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REVIEW

Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater

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ABSTRACT

Context Large cell neuroendocrine carcinomas of the ampulla of Vater are rare and confer a very poor prognosis despite aggressive therapy. There are few case reports of large cell neuroendocrine carcinomas of the ampulla of Vater in the literature and to date no studies have been done to establish optimal management. We describe a pooled case series from published reports of neuroendocrine carcinomas of the ampulla of Vater including a case which presented to our institution. **Methods** A narrative review was undertaken including all published English case reports of large cell neuroendocrine carcinomas of the ampulla of Vater. Our primary outcome was to determine overall survival. **Results** Twenty cases of large cell neuroendocrine carcinomas of the ampulla of Vater were identified. Seventy-six percent of patients were reported to have died of disease with mean survival of 11.8 months. Twenty percent of the tumours were associated with an adenoma. The approximate median survivals were 15 months for those with an associated adenoma and 11 months without. **Conclusions** This pooled analysis demonstrates both the rarity and poor prognosis of large cell neuroendocrine carcinomas of the ampulla of Vater. Although surgical resection is the mainstay of treatment, we review common adjuvant chemotherapy regimes. Prognosis may be improved when these tumours are associated with adenomas, however, more studies are needed.

INTRODUCTION

Neuroendocrine carcinomas of the ampulla of Vater are rare, accounting for less than 2% of all ampullary tumours [1]. They constitute a wide spectrum of neoplastic activity, both from the clinical and pathological perspective [2]. Given the clinico-pathological diversity, bespoke classification systems have been fraught to date.

Large cell neuroendocrine carcinomas (LCNECs) are highly aggressive [3] with a tendency for distant metastases and thus a poor prognosis [4]. Currently, there are numerous classification systems for LCNECs including the 2010 WHO classification [5], European Neuroendocrine Tumour Society (ENETS) grading system (2006) and the American Joint Committee on Cancer/Union for International Cancer Control (AJCC-UICC) system (2010) [6]. A recent study [7] has identified discrepancies between the aforementioned classification systems; however, regardless of the staging system employed LCNECs are aggressive tumours conferring extremely poor prognosis [8]. As reported by Nassar *et al*. [9], LCNECs are often associated with adenomas, although whether this has any clinical relevance remains unknown.

As LCNECs rarely occur in sites outside the tracheobronchial tree [10], there is a relative paucity of case reports in the literature of LCNECs of the ampulla of Vater. Due to this rarity there is unlikely to be randomised data or large case series to clearly establish optimal adjuvant treatment, thus evidence will always be low level [11]. It is difficult to know whether these ampullary located LCNECs should be treated differently to LCNECs on the whole, similar to the outcome differences seen in ampullary *versus* ductal adenocarcinoma of the pancreas. We describe a pooled case series from published reports of LCNECs of the ampulla of Vater, with the addition of a case which presented to our institution (AMNCH: Adelaide and Meath National Children's Hospital) (Table 1, Figure 1).

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Key words Ampulla of Vater; Carcinoma, Large Cell

Abbreviations AMNCH: Adelaide and Meath National Children's Hospital; HGNEC: high grade neuroendocrine carcinoma; LCNEC: large cell neuroendocrine carcinoma

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METHODS

An inclusive narrative review methodology was undertaken. In addition, we briefly review the diagnostic modalities used and the treatment decisions made in the case which presented to our institution. Electronic literature searches were conducted using

Table 1. Summary of cases of large cell neuroendocrine carcinomas reported in the literature.

Reference	Age (years)	Sex	No. of positive lymph nodes	Metastasis	Associated component	Ki-67 index	Follow up	Adjuvant therapy
AMNCH Case	52	Male	1	Liver	Villous adenoma	70%	Alive with disease at 20 months	Chemotherapy (cisplatin, etoposide, mannitol)
Cavazza *et al*. (2003) [3]	74	Female	Absent	Liver, L2-L3 vertebrae	Absent	NA	Died at 8 months	No chemotherapy (patient declined), palliative radiation
Cheng *et al*. (2004) [29]	55	Female	2	Liver, peritoneal seeding	Well-differentiated adenocarcinoma	60%	Died at 6 months	No adjuvant therapy (patient declined)
Hartel *et al*. (2004) [19]	44	Female	2	Absent	Absent	NA	NA	No adjuvant therapy
Nassar *et al*. (2005) [9]	61	Male	1	NA	Adenoma	NA	Died at 15 months	NA
	75	Male	1	NA	Absent	NA	Died at 30 months	NA
	84	Male	3	NA	Adenoma	NA	Died at 13 months	NA
	50	Female	5	NA	Absent	NA	Died at 16 months	NA
	77	Male	1	NA	Adenoma	NA	No disease at 17 months	NA
	80	Male	1	NA	Absent	NA	Died at 16 months	NA
	65	Male	4	NA	Absent	NA	No disease at 10 months	NA
	68	Female	4	NA	Absent	NA	Died at 4 months	NA
Huang *et al*. (2006) [30]	59	Male	5	Liver, peritoneal seeding	NA		Died at 10 months	Chemotherapy (cisplatin, cyclophosphamide)
Selvakumar *et al*. (2006) [1]	48	Male	2	Liver	NA	NA	NA	No documented adjuvant therapy
Liu *et al*. (2008) [16]	70	Female	Absent	Absent	Ductal adenocarcimona	90%	No disease at 1 month	No documented adjuvant therapy
Shu *et al*. (2006) [4]	76	Female	4	Liver, peritoneal seeding	Tubulovillous adenoma	NA	Died at 4 months	No adjuvant therapy (patient declined)
Selvakumar *et al*. (2008) [8]	47	Female	NA	NA	NA	NA	Died at 11 months	Chemotherapy
	45	Male	NA	NA	NA	NA	Died at 7 months	Chemotherapy
Stojsic *et al*. (2010) [10]	60	Male	NA	Liver	NA	41%	NA	Chemotherapy (etoposide, cisplatin)
Sunrose *et al*. (2011) [15]	73	Female	2	Liver, bone	Adenocarcinoma + squamous cell carcinoma	NA	Died at 13 months	Chemotherapy (cisplatin, irinotecan)

NA: information not available
AMNCH: Adelaide and Meath National Children's Hospital

MEDLINE (PubMed) from 1 January 2000 to 31 August 2011. All English case reports of LCNECs of the ampulla of Vater were selected. The selected search terms and related MESH headings were: "large", "neuroendocrine" and "ampulla". In each of the cases selected, the diagnostic criteria for LCNEC of the lung proposed by Travis *et al*. [12] were satisfied. According to these criteria, tumours are described as having cells at least three times larger than cells of a small cell carcinoma, neuroendocrine morphology (organoid growth pattern, cellular palisading, rosette formation) and an irregular chromatin pattern with brisk mitotic activity [13] (Figure 2a). These criteria were updated in the 1999 WHO classification [14], which added additional criteria including a high mitotic rate of greater than 11 mitoses (when 10 high-power fields of 2 mm^2 were examined), extensive necrosis and immunohistochemical evidence of neuroendocrine differentiation. The selected cases also fulfill these additional criteria with all LCNECs in our series immunostaining positive for neuroendocrine markers (Figure 2b). The primary outcome of interest was to determine the overall survival in this rare patient group. The secondary outcome was to determine if having an adenoma in association with a LCNEC improves prognosis.

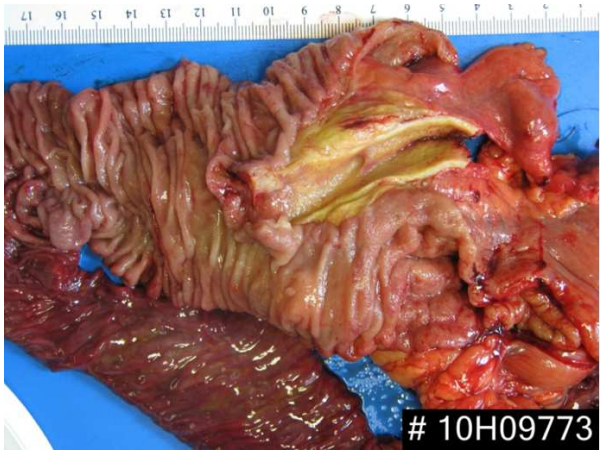

Figure 1. Macroscopically, a 1.5x1.5 cm circumferential fleshy ulcerated tumour is present surrounding the ampulla.

A database was constructed including: patient demographics; number of lymph nodes positive for metastases; sites of metastases; presence of a concomitant adenoma or other invasive component and the Ki-67 index of the tumour. We assessed patient status as no evidence of disease, alive with disease, and all cause mortality. The follow-up was recorded in months. The authors of the papers were contacted where data relevant to our study was not provided in the publication.

STATISTICS

A Kaplan-Meier curve was constructed to compare those ampullary LCNECs with and without associated adenomata. Log rank was used in the comparison with specific attention to the limited numbers available. The statistical analysis was made by means of the IBM SPSS (Armonk, NY, USA; version 18).

RESULTS

A total of 20 cases of LCNEC of the ampulla of Vater, including one case (AMNCH case) that presented to our institution, were identified.

Our incident case presented with obstructive jaundice. Hepatobiliary ultrasonography (US), magnetic resonance cholangiopancreatography (MRCP) and contrast computerised tomography of the abdomen (CT) showed intra- and extra-hepatic bile duct

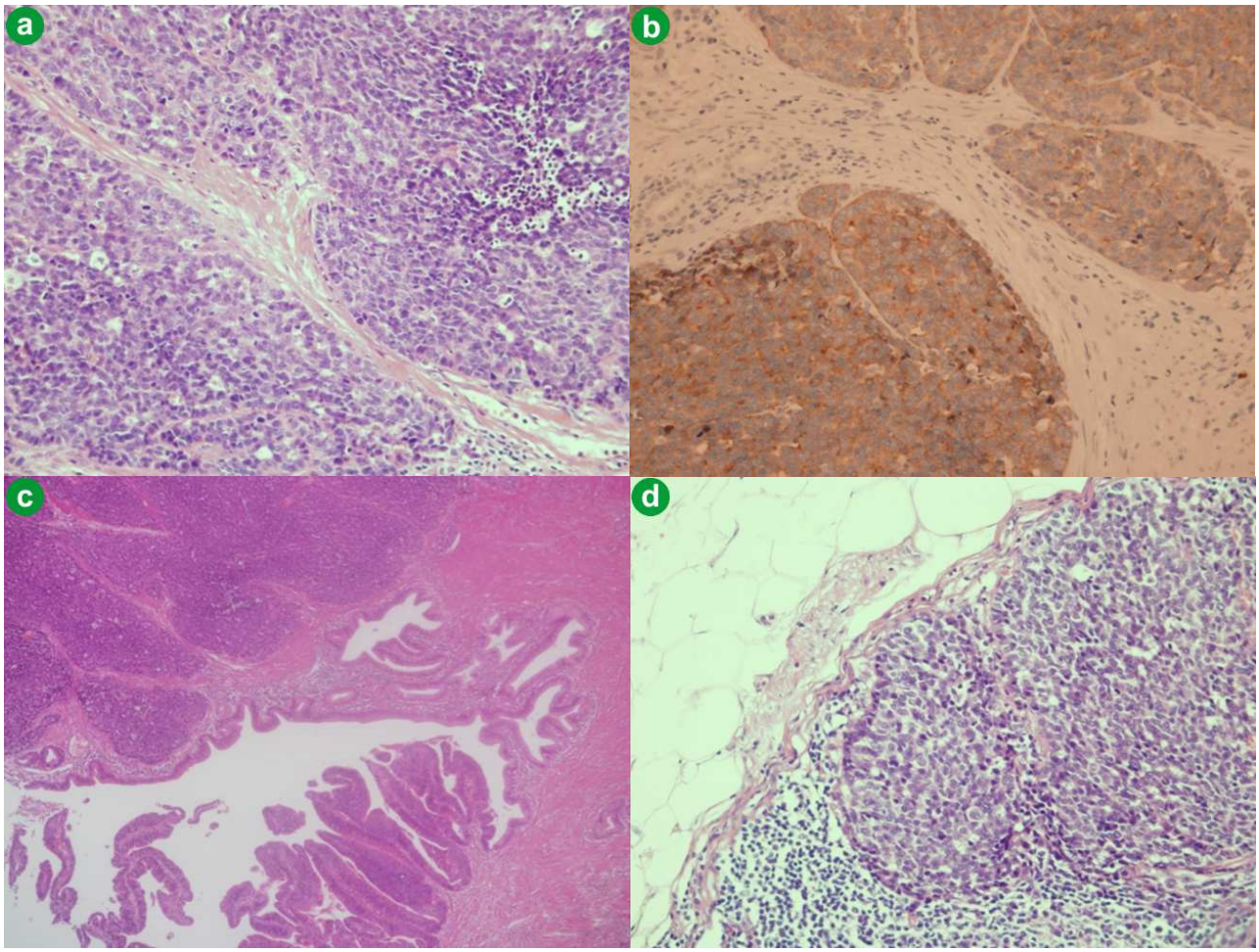

Figure 2. a. On high power magnification, the neoplastic cells are arranged in well defined solid nest and rosettes with oval vesicular nuclei containing occasional prominent nucleoli. Areas of necrosis are present. **b.** Tumour cells show strong immunohistochemical detection for synaptophysin. **c.** Large cell neuroendocrine carcinoma of the ampulla of Vater (top left of field), which is adjacent to a residual villous adenoma of the ampulla with low grade dysplasia (bottom of field). **d.** Regional lymph node metastasis. Magnifications: 200x, 200x, 20x, and 200x for **a.**, **b.**, **c.**, and **d.**, respectively).

dilatation, with a possible obstructing lesion at the ampulla of Vater. Endoscopic retrograde cholangiopancreatography (ERCP) showed an ulcerated irregular ampulla of Vater. Biopsy was positive for poorly differentiated adenocarcinoma, favouring ductal type. The patient underwent a pancreaticoduodenectomy. Histological examination of the surgical specimen confirmed a high-grade large cell neuroendocrine carcinoma of the ampulla of Vater, arising in association with an ampullary adenomatous polyp. He subsequently underwent four cycles of adjuvant chemotherapy (cisplatin, etoposide, mannitol). Sixteen months post-chemotherapy he was diagnosed with liver metastases. He is currently being considered for liver resection of the neuroendocrine tumour metastases on a supra-selected basis.

Table 1 provides a summary of the main clinical and pathological findings. The patients included 11 men and 9 women, ranging in age from 44 to 84 years (mean age 63 years). Four patients (20.0%) presented below the age of 50 years. All patients received surgical intervention with a pancreaticoduodenectomy. Six of the 20 patients (30.0%) received adjuvant chemotherapy. Four of the 6 patients (66.7%) who received adjuvant chemotherapy died of disease with a mean survival of 10.3 months. One patient received palliative radiation.

Overall, 13 of 17 (76.5%) patients with available follow up (range of follow up: 4-30 months) died of disease with a mean survival of 11.8 months despite complete surgical resection with pancreatico-duodenectomy. Three patients were alive with no evidence of disease at 1, 10 and 17 months, respectively. The patient who presented at our institution is alive with liver metastases at 20 months.

The patient presenting at our institution (Table 1; AMNCH case) had a villous adenoma associated with the LCNEC (Figure 2c). An associated adenoma was also found in 4 of the reported cases in the literature. The median survivals approximate 15 months for those with associated adenoma and 11 months without. This is not a statistically significant difference (Figure 3; Log rank P=0.420).

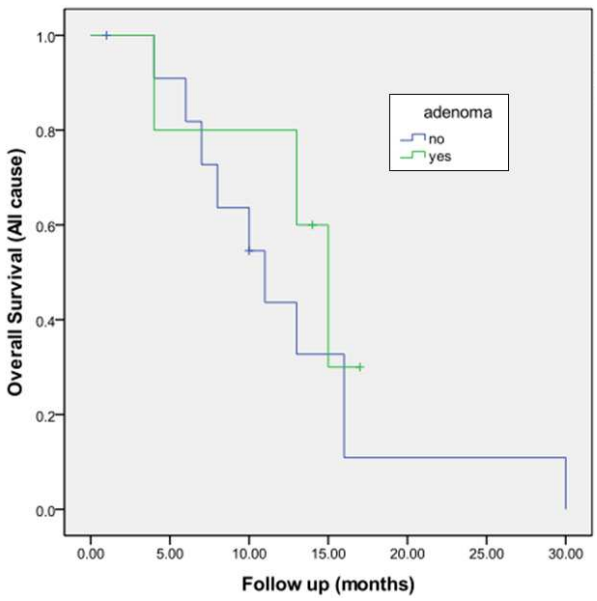

Figure 3. Overall survival (death for all causes) with and without documented associated adenoma. Given the low overall number the survival curve is a crude indicator only (n=17; Log rank, P=0.420).

Apart from adenomata, some other tumours had carcinoma associations. The LCNEC described by Liu *et al*. [1] was associated with an adenocarcinoma. Sunrose *et al*. [15] described a patient who had an adenocarcinoma with a squamous cell component associated with a LCNEC.

Lymph nodes were positive for metastases in 15 out of 17 cases (88.2%; Figure 2d), with a mean number of 2.2 nodes involved. The Ki-67 index was recorded in 4 cases, ranging from 41 to 90%. The commonest site of distant metastasis was the liver, with 8 out of 10 cases (80.0%) with recorded metastatic status being positive for liver metastasis. Other documented sites of metastasis were the peritoneum and bone.

DISCUSSION

Large cell neuroendocrine carcinomas of the ampulla of Vater are uncommon [2] and confer a poorer prognosis than both carcinoids and adenocarcinomas [16]. In a USA population-based study by Albores-Saavedra *et al*. [2], 6,081 cases of malignant neoplasms of the ampulla of Vater were reported between 1973 and 2006. Of these, 57 were high-grade neuroendocrine carcinomas (HGNECs), including only 6 LCNECs which were not discussed separately (hence unable to be included in our analysis). This leads to a very limited data set upon which to extrapolate adjuvant strategies for LCNECs.

In our pooled analysis, 76% of patients died with a mean survival of less than 12 months with the majority of patients developing metastases. Most patients had lymph nodes positive for metastases, further supporting that these tumours behave in an aggressive fashion. These results confirm the extremely poor prognosis associated with these tumours. Surgical resection was performed in all cases and, despite complete surgical resection, survival data in our pooled series is dismal.

The correct diagnosis and treatment of neuroendocrine tumours remains a challenge [17]. Biopsies obtained by ERCP may only achieve an accurate pre-operative diagnosis in approximately 14% of cases [18]. Often, these tumours are submucosal and therefore are undetectable in biopsy specimens [19]. In the case that presented to our institution, the pre-operative diagnosis, made by ERCP, was of poorly differentiated adenocarcinoma. After immunohistochemical analysis of the surgical specimen, the diagnosis was confirmed as LCNEC. Thus, this emphasises that the correct diagnosis is usually made after examination of the surgical specimen using histological and immunohistochemical techniques [1]. In a series of HGNECs of the ampulla of Vater by Nassar *et al*. [9], adenomas were associated with half of the cases.

Nassar *et al*. [9] reported 14 cases of HGNECs, of which 8 were LCNECs. Three of these cases of LCNECs were associated with concomitant adenomas. It has been proposed that this may indicate a common pathological origin for HGNECs and adenocarcinomas of the ampulla of Vater [4]. Due to the small number of reported cases of LCNECs associated with adenomas it is difficult to ascertain if there is an increase in survival in a patient with a LCNEC and a concomitant adenoma. As shown in the pooled series, 5 of the 14 cases with available data were associated with a concomitant adenoma. The median survivals approximate 15 months for those with associated adenoma and 11 months without. This is not a statistically significant difference and therefore difficult to draw any robust conclusion.

Surgical resection is the mainstay of treatment of neuroendocrine carcinomas and is currently the only treatment modality offering a potential cure [20]. All the patients in Table 1, including our incident case, underwent a pancreaticoduodenectomy. As LCNECs of the ampulla of Vater are so rare, there are no specific treatment strategies and all therapy must be individually tailored to the patient. Traditionally, first-line systemic adjuvant chemotherapy for high-grade, poorly differentiated neuroendocrine tumours is with cisplatin and etoposide [21]. In a study using these chemotherapeutic agents, a response rate of 67% was observed with a 19-month median survival [22]. Six of the 20 patients in Table 1 received adjuvant chemotherapy. Four patients who received adjuvant chemotherapy died of disease with a 10.3-month mean survival. The patient who presented to our institution received adjuvant chemotherapy and is alive with disease at 20-month follow up. Given this dismal data, there is an urgent need for more effective post-surgical adjuvant chemotherapy.

To date no studies have been done to establish optimal treatments for LCNECs of the ampulla of Vater, so currently we can only extrapolate data for other neuroendocrine carcinomas and apply it to patients presenting with LCNECs of the ampulla of Vater. As with LCNEC of the ampulla of Vater, LCNEC of the lung also carries a very poor prognosis [23]. Similarly, the optimal treatment for LCNEC of the lung has not yet been determined [24]. This said, it is known that surgical intervention alone is insufficient to treat pulmonary LCNECs [25] and it is necessary that patients receive adjuvant therapy [26].

Forty-six to 93% of patients with neuroendocrine tumours will have liver metastases at the time of diagnosis [27]. Patients who undergo a surgical liver resection usually have a more favourable outcome as compared with other therapies. Unfortunately only a small number of patients with metastatic neuroendocrine tumours are suitable surgical candidates [28].

In conclusion, the pooled case series of primary large cell neuroendocrine carcinomas of the ampulla of Vater confirms the rarity and poor prognosis associated with this disease. This limited data set provides no support that LCNECs of the ampulla of Vater behave in a more indolent way than non-ampullary LCNECs. There may be marginally improved prognosis if the LCNECs are associated with an adenoma but data sets are too small to confirm at present. More data and therapies, especially effective adjuvant chemotherapies, are urgently needed to help improve the survival rates of patients with LCNECs, a rare but aggressive tumour.

Conflict of interest None

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