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SMALL CELL NEUROENDOCRINE CARCINOMA OF HYPOPHARYNX – JOURNEY TO DIAGNOSIS AND TREATMENT.

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ABSTRACT

Neuroendocrine tumours are rare and aggressive heterogenous histologic group of tumours with a wide spectrum of differentiation. They are divided into 3 categories according to its grade, clinical behaviours and prognosis; well-differentiated or low-grade, moderately differentiated or intermediate-grade, and poorly differentiated or high-grade based on the 2017 World Health Organisation Classification for Head and Neck Tumours. They commonly originate at larynx, with only 4% arising from the hypopharynx. Experience regarding diagnosis and treatment of hypopharyngeal NEC cancer are scarce and are mostly consisted of case studies or small case series.[5] Here, we report a rare case of hypopharyngeal small cell type NEC malignancy and discuss the clinical manifestation, pathway to diagnosis and treatment.

Keywords: Chemotherapy, Elderly, Hypopharynx, Neuroendocrine malignancy, Radiation therapy.

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ABSTRACT

Neuroendocrine tumours are rare and aggressive heterogenous histologic group of tumours with a wide spectrum of differentiation. They are divided into 3 categories according to its grade, clinical behaviours and prognosis; well-differentiated or low-grade, moderately differentiated or intermediate-grade, and poorly differentiated or high-grade based on the 2017 World Health Organisation Classification for Head and Neck Tumours. They commonly originate at larynx, with only 4% arising from the hypopharynx. Experience regarding diagnosis and treatment of hypopharyngeal NEC cancer are scarce and are mostly consisted of case studies or small case series.[5] Here, we report a rare case of hypopharyngeal small cell type NEC malignancy and discuss the clinical manifestation, pathway to diagnosis and treatment.

Keywords: Chemotherapy, Elderly, Hypopharynx, Neuroendocrine malignancy, Radiation therapy.

INTRODUCTION

Neuroendocrine (NEC) tumours are rare malignancy which comprises of 0.49% of all malignancies.[1] It is an aggressive heterogenous histologic group of tumours with a wide spectrum of differentiation and is divided into 3 categories according to its grade, clinical behaviours and prognosis; well-differentiated or low-grade, moderately differentiated or intermediate-grade, and poorly differentiated or high-grade based on the 2017 World Health Organisation Classification for Head and Neck Tumours.[2] The poorly differentiated or high-grade NEC is further differentiated into small cell (SmCC) or large cell and is usually of pulmonary origin, however, there are also recognized extrapulmonary sites.[3]

NEC tumours in the head and neck are quite rare and most commonly originate at

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larynx.[4] The hypopharynx is the most uncommon site which comprises only 4%.[4] Experience regarding diagnosis and treatment of hypopharyngeal NEC cancer are scarce and are mostly consisted of case studies or small case series.[5] Here, we report a rare case of hypopharyngeal small cell type NEC malignancy and discuss the clinical manifestation, pathway to diagnosis and treatment.

CASE REPORT

A 70-year-old Malaysian woman presented to our clinic with foreign body sensation in the throat for two weeks associated with hoarseness. She was still able to take solid food. She had no aspiration symptoms and otalgia. She had underlying diabetes mellitus and hypertension. She was an active smoker who smoked 10 sticks per day for the past 50 years. Her family history was non-contributory.

Clinically, her voice was hoarse. However, she did not have stridor. Examination of the neck revealed no enlargement of cervical lymph nodes. A bedside laryngoscopic examination using a 70 degree-angled endoscope showed a hypopharyngeal fungating mass obliterating the left arytenoid and causing narrowing of the laryngeal inlet (Figure 1). Bilateral vocal cords were mobile but with narrow airway inlet due to the mass effect. A computed tomography (CT) from the base of skull till pelvis showed hypopharynx lesion with locoregional mass effect measuring 1.5cm x 2.6cm x 1.7 cm with enlarged cervical lymph node and spiculated solid lung nodule measuring 1.8cm x 2.1cm x 1.9cm suggestive of metastasis (Figure 2). The tumour was staged as T2N2M1 based on TNM staging.

She subsequently underwent tracheostomy under local anaesthesia followed by direct laryngoscopy, bronchoscopy, esophagoscopy and biopsy under general anaesthesia. Intraoperatively, a fungating mass was seen

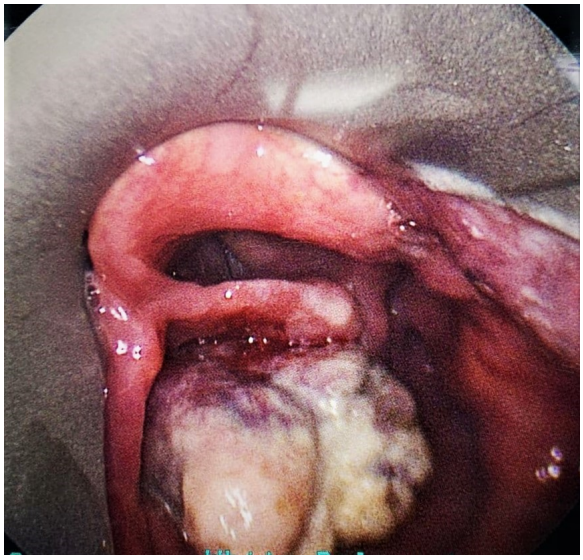

Figure 1: : Endoscopic view showed a fungating mass arising from the left pyriform fossa.

arising from left pyriform fossa apex, involving medial and lateral wall of pyriform fossa, displacing the left arytenoid anteriorly causing the laryngeal inlet to be narrow. The mass was friable and bleed on touch. Debulking surgery of tumour was done. Other structures including vocal cords, subglottic region, trachea and oesophagus were normal.

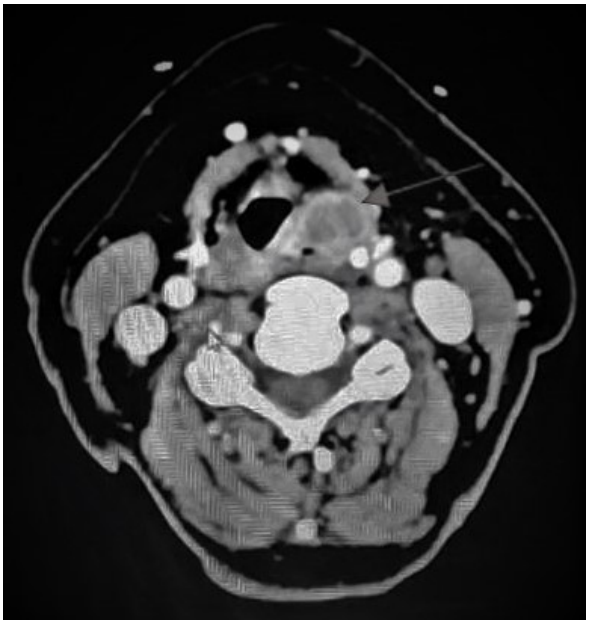

Figure 2: : Axial view of CT neck shows a hypodense lesion at left hypopharynx (red arrow) that causes mass effect causing slight narrowing of the hypopharynx.

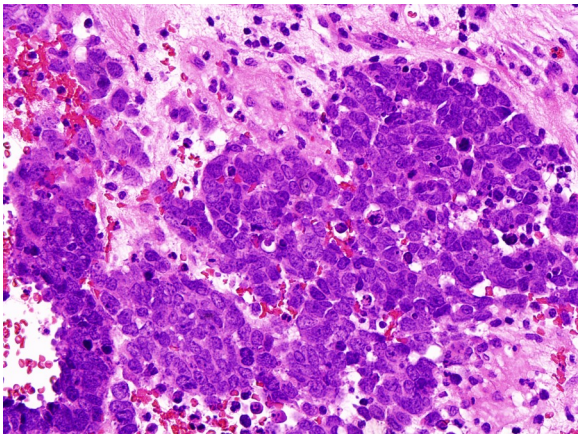

Figure 3: Light microscopy shows round to oval with some spindled shaped nuclei with salt and pepper chromatin pattern and scanty cytoplasm. (Magnification x40

Histopathological examination revealed a tumour with cells arranged in trabeculae and nested pattern accompanied by desmoplastic stroma and necrotic area. The cells were round to oval with spindled shaped nuclei with salt and pepper chromatin and scanty cytoplasm (Figure 3). These histopathological characteristics were compatible with small cell NEC carcinoma. Immunohistochemical analyses showed neuroendocrine features which were immunopositive with PanCK, CK7, chromogranin, Synaptophysin and CD56. The tumour cells were negative for CK20, LCA, S100, CK5/6 and TTF-1. Mitotic figures and apoptotic bodies were frequently seen. Ki-67 mitotic index achieved 80%.

As the tumour was inoperable, she was seen by oncologist and was scheduled for 6 cycles of palliative chemotherapy of Carboplatin and Etoposide. A CT scan done after the 3rd cycle of chemotherapy showed a good response where there was a reduction in the size of the hypopharyngeal tumour and cervical lymph node and a stable lung nodule. She then continued the remaining 3 cycles of chemotherapy followed by radical radiotherapy of 70Gy with 35 fractions for 7 weeks.

DISCUSSION

Neuroendocrine (NEC) cancers are made up of a combination of nerve cells and hormone-producing endocrine cells.[6] Neuroendocrine cells are found throughout the body which makes the tumour to arise from any organ but commonly from pulmonary and gastrointestinal system.[1,6,7] Olofsson and van Nostrand have been credited with the first case of primary extrapulmonary NEC in 1972 which originated from head and neck. Since then, NEC tumour arising from multiple sites of head and neck were reported which originated from larynx, paranasal sinuses, and salivary glands.[3,4] However, hypopharynx is a rare site for occurrence of NEC malignancy with pyriform sinus is the usual site of hypopharynx for occurrence as presented in this case report.[3]

NEC carcinoma is usually indistinguishable from squamous cell carcinoma (SCC) of hypopharynx as patients have similar symptoms and clinical features. Dysphagia and neck mass are the most common symptoms reported associated with weight loss, dyspnea, hoarseness and throat pain.[4] As in this case, patient had dysphagia and hoarseness.

NEC malignancy of hypopharynx is rare that a definite diagnosis is essential to determine the management plan. Histopathological investigation gives a definitive diagnosis. When NEC malignancy is found at an unusual anatomical site, routine immunohistochemical staining leads to an appropriate diagnosis.[3] In this case, histopathological examination showed a neuroendocrine tumour that were immunopositive with PanCK, CK7, chromogranin, Synaptophysin and CD56. The Ki-67 mitotic index achieved 80%. A high Ki-67 proliferation index suggested highly proliferative malignancy. The Ki-67 expression also gives criteria to determine the growth fraction of individual tissues and tumours.[4] Takagawa et al presented a case report of a patient with primary hypopharyngeal NEC with distant metastasis with high Ki-67 positivity

similar to this case.[7]

NEC carcinoma is an aggressive tumour with malignant characteristics of high proliferative activity, poorly differentiated, and high incidence of distant metastases.[7] In view of the lung metastases, palliative treatment was recommended for our case.

Until today, there is no consensus on the treatment of hypopharynx NEC carcinoma. However, a multimodal treatment combining chemotherapy, radiation therapy, and surgery is usually employed. Unfortunately, NEC has a poor prognosis with extremely poor outcome. [7] Surgical treatment is not always used as a treatment modality because it decreases the quality of life postoperatively. Thus, an oncological modality of chemoradiotherapy is preferred as it aids in organ preservation. [4] Nakahira et al in their case report showed successful local control of the primary tumour regardless of the treatment modality used. This suggests that an organ preservation strategy with platinum-based chemotherapy and concurrent radiotherapy for the primary lesion is also reasonable for neuroendocrine tumour of the hypopharynx. [3] In our case, the patient underwent 3 cycles of chemotherapy of Carboplatin and Etoposide which showed a good response. Thus, she was given another 3 cycles of chemotherapy followed by radical radiotherapy. Platinum based chemotherapy has been primary choice of treatment in NEC. In a study done by Lee et al., samples from NEC patients received front line regimen of platinum-based chemotherapy showed low expression of hypoxia-inducible factor-1α which plays as a predictor of better prognosis among NEC patients.[4]

Oncological research is advancing day by day towards finding efficient therapies. Treatment of extrapulmonary NEC is mainly based on the knowledge of small cell lung carcinoma (SCLC). Recently, combination chemotherapy using etoposide and platinum with immune checkpoint inhibitors are being used in advance SCLC. Immune checkpoint inhibitors show a successful treatment rate due to high immunogenicity and high tumour burden which are linked to chronic tobacco exposure which is commonly seen in larynx and hypopharynx NEC. This knowledge and clinical similarities between these diseases could support usage of this choice of treatment in primary or recurrence hypopharyngeal NEC.[8]

Immunotherapy can potentially be a better choice of modality of treatment for NEC tumours. However, no optimum strategy has been proved yet. More research needs to be done on treatment strategies for hypopharyngeal NEC including combination therapy of chemoradiotherapy, immunotherapy and immune check point inhibition.[9]

CONCLUSION

The present case report emphasizes the importance of pathological identification of NEC carcinoma from other oncological tumours as management and prognosis differs. NEC carcinoma of the hypopharynx has a more aggressive characteristic and poor prognosis compared to other NEC carcinoma. However, there are no standard guidelines on management of hypopharynx NEC and further research in the area of combination therapy of chemoradiotherapy, immunotherapy and immune check point inhibition is needed.

CONFLICT OF INTEREST

The author's declare no conflict of interest.

PATIENTS CONSENT FOR PUBLICATION

Consent was obtained from the patient for the publication of this case and images.

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