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Review Article

Childhood Nasopharyngeal Carcinoma-A Brief Review

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare disease in most parts of the globe but particularly concentrates in China and Southeast Asia. In Bangladesh, we come across a significant number of cases of Childhood NPCs. Childhood nasopharyngeal carcinoma almost always have the undifferentiated variant of the disease, which is associated with advanced regional spread and distant metastasis. Both genetic and environmental factors contribute to the development of nasopharyngeal carcinoma. Because childhood NPC has close association with EBV infection, WHO type III histology, and very high incidence of advanced- stage disease, it should be treated as a distinct entity. It is important for our physicians to be aware of the possibility of the disease among our children. In this review paper authors discus the predisposing factors, pathogenesis, diagnostic tools and treatment pattern of Nasopharyngeal carcinoma in children.

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant condition arising from the epithelial lining of the nasopharynx, a structure situated within the area behind the nasal cavity. This is quite an inaccessible site. When a tumour develops here, the subjective signs are poor and usually they become evident only when it has progressed considerably. Early diagnosis is therefore very difficult.

Nasopharyngeal carcinoma is one of the few malignant tumours in childhood that emerge from the epithelium. It is distinguishable from the adult form of the disease due to its close association with Epstein-Barr virus (EBV) infection, its undifferentiated histology and the high incidence of regionally advanced disease.

Childhood nasopharyngeal carcinoma has distinct epidemiological, histopathological, and clinical characteristics. In pediatric population, most nasopharyngeal malignancies are histologically classified as Undifferentiated carcinoma and lymphoepithelial carcinoma.[1]

Pathophysiology

Environmental Factors

Occupational hazards including exposures to formaldehyde, dust and smoke particulate, and certain aromatic hydrocarbons, have been investigated as risk factors for nasopharyngeal cancer.[2]

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The consumption of salted fish and other salt-preserved foods, including eggs, leafy vegetables & roots, in early childhood has documented as a substantial risk for the development of nasopharyngeal cancer in Malaysian Chinese.[5]

Epstein-Barr Virus

The link between nasopharyngeal cancer and Epstein Barr virus was first observed in 1966, when the sera of patients with the malignancy were found to manifest precipitating antibodies against cells infected with the virus.[6]

Subsequent studies have described elevated levels of IgG and IgA antibodies directed against particular components with nasopharyngeal cancer.[7,8]

Genetic Susceptibility

Genetic susceptibility has also been proposed as a risk factor for the development of the disease. Haplotypes that have been associated with the malignancy include certain human leukocyte antigens (HLA), including HLA - A2, HLA - B 46 and HLA - B 58.[9]

Clinical Presentation

History

Nasopharyngeal carcinoma rarely comes to medical attention before it has spread to regional lymph nodes. Enlargement and extension of the tumour in the nasopharynx may result in symptoms of nasal obstruction (eg. congestion, nasal discharge, bleeding), change in hearing (usually associated with blockage of the Eustachian tube, but direct extension into ear is possible), and cranial nerve palsies (usually associated with extension of the tumour into the base of the skull).[10,11,12]

Physical Findings

The most common physical finding is a neck mass, which is observed in 80% of patients.[13] Painless firm lymph node enlargement is present. Neck involvement is often bilateral; the most common nodes involved are the jugulodigastric and upper and middle jugular nodes in the anterior cervical chain.

Another common presenting sign is unilateral serous otitis as a result of Eustachian tube occlusion by the primary tumour.[8]
Cranial nerve infiltration with resultant palsy may also be present.[8,14]

The differential diagnosis of nasopharyngeal cancer includes other nasopharyngeal or sinusoidal masses (eg. Lymphoma, including Hodgkin's disease and lethal midline reticulosis), Wegners granulomatosis and mucocele.

Histopathology

The World Health Organization (WHO) has classified NPC into three subtypes: Type I is keratinizing squamous cell carcinoma; Type II is a nonkeratinizing epidermoid carcinoma; and Type III is undifferentiated carcinoma. The neoplastic element is epithelial , although in tumours of WHO type II & III, lymphoid, plasmoid and eosinophilic cell infiltration is common. Type I is characterized by Keratin production. In Type II there are groups or bundles of cells with fusiform and oval nucleus and scant cytoplasm; Type IIa shows pleomorphism, whereas in Type IIb , lymphoid infiltration is prominent. In Type III, also referred to as lymphoepithelioma or Schminke tumour, undifferentiated round cells with prominent nucleoli are the major cell type. This subgroup is characterized by nonmalignant lymphoid penetration. Large nucleoli and eosinophilic cytoplasm are specific type IIIa, whereas small nucleoli and basophilic structure indicate type IIIb.[11,15] The most common histopathological type in children is WHO Type III.[16]

Diagnosis

Clinical examination reveals cervical lymphadenopathy, a nasopharyngeal mass mostly on the lateral or roof, or cranial nerve palsies. Computed tomography (CT) and magnetic resonance imaging (MRI) should be used to assess the extent of local tumour growth and base of skull involvement. MRI is more sensitive than CT for detection of the primary tumour and the extent of regional spread including nodal metastasis and perineural extension; CT is better than MRI for identification of bone erosion.[17]

Table I shows the histopathological classification systems for NPC.[15]

Classical scheme	WHO scheme	Cologne modification WHO
SCC, keratinising	SCC	Type I
SCC, non-keratinising	Non-keratinising Ca	Type IIa (NKC with no lymphoid infiltration)
Transitional cell Ca		
Intermediary cell Ca		
LymphoepithelialCa	Non-keratinising Ca	type IIb (NKC with lymphoid infiltration)
Undifferentiated Ca	Undifferentiated Ca	Type IIIa (undifferantiated)
(anaplastic)		
Clear-cell Ca		Ca with no lymphoid infiltration
Lymphoepithelial Ca		Type IIIb (undifferentiated)
(Schmincke type)		Ca with lymphoid infiltration

WHO- World health Organization ; SCC- squamous-cell carcinoma; Ca-carcinoma; NKC-non-keratinising carcinoma.

For a definitive diagnosis an endoscopic examination and a biopsy from primary tumour should be done.

Chest radiographs along with CT, bone scans, and liver ultrasonography are the main investigation procedures for evaluation of distant metastasis. An aspiration biopsy of Bone marrow should be done for patients with advanced disease and , for patients with base of skull involvement, a cytological analysis of cerebrospinal fluid samples is appropriate. Furthermore, complete blood counts, Serum lactic acid dehydrogenase (>500 IU / ml indicates poor prognosis), and liver function tests should be done. The American joint committee for cancer staging system [18] is commonly used for staging of NPC which is displayed in table-II.

Table-II

T stage Extent of primary tumour			
T1	Confined to nasopharynx		
T2	Extends to oropharynx or nasal cavity		
2a	Without parapharyngeal extension		
2b	With parapharyngeal extension		
T3	Invades bones paranasal sinuses		
T4	Involvement of cranial nerves, intracranial contents, infratemporal fossa, hypopharynx,or orbit		
N stage Lymph-node disease			
N0	No lymph-node metastases		
N1	Unilateral lymph node(s) < 6cm		
N2	Bilateral lymph nodes < 6 cm		
N3	Metastases in lymph nodes		
3a	Greater than 6 cm		
3b	With extension to the supraclavicular fossa		
M stage Distant metastases			
M0	Absent		
M1	Present		
Stage group	T stage	N stage	M stage
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
	T1-T3	N1	M0
III	T3	N0-1	M0
	T1-T3	N2	M0
IVA	T4	N0	M0
IVB	T1-4	N3	M0
IVC	T1-4	N0-3	M1

Treatment

A. Surgery

NPC is considered unresectable due to complex anatomical location only. However, radial neck dissection is appropriate if the primary tumour seems to be controlled and if persistent neck nodes following chemoradiation, or isolated recurrence in the neck occurs after radiotherapy.[3,10]

B. Radiotherapy

Nasopharyngeal cancer has traditionally been treated with full course radiotherapy. Treatment result are more favorable in early stage of disease. .Undifferentiated NPC, which is common in children, is very sensitive to radiation so external radiation therapy has been the mainstay of treatment.[16,22]With radiotherapy alone, 5 year survival has been reported as 20-60% in most paediatric series.[13,23] Doses of 50-70 GY directed to the primary tumour are recommended for patients older than 10 years and a 5-10% reduction in this dosage is recommended for children younger than 10 years of age.

C. Chemotherapy

In most childhood cancers, including EBV-related lymphoid malignant diseases, the use of radiotherapy is limited or substituted by systemic chemotherapy. The poor overall survival and high incidence of systemic failure in children with locally advanced NPC has led to the investigation of two different chemotherapy schedules; before(neoadjuvant) and after (adjuvant) radiotherapy.During the past 10 years, administration of adjuvant and neoadjuvant cisplantin based chemotherapy gained popularity. This approach is used with the aim of early eradication of microscopic disease and decrease in primary tumour mass before and after radiation.[13,15]

Most chemotherapy combinations used in paediatric series include Cisplatin plus Fluorouracil, Cisplatin plus Epirubicin and Bleomycin, Cisplatin plus Methotrexate and Fluorouracil, or Cisplatin plus Methotrexate,Bleomycin and Vinblastine.[24,25]

D. Immunotherapy

Due to the characteristic disturbed immunoregulation in patients with NPC, immunostimulative interferon therapy in addition to chemoradiotherapy is used. Several studies have shown that interferon-b has antitumour effects in EBV-positive NPC; it is antiproliferative and directly cytotoxic to tumour cells.[15]

Immunotherapy with anti-EBV T cells may be another promising approach in the treatment of EBV-related NPC.[26]

Conclusion

Childhood NPC is not a rare disease in this subcontinent. It is rather common in Southeast Asia and we often encounter these cases in our routine medical practice. The variations in incidence of NPC between different geographical and ethnic groups indicates that both genetic and environmental factors contribute to its development. The uniqueness of the disease extends to treatment policy and make NPC the only childhood disease in which radiotherapy is the primary treatment for locally and regionally confined stages. Also early administration of our effective chemotherapeutic agent is needed for treatment of Childhood NPC.

Because of a gradually increased incidence of the disease in this territory nasopharyngeal cancer should be kept in mind when signs or symptoms of ear , nose and throat disease are present in our patients.

References

1. Lombardi F, GasparíniM, Gianni C, De Marie M et al. Nasopharyngeal carcinoma in childhood. Med Pediatr Oncol 1982;10(3):243-50.
2. Farrow DC, Vaughan TL, Berwick M, Lyrich CF, et al. Diet and nasopharyngeal cancer in a low risk population.Int J Cancer 1998;78:675-79.
3. Vaughan TL, Stewart PA, Teschke K, Lynch CF, et al. Occupational exposure to formaldehyde and wood dust and nasopharyngeal cancer.Occup Environ Med 2000;57:376-84.
4. Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, et al. Occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers

among U S men aged 30-60.Am J Ind Med 2000;37:532-41.

5. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ et al. Nasopharyngeal carcinoma in Malaysian Chinese : salted fish and other dietary exposures. Int J Cancer 1998;77:228-35.

6. Old LJ, Boyse EA, Oettgen HF,de-Harven E et al. Precipitating antibody in human serum to an antigen present in cultured Burkitt's lymphoma cells. Proc Natl Acad Sci U S A 1966;56:1699-704.

7. Collins SL. Squamous cell carcinoma of the oral cavity and oropharynx in: Ballenger JJ,Snow JB,jr.eds. Otorhinolaryngology: head and neck surgery 15th ed.Media,Pa : Williums & Wilkins,1996:249-368.

8. Vasef MA,Ferlito A, Weiss LM.Nasopharyngeal carcinoma, with emphasis on its relationship to Epstein-Barr virus. Ann Otol Rhinol Laryngol 1997;106:348-56.

9. Ren EC, Chan SH. Human leukocyte antigens and nasopharyngeal carcinoma.Clin Sci [colch] 1996;91:256-58.

10. Cvitkovic E, Bachouchi M, Armand JP. nasopharyngeal carcinoma : biology, natural history and therapeutic implications. Hematol Oncol Clin North Am 1991: 5: 821-23.

11. Douglass EC, Pratt CB. managament of infrequent cancers of childhood. In: Pizzo PA, Poplac DG.(Eds) 1997;Principles and practice of pediatric oncology 3rd edn.pp.997-1003.

12. Corey JP, Nalbone VP, Ng BA. Anatomic correlates of acoustic rhinometry as measured by rigid nasal endoscopy. Otolaryngol Head Neck Surg 1999; 121: 572-76.

13. Serin M, Erkal H, Elhan AH, C□akmak A. Nasopharyngeal carcinoma in childhood and adolescence. Med Pediatr Oncol 1998; 31: 498-505.

14. Alton M, Find A, Dupuis O,Cvitcovic E et al. Undifferentiated nasopharyngeal cancer (UCNT). Current diagnostic and therapeutic aspects. Int J Radiat Oncol Biol Phys 1995;32: 859-77.

15. Mertens R, Granzen B, Lassay L, et al. Nasopharyngeal carcinoma in childhood and adolescence. Cancer 1997: 80: 951-59.

16. Ayan I, Altun M. Nasopharyngeal carcinoma in children: retrospective review of 50 patients. Int J Radiat Oncol Biol Phys 1996; 35: 485-92.

17. Chan ATC, Teo PML, Johnson PJ. Nasopharyngeal carcinoma. Annal Oncol 2002; 13: 1007-15.

18. Fleming ID, Cooper J, Henson DE, et al. American Joint Committee on Cancer cancer staging manual. 1997; Philadelphia: Lippincott-Raven.

19. Geara FB, Sanguineti G, Tucker SL,Garden AS, et al. Carcinoma of the nasopharynx treated by radiotherapy alone : determinants of distant metastasis and survival. Radiother Oncol 1997; 43: 53-61.

20. Decaussin G, Lammali FS, Turenne-Tessier M, et al. Expression of BARF1 gene encoded by Epstein-Barr virus in nasopharyngeal carcinoma biopsies. Cancer Res 2000; 60: 5584-88.

21. Vokes EE,Liebowitz DN,Weichselbaum RR. Nasopharyngeal Carcinoma.Lancet 1997;350 : 1087-91

22. Sham JST, Poon YF, Wei WI, Choy D. Nasopharyngeal carcinoma in young patients. Cancer 1990; 65 : 2606-10.

23. Preciado MV, Chabay PA, Mattew EN, et al. Epstein Barr virus associated paediatric nasopharyngeal carcinoma: its correlation with p53 and BCL-2 expression. Med Paediatric Oncol 2002; 38: 345-48.

24. Jenkin RDT, Anderson JR, Jereb B, et al. Nasopharyngeal carcinoma - a retrospective review of patients less than thirty years of age : a report of children's Cancer study group. Cancer 1981;47: 360-66.

25. Gasparini M, Lombardi F, Rottoli L, et al. Combined radiotherapy and chemotherapy in stage T3 and T4 nasopharyngeal carcinoma in children.J Clin Oncol 1988;6: 491-94.

26. Lee SP, Chan ATC, Cheung ST, et al. Cytotoxic T lymphocyte control of Epstein-Barr virus in Nasopharyngeal carcinoma(NPC): EBV-specific CTL response in the blood and tumour of NPC patients and the antigen processing function of the tumour cells. J Immunol 2000;165: 573-82.

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