Case Report

Five-year disease-free survival of Epstein-Barr virus-associated locoregionally advanced undifferentiated nasopharyngeal carcinoma patients treated with chemo-radiotherapy: a case report

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Background: Nasopharyngeal carcinoma (NPC) is a tumor caused by epithelial cells covering the surface of the nasopharynx. NPC only accounted for less than 1% of all cancers diagnosed worldwide. However, the global incidence rates are highest in southern China. We report a case of local advanced undifferentiated NPC [specifically, vesicular nucleus cell carcinoma (VNCC) of NPC]. Long-term disease-free survival (DFS) of a patient with stage IVA NPC is reported.

Case Description: A 42-year-old male presented with a 4-month history of rhinorrhea and a lump in the left neck. The positron emission tomography (PET) showed local invasion to the surrounding tissues, specifically, the tumor invaded the brain. The pathological diagnosis was VNCC, the Epstein-Barr virus (EBV) was positive in tumor tissues by *in situ* hybridization. and the clinical diagnosis was stage IVA of NPC. The patient was treated with induction chemotherapy (IC) with gemcitabine and cisplatin (GP) followed by cisplatin/radiotherapy. The tumor lesions complete response (CR) after concurrent chemo-radiotherapy (CCRT).

Conclusions: To date, the DFS time has been more than 5 years. IC with GP followed by CCRT should be the first choice of treatment for patients with locoregionally advanced NPC. In recent years, more and more studies have shown the efficacy of immunotherapy in treating recurrent or metastatic NPC patients, especially in patients or are programmed death-ligand 1 (PD-L1)-positive or have a high tumor mutation burden. In the future, immunotherapy may become a standard treatment in clinic and bring longer survival to patients.

Keywords: Nasopharyngeal carcinoma (NPC); induction chemotherapy (IC); intensity-modulated radiotherapy; Epstein-Barr virus (EBV); case report

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Introduction

Nasopharyngeal carcinoma (NPC) is not a common cancer. In 2018, NPC only accounted for 0.7% of all cancers diagnosed worldwide. Notably, the global incidence rates of NPC are highest in Southeast Asia (especially southern China), Micronesia/Polynesia, Eastern Asia, and North Africa (1). Vesicular nucleus cell carcinoma (VNCC) is a pathological type of undifferentiated carcinoma. The typical characteristics of VNCC are an Epstein-Barr virus (EBV)-associated carcinoma, poorly differentiated or undifferentiated cancers, a high sensitivity to radiotherapy, and frequent metastasis to the regional lymph nodes at an early stage (2). Due to the complexity of its anatomic location and high sensitivity to radiotherapy, radiotherapy-based comprehensive treatment is the main treatment for NPC. Radiotherapy can improve the cure rate of early NPC (3). However, the 5-year overall survival (OS) rates of stage III and stage IV NPC patients with the addition of chemotherapy to radiotherapy are only 53–81.8% and 28–66.39% (4), respectively. Thus, the efficacy of local advanced NPC treatments needs to be improved. A combination of radiotherapy and chemotherapy is the main treatment for locoregionally advanced NPC. In this article, we report the case of a patient who received induction chemotherapy (IC) with gemcitabine and cisplatin (GP) and concurrent chemo-radiotherapy (CCRT) to treat locoregionally advanced undifferentiated NPC, and has achieved more than 5 years of disease-free survival (DFS).

We present the following article in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-168/rc).

Case presentation

A 42-year-old (non-smoking, and non-drinking) male presented with a 4-month history of rhinorrhea, and a lump in the left neck. A positron emission tomography (PET) image showed an irregular soft-tissue density lump in the left nasal cavity and parapharyngeal space (around the carotid sheath) with a maximum standardized uptake value (SUVmax) value of 3.8. The mass extended deep into the parotid gland, and had adjacent soft tissue involvement (of the medial pterygoid, lateral pterygoid muscles, and oropharynx). The tumor invaded the brain through the adjacent left skull base, and wrapped around the left internal carotid artery. Bilateral metastasis was found in area IIA of the cervical lymph nodes, but no distant metastasis was found (see *Figure 1A*,*1B*). A biopsy of the left cervical lymph node revealed undifferentiated carcinoma metastasis (lymphoepithelioma-like carcinoma) (see *Figure 2A*,*2B*). The patient's immunohistochemistry results were as follows: cytokeratin 5/6(+), p53(+), p40(+), and Ki-67(+, 30%). Additionally, in-situ hybridization of the EBV-encoded ribonucleic acid showed the localization of EBV genomes within the nuclei of tumor cells (see *Figure 2C*), and a gene chip test revealed the patient was negative for human papillomavirus. Thus, the patient was diagnosed with stage IVA undifferentiated NPC (T4bN2bM0).

From August 22, 2016 to October 25, 2016,4 cycles of chemotherapy were administered to the patient as follows: 1.6 g of gemcitabine (1,000 mg/m^2) on days 1 and 8, and 40 mg of cisplatin (75 mg/m^2) on days 1–3. Next, concurrent cisplatin with intensity-modulated radiotherapy was performed. The radiotherapy was completed in January 2017. After 2 cycles of chemotherapy, the cervical mass had shrunk and was without rhinorrhea. The tumor was further reduced, and the patient's symptoms had clearly improved at the end of 4 cycles. Magnetic resonance imaging (MRI) showed a complete response (CR) after 1 month of CCRT (see *Figure 3A*). On January 7, 2020, another MRI examination indicated that the tumor continued to show a CR (see *Figures 3B*,*4*). After treatment, the patient was reviewed regularly. To date, no recurrence or metastasis has been found, and the patient had a DFS time of more than 5 years. During the treatment, the patient experienced a grade II gastrointestinal response and grade III myelosuppression.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

EBV infection is an etiological factor in the development of NPC (5). A multivariate analysis showed that EBV status was an independent prognostic factor for OS (P=0.026) and DFS (P=0.03); however, stage is still the most important prognostic factor for locally advanced NPC (6). One study has shown that the EBV genome is detected in most NPC patients, and the level of the EBV-related antibody in NPC patients' serum is significantly higher than that in normal

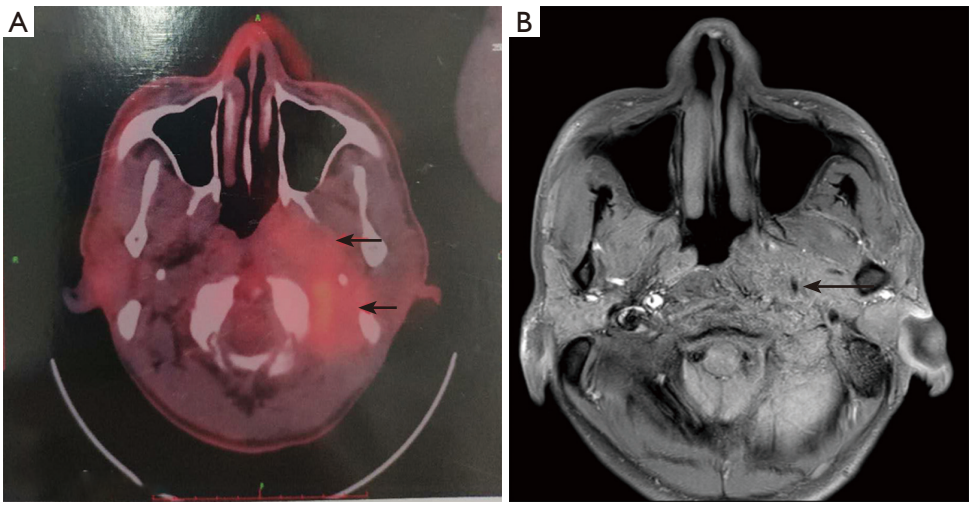

Figure 1 Patient's imaging results before treatment. The arrow indicates the tumor area. (A) PET showed a soft-tissue lump in the left wall of the nasopharynx (SUVmax 3.8), down to the level of the oropharynx, up into the brain, and multiple enlarged lymph nodes in the double neck area II. (B) Before treatment, MRI showed irregular long T1 and iso-T2 signals in the left parapharyngeal space. The boundary of the lesion was unclear. The mass invaded the nasopharynx, went outward to the parotid gland, upward to the left external auditory meatus, through the foramen magnum, and the skull base to the left of the cavernous sinus and posterior cranial fossa, and destroyed the adjacent bone. PET, positron emission tomography; SUVmax, maximum standardized uptake value; MRI, magnetic resonance imaging.

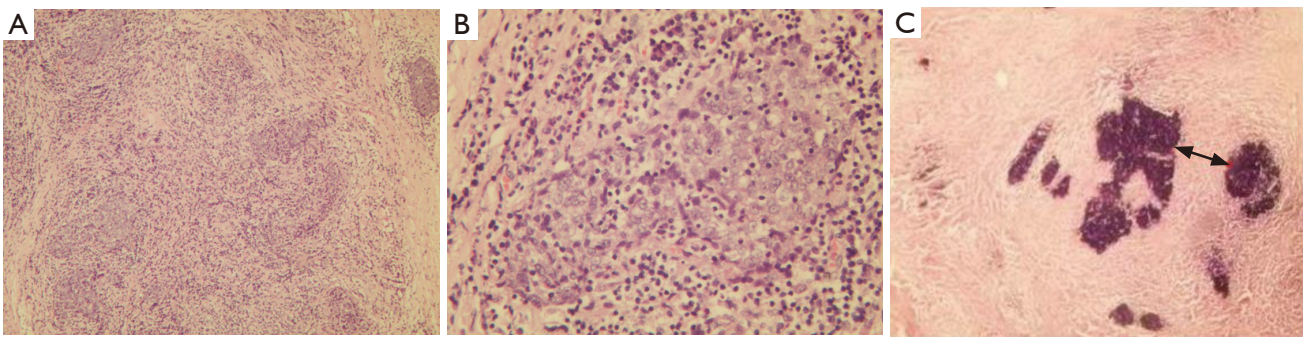

Figure 2 Immunohistochemical staining and EBV expression in tumor tissues. (A,B) Representative images of hematoxylin and eosin-stained NPC tissues. The cancer cells were composed of diffuse syncytial cells, and were associated with the inflammatory infiltration of the lymphocytes and plasma cells. There were vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm in the cells [(A) 100× and (B) 400×]. (C) The arrow points to EBV positive by *in situ* hybridization [(C) 100×]. EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma.

people (7). In this case, the patient was found to be EBV positive by in-situ hybridization, the OS of the patient reached more than 5 years. We only detected EBV before treatment and did not regularly monitor EBV during treatment. In the future, changes in EBV should be checked regularly in similar cases.

The basic principle of NPC is highly sensitive to radiation therapy (8). For patients with stage III or stage IV NPC, radiotherapy alone is not enough. Currently, there is evidence of the benefits of combined chemotherapy and concurrent systemic therapy/radiotherapy for patients with locoregionally advanced NPC (9). A 2016 NCT01528618 clinical trial showed that gemcitabine combined with cisplatin prolonged the progression-free survival (PFS) and objective response rate (ORR) of patients with metastatic or recurrent NPC (10). These results provide strong evidence for the standard first-line treatment of metastatic or recurrent NPC. In the study, 83% of the patients had

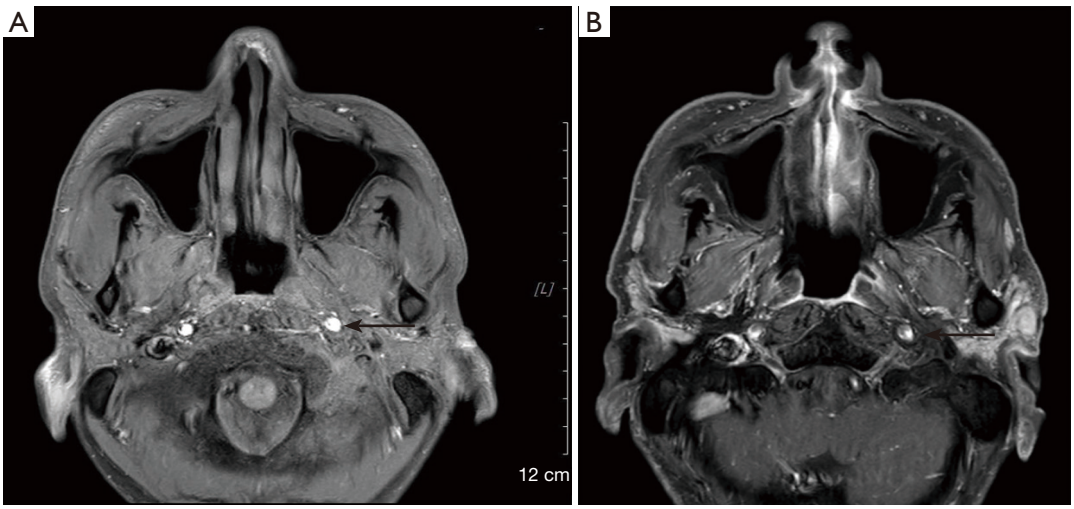

Figure 3 Response of the main lesion estimated by computed tomography. (A) After 2 cycles, the tumor was significantly smaller than before, and partial enhancement was shown by enhanced MRI. The arrow indicates the tumor area. (B) Enhanced MRI examination indicated that the tumor continued to show a CR on January 7, 2020. The soft tissue of the nasopharynx was slightly thick, the left pharyngeal recess was narrowed, and the bone structure of the left skull base was disordered. The arrow points to the area where the tumor disappears. MRI, magnetic resonance imaging; CR, complete response.

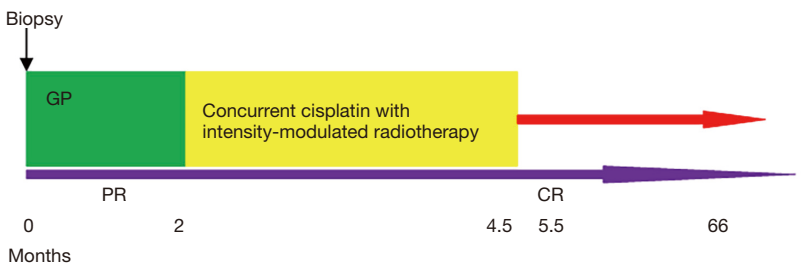

Figure 4 Timeline and duration of each treatment. Illustration of the treatment received by the patient and the corresponding PR and CR in months. GP, gemcitabine and cisplatin; PR, partial response; CR, complete response.

undifferentiated cancer (10). Based on the study, the National Comprehensive Cancer Network (NCCN) guidelines recommended GP as a first-line regimen (category 1) for patients with recurrent, advanced or unresectional NPC in 2018 (11). Clinically, nearly 60% of new patients with NPC were diagnosed with locoregionally advanced disease (12). For such patients, the NCCN recommends IC followed by systemic therapy/radiotherapy. Gemcitabine/cisplatin is a category 1 preferred option, but only for EBV-associated disease (10). After IC with GP, CCRT significantly improved OS and recurrence-free survival in locoregionally advanced NPC patients (13). The subgroup analysis further showed that gemcitabine plus cisplatin had a longer survival on T4 and N2. Additionally, the GP regime was well tolerated, and nearly 97% of the patients completed IC. The high completion rate of the GP regimen provides a basis for the treatment of NPC (14).

Based on treatment regimens for locoregionally advanced NPC recommended by the guidelines, the patient in this report received 4 IC cycles of the GP regimen followed by concurrent cisplatin/radiotherapy. After 2 IC cycles, the rhinorrhea was significantly reduced. MRI showed that the cervical bulk was shrunk. After 4 IC cycles, the mass shrank further and no rhinorrhea was observed. During the treatment, the patient had a grade III suppression of the bone marrow and a gastrointestinal reaction, remission was achieved after administration of granulocyte colony stimulating factor and 5-hydroxytryptophan receptor

antagonists, respectively. To date, no tumor recurrence or metastasis has been found, and the patient's OS time is nearly 5 years. Locoregionally advanced NPC has a high rate of local recurrence (15–40%) and distant metastasis, and the 5-year survival rate is <50% (15). As the patient had a perfect response, and a long survival, we have reported this case here.

This case was a patient with EBV-positive stage IVA NPC, whose tumor invaded the brain and had no chance of surgery. He underwent IC with GP followed by CCRT. So far, DFS is more than 5 years. The deficiency of this case was that the patient was not tested for PD-L1.

In recent years, more and more studies have shown the efficacy of immunotherapy in treating recurrent or metastatic NPC patients, especially in patients or are programmed death-ligand 1 (PD-L1)-positive or have a high tumor mutation burden (16-20). Undifferentiated NPC is associated with EBV. In 2020, the American Society of Clinical Oncology reported that plasma EBV changes can be used as an effective biomarker to predict the efficacy of immune checkpoint inhibitors, and suggested that immunotherapy may be a potential therapeutic approach. In the KEYNOTE-028 study (17), PD-L1 positive patients with recurrent or metastatic NPC were treated with pembrolizumab, and had an ORR of 25.9% and a median OS time of 16.5 months. In the NCI-9742 study (18), PD-L1 positive patients with recurrent or metastatic NPC received nivolumab, and had an ORR of 62% and a median OS time of 17.08 months. In the CAPTAIN-1st study, PFS was significantly longer in the camrelizumab plus GP group [median: 9.7 (95% confidence interval: 8.3–11.4) months] than the placebo group [median: 6.9 (95% confidence interval: 5.9–7.3) months] (19). Thus, the above clinical studies have shown immunotherapy significantly improves the survival time of patients. The DFS of this patient was significantly higher than that reported for patients in clinical trials who have received CCRT and immunotherapy; thus, treatment in this case was successful.

Conclusions

Undifferentiated NPC is a malignant tumor with cervical lymph node metastasis, which is highly related to EBV. Compared to other tumors in the nasal cavity, it has a better response to chemo-radiotherapy, and NPC patients have a good prognosis. In this report, the patient was treated with IC followed by systemic therapy/radiotherapy, and achieved long-term DFS.

Immunotherapy has an effect in treating many malignant tumors. Patient survival can be extended by 4 months with subsequent-line immunotherapy alone. The NCCN guidelines recommend programmed cell death protein 1inhibitors as a subsequent-line treatment for advanced and recurrent NPC patients who are PD-L1-positive, have the non-keratinizing disease, or a high tumor mutation burden (17,20). In the future, patients with NPC may have more treatment opportunities and longer survival rates.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-168/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-168/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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