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Original Research Article

Metastatic nasopharyngeal carcinoma presenting with palpable neck nodes-A look at clinical presentation and literature review on screening

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ABSTRACT

Background: Nasopharyngeal carcinoma in Nagaland has the highest age adjusted rates for both men (14.4 /100,000) and women (6.5 /100,000) in India. Most of the patients presents with usual vague symptoms related to mass in nasal cavity and higher clinical stage which affects the treatment outcome. The aim of this study is to present 34 cases of patients with Nasopharyngeal carcinoma initially presenting with palpable neck nodes and discuss the clinical findings and literature review on screening methodology with focus on Plasma EBV DNA.

Materials and Methods: Retrospective analysis of all cases of metastatic nasopharyngeal carcinoma diagnosed by Fine needle aspiration cytology on palpable cervical lymph node and histologically confirmed by endoscopic biopsy.

Results: Total of 34 cases were included with 23 men and 11 women. The age ranged from 16 to 79 years with average of 46.6 years. The most common clinical presentation was painless neck swelling followed by epistaxis. 33/34 cases are of Non keratinizing undifferentiated nasopharyngeal carcinoma. Majority of the cases presented in stage III (19/34) followed by stage IV (10/34).

Conclusion: Nasopharyngeal carcinoma is a major health problem in Nagaland. Development of a good NPC screening protocol including molecular techniques remains to be explored, in order to develop and contribute to the early detection of the disease and a favourable treatment outcome.

1. Introduction

Nasopharyngeal carcinoma is a carcinoma arising from the nasopharyngeal epithelial lining that shows histologic or ultrastructural evidence of squamous differentiation.[1] WHO classifies the malignancy into three morphological subtypes; keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma (differentiated and undifferentiated) and basaloid squamous cell carcinoma. The non-keratinizing and basaloid squamous cell variant are known to occur at an early age and have better response to radiotherapy,[2] however, the prognostic significance of the histologic subtypes has not reached a consensus.[3]

1.1. Demography

The carcinoma has a unique geographical and demographic distribution with differences in the predominance of the histological subtypes found in the endemic and non-endemic region. Globally cases are < 3 per 100,000 person-year and the keratinizing squamous subtypes more frequent in non-endemic areas.[4] The carcinoma is endemic in Northern and Eastern Africa and Eastern and Southeastern Asia[5] with the highest incidence in Southern China with 30 cases per 100,000 persons annually.[6] Nagaland, a small state situated in the North-eastern part of India with a

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population of 19.7 lakhs has the highest incidence of Nasopharyngeal carcinoma in the country, with an incidence of 14.4 /100,000 for men and 6.5 /100,000 for women according to national cancer registry programme, Indian council of medical research between 2012-2016 (report of national cancer registry programme, 2020)

We intent to address this regional cancer burden by highlighting the clinical profile of all palpable metastatic cervical lymph nodes initially diagnosed on FNAC and do a literature review focussing on screening for early detection of the cancer.

2. Material and method

2.1. Case definition

All patients with FNAC done on palpable neck nodes showing findings of metastatic disease and nasal endoscopic biopsy showing features of nasopharyngeal carcinoma and with available CT scan or MRI of head and neck.

Retrospective analysis of all metastatic NPC initially diagnosed with FNAC and primary confirmed by biopsy from nasopharynx. Only cases with biopsy proven nasopharyngeal carcinoma obtained from nasal endoscopy were included in the study. Data of their clinical presentation and the level of the palpable lymph node involved were obtained and analysed. The clinical staging was made from the radiology report.

2.2. Approval

The study has been approved by the Institute's Ethics committee.

3. Results

A total of 34 patients were diagnosed with nasopharyngeal carcinoma after the initial FNA cytology (Figure 1) suspicion on lymph node. 23 were men and 11 women patients. The age ranged from 16 to 79 years with average of 46.67. The average age group among women is 42.18 and men is 48.82. The most common presenting symptoms were painless neck swelling followed by epistaxis. The median time for onset of symptoms to diagnoses of disease is 4.5 months.

Level II cervical lymph node was the most common site diagnosed on FNA in 17 cases. The left sided cervical lymph nodes were more frequently involved in 19 cases followed with 9 cases involving the right side and 6 cases had bilateral cervical node involvement.

Majority of the cases presented in stage III (19/34) followed by stage IV (10/34) and rest stage II (5/34). Majority of biopsy (33/34) from the nasopharynx were classified as Non-keratinizing undifferentiated nasopharyngeal carcinoma (Figure 2) and only one case show histological pattern of non-keratinizing differentiated nasopharyngeal carcinoma (Figure 3).

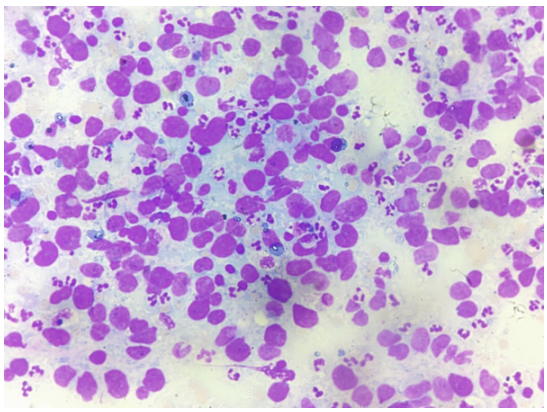

Fig. 1: Fine needle aspiration cytology showing metastatic cells from cervical lymph node.Leishman and Geimsa stain 40x.

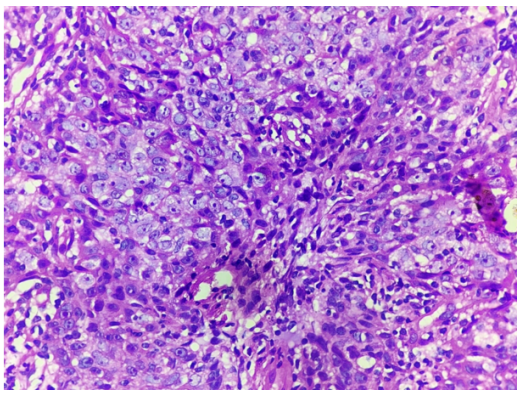

Fig. 2: H&E stain from nasopharyngeal mass showing features of Non-Keratinizing Undifferentiated Nasopharyngeal carcinoma, 40x.

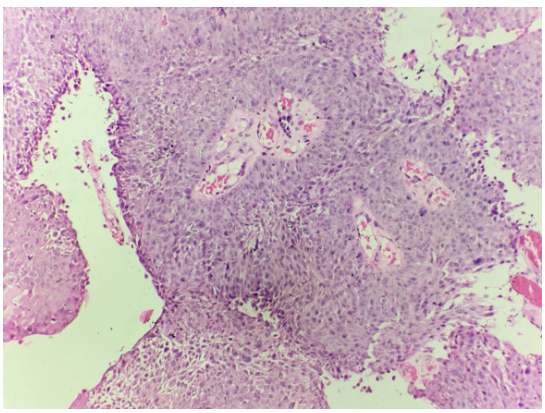

Fig. 3: H&E stain showing features of non-keratinizing differentiated nasopharyngeal carcinoma, 40x.

Table 1: Showing the cases with demographics, clinical presentation, staging and histology of the tumour.

S.No	Age	Sex	Duration of symptoms	Symptoms	Palpable Lymph node level	Histology	Clinical staging
1.	28	M	3 months	Painless neck swelling, epistaxis	Left level III	Non-keratinizing undifferentiated NPC	III
2.	33	M	1 month	Painless neck swelling	Left level III	Non-keratinizing undifferentiated NPC	IV A
3.	55	M	3 months	Headache, rhinolalia aperta	Left level II	Non-keratinizing undifferentiated NPC	III
4.	27	M	3 months	Painless neck swelling	Right level II	Non-keratinizing undifferentiated NPC	III
5.	60	M	3 months	Painless neck swelling	Left level II , V	Non-keratinizing undifferentiated NPC	II
6.	79	M	2 months	Neck swelling with headache	Left level II, Right Supraclavicular	Non-keratinizing undifferentiated NPC	II
7.	55	M	5 months	Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	II
8.	60	M	5 months	Nasal discharge with tinnitus	Left level II ,V	Non-keratinizing undifferentiated NPC	III
9.	38	M	1 year	Constitutional symptoms Painless neck swelling	Right level II	Non-keratinizing undifferentiated NPC	IV A
10.	62	M	3 months	Right sided ear ache	Right level II	Non-keratinizing undifferentiated NPC	III
11.	55	M	17 months	Nasal blood discharge with Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	III
12.	40	M	2 months	Painless neck swelling	Left level IIA, IIB	Non-keratinizing undifferentiated NPC	IVA
13.	27	M	3 months	Facial palsy	Left level IIA, IIB	Non-keratinizing undifferentiated NPC	III
14.	60	M	5 months	Epistaxis with otalgia	Right level III	Non-keratinizing undifferentiated NPC	III
15.	58	M	1 year	Painless neck swelling with facial palsy	Bilateral level II	Non-keratinizing undifferentiated NPC	II
16.	54	M	20 days	Painless neck swelling	Left level III	Non-keratinizing undifferentiated NPC	III
17.	41	M	6 months	Painless neck swelling	Left level III	Non-keratinizing undifferentiated NPC	II
18.	64	M	8 months	Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	IV
19.	65	M	1 month	Nasal blockage	Bilateral level V	Non-keratinizing undifferentiated NPC	III
20.	35	M	5 month	Painless neck swelling	Right level IB	Non-keratinizing undifferentiated NPC	IV A
21.	44	M	5 month	recurrent nasal bleeding	Right level II	Non-keratinizing undifferentiated NPC	III
22.	43	M	1 year	Painless neck swelling with nasal blockage for	Left level II	Non-keratinizing undifferentiated NPC	IV A
23.	40	M	5 month	Painless bialateral neck	Bilateral level II	Non-keratinizing undifferentiated NPC	IV A
24.	66	F	3 months	bilateral Painless neck swelling	Right level IB, II Left level V	Non-keratinizing undifferentiated NPC	IV A
25.	43	F	6 months	Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	III
26.	16	F		Painless neck swelling with epistaxis	Bilateral level V	Non-keratinizing undifferentiated NPC	III
27.	25	F	6 months	Painless neck swelling	Right level II	Non-keratinizing undifferentiated NPC	III
28.	42	F	3 months	Painless neck swelling	Right level II, III	Non-keratinizing undifferentiated NPC	III
29.	45	F	3 months	Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	IV A
30.	52	F	6 months	Painless neck swelling	Left level III	Non-keratinizing undifferentiated NPC	IV A
31.	30	F	3 months	Painless neck swelling	Left level II	Non-keratinizing undifferentiated NPC	III
32.	50	F	5 months	Painless neck swelling	Right level II	Non-keratinizing undifferentiated NPC	III
33.	40	F	1 month	Painless neck swelling	Left level II	Non-Keratinizing Differentiated NPC	II
34.	55	F	6 months	Recurrent epistaxis	Left level II, III	Non-keratinizing undifferentiated NPC	III

4. Discussion

NPC is an uncommon disease in India with high cases seen in the state of Nagaland. It presents with vague symptoms and has the highest preponderance for regional lymph node metastasis as compared with other head and neck squamous cell carcinoma.[7] FNAC is a very useful tool in the primary assessment of head and neck swelling, particularly in occult carcinomas, FNA results may be the only indication for searching primary in the nasopharynx[8] making the technique very useful as it also enables to discriminate benign from malignant conditions and its rapid assessment makes the technique a very important part of surgical pathology.[9] Aspirate findings from metastatic NPC can be confused with other malignant conditions particularly Hodgkin's Lymphoma and other metastatic carcinomas, however, careful studies of the cytological and architectural findings are key in giving the right diagnosis.[8,10]

In our study, men patients were predominant, a well-established fact seen in other studies as well[11,12] with as much as double or triple the cases compared to women patient in high risk population[1]. Women patients with NPC are shown to have better survival rates as compared to the men counterpart with similar stage of the disease.[13]

Our study (Table 1) showed the average age of patients at 46.67 years ranging from 16 to 79 years. In high risk population the incidence of NPC peaks at 40-60 years which rises after 30 years of age.[14] Studies on retrospective analysis in children and adolescent with NPC has showed better overall survival rates in younger individuals.[15,16] Although staging in younger patients do not have a significant difference at presentation as seen in a study done by Yan et al in 185 cases of patients aged less than 21 years where around 90% of the cases were stage III and stage IV.[17]

Our study showed that the median time for onset of symptoms to diagnoses of disease is 4.5 months, this was comparable in a study finding of 158 patients composed of children and adolescents which was 4.8 months[15] but in a larger sample size of 4768 patients[18] the mean duration was 8 months. This is variable and perhaps dependent on multiple factors such as the level of health care system established in the region and health seeking behaviour of the patients.

Studies have shown that the most common presenting symptoms for NPC is palpable neck lump, nasal obstruction and epistaxis.[11,18,19] Most of our patient also presented with painless neck swelling 76.47% (26/34) followed by epistaxis 20.5 % (7/34). Majority of the palpable lymph nodes in our study were on the left side 55.8 % (19/34) whereas in one prospective study of 271 cases, majority of the cases had bilateral cervical lymphadenopathy 39.2%.[7] This may be due to fact that we included only palpable neck nodes.

A Meta-analysis of 411 original article and 13 studies which had 2920 cases of NPC reveal that the most frequent involved groups of lymph nodes were the level II neck node (70%) and retropharyngeal node (69%).[20] We also found similar findings in our study with level II lymph node involvement in 44% (15/34) as compared with the second frequent involvement of the level III lymph node at 20% (6/34). The involved groups of lymph nodes are also important to note as seen in a study by Chaoyang Jiang et al, which showed that metastasis to lymph node posterior to level V had independent prognostic factor for Distant metastasis free survival.[21]

The biopsy obtained by nasal endoscopy in our study showed that non-keratinizing undifferentiated carcinoma (33/34) was seen in almost all the cases. This is the major histological subtype seen in endemic regions.[13]

In early disease, radiation is the standard treatment for primary tumour and cervical nodes[22,23] and at least one level beyond the clinical extent of disease should be given a prophylactic irradiation as the pattern of metastasis of nasopharyngeal carcinoma to lymph nodes is by orderly spread down the neck in a predictable pattern.[7] However, in locally advanced disease there are evidences which showed improvement in overall survival with induction chemotherapy followed by concurrent chemoradiotherapy.[24] The same treatment is followed in our setting as most of the patients in our institution presents with locally advanced disease.

The most commonly used staging system is the American Joint Committee on Cancer in English literature. Majority of our patients presented in stage III and stage IV disease. As treatment and management of NPC relies mostly on the staging, NPC detection of the disease at an early stage is one of the major problems.[25] Many studies have shown that majority of the patients present with stage III and IV disease[19] with 5-year survival rates of 90% in early disease and less than 50% in metastatic disease.[26]

Though FNAC, nasal endoscopy and imaging remains the standard practice for diagnosing NPC, our study shows that many of the cases presented at late stages. Which implies the importance of an early detection of NPC. As the treatment for nasopharyngeal carcinoma is stage dependent with radiation alone being the main treatment of choice for early-stage disease and concurrent radiation and chemotherapy for advanced disease[27] the value for detection of early disease becomes paramount which will require a good screening method. Screening is done with objective of discovering disease in an apparently healthy individual who are in fact suffering from the disease. There is some principle to be followed for disease screening such as, the disease of interest should have an important health problem to the community, an acceptable treatment should be already established with facility for diagnosis and treatment made available, the test should be acceptable

to the population, natural history of the disease should be well known and the case-finding should be economically balanced and the process should be continuous.[28] A study on screening in a risk population showed detection of NPC at stages I, II, III-IVB, and IVC at 43%, 24%, 32%, and 1% respectively as compared with those with usual care without screening at 6%, 29%, 54%, and 11%.[29] This shows the value of screening for NPC. Endoscopy plays a key role in detecting the early NPC lesions, and endoscopic biopsy enables their definitive diagnosis. When NPC is strongly suspected, considering early diagnosis of NPC, appropriate imaging examinations and/or biopsy of the nasopharyngeal mucosa are recommended even if the mucosal surface exhibits normal appearance.[30]

Epstein-Barr virus (EBV) infection plays an important role in the pathogenesis of NPC.[31] However, the EBV virus is also known to be associated with other malignancies such as Burkitt's lymphoma, Hodgkin's lymphoma and B cell lymphomas.[32] The tumour cell has been shown to harbour the virus as the EBV virus has been extracted in most of the cases in endemic areas. It has also been shown that the EBV DNA can be extracted by PCR in a study by Mutirangura et al, in which EBV DNA in cell free serum has been demonstrated in 13 out of 42 NPC patients and none in 82 healthy subjects using PCR.[33] Because of the close relationship between EBV and NPC, the possibility of using circulating EBV DNA as a tumor marker for NPC has been explored. Different modes of screening for NPC have been studied. Comparative study of two EBV DNA (BamHI-W 76 bp and EBNA1 99 bp) and four anti-EBV antibodies (early antigen [EA] IgA, EA IgG, EBNA-1 IgA and VCA) showed that plasma EBV DNA have excellent test-retest reliability and higher sensitivity of 96.7% to detect stage I NPC[34] while in another study EA-IgA is suitable for the diagnosis but not NPC screening.[35] Study by Chan et al also suggested that plasma EBV DNA was more sensitive than EBV IgA serology in the NPC screening context.[36] In a large screening of 20,174 participants in an endemic region using plasma EBV DNA the sensitivity and specificity was found to be 97.1 % and 98.6% respectively. The study used MRI and endoscopic examination to diagnose 34 participants with NPC.[37] It is important to note that multiple factors may affect the sensitivity and specificity of plasma EBV DNA test such as the histologic types, small-volume disease in early-stage, recurrent/metastatic NPC with a defective secretion of viral genomes, and environmental factors.[38] Plasma EBV DNA should be used with caution as a screening method, as a study by Nicholls et al[39] found Negative plasma EBV in histologically confirmed NPC in 518 patients without metastasis in 15.1% of cases.[40] Therefore, the association of Plasma EBV DNA with stage I NPC is still controversial.[35]

Few other limitations of plasma EBV DNA is that it cannot be used to differentiate between patients who had local remission and local persistence.[41] A way to overcome the limitations is by addition of other test modalities and epidemiological risk factors. Leung et al showed a diagnostic sensitivity of 99% when EBV DNA and IgA-VCA were used together in 139 new cases of NPC with control of 178 healthy individuals.[42] Addition of Comprehensive risk score (CRS) based on epidemiological risk factors: smoking status, salted-fish consumption, educational level, and family history of NPC, two human HLA SNPs (host genetic susceptibility) and EBV genetic variant can improve the antibody serology test ELISA based EBV nuclear antigen 1 (EBNA1/IgA) which is currently used in Southern China for screening, has an improved positive predictive value of 4.7% to 43.24%.[41]

Plasma EBV DNA detection in NPC patients by many studies have highlighted its importance in the management of cancer patients, ranging from early cancer screening to the detection of residual disease after treatment. However, due to limited resources and facilities, the potential use of plasma EBV DNA detection is not possible even though NPC remains the number one prevalent cancer in the state of Nagaland.

5. Conclusion

FNAC, nasal endoscopy, and imaging remains the standard tools for the diagnosis of NPC in our study. Though Plasma EBV DNA detection is a promising and a possible biomarker for NPC as evident by many studies, a large lacuna of knowledge and questions remain to be answered in this part of the country as no studies of the association of EBV with NPC has been comprehensively conducted.

The development of a good NPC screening protocol including molecular techniques remains to be explored, in order to develop and contribute to the early detection of the disease and a favourable treatment outcome.

6. Abbreviations

EBV: Epstein-Barr virus, NPC: Nasopharyngeal carcinoma, EBC viral capsid antigen (EBV-VCA), EBV early antigen (EBV-EA), FNAC: Fine needle aspiration cytology.

7. Source of Funding

The authors did not receive any external financial aid for the study.

8. Conflict of Interest

The authors have no conflict of interest in this study.

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