



# Neoadjuvant chemotherapy combined with immunotherapy for pulmonary large-cell neuroendocrine carcinoma: a case report

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**Abstract:** Lung cancer can be divided into small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC can be further divided into squamous cell carcinoma, adenocarcinoma, and large-cell neuroendocrine carcinoma (LCNEC). At present, our understanding of LCNEC is limited. LCNEC is a rare condition but is highly malignant with a poor prognosis. The mean age of onset was about 65 years old, and was highly correlated with smoking. Although many treatment methods, including surgery, radiotherapy, and chemotherapy, are available, the therapeutic effect was limited and there is still a lack of clear guidelines and recommendations for its therapy. At present, immunotherapy is rapidly developing, and its application in lung cancer is increasing. However, there is limited literature about immunotherapy in LCNEC. Here, we present a case of LCNEC at stage IIIA, which involved a 64-year-old man with a 30-year history of smoking. Enhanced chest radiography indicated a malignant tumor in the upper lobe of the left lung. We treated this patient with neoadjuvant chemo-immunotherapy with albumin paclitaxel, carboplatin, and sintilimab. We also performed postoperative chemo-immunotherapy the same as before surgery. The patient has well tolerated this treatment and remains under postoperative observation for 6 months at the time of writing.

**Keywords:** Large-cell neuroendocrine carcinoma; neoadjuvant therapy; chemotherapy; immunotherapy

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## Introduction

Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a clinically rare, high-grade neuroendocrine lung cancer, the incidence of which is low, ranging from 2.4% to 3.1% (1,2). It was first named by Travis *et al.* in 1991 (3). Owing to its lack of specific clinical manifestations, the high degree of malignancy and the difficulty in early diagnosis, about 40% of patients with LCNEC were reported to be at stage IV when diagnosed, in whom resection was not possible (4). However, neoadjuvant therapy is still not well defined for the treatment of unresectable pulmonary large-cell neuroendocrine carcinoma. We present a rare case of

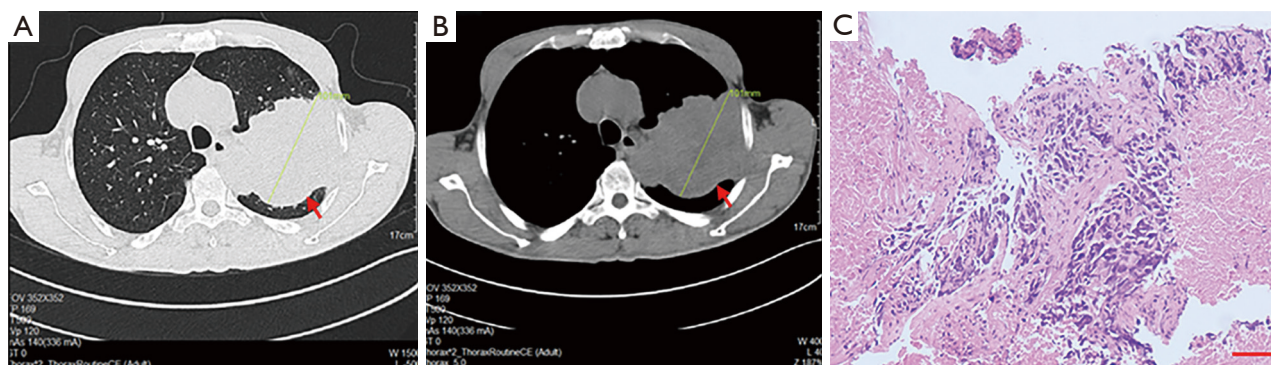
a 64-year-old male patient with stage IIIA LCNEC, who showed a good response to neoadjuvant chemotherapy combined with immunotherapy and obtained the opportunity to undergo surgical treatment. We present the following case in accordance with the CARE reporting checklist.

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## Case presentation

A 64-year-old man was admitted to hospital in January

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**Figure 1** Enhanced chest radiography and pathology before chemo-immunotherapy. (A,B) Enhanced CT revealed a malignant tumor in the upper lobe of the left lung of about 10.1 cm. The lesion is identified with a red arrow. (C) Pathological examination of CT-guided percutaneous biopsy specimen showed non-small cell carcinoma with HE staining. The scale bar indicates 100  $\mu\text{m}$ . CT, computed tomography; HE, hematoxylin and eosin.

2020 with the chief complaint of dizziness for more than 10 days, in whom a lung shadow had been found for 4 days. The patient had a history of smoking for 30 years. Physical examination showed no enlarged lymph nodes in the neck or clavicle. The left lung breath sound was significantly lower than normal, while that of the right lung was normal. Enhanced chest CT indicated a malignant tumor of about 10.1 cm in the upper lobe of the left lung with obstructive pneumonia, while a few lymph nodes near the bronchus were enlarged (*Figure 1A and B*). No distant metastasis was identified. The patient underwent CT-guided percutaneous biopsy. Pathological examination showed non-small cell carcinoma. Immunohistochemical staining revealed negativity for thyroid transcription factor 1, napsin A, synaptophysin, chromogranin A, CD56, protein 40, and protein 63, but positivity for CK (AE1/AE3) and P53, a Ki-67 index of 70%, with only focal positive of cytokeratin 5/6 (*Figure 1C*). Gene analysis showed negative findings for the expression of PD-L1, EGFR, ALK, MET, ROS1, HER2, KARS, and BRAF. Based on the above results, this patient was diagnosed clinically with stage IIIA (cT4N1M0).

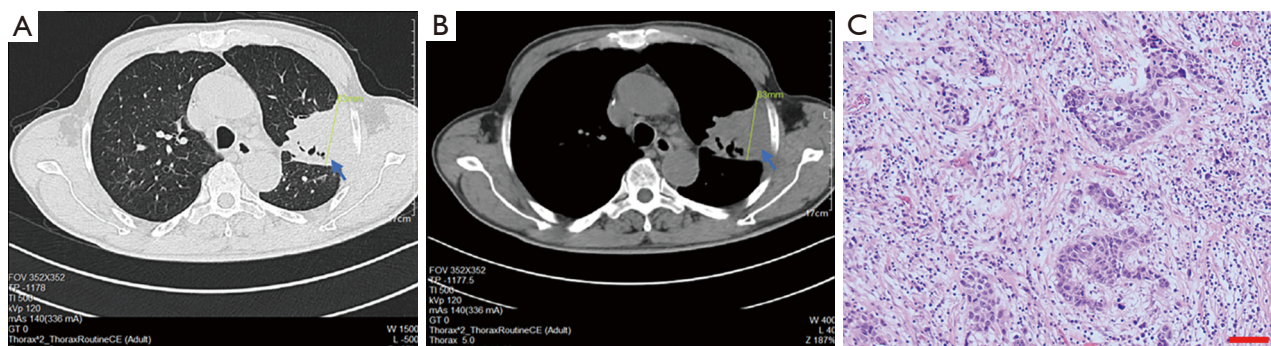
After two cycles of albumin paclitaxel, carboplatin, and sintilimab chemo-immunotherapy, grade II bone marrow suppression appeared, after which treatment with recombinant human granulocyte colony-stimulating factor was performed and improved the white blood cell count. We reexamined the patient using enhanced chest CT, which showed left lung carcinoma that was significantly smaller than before, with a longest diameter of 6.3 cm, along with mild mediastinum and left hilum bronchus lymph

node enlargement. There was still no distant metastasis during this examination, and the yield clinical stage was ycT3N1M0, IIIA. The efficacy of neoadjuvant therapy achieved partial remission (*Figure 2A and B*). According to the evaluation of thoracic surgeons, the left lung lesion was resectable and had the indication of an operation.

In April 2020, the patient underwent left upper lobectomy and mediastinal lymph node dissection. Postoperative pathology showed large-cell carcinoma with a small focus of neuroendocrine differentiation, without vascular invasion, nerve invasion, pleural invasion, airway spread, and lymph node metastasis. The tumor bed size was 7.5 cm  $\times$  4 cm, with two focal residual carcinomas, of 0.6 cm  $\times$  0.3 cm and 0.5 cm  $\times$  0.4 cm in size. Upon immunohistochemical staining of these two tumor lesions, one was CD56-negative and cytokeratin5/6 positive in few cells, while the other was CD56-positive (a small minority, about 15%) and cytokeratin5/6-negative, with other markers being consistent with the puncture sample. The yield pathological stage was ypT1bN0M0. The pathological remission grade after neoadjuvant therapy was grade IIb left residual tumor cells <10%. Main pathological remission (MPR) was achieved (*Figure 2C*).

After the operation, albumin paclitaxel, carboplatin, and sintilimab chemo-immunotherapy was continued for another two cycles. The patient had a mild rash, which was improved by symptomatic treatment. In general, the patient well tolerated the treatment and is still under postoperative observation.

All procedures performed in studies involving human participants were in accordance with the ethical standards



**Figure 2** Enhanced CT and pathology after chemo-immunotherapy. (A,B) Enhanced CT after two cycles of neoadjuvant chemo-immunotherapy showed that the left lung carcinoma was significantly smaller than before. The lesion is identified with a blue arrow. (C) Postoperative pathology under HE staining. The scale bar indicates 100  $\mu$ m. CT, computed tomography; HE, hematoxylin and eosin.

of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Discussion

Although the incidence of pulmonary large-cell neuroendocrine carcinoma is relatively low, its incidence is gradually increasing (4,5). LCNEC tends to occur in elderly men with a history of heavy smoking, and its clinical manifestations show a lack of specificity, including cough, hemoptysis, dyspnea, carcinoid syndrome, and asymptomatic nodules (6). In addition to the nonspecificity of symptoms, it is difficult to diagnose and has a poor prognosis. For some patients, preoperative pulmonary puncture or bronchoscopy specimens only with a small sample size could not identify cases as LCNEC, so nearly half of patients with large-cell carcinoma were reported to be at an unresectable advanced stage (4). Our case fits such a diagnostic situation in that preoperative biopsy only revealed undifferentiated carcinoma, while postoperative pathology confirmed large-cell neuroendocrine carcinoma in one of two tumor lesions. This suggests that the reliability of diagnosis of large-cell neuroendocrine carcinoma based on small samples should be evaluated carefully by clinicians. At the same time, we guessed that neoadjuvant therapy might also affect the proportion of neuroendocrine expression in different tumor cells. More research is required to clarify this. There is also no standard treatment for pulmonary large-cell neuroendocrine carcinoma; although platinum/etoposide chemotherapy or the same plan as non-small cell lung cancer (NSCLC) was recommended in the American Society of Clinical Oncology guidelines (7), the treatment effect and the

disease remission rate were not satisfactory. A multi-center retrospective study indicated that SCLC-based regimens were associated with better survival outcomes than NSCLC regimens (8). At present, the optimal treatment remains controversial. Gene sequencing revealed that pulmonary large-cell neuroendocrine carcinoma had three types, namely, SCLC-like, NSCLC-like, and carcinoid-like, and its corresponding mutations also had specificity (9). This may be the reason for the difference in sensitivity to chemotherapy in LCNEC. Therefore, according to the clinical characteristics, metastasis pattern, and treatment response, experts have pointed out that patients with LCNEC in the early stage have a condition more similar to NSCLC, so an NSCLC chemotherapy regimen may be adopted, while LCNEC in the advanced stage is more similar to SCLC, for which an SCLC chemotherapy regimen has been recommended (4,5).

Surgery is the preferred treatment for early LCNEC, but it has a high recurrence rate and is not highly sensitive to chemotherapy (5,10,11). Therefore, there is a need for further study of adjuvant therapy after surgery. At present, chemotherapy and/or radiotherapy are mainly used for advanced patients, and platinum-based systemic chemotherapy is mainly used for metastatic or recurrent patients (10). Those who received platinum-based adjuvant chemotherapy had a notably lower rate of recurrence than those without adjuvant chemotherapy (12). Adjuvant chemotherapy is potentially beneficial for the early phase as well. For example, adjuvant chemotherapy based on platinum has been reported to prolong LCNEC patients' overall survival in the early stage (13).

However, a portion of patients have lost the opportunity to undergo surgery by the time of initial diagnosis, for whom neoadjuvant therapy may make sense. A single-

center study found that the effective rate was 68% among 22 patients receiving neoadjuvant therapy containing platinum (14). Another study pointed out that neoadjuvant chemotherapy's partial response rate (mainly platinum–etoposide) was 75% in LCNEC (15). However, the role of neoadjuvant therapy has not been studied in detail. Cases of large-cell neuroendocrine carcinoma are rare, so it is very difficult to accumulate a large range of samples as evidence. The value of neoadjuvant therapy for the treatment of LCNEC is still under discussion.

In the text above, the use of chemotherapy as neoadjuvant therapy has been discussed, but the role of immunotherapy in adjuvant or neoadjuvant therapy for large-cell neuroendocrine carcinoma of the lung remains to be determined. In recent years, the addition of immunotherapy to adjuvant and neoadjuvant therapy has achieved surprisingly high remission rates in lung cancer. Borghaei *et al.* indicated that overall survival was longer with nivolumab (approximately 12.2 months) than in the docetaxel group (approximately 9.4 months) in NSCLC (16). Regarding atezolizumab, Rittmeyer *et al.* obtained the same result, with overall survival with atezolizumab being longer than in the docetaxel group (17). Moreover, in a phase II clinical study, among 21 patients with operable early stage (stages I–IIIA) NSCLC who received two cycles of nivolumab treatment before the operation, about 45% achieved a major pathological response (MPR) (18). However, the data on LCNEC are insufficient. In addition, because LCNEC is so rare, there have been no clinical trials to examine the effect of immune-neoadjuvant therapy.

In this case, the stage IIIA pulmonary large-cell neuroendocrine carcinoma achieved PR after two cycles of neoadjuvant chemotherapy combined with immunotherapy, and the patient obtained the opportunity to undergo surgical treatment. Postoperative pathology confirmed large-cell carcinoma of the lung with 15% neuroendocrine carcinoma in one of the lesions. Another two cycles of adjuvant treatments were completed after the operation. Throughout the treatment, the patient tolerated it well, with no significant side effects, and the neoadjuvant therapy successfully reduced the size of the tumor, which was then removed.

In conclusion, there is a need for further studies of pulmonary large-cell neuroendocrine carcinoma to prove the efficacy and safety of neoadjuvant immunotherapy. Although it is difficult to draw definitive conclusions based on such limited experience, our case report may provide a reference for treatment among our peers.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/apm-20-2536>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-2536>). The authors have no conflicts of interest to declare.

*Ethical Statement:* 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. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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