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CASE REPORT

Trends in Otorhinolaryngology
Head and Neck Surgery

Large cell neuroendocrine carcinoma of hypopharynx: A distinct histopathological entity

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Abstract

Aim: *To present a case of large cell neuroendocrine carcinoma (LCNEC) involving the hypopharynx focusing on the histopathological diagnosis, radiological investigations and oncology treatment.*

Methodology: *A case report with relevant literature review*

Case report: *A 71-year-old Caucasian male presented with a four-month history of right sided sore throat, a one-month history of feeling something stuck in his throat at the level of the larynx associated with a deeper voice and two weeks history of right referred otalgia. On examination his voice has a rough but there was no stridor. There was a 2 x 2 cm node palpable in the right neck level II. Flexible pharyngolaryngoscopy revealed an exophytic growth on the right aryepiglottic fold that was covering the whole of the glottis. However, panendoscopy showed a large exophytic mass filling up the right piriform fossa involving the adjacent aryepiglottic fold and the postcricoid region. The biopsy confirmed the LCNEC and the fine needle aspiration cytology showed metastasis in his neck. The scans did not show any widespread disease in the body. He was managed in the multidisciplinary team setting and was treated with chemoradiotherapy.*

Conclusion: *LCNEC involving the hypopharynx is an extremely rare clinical entity with poor prognosis. Early diagnosis and radical treatment with chemoradiotherapy would appear to be an acceptable treatment option.*

Keywords: *neuroendocrine carcinoma; large cell neuroendocrine carcinoma; hypopharynx; histopathology; chemoradiotherapy; prognosis*

Introduction

Neuroendocrine carcinomas (NEC) in the head and neck region is a rare entity, accounting for 0.49% of all malignancy [1]. In the 2017 edition of the WHO Blue Book "Tumours of the Head and Neck", improvement in the terminology and classification of NEC had been made, dividing these into well-, moderate- and poorly-differentiated NEC. The latter is further divided into small cell NEC and large cell NEC (LCNEC) [2]. LCNEC which was previously associated in the WHO 2005 edition with atypical carcinoid/moderately differentiated NEC, grade II, has now been reclassified into the group of poorly differentiated NEC, grade III, displaying a specific morphology and poorer prognosis [2-4]. Extra-pulmonary LCNECs arising in the head and neck region occur most frequently in the larynx and paranasal sinus, and rarely in the hypopharynx [3,5].

To the best of our knowledge there are only 4 published cases of LCNEC in the hypopharynx, including a case in a series of 8 patients with mucosal LCNEC in the head and neck region. We present a case of LCNEC involving the hypopharynx, our clinical experience in the management of LCNEC and review of relevant literature.

Material and Methods

A 71-year-old Caucasian male presented with a four-month history of right sided sore throat, four-week history of feeling something stuck in his throat at the level of the larynx associated with a deeper voice and two-week history of right referred otalgia.

On examination his voice was a bit rough but there was no stridor. There was a 2 x 2 cm node palpable in the right neck level II region. Flexible nasolaryngoscopy revealed an exophytic growth on the right aryepiglottic fold that was covering the whole of the glottis. The CT scan showed tumour extending from the right side of the epiglottis along the aryepiglottic fold into the pyriform sinus, the right paraglottic fat across the midline at the level of the glottis. There were large right-sided cervical lymph nodes with a maximum short axis diameter of 15 mm. The lungs were clear. The mediastinum was normal. Radiologically, appearances were suggestive of a supraglottic tumour with ipsilateral lymphadenopathy and no distant metastases although indeterminate left adrenal nodule (T3 N2b M0).

However, panendoscopy showed a large exophytic mass filling up the right piriform fossa involving the adjacent aryepiglottic fold and the post-cricoid region (Figure 1).

The biopsy confirmed the LCNEC and the fine needle aspiration cytology showed metastasis in his neck (Figure 2).

The PET scan did not show any widespread disease in the body. He was managed in the multidisciplinary team setting and was treated with chemoradiotherapy. He received 65 Gy in thirty fractions to the primary tumour site and involved nodal levels simultaneously with 54 Gy in thirty fractions to the remainder of his bilateral neck nodal levels concurrently with Cisplatin and Etoposide delivered every three weeks.

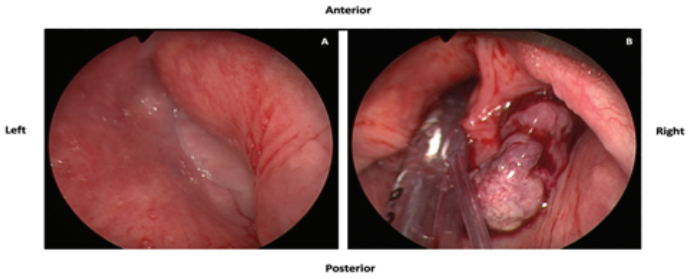

Figure 1: *Endoscopic photograph showing an exophytic tumour mass in the right pyriform fossa attached to its medial wall and involving the post-cricoid region. In comparison the left pyriform fossa is clear.*

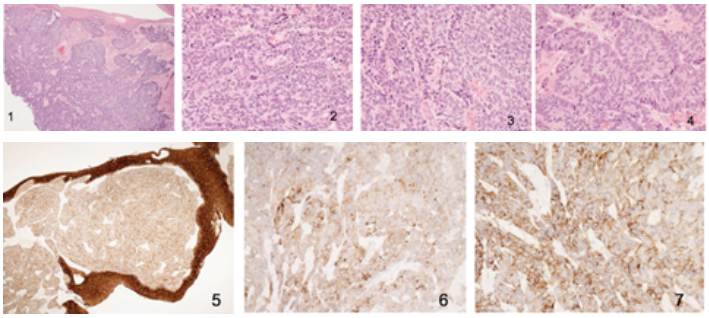

Figure 2: *Histological slides of LCNEC.*
1. Squamous mucosa with extensive subepithelial carcinoma which is architecturally trabeculated and solid with hyperchromatic nuclei; 2. Solid and trabeculated tumour with hyperchromatic nuclei and numerous mitoses; 3. More solid tumour in which the cells have little cytoplasm and slightly granular nuclei with mitoses (more small cell carcinoma-like); 4. Trabeculated and nested tumour with peripheral palisading in which the cells have plentiful cytoplasm and small nucleoli, still with numerous mitoses; 5. Immunohistochemistry: positive cytokeratin; the surface squamous epithelium has slightly darker staining than the tumour; 6. Immunohistochemistry: positive synaptophysin (neuroendocrine marker); 7. Immunohistochemistry: positive CD56 (neuroendocrine marker).

He continued to attend the head and neck oncology follow up clinic at 2-3 months interval for 30 months after completion of his treatment. On each visit there was a satisfactory appearance of his upper aerodigestive tract (Figure 3). Then he presented with 4 days history of blood-stained mucus expectoration, worsening dysphagia and intermittent right referred otalgia. The flexible laryngoscopy did not show any evidence of local disease recurrence. However, the CT scan showed possible disease recurrence in the right hypopharynx (Figure 4). It showed a 3 cm lobulated tumour mass centered on the right pyriform fossa but extending superiorly into involve the aryepiglottic fold and the pre epiglottic space and base of tongue. Laterally there is infiltration of the right thyroid lamina and posteriorly the tumour abuts the posterior pharyngeal wall but does not infiltrate the prevertebral muscles. There was a suspicion of mediastinal metastatic disease. The PET scan showed "there is an intense uptake in relation to the right pyriform fossa and right aryepiglottic fold. This extends laterally with involvement of the right thyroid cartilage. A subcentimetre right paratracheal node demonstrates similar intensity uptake and is regarded as suspicious for an involved node. The ill-defined plaque-like soft tissue adjacent to the left main bronchus demonstrates low to moderate uptake and is indeterminate".

Panendoscopy under general anaesthetic did not show any

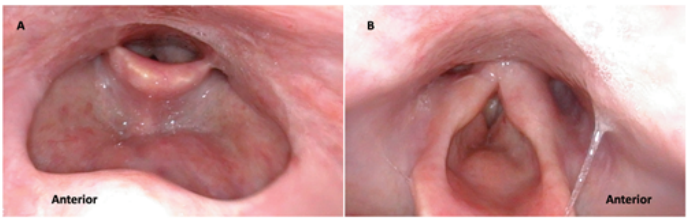

Figure 3: *Complete response to treatment as documented by endoscopic surveillance in the head and neck oncology follow up clinic. The tongue base and epiglottis (A); Supraglottis, glottis and bilateral pyriform fossae clear of disease*

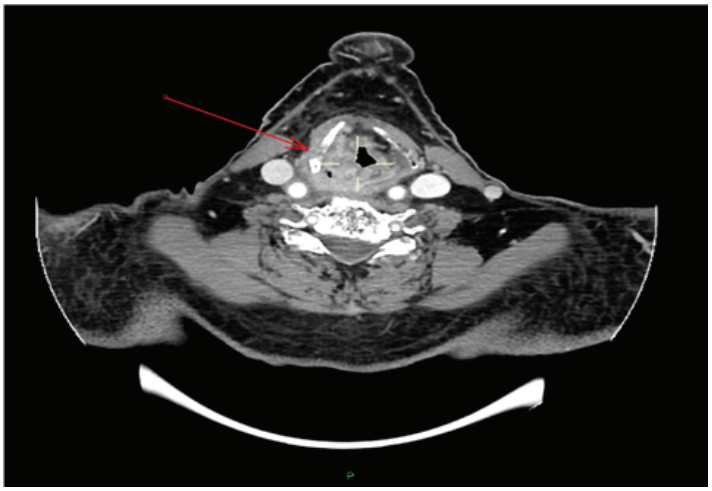

Figure 4: *CCT scan showing right hypopharynx fullness*

mucosal abnormality but deep submucosal biopsies were taken from the right hypopharynx. To our surprise the histology showed a squamous cell carcinoma in his right hypopharynx. There was definite squamous morphology with no neuroendocrine features or neuroendocrine positivity.

He received further radical radiotherapy. Unfortunately, he continued to deteriorate with disease progression and within 6 months passed away peacefully with aspiration pneumonia.

Results

In the past decade, LCNEC has received considerable interest and discussion amongst pathologists and clinicians. Hypopharyngeal cancer often present at more advanced stage III and IV (80%) partly attributed to the anatomy and location of the hypopharynx. The cardinal symptoms of hypopharyngeal cancer are neck mass with approximately half of patients presenting with this; well localised sore throat and associated referred ear pain on swallowing; progressive dysphagia result in significant weight loss; and hoarseness with our without upper airway obstruction as late symptom of the disease [6]. Our patient had presented with most of these symptoms apart from the upper airway obstruction.

Histologically, LCNEC grows in nests, with occasional rosette formation and nuclear palisading. It is composed of large, polygonal cells with a low nuclear- cytoplasmic ratio, coarse nuclear chromatin, sometimes with a speckled salt-and-pepper quality, and a single prominent nucleolus. A high mitotic rate (>10 mitoses/2 mm2 or 10 high power fields) with extensive necrosis is usually observed [8]. Ki67 index reportedly has a prognostic

significance, as well as the grading and staging of the disease [9]. Poorly differentiated NEC are immunopositive for at least one neuroendocrine marker (chromogranin, synaptophysin, or CD56) and low molecular weight cytokeratins, while TTF-1 is variably positive (Figure 1). Our patient had shown immunopositivity to more than one neuroendocrine marker. In the differential diagnosis, poorly differentiated NEC should be distinguished from basaloid squamous carcinoma, malignant lymphoma and malignant melanoma [2].

A recent meta-analysis published of 436 cases of laryngeal NECs, only 29 were LCNECs. Nearly 42% were small cell NECs followed by moderately differentiated NECs. There was a male preponderance of 3:1 for all subtypes except for well-differentiated NECs which gender predilection was not found. Majority of patients had a history of smoking (73-94%) and most often located in supraglottis (60-96%) [10]. Recent data also showed that the poorly differentiated laryngeal NECs are not associated with hrHPV infection, unlike the tumors at the other sites [11,12].

Management of LCNEC remains a challenge due to the inadequate understanding on this rare malignancy. Early diagnosis and radical treatment with chemoradiotherapy has been widely accepted as the treatment option. Hijoka et al. had observed in their cohort of pancreatic NEC, those with poorly differentiated NEC responded to platinum-based chemotherapy as oppose to those well-differentiated NEC. They have therefore recommended that this should be administered as first-line regimen [7]. Moertel et al. and Mitry et al. in their case series reported a 42– 67% response rate of high-grade NECs (from different primary sites) to cisplatin and etoposide, with a median response duration of 8–9 months and median overall survival of 15– 19 months. However, the authors have not distinguished their high-grade NECs, hence it is unclear the response of this oncologic regime in LCNEC [13,14]. The North American Neuroendocrine Tumour Society (NANETS) Consensus guideline (2010) had also recommended platinum and etoposide as the first-line chemotherapy for metastatic high-grade extrapulmonary NECs [9]. Lee et al. had reported a case of hypopharynx LCNEC treated with this combination but the tumour was resistant to the treatment [15]. Milroy described a 60-year-old man who presented with a composite squamous cell carcinoma and LCNEC of the hypopharynx without evidence of metastatic disease. Their patient showed complete disease response and no recurrence 15 months after the initial diagnosis with chemoradiotherapy (vincristine, bleomycin, methotrexate and folinic acid) [16]. Kusafuka et al had reported a case of hypopharyngeal LCNEC (T2N1) in their series of 8 patients with mucosal LCNEC in the head and neck region treated with unspecified surgery and chemotherapy died 90 months after diagnosis. The other 7 patients in their series died between 15 to 50 months despite surgery with or without oncologic treatment [17]. Our patient was treated with concurrent chemotherapy (cisplatin and etoposide) and radiotherapy.

In the NANETS Consensus guideline report, the 5-year disease-specific survival of NEC in the lung and thymus was 100% for well-differentiated NEC (carcinoid), 53% for moderately differentiated NEC (atypical carcinoid), 19% for SmCNEC, and 15% for LCNEC [10]. Lewis et al reported that 88% of patients with laryngeal LCNEC died of the disease [18]. Therefore, LCNEC in the head and neck region has a poor prognosis with most patients develop distant metastases and dying of disease within 2 years [19]. Thus new therapies are essential to improve long-term survival.

In conclusion, large cell neuroendocrine carcinoma (LCNEC) involving the hypopharynx is an extremely rare clinical entity. Publication prior to the WHO Blue Book in 2017 [2], LCNEC had been associated with atypical carcinoid tumour. However, it is now recognized as an aggressive high grade poorly differentiated NEC with a very poor prognosis. There is much still remains to be learned about the race, sex, primary tumor site distribution, and survival patterns in patients with these diseases to facilitate a more personalized treatment of the patients, particularly in the head and neck region, with this rare malignant neoplasm.

Acknowledgements

Dr P Brown, consultant Pathologist, ARI, Aberdeen, UK.

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Rec: 03 Oct 2021; **Acc**: 11 Nov 2021; **Pub**: 14 Nov 2021

Trends Otorhinolaryngol Head Neck Surg. 2021;1(1):105
DOI: 10.36879/TOHNS.21.000105