

EBV-positive large-cell and small-cell neuroendocrine carcinoma of the nasopharynx: A case report and review of the literature

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Abstract. Neuroendocrine carcinoma (NEC) of the nasopharynx is rare and its clinical and pathologic characteristics have remained to be fully elucidated. The present study reported on a case of Epstein-Barr virus (EBV)-positive NEC of the nasopharynx that exhibited features of large-cell NEC and small-cell NEC, as confirmed by immunohistochemical staining. The patient received three cycles of induction chemotherapy (with docetaxel-cisplatin) that was followed by concurrent chemoradiotherapy (a total of 70 Gy delivered in 33 fractions). Remission of the tumor was achieved and no recurrence or metastasis was detected 6 months after treatment. This is the first report of a patient with EBV-positive large-cell and small-cell NEC of the nasopharynx. The patient achieved good complete remission. Based on the features of this case and a literature review, it was concluded that immunohistochemical staining is important for the differential diagnosis of NEC. Furthermore, there is currently no standard treatment and thus, further clinical information on similar cases is required to optimize treatment outcomes.

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in North Africa, Southeast Asia and, most notably, South China (1). According to the current World Health Organization (WHO) classification of pathological subtypes, NPCs are grouped

into i) non-keratinizing squamous cell carcinoma, ii) keratinizing squamous cell carcinoma and iii) basaloid squamous cell carcinoma (2). The first group is further subdivided into non-keratinizing differentiated carcinoma and non-keratinizing undifferentiated carcinoma, which is dominant in endemic areas (2,3). Neuroendocrine carcinoma (NEC) is a poorly differentiated neuroendocrine neoplasm that is classified as small-cell NEC and large-cell NEC and may occur in the nasopharyngeal area (4). However, the recent WHO classification of nasopharyngeal malignant epithelial tumors does not include NEC (2). According to the 5th edition of the WHO Classification of Head and Neck Tumors, the literature so far indicates that the larynx is the most common site of occurrence of NECs of the head and neck and accounts for 60% of all head and neck NECs (4). The sinonasal tract is a distant second and accounts for 35%; however, unpublished observations and day-to-day clinical experience may significantly contradict these statistics and indicate that the sinonasal tract is the single most common site of occurrence of head and neck NECs (4). However, to the best of our knowledge, only sporadic cases of nasopharyngeal NECs have been reported (5-22). The present study contributed to the literature and statistics on nasopharyngeal NEC by describing a rare case of high-grade nasopharyngeal NEC that exhibited features of large-cell NEC and small-cell NEC and compared the present case with previously reported cases. In addition, an updated review of nasopharyngeal NECs reported in the literature up to May 2022 was provided.

Case report

A 34-year-old female visited the ear, nose and throat clinic of Panyu Central Hospital (Guangzhou, China) in September 2021, due to paroxysmal pain in the cheek for nearly half a year. Nasopharyngeal examination revealed a lump with an irregular surface. Biopsy of the nasopharyngeal mass and examination of the sample indicated that the mass contained invasive cancerous cells arranged in clumps with eosinophilic cytoplasm. Tumor tissue specimens were fixed, sectioned and stained according to standard procedures. Hematoxylin and eosin staining was performed on the tissue samples. This was followed by immunohistochemical staining in an automated Roche BenchMark1 instrument (Roche Diagnostics) according to the manufacturer's instructions with standard positive and negative controls using the following mouse monoclonal

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Abbreviations: NPC, nasopharyngeal carcinoma; WHO, World Health Organization; NEC, neuroendocrine carcinoma; CK, cytokeratin; NSE, neuron-specific enolase; TTF-1, thyroid transcription factor-1; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; MRI, magnetic resonance imaging; EGFR, epidermal growth factor receptor

Key words: nasopharyngeal carcinoma, neuroendocrine carcinoma, large-cell neuroendocrine carcinoma, small-cell neuroendocrine carcinoma, Epstein-Barr virus

antibodies: CD56 (cat. no. MAB-0743), synaptophysin (cat. no. MAB-0742), cytokeratin (CK; cat. no. MAB-0671), Ki-67 (cat. no. MAB-0672), neuron-specific enolase (NSE; cat. no. MAB-0791; all from Fuzhou Maixin Biotech Co., Ltd.) and thyroid transcription factor-1 (TTF-1; cat. no. ZM-0270; OriGene Technologies, Inc.). The expression of epidermal growth factor receptor (EGFR) was tested by using rabbit monoclonal antibody (RMA-0804, Fuzhou Maixin Biotech Co., Ltd.). All the antibodies were ready-to-use and optiview diaminobenzidine (DAB) Immunohistochemistry (IHC) Detection kit (Roche) was used, which was conducted according to the manufacturer's instructions. The nuclei of the tumor cells were large, hyperchromatic or vacuolar, with partially visible nucleoli and obvious heterogeneity (Fig. 1). The Ki-67 index was high at 80%. The cells were immunopositive for CD56, synaptophysin and CK, and negative for NSE and TTF-1 (Fig. 2). Based on these features, the nasopharyngeal lump was identified as a high-grade neuroendocrine carcinoma that exhibits the features of large-cell NEC and small-cell NEC. *In situ* hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) (23), which was performed with an EBER detection kit (ISH-7001; OriGene Technologies, Inc.) according to the manufacturer's instructions, indicated that the sample was positive for EBER (Fig. 2).

The patient was admitted for clinical staging of the carcinoma. Magnetic resonance imaging of the nasopharynx and neck confirmed the presence of a massive lump (42x49x31 mm) in the nasopharynx that had invaded the bone of the skull base and cavernous sinus, and also involved the right retropharyngeal lymph node and right cervical lymph node (Fig. 3). Computed tomography (CT) imaging of the chest and abdomen did not reveal anything remarkable and no tumors were found at any other sites. Based on these findings, the tumor was staged as T4N1M0 and the patient received three cycles of induction chemotherapy (with docetaxel-cisplatin) that was followed by concurrent chemoradiotherapy with triweekly cisplatin and a total dose of 70 Gy delivered in 33 fractions. The treatment was well tolerated and the patient completed the scheduled treatment. The patient was followed up every three months in the first two years after treatment. Remission of the tumor was achieved and no recurrence or metastasis was detected 6 months after the treatment (Fig. 4).

Literature review

The PubMed database was searched for articles published up to May 2022 in any language, as well as their references, using the following search terms: 'Neuroendocrine carcinoma', 'small cell cancer', 'small cell neuroendocrine carcinoma', 'large cell cancer', 'large cell neuroendocrine carcinoma', 'nasopharynx' and 'nasopharyngeal cancer'. The epidemiologic features, therapeutic strategies and survival status of the reported cases, including the present case, were collected and summarized.

Discussion

The present study described a rare case of EBV-positive large-cell and small-cell NEC of the nasopharynx. To the best of our knowledge, this is the first reported case of

nasopharyngeal NEC that exhibits the features of large-cell and small-cell carcinomas.

The literature review revealed that in a population-based study, only 60 cases of nasopharyngeal small-cell carcinoma were identified among 13,993 cases of nasopharyngeal cancer that were extracted from the Surveillance, Epidemiology, and End Results database, and there are only 16 literature reviews on nasopharyngeal small-cell carcinoma (9). Furthermore, another five cases were reported, including one case of non-small cell neuroendocrine carcinoma and four cases of EBV-positive large-cell neuroendocrine carcinoma (6,10,13,15,19). In addition, one case of human papillomavirus-associated small-cell carcinoma was reported (22). The present case was confirmed based on positive immunostaining for CD56, synaptophysin and CK. TTF-1 has been found to be positive in cases of extrapulmonary small-cell carcinoma, but the tumor in the present case was negative for TTF-1. The patient of the present study was finally diagnosed as having high-grade NEC with the features of large-cell and small-cell NEC after a number of consultations with pathologists, and it was thus distinguished from previously reported cases of NEC (5-22). In the present case, the tumor was in a locally advanced stage and had a high Ki-67 index, which is regarded as a marker of cell proliferation, aggressive biological behavior and poor prognosis (24,25). The median overall survival of patients with small-cell carcinoma of the nasopharynx is 18 months, which is much shorter than that of patients with nasopharyngeal carcinoma (9). In the present case, the patient responded well to the treatment and no tumor recurrence was noted at the 6-month follow-up. However, given its poor prognosis, consistent and careful follow-up is warranted in this case.

EBV infection is common worldwide and is associated with infectious mononucleosis, Burkitt's lymphoma, classical Hodgkin's lymphoma, gastric cancers and NPC (26). Almost 98% of NPC cases are closely related to EBV infection (27), which may promote the progression of NPC (28). A large number of studies have indicated that the level of free EBV DNA in the plasma of patients with NPC is highly correlated with its prognosis and is widely used as a clinical marker in the clinical diagnosis and monitoring of NPC (1,29). In the present case, the carcinoma was positive for EBER. This indicates that it may be related to EBV infection. However, the carcinoma was consistently negative for plasma EBV DNA during the diagnosis and treatment process, probably due to the sensitivity, specificity and accuracy of plasma EBV DNA detection at our hospital. There is no internationally recognized EBV DNA standardized testing process and comparatively large interlaboratory variability, even for the same assay using identical procedures without harmonization (1,30,31). Furthermore, in previous studies, small-cell cancers were not associated with EBV infection (5,9,11,22), while non-small cell cancers, including large-cell cancers, were associated with EBV infection (6,10,13,15,19). Therefore, it was still confirmed that NEC was associated with EBV infection in the present case.

In the present case, the tumor was negative for EGFR. In contrast to the present findings, it has been reported that EGFR overexpression is a potential prognostic biomarker for advanced-stage patients with a poor outcome and is relatively common in NPC (32). Furthermore, EGFR is highly expressed in EBV-infected cells and may promote the

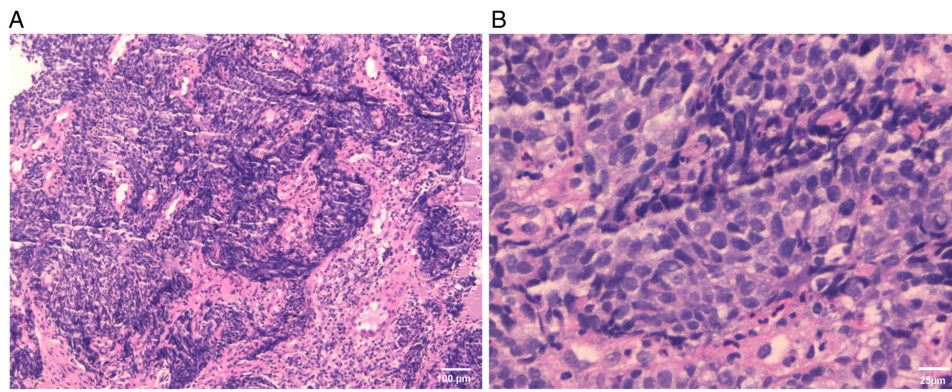


Figure 1. Morphological features of the tumor cells. The nuclei of the tumor cells were large, hyperchromatic or vacuolar, with partially visible nucleoli and obvious heterogeneity. (A) Magnification, x100; scale bar, 100 μ m. (B) Magnification, x400; scale bar, 25 μ m.

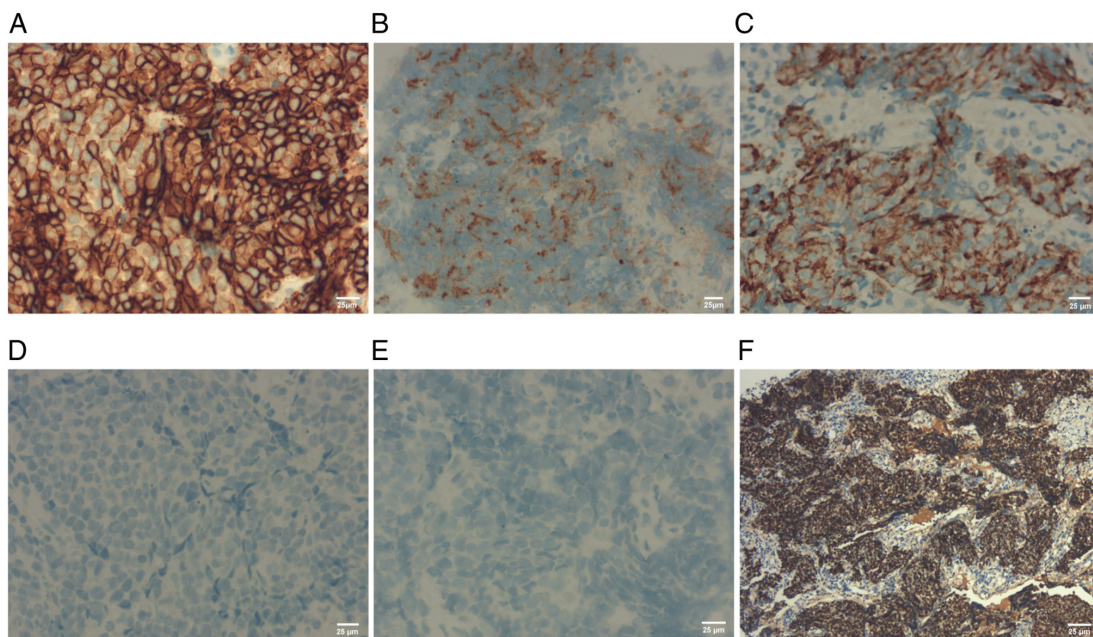


Figure 2. Immunohistochemical features of the tumor. The tumor was immunopositive for (A) CD56, (B) synaptophysin and (C) CK and negative for (D) NSE and (E) TTF-1. (F) The tumor was positive for EBV according to the result of *in situ* hybridization (magnification, x400; scale bars, 25 μ m). CK, cytokeratin; NSE, neuron-specific enolase; TTF-1, thyroid transcription factor-1; EBV, Epstein-Barr virus; EBER, Epstein-Barr virus-encoded RNA.

neoplastic transformation of EBV-positive cells; importantly, EGFR may be necessary for the internalization and fusion of EBV in NPC cells (28). However, only a small amount of information regarding EGFR expression is available (5-22), despite non-small cell cancers, including large-cell cancers, being associated with EBV infection (6,10,13,15,19). These results indicate that the biological behaviors of NECs of the nasopharynx may be different from those of common nasopharyngeal carcinomas. Therefore, their diagnosis requires further investigation into the biological behaviors through the study of additional cases in the future.

Due to its rarity, the treatment of NEC of the nasopharynx is challenging. The current strategies include chemotherapy and radiotherapy, and surgery is also considered in patients with early-stage NEC (9,14). Based on the findings of a population-based study, patients who received radiotherapy had prolonged overall survival and the radiotherapy dose was >60 Gy in most cases (9). Furthermore, most of the

reported cases were treated with radiotherapy (with a dose 70 Gy in the majority of the cases) and chemotherapy (with cisplatin-etoposide treatment in most cases) (10,12,15,16,22). However, most of the chemotherapy regimens have been described for small-cell cancer of the lung, for which the classic and conventional chemotherapy regimens include cisplatin-etoposide and cisplatin-irinotecan, which are regarded as first-line chemotherapy regimens. Paclitaxel, docetaxel and other regimens are also effective for lung small-cell cancer (33,34). By contrast, there is no consensus regarding treatment strategies for large-cell NEC. Typically, patients with lung large-cell NEC receive the same treatment as patients with non-small cell carcinoma, with the cisplatin-etoposide regimen being one of the most common choices (35,36). The docetaxel-cisplatin regimen is recommended by the guidelines for nasopharyngeal carcinomas according to the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology (37).

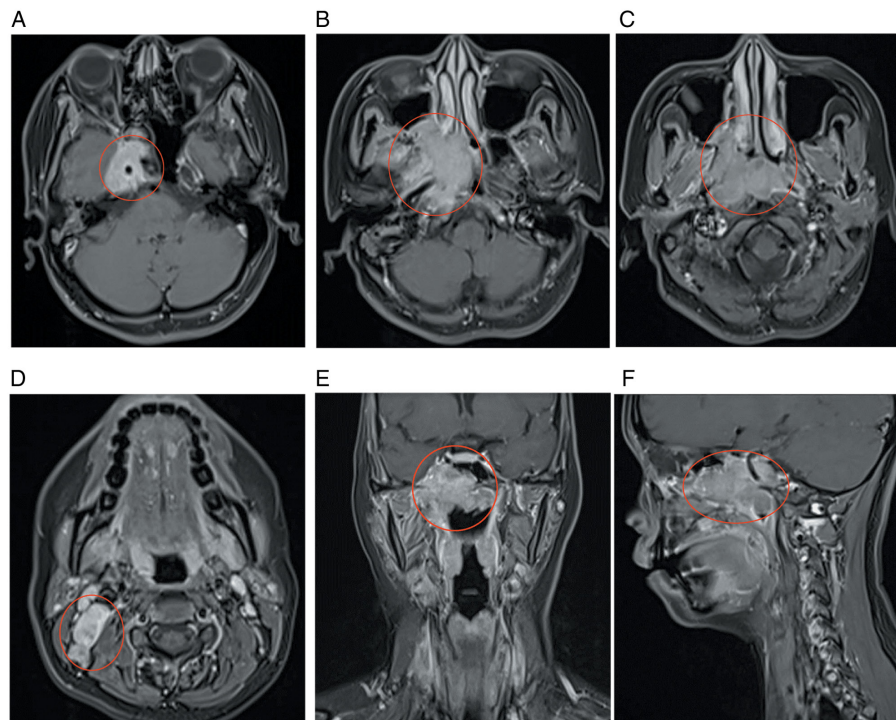


Figure 3. Pretreatment MRI findings of the patient. The scan depicted a lump in the nasopharynx that had invaded the bone of the skull base and cavernous sinus and also involved the right retropharyngeal lymph node and right cervical lymph node (in red circles). (A) Tumor invaded cavernous sinus and (B) the tumor invaded the bone of the skull base. (C) The lump in the nasopharynx in transverse section. (D) The right cervical lymph node. (E) The lump of nasopharynx in coronal section. (F) The lump of nasopharynx in sagittal section.

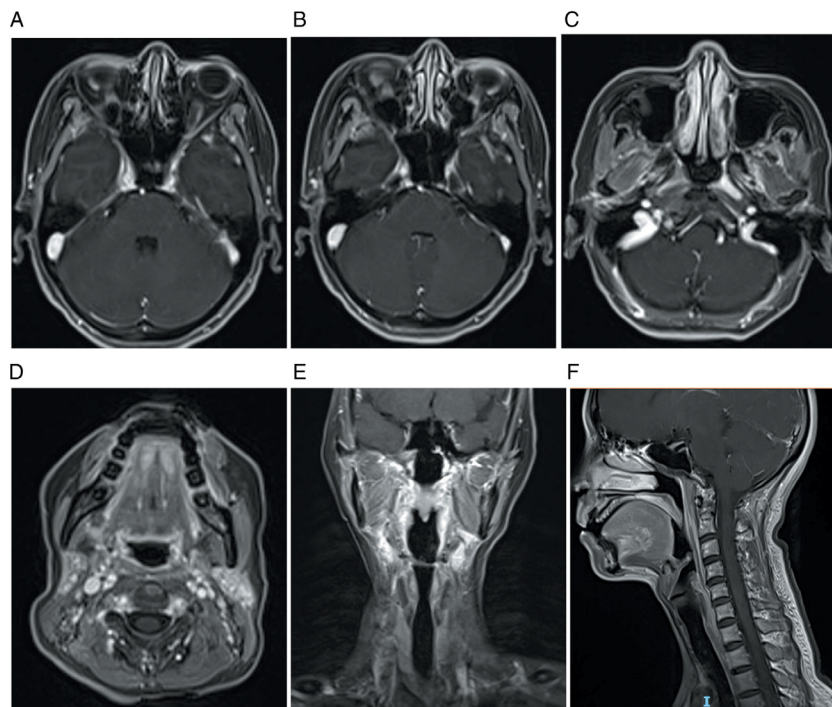


Figure 4. Posttreatment MRI findings of the patient. MRI scans taken 6 months after treatment indicated complete remission of the tumor, as no lump was observed in the nasopharynx or neck. (A) Complete response in cavernous sinus, (B) complete response in the bone of the skull base. (C) Complete response in the nasopharynx in transverse section. (D) Complete response of the right cervical lymph node. (E) Complete response in nasopharynx in coronal section. (F) Complete response in nasopharynx in sagittal section.

Accordingly, in the present case, the patient received three cycles of induction chemotherapy with docetaxel-cisplatin and then concurrent chemoradiotherapy (70 Gy delivered in

33 fractions). After the treatment was completed, complete remission of the tumor was observed. However, further follow-up is required to determine the long-term survival

outcomes and these results may contribute to pooled statistics regarding the survival outcomes in combination with other studies.

In conclusion, the present study was the first, to the best of our knowledge, to report on a patient with EBV-positive large-cell and small-cell NEC of the nasopharynx. Immunohistochemical staining is the gold standard for diagnosis and the immunohistochemical findings in this case clearly indicated large-cell and small-cell carcinoma features and the presence of EBER. There is no standard treatment, but the patient achieved good complete remission with the standard chemoradiotherapy protocol for nasopharyngeal carcinomas. Reports on more such cases in the future will shed light on the clinical behaviors of this rare group of nasopharyngeal malignant tumors and aid its diagnosis and treatment. In addition, multidisciplinary consultation may be a good strategy to determine the appropriate treatment and achieve optimal treatment effects.

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Availability of data and materials

The data are available from the corresponding author upon reasonable request.

Authors' contributions

GRZ conceived and designed the study. ZS and HWY acquired the data and acquired and provided the radiology images. ZS and HWY contributed to the study design and analyzed and interpreted the data. GRZ supervised the study. ZS and HWY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This case report was reviewed and approved by the Institutional Ethics Committee of Panyu Central Hospital (Guangzhou, China).

Patient consent for publication

Written informed consent for publication of anonymous case information was provided by the patient.

Competing interests

The authors have no competing interests to declare.

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