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Case Report

Familial clustering of nasopharyngeal carcinoma in the family of an adolescent with nasopharyngeal carcinoma

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ABSTRACT

Background. Nasopharyngeal carcinoma (NPC) is one of the rare malignant diseases of childhood, of which only 1% occurs in children. In recent years, genetic factors have attracted attention in NPC. A very limited data have been reported about clustering within families.

Case. Herein, the familial clustering of nasopharyngeal carcinoma in the family of an adolescent with nasopharyngeal carcinoma is presented.

Conclusions. There is familial clustering in nasopharyngeal carcinoma (NPC), but our knowledge on this subject is limited, especially in children or adolescent populations. Therefore, we should be more careful in NPC in childhood, especially in first-degree relatives.

Key words: adolescent, nasopharyngeal carcinoma, familial nasopharyngeal carcinoma.

Nasopharyngeal carcinoma (NPC) is one of the rare malignant diseases of childhood, of which only 1% occurs in children.[1] Some subjects in NPC are well known, including geographical and ethnic distribution, the bimodal age distribution in some countries, a 2-3 times higher diagnosis in males than females, and the association with Epstein-Barr virus (EBV). NPC is common in Southern China, Southeast Asia, the Mediterranean basin countries, and Alaska but rarer in Japan, Europe, and North America. It is bimodal in some populations in North America and the Mediterranean region. Moreover, the similarity between age distribution patterns has been hypothesized to be related to the similarity of latency patterns as in NPC and Hodgkin lymphoma.[2]

In recent years, genetic factors have attracted attention in NPC.[3] A very limited data have been reported about clustering within families.[4-9] Studies suggest that having a first-degree relative with NPC increases the risk of NPC sevenfold, and therefore recommend screening for NPCs among first-degree relatives.[5,10] The rate of familial NPC was reported as 15.5%. Additionally, the influence was more common among siblings, with a relatively short interval between affected siblings.[5] Studies associated NPC with human leukocyte antigens (HLA) and emphasized a possible relationship between NPC and especially human leukocyte antigen (HLA-A).[11-13] In a genome-wide search conducted in families at high risk for NPC, the evidence of a major susceptibility locus for NPC on chromosome 4 in a subset of families was determined.[14] However, our knowledge of NPC and genetics is quite limited. Additionally, familial clustering has not been emphasized much in childhood NPC series.[15-18]

Herein, familial clustering of NPC in the family of an adolescent with NPC is presented with a related literature review.

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Case Report

A 17-year-old male applied to the dentist because of new-onset toothache and neck swelling. The patient was referred to our hospital after the dentist detected a mass. The patient's medical history was unremarkable, but his family history revealed that one of his aunts and two uncles had NPC and one of his uncles died due to NPC (Fig. 1). Initial physical examination revealed a firmly fixed mass of 70 × 80 mm in the left angle of the mandible and 50 × 30 mm conglomerated lymphadenopathy in the left cervical region. Additionally, the oropharyngeal examination determined an anteriorly deviated left tonsil due to the mass. The patient did not have any other findings including café au lait spot on physical examination. The complete blood count and biochemical analyses were within normal limits.

The imaging studies revealed a normal chest computed tomography. Computed tomography and magnetic resonance imaging (MRI) revealed a 65 × 55 × 45 mm mass on the left side of the nasopharynx, which obstructs the torus tubarius and eustachian tube (Fig. 2). Additionally, 35 × 25 mm conglomerated lymphadenopathy was detected in the left submandibular and upper cervical region. 18-F FDG PET/CT images revealed a mass on the left of the nasopharynx (SUV_{max}: 15) and lymphadenopathies (SUV_{max}: 16.2) in the area that extend to the left parapharyngeal in the left upper and lower cervical region.

Undifferentiated NPC was diagnosed from the pathological examination of the nasopharyngeal mass biopsy. The patient was staged as IVA (T4N1M0) according to the American Joint Committee on Cancer NPC staging classification after a metastatic work-up completion. Polymerase chain reaction analysis of EBV DNA in the sera was 33,000 ug/dL (N: 0–1000 ug/dL). The patient was instituted on an NPC chemotherapy regimen containing cisplatin, docetaxel, and 5-fluorouracil.[18] Complete response was achieved after the fourth cycle of chemotherapy. Intensity-modulated radiotherapy (IMRT) with megavoltage (6 MV photon) radiotherapy was delivered once daily to the primary tumor and regional lymph nodes. The gross tumor volume included the disease in the primary lesion and cervical lymph nodes as observed on MRI studies with gadolinium contrast (T1 and T2 sequences). The clinical target volume included the gross tumor volume and all sites of potential subclinical disease with 1-cm margins. An additional margin of 3 mm (depending on local policy) was added to define the planning target volume. The primary tumor received a total dose of 70 Gy and 66 Gy for those with involved left level IB and II cervical lymph nodes. All nasopharyngeal regions, including

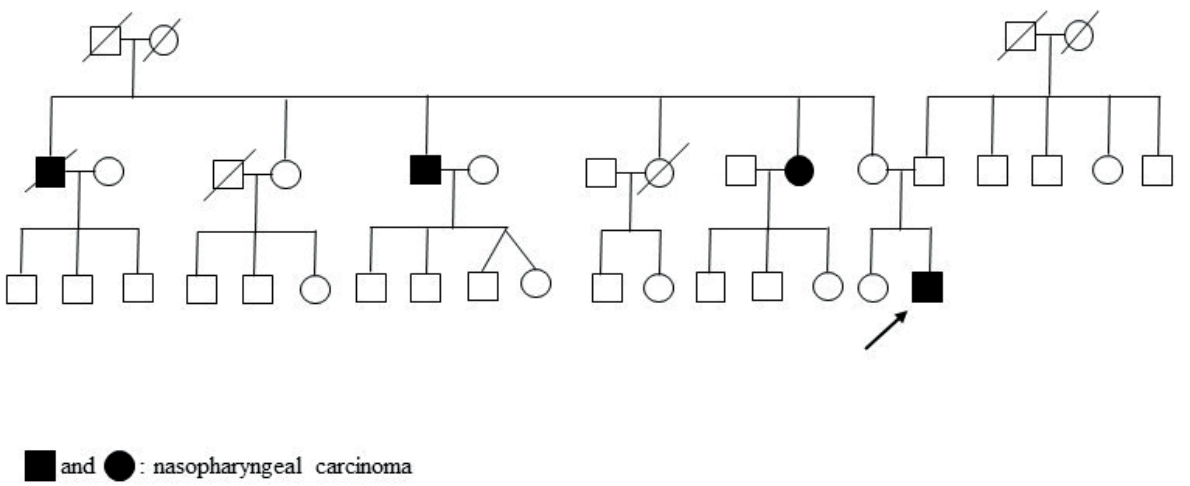

Fig. 1. The familial clustering of nasopharyngeal carcinoma on the patient's pedigree.

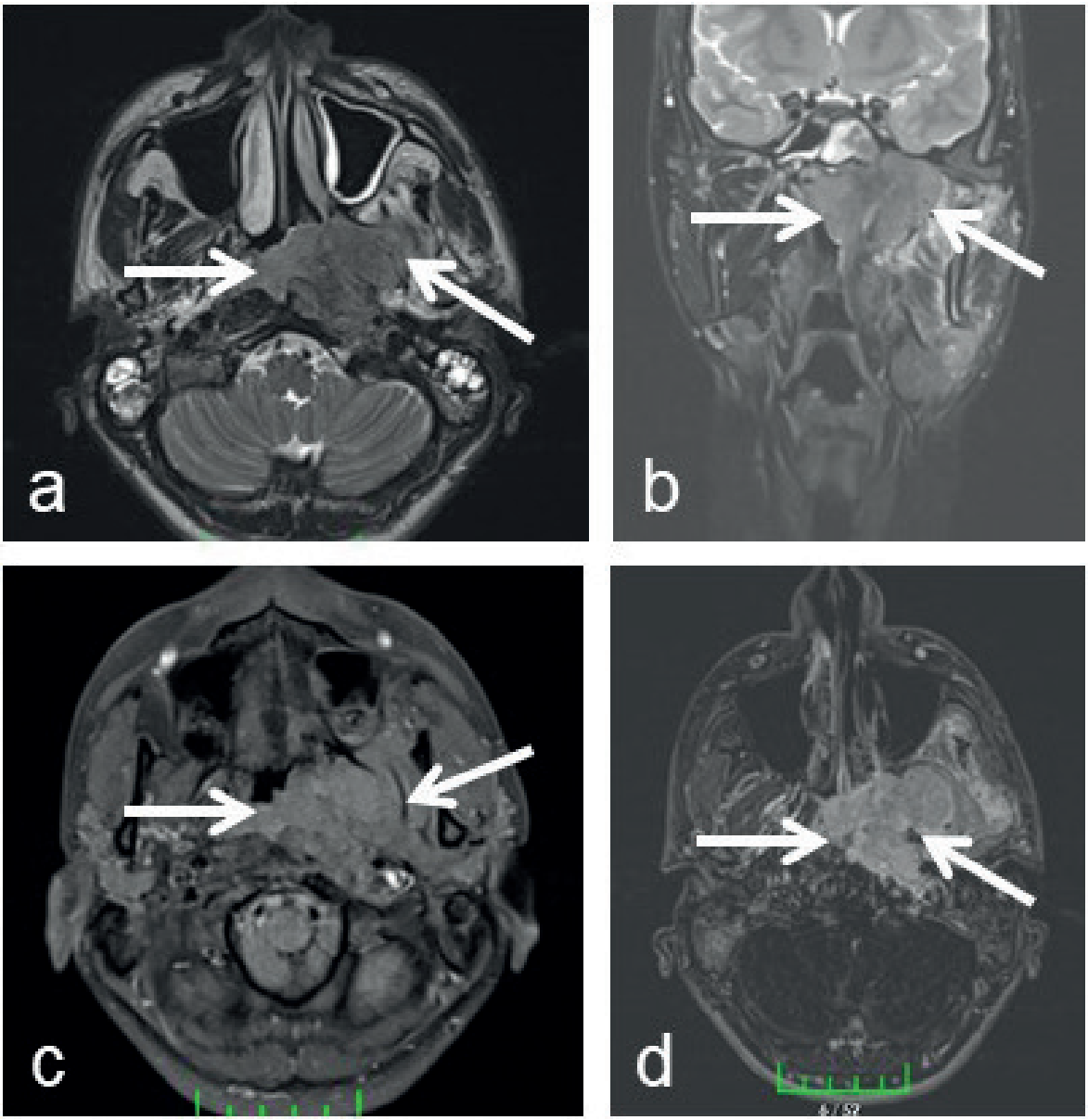

Fig. 2. Axial T2 (a), coronal T2 (b), fat-suppressed precontrast axial T1 (c), fat-suppressed postcontrast axial T1-weighted images (d) show a mass lesion filling the nasopharynx with marked contrast enhancement.

clivus and skull base, received a total dose of 60 Gy, whereas uninvolved regional lymphoid areas were irradiated with a total dose of 54 Gy with a simultaneous integrated boost technique for 33 fractions. The patient has been in follow-up for 6 months with the tumor-free disease.

Our patient, his uncle, and his aunt were taken into genetic analysis. However, mutations in known cancer susceptibility genes including *APC, ATM, BARD, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PRSS1, PTEN, RAD50, RAD51C, RAD51D, SLX4, SMAD4, STK11, TP53*, and *VHL* were not detected.

Written consent for publication of this case report and accompanying images was obtained from the patient and the parents of the patient.

Discussion

NPC is a rare malignant childhood disease, with interesting epidemiological features, such as geographic and ethnic distribution, gender and age distribution, and secular trend, and etiological features such as EBV, Human Papillomavirus (HPV), diet, and heredity.[1,3]

NPC is endemic in Southern China, including Hong Kong, whereas rare in the United States and Western Europe. Southeast Asia, North Africa, the Middle East, and the Arctic are intermediate-risk regions. The age distribution has peaked in the sixth decade in high-risk regions; bimodal age distribution can be seen in some regions, such as Southeast Asia, the Middle East/North Africa, and the United States (minor first peak in adolescents and young adults); and its incidence increases with age in low-risk regions. The median age of diagnosis is 13 years and the first peak of incidence in childhood is 10-20 years. The age distribution is different in these endemic regions. Children under the age of 16 years account for 1–2% of all NPC in China, while in the Mediterranean basin and Africa they account for 10-18%. Sex ratio ranges from 1.7 to 4.8 in the pediatric series. The geographic variation of NPC supports the fact that it develops with a multifactorial etiology.[19,20]

Viral infections, EBV, lifestyles, and especially dietary habits are among the main causes of high-risk incidence in endemic or intermediate-risk regions.[1,3] In endemic populations, the risk appears to be due to an interaction of several factors: EBV infection, environmental factors (such as high consumption of preserved foods and smoking), and genetic predisposition. In addition, the increased incidence in younger adults in high- and intermediate-risk areas suggests that exposure to a common pathogen at a young age is a determining factor.[3,21] In the last few decades, a decreased incidence of NPC has been observed in some endemic areas such as Hong Kong, Singapore, and Taiwan. The reasons for this decline are not exactly known; however, the role of lifestyle changes associated with rapid economic development is considered.[22]

There is ample evidence supporting the role of EBV as a primary etiologic agent in the pathogenesis of nasopharyngeal carcinoma. This includes detection of gene expression of both EBV DNA and EBV in precursor lesions and tumor cells, and it is also important that the nonkeratinizing subtype accounts for most cases in endemic areas (> 95%) and is predominantly associated with EBV infection.[23] Another viral pathogen less associated with nasopharyngeal carcinoma is HPV, and this pathogen is usually observed in nonendemic areas.[24] Dietary habits which contain salt-cured food, high consumption of preserved or fermented foods can lead to NPC. Because they contain high levels of nitrosamines that are direct genotoxins and EBV reactivating substances.[3]

In NPC, heredity is also emphasized, although detailed information is limited about its etiopathogenesis, unlike EBV and diet.[1,3] However, in recent years, rare publications on genetic clusters increased interest in genetics in NPC. Some NPC-associated chromosomes have also been reported. These are 3p21.31-21.2, 4p15.1-q12, and 4.[6,14] The rate of familial NPC was reported as 15.5%. Additionally, the influence was more common among siblings, with a relatively short interval between affected siblings.[5] For example, a case-control study from Taiwan suggests that having a first-degree relative with NPC increases the risk sevenfold.[10] A study from Sweden, where NPC is not endemic, investigated the cancer risk in the relatives of patients with NPC and revealed that relatives of NPC propands are at risk for both NPC and other cancers. Additionally, they concluded that the environmental risk factors, such as EBV infection and smoking, could explain this association, but that the shared genetic predisposition should not be ignored.[9] Another study emphasized the risk factors of NPC, such as environmental factors and dietary habits, as well as the possible association of *CYP2E1* polymorphism with familial NPC.[8,25] There were familial clusters; however, no

difference was found between familial and sporadic cases in demographic and clinical features.[10]

Generally, screening for first-degree relatives, especially siblings, of individuals with NPC is recommended; however, more information is necessary on NPC and genetics.

No familial NPC was reported in the large childhood NPC series from Turkey.[15-17,26] Herein, we present the familial clustering of NPC in the family of an adolescent with NPC. To our knowledge, it is the first reported familial NPC cluster in Turkey. However, so far, mutations in known cancer susceptibility genes were not detected.

In conclusion, there is familial clustering in NPC, but our knowledge on this subject is limited, especially in children or adolescent populations. Therefore, we should be more careful in NPC in childhood, especially in first-degree relatives.

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Ethical approval

Written consent for publication of this case report and accompanying images was obtained from the patient and the parents of the patient.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YK, BK, AOÇ; data collection: MD, BK; analysis and interpretation of results: YK; draft manuscript preparation: YK, BK, KE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. Lancet Oncol 2003; 4: 13-21. https://doi.org/10.1016/s1470-2045(03)00956-2
2. Barista I, Varan A, Ozyar E. Bimodal age distribution in Hodgkin's disease and nasopharyngeal carcinoma. Med Hypotheses 2007; 68: 1421. https://doi.org/10.1016/j.mehy.2006.11.014
3. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. Lancet 2016; 387: 1012-1024. https://doi.org/10.1016/S0140-6736(15)00055-0
4. Jia WH, Feng BJ, Xu ZL, et al. Familial risk and clustering of nasopharyngeal carcinoma in Guangdong, China. Cancer 2004; 101: 363-369. https://doi.org/10.1002/cncr.20372
5. Loh KS, Goh BC, Lu J, Hsieh WS, Tan L. Familial nasopharyngeal carcinoma in a cohort of 200 patients. Arch Otolaryngol Head Neck Surg 2006; 132: 82-85. https://doi.org/10.1001/archotol.132.1.82
6. Venugopal R, Bavle RM, Konda P, Muniswamappa S, Makarla S. Familial cancers of head and neck region. J Clin Diagn Res 2017; 11: ZE01-ZE06. https://doi.org/10.7860/JCDR/2017/25920.9967
7. Huang SF, Hsiao JH, Young CK, et al. Familial aggregation of nasopharyngeal carcinoma in Taiwan. Oral Oncol 2017; 73: 10-15. https://doi.org/10.1016/j.oraloncology.2017.07.020
8. Yang XR, Diehl S, Pfeiffer R, et al. Evaluation of risk factors for nasopharyngeal carcinoma in high-risk nasopharyngeal carcinoma families in Taiwan. Cancer Epidemiol Biomarkers Prev 2005; 14: 900-905. https://doi.org/10.1158/1055-9965.EPI-04-0680
9. Liu Z, Fang F, Chang ET, Ye W. Cancer risk in the relatives of patients with nasopharyngeal carcinoma-a register-based cohort study in Sweden. Br J Cancer 2015; 112: 1827-1831. https://doi.org/10.1038/bjc.2015.140
10. Ung A, Chen CJ, Levine PH, et al. Familial and sporadic cases of nasopharyngeal carcinoma in Taiwan. Anticancer Res 1999; 19: 661-665.

11. Hildesheim A, Apple RJ, Chen CJ, et al. Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 2002; 94: 1780-1789. https://doi.org/10.1093/jnci/94.23.1780

12. Lu CC, Chen JC, Jin YT, Yang HB, Chan SH, Tsai ST. Genetic susceptibility to nasopharyngeal carcinoma within the HLA-A locus in Taiwanese. Int J Cancer 2003; 103: 745-751. https://doi.org/10.1002/ijc.10861

13. Hu SP, Day NE, Li DR, et al. Further evidence for an HLA-related recessive mutation in nasopharyngeal carcinoma among the Chinese. Br J Cancer 2005; 92: 967-970. https://doi.org/10.1038/sj.bjc.6602347

14. Feng B-J, Huang W, Shugart YY, et al. Genome-wide scan for familial nasopharyngeal carcinoma reveals evidence of linkage to chromosome 4. Nat Genet 2002; 31: 395-399. https://doi.org/10.1038/ng932

15. Serin M, Erkal HS, Halil Elhan A, Çakmak A. Nasopharyngeal carcinoma in childhood and adolescence. Med Pediatr Oncol 1998; 31: 498-505. https://doi.org/10.1002/(sici)1096-911x(199812)31:6<498::aid-mpo6>3.0.co;2-o

16. Küpeli S, Varan A, Ozyar E, et al. Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. Pediatr Blood Cancer 2006; 46: 454-458. https://doi.org/10.1002/pbc.20433

17. Ozyar E, Selek U, Laskar S, et al. Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma: a Rare Cancer Network study. Radiother Oncol 2006; 81: 39-46. https://doi.org/10.1016/j.radonc.2006.08.019

18. Casanova M, Özyar E, Patte C, et al. International randomized phase 2 study on the addition of docetaxel to the combination of cisplatin and 5-fluorouracil in the induction treatment for nasopharyngeal carcinoma in children and adolescents. Cancer Chemother Pharmacol 2016; 77: 289-298. https://doi.org/10.1007/s00280-015-2933-2

19. Casanova M, Bisogno G, Gandola L, et al. A prospective protocol for nasopharyngeal carcinoma in children and adolescents: the Italian Rare Tumors in Pediatric Age (TREP) project. Cancer 2012; 118: 2718-2725. https://doi.org/10.1002/cncr.26528

20. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al. Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. Cancer 2005; 103: 850-857. https://doi.org/10.1002/cncr.20823

21. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15: 1765-1777. https://doi.org/10.1158/1055-9965.EPI-06-0353

22. Lee AWM, Foo W, Mang O, et al. Changing epidemiology of nasopharyngeal carcinoma in Hong Kong over a 20-year period (1980-99): an encouraging reduction in both incidence and mortality. Int J Cancer 2003; 103: 680-685. https://doi.org/10.1002/ijc.10894

23. Young LS, Dawson CW. Epstein-Barr virus and nasopharyngeal carcinoma. Chin J Cancer 2014; 33: 581-590. https://doi.org/10.5732/cjc.014.10197

24. Huang WB, Chan JYW, Liu DL. Human papillomavirus and World Health Organization type III nasopharyngeal carcinoma: multicenter study from an endemic area in Southern China. Cancer 2018; 124: 530-536. https://doi.org/10.1002/cncr.31031

25. Hildesheim A, Anderson LM, Chen CJ, et al. CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 1997; 89: 1207-1212. https://doi.org/10.1093/jnci/89.16.1207

26. Kebudi R, Buyukkapu SB, Gorgun O, et al. Nasopharyngeal carcinoma in children: Multimodal treatment and long-term outcome of 92 patients in a single center over a 28-year period. Pediatr Blood Cancer 2021; 68: e29372. https://doi.org/10.1002/pbc.29372