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Case Report

Neuroendocrine tumour of a larynx in 70-year-old man: a rare entity and a diagnostic challenge

Nida Shabbir[1], Ajay K. Singh[1], Manish Chandra[2], Sumaira Qayoom[1]*

[1]Department of Pathology, King George's Medical University, Lucknow, Uttar Pradesh, India
[2]Department of Otolaryngology, King George's Medical University, Lucknow, Uttar Pradesh, India

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***Correspondence:**
Dr. Sumaira Qayoom,
E-mail: qayoomsumaira@gmail.com

ABSTRACT

Neuroendocrine tumours of the larynx are rare yet neuroendocrine tumors is the second most common larynx tumour. According to the World Health Organization (WHO) 2022 classification, neuroendocrine tumours (NET) can be classified into well-differentiated, moderately differentiated and poorly differentiated. Well-differentiated NETs (typical carcinoids) of the larynx are rare and largely published as case reports. We present a case of a 70-year-old male with a history of hoarseness of voice for 1 year. Grossly, the tumour was globular and encapsulated. Based on histopathological features and immunohistochemistry results, the final diagnosis of a well-differentiated Neuroendocrine tumour was rendered. For carcinoid tumours of the larynx, conservative surgical resection is the preferred treatment without elective neck dissection. This tumour has a favourable prognosis, rare recurrences, and minimal metastasis.

Keywords: Immunohistochemistry, Neuroendocrine tumors, Larynx, Typical carcinoid

INTRODUCTION

In 1980, Markel et al published the first histological description of laryngeal 'carcinoid,' a lesion of the larynx.[1] Duvall et al reported the first well-documented case of laryngeal "carcinoid" in 1983.[2] Following squamous cell carcinomas, second most common tumor involving larynx is neuroendocrine tumor. According to World Health Organization (WHO), there are four types of neuroendocrine tumours (NETs): atypical carcinoid tumors, typical carcinoid small-cell neuroendocrine carcinomas, and paragangliomas.[3,4] A revised WHO classification series explained terms like well-differentiated neuroendocrine carcinoma (WD-NEC) and moderately-differentiated neuroendocrine carcinoma (MD-NEC), as well as poorly differentiated neuroendocrine carcinomas.[4] To accurately diagnose tumors, we must distinguish between tumors originating from epithelial and those with neural origins. In terms of epithelial origin tumors, there are WD-NECs, MD-NECs, small cell neuroendocrine carcinomas, and large cell neuroendocrine carcinomas; whereas neurons are the source of paragangliomas.[1] The frequency of carcinoid tumors is lower than that of other laryngeal neuroendocrine tumors. To the best of our knowledge (google search, PubMed, google scholar) approximately 21 cases are reported till date. Here, we describe a rare case of a laryngeal Well differentiated neuroendocrine tumor and discuss the morphological and immunohistochemical aspects.

CASE REPORT

The 71-year-old male presented with hoarseness of voice and intermittent haemoptysis over the past year. A history of substance abuse has been documented in the form of smoking and tobacco chewing for over 50 years. On physical examination, there was no lymphadenopathy, and the rest of the systems were within normal limits. On computed tomography (CT), an ill-defined

heterogeneously enhancing soft tissue lesion measuring 2.0×1.3 cm mass was seen in the supraglottic region involving the left aryepiglottic fold, superiorly extending into pre-epiglottic space and inferiorly extending up to the level of false cord. Routine investigations including complete blood count, erythrocyte sedimentation rate, renal function tests, liver function tests, random blood sugar levels, and electrolytes were within normal range. Direct laryngoscopy revealed polypoidal laryngeal mass with a smooth surface was seen which was excised and sent for histopathologic examination. On gross examination, the tumor was greyish white, globular, encapsulated measuring 1.2×1.0 cm. Cut surface showed grey white homogeneous areas. Histopathological examination revealed well-encapsulated tumors (Figure 1a) arranged in nests and lobules separated by thin fibrous septa (Figure 1b). Individual tumor cells have round to oval nuclei, displaying a 'salt and pepper' chromatin pattern and a moderate amount of granular eosinophilic cytoplasm (Figure 1c).

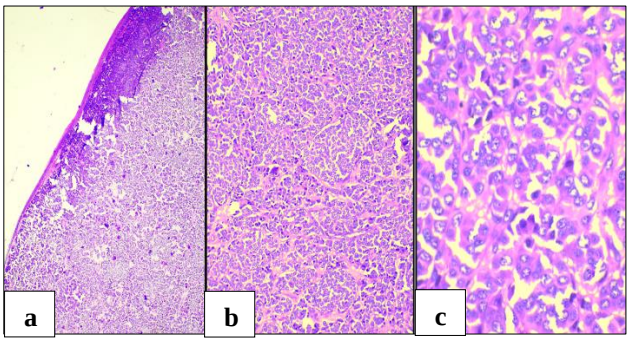

Figure 1 (a-c): Section shows encapsulated tumor (H&E, a, 40X) disposed in nests and lobules separated by thin fibrous septa (H&E, b, 100X). Individual tumor cells are round to oval with stippled chromatin, conspicuous nucleoli and moderate eosinophilic cytoplasm (H&E, c,400X).

There was no marked pleomorphism or necrosis. As a result of the above histomorphology, the following differential diagnosis was considered: Neuroendocrine tumour, paraganglioma, granular cell tumours, and soft part sarcoma. On immunohistochemistry (IHC), the tumour cells show strong immunopositivity for AE1/AE3, chromogranin, synaptophysin and calcitonin (Figure 2a-d). S100 is positive in interspersed sustentacular cells (Figure 2e). Tumor was negative for P40, desmin, CD56, vimentin, P53 and SMA (Figure 2f-k). Mib 1 labelling index was 12% (Figure 2l). Based on histomorphology and IHC findings the final diagnosis of a well differentiated neuroendocrine tumour of the larynx was made (Table 1).

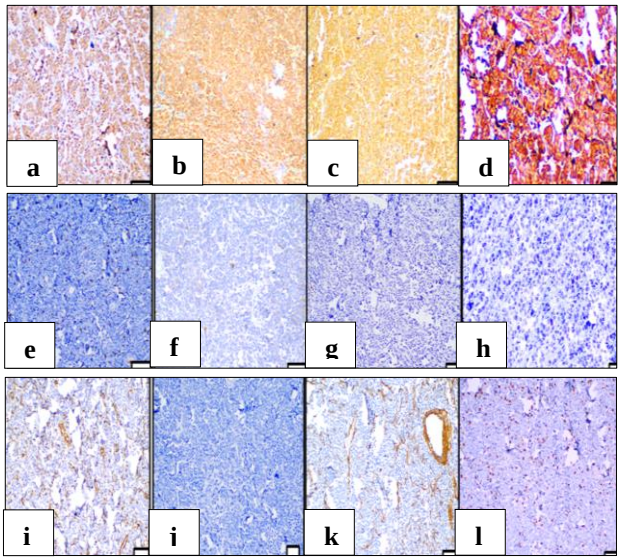

Figure 2: Tumor cells were strongly positive for (a) AE1/AE3, (b) synaptophysin, (c) chromogranin, and (d) calcitonin; (e) S-100 highlighted interspersed sustenacular cells; tumor cells were negative for (f) p40, (g) desmin, (h) CD56, (i) vimentin, (j) p53, and (k) SMA; and (l) Mib1 labelling index was 12%.

Table 1: Immunohistochemistry findings in NET and its differential diagnosis.

Differntial diagnosis	CK	Synaptophysin	Chromogranin	S100	SOX10	Vimentin	Ki67 (%)
Well differentiated NET (typical carcinoid)	+	+	+		-	-	<20
Moderately differentiated NET (atypical carcinoid)	+	+	+	+	-	-	>20
Paraganglioma	-	+	+	+	-	-	<10
Granular cell tumors	-	-	-	+	+	-	<10
Soft part sarcoma	-	-	-	-	-	+	<10

DISCUSSION

WHO defined four different types of neuroendocrine tumor of the larynx: typical carcinoid tumor, atypical carcinoid tumor, small-cell neuroendocrine tumor, and paraganglioma.[5] Even though in head and neck region, NET's involve larynx most commonly yet typical carcinoid tumor in the larynx is very uncommon and accounts for 0.5% to 1% of all epithelial neoplasms. An excellent prognosis has been established for this well-differentiated malignant lesion, with demonstrated capabilities for both regional and distant metastases. Male patients have a slight predominance with a 3:1 male-to-female ratio and usually present in sixth to eight decade of life.[4,6] Smokers and non-smokers are equally at risk for these tumors. Torrente et al found the significant

association of NECs with human Papilloma virus infection.[7] There are numerous schools of thought concerning the origin of this tumor. Some say it grows from Kulchitsky-like argyrophilic cells in the laryngeal mucosa that are similar to those in the bronchial mucosa, while others suggest it develops from pluripotent stem cells in the surface epithelium.[8] As a result of the release of several neuroendocrine hormones like serotonin, growth hormone, insulin, gastrin, glucagon, CgA and calcitonin neuroendocrine carcinomas can be detected by IHC and serological methods. In most cases, serum CgA and calcitonin levels are the most commonly measured hormone. The serum CgA level plays role in determining treatment response and prognosis as its levels have significant correlation with tumor volume, differentiation, and secretory activity.[9]

The most common site for origin is the supraglottic larynx, especially the arytenoid of the aryepiglottic fold as these areas contain abundant numbers of neuroendocrine cells. The patients present with non-specific symptoms like hoarseness, dysphagia, sore throat and duration of symptoms may vary from 4 weeks to 10 years.[10] Lymph nodal metastasis is rare in typical carcinoid tumor but may be seen in extended follow-up.[11] Ferlito et al have reported liver metastasis in one case associate with carcinoid syndrome.[12] Hemalatha et al also reported a case of carcinoid with lymph node metastasis.[13] Similarly, Van der Laan et al concluded that distant metastasis is extremely low in well- differentiated NET of larynx but could be upto 90% in moderately and poorly differentiated NET of larynx.[14]

Grossly, the tumor presents as a submucosal or polypoid mass with an average size of 0.3-4 cm. Microscopically, the tumor cells are small to medium sized with mild to moderate pleomorphism, round to oval nuclei, salt-pepper chromatin, inconspicuous nucleoli and moderate amount of clear to pale eosinophilic cytoplasm.[15] Significant pleomorphism or atypia is not seen. In well-differentiated NETs, mitotic activity is very low (<2 per 10 high power fields), necrosis is absent, very rarely with perineural and vascular invasion.[16] In addition to focal "Zellballen" arrangements, oncocytic/oncocytoid cells may also be detected. On histomorphology, well differentiated NET closely resembles paraganglioma which can be differentiated on immunohistochemistry. NET are strongly positive for synaptophysin, chromogranin, CD56 and AE1/AE3, negative for S-100 and GATA-3 while paraganglioma are negative for AE1/AE3 and positive for GATA.[17] Some paragangliomas stain positive for AE1/AE3 but stain is either weak or focal.[18] NETs are consistently positive for low–molecular-weight cytokeratin (CK7, CK8, CK18, CK19, CK20), epithelial membrane antigen, and carcinoembryonic antigen.[3,5] MIB1/Ki67 index is <20%. The use of Ki67 labelling index is controversial however, many studies have suggested that Ki67 index should be low in the setting of WD-NEC (<20%). As in our case, Ki67 is 15%. On histomorphology, WD-NEC is differentiated from MD-NEC on the basis of mitotic rates, cell size, nucleoli prominence, and necrosis presence. Specific histological criteria for distinguishing WDNEC and MD-NEC are mitotic counts (<2 per high power field) and the absence of necrosis which are most reliable features for WD-NEC. The presence of these features may be poorly represented in small, incisional biopsies, making diagnosis challenging. As paragangliomas are negative for cytokeratins and include a subpopulation of peripheral S100-positive, sustentacular cells around tumor nests, it is relatively easy to distinguish them from paragangliomas.[19]

Surgical excision is the treatment of choice. For desirable functional results and lower morbidity, minimally invasive approaches (transoral CO2 laser or transoral robotic approach) are recommended. According to van der Laan et al, the 5-year disease-specific survival rate of typical carcinoid tumors is 100%, and local excision alone can cure them.[14] Can laryngeal WD-NECs metastasize? Ultimately, this is the question that matters. A similar clinical dilemma exists in other organs as well. For example, there is a difference in metastatic rate between ileal and gastric "carcinoids". Hence, the importance of defining the true metastatic potential of WDNEC in the larynx cannot be overstated.

CONCLUSION

Last but not least, precise diagnosis and definitive tumor subtyping based on histomorphological features in conjunction with immunohistochemistry are key in the management of neuroendocrine neoplasms. There are significant differences in the treatment modalities and prognostic factors between the various entities in this group. It is important for pathologists to employ the current classifications and diagnostic criteria for WD-NEC and MD-NEC to differentiate them. Diagnostic and treatment of laryngeal WD-NEC should not be based on the assumption that it is an indolent tumor but rather on the assumption that it is a low-grade carcinoma with the potential to metastasize.

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