

# Clinical Presentation and Treatment Strategies for Laryngeal Neuroendocrine Carcinoma: Insights from: A Rare Case

Rahul Dhama<sup>1</sup>, Winsome Kumar<sup>2</sup>, Anu Agrawal<sup>3</sup>,  
Navaudhayam Ranganathan<sup>4</sup>, Akhilesh Mishra<sup>5</sup>

<sup>1,2</sup>PG Resident, VMMC and Safdarjung Hospital

<sup>3</sup>MD, DNB, VMMC and Safdarjung Hospital

<sup>4,5</sup>MD, VMMC and Safdarjung Hospital

## Abstract

**Introduction** -Neuroendocrine neoplasms (NEN) of the larynx are very rare, accounting for <1% of all laryngeal carcinomas. Based on the 2022 IARCH/WHO classification, NENs are characterised as well-differentiated neuroendocrine tumours (NET), which can further be divided into grades 1-3 based on Ki-67 levels and mitotic count, or poorly differentiated neuroendocrine carcinomas (NEC) consisting of small cell carcinoma and large cell carcinoma. In this case report, we describe a rare presentation of NEC of the larynx encountered in a 54-year-old man and how diagnostic and therapeutic dilemmas unfolded.

**Case description:** A 6-month history of breathing and swallowing difficulties led to a tracheostomy due to stridor, in the emergency department. Imaging revealed a soft tissue mass involving the supraglottic larynx but no significant associated cervical lymphadenopathy. The biopsy from the growth was suggestive of poorly differentiated NEC as an AJCC stage cT3N0M0. However, there was local progression post-initial treatment with vincristine, doxorubicin and cyclophosphamide (VAC). The chemotherapy regimen was switched to carboplatin and etoposide. The patient received definitive radiation therapy and completed the planned dose of radiation. After 10 months of disease-free interval, there was local recurrence with lung nodules that prompted rechallenge with platinum and etoposide. The patient is doing well and remains clinically and radiologically stable to maintenance therapy with carboplatin & etoposide.

**Conclusion:** NENs of the larynx and especially NECs, are difficult to diagnose as they are rare and have varied molecular profiles. Its management frequently calls for multimodal approaches with chemotherapy and radiation therapy. Due to the developments in diagnostic and therapeutic modalities, our knowledge of NENs has been enhanced which contributed to better practice standards. Nevertheless, standardized treatment strategies remain to be determined by large cohort studies and comprehensive molecular profiling that can determine improved clinical outcomes.

## Introduction:

Neuroendocrine neoplasms of the larynx are sporadic and constitute <1% of all laryngeal carcinomas [1]. According to IARC/WHO 2022, neuroendocrine neoplasm is divided into two broad categories - 1) Well-differentiated Neuroendocrine Tumor (NET), which is further divided into Grade 1, 2 & 3 and 2) Poorly

differentiated Neuroendocrine Carcinoma (NEC), which is further of two types: - i) small cell NEC & ii) large cell NEC [2].

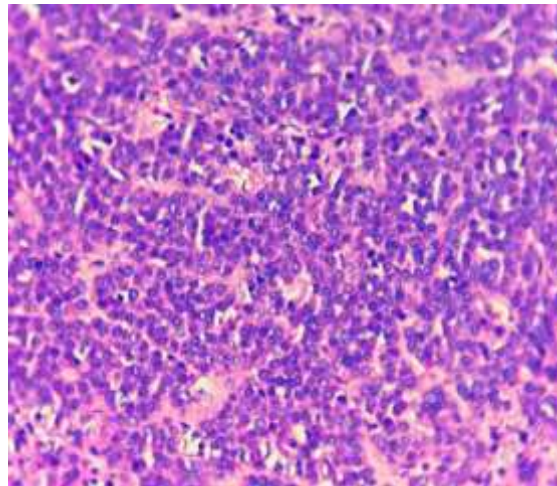
Primary NECs of the larynx are uncommon. The most common subsite involved is the supraglottic region, particularly the aryepiglottic fold followed by arytenoid and epiglottis [4,5]. Smoking is one of the most important known risk factors for neuroendocrine carcinoma of the larynx having male predominance with a male: female incidence ratio of 3:1 [5]. We discuss a rare case report on NEC of the larynx and the challenges faced in diagnosing and managing the same.

### **Case History:**

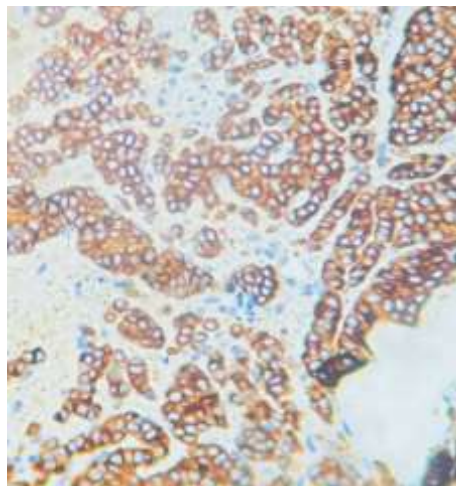
A 54-year-old male presented with complaints of difficulty in breathing and swallowing which started six months before presentation. He presented to the emergency with stridor and increased difficulty in breathing for which he underwent emergency tracheostomy. He was referred to an oncologist who obtained dedicated contrast-enhanced computed tomography (CECT) of the neck which showed an enhancing soft tissue mass lesion involving the left side of aryepiglottic fold, left side epiglottis, pre-epiglottic fold, para-laryngeal fat & false and bilateral true vocal cords. There was no significant cervical lymphadenopathy. Biopsy from the growth showed stratified squamous epithelium along underlying lobules of poorly differentiated mitotically active malignant epithelial cells with a moderate amount of pink cytoplasm and distinct peripheral palisading with the presence of rosetting and increased mitoses. On immunohistochemistry, pan-cytokeratin (CK), synaptophysin and nonspecific enolase (NSE) were positive. The diagnosis of neuroendocrine carcinoma of the larynx was made and staged as AJCC cT3N0M0.

The patient received three cycles of vincristine at  $1.5\text{mg}/\text{m}^2$  capped at a maximum  $2\text{mg}/\text{m}^2$ , doxorubicin at  $75\text{mg}/\text{m}^2$  and cyclophosphamide at  $1200\text{mg}/\text{m}^2$  3 weekly for 3 cycles outside. Reassessment CECT face and neck showed local progression with the increase in size of primary. The patient received four cycles of cisplatin at  $45\text{mg}/\text{m}^2$  and etoposide at  $130\text{mg}/\text{m}^2$ , there was symptomatic, clinical and radiological response. The patient received definitive radiation therapy to a total dose of 66Gy in 33 fractions at 2Gy per fraction over 6 weeks with concurrent cisplatin  $40\text{mg}/\text{m}^2$  weekly. The patient developed grade 2 neutropenia in the second week hence concurrent chemotherapy was stopped and was continued with radiation therapy to a total dose of 66Gy with bilateral parallel opposed face and neck field in phases. Phase I was planned to a dose of 46 Gy in 23 fractions and phase II being off cord to a dose of 22 Gy in 11 fractions at 2 Gy per fractions. He was on follow-up with clinical examination and indirect laryngoscopy.

There was disease free interval of 10 months. At 10 months, CECT of face, neck and chest was done which was suggestive of local recurrence with lung nodules. He was staged as rcT4aN0M1 and was rechallenged with platinum and etoposide 3 weekly for four cycles. Post 4 cycles, he was clinically and radiologically stable, hence is continued on carboplatin and etoposide as of now.



**Figure 1 - Section shows stratified squamous epithelium with poorly differentiated mitotically active malignant epithelial cells with presence of rosetting, distinct peripheral palisading and increased mitosis.**



**Figure 2 - Section shows tumor cell positivity for synaptophysin.**

## **DISCUSSION:**

Neuroendocrine tumor commonly arises in the gastrointestinal or respiratory systems and rarely in the head and neck region [6]. Larynx is the most common site of the neuroendocrine tumor in the head & neck region, and it is the most common non-epidermoid laryngeal carcinoma and consists of 0.5 to 1% of all epithelial cancer and mostly occurs in the supraglottic region [1]. Neuroendocrine carcinoma of the larynx has unique diagnostic and therapeutic challenges due to its rarity and heterogeneous molecular profile with various histological subtypes [2]. Small-cell neuroendocrine carcinoma is the most aggressive variant followed by large-cell neuroendocrine carcinoma, and carcinoid tumors are the least aggressive among NENs [7].

Patients with neuroendocrine carcinoma of the larynx present with symptoms such as hoarseness of voice, dysphagia, and sore throat. These symptoms, however, are common to many laryngeal disorders, necessitating a high index of suspicion and thorough diagnostic evaluation [3]. Diagnosis of the condition may be delayed as it is a rare condition and diagnosis is made based on the biopsy for obtaining tissue for histological examination for confirming the neuroendocrine nature of the tumor and distinguishing it from

other laryngeal malignancies. Morphological characteristics of NECs on light microscopy are peripheral palisading of tumor nests, trabeculae, glandular differentiation, and rosette formation. Immunohistochemical markers such as chromogranin A, synaptophysin, and CD56 are necessary to diagnose a tumor as NEC [8].

Management of neuroendocrine carcinoma depends upon stage and subtype. Multimodality treatments are used for neuroendocrine carcinomas incorporating surgery, chemotherapy, and radiotherapy. The most used first-line chemotherapy regimen for NEC larynx is cisplatin and etoposide and second-line chemotherapy is paclitaxel and carboplatin [9].

Radiation therapy plays a crucial role in the management of neuroendocrine carcinoma of the larynx. For small-cell and large-cell neuroendocrine carcinomas chemo-radiation have shown to improve overall survival rates and local control [7]. As the field of radiation therapy is continuously evolving with newer and more conformal techniques leading to dose escalation, leading to enhanced treatment efficacy with minimum toxicity.

The prognosis for neuroendocrine carcinoma of the larynx also depends upon stage and subtype. Small cell neuroendocrine carcinoma has a poorer prognosis due to early metastasis and aggressive nature. Large cell neuroendocrine carcinoma has a comparatively better prognosis but depends upon tumor size and local involvement. Whereas the carcinoid tumors have the best prognosis [7].

In summary, neuroendocrine carcinoma of the larynx represents a heterogeneous group of tumors with variable clinical outcomes and prognoses. With the advancement of technology in both diagnostic and therapeutic methodologies, we now have a better understanding of this heterogeneous group of neuroendocrine neoplasms. However, there are no prospective or randomized control trials to support the treatment guidelines as of now in the NEC of head and neck.

### Conclusion:

Laryngeal NENs present significant diagnostic and therapeutic challenges due to their rarity and overlapping clinical presentation with other histologies, requiring careful diagnosis and treatment. Our understanding of NENs is evolving with continued new research output, particularly with new biomarker studies. Further research with large cohort studies, comprehensive molecular profiling and a multidisciplinary approach is necessary to refine treatment protocols and improve local control and clinical outcomes.

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