Lung cancer is one of the leading causes of cancer-related mortality worldwide. Anaplastic lymphocyte kinase (ALK) rearrangements are driver genes in non-small cell lung cancer (NSCLC), accounting for 2%–7% of NSCLC. EML4-ALK is the most common ALK gene arrangement, and some non-canonical ALK fusions have been reported. For advanced ALK-positive NSCLC, alectinib is recommended as first-line treatment. No differences were observed in the results of different EML4-ALK variants with alectinib in the ALEX trial; however, further studies are needed to confirm the efficacy of alectinib in other non-canonical ALK fusions compared with that in EML4-ALK.

This is the first report of a lung adenocarcinoma patient harbouring a CCDC85A-ALK rearrangement that showed a remarkable response to alectinib. This case suggests that alectinib is an option for NSCLC patients with uncommon ALK gene rearrangements.

CASE REPORT

A Chinese man was hospitalized in April 2020 with an irritating dry cough and chest pain for more than 1 month. PET/CT showed a large hypermetabolic lesion (ca. $76 \times 92 \times 97 \text{ mm}^3$) in the right mediastinum, straddling the anterior, middle and posterior mediastinum and protruding into the lung field and involving the adjacent pleura. In the mediastinum (4R group), the lymph nodes were enlarged and metabolically active. Lymph node metastasis was suspected (Figure 1). Under CT guidance, a lung biopsy was performed. The pathological diagnosis was confirmed as poorly differentiated lung adenocarcinoma (Figure 1). The immunohistochemistry was CD30(−), CK(partial+), TTF-1(focal+), P40(−), CK7(−), vimentin(+), CD7(−), calretinin(−), Ki-67(70%+), CK(35BH11) (focal+), CgA(−), CK8/18(partial+), Syn(−) and ALK(D5F3)(+).

To explore potential targeted therapies, next-generation sequencing (NGS) was performed on the pulmonary biopsy tumour tissue and a blood specimen. This revealed a CCDC85A-ALK fusion variant and missense mutation of exon 8 (p.P540S) (Figure 2). The patient refused radiotherapy and chemotherapy, but agreed to take alectinib (600 mg bid).

After 2 weeks of alectinib, the tumour was markedly smaller on CT. The patient tolerated the alectinib well, with a sustained partial response (Figure 3). Periodic re-examination has detected no obvious adverse reactions.
FIGURE 1 (A–D) PET/CT showed that there were large hypermetabolic lesions in the right mediastinum, which straddled the anterior, middle and posterior mediastinum, and protruded into the lung field and involved the adjacent pleura. (E) The histology of adenocarcinoma with poor differentiation. (F) ALK (+) IHC using the D5F3 ALK antibody.

FIGURE 2 (A) Integrative Genomics Viewer snapshot of CCDC85A-ALK by next-generation sequencing (NGS). (B) A schematic representation of the CCDC85A-ALK fusion. Exons 1-2 (1-413aa) region of CCDC85A gene and ALK (exon 20), with a hypothetical CCDC85A-ALK fusion. (C) We used the Coils server (https://embnet.vitali.ch/software/COILS_form.html) to compare the amino acid sequence of CCDC85A gene to a database of proteins known to form coiled coils and found that the probability of a coiled coil domain at the exons 1-2 (1-413aa) region of CCDC85A gene being present is almost 100%. The x-axis represents the position in the protein by amino acid number, and the y-axis shows how strongly that region is predicted to form a coiled coil domain. ‘Window’ refers to the width of the amino acid ‘Window’ that is scanned at one time.
**DISCUSSION**

Anaplastic lymphocyte kinase is a transmembrane protein and an insulin receptor tyrosine kinase. Echinoderm microtubule-associated protein-like 4 (EML4)-ALK is the most common ALK gene arrangement, and it is found in 3%-13% of NSCLC. Different ALK fusion genes and EML4-ALK variants have been reported in NSCLC, and they respond to ALK inhibitors differently.

The incidence of uncommon ALK gene rearrangements in ALK-positive Chinese NSCLC is 18%-19%, and the clinical efficacy of ALK inhibitors needs further study. In this case, a rare gene fusion had a marked clinical response to alectinib, a highly ALK selective inhibitor recommended as a first-line drug for advanced ALK-positive NSCLC. The Global Phase III ALEX Study confirmed the superior efficacy of alectinib versus crizotinib in untreated ALK-positive NSCLC. The median progression-free survival was 34.8 months with alectinib and 10.9 months with crizotinib. In our case, the tumour shrank markedly after the patient had taken alectinib for 2 weeks.

In this patient, NGS showed that the ALK gene possessed a CCDC85A-ALK fusion variant due to the rearrangement of exon 2 of CCDC85A and exon 20 of ALK. We predicted that the CCDC85A gene had a coiled coil domain, which is thought to drive the dimerization of the ALK fusion protein and activate self-phosphorylation of the ALK kinase domain in the fusion protein, triggering ALK downstream signalling pathways. This is the first discovery of a CCDC85A-ALK rearrangement in a lung adenocarcinoma patient before treatment. We speculated that this fusion constitutively activated kinase participating in tumorigenesis and cancer progression, and increased the sensitivity of the tumour to ALK kinase inhibitors (Figure 2).

This is only one case report, and the long-term efficacy of alectinib in this patient will require further observation. The lack of in vitro studies of the signal pathway caused by the fusion, and its sensitivity to various ALK kinase inhibitors is also a deficiency of this report.

In summary, this is a successful case of a lung adenocarcinoma patient receiving an ALK kinase inhibitor. This case suggests that the newly found CCDC85A-ALK fusion is sensitive to alectinib. These findings demonstrate the importance of NGS in the diagnosis of and treatment for patients with NSCLC. NGS may identify more rare mutations, provide more comprehensive mutation information for clinicians and NSCLC patients, and help in the selection of appropriate treatments.

**AUTHOR CONTRIBUTIONS**

Jieheng Lin: Conceptualization (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal).

Wenping Wang: Data curation (equal); formal analysis (equal).

Jietao Lin: Data curation (equal); methodology (equal); supervision (equal).

Ruilian Chen: Data curation (equal); writing – original draft (equal).

Yang Cao: Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).

**CONFLICT OF INTEREST**

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associational interest that represents a conflict of interest in connection with the work submitted.
DATA AVAILABILITY STATEMENT
Data available on request due to privacy/ethical restrictions.

CONSENT STATEMENT
The patient had signed informed consent prior to his hospitalization that biological specimens collected during his hospitalization might be used for scientific research.

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