Case Report
Metastasis of nasopharyngeal carcinoma: a case report and review

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Abstract: Nasopharyngeal carcinoma (NPC) is one of the most common epithelial malignancies in the head and neck region with a marked racial predilection in Southern Chinese, which metastasize to parotid gland, and it is extremely rare. In these populations, it is usually associated with Epstein-Barr virus (EBV). The existence of EBV in tumor cells, aberrant type of antibodies against EBV antigens in patient sera, and the same increased viral DNA in patient circulation as nasopharyngeal region highlights the role of EBV during NPC development. Here we report a rare case of parotid gland metastasis of nasopharyngeal carcinoma. A 37-year-old male, was admitted to Peking University Shenzhen Hospital for diagnosis of a pre-existent (half-year) painless mass in the left parotid region. A 3.5 cm mass was found in the left parotid. It was firm, fixed and medium hardness. On the basis of clinical medical history, morphological, immunohistochemical and molecular biology findings, a diagnosis of stage II, Epstein Barr-virus positive, parotid gland metastasis of nasopharyngeal carcinoma and nasopharyngeal non-keratinizing carcinoma were made. The primary symptom of parotid gland mass with NPC is often misdiagnosed, which has been admitted to be a pivotal cause of therapy failure in patients.

Keywords: Parotid gland metastasis, nasopharyngeal carcinoma, Epstein-Barr virus, clinicopathological feature, therapy

Introduction

A variety of metastatic neoplasms can present as masses in the parotid gland. Approximately 25% of malignant parotid tumors are metastases originating from head and neck tumors i.e. face, oral cavity, and oropharynx. Squamous cell carcinoma and malignant melanoma are one of the most common ones among malignant parotid tumors [1-3]. However, parotid gland tumors metastases originating from nasopharyngeal carcinoma (NPC) are extremely rare, and according to a recent study reported by Francis CH Ho et al, low-risk node groups included the supraclavicular, levels IA/IB and VI nodes, and parotid nodes with involvement rates at 3%, 0%, 3%, 0%, and 1%, respectively [4]. NPC is a common malignant head and neck cancer, especially in Southern China, where the annual incidence is 15-25 cases per 100,000 [5]. It has a high preference for local lymph node metastasis, and over 80% of cases presented with lymphadenopathy at diagnosis. Its etiology includes genetic epigenetic, background and environmental factors [6]. EBV infection belongs to environmental factors, which has attracted increasing attention, and a large number of emerging evidences have elucidated the close relationship between EBV and NPC [7, 8]. Illocosomal EBV infection in human suggests that most individuals carry EBV-infected cells, whereas a direct causal relationship between both events were difficult to establish by mere detection of the virus in individual with tumor, but instead requires definite detection of viral nucleic acids or viral proteins in the tumor cells. The diagnosis of parotid metastasis in NPC is primarily based on magnetic resonance imaging (MRI) and/or transnasal endoscopic biopsy. Compared with biopsy, MRI is a noninvasive and tremendous useful in the evaluation of cervical and retropharyngeal lymphadenopathy, which is the commonly used method for discrimination between benign and malignant parotid masses [9-11]. Histologically, the nasopharyngeal stroma is so full of lymphoid tissue
and lymphaticplexus that usually involves reactive lymphoid follicles, and many small lymphoid cells infiltrate the epithelium commonly. Radiotherapy is the most efficacious therapeutic approach for NPC and the conventional dose of radiotherapy is between 60 and 70 Gy, while chemotherapy is also needed in advanced disease [12]. Although the incidence of parotid gland metastasis of nasopharyngeal carcinoma is quite low, it should always be considered in the differential diagnosis of a parotid mass.

In this study we focused on reviewing and investigating English literatures with reference to this rare metastatic site over the past two decades, the diagnosis of parotid gland metastasis and the advancing of the therapeutic methods in patients with metastasis of NPC to the parotid gland.

**Case report**

In September 2015, a 37 years old male, which was born and lived in Guangdong Province, was...
admitted to Peking University Shenzhen Hospital for diagnosis of a pre-existent (half-year) painless mass of the left parotid region, with progressive-growing since he perceived. Initial diagnosis was the left parotid gland mass. During examination, a medium hardness tumor was visible, which was fixed to the underlying soft tissues in the left parotid gland and the size is about 2.9 cm × 4.0 cm × 3.5 cm with a defined boundary. Several tender and unfixed lymph nodes could be palpated in bilateral neck. There were no lesions found in skin of the cervical region in appearance and the oral cavity. No facial nerve palsy was presented. During his illness, there had been no symptoms of headache, abnormal deglutition, nasal occlusion or blood-stained nasal discharge. A normal thoracic image was presented by chest X-ray. Serum anti-EBV antibodies was positive (Titers: VCA-IgA was >1:10 and EA-IgA was >1:10), other laboratory data were within the reference range. Magnetic resonance imaging (MRI) of head and neck region delineated a 2.9 cm × 4.0 cm × 3.5 cm well-circumscribed mass located on the superficial lobe of the left parotid (Figure 1), the mass exhibited isointensity or hypointense signal on T1-weighted images and hyperintensity on T2-weighted images, with a moderately enhanced effect; the top left retropharyngeal wall showed abnormal enhanced signal and 9.4 mm × 5.6 mm size of oval spot (Figure 1), suggesting further examination; multiple abnormal enlargement of the lymph nodes were identified in the area of bilateral carotid sheath and the bigger one was measured about 1.5 cm × 0.6 cm in size. Nasopharyngoscopy examination revealed an ill-defined elevated lesion in the top left retropharyngeal wall which suspected as a neoplasm. The patient was otherwise well, with no other significant evidences in the medical history.

Then, a rhinopharyngeal biopsy of the neoplasm was performed. The specimen was pale in color and the histopathological examination of a tissue sample revealed an abnormal tumor nests of undifferentiated epithelial cells closely mixed with lymphocytes. The tumor cells showed an indistinct cell borders, bare nuclei, vesicular nuclei, and situated centrally in the nucleolus (Figure 2). Immunohistochemically and in situ hybridization, the tumor cells were widely positive for pan cytokeratin (PCK), cytokeratin 5/6 (CK5/6) and p63 (Figure 3), EBV-encoded RNA was widely positive in undifferentiated carcinoma (Figure 4), thus, with taking the results of MRI features, immunohistochemical and in situ hybridization of specimens, and basic information of patient, including ethnic, birthplace, EBV infection into consideration, the diagnosis of non-keratinizing undifferentiated carcinoma of the nasopharynx was established. Under general anesthesia, left parotidectomy with resection of several satellite lymph nodes and neck dissection and the left parotid duct resection were performed, and pathological examination revealed morphological features of the left parotid gland tumor identical to the specimen from rhinopharyngeal biopsy and the tumor cells were diffusely posi-
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tive for PCK, CK5/6 and p63 in immunohistochemical (Figure 3), resection of the left parotid duct was also positive for PCK and CK5/6 (Figure 5), however, there were no tumor cells observed in histopathology of satellite lymph nodes of left parotid gland. The safe margin status exhibited no malignancy, no extracapsular extension, and no lymphovascular or perineural invasion. To conclu, a final diagnosis of Epstein-Barr virus-associated parotid gland metastasis of nasopharyngeal carcinoma was determined. After one month of surgery, a dose of 50 Gy intensity-modulated radiotherapy (IMRT) was suggested and he accepted that treatment. Clinical and instrumental examination every three months in the first year after therapy and every six months thereafter excluded local and distant recurrences. The patient

Figure 3. Immunohistochemical staining of nasopharyngeal carcinoma, the left parotid gland tumor. Thetwo tissues were positive for PCK (A1, A2), CK5/6 (B1, B2) and p63 (C1, C2) (× 400).
was living a normal life with a good condition at the time of last follow up in October 2016.

**Discussion**

NPC is relatively uncommon in the western countries, however, incidence of NPC is high in southern China and Southeast Asia, especially in the Guangdong Province. NPC has a high tendency for regional lymph node metastasis, lymphadenopathy occurs in almost 84.9% of patients after diagnosis [4]. The pattern of nodal metastasis in NPC follows an orderly spread down the neck with rare node skipping; the retropharyngeal space is the most commonly involved regions, and the sequence of incidence level is as follows: levels II, III, IV, V, IB and the supraclavicular nodes [4]. According to the latest International Consensus Guidelines for nodal levels, the parotid lymph nodes were classified as level VIII; it has an extremely low risk metastasis from the nasopharynx. In Francis CH Ho et al [4] meta-analysis of clinical evidence study, the nodal stations may be divided into high, intermediate and low risk groups, and the low risk group of draining nodes in NPC include the supraclavicular as well as parotid lymph nodes, with an incidence of involvement at 8.8% and 0.9%, respectively. NPC can metastasize to the parotid gland lymph nodes (PLNs) via three approaches: (1) lateral retropharyngeal lymph nodes to the parotid gland tissue; (2) superior deep cervical lymph nodes; and (3) parotid gland tissue involvement. It can also infiltrate the parotid gland tissue directly by the primary lesion in the nasopharynx via peripharyngeal space. In term of our case, the major pathway of invading the

![Figure 4](image1.png) Nasopharyngeal carcinoma associated with Epstein-Barr virus. A and B. In situ hybridisation with EBER probes revealing extensive positivity in the tumor cells (× 100 and × 400, respectively).

![Figure 5](image2.png) Immunohistochemical staining of left parotid duct. The tissues were positive for PCK (A), CK5/6 (B) (× 400).
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parotid gland tissue is via the peripharyngeal space considering the MRI which revealed the tumor with a sprawl pattern of growth in all directions, pushing the left parotid gland backward, and creeping into the left peripharyngeal space by surrounding ramus of mandible. However, there is another possibility of invasion, the tumor cells of left retropharyngeal wall could be planted in the left parotid gland through parotid duct. The positive for PCK, CK5/6 and tumor cells infiltrating were obviously detected in the resection of left parotid duct.

The definite diagnosis of PLN metastasis in the present case study was mainly based on MRI and nasopharyngoscopy examination rather than fine-needle aspiration cytology (FNAC) or radiologic criteria [13] because of these reasons. First of all, NPC is mainly staged by MRI. FNAC is an invasive examination and easy to generate needle-path tumor implantation, seldom executed in patients with parotid lesions, unless pathologic verification of the primary tumor is unavailable. The second, radiologic criteria for PLN metastasis have not been admitted yet, and during process of surgery, the PLNs are not resected routinely, therefore, the radiologic criteria, is unable to be applied to the PLNs, which based on clinicopathologic analysis of the neck lymph nodes in dissection specimens [13]. The third, Once a patient with (or without) EBV infection has a suspected neoplasm that was detected in nasopharynx or neck by MRI, a careful nasopharyngoscopy examination is essential and, if relevant, random nasopharyngeal biopsy must be performed. The principal differential diagnosis of our case is lymphoepithelial carcinoma (LEC), which is also a rare and unique malignant salivary gland tumor with morphological characteristics identical to that of metastatic nasopharyngeal carcinoma. Morphologically, parotid gland metastasis of nasopharyngeal carcinoma is difficult to distinguish from LEC of the parotid gland, which has extremely similar architectural and cytological features which is a lymphoid rich tumor composed of sheets and nests of large vesicular cells with prominent nucleoli and syncytial cytoplasm, the same ethnic predilection, and a strong association with EBV infections. Thus, a careful nasopharyngoscopy examination is necessary for detection of primary tumor and definite diagnosis, then, if positive results were presented, multiple nasopharyngeal biopsies must be executed.

To the best of our knowledge, a retrospective review of English literatures and abstracts analyzing the distant metastasis status of patients with NPC was performed by searching electronic database PUBMED from 1995 to 2015. Patients who was previously treated or present with recurrence of disease were excluded from analysis, or had received MRI examination of the neck and nasopharynx. Altogether, 7958 cases with NPC of 14 included studies were

### Table 1. Clinical characteristics of the 7958 patients with NPC of 14 included studies

<table>
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Abbreviations: Ab, abnormal; LN, lymph nodes; R LN, Retropharyngal LN; SCF, supraclavicular fossa.
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included in the study. A total of 7069 (88.83%) patients involved abnormal lymph nodes and, the detailed distribution were summarized in Table 1 [14-27]. 96 PLN metastases were detected in 7069 patients; the incidence of PLN metastasis was 1.21%, which is identical to the rates reported in former study [4]. Although such a low incidence it is, reports of long-term survival inpatients with PLN metastasis at presentation are rare. The earlier diagnosis and aggressive treatment for patients with parotid gland metastasis of nasopharyngeal carcinoma may better improve the outcomes and the PLN metastasis with NPC misdiagnoses should be avoided as possible. In clinical practice, a combination of radio/chemotherapy is currently the gold standard but the rates of failure arising from 7% up to 58%. Because EBV infection is closely linked to NPC development and the current NPC therapy is based on radiochemotherapy which is affected by severe side effects and high rate of recurrences, many efforts were made to develop an effective treatment against EBV latent cycle, moreover, many studies on EBV directed therapy and their application on NPC have been made in last few years. Future researches on this topic are warranted. The optimal treatment for patients with NPC who involved in PLN metastasis is controversial. In the present case, we recommend the removal of partial parotidectomy and parotid tail nodes. However, there is still controversy on the selection of surgery to treat metastasis to parotid lymph nodes; while some surgeons prefer superficial parotidectomy, others prefer complete parotidectomy. Facial nerve preservation should be attempted unless the nerve is grossly involved with the tumor.

In conclusion, PLN metastasis from NCP is highly rare that often being neglected. According to a retrospective review of English literatures, the incidence of PLN metastasis was only 1.21% over the past two decades and, its treatment has not been standardized. Thus, in order to improve the clinical outcome and quality of life, therapeutic decision-making rely on the clinical disease extent, and surgery and/or chemoradiation therapy must be tailored to the individual patient. A careful nasopharyngoscopy examination is necessary for patients who were suspected PLN metastasis from NPC. The earlier the diagnosis and more aggressive of the treatment for patients with parotid gland metastasis of nasopharyngeal carcinoma may better improve outcomes.

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Disclosure of conflict of interest

None.

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References


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