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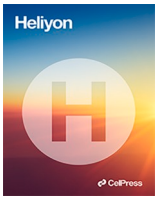

Case report

Complete response in patient with locally advanced lung large cell neuroendocrine carcinoma under sintilimab plus platinum-based chemotherapy: A case report

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ABSTRACT

Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is an uncommon subtype of lung cancer with bleak prognosis. Its optimal treatment remains undetermined due to its malignancy. A 66-year-old man diagnosed with unresectable locally advanced LCNEC exhibited partial radiographic response to chemo-immunotherapy. He underwent salvage surgery after 4 rounds of docetaxel/nedaplatin (DP) regimen plus sintilimab, a highly selective monoclonal antibody which targets human anti-programmed death-ligand 1 (PD-L1). In addition, the pathologic examination of the excision demonstrated that there were no viable residuary tumor cells. This case indicates that neoadjuvant chemo-immunotherapy might benefit patients with locally advanced LCNEC, which deserves further investigation.

1. Introduction

As a rare but destructive malignancy, pulmonary large-cell neuroendocrine carcinoma (LCNEC) is most common among older adult males who have been smoking for decades [1], accounting for <3% of lung carcinomata [2]. Due to its rarity, there have been no extensive, prospective, and randomized clinical tests. Hence, determining its optimal therapy remains challenging. In pathological

Abbreviations: LCNEC, large-cell neuroendocrine carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; PET-CT, positron emission tomography combined with computed tomography; NGS, next-generation sequencing.

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performance, it has the properties of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [3], making its classification controversial. In the 2015 World Health Organization Classification of Lung Tumors, LCNEC was classified as a neuroendocrine tumor. The treatment strategy regarding the National Comprehensive Cancer Network was formulated based on the NSCLC project. In the early stages of LCNEC, there are no obvious symptoms. By the time patients do develop symptoms and seek treatment, they are often in the advanced stages, or are at least locally advanced. LCNEC has bleak prognosis, with a <5% survival rate at stages IIIB–IV [4]. Surgical treatment, which is insufficient for the advanced types, remains recommended. Hence, neoadjuvant chemotherapy, radiotherapy, immune checkpoint inhibitors (ICIs), and other treatments are typically required.

Herein, a locally advanced LCNEC with complete response is reported. The patient received surgery after sintilimab plus platinum-based chemotherapy. The case indicated that neoadjuvant chemo-immunotherapy might benefit patients with locally advanced LCNEC.

2. Case presentation

In June 2020, a 66-year-old man, who had been smoking, was hospitalized with a 6-month history of cough and an Eastern Cooperative Oncology Group Performance Status of 1 point (ECOG 1). He was 1.7 m tall and weighed 56.5 kg. The patient had nothing notable in his medical history nor any previous treatment history. The combined computed tomography and fluorodeoxyglucose positron emission tomography (FDG PET-CT) revealed a 6.5 × 7.8 × 7.0 cm mass in his right lung's superior lobe with mediastinal invasion in his right hilar lymph nodes and mediastinal lymph nodes in station 4R metastases (Fig. 1). He was diagnosed with cT4N2M0 according to the TNM classification 8th edition, which is consistent with the cIIIB stage. Afterward, he underwent a CT-

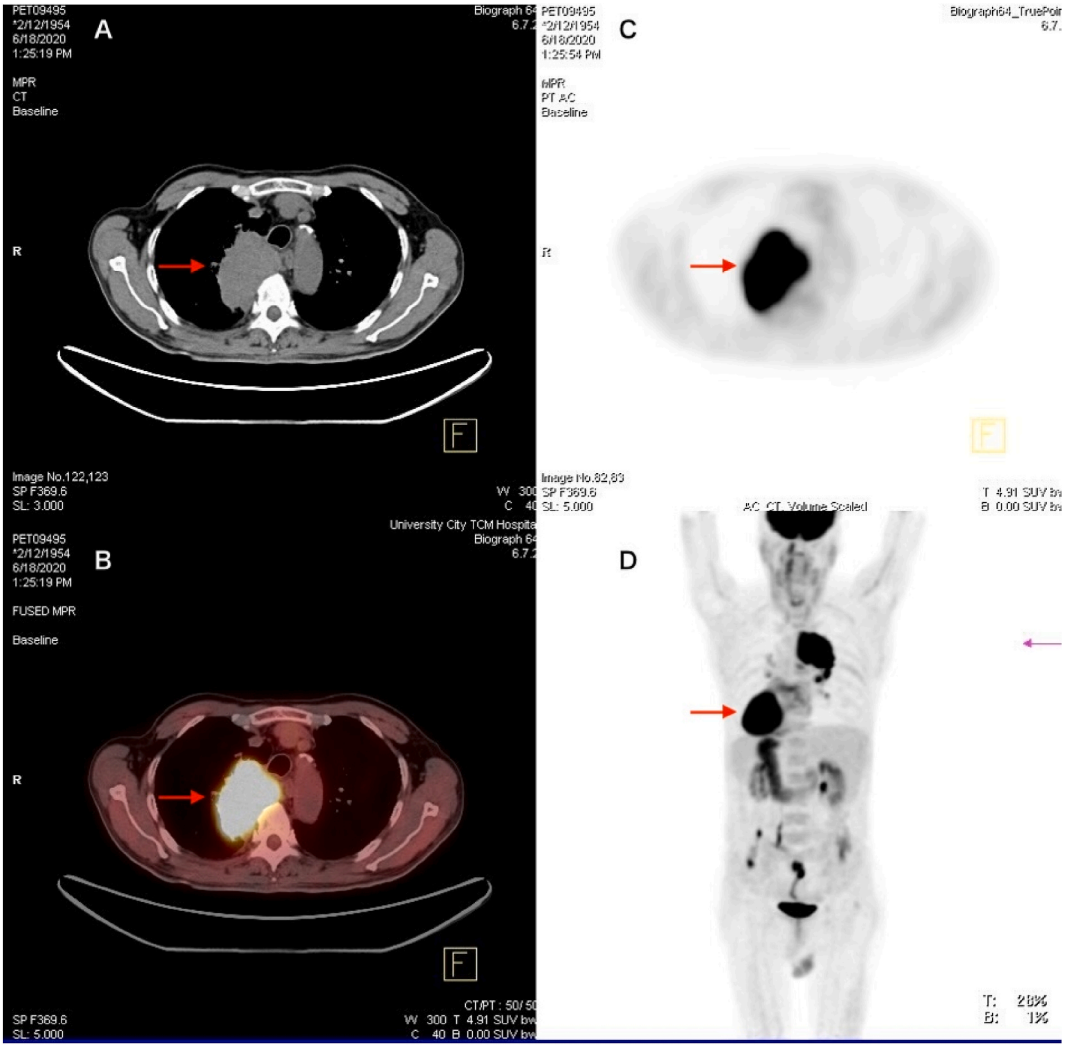

Fig. 1. Evaluation by FDG PET-CT during the diagnostic process. The mass in the right lung's superior lobe (indicated by arrow) was identified as the primary tumor.

guided percutaneous transthoracic needle aspiration biopsy, implying a poorly differentiated LCNEC. Immunohistochemistry detected PD-L1 expression in 10% of the cancer cells (Fig. 2), whereas no ALK or ROS-1 expression was observed. No TKI-targetable mutations were detected by next-generation sequencing (NGS).

Therefore, the patient underwent 4 cycles of chemotherapy with docetaxel (100 mg, every 3 weeks, Cisen Pharmaceutical Co., Ltd.) and a nedaplatin (100 mg, every 3 weeks, Simcere Pharmaceutical Group Ltd.) regimen plus sintilimab (200 mg, every 3 weeks, Innovent Biologics, Inc.) from July 2020 to September 2020. After the treatment, chest CT scan images demonstrated that the tumor had shrunk (Fig. 3). Following the Response Evaluation Criteria in Solid Tumors (version 1.1) guidelines, the patient was found to exhibit partial response.

Given his tumor response, and also that he was only 66 and had good ECOG performance status (ECOG 0 after the treatment), right upper lobectomy with the right hilar lymph node and mediastinal lymph node dissection (MLND) with lysis of pleural adhesions were performed on October 16, 2020. The histological examination of the excisional lung and lymph nodes indicated that there were no viable tumor cells (Fig. 4). Therefore, the result of the pathological TNM classification 8th edition was ypT0 ypN0 (R0). After surgery, sintilimab was continued while an additional 4 cycles of DP regimen chemotherapy were completed. Thereafter, the patient maintained monthly sintilimab until May 2023. No tumor recurrence or metastasis were found in the patient after regular CT scans and blood examination. His last examination was on March 23, 2023. Unfortunately, on June 20, 2023, the patient suddenly began suffering from slurred speech and slow reaction. After completing relevant examinations at the local hospital, he was diagnosed with bacteremia and intracranial infection, the latter induced by *Fusobacterium nucleatum* and *Cutibacterium acnes*. The treatment was ineffective and he died on July 29; during this period, no recurrence or metastasis of the tumor was found via CT scan.

3. Discussion

As a pathological subtype of pulmonary neuroendocrine carcinoma with the characteristics of high invasiveness and poor prognosis, LCNEC is highly correlated with smoking [5]. LCNEC is a type of biologically destructive cancer whose presentation resembles that of small cell carcinoma [6]. Most patients are diagnosed at advanced stages when surgical treatment is limited and the recurrence risk is high. Hence, a systemic treatment is needed to improve the curative effect.

Due to its rarity, the optimal treatment for LCNECA remains unestablished. The primary recommended treatments for LCNEC are the same as those recommended for NSCLC. Most patients diagnosed with early-stage LCNEC undergo surgery while those at the middle or advanced stages receive multidisciplinary treatment. Most LCNEC patients in the early stages receive operative treatment [7], but surgery alone is insufficient. Iyoda et al. retrospectively analyzed 335 patients with pathologic stage IA NSCLC, and found that large-cell neuroendocrine carcinoma was an unfavorable prognostic indicator [8]. Thus, mere surgical resection is inadequate for LCNEC treatment. Saji et al. assessed the curative effect of perioperative chemotherapy on patients with totally excisional LCNEC. They found that the risk of death among those who had undergone surgery alone was 9.5 times higher than that of those who had received surgery combined with chemotherapy. Therefore, perioperative chemotherapy is needed to increase the survival rate of patients with LCNEC [9]. The most extensively applied chemotherapy treatment has been the platinum-based VP-16 in combination with CPT-11 [9]. Sun et al. assessed whether the treatment for advanced LCNEC should resemble that of SCLC or NSCLC. Similar to SCLC, the therapy is more fitting for advanced-stage LCNEC than it is for NSCLC [10,11].

As a biologically heterogeneous group of tumors, LCNEC consists of distinct subtypes in terms of genomic signatures, i.e., the SCLC-like subgroup (TP53+RB1 co-mutation/loss and other SCLC-type alterations), the NSCLC-like subgroup (scarcity of co-altered TP53+RB1 and the ubiquitous NSCLC-type mutations [STK11, KRAS, and KEAP1]), and carcinoid-like subgroup (MEN1 mutations and low mutation burden) [12]. The tumor of the patient in the present study was examined through NGS which revealed RB1 (c.1759G > T [p.E587*]) mutation, KEAP1 (c.1436A > T [p.D479V]) mutation, STK11 (c.616del [p.A206fs]) mutation, TP53 (c.230del [p.P77fs]) ERBB2 (c.3283G > A [p.A1095T]) mutation, SMARCA4 (c.2921C > T [p.P974L]) mutation, and SMAD4 (c.473T

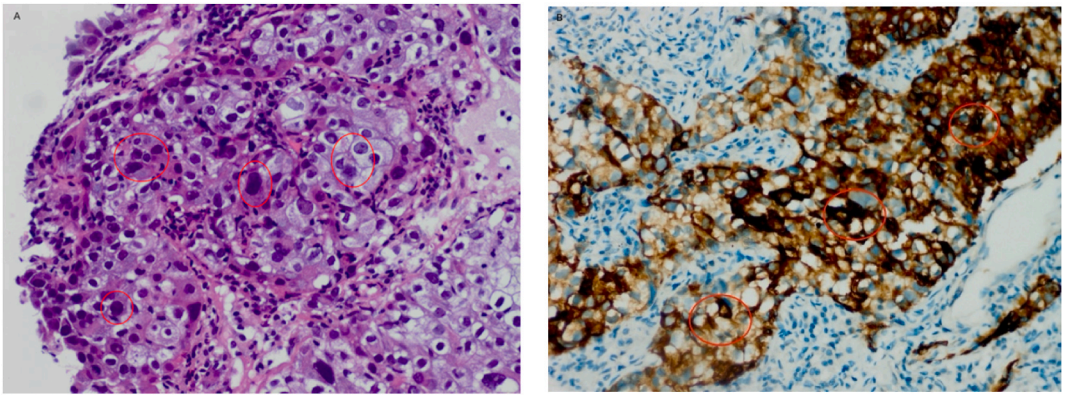

Fig. 2. Pathology during the diagnostic process. (A) Hematoxylin and eosin (HE) staining indicated neoplastic cells that possessed morphologic properties of NSCLC (indicated by circle). (B) Immunohistochemistry detected diffuse cytokeratin expression, which facilitated the diagnostic process of lung LCNEC (indicated by circle). Picture magnification: 20 × , 50 μm scale bar.

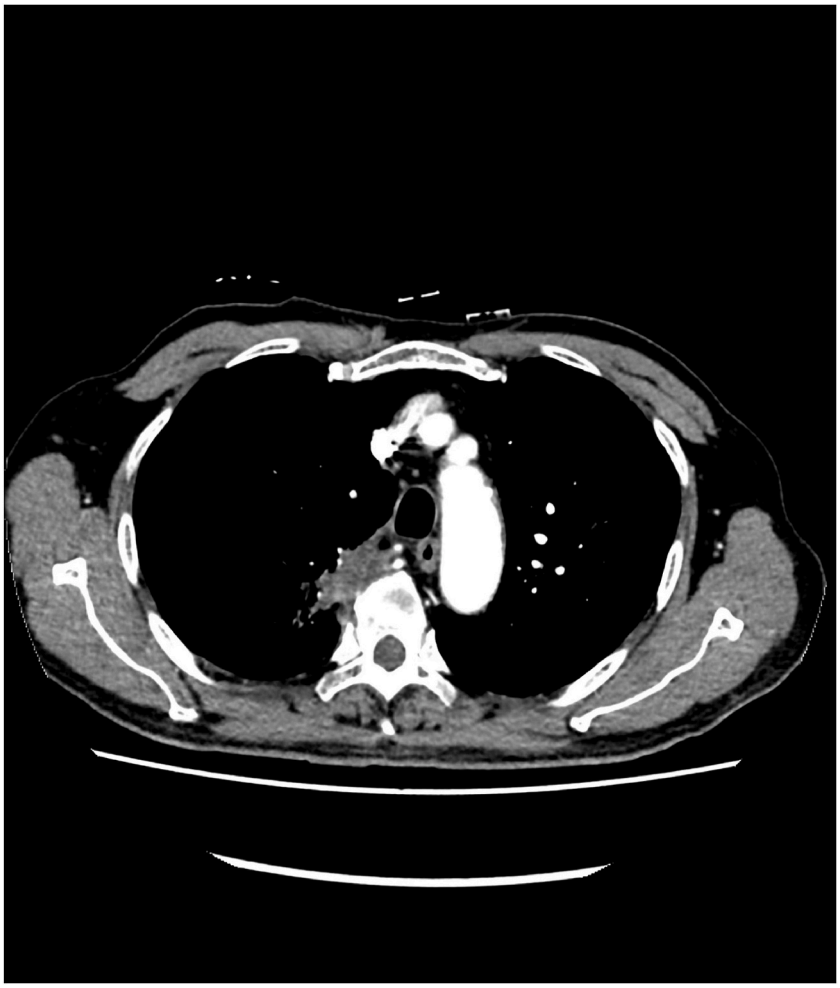

Fig. 3. CT scan indicated that the tumor in the right lung had shrunk.

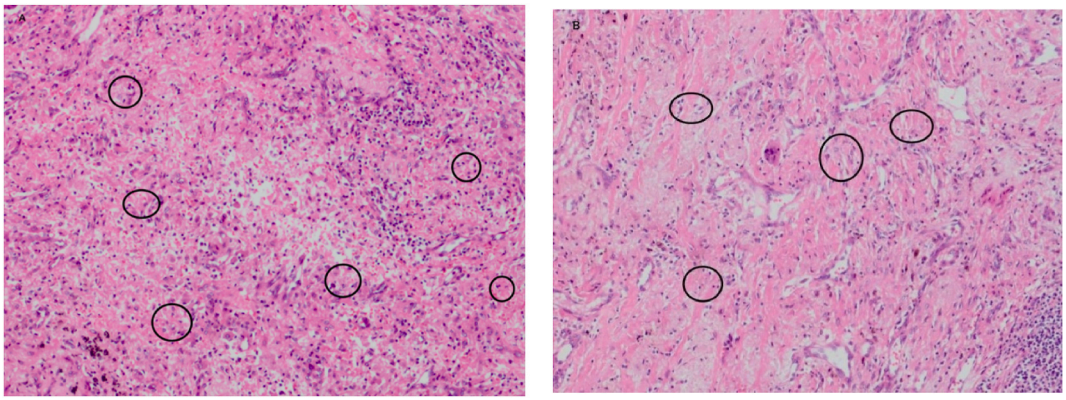

Fig. 4. During the surgery. (A) HE stains indicated a phagocytic reaction in the earlier cancer tissue's necrotic area without carcinoma cells that could survive (indicated by circle). (B) HE dyeing displays collagen fiber hyperplasia in the earlier carcinoma tissue's gangrenous region without residuary carcinoma cells that could survive (indicated by circle). Photo amplification: 50 μm scale bar, 20 × . Color online. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

> A [p.V158E]) mutation. Considering the patient's molecular characteristics accompanied with NSCLC-type (STK11 and KEAP1) and SCLC-type mutations (TP53 and RB1), we treated him with a DP regimen that was effective for both diseases.

PD-1 inhibitors such as pembrolizumab and nivolumab are ICIs that have been demonstrated to increase the overall survival rate of patients with advanced-stage NSCLC [13,14]. However, data on ICIs' curative effect on L-LCNEC have been limited, mostly coming from small sample clinical trials or case reports. Sherman et al. assessed 37 patients diagnosed with advanced-stage LCNEC, finding that ICI-treated patients showed a longer median OS because the diagnosis for their advanced-stage diseases took longer than those who had received different treatments [15]. Against this backdrop of insufficient data about ICIs' curative effect on advanced LCNEC, the application of ICIs plus chemotherapy remains unclear. The NADIM study indicated that neoadjuvant chemoimmunotherapy would transform the comprehension of locally advanced-stage NSCLC from a potentially fatal carcinoma into a treatable one [16]. There is some data about the curative effect of neoadjuvant chemoimmunotherapy on patients with advanced-stage LCNEC. The patient with LCNEC exhibited complete tumor response after receiving platinum-based chemotherapy plus sintilimab. As a highly selective fully human monoclonal antibody, sintilimab can block the contact between PD-1 and its ligand PD-L1. According to relative preclinical data, sintilimab possesses a binding site that differs from that of nivolumab or pembrolizumab, and possibly has higher affinity against PD-1 [17]. The ORIENT-11 study indicated that for patients diagnosed with advanced or metastatic nonsquamous NSCLC, the combination of sintilimab with pemetrexed/platinum chemotherapy could cause longer PFS than with chemotherapy alone [18]. Similarly, the postoperative pathology of the patient in the present study showed complete response, implying that sintilimab and chemotherapy achieved a synergistic anticancer effect. Although the patient passed away, the cause of death was not related to the tumor. The patient's overall survival time was 37 months, which exceeds the average survival time of 16.1 months [19]. However, infection is one side effect of PD-1 inhibitors, and whether this patient's systemic infection was related to the side effects of PD-1 inhibitors is worthy of further investigation [20]. However, such serious side effects are rare in clinical practice, and the positive therapeutic effect of immune drugs on tumor therapy should not be discounted.

4. Conclusion

LCNEC is an uncommon subgroup of lung cancer with bleak prognosis. Although the curative effect of ICIs on LCNEC remains unevaluated, they might offer certain advantages regarding patient survival. The combination of immunotherapy and chemotherapy has proven to prolong the life expectancy of patients with advanced NSCLC. In previous studies, neoadjuvant chemoimmunotherapy has transformed some cases of advanced NSCLC into a curable disease. Nonetheless, further studies are still needed to confirm the effect of neoadjuvant chemoimmunotherapy on advanced LCNEC.

5. Consent

The patient provided informed consent for the publication of this case report and relative images, a copy of which is available from the editor-in-chief of this journal upon request.

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Data availability statement

All data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Jinpeng Huang: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Feiye Wang:** Writing – original draft, Investigation. **Xiaohua Du:** Data curation. **Yongfeng Li:** Data curation. **Yuanyuan Zhuang:** Data curation. **Ziyan Gan:** Data curation. **Shunqin Long:** Data curation. **Wanyin Wu:** Writing – review & editing, Funding acquisition, Conceptualization. **Xiaobing Yang:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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