Mandibular Metastasis from Nasopharyngeal Carcinoma

ABSTRACT

Objective: To describe a case of mandibular metastasis from nasopharyngeal carcinoma and review the literature.

Methods: Design: Case Report Setting: Tertiary Public University Hospital Patient: One

Result: A 42-year-old Malay gentleman underwent concurrent chemoradiotherapy (CCRT) for T4N2M0 (Stage IVa) nasopharyngeal carcinoma (NPC) non-keratinizing type (WHO II). Upon completion of CCRT, he developed metastasis to the left body of the mandible that increased in size despite three cycles of adjuvant intravenous chemotherapy. Hemi-mandibulectomy was deferred due to recent irradiation and a further 15 fractions of boost radiotherapy reduced the mandibular metastasis in size but it has remained the same after six months follow up.

Conclusion: Nasopharyngeal carcinoma (NPC) is a common malignancy in Oriental Asia and the South East Asian regions. It has the highest rates of nodal and distant metastases among all head and neck cancers. Distant metastasis to bone is common but we could find no previous report of mandibular bone involvement in the literature. Radiotherapy remains the main treatment modality and combination with chemotherapy has been shown to improve survival of patients. There are studies on nasopharyngeal carcinoma tumour markers for diagnosis and disease process follow up but these are still inconclusive.

Keywords: nasopharyngeal carcinoma, bones, mandible, metastasis.
The patient underwent concurrent chemoradiotherapy (CCRT) consisting of 35 sessions of fractionated radical radiotherapy (total of 60 Gy) with weekly intravenous (IV) Cisplatin 30mg/m².  

Upon completion of the CCRT, he developed a slightly tender swelling of the left mandible. Examination revealed a firm, diffuse 3 x 3 cm swelling in the labial sulcus of the left body of the mandible with reddish overlying mucosa. There was no bleeding or purulent discharge noted. Fine needle aspiration cytology revealed metastatic carcinoma. He then proceeded with 3 cycles of adjuvant intravenous chemotherapy (5-flourouracil and Cisplatin).

Upon completion of the adjuvant chemotherapy, the mandibular swelling increased in size and was bony-hard and moderately tender on intra- and extra-oral palpation. Orthopantomogram (OPG) showed swelling increased in size and was bony-hard and moderately tender (5-flourouracil and Cisplatin).

He was prescribed a further 15 fractions of boost radiotherapy (total of 20 Gy) localized to the affected mandible. The swelling reduced in size to 1 x 1 cm upon completion of the boost radiotherapy.

Six months after the boost RT, the swelling on the mandible remained the same but there was no local recurrence at the primary site. Surgery remains an option if the swelling increases in size again.

**DISCUSSION**

NPC has one of the highest rates of nodal and distant metastases among head and neck cancers. About 75% of NPC patients have enlarged nodes at presentation. The clinically important commonly involved lymph nodes are the retropharyngeal (82%), cervical level II (95.5%), III (60.7%) and IV (34.8%).

The common distant metastatic sites are bones, lungs and liver in descending order of frequency. Distant metastases usually develop within a 3-year period and there is an association between distant metastases and the nodal (N) staging. There are also case reports of rare sites of distant metastases to the thyroid glands, choroid of the eye and skin.

Skeletal involvement usually affects the spine (59.6%) and pelvis (16.3%), followed by femur (9.9%), ribs and sternum (7.8%) and humerus (5.0%). On X-ray, lesions are mostly lytic (66%), sclerotic (21%) and mixed lytic and sclerotic (12.8%). This unusually high incidence of mixed and sclerotic bony secondaries is unique in head and neck cancer. The role of bone scanning of asymptomatic skeletal metastases on presentation of NPC patients is limited by its low sensitivity and specificity. Thus, bone scintigraphy is not recommended as part of a routine staging investigation for NPC on top of its low cost-effectiveness. However, it should be an option for NPC patients with higher risk for distant metastasis (advanced T or N staging, male and older age). Chua et al. compared 4 diagnostic panels for distant metastasis staging (1. chest X-ray, liver ultrasound, and skeletal scintigraphy; 2. CT of the thorax, abdomen and skeletal scintigraphy; 3. (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) and 4. Integrated FDG-PET/CT). Results showed that integrated FDG-PET/CT was the most specific (83.3%), sensitive (97.2%) and accurate (96.2%) modality to detect distant metastasis. However, this investigation is limited also by its cost and availability. Even though distant metastasis to bone from NPC is common, we could find no previous report of mandibular involvement in the literature based on a PubMed search of MEDLINE as well as Ovid and Google.

Intrathoracic metastases incidence has been reported as high as 8-13%. About 64% of all patients with lung metastasis have thoracic lymphadenopathy especially involving the hilar nodes. It is also interesting to note that instead of solitary deposits, there is a 12% incidence of lung lesions of the cavitary type (usually associated with squamous cell carcinoma). Liver metastasis is also common in NPC patients (36% of distant metastases). Like other cancers, the metastasis of nasopharyngeal carcinoma involves several theoretical sequential steps. Metastatic tumour cells must separate from other cells by losing the function of E-cadherin and beta-catenin. Then the cells migrate through the basement membrane into the circulation (blood or lymphatic). Although these tumour cells are vulnerable to the host immune system, some may escape and adhere to vascular endothelium and invade the susceptible organ parenchyma.
Organ metastases usually could be predicted by the location of the primary tumour and its vascular and lymphatic drainage. However, as seen in this case, the natural drainage pathways do not always explain the site of metastasis. Probable mechanisms include expression of adhesion molecules on cell membranes by the metastatic tumour cells whose ligands are expressed on the endothelium of target organs or the use of chemokines by tumour cells to reach specific organs.\textsuperscript{15} Many different NPC tumour markers (E-cadherin, \(\beta\)-catenin, \(\beta\)-2-microglobulin, LMP2A)\textsuperscript{16-18} and NPC cell lines (5-8F- GFP and 6-10B-GFP)\textsuperscript{20} for NPC have been studied but their clinical relevance still remains inconclusive.

Rare distant metastases may happen in patients with NPC. A study by Pegtel \textit{et al.}\textsuperscript{16} on Epstein-Barr Virus (EBV) and non-keratinizing NPC showed that there was a link between LMP2A expression (latent protein expressed on EBV-infected epithelial cells), ITG alpha6 expression (cellular protein associated with cellular migration in vitro and metastasis in vivo), epithelial cell migration and NPC metastasis. The results suggest that EBV infection may contribute to higher incidence of metastasis in NPC progression. There is further need for laboratory research in this relevant topic for definite treatment regarding EBV infection in humans. Nevertheless, EBV serology was not available prior to treatment of our patient as it is not a routine test in our clinical setting.

### ACKNOWLEDGEMENTS

We are grateful to Prof. Prepageran Narayanan (FRCS) from the University Malaya of Kuala Lumpur for reviewing this paper.

### REFERENCES