



# Cutaneous Metastasis of Laryngeal Neuroendocrine Carcinoma: a Case Report

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Received: 11 December 2018 / Accepted: 2 May 2019 / Published online: 28 May 2019  
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## Background

Laryngeal neuroendocrine carcinomas (LNECs) are rare, constituting < 1% of all tumors of the larynx [1]. Approximately 550 cases have been reported in literature till date. There are four histological subtypes distinguished based on the extent of differentiation and cell size. The atypical carcinoid tumor/moderately differentiated is the most frequent of all LNECs, followed by the small cell neuroendocrine carcinoma, paraganglioma and the typical carcinoid (well differentiated) [1, 2]. Lymph node metastases are often present. Other sites of metastases includes- bone, skin (22%), subcutaneous tissues, distant lymph nodes and lung with a poor 5-year survival rate. Fine needle aspiration cytology (FNAC) can be used as a minimally invasive tool for diagnosis in metastatic cases and obviate the need for biopsy [3]. There is limited literature on the role of FNAC as an investigating tool for such patients. We report a 60-year-old male patient with metastatic neuroendocrine carcinoma to lymph node and skin, which developed 2 years after primary diagnosis.

## Case Presentation

A 60-year-old male presented with left neck swelling along with multiple nodular lesions over the abdomen and back for 1

month. He was a chronic bidi smoker since last 40 years. Previous surgery and histopathology report 2 years ago, had shown a neuroendocrine carcinoma, moderately differentiated (grade II) in right aryepiglottic fold. Currently on examination patient had swelling in right level Ib cervical region measuring 2 × 1.5 cm and was well defined, soft, non-tender. No other lymph nodes were palpable. There were multiple subcentimetric, non-tender subcutaneous swellings over the left anterior abdomen wall and right scapular region (Fig. 1a–c). USG neck revealed well-defined solid non-necrotic node with central echogenicity on the right side measuring 2 × 1.1 cm in size.

FNAC of right cervical lymph node as well as abdominal subcutaneous swelling and right scapular region were done using 23-gauge needle and rapid on-site screening was done using toluidine blue stain. The smears from all the three sites were cellular and showed loose clusters and singly dispersed cells with stippled chromatin and prominent nucleoli (Fig. 2a, b). A provisional diagnosis of metastatic carcinoma was given. Following toluidine blue, smears were sent for routine PAP and Giemsa staining along with cell block preparation. The routine cytological stained slides revealed high cellularity with monotonous singly dispersed cells and loose clusters of cells. Focal areas of rosetting were also seen. The tumor cells had eccentric nuclei with high n/c ratio, stippled chromatin and occasional prominent nucleoli. There were also seen some multinucleated tumor giant cells (Figs. 2c, d and 3a, b). Cell block smears had similar morphology of tumor cells (Fig. 3c). Immunohistochemistry from cell block showed strong positivity for synaptophysin and chromogranin (Fig. 3d). A final diagnosis of metastatic neuroendocrine carcinoma was given. The patient was then sent for whole-body PET scan with i.v. inj of 4.59 mCi of <sup>18</sup>F-FDG which revealed metabolic activity in the aryepiglottic fold with cervical and mediastinal lymphadenopathy along with emphysematous changes in bilateral lung parenchyma (Fig. 1d–e). Currently, the patient is under conservative follow-up owing to poor socioeconomic status and disseminated metastasis.

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**Fig. 1** a, b, c Swellings over right level Ib cervical region measuring  $2 \times 1.5$  cm, well defined, soft, and non-tender. Also seen were multiple subcentric subcutaneous swellings over the left anterior abdomen wall and right scapular region. d, e, f Whole-body PET scan revealed metabolic

activity in the aryepiglottic fold with cervical and mediastinal lymphadenopathy along with emphysematous changes in bilateral lung parenchyma

## Discussion

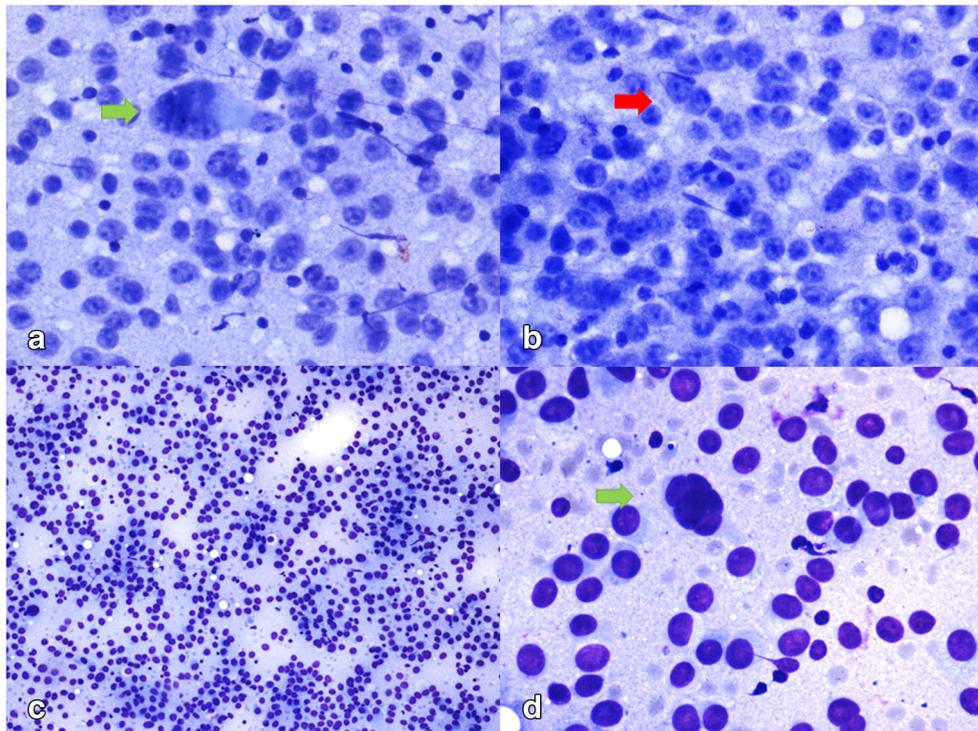
Neuroendocrine tumors (NETs) of the larynx are a heterogeneous group of neoplasms accounting for 0.6–1% of laryngeal neoplasms [1]. About 550 cases have been reported in the literature, the first in 1969 by Goldman et al. [4]. The origin of such tumors has not been clearly identified, but there is a belief that the precursor cells belong to the diffuse neuroendocrine system. It is the most common non-epidermoid tumors of the larynx and mainly affects males (M:F 3:1) with a median age of diagnosis being 36–83 years (mean age 61 years). The most important recognized risk factor is history of smoking in > 70% patients [5].

Neural (paraganglioma) and epithelial origin (typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma) can be distinguished based on pathological features [5]. Atypical carcinoid (54%) was the most frequent type, whereas typical carcinoid

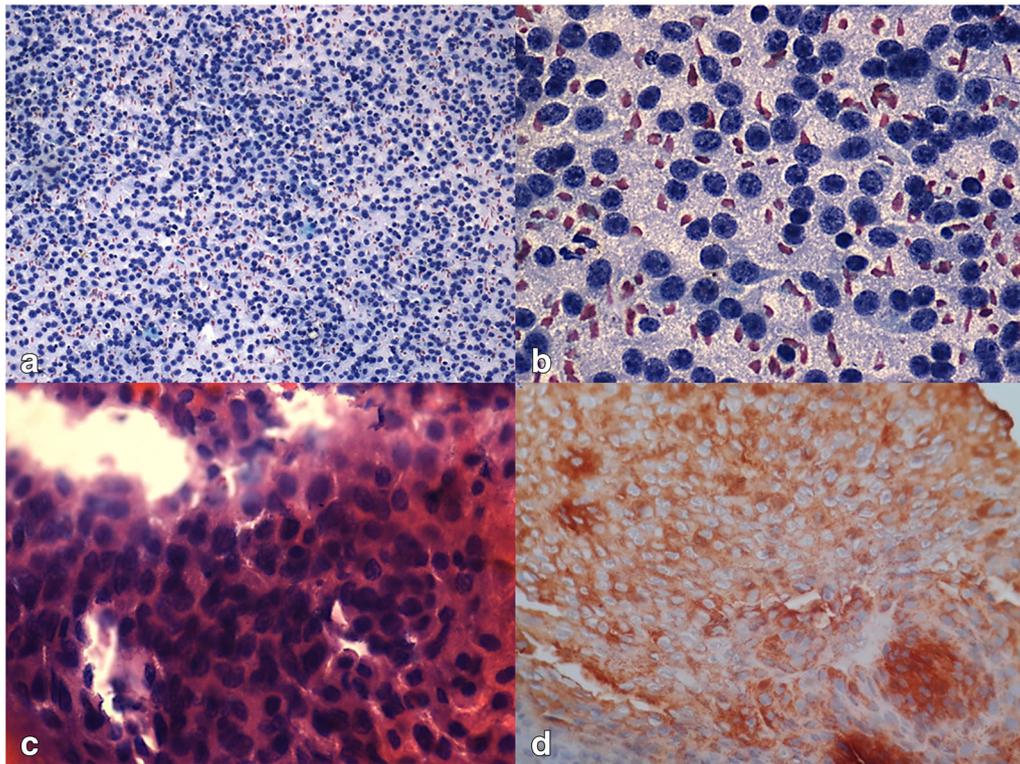
was very rare (3%) [2]. The supraglottic region is the most common site (90% of cases in aryepiglottic fold, arytenoid and epiglottis), and small cell carcinoma presents a more homogeneous involvement of the whole organ [5, 6].

Clinical presentations are not characteristic and may differ according to the extent and the site of disease. The most common symptoms are hoarseness in voice, difficulty in swallowing, pain, hemoptysis and shortness in breath [5]. Associated paraneoplastic syndrome is exceptionally rare [2]. The prognosis and biological behavior of laryngeal NETs vary widely according to the histological tumor type, i.e., typical carcinoids and paragangliomas have a smoldering clinical course and rarely metastasize. Atypical carcinoids show an intermediate behavior, while small cell and large cell neuroendocrine carcinomas are very aggressive tumors [2, 7].

Metastatic sites include the cervical and distant lymph nodes, lung, bones, skin, subcutaneous tissues, mediastinum, liver, heart, pancreas, diaphragm, peritoneum, gastrointestinal tract,



**Fig. 2** a, b, c, d Cytosmears were cellular and showed singly dispersed cell with stippled chromatin and prominent nucleoli. Few multinucleated tumor giant cells (green arrow) and focal areas of rosettoid pattern were also seen (red arrow) (TB  $\times 40$  and Giemsa  $\times 10, \times 40$ )



**Fig. 3** a, b Cytosmears showed tumor cells with eccentric nuclei, high n/c ratio, stippled chromatin, and prominent nucleoli. c, d Cell block smears also had similar morphology of tumor cells. Immunohistochemistry showing strong positivity for synaptophysin. (PAP  $\times 10, \times 40$ , H&E  $\times 40$ , IHC  $\times 40$ )

prostate, breast, brain, dura mater, pleura, testicles and muscles [8]. The most common site of metastases is the lymph node (43%), followed by skin and subcutaneous tissue (22%). In cutaneous metastasis, the lesions can be single or multiple nodules, non-ulcerated, painless and of slow growth, ranging from 0.5 to 2.5 cm in diameter. The location was most frequently on the cephalic segment (typical) or trunk [9].

FNAC can play an important role in rapid diagnosis of neuroendocrine tumors. On FNAC, NET findings are distinctive enough, with or without ancillary tests such as electron microscopy or immunocytochemistry. The “neuroendocrine” round-to-oval nuclei, stippled nuclear chromatin, inconspicuous nucleoli and plexiform background of small blood vessels with adherence of cells to vascular core are distinctive. Plexiform vascular pattern may not be an obvious feature in metastases [5]. NETs stain for synaptophysin (100%), cytokeratin (96%), chromogranin A (94%), calcitonin (80%), CEA (75%), somatostatin (50%), serotonin (21%) and adrenocorticotrophic hormone (17%) [2].

Surgery is preferred and a partial or total laryngectomy may be done depending on the site of the tumor. In view of the high incidence of cervical lymph node metastasis, a neck dissection even when the lymph nodes are clinically negative can be performed. CO<sub>2</sub> laser/somatostatin/chemotherapies/electrochemotherapy can be used for multiple skin metastases and were all unsatisfactory [1, 10–12].

The prognoses of patients with atypical laryngeal carcinoids are relatively poor; the 3-, 5-, and 10-year survival rates were 44.0%, 22.0% and 13.0% [1, 2]. The cause of death is due to metastatic disease rather than local recurrence. Although the incidence of cutaneous and subcutaneous metastases from atypical laryngeal carcinoids is approximately 22%, few systematic analyses of clinical manifestations or treatment of such metastases have been reported [11]. The mechanism by which distant metastasis and local recurrence develop remains unclear, so does the relevant prognostic factors [1].

LNECs are rare and metastasis to multiple sites carries very poor prognosis. Lymph node and skin metastases have rarely been reported on cytology. FNAC with onsite evaluation can avoid the need for invasive procedure. Radiotherapy and chemotherapy have not been of much success in these patients.

**Authors' Contributions** TS carried out data acquisition, data analysis, and manuscript preparation and will stand as guarantor also. KK carried out concepts and design, literature search, and participated in clinical study. MA carried out concepts and design and literature search. All the authors have read and approved the final manuscript.

**Data Availability** All the data regarding the findings are available within the manuscript.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Consent to Publish** Written consent for publication for this case study and any additional related information were taken from the patient involved in the study.

**Abbreviations** CEA, carcinoembryonic antigen; FDG, fludeoxyglucose; FNAC, fine needle aspiration cytology; LNEC, laryngeal neuroendocrine carcinomas; NETs, neuroendocrine tumors; PAP, Papanicolaou; PET, positron emission tomography

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