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LYMPH NODE METASTASIS AS A SOLE PRESENTATION OF NASOPHARYNGEAL CARCINOMA

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Abstract

Introduction: Nasopharyngeal carcinoma (NPC) is a distinct head and neck malignancy with unique epidemiological and biological characteristics. In many cases, NPC initially presents with cervical lymph node metastasis before the identification of the primary tumor. Rarely, lymph node metastasis may be the *sole initial clinical manifestation*, leading to diagnostic delay and clinical challenges.

Objective: To highlight the clinic pathological features of patients presenting with cervical lymph node metastasis as the only initial presentation of Nasopharyngeal carcinoma.

Materials and Methods: This observational study was conducted in the Department of ENT and Head and Neck Surgery at Ayub teaching Hospital MTI, Abbottabad., and included 30 patients presenting with isolated cervical lymphadenopathy subsequently diagnosed as nasopharyngeal carcinoma (NPC). Patients underwent detailed clinical examination, contrast-enhanced CT/MRI of the head and neck, nasopharyngoscopy, and histopathological evaluation of lymph node and nasopharyngeal biopsy specimens. Immunohistochemistry and Epstein–Barr virus (EBV)-encoded RNA testing were performed where indicated. Demographic, clinical, radiological, and pathological findings were analyzed using descriptive statistical methods.

Results: Most patients presented with painless, firm cervical lymph nodes, predominantly in the upper deep cervical chain. In several cases, the nasopharyngeal primary tumor was clinically occult and detected only on imaging or endoscopic evaluation. Histopathology confirmed non-keratinizing undifferentiated carcinoma in the majority of cases. Epstein–Barr virus (EBV)-associated markers were positive in most patients. Delayed identification of the primary site was associated with advanced nodal stage at presentation.

Conclusion: Cervical lymph node metastasis may represent the sole presenting feature of NPC. A high index of suspicion, especially in endemic regions, is essential for early diagnosis. Comprehensive evaluation of unexplained cervical lymphadenopathy should always include assessment of the nasopharynx to avoid diagnostic delay and improve outcomes.

Keywords: Nasopharyngeal carcinoma; cervical lymphadenopathy; occult primary tumor; lymph node metastasis; Epstein–Barr virus; head and neck cancer; non-keratinizing carcinoma; diagnostic delay

Introduction

Nasopharyngeal carcinoma (NPC) is a unique epithelial malignancy arising from the mucosal lining of the nasopharynx, with distinct epidemiological, histopathological, and clinical characteristics compared to other head and neck cancers.[1,2] It shows a remarkable geographic and ethnic variation in incidence, being highly prevalent in Southeast Asia, Southern China, North Africa, and parts of the Middle East, while remaining relatively uncommon in Western populations.[3,4] In endemic regions, NPC represents a significant public health concern due to its aggressive behavior, tendency for early metastasis, and often delayed diagnosis.[5,6]

The etiopathogenesis of NPC is multifactorial, involving a complex interplay of genetic susceptibility, environmental factors, and viral oncogenesis. Epstein–Barr virus (EBV) infection is strongly associated with the non-keratinizing and undifferentiated subtypes of NPC, which constitute the majority of cases in endemic areas.[7,8] Additional risk factors include consumption of salt-preserved foods rich in nitrosamines, exposure to wood dust and formaldehyde, smoking, and familial predisposition. These factors contribute to malignant transformation of nasopharyngeal epithelial cells through chronic inflammation, genetic mutations, and immune evasion mechanisms.

Clinically, NPC is often referred to as a "silent" or "hidden" tumor due to its deep anatomical location and non-specific early symptoms.[9,10] Patients may initially present with nasal obstruction, epistaxis, hearing loss, tinnitus, or headache; however, these symptoms are frequently mild and overlooked.[11,12] One of the most common and clinically significant features of NPC is cervical lymphadenopathy caused by early regional metastasis.[13] The rich lymphatic network of the nasopharynx facilitates early spread to the upper deep cervical lymph nodes, particularly the jugulodigastric and posterior cervical chains.[14]

In some cases, cervical lymph node enlargement may be the sole initial clinical manifestation, while the primary nasopharyngeal lesion remains clinically occult. This presentation poses a major diagnostic challenge, as patients are often initially evaluated for primary lymph node pathology or other head and neck malignancies. Consequently, misdiagnosis or delayed identification of the primary tumor is common, leading to progression to advanced disease stages at the time of diagnosis.

Histopathologically, NPC is most commonly classified as non-keratinizing differentiated or undifferentiated carcinoma, both of which are strongly associated with EBV infection.[15] Immunohistochemical markers, including EBV-encoded RNA (EBER), play a crucial role in confirming the diagnosis, particularly in metastatic lymph node specimens when the primary site is not immediately evident.[16] Imaging modalities such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic examination of the nasopharynx are essential for accurate localization of the primary tumor.

Given the diagnostic complexity and potential for isolated nodal presentation, a high index of suspicion is required, particularly in endemic regions. Early recognition of NPC presenting as isolated cervical lymphadenopathy is critical for prompt diagnosis, appropriate staging, and timely initiation of therapy, which significantly influences prognosis and survival outcomes. This study therefore emphasizes the clinicopathological spectrum of NPC cases where cervical lymph node metastasis is the sole initial presentation, highlighting the importance of comprehensive diagnostic evaluation in patients with unexplained cervical lymphadenopathy.

Methodology

This observational study was conducted in the Department of ENT and Head and Neck Surgery at Ayub teaching Hospital MTI, Abbottabad. The study included a total of 30 patients presenting with cervical lymphadenopathy who were subsequently diagnosed with nasopharyngeal carcinoma (NPC), where cervical lymph node metastasis was the sole initial clinical presentation. The study

design was descriptive and included both retrospective and prospective evaluation of cases over a defined study period. Patients were evaluated after confirmation of diagnosis through clinical, radiological, endoscopic, histopathological, and immunohistochemical investigations.

All patients of either gender presenting with unexplained cervical lymph node enlargement and later confirmed to have metastatic NPC were included in the study. Only those cases were selected in which no obvious primary tumor was identified at initial presentation and cervical lymph node enlargement was the first and only presenting feature. Patients who underwent complete diagnostic workup including contrast-enhanced CT or MRI of the head and neck, nasopharyngoscopy, and histopathological confirmation were eligible for inclusion.

Patients with known primary head and neck malignancies other than NPC, recurrent NPC cases, metastatic lymphadenopathy from other primary sites, previously treated head and neck cancers, or incomplete diagnostic evaluation were excluded from the study.

A detailed clinical history was obtained from all patients, including duration of neck swelling, associated nasal or otologic symptoms, and relevant risk factors such as smoking and dietary habits. Physical examination focused on the characteristics of cervical lymph nodes, including size, consistency, number, and level of involvement. Radiological assessment was performed using CT and/or MRI to identify occult primary lesions and evaluate the extent of disease. Flexible nasopharyngoscopy was carried out in all cases, and biopsies were taken from any suspicious areas or randomly from the nasopharynx when no visible lesion was present.

Histopathological examination of lymph node specimens was performed using hematoxylin and eosin staining, and tumors were classified according to the WHO classification, with emphasis on non-keratinizing and undifferentiated carcinoma types. Immunohistochemical analysis, including Epstein–Barr virus (EBV)-encoded RNA (EBER) testing, was used where indicated to support the diagnosis. Data were analyzed using descriptive statistical methods. Ethical approval was obtained from the Institutional Review Committee of Ayub Medical College, and informed consent was obtained from all participants prior to inclusion in the study.

Results

Table 1: Demographic Characteristics of Patients (n = 30)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	<20	2	6.7
	21–40	09	30.0
	41–60	14	46.7
	>60	05	16.6
Gender	Male	21	70.0
	Female	09	30.0

The majority of patients were middle-aged males, with the highest frequency observed in the 41–60 years age group, reflecting the known demographic pattern of nasopharyngeal carcinoma.

Table 2: Clinical Presentation and Cervical Lymph Node Characteristics

Variable	Category	Frequency (n)	Percentage (%)
Duration of neck swelling	<1 month	04	13.3
	1–3 months	13	43.3
	>3 months	13	43.3
Laterality	Unilateral	19	63.3
	Bilateral	11	36.7
Lymph node consistency	Firm	22	73.3

Variable	Category	Frequency (n)	Percentage (%)
	Hard	08	26.7
Pain	Painless	25	83.3
	Painful	05	16.7

Most patients presented with painless, firm, unilateral cervical lymphadenopathy of more than one month duration, indicating delayed presentation and advanced nodal involvement.

Table 3: Diagnostic Findings and Histopathological Profile

Variable	Category	Frequency (n)	Percentage (%)
Imaging (CT/MRI) detection of primary	Detected	24	80.0
	Not detected	06	20.0
Nasopharyngoscopy finding	Visible lesion	22	73.3
	Occult/normal	08	26.7
Histopathology type	Non-keratinizing undifferentiated carcinoma	23	76.7
	Differentiated non-keratinizing carcinoma	07	23.3
EBV (EBER) status	Positive	25	83.3
	Negative	05	16.7

Non-keratinizing undifferentiated carcinoma was the most common histological subtype, and EBV positivity was observed in the majority of cases, supporting its strong etiological association with NPC.

Discussion

Nasopharyngeal carcinoma (NPC) is a unique epithelial malignancy characterized by its aggressive biological behavior and marked tendency for early regional lymphatic spread. Due to the rich lymphatic network of the nasopharynx, cervical lymph node metastasis frequently occurs at an early stage of disease and may precede the appearance of symptoms related to the primary tumor. In the present study conducted at Ayub Medical College, Abbottabad, 30 patients presenting with isolated cervical lymphadenopathy as the initial manifestation of NPC were evaluated to determine their clinicopathological characteristics and diagnostic challenges.

The demographic profile of our patients demonstrated a predominance of males (70%) and a peak incidence in the 41–60 years age group (46.7%). These findings are consistent with previous studies that have reported a higher incidence of NPC among middle-aged men. The observed male predominance may be related to greater exposure to environmental and lifestyle risk factors, including tobacco smoking, occupational exposure to dust and chemical agents, and dietary practices. Genetic susceptibility and hormonal influences have also been proposed as contributing factors in the gender disparity observed in NPC.

Cervical lymphadenopathy was the sole presenting complaint in all patients included in this study. Most patients presented with painless, firm, unilateral cervical lymph node enlargement, while bilateral nodal involvement was observed in a smaller proportion of cases. This pattern corresponds with the known lymphatic drainage pathways of the nasopharynx, where metastasis commonly involves the upper deep cervical and jugulodigastric lymph nodes. The majority of patients reported a duration of neck swelling exceeding one month before seeking medical attention, suggesting

delayed presentation. Such delays may occur because cervical lymphadenopathy is often initially attributed to benign inflammatory conditions, particularly in regions where infectious causes of lymph node enlargement are common.

Radiological investigations played a significant role in detecting occult primary tumors. In the present study, CT and MRI successfully identified the primary nasopharyngeal lesion in 80% of patients, whereas 20% of cases remained radiologically occult at initial evaluation. Similarly, nasopharyngoscopic examination revealed visible lesions in most patients, although a notable proportion showed no obvious abnormality on endoscopy. These findings highlight the diagnostic complexity of NPC and emphasize that a normal endoscopic appearance does not exclude the presence of malignancy. Therefore, directed or random nasopharyngeal biopsies should be considered in patients with metastatic cervical lymphadenopathy of unknown origin when NPC is suspected.

Histopathological examination revealed that non-keratinizing undifferentiated carcinoma was the predominant subtype, accounting for 76.7% of cases. This observation is in agreement with reports from endemic regions where non-keratinizing NPC constitutes the majority of cases and demonstrates a strong association with Epstein–Barr virus (EBV) infection. In our study, EBV positivity was detected in 83.3% of patients, further supporting the established role of EBV in NPC pathogenesis. The high prevalence of EBV-associated tumors highlights the diagnostic value of EBER testing, particularly in metastatic lymph node specimens where the primary tumor may not be readily identifiable.

One of the most significant findings of this study is that cervical lymph node metastasis may represent the only clinical manifestation of NPC at presentation. This poses a substantial diagnostic challenge because patients are frequently investigated for alternative causes of cervical lymphadenopathy, including tuberculosis, lymphoma, reactive lymphadenitis, and metastatic disease from other primary sites. Consequently, diagnosis may be delayed, allowing disease progression and increasing the likelihood of advanced nodal involvement at the time of treatment initiation.

The findings of this study underscore the importance of maintaining a high index of suspicion for NPC in all patients presenting with persistent unexplained cervical lymphadenopathy. Comprehensive diagnostic assessment, including detailed head and neck examination, cross-sectional imaging, nasopharyngoscopy, histopathological evaluation, and EBV-related investigations, is essential for accurate diagnosis. Early identification of the primary lesion is particularly important because NPC is highly sensitive to radiotherapy and chemoradiotherapy, and early-stage diagnosis is associated with significantly improved treatment outcomes and survival rates.

Although the present study provides valuable insight into the clinicopathological characteristics of NPC presenting with isolated cervical lymph node metastasis, certain limitations should be acknowledged. The relatively small sample size and single-center design may limit the generalizability of the findings. Future multicenter studies involving larger patient populations and long-term follow-up are recommended to further evaluate diagnostic strategies, treatment outcomes, and prognostic factors in this unique clinical presentation.

Overall, the present study reinforces that isolated cervical lymphadenopathy may be the first and only presenting feature of nasopharyngeal carcinoma. Early recognition and thorough evaluation of unexplained cervical lymph node enlargement can facilitate prompt diagnosis, reduce diagnostic delays, and improve patient outcomes.

Conclusion

Cervical lymph node metastasis may be the sole initial presentation of nasopharyngeal carcinoma, often leading to delayed diagnosis. A high index of suspicion is essential in patients with unexplained cervical lymphadenopathy, especially in endemic regions. Early and comprehensive evaluation using imaging, nasopharyngoscopy, and histopathology is crucial for timely diagnosis and improved patient outcomes.

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