

CASE REPORT

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Neoadjuvant immunochemotherapy for pulmonary large-cell neuroendocrine carcinoma: case report

Chang Xu¹, Guangyin Zhao¹, Hongyu Zhang¹, Di Ge¹ and Jie Gu^{1*}

Abstract

Background Pulmonary large-cell neuroendocrine carcinoma (pLCNEC) represents a rare malignancy characterized by its aggressive behavior and a notably high recurrence rate. Remarkably, there is currently no established standard treatment protocol for this condition.

Case description In this report, we present an intriguing case of pLCNEC diagnosed at clinical-stage IIB. This case involves a 64-year-old man with a smoking history spanning four decades. In our approach, we initiated a course of neoadjuvant chemotherapy in combination with pembrolizumab, administered for two cycles prior to surgical resection. This innovative treatment strategy resulted in a significant pathological response, culminating in a major pathological remission (MPR). As of the time of composing this report, the patient has been diligently monitored for 39 months post-surgery, exhibiting no indications of recurrence, and has demonstrated exceptional tolerance to the entire treatment regimen.

Conclusions We have first reported a clinically successful case of neoadjuvant combination chemotherapy with pembrolizumab in the treatment of pLCNEC. This case offers promising clinical insights and suggests that this therapeutic approach could be a viable option for managing pLCNEC.

Keywords pLCNEC, Neoadjuvant immunochemotherapy, MPR, Case report

Background

A new classification within the spectrum of pulmonary neuroendocrine tumors, pulmonary large-cell neuroendocrine carcinoma (pLCNEC), was originally proposed by Travis et al. in 1991 [1]. The incidence of pLCNEC is 2.1–3.5% of all lung cancer cases. Currently, a universally accepted standard treatment regimen for pLCNEC is notably absent, with surgery being recommended as

the primary approach for patients deemed suitable for resection. The 5-year survival rate for surgically managed patients ranges only from 13 to 57% [2]. Moreover, the landscape of neoadjuvant therapy for unresectable pLCNEC remains ill-defined, primarily due to the limited availability of data. Nevertheless, some studies have revealed that neoadjuvant chemotherapy shows great potential in the treatment of pLCNEC [2–4]. In this report, we share a compelling clinical case of pLCNEC, demonstrating a major pathological remission (MPR) following neoadjuvant combined chemotherapy with pembrolizumab.

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Case presentation

A 64-year-old man, who had been a smoker for four decades, was admitted to the hospital in January 2020 after the discovery of pulmonary space-occupying lesions during a routine physical examination three months earlier. An enhanced chest computed tomography (CT) scan revealed a large mass, measuring up to 36*28 mm in its maximum cross-section, along with a small, solitary nodule with a diameter of 9 mm in the right lower lobe. Subsequent Positron Emission Tomography (PET)-CT imaging disclosed that the large mass exhibited malignancy, with a standardized uptake value (SUV) of 20.2, while the smaller nodule was identified as a satellite lesion with an SUV of 2.3. No enlarged lymph nodes or distant metastases were detected. The patient underwent CT-guided percutaneous biopsy. Immunohistochemical analysis revealed negativity for thyroid transcription factor 1, napsin A, synaptophysin, CD56, protein 40, and protein 63, but positivity for CK7, a Ki-67 index of 80%, with only partial positivity for chromogranin A. Two experienced pathologists were invited to review the section of the medical record and found the morphology was consistent with the manifestation of large cell neuroendocrine carcinoma. Based on these findings, the patient was considered as LCNEC at clinical stage IIB (cT3N0M0).

For treatment, we initiated neoadjuvant chemotherapy combined with pembrolizumab, administering two cycles at three-week intervals. The patient's body surface area is about 1.6 square meters. The treatment regimen is paclitaxel 135 mg/m² + cisplatin 75 mg/m² + pembrolizumab 100 mg (Fig. 1A). Following these two cycles of immunochemotherapy, a reevaluation through enhanced chest CT indicated substantial reductions in both lesions, constituting a partial response (PR) according to efficacy assessment criteria (Fig. 1B). Subsequently, a right lower lobectomy and systemic lymphadenectomy were successfully performed 23 days after the last therapy (C2D1+23 days).

Postoperative pathology confirmed large-cell neuroendocrine carcinoma, with a major pathological remission (MPR) achieved, characterized by only a small amount of residual carcinoma tissue (<5%) and a tumor bed size of 2.0×1.5 cm, accompanied by fibrous hyperplasia, inflammatory cell infiltration, and histiocytic reaction. Immunohistochemical staining corroborated the biopsy results, and no signs of lymph node metastases were identified. The TNM stage was downgraded to ypT1bN0M0 IA2. The patient was discharged just five days following the surgery without any significant in-hospital complications. The same immunochemotherapy regimen was administered for two additional cycles, and the patient exhibited only mild anorexia throughout the treatment, demonstrating excellent tolerance. To date, the patient

has been followed up for 33 months and remains in excellent health, with no evidence of recurrence or metastases.

Discussion and conclusions

Clinical data regarding pLCNEC are scarce due to its low incidence. The treatment landscape for LCNEC remains a subject of controversy. Notably, Rekhtman et al. proposed a molecular categorization of LCNEC into NSCLC-like LCNEC and SCLC-like LCNEC based on next-generation sequencing [5]. In the NSCLC-like LCNEC subgroup, mutations in KRAS, serine/threonine kinase 11 gene (STK11)/kelch-like ECH associated protein 1 gene (KEAP1), and TP53 were prevalent, while the SCLC-like LCNEC subgroup exhibited predominant RB1 and TP53 inactivation [6].

Sun et al. conducted research indicating that the SCLC-regimen displayed superior prognosis and objective response rates in advanced pLCNEC compared to the NSCLC-regimen. This observation aligns with the demonstrated efficacy of platinum compounds and taxanes in advanced disease [7]. Although surgery stands as the optimal treatment for early pLCNEC, some patients may derive benefits from neoadjuvant therapy, especially if surgical intervention is not feasible at the time of initial diagnosis. A single-center study reported a high response rate of 68% to platinum-based neoadjuvant therapy in 22 patients [3]. Another retrospective analysis pointed out that perioperative chemotherapy, including preoperative chemotherapy, may be beneficial in patients with resected LCNEC [4]. Saji H. also reported response rates of about 80% with neoadjuvant chemotherapy, indicating that neoadjuvant chemotherapy may favor survival [8]. Nevertheless, the role of neoadjuvant therapy in LCNEC treatment remains under active investigation.

Recent years have seen a phase II clinical study showing that neoadjuvant nivolumab could induce a major pathological remission (MPR) in 45% of resected tumors in NSCLC [9]. Furthermore, immunotherapy treatment, such as immunotherapy, has shown better overall survival and safety benefits versus docetaxel in NSCLC, based on results from OAK [10]. Despite the limited data available for pLCNEC, our case provides support for the positive influence of immune-neoadjuvant therapy and underscores the synergistic effect of neoadjuvant immunochemotherapy in pLCNEC. In our case, a clinical-stage IIB pLCNEC achieved a partial response (PR) after two cycles of neoadjuvant immunochemotherapy, and the patient underwent surgery with remarkable tolerance throughout the treatment. Postoperative pathology confirmed an MPR with less than 5% residual carcinoma tissue. The same immunochemotherapy regimen was continued for an additional two cycles after the operation. At the latest follow-up, the patient remained in good health with no signs of tumor recurrence. We

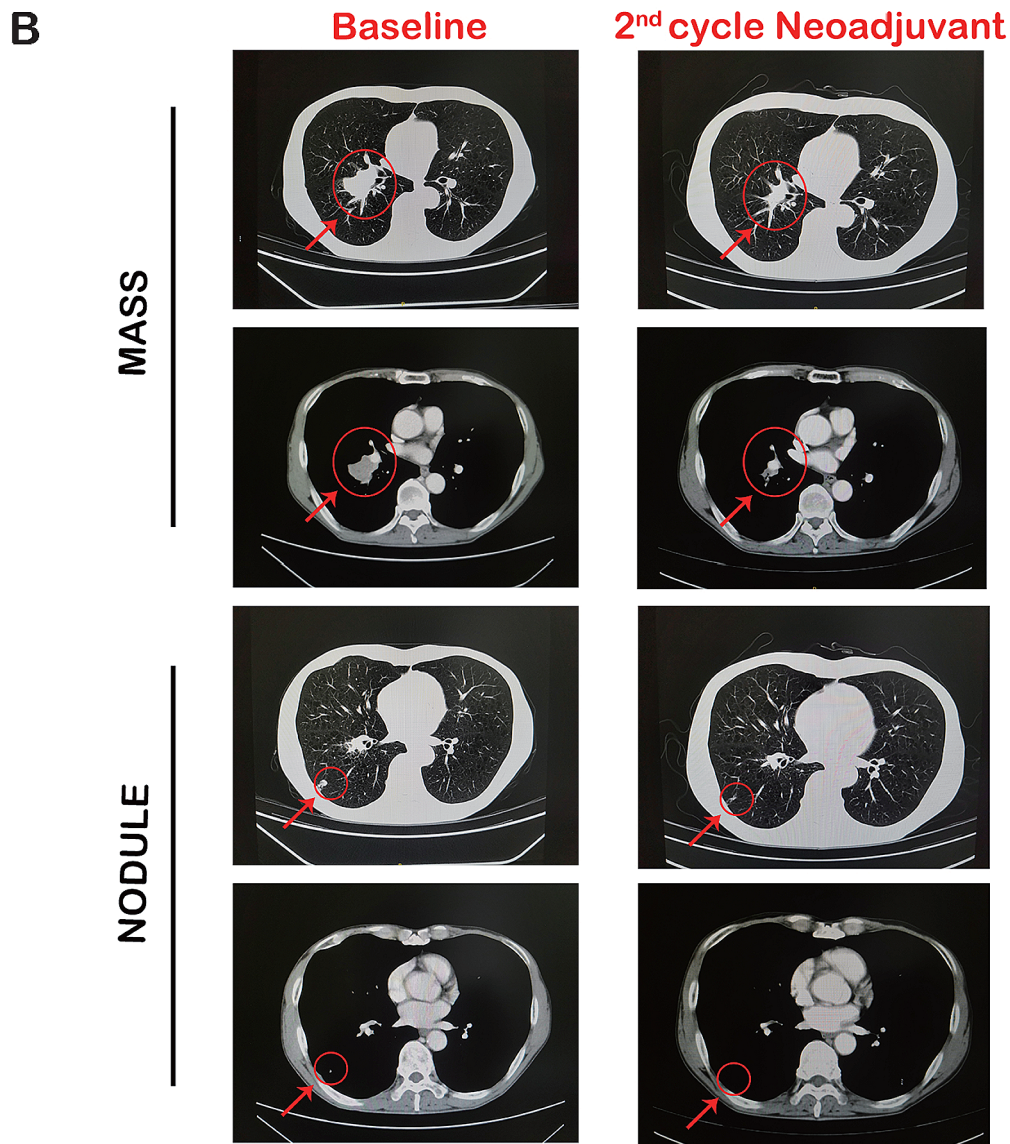
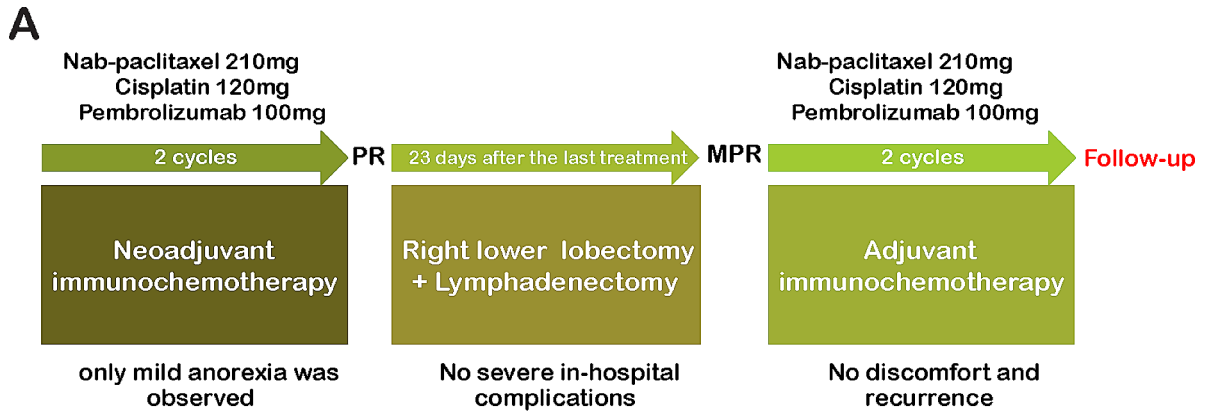


Fig. 1 Disease evolution and treatment timeline under neoadjuvant immunochemotherapy. (A) The timeline therapy administration from the episode of treatment. PR, partial response; MPR, major pathological remission. (B) Computed tomography scan showed dynamic changes of lesions in radiology and revealed a partial response of disease after 2 cycles of immunochemotherapy

hypothesize that chemotherapy-induced tumor cell death and the substantial release of tumor antigens triggered a robust and sustained response to immune checkpoint inhibitors (ICIs) through immune activation.

In conclusion, we report a clinically successful case of neoadjuvant combination chemotherapy with pembrolizumab in pLCNEC. We advocate for clinical trials to validate the clinical significance of neoadjuvant immunotherapy in pLCNEC. In summary, neoadjuvant immunotherapy may indeed represent a clinically viable option for the treatment of pLCNEC.

Abbreviations

IRB	Institutional Review Board
pLCNEC	pulmonary large-cell neuroendocrine carcinoma
MPR	major pathological remission
CT	computed tomography
PET	positron emission tomography
PR	partial response

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Not applicable.

Author contributions

CX analyzed and interpreted the patient data, and was a major contributor in writing the manuscript; GZ suggested improvements and helped revise the work; HZ contributed to the collection and assembly of data; JG provided study materials and patient data; DG was in charge of project administration. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

The publication of data received ethical approval from the Zhongshan Hospital's ethics committee. The patient provided informed written consent for the publication of their case data.

Conflict of interest

The authors declare no potential conflicts of interest.

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