Case Report

Beware the Retrobulbar Optic Neuritis Diagnosis

Kealan McElhinney\textsuperscript{a}  Maedbh Rhatigan\textsuperscript{a}  Zornitsa Tsvetanova\textsuperscript{b}
Conor O’Keane\textsuperscript{b}  Patricia Logan\textsuperscript{a}

\textsuperscript{a}Department of Ophthalmology, Mater Misericordiae University Hospital, Dublin, Republic of Ireland; \textsuperscript{b}Department of Pathology, Mater Misericordiae University Hospital, Dublin, Republic of Ireland

Keywords
Optic neuropathy · Compression · Orbital lymphoma

Abstract
A 48-year-old gentleman presented to the ophthalmology department with progressive monocular vision loss, a relative afferent-papillary defect, decreased color perception, headache, proptosis, and retro-orbital pain. This particular patient’s demographics and disease course did not suggest a “typical” retro-bulbar optic neuritis and highlights the importance of avoiding presumptive steroid treatment in such “atypical” cases. Further investigations revealed a compressive optic neuropathy secondary to an orbital tumor (B-cell non-Hodgkin’s lymphoma) and were subsequently treated by a multi-disciplinary approach. Early detection and commencement of treatment is a crucial determining factor in orbital lymphoma prognosis and is therefore an important differential diagnosis for an ophthalmologist to consider when evaluating patients with “atypical” optic neuropathies.

Introduction
Optic neuropathy is a common predicament for a practicing ophthalmologist, often presenting with monocular progressive loss of visual acuity and visual field, dyschromatopsia, relative afferent-papillary defect, and associated retro-orbital pain [1]. On examination, the optic nerve head may appear swollen and normal, or may show signs of optic nerve pallor (optic atrophy) after 4–6 weeks. Optic nerve damage may be caused by a range of insults including compression, ischemia, metabolic, infection, inflammation, infiltration, hereditary, or trauma [2].
A 48-year-old white Irish gentleman presented to the eye casualty with progressive monocular central vision loss over the preceding 2 weeks with associated photosensitivity, facial pain, and headache. The patient’s past medical history included bilateral dacryocystorhinostomy, asthma, eczema, and ex-smoker (10 pack years). Prior to presentation, the patient took no regular medications and only reported intermittent unilateral upper limb sensory disturbances and no other systemic symptoms. On evaluation in the eye clinic, best corrected Snellen visual acuity measured 6/18 on the right and 6/9 on the left. Physical examination showed a right-sided relative afferent pupillary defect and reduced color vision (Ishihara plate score of 9/13 on the right and 13/13 on the left). Slit-lamp examination showed normal anterior segments with bilateral intraocular pressures of 17 mm Hg. Dilated funduscopy was unremarkable with no evidence of macular, fundal, or optic nerve abnormalities. There were no abnormalities in extra-ocular motility or ophthalmoplegia and no evidence of ptosis, eyelid edema or retraction, or lid lag. The initial working diagnosis was retrobulbar optic neuritis (RBON).

The differential diagnosis included optic neuropathy (inflammatory, ischemia, compressive, hereditary, toxic/nutritional, traumatic, and paraneoplastic), retinopathy (paraneoplastic, inherited retinal disorder), space occupying lesion in the orbit or optic pathway (inflammatory disorders, malignant neoplasms). Outpatient magnetic resonance imaging (MRI) of the brain was requested to be performed with immediate follow-up in the neuro-ophthalmology outpatient clinic. At this outpatient appointment 4 weeks following initial presentation, it was noted that the best corrected Snellen visual acuity now measured 6/60 in the right eye with a score of 1/13 on Ishihara plates. On exophthalmometer evaluation, a 3 mm proptosis was noted for the right eye in comparison with left eye. Furthermore, interim Humphrey and Octopus visual field testing revealed monocular paracentral vision loss with sparing of the superior nasal quadrant (shown in Fig. 1).

MRI brain and orbits with contrast were performed which revealed a well-defined soft tissue lesion of the orbital adnexa infiltrating through different spaces including orbital apex, posterior aspect of the orbit, anterior cavernous sinus, superior orbital fissure, infratemporal fossa, and nasal cavity medially (shown in Fig. 2). This patient was thusly admitted for urgent investigation with input from multi-disciplinary specialists.

Blood testing revealed no abnormalities on full blood count, urea and electrolytes, liver function testing, inflammatory markers (C-reactive protein, erythrocyte sedimentation rate).
thyroid functioning testing, connective-tissue disease screen, antineutrophil cytoplasmic antibodies, or atypical bacterial/viral serology (HIV, HSV, VZV, CMV, HCV, Lyme, tuberculosis). Computed tomography imaging the neck, thorax, abdomen, and pelvis revealed an enlarged lymph node in the left cervical and left iliac chain regions. Subsequent biopsy of an enlarged (1.4 cm) left level 2 cervical lymph node by ultrasound-guided core needle biopsy showed histological features of atypical lymphoid infiltrates with sheets of small-sized B cells that stained positively for CD20. The cells showed some co-expression of CD10 and low proliferation index of 10–20%. The features were diagnostic of B-cell non-Hodgkin’s lymphoma (NHL) (shown in Fig. 3).

Immunoglobulin gene rearrangements were assessed by PCR, which indicated the presence of a monoclonal B-cell population. However, the B-cell clonality not necessarily confirms malignancy as it can be observed in chronic immune process such as viral, bacterial, and autoimmune stimuli, where abnormal cell proliferation may not yet have spread beyond the site of inflammation [3].

Evaluation of the main lesion required obtainment of ethmoidal biopsies through functional endoscopic sinus surgery. Histological assessment confirmed morphological features of a B-cell NHL, which required further immunophenotyping. The tumor cells were found to strongly express CD20 and be negative for cyclin D1, CD57, TdT, and MUM1. Numerous admixed reactive T cells showed variable positivity with CD3, CD5, CD4, CD8 markers. CD10 and BCL6 showed variable positivity. CD23 highlighted the meshwork of the follicular dendritic cells only. Proliferative index, MIB1, remained low 10–20%. The final diagnosis of extranodal marginal zone was reached by method of exclusion, as no specific diagnostic marker is currently available, making the diagnosis challenging (shown in Fig. 3).

**Discussion/Conclusion**

In clinical practice, optic neuropathy is often given a presumptive diagnosis of RBON. We highlight this unusual case presentation to underpin the value of thorough investigation into and the importance of avoiding a presumptive diagnosis of RBON. Pre-emptive steroid treatment in such patients may mask underlying sinister pathologies and ultimately as highlighted by the optic neuritis...
treatment trial does not improve final visual outcomes following optic neuritis [4]. Furthermore, in patients with atypical features (age, gender, visual acuity not improving after 6–8 weeks, examination findings) not in keeping with a “classic” RBON, we advise a conservative approach regarding steroid usage. This particular patient’s demographics and disease course did not suggest a “typical” RBON, and thus, withholding steroid treatment avoided unwanted shrinkage of the compressive lesion and ensured a tissue biopsy/diagnosis with subsequent prompt correct treatment.

Optic nerve damage may be caused by a range of insults including compression, ischemia, metabolic, infection, inflammation, infiltration, hereditary, or trauma [2]. Compressive optic neuropathy arises from an extrinsic or intrinsic lesion exerting a mass effect anywhere along the course of the optic nerve—the most susceptible points are at the orbital apex and the optic canal [5]. Compressive force upon the optic nerve impairs signal transmission and axoplasmic flow while also compromising vascular supply resulting in ischemia. Compressive optic neuropathy may be caused by infectious, inflammatory, vascular, traumatic, or neoplastic etiologies [6]. Associated symptoms vary depending on the location of the lesion leading with monocular visual loss seen in lesions of the orbital optic nerve and binocular vision loss associated with midline lesions (pituitary adenoma, craniopharyngioma, meningioma, giant aneurysms) or bilateral orbital lesions (thyroid disease, sarcoidosis). Furthermore, anterior optic nerve compression is associated with optic nerve head edema [7].

Lymphomas are malignancies of lymphoreticular origin and are divided into Hodgkin’s and NHL [8]. Orbital lymphomas are uncommon, comprising 1% of all NHL, and may be primary orbital tumors (particularly in over 60-year-olds) or secondary orbital involvement in approximately 1–2% of systemic lymphomas [9]. Over half of all orbital malignancies are
NHL, most commonly extranodal marginal-zone B-cell lymphomas, also called mucosa-associated lymphoid tissue-type lymphoma [10, 11]. Mucosa-associated lymphoid tissue lymphoma was initially discovered in the stomach in association with Helicobacter pylori infection and has been described in other sites, including the orbit [12]. Recent data have suggested that other infections such as Chlamydia psittaci and Campylobacter jejuni, and autoimmune disorders (Sjogren, systemic lupus erythematosus) may also be a trigger for this type of lymphoma [13]. These tumors typically show immunopositivity for CD19 and CD20, but no pathognomonic markers are currently available, making the diagnosis challenging [14]. Ocular extranodal marginal-zone B-cell lymphomas are associated with an excellent prognosis [15].

Orbital tumors are associated with signs and symptoms of vision loss, lid edema, extra-ocular motility limitation, diplopia, proptosis, photophobia, eye pain, and conjunctival chemosis/injection. Early detection and treatment commencement is a crucial determining factor in orbital lymphoma prognosis. It is therefore an important differential diagnosis for an ophthalmologist to consider when evaluating patients with “atypical” optic neuropathies. Ophthalmologist-led recognition of the ocular manifestations of this malignancy is essential to ensure prompt investigation, management, and multi-disciplinary follow-up.

In conclusion, this rare case demonstrates how NHL can present atypically and may be mistaken for other etiologies. A high degree of suspicion should be maintained when monocular optic neuropathies do not comply with a “typical” RBON history of presenting complaint and should thusly be thoroughly investigated.

**Statement of Ethics**

Written informed consent was obtained from our patient for publication of the details of their medical case and any accompanying images. Case reports are exempt from Ethic Committee approval in Ireland as per HSE guidelines. https://www.hse.ie/eng/services/list/5/publichealth/publichealthdepts/research/rec.html.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

No funding received for this case report.

**Author Contributions**

Kealan McElhinney – responsible for the acquisition, analysis, or interpretation of data for the work from an ophthalmology perspective. Maedbh Rhatigan – drafting of the article and revisions. Zornitsa Tsvetanova – responsible for the acquisition, analysis, or interpretation of data for the work from a histopathology perspective. Conor O’Keane – conception or design of the work from a histopathology perspective. Patricia Logan – overall lead and conception or design of the work from an ophthalmology perspective.
Data Availability Statement

All data generated or analyzed during this case report are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Prasad S, Volpe NJ, Balcer LJ. Approach to optic neuropathies: clinical update. Neurologist. 2010;16(1):23–34.
2. Bastakis GG, Ktiena N, Karageoge D, Savvaki M. Models and treatments for traumatic optic neuropathy and demyelinating optic neuritis. Dev Neurobiol. 2019;79(8):819–36.
3. Sohn EJ, Ahn HB, Roh MS, Jung WJ, Ryu WY, Kwon YH. Immunoglobulin G4 (IgG4)-positive ocular adnexal mucosa-associated lymphoid tissue lymphoma and idiopathic orbital inflammation. Ophthalm Plast Reconstr Surg. 2018;34(4):313–9.
4. Beck RW. Treatment of acute optic neuritis. Arch Ophthalmol. 2008 Jul 14;126(7):994.
5. Rodriguez-Beato FY, De Jesus O. Compressive optic neuropathy. Treasure Island, FL: StatPearls; 2020.
6. Sheremet NL, Khanakova NA. Etiology and diagnostics of compressive optic neuropathies. Vestn Oftalmol. 2018;134(6):72–82.
7. Dworak DP, Nichols J. A review of optic neuropathies. Dis Mon. 2014;60(6):276–81.
8. Caponetti G, Bagg A. Demystifying the diagnosis and classification of lymphoma: a hematologist/oncologist’s guide to the hematopathologist’s galaxy. J Community Support Oncol. 2017;15(1):43–8.
9. Demirci H, Shields CL, Shields JA, Honavar SG, Mercado GJ, Tothova J. Orbital tumors in the older adult population. Ophthalmology. 2002 Feb 15;109(2):243–8.
10. Margo CE, Mulla ZD. Malignant tumors of the orbit. Ophthalmology. 1998 Jan;105(1):185–90.
11. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer. 1983 Oct 15;52(8):1410–6.
12. Ishii Y, Tomita N, Takasaki H, Ogusa E, Hattori Y, Matsuura S, et al. Clinical features of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. Hematol Oncol. 2012 Dec;30(4):186–9.
13. Koller MC, Aigelsreiter A. Chlamydia psittaci in ocular adnexal MALT lymphoma: a possible causative agent in the pathogenesis of this disease. Curr Clin Microbiol Reports. 2018;5(4):261–7.
14. Nakamura S, Ponzoni M. Marginal zone B-cell lymphoma: lessons from Western and Eastern diagnostic approaches. Pathology. 2020;52(1):15–29.
15. Eckardt AM, Lemound J, Rana M, Gelrich NC. Orbital lymphoma: diagnostic approach and treatment outcome. World J Surg Oncol. 2013;11:73.