CASE REPORT: A PATIENT WITH LARGE CELL NEUROENDOCRINE CARCINOMA OF UNKNOWN ORIGIN ACHIEVED AN EXCELLENT RESPONSE TO TEMOZOLOMIDE TREATMENT AFTER FAILURE OF TWO PREVIOUS CHEMOTHERAPY REGIMEN

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ABSTRACT

Abstract: Large-cell neuroendocrine carcinoma of unknown primary origin is a rare entity with limited data, primarily from retrospective analyses or case reports. We herein present the case of a 71-year-old female with stage IV disease and extensive nodal involvement. After limited success with Etoposide-Carboplatin and then FOLFIRI, the patient achieved a remarkable clinical and radiological response to Temozolomide. Through this case, we summarized key clinical, paraclinical, and treatment outcome data from the literature.

Keywords: Euroendocrine carcinoma, Cancer of unknown primary, Temozolomide.

1. INTRODUCTION

Cancers of unknown primary account for approximately 2% of all malignancies, among which neuroendocrine tumors represent less than 5%. Large-cell neuroendocrine carcinoma of unknown primary is an exceptionally rare entity, with very limited data available in the literature. Most retrospective analyses have focused on neuroendocrine carcinomas (NECs) in general, with little attention given to the large-cell subtype specifically.

As with other forms of NEC, first-line treatment for stage IV disease typically consists of a Platinum-Etoposide doublet. Although response rates are relatively favorable (approximately 60-70%), the duration of response is generally short. In subsequent lines of therapy, regimens such as Irinotecan, Paclitaxel, Topotecan, and Temozolomide have demonstrated low disease control rates, and no regimen has consistently shown clear superior efficacy.

Herein, we report a clinical case of stage IV large-cell neuroendocrine carcinoma of unknown primary that achieved a remarkable response to Temozolomide as third-line therapy.

2. CASE REPORT

Our case was a 71-year-old female with no significant past medical history. She presented to K Hospital due to self-examination of a left cervical lymph node. Her performance status was generally good. Peripheral lymph node

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examination revealed a left supraclavicular lymph node approximately 2 cm in size, firm, and with limited mobility. No other abnormalities were identified on systemic examination.

An excisional biopsy of the cervical lymph node was performed. Histopathological examination and immunohistochemistry confirmed large-cell neuroendocrine carcinoma (LCNEC), with the following profile: Chromogranin (+), synaptophysin (+), CDX-2 (−), napsin A (−), and TTF-1 (−).

A whole-body PET-CT scan demonstrated hypermetabolic lymphadenopathy involving cervical levels IV–V (maximum diameter 26 mm, SUVmax 10.1), mediastinal lymph nodes (maximum 14 mm, SUVmax 5.6), and abdominal lymph nodes predominantly in the right renal hilum region (maximum 17 mm, SUVmax 8.4). Based on clinical and imaging findings, the patient was diagnosed with neuroendocrine carcinoma of unknown primary, stage IV. Additional biomarkers, including PD-L1 expression and microsatellite instability (MSI) status, were negative.

Following multidisciplinary discussion and consultation with the patient and her family, first-line chemotherapy with Etoposide–Carboplatin was initiated. The treatment was well tolerated, with only mild fatigue lasting 3–5 days after each cycle and no other reported adverse events. After three cycles of EP, clinical examination showed minimal change in the size of the left supraclavicular lymph node. Computed tomography (CT) imaging demonstrated stable disease, with no significant change in cervical, mediastinal, or abdominal lymph nodes and no new lesions.

Given the patient's and family's preference for a more aggressive approach, Atezolizumab (anti–PD-L1) was added to the regimen (EP–Atezolizumab). However, after three cycles, the best response remained stable disease, with a 16% increase in the sum of lesion diameters (SLD) according to RECIST 1.1 criteria. Maintenance therapy with Atezolizumab was subsequently administered.

After two cycles of maintenance therapy, the patient reported enlargement and increased pain of right cervical lymph nodes. Follow-up CT imaging revealed disease progression, with enlargement of all previously identified lesions, including cervical lymph nodes (largest 28 × 39 mm), mediastinal lymph nodes (largest 30 × 46 mm), and retroperitoneal lymph nodes (largest 24 × 42 mm).

Considering the patient's relatively preserved condition and strong treatment intent, second-line chemotherapy with FOLFIRI was initiated. After four cycles, the disease continued to progress clinically and radiologically. The patient developed worsening abdominal pain, occasionally severe. CT imaging showed further enlargement of lymph node masses, with the largest abdominal lesion measuring 38 × 54 mm, associated with surrounding infiltration, consistent with the patient's symptoms.

After two lines of combination chemotherapy with suboptimal response and declining performance status, treatment options were discussed, including best supportive care versus exploratory oral chemotherapy with temozolomide. The patient and her family opted for the latter. Temozolomide was administered at a dose of 150-200 mg/m²/day orally on days 1–5 of a 28-day cycle. No dose reduction was required. The treatment was well tolerated. No grade ≥3 hematologic or non-hematologic toxicities were observed. The patient reported only mild fatigue (grade 1–2).

Remarkably, within the first month of Temozolomide therapy, the patient demonstrated significant clinical improvement. Bilateral

cervical lymph nodes decreased in size from approximately 4 cm to 1 cm. Abdominal pain resolved completely.

After two months of treatment, imaging assessment showed a near-complete response. The largest cervical lymph node decreased from 40 × 42 mm to 7 mm, the largest mediastinal lymph node from 30 × 46 mm to 12 mm, and abdominal lymphadenopathy was no longer detectable (previously up to 38 × 54 mm). Tumor markers also showed a dramatic decline: neuron-specific enolase (NSE) decreased from 4720 to 14 ng/mL, and pro-gastrin-releasing peptide (proGRP) from >5000 to 145 pg/mL.

The disease remained stable after four months of treatment. However, at the six-month evaluation, lymph node lesions began to increase in size again, with the largest cervical, mediastinal, and retroperitoneal lymph nodes measuring 14 mm, 24 mm, and 20 mm, respectively. At this stage, the patient and her family decided to discontinue specific anti-cancer treatment and focus on palliative care.

3. DISCUSSION

Cancers of unknown primary account for approximately 2% of all malignancies, of which neuroendocrine tumors comprise less than 5%. Neuroendocrine carcinomas (NECs) are poorly differentiated neoplasms that are typically diagnosed at an advanced or metastatic stage and are associated with a poor prognosis.

In patients with NEC of known primary origin, the literature reports high response rates (approximately 66%) with Platinum-based chemotherapy (Carboplatin or Cisplatin) in combination with Etoposide. Similarly, this doublet regimen has demonstrated activity in NEC of unknown primary and is considered the standard first-line treatment. In the largest published case series to date (n = 99), the objective response rate (ORR) reached up to 70.[1]

More recently, immune checkpoint inhibitors (ICIs) have demonstrated clinical efficacy in neuroendocrine malignancies such as Merkel cell carcinoma of the skin and small-cell lung cancer. However, data supporting their benefit in other neuroendocrine tumor subtypes remain limited. The non-randomized prospective LANCE study, published in June 2024, evaluated the addition of atezolizumab to standard chemotherapy in the first-line treatment of large-cell neuroendocrine carcinoma (LCNEC) of the lung. Owing to the rarity of this disease, only 17 patients were enrolled, including 10 patients treated with four cycles of Etoposide–Carboplatin plus Atezolizumab followed by maintenance therapy with the checkpoint inhibitor, and 7 patients treated with chemotherapy alone.

After a median follow-up of 23.3 months, the Atezolizumab-containing arm demonstrated improved 24-month overall survival (OS) rates (45.7% vs. 14.3%) and longer median OS (not reached vs. 8.2 months; hazard ratio [HR] = 0.37; 95% confidence interval [CI], 0.10–1.05) compared with the EP-only arm. Although limited by the small sample size, these findings provide preliminary evidence supporting the addition of Atezolizumab to first-line chemotherapy in metastatic pulmonary LCNEC.

Based on the findings of the LANCE study, we incorporated atezolizumab into the EP regimen in our patient with the aim of achieving a deeper and more durable response. With this first-line approach, the patient achieved a progression-free survival (PFS) of 6 months, which represents a clinically meaningful outcome in the context of the poor prognosis associated with LCNEC.

In subsequent lines of therapy, according to the National Comprehensive Cancer Network guidelines, several regimens have demonstrated clinical activity, primarily based on retrospective

studies, including FOLFOX, FOLFIRI, and temozolomide with or without capecitabine. In a retrospective analysis of 64 patients with extrapulmonary NEC who progressed after first-line platinum–etoposide therapy, regimens such as irinotecan, paclitaxel, topotecan, temozolomide, and paclitaxel–topotecan did not demonstrate clear superiority, with a median progression-free survival (PFS) of approximately 2 months and a median overall survival (OS) of 6–7 months. In our case, we selected the FOLFIRI regimen to optimize treatment tolerability and preserve quality of life. However, after only four cycles (approximately 2 months), the disease continued to progress both clinically and radiologically.

In the absence of standard third-line therapy for extrapulmonary NEC, temozolomide was selected based on its oral administration, tolerability, and reported activity in retrospective studies. Additionally, the patient's declining performance status and preference favored a less intensive regimen. Administered on a 5-day schedule every 28-day cycle, this regimen is convenient, does not require hospitalization, and is associated with a favorable toxicity profile. Moreover, the continuation of active anticancer therapy contributed positively to the patient's psychological well-being and treatment outlook. The patient achieved a near-complete response at the first evaluation after 2 months of treatment, with disease stabilization maintained for up to 6 months. Given the rarity of large-cell neuroendocrine carcinoma (LCNEC) of unknown primary, available evidence is limited and largely derived from retrospective analyses and case reports. Consequently, treatment recommendations are often extrapolated from data on small-cell neuroendocrine carcinoma, particularly small-cell lung cancer, due to shared histopathological characteristics. Evidence regarding the efficacy of temozolomide in LCNEC of unknown primary remains particularly scarce.

In a phase II study (2021) by Noritoshi Kobayashi et al., evaluating temozolomide monotherapy following platinum–etoposide therapy, only one patient with unknown primary tumor was included among 13 patients with extrapulmonary NEC. Unlike our case, that patient experienced disease progression at the first assessment, with a progression-free survival (PFS) of only 1.8 months. Another retrospective analysis by Staffan Welin et al. (2011) evaluated temozolomide, with or without capecitabine, in patients with extrapulmonary NEC. However, only 5 of 25 enrolled patients had tumors of unknown primary origin, and detailed data regarding histological subtypes (large-cell vs. small-cell), treatment response, and survival outcomes for this subgroup were not specifically reported. Taken together, our case represents one of the few reports demonstrating a significant clinical benefit of temozolomide in a patient with stage IV large-cell neuroendocrine carcinoma of unknown primary.

Are there any factors that may predict response to Temozolomide in neuroendocrine carcinoma? A meta-analysis of 11 studies demonstrated that patients with neuroendocrine tumors harboring O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation or low MGMT protein expression achieved higher objective response rates to alkylating agents than those without these features. [5]

The MGMT gene is located on chromosome 10q26 and encodes a DNA repair enzyme capable of rapidly reversing DNA damage induced by alkylating agents, thereby maintaining genomic stability.[6] The promoter region of the MGMT gene contains 97 CpG sites. Methylation of these CpG sites may lead to alterations in chromatin structure, inhibit the binding of transcription factors to the promoter region, and ultimately result in gene silencing. In other words, MGMT promoter methylation suppresses MGMT enzyme

activity, rendering tumor cells more sensitive to alkylating agents such as temozolomide. However, in routine clinical practice at K Hospital, as well as in Vietnam more broadly, testing for MGMT promoter methylation status is not yet widely available and remains costly.

Despite the remarkable response observed in this case, the efficacy of temozolomide in LCNEC remains uncertain due to limited data and heterogeneity of reported studies. The observed benefit may reflect underlying biological factors, including potential MGMT deficiency, although this was not assessed in our patient.

4. CONCLUSION

We report a case of stage IV large-cell neuroendocrine carcinoma of unknown primary that achieved a dramatic response to temozolomide. This case provides additional clinical evidence supporting the potential role of temozolomide in this rare and challenging disease.

REFERENCES

[1]. Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. *Semin Oncol*. 2009;36(1):52-59. doi:10.1053/j.seminoncol.2008.10.003

[2]. Evangelou G, Trontzas IP, Gkiozos I, et al. The Effectiveness of Atezolizumab in Metastatic Large Cell Neuroendocrine Carcinoma of the Lungs: Insights from the LANCE Pilot Study. *Biomedicines*. 2024;12(6):1161. doi:10.3390/biomedicines12061161

[3]. Kobayashi N, Takeda Y, Okubo N, et al. Phase II study of temozolomide monotherapy in patients with extrapulmonary neuroendocrine carcinoma. *Cancer Sci*. 2021;112(5):1936-1942. doi:10.1111/cas.14811

[4]. McGarrah PW, Leventakos K, Hobday TJ, et al. Efficacy of Second-Line Chemotherapy in Extrapulmonary Neuroendocrine Carcinoma. *Pancreas*. 2020;49(4):529-533. doi:10.1097/MPA.0000000000001529

[5]. Qi Z, Tan H. Association between MGMT status and response to alkylating agents in patients with neuroendocrine neoplasms: a systematic review and meta-analysis. *Biosci Rep*. 2020;40(3):BSR20194127. doi:10.1042/BSR20194127

[6]. Travis WD. Pathology and diagnosis of neuroendocrine tumors: lung neuroendocrine. *Thorac Surg Clin*. 2014;24(3):257-266. doi:10.1016/j.thorsurg.2014.04.001

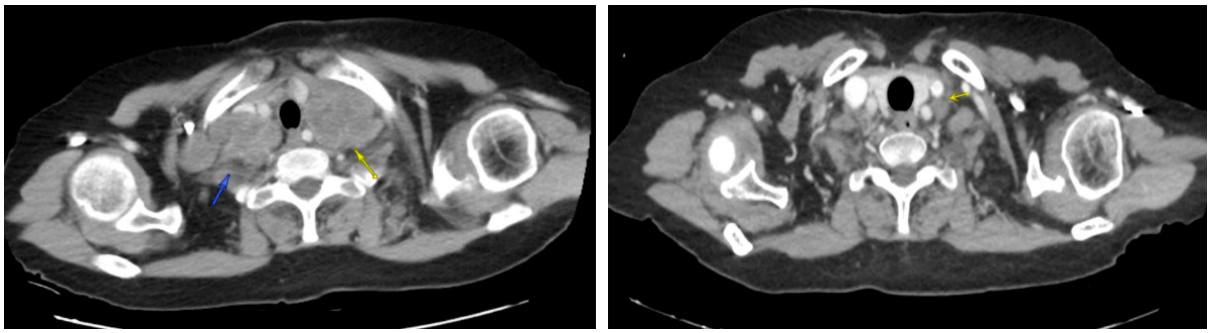

Figure 1. CT scan of the neck before and after Temozolomide treatment

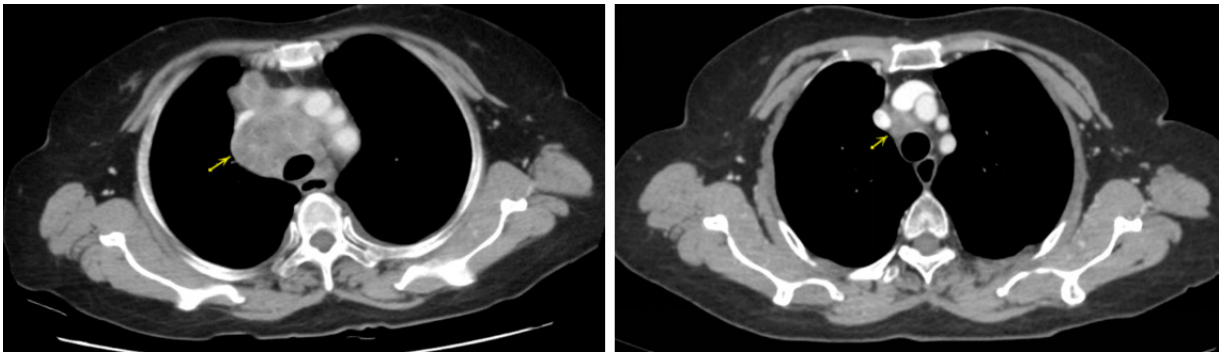

Figure 2. CT scan of the chest before and after Temozolomide treatment

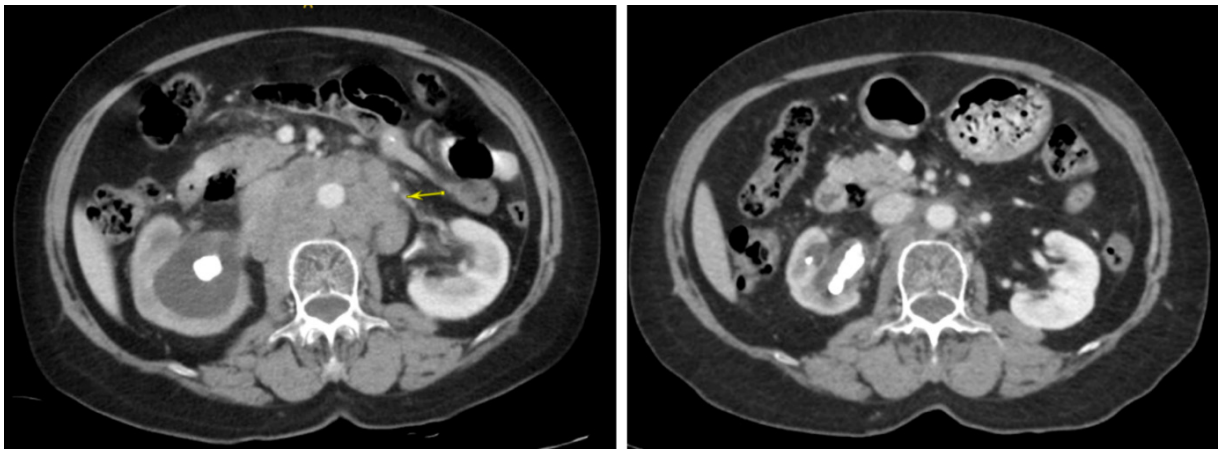

Figure 3. CT scan of the abdomen before and after Temozolomide treatment