Nasopharyngeal carcinoma presenting as an inconspicuous primary lesion with extensive cavernous sinus involvement and temporal lobe extension: a case report and review of literature

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Introduction
Nasopharyngeal carcinoma (NPC) is a head and neck cancer arising out of the epithelium of the nasopharynx. There is an annual incidence of 0.5–2.0 cases per 100,000 in the US and Europe, although numbers as high as 25 per 100,000 may be seen in endemic countries such as China [1]. Males are at an increased risk and while there has been evidence of a link to dietary practices in endemic areas, the vast majority of data suggest Epstein–Barr virus (EBV) as the predominant pathogenic factor in NPC [2, 3]. Given the association with EBV, the histology and natural history of NPC differ from most other cancers of the head and neck. Treatment of early and locally advanced disease is typically nonsurgical because of the proximity of nearby vital structures. Thus, there is a strong role for noninvasive therapy in the form of radiation ± chemotherapy, which is considered standard of care for this disease [4].

Detection of nodal metastasis in the neck or spread to adjacent structures including the skull base, nasal cavity, sphenoid bones, pterygoids, prevertebral muscles, and oropharynx with occult or frank primary disease is relatively common in NPC [5, 6]. In contrast, intracranial extension of NPC is not as common especially in the absence of an...
obvious primary lesion [7]. In this case report, we discuss a patient with a diagnosis of NPC that presented with extensive skull base disease and metastasis to the right temporal lobe with subtle findings in the nasopharynx.

**Case Report**

In December 2013, a previously healthy 37-year-old man from the Middle East presented to his local ophthalmologist with diplopia and right-sided cranial nerve VI palsy. He had a 12 pack/year smoking history but was otherwise absent known cancer risk factors. Magnetic resonance imaging of the brain (MRI-brain) and face/orbit (scan of skull base that included cavernous sinus and orbital apex), with and without contrast in addition to examination by a neurosurgeon (December 2013), was reportedly normal. Worsening symptoms led to a repeat MRI-brain and face/orbit, with and without contrast 4 months later (March 2014). The report described a well-circumscribed, intense homogeneous enhancement of an extracranial mass involving the cavernous sinus that was T1 isointense and T2 hyperintense, consistent with a cavernous sinus meningioma. Nasopharyngeal fullness was also described, but there was no suspicious mass or lesion. The patient received medical treatment for sinus infection and congestion. No biopsy of the nasopharynx or CSF evaluation was performed as it was presumed to be a cavernous sinus meningioma by his treating neurosurgeon. This physician recommended that the patient receives Gamma knife stereotactic radiosurgery and he received a single fraction of 12 Gy to the 50% isodose line with an excellent response in neurologic symptoms initially. Per outside documentation, there were no radiation or medical oncologists at the hospital that the patient received radiosurgery. A few months later (May 2014), he developed progressive right-sided facial paresthesias, hearing loss, periocular pain, and numbness. An outside physician reinterpreted the patient’s March 2014 MRI at this time and described nasopharyngeal fullness with an enhancing mass extending through the foramen lacerum and carotid canal to the cavernous sinus, bony skull base, sphenoid sinus, and bilateral retropharyngeal nodes. A repeat MRI-brain and cavernous sinus/orbital apex with and without contrast at this time demonstrated a progressive, enhancing cavernous sinus mass with extensive skull base involvement and a new 1.5 cm cystic mass in the right temporal lobe (Fig. 1). He was referred to an ENT (June 2014) who described a retracted right tympanic membrane and a soft tissue mass in the right nasopharyngeal region on endoscopic exam. For 6 months, the patient was lost to follow-up as he sought secondary opinions. An eventual biopsy of the right nasopharynx was performed (December 2014) which demonstrated an undifferentiated nasopharyngeal carcinoma (WHO grade III) (Fig. 2) with Epstein–Barr virus (EBV) positivity,

**Figure 1.** Post-Gammaknife MRI-Brain and Cavernous Sinus/Orbital Apex. Axial T2 precontrast slice, white-dashed arrow identifies residual right cavernous sinus disease. Solid white arrow identifies right temporal lobe mass.

**Figure 2.** Histological Specimen from Nasopharynx Biopsy. (A) 10X magnification hematoxylin- and eosin-stained pathologic specimen of nasopharynx biopsy. Image identifies sheets of cancerous cells with high nucleus-to-cytoplasmic ratio. (B) 20X magnification hematoxylin- and eosin-stained pathologic specimen of nasopharynx biopsy. Large nuclei of cancerous cells are better visualized.
suggesting a stage IV (T4 N2 M1; AJCC 7th Edition) nasopharyngeal carcinoma. The patient received three cycles of cisplatin and 5-FU chemotherapy with a favorable treatment response on a restaging MRI-brain and cavernous sinus/orbital apex (March 2015).

He was subsequently referred to M.D. Anderson Cancer Center (Houston, TX) and underwent multidisciplinary evaluation by Head and Neck Surgery, Head and Neck Radiation Oncology, Medical Oncology and Neurosurgery. On fiberoptic endoscopy, there were subtle submucosal fullness and erythema in the right Rosenmuller fossa. A MRI-brain and cavernous sinus/orbital apex with and without contrast performed here (June 2015) showed a complex finding of enhancing disease in the skull base involving the cavernous sinus, Meckel’s cave, foramen ovale, and a large cystic, rim enhancing temporal lobe mass that measured 5.0 cm × 4.3 cm (Fig. 3A). There was no evidence of gross disease in the nasopharynx, but concerning enhancement was seen in the masticator space (Fig. 3B). A PET/CT showed FDG-avidity involving the right foramen ovale into the masticator space. The nasopharynx did not reveal FDG-avid regions (Fig. 3C). A computed tomography scan of the bilateral neck demonstrated involved left level II neck and bilateral retropharyngeal lymph nodes suggesting N2 disease (Fig. 3D). The patient developed worsening headaches, nausea, and right-sided trigeminal nerve symptoms and was started on oral steroids and underwent a right temporal craniotomy and resection of the temporal lobe mass. Pathological analysis of the resected temporal mass was consistent with nasopharyngeal carcinoma (Fig. 4). A 50-panel gene somatic mutation analysis panel was performed that was negative for genes tested, including BRAF, KRAS, and EGFR. Postoperative MRI-brain and cavernous sinus/orbital apex performed immediately after surgery showed a gross total resection of the temporal lobe mass and gross disease in the skull base as described extending into the masticator space (Fig. S1). He was dispositioned to radiation therapy and received volumetric modulated arc therapy (VMAT) using 6 MV photons and 2 arcs (Fig. 5). The gross disease in the nasopharynx and neck received 70 Gy in 33 fractions, whereas dose to gross

Figure 3. Postchemotherapy MRI-Brain and Cavernous Sinus/Orbital Apex. (A) Coronal T1 postcontrast slice, solid white arrow identifies right temporal lobe mass. Dashed white arrow identifies residual cavernous sinus disease. White bracket indicates the likely path of spread from the right cavernous sinus to the right temporal lobe. A hyperintense track is observed between the inferior right cavernous sinus and temporal lobe lesions. (B) Axial T1 postcontrast slice, white asterisk identifies no evidence of disease in nasopharynx. Solid white arrow identifies right masticator space enhancement. (C) Fused PET/CT. FDG avidity is demonstrated in the right foramen ovale and right masticator space. (D) CT of the bilateral neck demonstrating involved left level II (white-dashed circle) and right retropharyngeal lymph nodes (dashed arrow).
disease in the skull base was limited to 66 Gy due to proximity to critical structures. The postoperative intracranial tumor bed and high-risk subclinical disease sites were treated to 59.4 Gy and areas of lower risk subclinical disease received 57 Gy. Chemotherapy was delivered as weekly paclitaxel (20 mg/m²) and carboplatin (AUC 1.5).

Radiation therapy was well tolerated. Acute toxicities from radiation therapy included CTCAE V.4 grade 3 dermatitis, grade 2 mucositis, and grade 2 dysgeusia. The mucositis and dermatitis symptoms were treated medically with complete resolution. He did develop peripheral neuropathy likely associated with chemotherapy. At his 6-month follow-up visit, he did not display adverse radiotherapy effects and exhibited improved periorcular pain. The patient continued to complain of stable right-sided facial paresthesias. MRI-brain and cavernous sinus/orbital apex with and without contrast obtained at this time revealed good treatment response with decreased enhancement in the intracranial surgical cavity and significantly reduced disease volume in the right cavernous sinus (Fig. 6A) and right masticator space (Fig. 6B).

Discussion

In this report, we discuss a case of nasopharyngeal carcinoma presenting to our institution with a cavernous sinus mass and temporal lobe metastasis, with subtle disease in the primary site. He was treated with chemotherapy and resection of the temporal lobe mass with pathology demonstrating nasopharyngeal carcinoma. He was staged as T4 N2 M1 and after multidisciplinary discussion, dispositioned to curative intent concurrent chemoradiotherapy with coverage of the nasopharynx, skull base, neck, and intracranial postoperative bed. On initial diagnosis, the patient’s most pronounced radiographic evidence of disease was in the cavernous sinus, which is a “medium-risk” site of involvement in NPC with an invasion rate of 17.9% [5].

Nasopharyngeal endoscopy is the gold standard for initial diagnosis of NPC [8]. In the present case, a nasopharyngeal endoscopy was performed after the patient was treated with stereotactic radiosurgery for a presumed cavernous sinus meningioma, which revealed submucosal fullness in the right nasopharynx that was not detected on corresponding MRI. An eventual biopsy of this region did confirm a diagnosis of NPC. It is unclear if a thorough
examination of the nasopharynx was performed during the initial diagnostic evaluation or whether the soft tissue abnormality in the nasopharynx formed after initial findings. This potential oversight underscores the value of a thorough multidisciplinary evaluation. The decision making of a team of physicians generally outperforms that of a single physician [9–11]. However, tumors located deep in the nasopharyngeal mucosa or within the pharyngeal recess may be missed on initial endoscopy or result in falsely negative biopsy as previously reported [12, 13].

A number of imaging studies can be used to identify NPC. MRI is the preferred imaging modality to detect and stage the primary disease [14] and may detect NPCs missed on endoscopic biopsy. A recent study examined the diagnostic accuracy of MRI and endoscopy in 246 patients with suspected NPC and found significantly improved sensitivity (100% vs. 88%, P = 0.003) and equivalent specificity (92% vs. 94%, P = 0.617) with MRI [14]. In addition, MRI is more sensitive and specific than single-photon emission computed tomography/computed tomography (SPECT/CT) and CT in identifying skull base invasion in patients with NPC, with CT having the lowest sensitivity among the three imaging modalities [15]. Positron emission tomography (PET) plays a significant role in defining metabolic activity of tumors, determining N and M staging, and assessing response to treatment [16] but is less useful for detection of primary disease [17]. A recent study found that the combined sensitivity for PET imaging to correctly identify T staging was 0.77 (95% CI: 0.59–0.95) while its ability to assess N and M staging was significantly better, with sensitivity of 0.84 (95% CI: 0.76–0.91) and 87% (95% CI: 0.74–1.00), respectively [18]. The patient in this case report had a post-biopsy PET scan that did not show clear evidence of disease in the nasopharynx despite pathologic confirmation for NPC on nasopharyngeal biopsy. Due to the relatively poor ability of PET imaging to assess T staging and identify primary disease, it is suggested that both MRI and PET should be used as part of routine staging for NPC. Although imaging is frequently necessary to aid in the diagnosis of primary disease, in the presented case, the initial imaging evidence led the clinician toward a different diagnosis. This is interesting given that many of the radiographic findings were suggestive of a nasopharyngeal primary.

In addition to the subtle imaging and endoscopic evidence of nasopharyngeal mass during initial work-up, this patient did not present with typical local signs/symptoms associated with a nasopharyngeal mass such as epistaxis, nasal obstruction, and nasal discharge [19]. Our patient initially presented with a cranial nerve VI palsy and diplopia consistent with a cavernous sinus lesion. He ultimately developed right-sided facial paresthesias, hearing loss, periorcular pain, and numbness as disease in the skull base progressed, which prompted the clinical team to question the original diagnosis of meningioma and proceed with further work-up.

In summary, we have reported an uncommon presentation of NPC where the patient was found to have a cavernous sinus mass and subsequent temporal lobe metastasis with subtle disease in the primary site that was recognized late in the patient’s management. In this particular case, the diagnosis of NPC was made after endoscopic evaluation that occurred a year after the patient’s initial presentation and multiple imaging studies. This case highlights the significance of recognizing the local extension patterns of NPC tumors and need for multidisciplinary cooperation among experts. Even with the best diagnostic imaging available, a primary diagnosis of NPC
can be missed even by an experienced radiologist. Review of the May 2014 imaging studies by our expert radiologist did show submucosal nasopharyngeal disease spread along its usual route into the foramen lacerum, carotid canal, hypoglossal canal, and foramen ovale into the cavernous sinus (Fig. S2). Finally, the presence of a necrotic left lateral retropharyngeal node on the MRI-brain and cavernous sinus/orbital apex with and without contrast (Fig. S3) was highly suggestive of NPC disease as involvement of retropharyngeal nodes are seen &gt;50% of NPC cases. Because NPC tumors often burrow submucosally, imaging, and nasopharyngeal endoscopy have complementary roles in evaluation. Thus, close cooperation between the clinician and radiologist should be maintained as new information is obtained to re-evaluate the differential diagnosis and when needed, expert opinion sought. It is the authors’ hope that this report will assist other clinicians by adding NPC to the differential diagnosis in patients presenting with skull base/intracranial disease where the site of primary disease is unclear.

Conflict of Interest
None declared.

Authorship
CP III—Primary author: wrote, structured, formatted case report, and generated all figures. SMM: was a primary contributor for introduction and case sections of report. LEG: provided expert interpretation and description of all radiographs presented in report. MSK: assisted in structuring and formatting case report. SMR: provided expert analysis of neurosurgical aspects of the patient’s case and assisted in writing discussion. SYS: provided expert analysis of surgical aspects of the patient’s case and assisted in writing discussion. ST: provided expert analysis of physics associated with patient’s radiation treatment and assisted in generation of figures. JP: conceived idea for and organized details of the case study and major contributing author to the introduction, case, and discussion sections.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Post-Temporal Lobe Resection MRI MRI-Brain and Cavernous Sinus/Orbital Apex.

Figure S2. Initial Imaging Before Treatment.

Figure S3. RP node prior to treatment.