CASE REPORT

Hypopharyngeal large cell neuroendocrine carcinoma

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SUMMARY

Neuroendocrine carcinoma (NEC) of the head and neck is rare. We report a case of a 56-year-old man with a 6-week history of dysphagia, a neck mass and weight loss. He was diagnosed with a hypopharyngeal large cell NEC (LCNEC) with metastases to multiple sites. He received two cycles of cisplatin and etoposide. Subsequent restaging scan revealed progressive disease. The patient declined further chemotherapy and died shortly after. This is the third case of LCNEC of hypopharynx reported in the English literature and the first to progress on platinum-based chemotherapy. Although LCNEC of the head and neck is still classified as an atypical carcinoid, there is increasing evidence it is a distinct clinicopathological entity that carries an especially poor prognosis. Currently, there is a paucity of data to guide treatment of this rare malignancy.

BACKGROUND

Neuroendocrine carcinomas (NECs) are rare, accounting for 0.49% of all malignancies.¹ Historically, they have been recognised as commonly arising from the gastrointestinal and pulmonary systems,¹ but, increasingly, they have been identified from any anatomical site.² Traditionally, they have been classified by histological grade into typical carcinoid (low grade), atypical carcinoid (intermediate grade) and small cell NECs (high grade). NECs arising in the head and neck are also well described, especially in the larynx and paranasal sinuses.^{3–4} Laryngeal NECs are in fact the second most common non-squamous neoplasm arising from this anatomical position.³

In recent times, a fourth clinicopathological entity—the large cell NEC (LCNEC)—has been recognised.^{5–6} There is well-established literature, particularly for pulmonary LCNEC, showing distinct outcomes compared to other NECs. The most common site for extrapulmonary LCNEC is the larynx, followed by the parotid gland, with sparse case reports also showing it to occur in the sinonasal tract, the oral cavity, the oropharynx, the hypopharynx and the submandibular gland.² The current literature on NECs of the hypopharynx is limited to a small number of case reports.^{7–13} We report only the third case of a hypopharyngeal LCNEC tumour.

CASE PRESENTATION

A 56-year-old man presented with a 6-week history of progressive dysphagia, hoarseness and an enlarging neck mass. He was an active heavy smoker and had a distant history of heavy alcohol intake.

On examination, he had a large right conglomerate nodal mass (levels II–III) and a smaller left level II node. He had no visible oral cavity lesions and was maintaining his own airway without stridor.

INVESTIGATIONS

Fiberoptic laryngoscopy revealed a large mass arising from the posterior hypopharynx. A CT scan of the neck ([figure 1](#)) again showed a large hypopharyngeal mass with near complete obliteration of the upper aerodigestive tract and bilateral cervical lymphadenopathy. A positron emission tomography scan further demonstrated fluorodeoxyglucose-avid distant metastases to mediastinal lymph nodes, lung, liver and bone, without correlative structural lesions in the bones. The patient was clinically staged as T_{4a}N₃M₁ (stage IV_c).

Biopsy of the hypopharyngeal mass ([figure 2](#)) revealed a superficially ulcerated and inflamed, poorly differentiated carcinoma composed of variably sized nests, ribbons and sheets of tumour cells displaying peripheral nuclear palisading within desmoplastic stroma. The tumour cells possessed moderate amounts of pale eosinophilic cytoplasm with enlarged pleomorphic hyperchromatic nuclei showing nuclear membrane irregularity and brandishing prominent nucleoli. Mitotic and apoptotic figures were abundant, with up to 90 mitotic figures per 10 high-power fields; and tumour nests revealed frequent central comedonecrosis. The tumour cell nuclei exhibited ‘salt and pepper’ chromatin, but there were no well-formed rosettes or organoid arrangements, and features of small cell carcinoma were not present. On immunohistochemical interrogation, the tumour cells stained strongly patchy AE1/3+, CD56+ and synaptophysin+, with isolated cells staining for chromogranin and p63. There was no immunolabelling for CK7, CK5/6, p16 and smooth muscle actin, and EBER-ISH was negative. The Ki67 mitotic index approached 70%. These features were considered diagnostic of LCNEC of the hypopharynx.

TREATMENT

The patient had a tracheostomy to secure his airway and a percutaneous endoscopic gastrostomy tube for nutritional support. As the patient had a secure airway and widely metastatic disease, he was treated with platinum/etoposide doublet therapy (cisplatin 80 mg/m² on day 1 and etoposide 100 mg/m² on days 1–3), rather than upfront radiotherapy.

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Figure 1 Coronal section (A) and cross-section (B) of the CT scan, which revealed a hypopharyngeal mass (yellow arrows) and right cervical lymphadenopathy (red arrow).

OUTCOME AND FOLLOW-UP

A restaging CT scan 3 weeks after the second cycle of chemotherapy revealed significant progressive disease. The patient declined further chemotherapy and was planned for palliative radiotherapy for local control. Unfortunately, he soon died of presumed cardiopulmonary arrest before he received any palliative radiotherapy.

DISCUSSION

While LCNECs of the head and neck remained grouped with atypical carcinoids in the 2005 WHO classification,¹⁴ the sparse but emerging data suggest that it should also be considered a separate entity in the head and neck region, as it is clinically more aggressive and carries a worse prognosis.^{15–18} In a recent meta-analysis of laryngeal NECs, van der Laan *et al*¹⁵ reported a higher early metastasis rate of laryngeal LCNECs compared to the rest of the atypical carcinoids (70% vs 30%), as well as poorer 5-year survival (15% vs 53%). Instead, the metastasis rate (70% vs 67%) and 5-year survival rate (15% vs 19%) of LCNECs more closely correspond with that of small cell NECs.

The poor prognosis of LCNECs was also supported by the case series of Lewis *et al*,¹⁶ which reported a disease-related mortality of 89%, with most deaths occurring within 3 years of diagnosis despite treatment.

Owing to inadequate data on this rare malignancy, management remains a clinical challenge. In van der Laan *et al*'s¹⁵ recent meta-analysis of laryngeal NECs, chemoradiotherapy appeared to be the best management option for small cell NECs, with increased 5-year disease-specific survival compared to other modalities (31% vs 13%). However, the small number of LCNEC in the meta-analysis was insufficient to draw therapeutic recommendations for LCNEC of the larynx. Given the significant burden of metastatic disease and lack of local symptoms (after palliative interventions), induction chemotherapy was the preferred initial approach in our patient.

Treatment decisions are often made based on extrapolation of data from high-grade NEC or from different anatomic sites. Case series by Moertel *et al*¹⁹ and Mitry *et al*²⁰ reported a 42–67% response rate of high-grade NECs (from different primary sites) to cisplatin and etoposide, with a median response

Figure 2 Histopathological features of the hypopharyngeal tumour. (A) Large nests and ribbons of tumour cells, many with central comedonecrosis (H&E stain; original magnification $\times 40$). (B) Tumour cells with fine and coarse chromatin, prominent nucleoli and increased nucleus-to-cytoplasm ratios; features consistent with large cell neuroendocrine carcinoma (H&E stain; original magnification $\times 400$). On immunohistochemistry, (C) neoplastic cells demonstrate focal strong staining for CD56 (original magnification $\times 100$) and (D) synaptophysin (original magnification $\times 100$).

Table 1 Response rate of high-grade neuroendocrine carcinomas to chemotherapy, by site and histology

Site	Histology	Number of patients	Stage	Treatment modalities	Treatment response	Survival
Gastrointestinal (not including hepatobiliary) ²⁵	High grade	18	Extended stage	Cisplatin+etoposide (6%) or cisplatin+irinotecan (94%)	0% CR, 37.5% PR	MS 14.9 months
Hepatobiliary ²⁵	High grade	16	Extended stage	Cisplatin+etoposide	0% CR, 12.5% PR	MS 7.8 months
Bladder ²⁷	Small cell	20	Heterogeneous, 45% extensive stage	Best supportive care (20%), or surgery, or RTx, or CTx (65%), or combination	50% CR to CTx, 25% PR to CTx	MS 10 months
Head and neck ²⁴	Mostly small cell	23	Heterogeneous, 61% stage IV	Definitive surgery±platinum-based CTx (39%) or definitive RTx±platinum-based CTx (61%)	100% CR to RTx, 75% CR to CTx	5-year OS 33%, 5-year DSS 25%
Head and neck ¹⁵	Large cell	29	Heterogeneous, 70% stage IV	Surgery only (43%), or RTx only (21%), or combination (36%)	Unclear	5-year OS 14%, 5-year DSS 15%
Lung ²⁸	Large cell	144	Heterogeneous, 50% stage I, 1% stage IV	Surgery (majority)±induction CTx (15%) or postoperative CTx (17%)	80% response to induction CTx	5-year OS 43%

CR, complete response; CTx, chemotherapy; DSS, disease-specific survival; MS, median survival; OS, overall survival; PR, partial response; RTx, radiotherapy.

duration of 8–9 months and median overall survival of 15–19 months. Unfortunately, these studies did not histologically distinguish their high-grade NECs, hence the relative proportion of large cell versus small cell within these high-grade NECs remains unclear. However, based on these two studies, the North American Neuroendocrine Tumour Society (NANETS) Consensus guidelines of 2010 recommended platinum and etoposide as the first-line systemic chemotherapy for high-grade extrapulmonary NECs (both small cell and large cell) with metastatic disease.²¹

Elsewhere in the body, the management of LCNECs of the lung has been more extensively studied. Rossi *et al*²² demonstrated, in a case series of surgically resected patients with LCNEC, that the use of standard chemotherapy (platinum and etoposide) for small cell lung cancer (SCLC) as adjuvant therapy was associated with superior median survival (42 vs 11 months) in comparison with the use of chemotherapy regimes that are more frequently used in non-SCLC (NSCLC) (cisplatin and gemcitabine, or carboplatin and paclitaxel, or cisplatin and vinorelbine). Similar, Sun *et al*²³ also reported non-statistically significant higher response rate and longer progression free survival when SCLC regimes (platinum and etoposide) were used as first-line chemotherapy for advanced LCNEC compared to NSCLC regimens. On the basis of these studies and the NANETS Consensus guidelines, we chose cisplatin and etoposide as the first-line chemotherapy for our patient.

There have been two reported cases of LCNEC of the hypopharynx with vastly different outcomes to that seen in our patient. In Kusafuka's¹⁷ case series of mucosal LCNEC of the head and neck region, a case of a 52-year-old man presenting with T2N1 hypopharyngeal LCNEC was included. He was treated with unspecified surgery and chemotherapy, and was alive 90 months after diagnosis.¹⁷ 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).¹⁰ He was treated with chemoradiotherapy (vincristine, bleomycin, methotrexate and folinic acid) and showed complete disease response and no recurrence 15 months after initial diagnosis.¹⁰ In contrast, our patient's tumour showed primary resistance to the combination of cisplatin and etoposide. To the best of our knowledge, ours is the first reported case of treatment refractory hypopharyngeal LCNEC in the literature.²⁴

One possible explanation for this outcome is the inherent aggressiveness and chemo-unresponsiveness of extrapulmonary

NECs in comparison to SCLC. This is demonstrated in Terashima *et al*'s²⁵ study, which compared the response of metastatic extrapulmonary NECs versus extended stage SCLC to platinum-based chemotherapy. In this study, metastatic extrapulmonary NECs had a significantly poor rate of response to platinum-based chemotherapy compared to extended stage SCLC (30.8% vs 77.8%). There is some evidence of differential response to chemotherapy of high-grade NECs according to site of origin, with response rates as low as 14% for gastrointestinal NECs,²⁶ and as high as 75% for non-sinonasal NECs of the head and neck.²⁴ Table 1 lists the response rates reported by site and histology for high-grade NECs.

Learning points

- ▶ Extrapulmonary large cell neuroendocrine carcinomas (LCNECs) occur most frequently in the larynx and paranasal sinus, and rarely in the hypopharynx.
- ▶ LCNEC is associated with a more aggressive clinical course and a worse prognosis compared with other neuroendocrine carcinomas (NECs).
- ▶ Currently, North American Neuroendocrine Tumour Society Consensus guideline of 2010 recommended platinum and etoposide as the first-line chemotherapy for metastatic high-grade extrapulmonary NECs.
- ▶ Many studies in the past did not histologically distinguish LCNECs from small cell NECs; instead, they were often grouped together as high-grade NECs. This has resulted in a paucity of data regarding optimal treatment specifically for LCNECs of the head and neck.
- ▶ Future studies should focus on identifying a better treatment strategy for extrapulmonary LCNECs. Furthermore, treatment may need to be individualised depending on the anatomical locations of the NECs.

Competing interests None declared.

Patient consent Obtained.

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