Nasopharyngeal Carcinoma Diagnostic Challenge in a Nonendemic Setting: Our Experience with 101 Patients

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Perm J 2017;21:16-180

E-pub: 06/05/2017

https://doi.org/10.7812/TPP/16-180

ABSTRACT

Introduction: We studied the presenting symptoms, time intervals, and workup involved in the diagnosis of nasopharyngeal carcinoma in an integrated health care system.

Methods: A retrospective chart review of all patients with a nasopharyngeal carcinoma diagnosis between 2007 and 2010 at Kaiser Permanente Northern California. Main outcome measures included diagnostic time intervals, presenting symptoms, diagnostic accuracy of nasal endoscopy, imaging, and diagnosis at first otolaryngologist (Oto-HNS) visit.

Results: This study included 101 patients: 70 (70%) were of Chinese or of Southeast Asian descent. The median time intervals along the diagnostic pathway were symptom onset to primary care physician visit, 6.0 weeks; primary care physician to Oto-HNS, 2.4 weeks; Oto-HNS to pathologic diagnosis, 1.1 weeks; and diagnosis to treatment onset, 5.5 weeks. The most common presenting symptoms were otologic issues (41, 41%), neck mass (39, 39%), nasal issues (32, 32%), and headache/cranial neuropathy (16, 16%). A nasopharyngeal lesion was detected in 54 (53%) patients after the first Oto-HNS visit. Among the initial nasal endoscopy reports, 32 (32%) did not reveal a nasopharyngeal lesion; 32 (32%) initial imaging studies also did not reveal a nasopharyngeal lesion. There was no correlation between diagnostic delay and disease stage.

Conclusion: Nasopharyngeal carcinoma presenting symptoms are extremely variable, and initial misdiagnosis is common. Median time from symptom onset to treatment was almost six months among patients studied. Nearly one-third of nasopharyngeal cancers were missed with nasal endoscopy and imaging. An understanding of the risk factors, presenting symptoms, and limitations associated with these diagnostic tests is necessary to support earlier detection of this insidious cancer.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is rarely diagnosed outside of the endemic areas of Southern China and Southeast Asia. In the US, NPC incidence is 0.7/100,000 per year.[1] As with other cancers, disease stage heavily influences prognosis, and efforts directed toward earlier diagnosis may improve survival. The largest study conducted to date in Hong Kong revealed that the mean symptom-to-diagnosis duration was 8 months and that earlier presentation correlated with improved 10-year survival.[2] To our knowledge, only a single study from 2001 described NPC in an American health care setting.[3] August et al reported a similar average symptom period of 7 months before diagnosis.[3] Considering the importance of early diagnosis, the frequency of delayed diagnoses, and the relative lack of literature on this topic, we sought to examine the pathway to NPC diagnosis in our health care system.

METHODS

The tumor registry at Kaiser Permanente Northern California was queried for all patients who received an NPC diagnosis between January 1, 2007, and December 31, 2010. Charts were reviewed for diagnostic time intervals, symptoms, nasopharyngoscopy findings, initial radiographic imaging reports, and initial diagnosis by an otolaryngologist (Oto-HNS). Images were reviewed with an experienced neuroradiologist in a nonblinded fashion.

RESULTS

During the study period, 101 patients met inclusion criteria (demographics are described in Table 1). Most patients (70, 70%) were of Chinese or Southeast Asian descent, and 70 (70%) were men. The mean age (± standard deviation) was age 52 (±13) years. Among patients, 64% had late-stage disease (stages III/IV) at the time of diagnosis.

Table 1. Patient demographics

Characteristic	Number (N = 101)
Mean age, years (SD)	52 (13)
Sex	
Men	70
Women	31
Race/ethnicity	
Chinese/Southeast Asian[a]	70
Caucasian	22
Hispanic	6
African American	3
Histology	
WHO I	10
WHO II/III	85
Unknown	6
AJCC stage, 7th edition	
Stage I	6
Stage II	31
Stage III	33
Stage IVa	15
Stage IVb	7
Stage IVc	9
T stage	
T1	31
T2	32
T3	13
T4	25

[a] Southeast Asian includes Filipino, Hmong, Laotian, Pacific Islander, and Vietnamese.

AJCC = American Joint Committee on Cancer; SD = standard deviation; WHO = World Health Organization.

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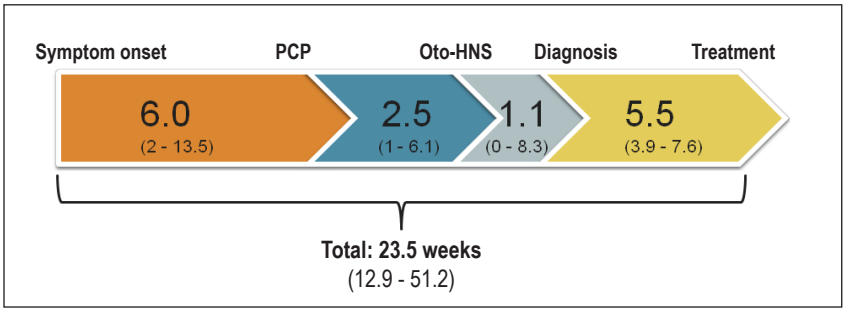

Figure 1. Median time intervals in weeks (interquartile ranges).

Oto-HNS = otolaryngologist; PCP = primary care physician.

The median diagnostic pathway time intervals are summarized in Figure 1. The longest interval was from symptom onset to initial visit with a primary care physician. The total median interval from symptom onset to treatment initiation was 23.5 weeks (interquartile range 12.9-51.2).

Presenting symptoms, which were extremely variable, were categorized into 4 groups (Figure 2). The most common symptoms were ear-related; neck masses were second most common. Among patients, 33 (33%) experienced symptoms from multiple categories.

At the first Oto-HNS visit, 54 (53%) patients had a nasopharyngeal lesion diagnosed (Figure 3). For the remaining patients, other diagnoses were made, most commonly middle ear effusion and neck masses. Nasopharyngoscopy was performed at the first Oto-HNS visit for 84 (83%) patients. Among initial endoscopies, 69 (68%) detected a nasopharyngeal lesion; the remaining results were documented as normal.

The first radiographic study was variable; magnetic resonance imaging (MRI) was most common (Table 2). Radiologists detected nasopharyngeal lesions in 68 of 101 (67%) patients. When the referring clinician indicated a nasopharyngeal lesion (42, 42% of the time), 39 (93%) imaging studies confirmed the abnormality. Among 59 (58%) imaging studies with other indications such as sinusitis or neck mass, only 28 (48%) imaging reports described a nasopharyngeal lesion. All the studies were reviewed again by a neuroradiologist in a nonblinded fashion, and NPC was identified for 30 (91%) of 33 patients who had false-negative imaging study results.

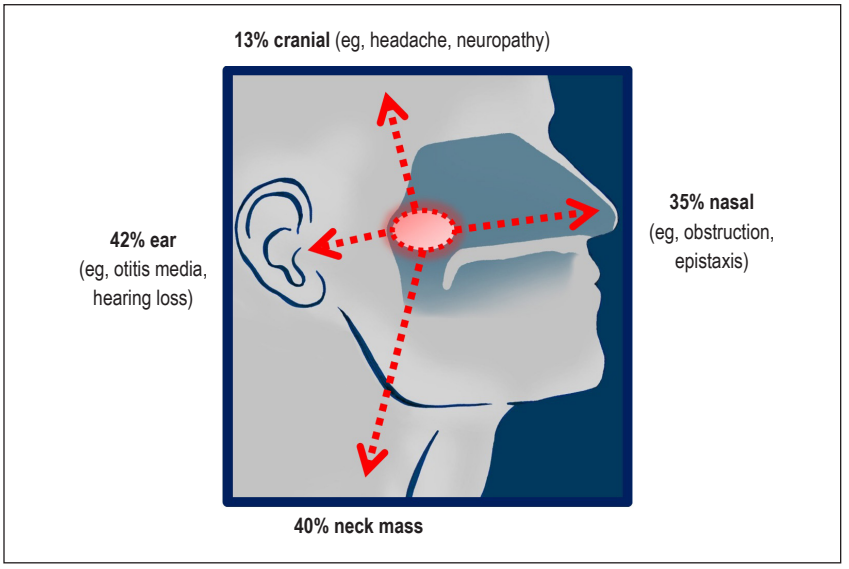

Figure 2. Nasopharyngeal carcinoma presenting symptoms.

Of the negative imaging studies, 13 (39%) were identified as suboptimal for evaluating the nasopharynx for these reasons: 1) fewer than two slices of the nasopharynx were captured, 2) lack of contrast, 3) lack of axial-oriented slices, and/or 4) dental artifact. Among the positive scans, only 1 (1.5%) was suboptimal.

Upon review of radiographic images, the tumor growth pattern in the nasopharynx was exophytic in 53 (52%) patients, endophytic in 29 (29%), both exophytic and endophytic in 15 (15%), normal in 1 (1%), and not included in the scan in 3 (3%). Mastoid opacification was found in 53 (52%) images. Sphenoid opacification was identified in 32 (32%) patients, and bony skull base erosion in 30 (30%).

Ultimately, a nasopharyngeal lesion was first detected with nasal endoscopy in 64 (63%) patients, with imaging in 33 (33%), and intraoperatively for 4 (4%).

DISCUSSION

In this study, a nasopharyngeal lesion was diagnosed after the first Oto-HNS visit for 54 (53%) patients. No nasopharyngeal abnormality was documented for the remaining patients. Most of these cases were initially misdiagnosed and patients were treated for other conditions such as eustachian tube dysfunction, sinusitis, or epistaxis without undergoing a cancer workup. However, the primary diagnosis was a neck mass for 10 (9%) patients, and neck imaging was obtained for 7 patients within 1 month of the initial visit. Because appropriate workups were initiated, we did not consider misdiagnosis as an issue for these patients. Although clinicians other than Oto-HNS are not expected to diagnose NPC, the high rate of misdiagnosis by Oto-HNS has not been well described. In part, this is attributable to the rarity of NPCs. In our health care system, which includes more than 3 million patient members (15% Asian), approximately 130 full-time Oto-HNS each averaged one NPC diagnosis every 4 years.

NPC is also challenging to diagnose because of its anatomic isolation. Most of these cancers remain clinically silent for a long period of time. Although one-third of patients presented with nasal symptoms

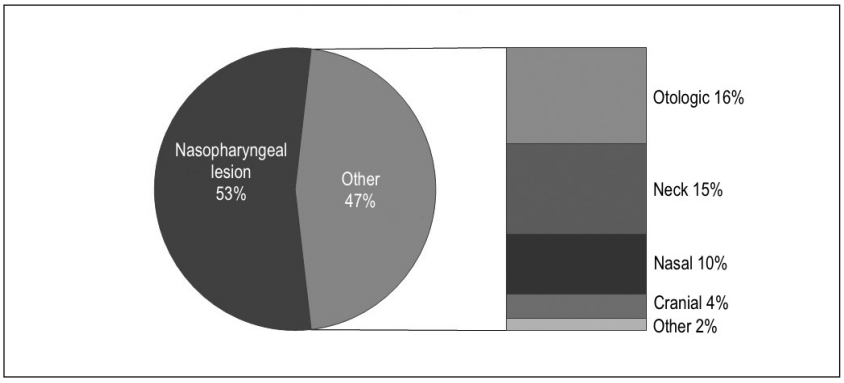

Figure 3. Initial diagnosis by otolaryngologist.

such as epistaxis and nasal obstruction, most presented only when the cancer began to affect the surrounding organs, causing ear symptoms or a neck mass.

Basic demographic data can be used to assess NPC risk in the context of clinical symptoms. Among our patients with NPC, 71 (70%) were men, and 83 (82%) were older than age 40 years. Although other head and neck cancers are rare in people younger than age 40 years, NPC does occur in young adults (18 [18%] of our patients were between ages 21 and 39; 71 [70%] were of Chinese or Southeast Asian ethnicity). This ethnic distinction is important: In our population, there were no patients with NPC of Indian, Korean, or Japanese descent. Other epidemiology studies confirm this ethnic predilection.[4] In parts of southern China, NPC is the second-most-common cancer among men, with an incidence 10 to 20 times that of nonendemic populations.[5] NPC etiology is thought to involve a combination of Epstein-Barr virus exposure and genetic susceptibility. Those who immigrate to the US from endemic areas are at higher risk for NPC than the general US population, but their risk is decreased when compared with risk for people living in China.[5]

Table 2. Initial radiographic scan type (N = 101)

MRI	34
CT neck	33
CT sinus	19
CT head	7
Positron emission tomography-CT	8

CT = computed tomography; MRI = magnetic resonance imaging.

Time Intervals

The median diagnostic pathway time intervals in Figure 1 appear to indicate an efficient pathway to diagnosis and treatment. However, the mean time intervals were much longer: Total time from symptom onset to treatment initiation was ten months. The much longer mean time intervals reflect the minority of patients whose care was substantially delayed by themselves or by their physicians. One-third of patients waited longer than three months before seeking medical attention. Considering that all of our patients had health insurance, this delay probably reflects the fact that they were not alarmed by symptoms such as hearing loss, neck masses, and nasal obstruction. Additionally, for one-third of patients, the Oto-HNS needed longer than one month to establish the correct diagnosis after the initial visit. Even when specialists are equipped with the proper technology with which to examine the nasopharynx, an NPC diagnosis can remain elusive.

Presenting Symptoms

NPC's presenting symptoms are, in descending order, ear-related issues, a neck mass, and nasal and cranial symptoms. This is in contrast to classic teaching, however, which states that a neck mass is the most common NPC presenting symptom.[6,7] Ear symptoms occur because the nasopharyngeal tumor compresses or obstructs the torus tubarius and leads to eustachian tube dysfunction, which can manifest as a middle ear effusion, acute otitis media, and conductive hearing loss. In Chinese or Southeast Asian men, new onset of these ear symptoms should trigger an examination of the nasopharynx. In our study, neck masses were usually referred appropriately by primary care physicians and worked-up efficiently by an Oto-HNS. However, several patients received misdiagnoses of lipoma, reactive lymphadenopathy, and neck abscess. Nasal symptoms such as obstruction, epistaxis, or sinusitislike symptoms were third most common upon presentation. These conditions often were initially treated with nasal steroids, antihistamines, or antibiotics by a primary care physician before referral to an Oto-HNS. Symptoms such as cranial neuropathy and headache occurred in 13 (13%) patients. Cranial neuropathies manifested most commonly as diplopia, followed by facial numbness, facial droop, and tongue numbness. One-third of patients had symptoms from multiple categories, and 42 different symptom combinations were seen. Such variation in symptomatology likely contributes to the challenge in diagnosis.

Nasal Endoscopy

Nasal endoscopy plays a crucial role in NPC diagnosis. It is performed in the Oto-HNS office with topical anesthetic in just a few minutes. For 84 (83%) patients, endoscopy was performed at the first Oto-HNS visit. Findings of the first nasopharyngoscopy were reported as normal for 32 (32%) patients. Of these patients with an initial negative nasal endoscopy result, 21 (66%) had T1/2 tumors, and 11 (34%) had T3/4 tumors. This false-negative rate is surprisingly high (especially for T3 and T4 tumors). These examination records were not available for our review, but we postulate several explanations. Among tumors, 29 (29%) were mostly endophytic on radiographic imaging; therefore, they were likely to be submucosal on endoscopic exam. Most tumors are thought to originate from the fossa of Rosenmüller, which is the posterolateral nasopharyngeal recess. This space is longer than 1 cm in depth and less than 5 mm wide in about 50% of people.[8] It is not always possible to visualize the entire fossa, so turning the endoscope 90° or approaching the fossa from the contralateral side may be necessary. We hypothesized that many Oto-HNS do not routinely visualize the fossa's entirety, thereby missing smaller NPCs.

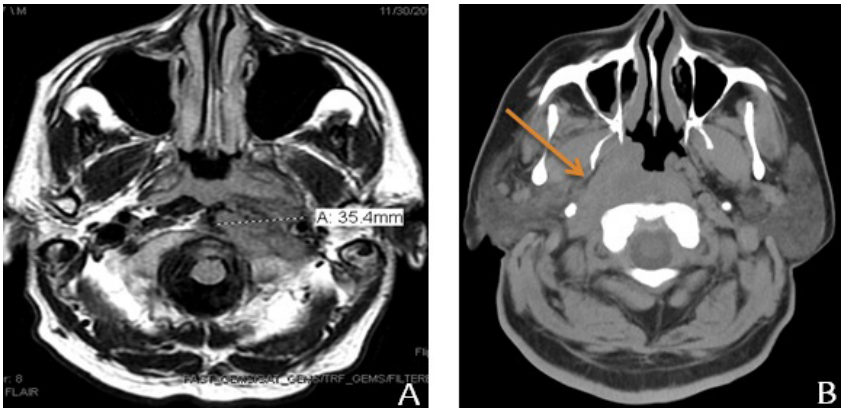

Figure 4. (A) Example of a T4b nasopharyngeal carcinoma (NPC) with an endoscopic examination that was initially normal. (B) Example of an endophytic NPC initially interpreted as normal on this computed tomography sinus scan without contrast. The arrow points to a tumor in the right parapharyngeal space.

The challenge associated with nasopharyngeal assessment was well described by Vlantis et al[9] in which a 44-point scoring system was used. This exceptionally thorough evaluation system probably would be more accurate than other evaluations, but the time required would pose a challenge in daily practice.

The nasopharyngoscopes used during this study were standard fiber optic scopes. Video nasopharyngoscopes have improved resolution and offer a larger field of view and recording/playback capabilities. These newer scopes have recently been adopted widely in our system; with improved visualization, the incidence of missed NPCs on nasal endoscopy should decrease.

The fact that most (64, 63%) NPCs in our study were first detected by nasal endoscopy underscores the importance of performing nasal endoscopy for high-risk patients at the initial Oto-HNS visit. High-risk patients include any patient from China or Southeast Asia who present with an ear complaint, neck mass, nasal obstruction or cranial symptoms. Considering that nasal endoscopy is relatively quick to perform and virtually risk free, the threshold for its use should be very low for high-risk patients. Additionally, an understanding of the high false-negative rate associated with this examination is important when interpreting the findings. When a high-risk and symptomatic patient has negative nasal endoscopic exam findings, MRI should be considered for further evaluation for NPC. Figure 4A provides an example of an NPC that went undetected on endoscopic exam; a large tumor is visualized on MRI.

Imaging

A nasopharyngeal lesion was not reported by the radiologist after viewing 33% of initial scans. During our rereview with our neuroradiologist, 91% of these scans revealed a nasopharyngeal lesion. Some lesions were subtle and probably detected on the basis of a priori knowledge of the presence of NPC; however, some lesions were obvious. The first imaging study technique was highly variable (Table 2), which reflects the assorted symptom indications and diversity among ordering physicians. One-quarter of first scans were ordered by a non-Oto-HNS.

Other studies that have examined the diagnostic accuracy of MRI for NPC found sensitivity to be higher than 90%.[10,11] However, these studies were performed in an endemic area on patients "suspected" to have NPC. In our study, the first imaging study was a computed tomography (CT) scan (neck, sinus, or head), MRI, or a positron emission tomography/CT scan in a nonendemic population for which a nasopharyngeal pathology was not suspected 58% of the time.

Although some scans were suboptimal for examination of the nasopharynx (eg, CT sinus and CT head), we contend that some of the false-negative scans can probably be explained by inattentional blindness.[12] For example, when the indication was sinusitis, the radiologist likely focused on the sinuses and missed NPC (Figure 4B provides an example of a false-negative imaging study). The high false-negative rate underscores the importance of clinicians communicating clinical context to radiologists when ordering scans. The challenge remains, however, that clinicians themselves often do not suspect NPC and do not communicate this need to the interpreting radiologist. Mastoid opacification was found in 53 (52%) patients and sphenoid opacification in 32 (32%) patients. To our knowledge, these radiographic findings were not previously reported as warning signs for NPC. Although the specificity of these signs is unknown, considering that our cohort was entirely patients with NPC, we feel these signs should prompt astute clinicians to closely scrutinize the nasopharynx in high-risk patients.

We did not find a correlation between prolonged diagnostic time intervals and disease stage. This may be explained mainly by the clinically silent nature of NPC. Even with prompt action by both patients and the health care system, many patients with NPC probably do not develop clinical symptoms until advanced T-stage disease or nodal positivity is present. Nevertheless, once these symptoms appear, patients must receive an efficient diagnosis.

The limitations of this study include its small size, its retrospective nature, and the availability of documentation and examination data. Patient-reported history is prone to recall bias, and documentation by physicians in the medical record was sometimes vague. Although we could review each radiographic study, review was not performed in a blinded fashion. Additionally, endoscopic examinations were unavailable for review. Finally, the study was conducted at a single institution in a limited geographic area (Northern California).

The Institute of Medicine's recent landmark report, *Improving Diagnosis in Health Care,*[13] highlighted the fact that scant data exist on diagnostic error. We hope that our study will provide necessary baseline data regarding NPC.

CONCLUSION

NPC is rarely encountered in our health care system and frequently is misdiagnosed. Thirty-two percent of nasopharyngeal cancers are difficult to visualize upon nasal

endoscopy, and 33% are missed upon an initial imaging study. This descriptive study of misdiagnosis incidence and patterns is a first step toward understanding the challenges associated with NPC diagnosis. Further work is required to implement changes that can reduce diagnostic error. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

Jason E Gilde, MD, created Figure 2.

Brenda Moss Feinberg, ELS, provided editorial assistance.

How to Cite this Article

Wang KH, Austin SA, Chen SH, Sonne DC, Gurushanthaiah D. Nasopharyngeal carcinoma diagnostic challenge in a nonendemic setting: Our experience with 101 patients. Perm J 2017;21:16-180. DOI: https://doi.org/10.7812/TPP/16-180.

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Diagnosis

The diagnosis of disease is often easy, often difficult, and often impossible.

— Peter Mere Latham, MD, 1789-1875, British physician
and medical educator, physician extraordinary to Queen Victoria