

Perioperative serplulimab-based chemoimmunotherapy in stage IV large cell neuroendocrine carcinoma of the lung: A case report

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Abstract. Large cell neuroendocrine carcinoma (LCNEC) is a rare and enigmatic tumor, characterized by neuroendocrine features and a poor prognosis similar to small cell lung cancer (SCLC). The present report details the case of a 45-year-old male with oligometastatic stage IV LCNEC who achieved clinical cure after undergoing perioperative immunochemotherapy. Despite the typical non-recommendation of surgery for stage IV cases, based on the insistence of the patient, the present study initiated three cycles of neoadjuvant therapy combining serplulimab (a programmed cell death protein 1 inhibitor) with chemotherapy, resulting in the radiological disappearance of the tumor. Pathological complete response was confirmed following resection of the primary tumor. The treatment continued with three cycles of adjuvant therapy using serplulimab and chemotherapy, followed by maintenance therapy with serplulimab alone. After 17 cycles of maintenance therapy, a positron emission tomography-computed tomography scan revealed a complete metabolic response of the metastasis, and radiological scans revealed no visible tumor

or distant metastasis, indicating a clinical cure. Event-free survival has exceeded 11 months, and overall survival has exceeded 14 months. The present case highlights the efficacy of immunochemotherapy in treating advanced LCNEC.

Introduction

Lung cancer is the most common malignant tumor type in the world (1). Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and highly aggressive malignancy, with an overall age-adjusted incidence rate of 0.3/100,000 in the United States between 2000-2013 (2). Characterized by rapid progression and poor prognosis, LCNEC presents limited therapeutic options (3). Although classified as a non-small cell lung cancer (NSCLC), LCNEC shares more similarities in biological behavior with SCLC (4). The high aggressiveness of LCNEC, along with the difficulties in diagnosis and nonspecific symptoms in the early stage of LCNEC, often lead to a stage IV diagnosis, reducing surgical opportunities (5,6). Furthermore, the rarity of LCNEC contributes to the lack of randomized clinical trial data. Consequently, the current first-line treatment for LCNEC typically involves a combination of platinum-etoposide chemotherapy and immunotherapy or palliative radiotherapy, resulting in unexpected 5-year OS rates ranging from 15 to 57% (7).

Historically, immunotherapy had been deemed unsuitable for lung cancer treatment due to weak immune responses (8). However, the discovery of immune checkpoints (ICPs) has revolutionized lung cancer treatment, enabling the integration of immunotherapy with various therapeutic strategies (9). ICPs are proteins produced by immune cells (such as T cells) and cancer cells, which result in cancer cells escaping immune-mediated tumor cell death; the application of checkpoint inhibitors (CKIs) targeting ICPs has yielded beneficial outcomes (9).

Programmed cell death protein 1 (PD-1), one of the most extensively studied ICPs, and its corresponding CKIs (PD-1 monoclonal antibodies) have been incorporated into lung cancer immunotherapy (10). PD-1 monoclonal antibodies have shown promising prospects in lung cancer clinical trials and are recommended in oncological guidelines in multiple countries (11). However, due to the rarity of LCNEC, clinical trials evaluating the efficacy of immunotherapy are currently focused on lung adenocarcinoma and squamous lung cancer.

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Abbreviations: LCNEC, large cell neuroendocrine carcinoma; pCR, pathological complete response; ICPs, immune checkpoints; CKIs, checkpoint inhibitors; PD-1, programmed cell death protein 1; CEA, carcinoembryonic antigen; UNL, upper normal limit; TSH, thyroid stimulating hormone; FT3, triiodothyronine; FT4, thyroxine; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; TTF-1, thyroid transcription factor-1; CK, cytokeratin; CgA, chromogranin A; Syn, synaptophysin; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer

Key words: chemoimmunotherapy, large cell neuroendocrine carcinoma, lung cancer, neoadjuvant

The present report presents a successful case of LCNEC treatment, involving a perioperative treatment with immunotherapy, which resulted in a pathological complete response (pCR) post-surgery.

Case report

In March 2023, a 45-year-old man visited Fujian Medical University Union Hospital (Fuzhou, China) to evaluate a pulmonary mass incidentally identified during a routine medical examination. The patient smoked an average of 30 cigarettes per day for 30 years but denied any respiratory or systemic symptoms. The patient experienced a significant weight loss of ~5 kg over the previous 3 months, and clinical assessment revealed a body mass index of 27.1 with an overweight status. The patient reported no family history of cancer or chronic diseases and considered himself generally healthy. Physical examination did not reveal any notable abnormalities. Comprehensive laboratory tests indicated a markedly elevated carcinoembryonic antigen (CEA) level at 73.3 ng/ml (Fig. 1B), 10-fold higher compared with the upper normal limit (UNL) of the normal reference range of <5 ng/ml. Thyroid function tests revealed suppressed thyroid stimulating hormone (TSH) levels (<0.01 mIU/l) and elevated free triiodothyronine (FT3) at 40.41 pmol/l (5-fold of UNL) and free thyroxine (FT4) at 63.89 pmol/l (3-fold of UNL), suggestive of hyperthyroidism (Fig. 1A). Chest computed tomography (CT) scan revealed a mass in the dorsal segment of the left lower lobe, measuring 0.8 cm, with enlarged lymph nodes at the left hilum and mediastinum (Fig. 2A and B). Positron emission tomography-CT (PET-CT) scan showed increased metabolic activity in the nodules in the left lower lobe, mediastinal and left hilar lymph nodes, as well as a hypermetabolic nodule in the left adrenal gland (Fig. 3A and B). Considering the small size of the pulmonary lesion and the concurrent hyperthyroidism of the patient, which posed a high anesthetic risk, an endobronchial ultrasound-guided transbronchial needle aspiration was performed to obtain mediastinal lymph node biopsy. However, the sample was insufficient for a definitive diagnosis. After multidisciplinary consultation it was decided to initially manage the thyroid hormone levels of the patient with thiamazole tablets to minimize medical harm. Subsequent thoracoscopic biopsy would be considered once the thyroid condition was controlled.

In May 2023, thyroid function tests revealed normalized levels of FT3 and FT4, with TSH remaining below detectable limits, indicating effective management of the hyperthyroidism (Fig. 1A). A slight elevation in CEA levels was noted compared with 2 months prior (Fig. 1B). Repeated chest and abdominal CT scans showed no significant changes in the pulmonary lesion, lymph nodes and adrenal nodule; brain MRI scans were unremarkable (data not shown). Subsequently, the patient underwent a thoracoscopic mediastinal lymph node biopsy. The tissue samples were fixed in a 10% neutral formalin solution for 24 h, followed by paraffin embedding and sectioning at a thickness of 4 μ m. After hematoxylin and eosin staining, the sections were examined using a light microscope at a magnification of 200x. Histopathological examination revealed heterogeneous tissue with poorly differentiated, large cells and scattered necrotic areas (Fig. 4A). Tissue paraffin

sections were immersed in citrate buffer (pH 6.0) and heated in a microwave oven for 15 min to induce epitope repair. The slides were then cooled for 20 min, rinsed with distilled water and rehydrated in a descending-gradient alcohol series. To block non-specific binding, sections were incubated with 5% BSA (cat. no. A8850; Beijing Solarbio Science & Technology Co., Ltd.) in PBS for 30 min at room temperature. Antibodies for immunohistochemical analysis were obtained from MXB Biotechnologies. thyroid transcription factor-1 (TTF-1) (1:200 dilution; cat. no. MAB-0677), cytokeratin (CK) (1:200 dilution; cat. no. Kit-0009), chromogranin A (CgA) (1:100 dilution; cat. no. MAB-0707) and synaptophysin (Syn) (1:150 dilution; cat. no. MAB-0742) antibodies were diluted in PBS and applied to the sections, which were then incubated at 4°C overnight. After washing, sections were incubated with goat anti-rabbit IgG H&L (HRP) (cat. no. ab6721; 1:200 dilution; Abcam) for 1 h at room temperature. The sections were stained with hematoxylin and observed under a light microscope at a magnification of x200. Immunohistochemical staining confirmed the pulmonary origin and neuroendocrine characteristics of the tumor cells: Positive for TTF-1, CK, CgA and Syn, but negative for programmed death-ligand 1 (PD-L1) evaluated by 22C3 (cat. no. SK006; 1:40 dilution; Dako; Agilent Technologies, Inc.) assays/kit (Fig. 4B-E). Due to economic factors, the patient underwent a few genetic tests against targeted therapeutic markers including *ALK*, *ROS1*, *RET*, *EGFR*, *KRAS*, *BRAF*, *PIK3CA*, *HER2* and *MET* mutations, all of which were negative.

Combining radiological and pathological findings, the patient was diagnosed with stage IV LCNEC of the lung, classified as cT1N2M1, with an Eastern Cooperative Oncology Group performance status of 1.

Treatment and outcome. Typically, patients with stage IV cancer are not considered surgical candidates. However, in the present case, the patient expressed a strong desire for surgery. Given the slow progression of the primary lesion and the general condition of the patient, a multidisciplinary team decided to proceed with neoadjuvant immunotherapy. The specific regimen included nab-paclitaxel (400 mg intravenously) plus cisplatin (150 mg intravenously) in combination with serplulimab (300 mg intravenously) every 3 weeks for three cycles. Concurrently, the patient continued thiamazole 20 mg per day to manage his thyroid function. Post-neoadjuvant therapy, a repeat CT scan of the chest and abdomen revealed no detectable nodule in the left lower lobe of the lung where the primary lesion was located, a significant reduction in mediastinal lymph nodes, and a shrunk of the adrenal lesion (Fig. 2C and D). Another multidisciplinary consultation considered that the patient might benefit from surgical resection of the primary lung tumor. The treatment strategy for the adrenal metastasis was left to be determined based on the response of the tumor to the immunotherapy. In August 2023, 31 days after completing three cycles of the neoadjuvant immunotherapy, the patient underwent left lower lobectomy and mediastinal lymphadenectomy. Postoperative pathology revealed no residual cancer cells in the tumor bed or lymph nodes (Fig. 4F). Immunohistochemical staining results were negative for CK, Syn, CgA, CD56, TTF-1 and P40, indicating a pCR.

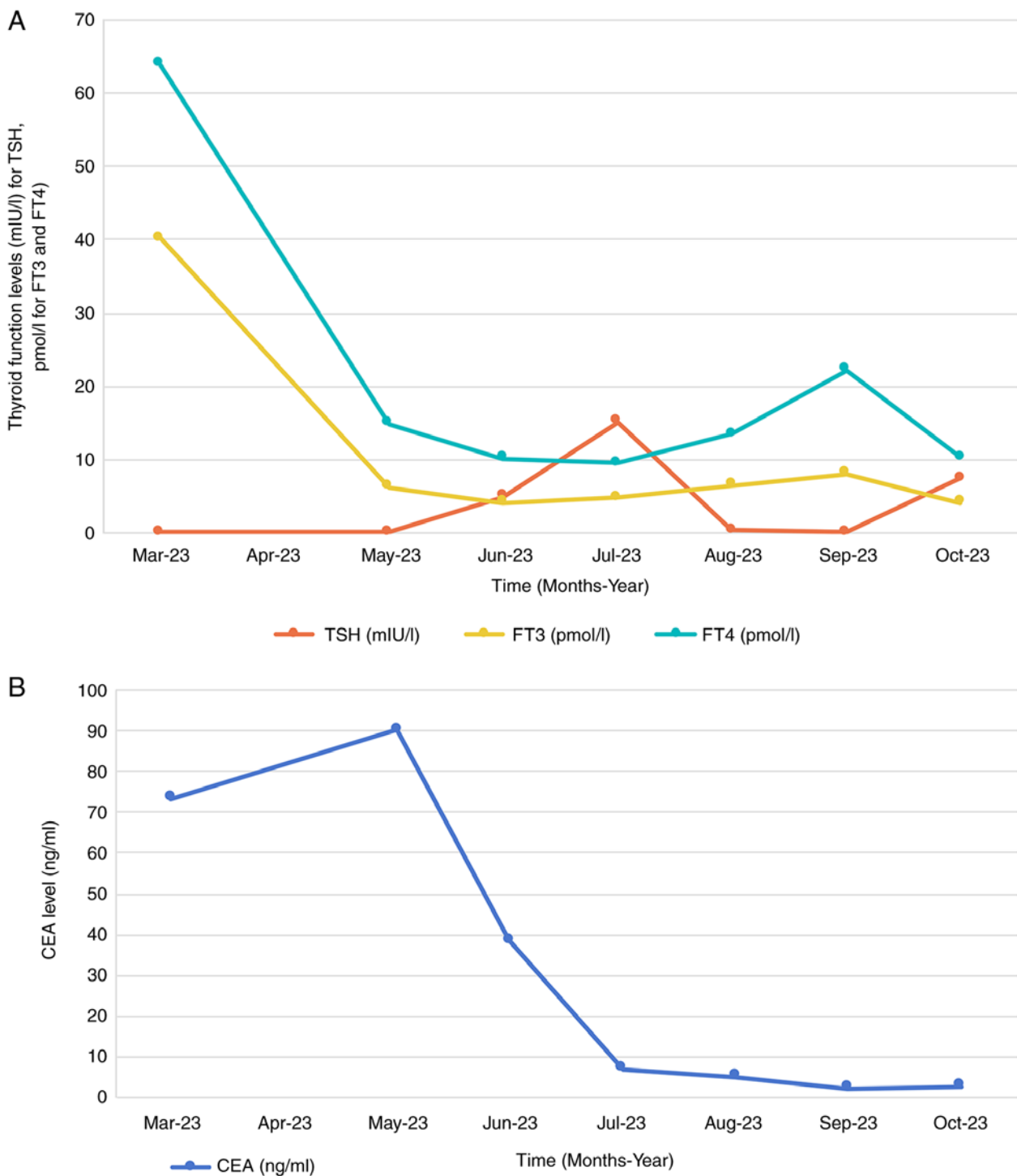


Figure 1. Changes in thyroid hormone and tumor biomarker levels during treatment. (A) The fluctuations in thyroid hormone levels, including TSH, FT3 and FT4. (B) The changes in the level of the tumor biomarker CEA. TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; CEA, carcinoembryonic antigen.

Despite the clear benefits of neoadjuvant and surgical treatments, the adrenal metastasis of the patient remained a concern. Therefore, the treatment plan was extended to include three additional cycles of adjuvant therapy using nad-paclitaxel (400 mg intravenously, D1, q3w), cisplatin (150 mg intravenously, D1, q3w) and serplulimab (300 mg intravenously, D1, q3w). This was followed by maintenance therapy with serplulimab alone. Throughout the treatment period, the patient experienced hypothyroidism (decreased FT3 and

FT4) in October 2023 and April 2024, and hyperthyroidism (increased FT3 and FT4) in January 2024, both of which were corrected with dose adjustments of the hyperthyroid medication. Otherwise, the patient had no other adverse effects.

As of July 2024, the patient has completed 17 cycles of the serplulimab maintenance therapy, and the PET-CT scan revealed a complete metabolic response of the adrenal metastasis, without any specialized intervention (Fig. 3C). Event-free survival has exceeded 11 months, and overall survival has

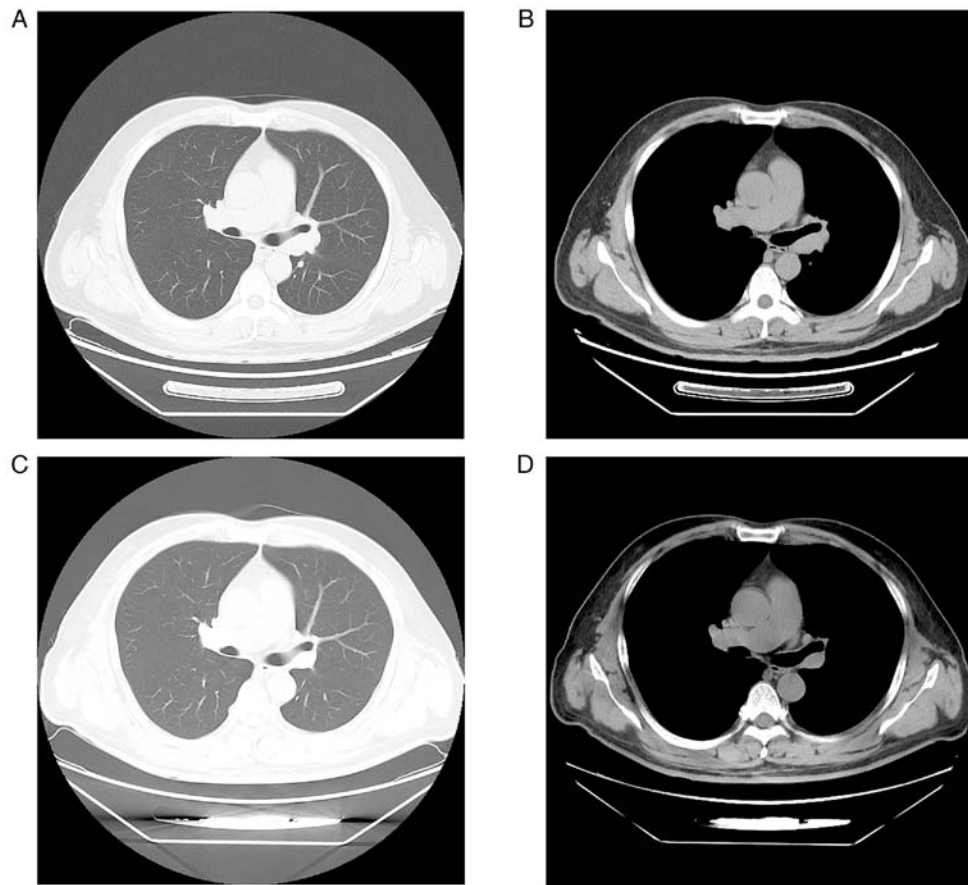


Figure 2. Pulmonary tumor response to neoadjuvant treatment by chest CT scans. (A) The primary lung tumor and (B) enlarged hilar lymph nodes at initial diagnosis. (C) The non-detectable of the primary lung tumor and (D) the shrunk size of the hilar lymph node post-neoadjuvant therapy. CT, computed tomography.

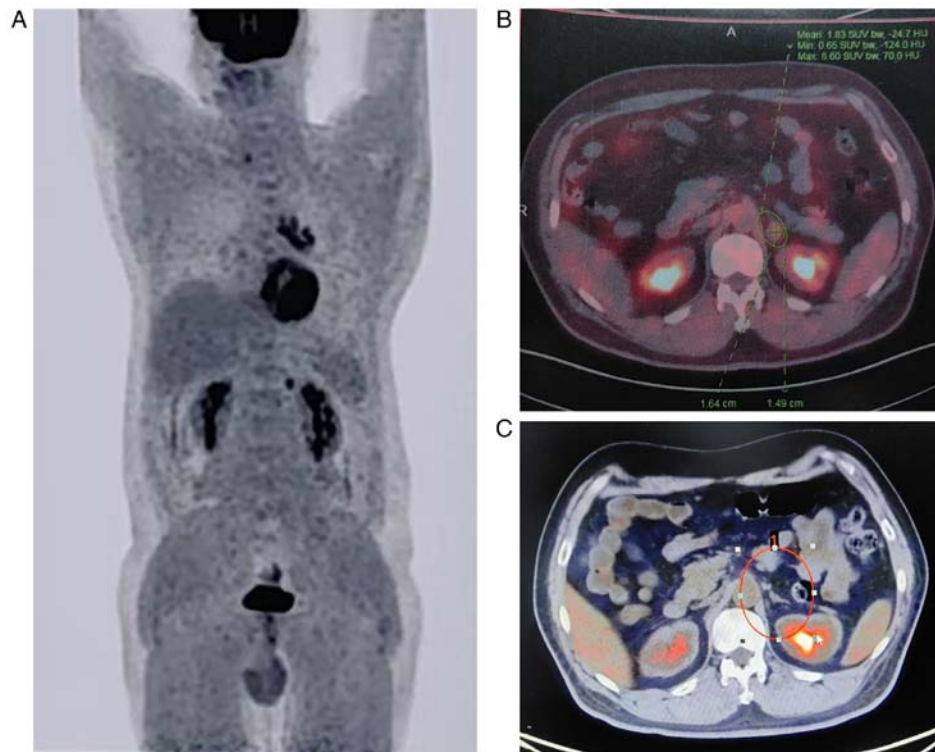


Figure 3. Adrenal metastasis metabolic response to immunotherapy by PET-CT. (A) PET-CT suggests a hypermetabolic nodule in the left adrenal gland. (B) The adrenal metastasis shown by PET-CT at the initial diagnosis. (C) The complete metabolic response of the adrenal metastasis following five cycles of adjuvant therapy. PET-CT, positron emission tomography-computed tomography.

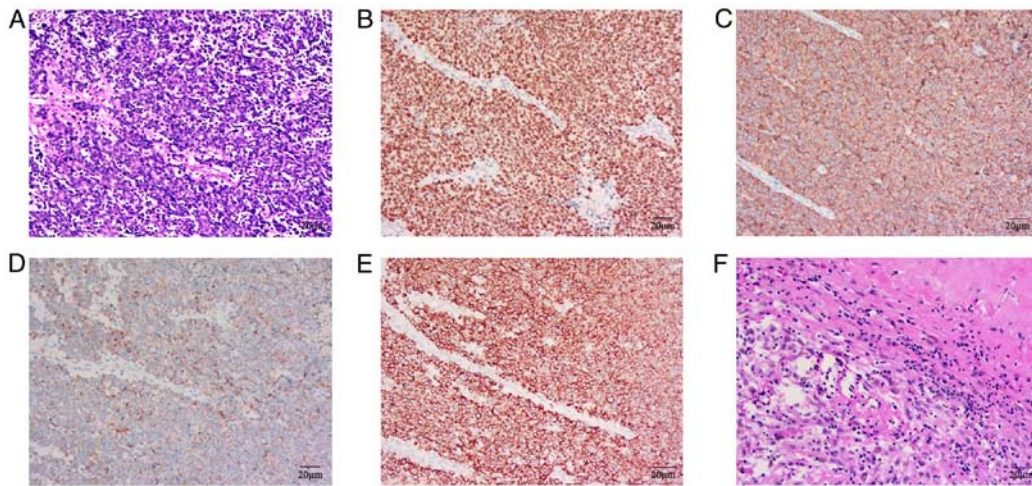


Figure 4. HE and IHC staining of tumor. (A) A HE-stained section of the lymph node biopsy at diagnosis. Positive expression of (B) TTF-1, (C) Syn, (D) CgA and (E) CK through IHC, respectively. (F) Surgically resected lymph node. Magnification, 200x. HE, hematoxylin-eosin; IHC, immunohistochemistry; TTF-1, thyroid transcription factor-1; Syn, synaptophysin; CgA, chromogranin A; CK, cytokeratin.

exceeded 14 months. The radiological scans showed no visible adrenal metastasis, no recurrence of the pulmonary lesion, and no evidence of distant metastasis, indicating a clinical cure. The treatment journey of this patient underscores the potential of tailored, multimodal oncological approaches in managing advanced lung cancer cases, even in cases that are traditionally deemed non-operable.

Discussion

LCNEC of the lung, originating from pulmonary argentaffin cells, is a rare and aggressive malignant tumor characterized by neuroendocrine morphology and differentiation (12,13). In 2021, the World Health Organization (WHO) classified LCNEC as a neuroendocrine carcinoma, highlighting its molecular subtyping, potentially contributing to the diagnosis and treatment (14). Although LCNEC is categorized as a type of NSCLC, it exhibits increased invasiveness and malignancy compared with other NSCLCs, with biological behavior similar to SCLC (15). Additionally, LCNEC is prone to chemoresistance, metastasis and recurrence, leading to poor prognosis (16). Due to its rarity, research on LCNEC is limited, resulting in a lack of epidemiological data and standardized treatment. Therefore, further research and clinical trials are necessary to explore effective treatment strategies and improve prognosis for patients with LCNEC.

Biomarkers play a pivotal role in the diagnosis of malignancies. In LCNEC, serum biomarkers such as CEA and pro-gastrin-releasing peptide are elevated (17). Additionally, neuron-specific enolase (NSE), a specific neuroendocrine marker for lung neuroendocrine tumors, is also increased in LCNEC cases (17). A study by Iyoda *et al* (18) analyzed serum biomarkers in LCNEC, identifying significant elevations in lactate dehydrogenase (LDH), tissue polypeptide antigen, CEA and NSE, with a minority of patients showing increased levels of α -fetoprotein (AFP), CA199 and CA125. These changes in biomarkers may contribute to diagnosing LCNEC, although further epidemiological validation is required. The histology of LCNEC typically reveals distinct necrotic areas, large

cells with abundant cytoplasm and high proliferative nuclei features (19). IHC analysis frequently demonstrates diffuse positivity for specific neuroendocrine markers such as CgA, Syn and CD56 in LCNEC (17,19,20). Approximately 84.4% of LCNEC cases express CK, and 54.8% express TTF-1 (21). Sturm *et al* (22) have suggested that TTF-1 expression may differentiate LCNEC from basaloid carcinoma. In the present case, the tumor histopathology revealed prominent large cells with scattered necrotic areas, and positive staining for TTF-1, CK, CgA and Syn. Considering the presence of hyper-metabolic nodules in the mediastinum and adrenal gland, the patient was diagnosed with stage IV LCNEC based on the 2021 WHO criteria for LCNEC (14). Additionally, the patient did not exhibit any definitive association of genotypic profiles with targeted therapies.

Currently, research on genetic mutation in LCNEC remains limited and lacks representativeness. Given the reliance of tumor cells on aberrant signaling pathways and survival mechanisms conferred by mutated genes, the disruption of these pathways typically results in cell cycle arrest or apoptosis (23). Statistics indicate the potential presence of mutations in genes such as TP53, RB1, STK11, KEAP1, KRAS, MEN1 and EGFR in LCNEC, and the mutation frequencies are markedly different in a previous study (21), with TP53 (82.3%) being the most common. In 2021, the WHO underscored the importance of genotypic profiling in LCNEC, suggesting that more studies on LCNEC genotyping are crucial as they could provide valuable insights and direction for subsequent treatment approaches (14). Additionally, the association between high tumor mutational burden (TMB) value and survival benefit of patients with lung cancer treated with ICIs has been shown in CheckMate 026 (24) and CheckMate 227 (25). Smoking is a significant risk factor for lung cancer, and previous study has shown that the TMB value in smoking patients was significantly higher (26). Garassino *et al* (27) have indicated that patients who smoke may benefit more from second-line immunotherapy than non-smoking patients. However, the relationships between tobacco exposure, TMB and survival benefits have not been yet fully elucidated.

Currently, there is no standardized treatment for LCNEC. Treatment for LCNEC is based on multidisciplinary strategies (including surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy), and platinum-based chemotherapy plays a pivotal role (16). Surgical intervention is generally suitable for stage I-III patients (28); however, the high rate of local and distant metastases (29), coupled with the insidious onset of the disease, leads to most patients being diagnosed at stage IV, resulting in adjuvant or multimodal treatments (16,30). Studies have shown that platinum-based regimens achieve an objective response rate of 59.1 to 73% in patients with LCNEC, significantly higher compared with other chemotherapy and offering improved OS benefits (30-32). The 2021 National Comprehensive Cancer Network guidelines recommend chemotherapy combinations for locally unresectable or metastatic lung neuroendocrine carcinomas (including LCNEC), and noted the limited efficacy of second-line and subsequent therapies (33). Targeted treatments for LCNEC [such as EGFR-TKIs (34,35), ALK inhibitors (36,37), anti-VEGF drugs and anti-c-KIT drugs (38)] are still under investigation, with their effectiveness in patients with LCNEC remaining contentious. Moreover, due to the genetic heterogeneity among LCNEC patients, targeted therapies are limited to personalized treatments (21).

PD-1 and its ligand PD-L1 combined with chemotherapy are standard treatment strategies for most advanced NSCLC and SCLC (39,40). However, the immunotherapy for LCNEC remains uncertain, and the benefits of CKIs still require exploration. Due to the rarity of LCNEC, there is little information on PD-1/PD-L1 expression and the efficacy of CKIs in LCNEC, and no clinical trials of immunotherapy have been conducted in patients with LCNEC, so reports and studies on the use of PD-1 monoclonal antibodies in LCNEC are limited (41). Prospective data on ICP in LCNEC are still lacking, and only some small-sample studies have evaluated PD-1 and PD-L1 expression in patients with LCNEC. Some studies have shown that the majority of patients included in LCNEC exhibit PD-1/PD-L1 positivity (42,43), but another portion of the studies have shown PD-L1 positivity in only a minority of samples (44,45). A retrospective study found only 10.4% of patients with LCNEC express PD-L1 (44). Such a discrepancy is most likely due to the small number of LCNEC samples included and warrants further study to determine the potential value of PD-1 applied to immunotherapy.

In the absence of specific clinical trials for patients with LCNEC, current data on the efficacy of immunotherapy for LCNEC come primarily from a small number of studies in a small sample of patients treated with CKIs. The University of Kentucky treated three patients with LCNEC with nivolumab after platinum-based chemotherapy progression disease, and all of whom achieved either a complete radiological response or stable disease (46). Levra *et al* (47) reviewed prognostic data on 10 patients with LCNEC treated with CKIs, of whom 6/10 had partial responses and 1/10 had stable disease with a median PFS of 57 weeks. A retrospective study reported the efficacy of nivolumab in 17 pretreated patients with stage III-IV LCNEC, showing a prolonged OS as second-line treatment or beyond (48). In addition, Zhang *et al* (49) described a case of a PD-L1-negative patient whose disease progressed rapidly after surgery and adjuvant

chemotherapy, but the patient achieved a complete response during nivolumab treatment. Sato *et al* (50) reported another patient with stage IV LCNEC negative for PD-L1 expression who responded to nivolumab. A retrospective study involving 37 patients with LCNEC, 11 were PD-L1 positive and received nivolumab or pembrolizumab treatment, with 60% achieving partial response (51). Another retrospective study that included 661 stage IV patients with LCNEC, 37 of whom underwent immunotherapy, evaluated the efficacy of immunotherapy and showed that immunotherapy is associated with improved overall survival, but propensity scores on the overall survival analysis show a non-significant trend in favor of immunotherapy (52). Although all of these studies have limitations and the relevance of LCNEC to immunotherapy is still under investigation, the results of all of the aforementioned studies suggest that PD-1 /PD-L1 expression and the use of CKIs have potential in the treatment of LCNEC.

Additionally, Wang *et al* (39) reported a case of a PD-1-positive but PD-L1-negative patient with LCNEC with disease progression after postoperative adjuvant chemotherapy, who was subsequently treated with pembrolizumab, with all visible lesions shrinking after one cycle and no new lesions; at 6 months later, the patient was still on pembrolizumab and continued to improve. This parallels the present case, where the PD-L1 negative patient showed sensitivity to perioperative immunochemotherapy with serplulimab, achieving complete response after three cycles of neoadjuvant therapy. Notably, the present patient with stage IV LCNEC was a controversial candidate for surgical intervention. However, with the favorable response of neoadjuvant treatment, as well as the patient's strong desire for surgery, the present study conducted the surgical resection of the primary lung tumor. Postoperative pathology confirmed a pCR, demonstrating the therapeutic potential of immunochemotherapy in the neoadjuvant setting. Following surgery, combined with adjuvant immunochemotherapy and radiotherapy targeting the adrenal metastasis, the patient experienced the disappearance of primary and metastatic lesions without recurrence, achieving a clinical cure.

Abnormal thyroid function is one of the common immune-related adverse reactions with an incidence of ~25% (53). Its main manifestations are hypothyroidism, hyperthyroidism or transient thyroiditis, but the mechanism of occurrence remains unclear (54). It has been shown that the interaction of PD-1-expressing lymphocytes and PD-L1-expressing thyroid cells can inhibit T-cell-mediated autoimmune responses, thereby protecting the thyroid gland (55). However, PD-1 monoclonal antibodies may block this interaction, thereby inducing T-lymphocyte infiltration within the thyroid gland, leading to abnormal thyroid function (56). In the present case, given that: i) The patient had a clear history of hyperthyroidism; ii) the thyroid function abnormalities of the patient during the treatment period showed alternating hyperthyroidism and hypothyroidism; and iii) that the thyroid function of the patient returned to normal after adjusting the dosage of the hyperthyroid medication, the present study hypothesized that the thyroid function abnormalities of the patient were mainly related to the dosage adjustment of the hyperthyroid medication, and that there was no clear and direct relationship with the immunotherapy.

The present case report is limited to a single case, and the detection of targeted therapeutic markers and ICPs in patients is not perfect. From our results, genetic testing did not provide a strong contribution to the subsequent treatment plan of the patient. Also, the present study was unable to indicate whether PD-1/PD-L1 could be used as a support for determining the treatment plan of the patient in this case. In addition, the follow-up of this patient was slightly shorter. Due to the rarity of LCNEC, there is an urgent need to investigate clinical trials of serplulimab in combination with chemotherapy in larger cohorts of patients with LCNEC to clarify the relationship between ICPs, CKIs and patient management and prognosis.

In conclusion, the present study provided novel evidence for the efficacy of immunochemotherapy in the perioperative treatment of patients with stage IV LCNEC, offering a novel approach to LCNEC management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SZ, CL and JD conceived and designed the study, analyzed and interpreted the data and approved the final version of the manuscript. MC performed follow-up of the case and drafted and critically revised the manuscript. YH and MC extracted the images and acquired the laboratory and clinical data. CC wrote the manuscript and acquired the laboratory and clinical data. BZ critically revised the manuscript for intellectual content and conceived and designed the study. All authors confirmed the authenticity of all the raw data, and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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