55% of patients with CNS lymphoma.⁴⁶ CSF should be sent for cytology, flow cytometry, and PCR. Cytology is the gold standard in the diagnosis of CNS lymphoma as it has high specificity (>95%), however lower sensitivity (<50%, 2-32%).^{7,46} The yield of cytologic studies varies widely and delays in processing, exposure to corticosteroids, and small sample volume may affect diagnostic value of the study.

Flow cytometry is useful in diagnosing lymphoma given the speed and quantitative nature of flow cytometric immunophenotyping analysis. Utility of flow cytometry analysis extends

beyond diagnosis of lymphoma, and can aid in determining prognosis as well as detecting drug resistance.⁴⁸ Up to 80% of lymphoma cases with CSF involvement were detected on the first lumbar puncture when CSF was analyzed with both cytology and flow cytometry.⁴⁶

Polymerase chain reaction (PCR) is a useful adjunctive test in diagnosing lymphomatous meningitis particularly when CSF sampling does not provide adequate morphologically recognizable malignant cells. The benefit of PCR lies in the exquisite sensitivity to detect tumor derived DNA. Detection of specific translocations such as t(14:18) and detection of T-cell and B-cell clonality may support a diagnosis of lymphomatous meningitis when cytology is non-diagnostic. Studies have reported high specificity (85%) and moderate sensitivity (58%) in the diagnostic ability of PCR; however, PCR should be used in conjunction with other methods of diagnosis and not be the sole basis for a diagnosis.^{44,46} Other molecular testing to consider include beta-2 microglobulin and lactate dehydrogenase isozyme 5 for all patients, and Epstein-Barr virus in immunocompromised patients. The future direction of molecular diagnostic testing currently includes proteomic analysis and MicroRNA expression of CSF. Improvement of these techniques may aid in pre-surgical diagnosis of CNS lymphoma.⁴⁶

VII. Optic Nerve Biopsy Indications and Techniques

Optic nerve biopsy is indicated when an optic nerve disease causes significant loss of vision despite empiric treatment, vision in the fellow eye is threatened, or systemic investigations are unsuccessful in determining the etiology of the optic neuropathy.³¹ An optic nerve biopsy can be helpful in cases in which an optic neuropathy is the presenting symptom of a lymphoma and the workup is negative; however, routine biopsy in patients with a history of systemic lymphoma is not necessary in most cases.

Methods for obtaining optic nerve tissue include image guided fine needle aspiration biopsy (FNAB), transconjunctival biopsy, and a neurosurgical approach. Image guided FNAB is infrequently utilized as the biopsy specimen obtained is small with tissue architecture not well preserved. In 2000, Dayan and colleagues described that intrinsic optic nerve biopsy, rather than a more invasive neurosurgical approach such as craniotomy, may be performed for a tissue diagnosis.¹³

Studies suggest that medial transconjunctival intrinsic optic nerve biopsy is safe and can preserve some vision.^{13,22} Several factors support the relative safety of a medial approach for optic nerve biopsy. Macular ganglion cell axons occupy the lateral portion of the optic nerve; thus, with a medial approach these nerve bundles and central vision are spared, and any residual visual field defects would be located in the peripheral temporal region, corresponding to loss of nasal retinal ganglion cells. Additionally, the ciliary ganglion is located lateral to the optic nerve and is less likely to be disrupted with the medial approach. The transconjunctival approach to the optic nerve begins with a peritomy sparing the lateral conjunctiva. The medial rectus is isolated then disinserted to provide access to the medial intraconal space. After optic nerve visualization, the anterior portion is exposed with malleable retractors. The optic nerve sheath is incised by grasping the sheath with toothed forceps and tenting it away from the underlying nerve. A rectangle or ellipse window of the

optic nerve sheath is carefully removed. Gündüz et al recommend 1cm long incision of the optic nerve sheath, then an oblong shaped incisional biopsy of the tumor about 0.5cm long.²² The underlying optic nerve is then biopsied by carving out a small block of tissue. Careful handling of the tissue avoids crush artifact which can obscure cytologic details. Both the nerve sheath and optic nerve biopsy should be sent for histopathological examination. Diathermy should be avoided to prevent thermal injury to the optic nerve. The medial rectus is sutured back to its insertion, and the overlying conjunctiva is closed.^{22,31} Biopsy specimens should be submitted in the following media for complete examination and classification of lymphoma: neutral buffered formalin for preservation of DNA and long term storage, a metal-based fixative (such as B5 Zenker's solution or zinc sulfate available commercially as B-plus TM from BBC Biochemical, Mt. Vernon, WA) for speedy fixation and optimal nuclear morphology, and Roswell Park Memorial Institute (RPMI) medium for flow cytometry.^{48,26} The low cellularity of CSF and optic nerve biopsy samples makes flow cytometry challenging. Ideally, 1 gram of optic nerve tissue is needed for flow cytometry studies, but can be less if the tissue is cellular.

Optic nerve biopsy should be done judiciously as it carries significant risk to patients who maintain good visual acuity despite lymphomatous involvement of the optic nerve.⁴¹ Limitations of a medial conjunctival biopsy include obtaining only a small amount of tissue for, as well as accessing only the most anterior portion of the optic nerve. Previously reported patients who underwent optic nerve biopsy for lymphoma had no significant visual deterioration.^{13,22,31} The surgical techniques in our two cases are as described above, and the decisions to biopsy was not difficult as both patients had no light perception vision.

VIII. Histopathologic Findings in Optic Nerve Biopsies

Lymphoid neoplasms are tumors composed of clonal populations of mature and/or immature B or T cells. B-cell lymphomas are relatively more common than T-cell lymphomas. In our survey of 24 cases, we encountered only 2 cases of definite T cell lymphoma (Table 2 and 4). When not specified, we presumed cases to be B-cell lymphomas. These lymphomas can be classified based on the level of cell differentiation or morphology, immunophenotype, genetic abnormalities, and clinical features. Cells are small to medium sized and typically show little pleomorphism.; however, high-grade lymphomas may show considerable nuclear pleomorphism. Based on the reported 12 cases of optic nerve biopsies, lymphoma can equally involve the nerve fiber bundles, fibrovascular pial septa, or both (3 cases each for intrinsic, leptomeningeal, and both). Most B-cell lymphomas have characteristic immunophenotypic profiles that are helpful in the diagnosis, whereas immune profiling is less useful in subclassifying T-cell lymphomas.^{6,26}

Immunohistochemical staining for specific markers is used to diagnose distinct clinical lymphoma entities. All lymphoid cells are reactive for CD45, also known as the leukocyte common antigen (LCA). Pan B-cell markers include CD 19, CD 20, CD 22 and certain low-grade B-cell lymphomas are reactive for CD 5 and CD 43 that are normally found on T-cells. Pan T-cell markers include CD 2, CD 3, CD 7, CD 4 and CD8.

A range of subtypes of lymphomas infiltrate the optic nerve as proven by biopsy. Most of these cases were of optic nerve involvement with CNS disease. The types of lymphoma that have infiltrated the optic nerve are summarized in Table 4. Kitzmann et al. reported a rare case of systemic peripheral T-cell lymphoma that directly infiltrated the optic nerve, with the tumor staining for CD3 and not for CD20. Zelefsky et al.'s case was positive for BCL2, and negative for CD5 and CD10, consistent with a diffuse small B cell type, originating from follicular center cells.⁵⁶

There are three reports of suspected lymphomatous optic nerve infiltration confirmed postmortem. Bullock et al. recounts a case of a patient with widespread poorly differentiated NHL. Autopsy findings revealed lymphomatous infiltration of the optic nerve, almost completely replacing a segment of nerve, with extensive necrosis and degenerated nerve bundles. Guyer et al. documented a case of systemic non-Hodgkins mixed cell (small and large) lymphoma, cleaved cell type with follicular and diffuse patterns that proceeded to infiltrate the pial septa of the optic nerve, causing extensive infarction and bilateral central retinal artery occlusions. The tumor was composed of cells with hyperchromatic nuclei and scant cytoplasm crowded in the extravascular area. Immunostaining was positive for leukocyte common antigen. Histologic findings in the optic nerve included dissolution of myelin, necrosis of nerve fiber bundles, and thrombus formation in the central retinal artery. Lee et al. reported a case of systemic NHL and concomitant acquired immunodeficiency syndrome with the bone marrow diffusely replaced by a uniform population of medium to large cells with a moderate amount of cytoplasm, irregular convoluted nuclei, finely granular chromatin and prominent nucleoli. These malignant lymphocytes had a Burkitt lymphoma cell-like appearance, immunohistochemically stained for CD20, and in situ hybridization revealed Epstein Barr Virus. Although the patient was treated with chemotherapy and was thought to be in clinical remission, he later presented with acute vision loss and other neurologic signs. The patient eventually died and autopsy showed both optic nerves densely infiltrated with malignant cells, bilateral necrotizing vasculitis and CRVOs of the retina, and lymphomatous involvement of the paraventricular regions of the brain. The optic nerves and brain contained areas of necrosis and reactive inflammation, thought to be the effects of prior treatment.

Less common are reports of isolated lymphoma of the anterior visual pathways (optic nerve, chiasm, optic tract, and lateral geniculate body)⁵⁶ and isolated optic nerve² with no other systemic involvement. Dayan et al. described a patient with bone marrow and peripheral blood findings of a low grade NHL positive for the B cell markers CD20, CD19, kappa light chain, and IgM. A complaint of blurring of vision prompted an optic nerve biopsy that also showed low grade NHL.¹³ Behbehani et al. reported a case of B-cell lymphoma of the optic nerve where optic nerve biopsy was done because there was no improvement with conservative treatment for 3 months for a presumed inflammatory infiltration. Frozen sections showed infiltration of the optic nerve by moderately pleomorphic B-cells around the blood vessels with scattered reactive T-cells. These cells stained positively for CD45 and CD 20.³

Lastly, in one case, small, immature, atypical lymphocytes with clumped chromatin consistent with small cleaved cell lymphoma were found in temporal artery and bone

marrow biopsies. An optic nerve biopsy was not performed, but an MRI was suggestive of optic nerve infiltration.⁴⁹

IX. Treatment and Follow up

There is no consensus on a standardized treatment for leptomeningeal lymphoma given the lack of randomized trials. Treatment options include high-dose intravenous chemotherapy, intrathecal chemotherapy, radiation therapy to sites of symptomatic disease, and high-dose corticosteroids. Most patients received radiation treatment for lymphomatous optic nerve involvement, and some were also treated with systemic chemotherapy, intrathecal chemotherapy, or intravenous corticosteroids.

One study reported that, after treatment of CNS recurrence in patients with NHL, analysis showed that intrathecal treatment did not result in meaningful responses, and radiation therapy frequently resulted in rapid, but transient, symptomatic relief.⁵¹ While chemotherapy is theoretically appealing as some agents cross the blood-brain barrier most patients had CNS relapse during or shortly after completing their treatment regimens.⁵¹ We recommended that treatment be individualized for each patient with consideration of type and staging of the systemic lymphoma.

X. Conclusion

Optic nerve metastasis of NHL should be considered in patients with a history of NHL who present with an optic neuropathy. The work up of a presumed optic nerve lymphoma should include neuroimaging and CSF evaluation, then careful consideration of an optic nerve, depending on the results of initial work up and other clinical findings. Our cases support local spread via the meninges in patients with concurrent CNS lymphoma and hematogenous dissemination in patients with systemic NHL as the usual routes optic nerve involvement. Treatments should be individualized and based on the lymphoma subtype and stage. Further studies are recommended to determine the appropriate utilization of optic nerve biopsies in optic nerve lymphoma.

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Figure 1.

Case 1. A. Fundus appearance showing optic nerve edema, vessel engorgement and intraretinal hemorrhages. B. MRI showing right optic nerve and optic nerve sheath swelling (arrow) compared with the left. C. Optic nerve biopsy showing distension of fibrovascular septa with lymphocytes and atrophy of nerve fiber bundles. D. Monotonous sheets of lymphocytes mainly in the fibrovascular pial septa with occasional cells present within the atrophic and necrotic nerve fibers. E. Higher magnification showing lymphocytes with round to oval, condensed nuclei and scant cytoplasm. F. Cells in the fibrovascular septa and nerve tissue stain for CD20. (C. hematoxylin and eosin 10 $\times$; D. hematoxylin and eosin 25 $\times$; E. hematoxylin and eosin 250 $\times$; F. peroxidase anti-peroxidase 100 $\times$)

Figure 2.

Case 2. A. Fundus appearance of left eye showing disc edema and mild pigmentary changes of the retina. B. MRI with gadolinium showing enhancement of the left optic nerve and optic nerve sheath (arrow) compared with the right. C. Optic nerve biopsy showing infiltration of the fibrovascular pial septa with lymphocytes and sparing of the nerve fiber bundles. D. Higher magnification of lymphocytes within the pial septa. E. Lymphocytes with hyperchromatic nuclei, occasional histiocytes with larger nuclei, and associated crush artifact. F. Lymphocytes within the fibrovascular pial septa staining positive for CD20. (C. hematoxylin and eosin, 25 $\times$; D. hematoxylin and eosin 100 $\times$; E. hematoxylin and eosin 250 $\times$; F. peroxidase anti-peroxidase, 25 $\times$)

Table 1
Cases of Lymphoma with Primary Optic Nerve Involvement

Year/ Author	Age/ Sex	Diagnosis	Initial Visual Symptom	Fundus Findings	Imaging	Lumbar Puncture	Type of Biopsy/ ON location	Treatment	Visual Outcome	Outcome
Strominger, 1993	69 F	Small cleaved cell	Decreased VA OS, VF defect OU	Engorged RV OS	MRI (+)	wnl	TAB	IVs, XRT	Improved VA	Death, 6 weeks
Dayan, 2000	74 F	Low grade B-cell	TVO OU, VF defect OU	ON edema OU	MRI (+)	High protein	ON/ INT	XRT	Improved VA	Remission
Behbehani, 2005	66 F	B-cell	Decreased VA OD, VF defect OD	ON edema, distended RV	MRI (+)	wnl	ON/ INT and LPM	XRT, IVc	Stable VA VF	n/a

F = female, OD = right eye, OS = left eye, OU = both eyes, TVO = transient visual obscurations, VA = visual acuity, VF = visual field, ON = optic nerve, RV = retinal veins, (+) = positive findings, wnl = within normal limits, TAB = temporal artery biopsy, INT = intrinsic optic nerve, LPM = leptomeningeal optic nerve, IVc = intravenous chemotherapy, IVs = intravenous steroids, XRT = radiation therapy, n/a = information not available

Table 2
Cases of Lymphoma with Optic Nerve Involvement and Central Nervous System Disease

Year/ Author	Age/ Sex	Diagnosis	Initial Visual Symptom	Timing of visual Symptom	Fundus Findings	Imaging	Lumbar Puncture	Type of Biopsy / ON location	Treatment	Outcome ^a
B-cell lymphomas										
Bullock, 1979	75 M	Poorly differentiated NHL	Decreased VA OD, Diplopia	1 mo after chemotherapy initiation	normal	CT (-) Orbital xray (+)	7 mononuclear cells, low glucose	ON at autopsy/ INT	XRT	Death, 31d
Guyer, 1990	57 F	Mixed cell NHL	Diplopia	5 mo after diagnosis, 1 mos after CNS involvement	CRAO	CT (-) Carotid dopplar (-)	Atypical lymphocytes, increased intracranial pressure	ON at autopsy/ LPM	IT, XRT	Death, 8wk
Zaman, 1993	42 F	Centroblastic NHL	Decreased VA OU	6 mo after chemotherapy	ON pallor, VF defect	CT (+), MRI (+)	wnl	No biopsy done	XRT	n/a
Saatci, 1999	14 M	Diffuse Large B-cell NHL	Decreased VA OS	5 mo after chemotherapy	CRAO, CRVO	MRI (+) periventricular tumor infiltration	High protein	No biopsy done	IVc, IVs, IT XRT	Death, 24mo
Lee, 2002	56 M	Large B-cell NHL	Decreased VA OS, CN5 palsy	4 mo after diagnosis	ON edema, RV engorgement, 4 quad IRH	MRI (+)	wnl	ON at autopsy/ LPM	IVs, XRT	Death, 3 weeks
El Kettani, 2006	75 M	Large B-cell NHL	Decreased VA OU, CN5 palsy	8 years after diagnosis	B ON edema	CT (+)	Atypical Lymphocytes	No biopsy done	IVc, IVs, IT	Death, 2 mo
Zelefsky, 2008	72 F	Diffuse small B-cell	Decreased VA OD, VF defect	Presenting symptom	ON pallor	MRI (+) chiasm and tract	n/a	ON/ INT and LPM	IVc, PO	Death, 3mo
Matsuyama, 2013	84F	Diffuse large B-cell NHL	Decreased VA OU	Presenting symptom	n/a	MRI (+) suprasellar tumor	n/a	fronto-temporal craniotomy	PO	n/a
Matsuyama, 2013	67M	Malignant Lymphoma	Decreased VA OD	Presenting symptom	n/a	MRI (+) chiasm	n/a	fronto-temporal craniotomy	IVc	Death, 39mo
Case 2, 2014	25 F	Burkitt Lymphoma	Decreased VA OS	After 6 cycles of chemotherapy	Normal	MRI (+) Trigeminal nerve involvement	wnl	ON/ LPM	XRT	Hospice care, 2mo
T-cell lymphomas										
Kitzmann, 2008	39 M	T-cell NHL	Decreased VA OU	After 2 cycles of chemotherapy	ON edema, flame hemorrhages, vein dilation, VF defects	MRI (+)	n/a	ON/ INT	IVc, XRT	Death, 3mo
Coleman, 2013	41M	Anaplastic Large T-cell NHL	Decreased VA OD, eye pain	Presenting symptom	n/a * asymmetric proptosis, ophthalmoplegia, chemosis	MRI (+) optic tract, chiasm, vasogenic edema of frontal lobe	n/a	total ethmoidectomy, maxillary antrostomy	IVc, XRT, PO	n/a

M=male, F=female, NHL = Non Hodgkins lymphoma, OD=right eye, OS=left eye, OU=both eyes, CN=cranial nerve, VF= visual field, mo = months, CNS=central nervous system, CRAO = central retinal artery occlusion, CRVO = central retinal vein occlusion, ON = Optic Nerve, , n/a = information not available, (-) = negative findings, (+) = positive findings, wnl = within normal limits, INT = intrinsic, LPM = leptomeningeal, IVc = intravenous chemotherapy IVs = intravenous steroids, IT = intrathecal chemotherapy, PO = oral steroids, XRT = radiation therapy,

* timing of death is with respect to onset of visual symptoms

Cases of Lymphoma with Optic Nerve Involvement and Systemic Disease

Table 3

Year/ Author	Age/ Sex	Diagnosis	Initial Visual Symptoms	Timing of Visual Symptoms	Fundus findings	Imaging	Lumbar Puncture	Biopsy	Treatment	Visual outcome	Outcome ⁺
Kattah, 1980	26 M	Poorly differentiated lymphocytic lymphoma	Decreased VA OD, VF defect OD	Onset of 5 th chemotherapy cycle	ON edema, peripapillary hemorrhage, OS – superonasal disc margin swelling	XRay (-), CT (-)	Atypical lymphocytes	No biopsy done	IVc, IT, PO, XRT	Improved VA & VF	Death, 7mo after visual symptoms
Kay, 1986	55 F	Undifferentiated histiocytic lymphoma	Decreased VA OS, VF defect OS	1 mo after chemotherapy completion	ON edema	CT (+)	Atypical lymphocytes, high ICP, low glucose, high protein	No biopsy done	IT, ITs, XRT	Improved VA & VF	n/a
Lanska, 1987	65 F	Diffused mixed lymphocytic / histiocytic	Decreased VA OS, VF defect OS	Onset of 6 th chemotherapy cycle, 5 mo after diagnosis	Normal	CT (+) *	High ICP	No biopsy done	IVs, IT, PO, XRT	Improved VA & VF	n/a
Siatkowski, 1992	21 M	Hodgkin's nodular sclerosis, Stage IIIB	Decreased VA OS, VF defect OS	2 yr after chemotherapy	ON edema, peripapillary hemorrhages	MRI (+)	High ICP	No biopsy done	IVs, XRT	Improved VA	Systemic recurrence, improved VA
Shukla, 2006	28 M	Marginal Zone B-cell NHL	Decreased VA OD	4 mo after remission	ON edema, CRAO, CRVO	MRI (+) CT (+)	n/a	No biopsy done	IVs, XRT	No improvement in VA, NVG	No systemic recurrence
Kim, 2010	2 F	Diffuse Large B-cell Lymphoma	Redness & Pain OD	6 mo after remission	ON edema, eyelid edema, conjunctival congestion, axial proptosis	CT (+)	wnl	No biopsy done	IV, IVs, IT, XRT	Improved neuroimaging	n/a
Sudhakar, 2011	44 M	Burkitt NHL	Decreased VA OS	After 4 th chemotherapy cycle	Mild ON edema	MRI (+)	Atypical lymphocytes high protein	No biopsy done	IV, IVs, IT, XRT	No improvement	n/a
Finke, 2012	51 F	B-cell Lymphoma, Stage IV	Decreased VA OD, VF defect OD	Onset of 5 th chemotherapy cycle	RAPD, otherwise wnl	MRI (+)	Atypical lymphocytes	No biopsy done	IV, IVs	Initial improvement in VA then decreased VA OU	Death, 6wks after visual symptoms
Case 1, 2014	65 F	Follicular B-cell NHL	Decreased VA OD	1 mo after chemotherapy, 1 yr after dx	ON edema, vein engorgement, ischemic macula, retinal hemorrhage	MRI (+)	wnl	ON/ INT and LPM	IT, XRT	No change in vision	n/a

M=male, F=female, NHL= Non Hodgkin's lymphoma, VA=visual acuity, OD=right eye, OS=left eye, VF=visual field, ON = Optic Nerve, CRAO=central retinal artery occlusion, CRVO=central retinal vein occlusion, RAPD=relative afferent pupillary defect, wnl = within normal limits, (+) =positive findings, (-) negative findings, ICP=intracranial pressure, INT=intracranial pressure, IT = intrathecal chemotherapy, IVs = intravenous steroids, PO = oral steroids, XRT = radiation therapy, n/a = information not available,

* initial CT scan & MRI wnl, follow up CT with findings

Table 4
Summary of 24 Cases of Lymphoma Involving the Optic Nerve

Biopsy Proven (number of cases)		
B-Cell Lymphoma	Presumed B-Cell Lymphoma	T-Cell Lymphoma
Small Cleaved Cell (1)	Poorly Differentiated NHL (1)	T-cell NHL (1)
Low Grade B-cell (1)	Mixed Cell NHL (1)	Anaplastic Large T-Cell (1)
Large B- Cell NHL (2)	Malignant Lymphoma (3)	
Diffuse Small B-Cell NHL (1)		
Diffuse Large B-Cell NHL (4)		
Burkitt Lymphoma (2)		
Follicular B-cell NHL (1)		
Not Biopsy Proven (number of cases)		
B-cell Lymphoma	Presumed B-Cell Lymphoma	
Centroblastic NHL (1)	Poorly Differentiated Lymphocytic Lymphoma (1)	
Marginal Zone B-cell NHL (1)	Undifferentiated Histiocytic Lymphoma (1)	
	Diffuse Mixed Lymphocytic / Histiocytic Lymphoma (1)	