CASE REPORT

Sinonasal Non-Hodgkin's Lymphoma with Skull Base Involvement

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ABSTRACT

Non-Hodgkin's lymphoma (NHL) is a rare tumor of the skull base. As the incidence of primary central nervous system (CNS) lymphoma has increased, atypical presentations involving the skull or cranial base exclusively have been reported. In immunocompetent patients with no previous history or predisposing factors, the diagnosis of primary NHL of the skull base may be delayed. We present four cases of nasal and paranasal sinus NHL with both skull base and intracranial involvement in immunocompetent patients. Clinicopathologic correlation suggests that cranial base and intracranial involvement with NHL represents advanced-stage primary sinonasal disease. Surgical biopsy before definitive treatment is recommended. Radiation therapy provides local control; adjuvant chemotherapy after primary radiation therapy may be required for recurrent disease.

KEYWORDS: Lymphoma, skull base, paranasal

Non-Hodgkin's lymphoma (NHL) represents 5% of head and neck malignancies, and it may involve almost any location in this region.^{1,2} As the reported incidence of primary central nervous system (CNS) lymphoma has increased,^{3,4} several atypical presentations of head and neck NHL involving the cranial base exclusively have been reported.⁵ In immunocompetent patients with no predisposing history, the disease may be

least suspected. The diagnosis may be further delayed by a differential diagnosis that includes more common malignancies of the head and neck region such as squamous cell carcinoma.^{6,7} We report four cases of nasal and paranasal sinus NHL with invasion of the skull base and intracranial space in immunocompetent patients. Clinical, histologic, and initial treatment outcomes are presented.

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CASE STUDIES

Case 1

A 64-year-old woman presented with a 3-month history of left-sided headaches and progressive loss of vision. Neurologic examination showed ptosis, homonymous hemianopsia, and faint light perception in the left eye. Loss of sensation in the ophthalmic and maxillary distributions of the trigeminal nerve on the left was also appreciated. The remainder of her neurologic examination was otherwise remarkable. Magnetic resonance imaging (MRI) confirmed abnormal soft tissue in the left ethmoid and sphenoid sinuses with extension into the left orbital apex and the floor of the left middle cranial fossa (Fig. 1A). Tumor could be visualized to a lesser extent in the anterior cavernous sinus (Fig. 1B). Computed tomography (CT) showed destruction of the ethmoid and sphenoid bones (Fig. 1C). Biopsy of this mass demonstrated a diffuse large cell malignant NHL, B-cell type (Fig. 2). Further evaluation (including CT of the skull base, chest, abdomen, and pelvis; cerebrospinal fluid (CSF) analysis; gallium scan; and bone marrow biopsy)

showed no evidence of immunosuppression, systemic disease, or other tumors. The patient was treated with intravenous steroids and focused radiation therapy (3600 centigray [cGy]) to the skull base. Intrathecal chemotherapy (methotrexate, cytarabine, and hydrocortisone) was administered for prophylaxis. Three months after therapy, the patient's disease remained unchanged on MRI. Systemic chemotherapy consisting of cyclophosphamide, vincristine, and adriamycin was therefore instituted. At a follow-up examination 12 months after the patient's initial presentation, MRI showed stable disease with partial regression of the middle fossa lesion.

Case 2

A 71-year-old man presented with visual disturbance, epistaxis, and difficulty breathing. Neurological examination revealed decreased right visual acuity. A right nasal mass was appreciated on physical examination. Plain radiographs of the skull showed a large, right-sided intranasal mass extending posteriorly to the nasopharynx and sphenoid

Figure 1 Case 1. (A) Gadolinium-enhanced axial T₁-weighted MRI shows abnormal soft tissue in the left ethmoid and sphenoid sinuses with involvement of the left orbital apex and the floor of the left middle cranial fossa. (B) Minimal involvement of anterior cavernous sinus. (C) CT shows bone destruction in the ethmoid and sphenoid sinuses.

Figure 2 Case 1. Hematoxylin and eosin (H&E) staining method. (A) 10 $\times$ magnification. (B) 10 $\times$ magnification, proliferating, large lymphoid cells of non-Hodgkin's lymphoma.

sinuses bilaterally. The mass also invaded the ethmoid sinuses and the right frontal sinus superiorly. Intranasal biopsy of this lesion demonstrated lymphosarcoma, reticulum cell type, retrospectively classified as malignant NHL. Further evaluation including a bone marrow biopsy showed no evidence of immunosuppression, systemic disease, or other tumors. The patient received focused radiation therapy (2900 cGy), with complete response.

Case 3

A 73-year-old man presented with left retro-orbital pain and diplopia. Physical examination showed decreased left visual acuity and ptosis on that side. CT showed a left frontal sinus mass with extension into the anterior ethmoid sinuses and orbital apex. MRI confirmed these findings and demonstrated minimal invasion of the frontal fossa. Biopsy demonstrated large-cell malignant NHL, positive for common leukocyte antigen. There was no evidence of distant or systemic disease, other malignancies, or immunosuppression. The patient received focused radiation therapy (4500 cGy) with complete response at a 3-month

follow-up examination. The patient remained disease free until his death at 20 months from unrelated medical treatment complications.

Case 4

An 83-year-old man presented with left-sided headache and diplopia. Neurologic examination was significant for decreased left visual acuity, limitation in left extraocular movement, and decreased sensation in the ophthalmic distribution of the left trigeminal nerve. MRI revealed an ill-defined, hyperintense mass centered within the frontal sinus with extension superiorly into the epidural space, inferiorly into the left frontonasal duct, and medially into the left ethmoid sinus (Fig. 3A). The left optic nerve was displaced inferiorly (Fig. 3B). A supraorbital craniotomy was performed, and a biopsy demonstrated malignant NHL, large cell, B-cell phenotype (positive for markers CD20, HLADR, and CD19). Further evaluation revealed no evidence of immunosuppression, systemic disease, or other tumors. The patient received focused radiation therapy (3900 cGy) with complete response on follow up MRI at 3 months.

Figure 3 Case 4. Gadolinium-enhanced T_1 -weighted MRI. (A) Coronal image reveals a hyperintense mass in the frontal sinus with epidural extension. (B) Sagittal view shows displacement of the left optic nerve inferiorly.

DISCUSSION

Lymphoma is characterized by abnormal proliferation of lymphoreticular tissue occurring nodally as Hodgkin's lymphoma or extranodally as NHL. In the head and neck region, extracranial NHL may occur as primary disease—primary head and neck NHL—or as part of disseminated disease.^{2,8,9} The head and neck region, especially Waldeyer's lymphatic ring, is the second most common site for involvement of extranodal NHL, the most common site being the gastrointestinal tract.¹ Primary sinonasal manifestation is less common, occurring in 6 to 13% of head and neck NHL.^{7,10}

Until recently, only a handful of cases of NHL involving the skull base had been reported in the literature.^{10–14} The disease was reported particularly in immunosuppressed patients,^{12,14} patients with known systemic disease,¹⁴ and Asians.^{11,13} The increasing incidence of NHL in the United States^{3,4} has been accompanied by several reports of atypical presentations of NHL in immunocom-

petent patients. Roman-Goldstein et al.⁵ reported two patients with disease involving primarily the cavernous sinus and one patient with disease limited to the internal auditory canal. Erlich et al.¹⁵ reported diffuse infiltration of lymphoma involving the calvarium and bone of the cranial base in a patient who presented with multiple cranial nerve palsies.

Secondary involvement of the skull base by NHL arising from adjacent head and neck structures has been recognized previously, albeit sporadically,¹⁶ in the setting of immunosuppression or disseminated disease,¹⁴ as well as in Asia.¹⁷ Skull base involvement associated with sinonasal lymphoma is rare. In several large series of NHL of the nasal cavity and paranasal sinuses, disease involving the cranial base has not been reported.^{6,10,18–20} The four cases described here represent more extensive disease involving the skull base and intracranial space than has previously been reported in immunocompetent patients with primary sinonasal NHL. Of particular significance is that three of

these four patients were diagnosed during the last decade, consistent with a nationally reported increase in the incidence of NHL.^{3,4}

The clinical presentation, disease stage, and Ann Arbor classification of our patients are summarized in Table 1. Presentation with progressive ophthalmoplegia in NHL involving the cranial base has previously been reported and reflects cranial base involvement, especially of the cavernous sinus.^{16,17} The male-to-female ratio of 3:1 and the average age of 72.7 years (range, 64 to 83 years) are consistent with data on the epidemiology of sinonasal NHL as a disease of the "elderly male."¹⁸⁻²⁰

In immunocompetent individuals presenting with ophthalmoplegia and symptoms referable to the sinonasal region and cavernous sinus, the diagnosis of NHL of the skull base is not readily made.^{1,6} This difficulty partly reflects that the clinical presentation and initial radiological features are similar to those associated with squamous cell carcinoma, a more common tumor of this region.⁶ Table 2 summarizes the sinonasal, intracranial, and bony involvement by disease in our cases. The imaging characteristics of NHL that involve the cranial base have previously been described.¹¹ As in our patients, lesions often appear isointense to gray matter on T₁-weighted images and slightly hypo-, iso-, or hyperintense on T₂-weighted or proton-density images. Skull base NHL often shows heterogeneous enhancement with gadolinium. Lesions in the intracranial epidural space may enhance en plaque (dural tail) or homogeneously; both features are reminiscent of meningioma.

Table 1 Demographics and Clinical Presentation

Case	Age (yr)/ Sex	CN Deficits	Ann Arbor	TNM
1	64/F	II, III, V ₁ , V ₂	1 _E	T4N0M0
2	71/M	II	1 _E	T4N0M0
3	73/M	II, III	1 _E	T4N0M0
4	83/M	II, III, V ₁	1 _E	T4N0M0

Ann Arbor, Ann Arbor classification; CN, cranial nerve; TNM, tumor-node-metastasis classification.

Table 2 Sinonasal, Intracranial, and Bony Involvement by Disease

Case	Fron	Ethm	Sph	Max	CS	IC	Bone Dest
1	+	++	+	—	+	Mid	+
2	+	++	+	—	+	Ant	+
3	++	+	—	—	—	Ant	+
4	++	+	—	—	—	Ant	+

Ant, anterior fossa; Bone Dest, bone destruction; CS, cavernous sinus; Ethm, ethmoid sinus; Fron, frontal sinus; IC, intracranial compartment; Max, maxillary sinus; Mid, middle fossa; Sph, sphenoid sinus; ++, primary focus; +, secondary involvement.

However, unlike meningioma, NHL does not induce hyperostosis of the adjacent bone. Instead, it may present variably with sclerotic or osteoblastic changes,¹ a permeative type of bone involvement that leaves the cortical outlines intact.⁹ Less frequently, a destructive, lytic pattern of bone involvement more characteristic of squamous cell carcinoma is present.⁶ In one patient (case 1) and in five patients reported by Han et al.,¹¹ cavernous sinus involvement by NHL was without luminal narrowing of the carotid arteries. This feature may serve as an additional criterion for differentiating between NHL and meningioma involving the skull base. Nonetheless, NHL involving the skull base is a "great mimic" of other pathologies in the region. The differential diagnosis is best resolved by surgical biopsy, as was performed in our patients.

The pathologically confirmed diagnosis of diffuse large cell lymphoma of B-cell origin in our patients is consistent with the predominant histologic grade reported in several series of nasal and paranasal NHL.^{10,18,19,22} For example, in a review of 16 patients presenting with NHL of the paranasal sinuses, Hausdorff et al.¹⁸ reported a predominance (81%) of diffuse large cell lymphomas of B-lineage (63%). Among 70 patients reported by Logsdon et al.,¹⁹ 60 (86%) were of a diffuse large cell histologic type. These observations suggest that extensive disease involvement of the skull base and cranial fossa may represent a clinically advanced stage of sinonasal NHL. Indeed, several investigators have noted that disease stage may be a

more important prognosticator for survival than histologic grade.^{10,21,22} The clinical significance of skull base and intracranial involvement on survival remains to be determined, however.

Traditionally, treatment of extranodal NHL has been dictated by the site of primary involvement, the histology, and the stage of disease. For stage I or II patients who have low-grade histology, primary radiation therapy has been considered adequate.²³ However, prognosis with radiation therapy alone is often poor even in early-stage disease. In one report, the 5-year survival rate did not exceed 12%.⁷ Consequently, combined-modality treatment with radiation and chemotherapy has recently been used with improved outcome.¹⁹ Concurrent with this evolution in the medical management of NHL, we have been able to obtain a complete response with radiation therapy alone in three of four patients with Ann Arbor stage 1_E disease. In one patient (case 1), radiation therapy alone resulted in a partial response; chemotherapy was therefore instituted and the disease stabilized at 12 months. The reason for initial treatment failure in this patient is unclear. Recurrence of extranodal NHL in the head and neck region after radiation therapy is usually in the form of distant spread. Local or regional recurrence, or both, is rarely reported, especially in stage 1_E disease.^{7,19} Furthermore, previous studies have not identified any specific histologic features associated with recurrence in B-lineage extranodal NHL.^{18,21} A poorer prognosis, however, has consistently been associated with T-lineage extranodal NHL.¹⁰ Technical considerations cannot be excluded, including the potential for a marginal miss at radiotherapy. Irrespective of disease stage, this factor may become increasingly important to the outcome of large tumors. Consequently, first-line combined modality therapy has been suggested for more advanced disease, including stages 1_E (T4), II, and IV.

In immunocompetent older patients presenting with a visual disturbance, partial or complete ophthalmoplegia, and imaging evidence of sinonasal disease with cranial base and/or intracra-

nial involvement, the possibility of NHL should be raised along with other more common lesions such as squamous cell carcinoma. The differential diagnosis is resolved by surgical biopsy. In our experience, local control may be achieved with primary radiation therapy, reserving combined modality treatment with appropriate chemotherapeutic agents and radiation for disease unresponsive to single therapy.

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