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Case Report

Laryngeal neuroendocrine tumour: a case report on a rare pathology

Anand Krishnan[1]*, Neha Salaria[2], Anju Singh[3], Shubham Mittal[4]

[1]Department of ENT, Parco Institute of Medical Sciences, Vatakara, Kozhikode, Kerala, India
[2]Department of ENT, BPS Government Medical College for women Khanpur Kalan, Sonepat, Haryana, India
[3]Department of ENT, Jaipur National University Institute for Medical Sciences and Research Centre, Jaipur, Rajasthan, India
[4]Department of ENT, Noida International Institute of Medical Sciences, Gautam Budh Nagar, Uttar Pradesh, India

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***Correspondence:**
Dr. Anand Krishnan,
E-mail: aakri007@gmail.com

ABSTRACT

Most of the laryngeal malignancies are squamous cell carcinomas. The neuroendocrine neoplasms (NENs) are rare tumours of larynx with high incidence of widespread metastases and poor prognosis. Here we are reporting an 87-year-old male with localised primary grade 3 neuroendocrine tumour with Ki67 positivity. He was treated with surgery followed by palliative radiotherapy and is on follow up. We report the rare case of laryngeal neuroendocrine tumour managed with direct laryngoscopic excision followed by radiotherapy.

Keywords: Laryngeal tumours, Neuroendocrine neoplasm, Carcinoids, Direct Laryngoscopy, Laryngeal malignancy

INTRODUCTION

Vast majority of the primary malignancies of the larynx some 85 to 90% of them are squamous cell carcinomas. Though very rare in occurrence, the most common non-squamous laryngeal neoplasms are neuroendocrine neoplasms (NENs) comprising less than 1% of all laryngeal tumours.[1] Laryngeal neuroendocrine neoplasms are categorized as divided into epithelial (carcinomas) and neural-type tumour (paragangliomas) on basis of tissue of origin. While paragangliomas are considered benign, carcinomas were categorized as, typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma.

WHO Blue Book 2007 has re-categorized Neuroendocrine neoplasms; well differentiated carcinoma or carcinoids, moderately differentiated carcinoma or atypical carcinoids and poorly differentiated neuroendocrine carcinomas.[2] The last one is again subdivided into small cell and the large cell subtypes. These tumours have a strong association with heavy tobacco use and mostly affect men in the older decades of life. NENs have high chance of early and widespread metastasis and poor prognosis.[3] Rarity of the tumour, variation in morphological and clinical picture and different classification systems make NENs an enigma in the larynx.

CASE REPORT

An 87-year-old male presented to the outpatient department with recurrent episodes of change in voice for 2 months. He also complained of occasional difficulty in swallowing and aspiration while swallowing. He was on regular treatment for systemic hypertension, diabetes mellitus and recently diagnosed diabetic kidney disease. On examination, he was active, alert, conscious and very cooperative.

A videolaryngoscopic evaluation revealed a 2×2 cm pedunculated fleshy mass at the level of supraglottic which was moving with respiration and phonation. The mass was reaching up to the level of upper border of epiglottis during expiration and till the level of vocal cords during inspiration (Figure 1). There was no ulcerative or proliferative component over the mass. The attachment of the mass was found to be towards the right aryepiglottic fold. Both the vocal cords were normal and mobile.

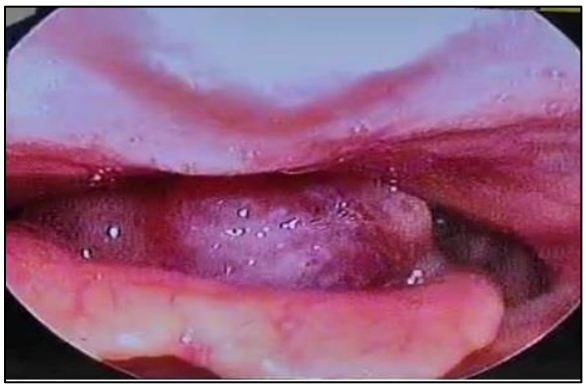

Figure 1: Video laryngoscopic evaluation of larynx showing ovoid mass reaching up to epiglottis. Lower attachment is not visible.

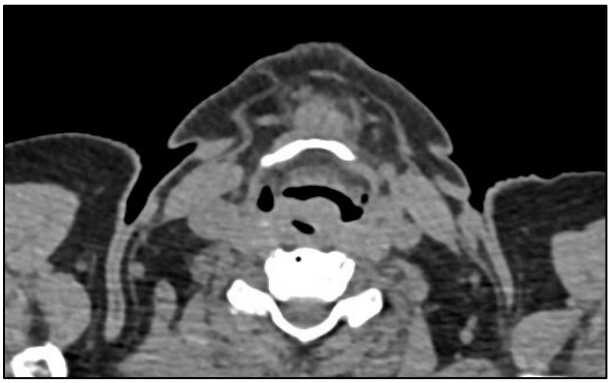

Figure 2: Computed tomography of neck axial section showing mass lesion in the larynx at the level of supraglottic and abutting the right aryepiglottic fold.

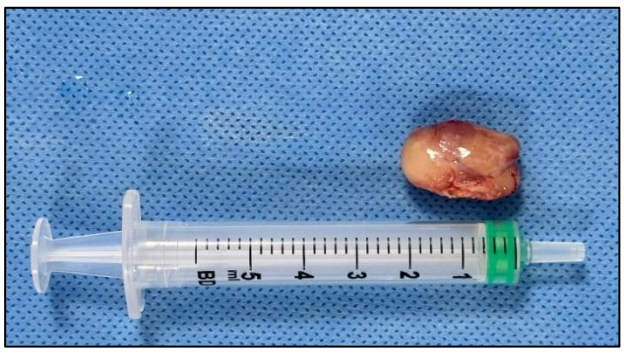

Figure 3: Showing the gross specimen of mass from larynx after direct laryngoscopic removal.

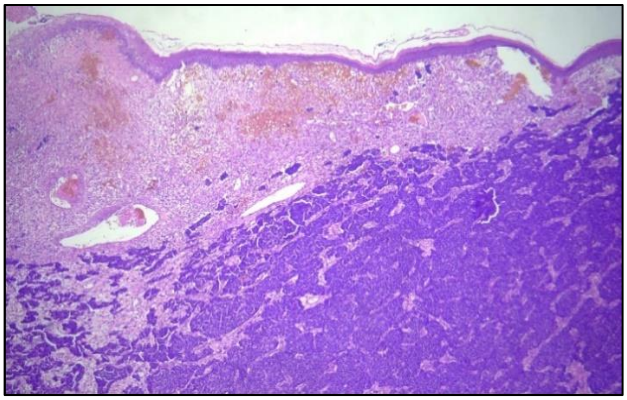

Figure 4: H&E-stained section 10x magnification showing polypoidal lesion lined by stratifies squamous epithelium with ulceration. Sub epithelial region show a cellular neoplasm composed of intermingling nests and sheets.

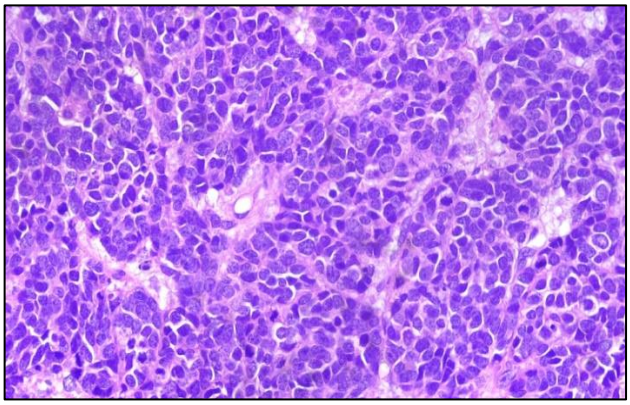

Figure 5: H&E stained 40x magnification section showing relatively small sized cells with round nucleus, stippled chromatin, inconspicuous nucleoli and scanty cytoplasm.

On working up the patient hematological investigations revealed high serum creatinine levels and a nephrology consultation was done to check the feasibility of doing contrast enhanced computed tomography. After intravenous hydration with normal saline, CECT was done in which a well-defined heterogeneously enhancing polypoidal soft tissue density mass lesion measuring approximately 24.0×17.4×12.0 mm was noted at the level of laryngeal inlet causing moderate luminal narrowing (Figure 2). No fat density areas/ calcifications/ central necrosis was seen within the lesion. No obvious lysis/ sclerosis of arytenoids was noted.

The lesion was found to extend adjacent to inter-arytenoid mucus fold and the adjacent posterior wall and was also seen abutting the right aryepiglottic fold laterally. The lesion was seen extending superiorly into lower aspect of laryngo-pharynx and abutting the posterior pharyngeal wall. A few sub centimetric cervical lymph nodes were noted in bilateral level II and III regions without evidence of central necrosis/

calcifications. No significantly enlarged lymph nodes were seen. Rest of the airway was patent. The trachea appeared normal. Vallecula, epiglottis and vocal cords appeared normal. Strap muscles were normal. A CECT of the thorax and ultra-sonogram of abdomen was done to rule out distant metastasis. A direct laryngoscopy was done under general anaesthesia for assessment and biopsy. Intraoperatively, the mass was found to be large, firm and mobile with a broad-based origin, arising from right aryepiglottic fold. An excision of the mass with cauterization of base was done and steroids were given considering the chance of post-operative stridor. Excised mass was sent for histopathology; patient was stable after procedure (Figure 3). Histopathology showed a polypoidal lesion lined by stratified squamous epithelium with sub epithelial region showing a cellular neoplasm composed of intermingling nests and sheets. Cells were relatively small sized with round nucleus, stippled chromatin, inconspicuous nucleoli, scanty cytoplasm and mitosis of 8-10/hpf was noted with stromal desmoplasia, suggestive of poorly differentiated high grade malignant small round cell neoplasm (Figure 4,5). Immunohistochemistry was done further, expressing Ki67 up to 60-70%, diffusely positive CK and focally positive chromogranin and synaptophysin. Thus, the overall pathologic features were suggestive of neuroendocrine tumour grade 3 with Ki67 positivity up to 60-70%. After a multidisciplinary meeting with radiation oncologist and pathologist, we decided to follow up the treatment with radiotherapy. Total of 66 Gy in 33 fractions were given. Follow-up endoscopic evaluations showed no residual lesion. Patient showed good tolerance and had complete recovery from all the symptoms.

Table 1: Depicting various classification systems suggested for neuroendocrine tumours.

Woodruf et al[6]	Wenig et al[7]	WHO[1]	WHO[1]	WHO[1]
Small cell	Well differentiated	Typical carcinoid	Typical carcinoid	Well differentiated
Large cell	Moderately differentiated	Atypical carcinoid	Atypical carcinoid small cell	Moderately differentiated
	Poorly differentiated	Small cell (oat cell)	Combined small cell and non-small cell	Poorly differentiated Small cell Large cell
		Intermediate cell		
		Large cell		

Table 2: comparison of different immunocytochemical antibodies and their association with different types of laryngeal neuroendocrine neoplasms.

Antibody	Carcinoid tumour	Atypical carcinoid tumour	Small cell neuroendocrine carcinoma	Paraganglioma
Cytokeratin	+	+	+	-
Epithelial membrane antigen	+	+	+	-
Carcinoembryonic antigen	+	+	+	-
Calcitonin	+	+	+/-	-
Chromogranin	+	+	+	+
Leu 7 (CD57)	+	+	+	+
CD56	+	+	+	+
Neuron-specific enolase	+	+	+	+
Protein gene product 9.5	+	+	+	+
Galanin	-	-	-	+
Bombesin	+	+	+	-
Somatostatin	+	+	+	+
Serotonin	+	+	+	+
Thyroid transcription factor-1	-	+/-	+/-	-
S-100 protein	-	-	-	+
Glial fibrillary acidic protein	-	-	-	+

DISCUSSION

Laryngeal neuroendocrine neoplasms are a rare type of malignant neoplasms with broad morphologic and clinical spectrum unified by shared histologic, immunohistochemical and ultrastructural characteristics.[4]

The first description of NENs was made in a single case report published by Goldman et al.[5] Woodruff et al classified laryngeal NENs into small cell and large cell types.[6] In 1988 Wenig et al, introduced a new classification of laryngeal NENs based on one existing for pulmonary neuroendocrine carcinomas.

The types mentioned in their classification were well differentiated, moderately differentiated and poorly differentiated synonymous with carcinoids, atypical carcinoids and small cell carcinomas in that order.[7] Thereafter many classifications and nomenclatures have been published in literature. In this case report we present a poorly differentiated high grade malignant small round cell laryngeal neuroendocrine tumour.

NENs show a predilection amongst patients between the ages of 55 to 75 years and incidence is more among men. It is considered that the high incidence of habits like tobacco and alcohol consumption is the cause for this sex disparity.[8] The clinical presentation and morphological appearance of the tumour varies greatly from squamous carcinomas which are more common in glottis. NENs are often located in the supraglottis rather than the glottis owing to the abundance of neuroendocrine cells in this area.[9-11]

Clinical presentations are usually of nonspecific symptoms like foreign body sensation, difficulty in swallowing, referred ear pain or change in voice as in any supra-glottic tumours.[12] Advanced diseases with metastasis to liver, lungs, bones and brain are seen in around two-third of patients.[13] Carcinoid syndrome and other paraneoplastic symptoms are rare in laryngeal NENs as most of them are non-secreting tumours.[1]

Histogenesis of the NENs has been an interesting topic in of discussion among pathologists. Located in the laryngeal respiratory epithelium's middle or basal layer are the neuroendocrine cells which are thought to be the precursor cells of laryngeal NENs whereas paraganglia cells of larynx giving rise to paragangliomas.14 Even a single tumour will show differentiation in diverging lines indicating the origin is from a common pluripotent primitive cell and not from any particular neuroendocrine precursor.[15]

Varying histopathology and heterogeneous nature of different entities under NENs led to confusing classifications and nomenclatures in the past. We intend to discuss two relevant classifications here (Table 1). Classically the laryngeal neuroendocrine neoplasms are classified into two main categories, neural (paragangliomas) and epithelial type tumours, later once again divided into carcinoid tumours, atypical carcinoid tumours and small cell undifferentiated carcinomas.[1] The latest (2022) WHO classification follows the IARC/WHO nomenclature framework.

A well differentiated neuroendocrine tumours are termed as neuroendocrine tumours (NET). They are graded according to necrosis, number of mitoses per 2 mm 2 and Ki67 positivity in to G1, G2 and G3. This system restricts the diagnostic term of neuroendocrine carcinoma (NEC) to poorly differentiated epithelial neuroendocrine neoplasms which is further divided into small cell and large cell neuroendocrine carcinomas based on cytomorphological characteristics.[16] This classification has got a strict correlation of morphology and immunohistochemical findings in the accurate diagnosis of neuroendocrine neoplasms.

Immunohistochemistry has proven to be the most useful tool in diagnosing different NENs with precision and differentiating them from other tumours with similar features in routine histological examination. In the current case discussed, Ki67 positivity up to 60-70%, diffusely positive CK and focally positive chromogranin and synaptophysin was found. Thus, the overall pathologic features were suggestive of Neuroendocrine tumour grade 3. Table 2 shows different laryngeal neuroendocrine neoplasms and specific immunohistochemical markers associated.[1]

Natural history and prognosis of NENs vary significantly among different subtypes. Typical carcinoids were previously considered to be indolent but later studies suggested loco-regional and distant metastasis in many cases. A 5-year survival rate of 48% was mentioned in a large series reported.[17] Atypical carcinoids are generally considered to be aggressive tomours.[18] Most of the cases show cervical lymph node and distant metastasis. 5-year survival of 40% has been reported in literature.[17]

Due to early distant metastasis, small cell neuroendocrine carcinomas have the very poor prognosis.[19] A 5-year survival rate of only 5% is reported in such cases.[20] Laryngeal paragangliomas are mostly benign in nature with only a few cases of metastatic disease reported.[13]

Management of different NENs vary greatly and is usually modified according to the extent of the disease also. Grade 2 NETs are usually managed by surgical removal. Chemo and radiation therapy are not regularly considered as options in such scenarios. But chemotherapy using combinations of cisplatin or etoposide are mainstay of management in case IC NECs. Sometimes this may be augmented with radiotherapy also.[4]

CONCLUSION

Early identification of histopathological subtype is crucial in management of neuroendocrine neoplasms. Owing to the scarcity of treatment algorithms, management is usually tailored to the patient according to extend of disease and subtype of tumour, some of which requires aggressive multidisciplinary treatment.

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