CASE REPORT

Orbital and Cavernous Sinus Lymphoma Masquerading as Post-Herpetic Neuralgia

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ABSTRACT

We report an unusual case of adult-onset B-cell lymphoma in the cavernous sinus presenting as post-herpetic neuralgia; additionally, we review the literature regarding primary B-cell lymphomas of the cavernous sinus. This case demonstrates the importance of maintaining a suspicion for malignancy when an atypical clinical course is seen, even when presented with seemingly common or innocuous disease.

KEYWORDS: cavernous sinus; lymphoma; post-herpetic neuralgia

INTRODUCTION

Primary central nervous system (CNS) lymphomas of the cavernous sinus are very rare. Most lymphomas in this region are metastases from another location or direct extension of nasopharyngeal tumours.^{1–3} To our knowledge, no cases have been reported in which post-herpetic neuralgia was the presenting symptom of primary lymphoma in the cavernous sinus.

CASE REPORT

A 70-year-old woman with facial pain, complete right ptosis, and constant diplopia was referred to the Neuro-ophthalmology Unit of the Wilmer Eye Institute at Johns Hopkins. Six months prior to presentation, the patient experienced a rash on the right side of her forehead, severe headache, and diplopia. She was diagnosed with herpes zoster ophthalmicus (HZO) and treated with valacyclovir, with resolution of double vision. Pregabalin was prescribed for pain but was minimally effective.

However, in the ensuing 6 months the patient experienced waxing and waning pain, variable ptosis of the

right eye, and mild anterior segment inflammation. Her vision was stable without diplopia. During these 6 months, she was seen by a primary care physician, ophthalmologist, and neurologist. Treatment for presumed post-herpetic neuralgia and zoster-related uveitis was attempted with various doses of oral pregabalin, acetaminophen/propoxyphene napsylate, gabapentin, and topical loteprednol etabonate; the uveitis resolved, whereas the pain did not.

The patient then experienced insidious weight loss of greater than 20 pounds, and 6 weeks later she developed complete ptosis of the right upper eyelid with diplopia (when the eyelid was manually elevated). Ophthalmologic examination revealed a pupil-involving right third nerve palsy and right facial numbness. Computerised tomographic (CT) angiography of the head was performed and no aneurysm was found. Magnetic resonance imaging (MRI) of the brain and orbits with gadolinium contrast showed a mass in the cavernous sinus ($2.7 \times 1.3 \times 1.8$ cm), with extension through the superior orbital fissure into the superomedial orbit (Figure 1). The radiologist's interpretation favoured schwannoma. Interestingly, an open MRI of the brain without a dedicated orbital protocol had been performed 5 months prior and was unremarkable.

The patient was then referred to our clinic for assessment. Best-corrected visual acuity was 8/200 OD and 20/200 OS (consistent with advanced cataract OS). Colour vision was intact to gross colour

Received 03 June 2010; revised 28 June 2010; accepted 28 June 2010

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recognition only on the right with 4/10 HRR plates read correctly on the left. Kinetic perimetry demonstrated a scotoma inferotemporally to the V4 test object in the right eye; the left eye was normal. The pupil was fixed on the right and reactive on the left with a dense right afferent pupillary defect. Extraocular movements of the right eye were nearly absent, with only slight intorsion of the globe during attempted downgaze. Movement of the left eye was normal. Corneal and facial sensation were abnormal on the right. There was complete right ptosis, with 3-mm proptosis and resistance to globe retropulsion. The optic nerves and maculae were of normal appearance.

The differential diagnosis included an inflammatory process (e.g. Tolosa-Hunt syndrome), a compressive lesion (e.g. meningioma), and neoplasia (e.g. schwannoma, lymphoma). A trial of corticosteroids was initiated along with continued pain management with pregabalin and acetaminophen/propoxyphene napsylate. Her visual acuity in the right eye improved to 20/60, but pain continued to worsen. An orbital biopsy was obtained via a right lateral orbitotomy; microscopic evaluation revealed large B-cell lymphoma. CT of the chest, abdomen, and pelvis showed no occult malignancy. Positron emission tomography (PET) CT scan demonstrated no disease other than of the orbit and middle cranial fossa. Bone marrow biopsy via aspiration did not show evidence of malignant cells. It was determined that the patient suffered from primary B-cell lymphoma of the cavernous sinus (Figure 2). Chemotherapy was initiated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. The

patient experienced pain relief and improved appetite. Visual acuity in the right eye improved to 20/25+1, the visual field expanded, and there was no afferent pupillary defect. Extraocular motility and levator function also improved, and proptosis was reduced.

FIGURE 1 MRI scan of brain and orbits. Axial (A, B) and coronal (C, D) T1 with gadolinium contrast images demonstrate a mass in the right cavernous sinus extending through the superior orbital fissure and into the intra-conal space of the right orbit.

FIGURE 2 Microscopic appearance of the lesion (20× magnification). (A) H&E staining. Immunohistochemical stains were positive for CD20 (B), CD45 (C), and Ki-67 (D), while negative for CD3 (E).

DISCUSSION

In this patient, 6 months elapsed between the onset of presumed post-herpetic neuralgia until diagnosis and treatment of B-cell lymphoma of the right cavernous sinus. Lymphomas can arise from any location within the body, most commonly manifesting as enlargement of lymph nodes.⁴ Extranodal origin occurs in 10–34% of cases.⁴ In the cavernous sinus, primary lymphomas are extremely rare; most cases of lymphoma in this area arise from metastatic spread or direct extension of regional tumours.² When lymphomas do occur in the cavernous sinus, presenting symptoms usually include headache, ptosis, and diplopia.^{1,2,4–8} No cases to our knowledge have described a primary lymphoma of the cavernous sinus presenting as post-herpetic neuralgia.

Only 10 cases of primary cavernous sinus lymphomas in adults have been reported (Table 1). The average age at presentation was 53 years old (range 37–77 years), and typical presenting symptoms included headache, ipsilateral dysaesthesia, and third nerve palsy. These symptoms can mimic other syndromes, particularly Tolosa-Hunt. Of the cases in which histologic type was reported, diffuse large B-cell lymphoma was most common, with one instance of diffuse small B-cell lymphoma, one of MALT lymphoma and one of

Burkitt lymphoma.^{1,2,4–7} Treatment regimens included a combination of resection, chemotherapy, and radiation therapy. Current recommendation for treatment includes CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy along with rituximab, a therapeutic antibody directed against the CD20 antigen present on B-cell lymphomas.^{9,10} Radiotherapy of 30–40 Gy also may be used.¹⁰ Patient outcomes varied dramatically, with one patient dying 20 days after onset of symptoms, and one patient surviving after 9 years (Table 1). Of the patients who died, the time from diagnosis until death was a mean of 16.6 months, median of 18 months, and range of 0.7–31 months. It must be noted that while the authors report these tumours as being primary central nervous system (CNS) lymphomas, not all describe a thorough search for systemic involvement. Up to 10% of presumed primary CNS lymphomas have evidence of systemic lymphoma at autopsy.¹¹ A thorough search for additional disease sites should include CT of the chest, abdomen, and pelvis; PET CT; and bone marrow biopsy.

Our patient's presenting symptoms were similar to those in previously described cases. What is unusual is the temporal association of her symptoms with HZO, which was manifest as the characteristic dermatomal rash in addition to diplopia and pain. When the patient

TABLE 1 Summary of 10 cases of primary cavernous sinus lymphomas in adults

	Age, Sex	Presentation	Location	Histologic type	Treatment	Patient outcome
Present case 2008	70, F	Facial pain, ptosis	Right cavernous sinus	DLBCL	Chemotherapy: CHOP	Currently alive and improving
Abalo-Lojo et al., 2007 ⁴	41, M	Tolosa-Hunt syndrome	Right cavernous sinus	DLBCL	N/A	Died, 20 days
Ronson et al., 2006 ⁵	53, F	Headache, diplopia, paraesthesia (left mouth), extremity ataxia	Right sphenoid sinus, right cavernous sinus	DLBCL	ResectionChemotherapy: CHOP and rituximabProton radiotherapy	N/A
Dufour et al., 2001 ⁶	37, F	Oculomotor paresis, retrobulbar pain	Cavernous sinus, superior orbital fissure	Burkitt's lymphoma	Chemotherapy	Alive after 9 years
Sanjeevi et al., 2001 ⁷	46, F	N/A	Cavernous sinus	MALT B-cell lymphoma	Partial excisionRadiation	N/A
Arimoto et al., 2000 ¹	59, F	Diplopia, right facial hypesthesia	Right cavernous sinus	DSBCL	Partial resectionPrednisoloneRadiation 40 Gy WB	N/A
Roman-Goldstein et al., 1998 ⁸	37, M	Tolosa-Hunt	Right cavernous sinus	Lymphoma	Radiation 3000 rads	Alive after 4 years
Roman-Goldstein et al., 1998 ⁸	62, M	Tolosa-Hunt	Left cavernous sinus	Lymphoma	16 procedures, radiation	Died, 18 months
Roman-Goldstein et al., 1998 ⁸	51, F	Diplopia	Left cavernous sinus	Lymphoma	Chemotherapy	N/A
Nakatomi et al., 1996 ²	77, M	Facial hypaesthesia, diplopia	Left cavernous sinus	DLBCL	Subtotal removalRadiation 37.5 Gy (WB), 33.6 (L)MTX, prednisolone	Died, 31 months

F = female; M = male; DLBCL = diffuse large B-cell lymphoma; DSBCL = diffuse small B-cell lymphoma; MALT = mucosa associated lymphoid tissue; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; N/A = not available.

was first diagnosed with HZO, an open MRI without dedicated orbital sequences was unremarkable; yet, 6 months later, a mass was clearly evident. A number of explanations are possible: the relationship may be purely coincidental, the lymphoma might have triggered HZO (or vice versa) or a common event may have led to both HZO and lymphoma.

The lymphoma might have preceded the HZO;¹² 15–25% of patients with Hodgkin disease and 10% of those with non-Hodgkin lymphoma have at least one zoster infection during the course of their disease.¹³ HZO-related inflammation in the cavernous sinus may incite an exuberant immune response in the cavernous sinus that becomes deranged, leading to lymphoma.² An immunocompromised state (postulated to occur in all individuals who are aged 50 and over) is a risk factor both for HZO and lymphoma.^{3,14,15} The typical symptoms of cavernous sinus lymphoma can present as facial dysaesthesia and ptosis, and may be mistaken for post-herpetic neuralgia.^{3,14,15}

It is impossible to determine if the lymphoma originated in the orbit or cavernous sinus. Diffuse large B-cell lymphoma comprised only 16% of lymphoid lesions in a recent series of 160 patients, whereas primary B cell lymphoma is the most common type in the CNS.¹⁶ In any case, lymphoma was likely present in the cavernous sinus and possibly mistaken for post-herpetic neuralgia during a 6-month period. In general, prognosis of primary CNS lymphomas is poor, with mean survival of 3–6 months without treatment, 15–45 months with radiation treatment, and 24 months with chemotherapy.^{17,18} In the case that this tumour had been a secondary lymphoma in the cavernous sinus, early diagnosis would still have been imperative. The clinical course is rapid, with an 8-month average survival time from onset of first presenting symptom.² The initial radiological interpretation of the mass strongly favoured schwannoma rather than lymphoma or other inflammatory disease, given the apparent confluence with the trigeminal nerve in the orbit, cavernous sinus, and in Meckel's cave. Nonetheless, we proceeded with biopsy because the patient's symptoms were not consistent with this diagnosis. Chronic granulomatous infection may present as a mass lesion and was considered as a possibility, although the patient did not have a high risk for mycobacterial exposure. Steroid use before biopsy of suspected lymphoma may result in rapid lysis of abnormal cells and an inconclusive biopsy. In this case, the size of the lesion and timely (within 8 days) biopsy allowed us to obtain the correct diagnosis before such an effect was seen.

Because of the poor prognosis of cavernous sinus lymphomas, whether primary or secondary, early

diagnosis is essential. In an ageing population, the likelihood exists that lymphoma of the cavernous sinus may masquerade as post-herpetic neuralgia. Our case demonstrates the need for clinician awareness and the importance of maintaining a broad differential diagnosis.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figure 2 of this article is available in colour online at www.informahealthcare.com/oph

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