Left total pneumonectomy performed after alectinib treatment for anaplastic lymphoma kinase-positive lung adenocarcinoma: a case report

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Background: Anaplastic lymphoma kinase (ALK) rearrangement generates an oncogenic ALK tyrosine kinase that activates numerous downstream signaling pathways, leading to increased cell proliferation and survival. About 5% of non-small cell lung cancer (NSCLC) patients are being diagnosed with tumor harboring ALK-positive. ALK rearrangement is an important molecular target for the treatment of NSCLC, and alectinib is a potent and highly selective second-generation ALK inhibitor. Alectinib as a neoadjuvant therapy has been reported in previous studies. However, cases of patients undergoing left total pulmonary resection after neoadjuvant therapy are rare.

Case Description: In this report, a 52-year-old Asian woman's chest computed tomography (CT) showed mass shadows in the left lung. Echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK) fusion variant was detected by next-generation sequencing. We administered the targeted drug alectinib at 600 mg twice daily for two and a half months. Positron emission tomography (PET)-CT examination showed that the left lung mass and lymph nodes were significantly reduced. The tumor node metastasis (TNM) stage was reduced from cT4N2M0, IIIb to ycT2aN0M0, IB. Then she underwent thoracoscopic transthoracotomy of the left total lung. Oral alectinib therapy was continued after surgery, and the follow-up duration was one year.

Conclusions: This case indicates that alectinib is feasible and has a good safety profile as a neoadjuvant therapy for ALK-positive NSCLC. But further research is needed to determine how long the treatment should last for patients to get the most benefit. There is also the problem of pulmonary fibrosis in the process of alectinib neoadjuvant therapy, which needs to be solved urgently.

Keywords: Alectinib; neoadjuvant; anaplastic lymphoma kinase inhibitor (ALK inhibitor); non-small cell lung cancer (NSCLC); case report

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Introduction

Neoadjuvant therapy has provided more surgical opportunities to patients with lung cancer. Chemotherapy is the main mode of neoadjuvant therapy, but its effect is limited, and preoperative chemotherapy alone can improve the 5-year survival rate by only 5% (1). The use of novel therapeutic agents in neoadjuvant therapy for non-small cell lung cancer (NSCLC) is an emerging area of research aimed at achieving higher cure rates, and it has shown good results in NSCLC patients without gene mutations (2). Although neoadjuvant therapy may sometimes delay surgery and carry the risk of disease progression, its advantages are well known. Alectinib is a potent and highly selective second-generation anaplastic lymphoma kinase (ALK) inhibitor for patients with ALK-positive NSCLC. ALNEO trial is a phase II, open-label, single-arm, multicenter study to assess the activity and safety of alectinib as neo-adjuvant therapy in patients with ALK-positive locally advanced stage III NSCLC is currently on going (3). There are no mature clinical data on the perioperative treatment of alectinib for ALK-positive NSCLC. Most data are derived from case reports or small-sample studies. However, all have shown good results. Therefore, in this case, we chose to use alectinib as the targeted drug for neoadjuvant therapy. We present this article in accordance with the CARE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-111/rc).

Highlight box

Key findings

- This case report describes a patient with anaplastic lymphoma kinase-positive (ALK-positive) lung adenocarcinoma who underwent a left total lung resection after significant tumor shrinkage following neoadjuvant therapy with alectinib. These results indicate that alectinib neoadjuvant therapy is very effective.

What is known and what is new?

- Alectinib has been previously studied as a neoadjuvant therapy in patients with ALK-positive lung adenocarcinoma, but left total pneumonectomy after neoadjuvant therapy is rare.
- Our patient underwent neoadjuvant therapy with alectinib and underwent left total pneumonectomy. The patient still had a good quality of life after one year of follow-up. This case proves that alectinib is safe and reliable as a neoadjuvant therapy.

What is the implication, and what should change now?

- Future studies should focus on the timing of alectinib neoadjuvant therapy and the most appropriate time of use after surgery.
- At the same time, we should also focus on the problem of pulmonary fibrosis in the course of alectinib neoadjuvant therapy, explore its mechanism and find out solutions.

Case presentation

A 52-year-old Asian woman presented with wheezing that was aggravated after activity had had no obvious inducement 6 months before admission. She had no fever, coughing, phlegm production, or chest pain. Ten days before presentation, she developed sudden hemoptysis. The patient remained in good health with no history of major diseases, smoking, or drinking or a family history of tumors. Chest computed tomography (CT) showed mass shadows in the hilum of the left lung and the soft tissue of the left mediastinum with a maximum cross-sectional area of 46 mm × 50 mm, as well as lymph node shadows beside the aortic arch. Lung cancer was considered to have invaded the mediastinum. The carcinoembryonic antigen concentration was 81.30 ng/mL (reference range, 0.00–5.00 ng/mL). Pathological biopsy by tracheoscopy showed invasive mucinous adenocarcinoma in the lower lobe of the left lung. According to the 8th tumor node metastasis (TNM) stage, the patient was cT4N2M0, IIIB.

Based on National Comprehensive Cancer Network (NCCN) guidelines, patients are recommended to undergo radical concurrent chemoradiotherapy. ALK [echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion positive] was detected by next-generation sequencing, with no other genetic variants. Alectinib is recommended as a first-line targeted drug for ALK-positive patients. According to some previous case reports, alectinib is better than traditional radiotherapy or chemotherapy in patients with locally advanced ALK-positive NSCLC. So after full disclosure and consultation with the patient and her family, we decided to give the patient the targeted drug alectinib, 600 mg twice daily for two and a half months. The carcinoembryonic antigen concentration was 5.63 ng/mL (reference range, 0.00–5.00 ng/mL), which was significantly lower than that before targeted therapy. After targeted therapy, pulmonary function testing revealed small airway dysfunction, slightly reduced diffusion function, and a normal ratio of residual volume to total lung capacity. Lung function was thus improved compared with that before treatment (*Table 1*).

Chest CT showed that the maximum cross-sectional area of the left lung tumor before targeted therapy was 46 mm × 50 mm. After treatment, the soft tissue mass in the left hilar area and the left mediastinum was significantly reduced,

Table 1 Changes in lung function

Lung function items	Before targeted therapy	After targeted therapy	Six months after surgery
VC (L)	1.82	2.72	1.64
FVC (L)	1.82	2.72	1.64
FEV1 (L)	1.41	2.05	1.28
FEV1/FVC (%)	77.63	75.53	78.2
MEF50 (L/s)	1.4	2.26	1.27
PEF (L/s)	3.96	5.72	3.7

VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; MEF50, maximal expiratory flow at 50% of forced vital capacity; PEF, peak expiratory flow; L, liter; s, second.

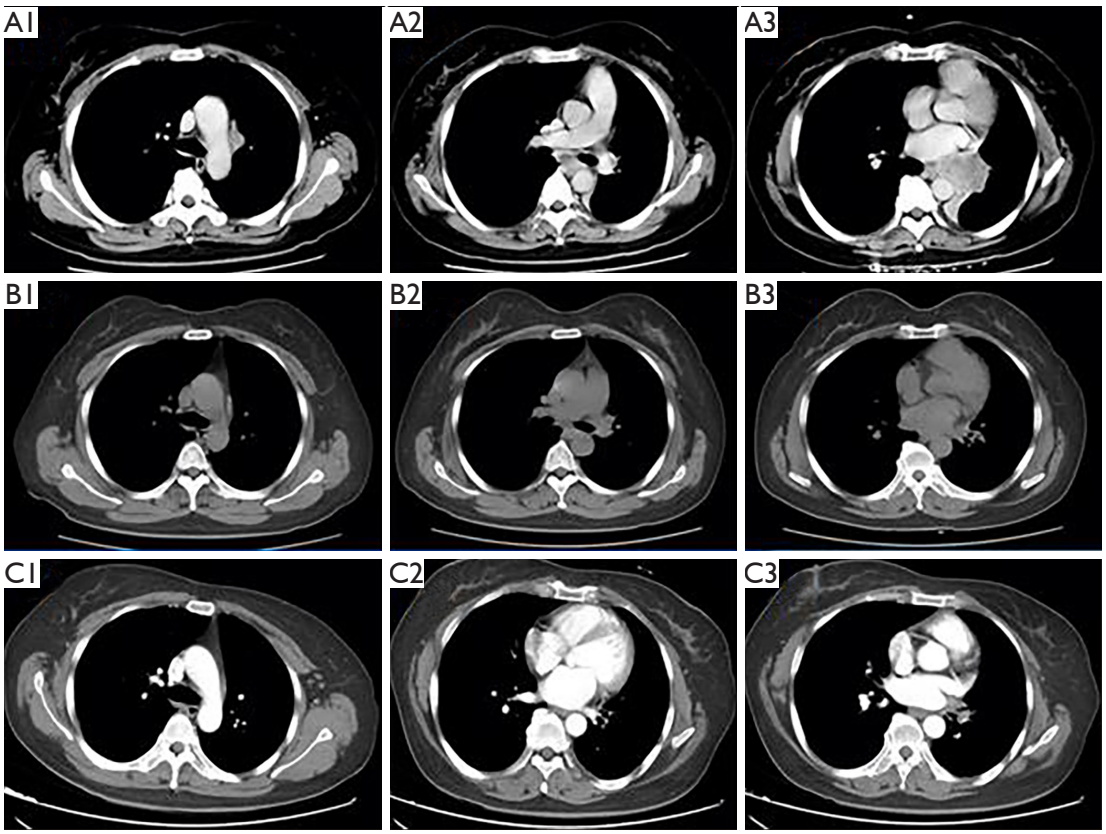

Figure 1 Chest CT before and after targeted therapy. (A1, A2, and A3) are before targeted therapy, maximum cross-sectional area of the tumor is 46 mm × 50 mm; (B1, B2, and B3) are 1 month after targeted therapy, maximum cross-sectional area of the tumor is 8 mm × 10 mm; and (C1, C2, and C3) are 2 months after targeted therapy, maximum cross-sectional area of the tumor is 5 mm × 8 mm. CT, computed tomography.

and the enlarged lymph nodes around the aortic arch and in the mediastinum were also significantly reduced (*Figure 1*). Two months after targeted therapy, positron emission tomography (PET) revealed a standardized uptake value of 3.9 for the tumor in the left hilar region, with no enlarged hilar or mediastinal lymph nodes or tracer accumulation. The maximum cross-sectional area of the left lung tumor after targeted therapy was 4 mm × 7 mm (*Figure 2*).

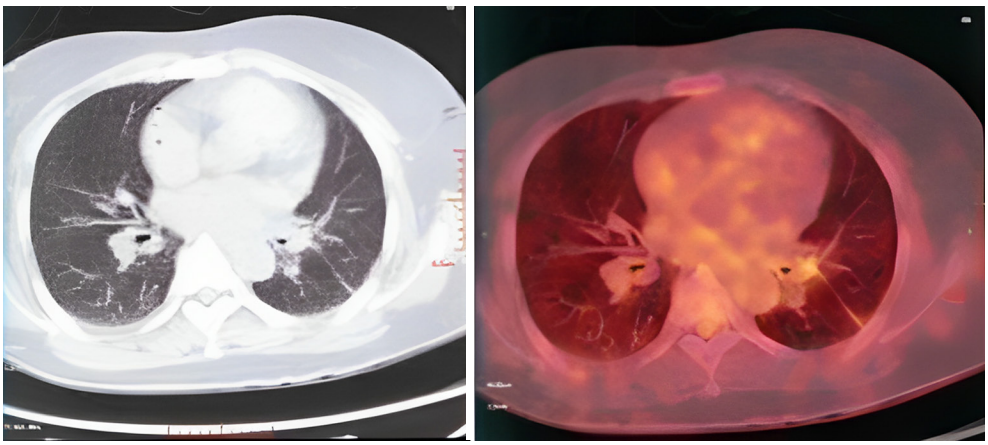

Figure 2 PET/CT after 2 months of targeted therapy. The maximum cross-sectional area of the tumor is 4 mm × 7 mm. PET/CT, positron emission tomography/computed tomography.

The comparison of bronchoscopy before and after the administration of targeted drugs is shown in *Figure 3*.

The patient's TNM stage was reassessed to ycT2aN0M0, stage IB. No abnormalities were found on brain magnetic resonance imaging (MRI) and abdominal CT. There were no contraindications to surgery. Subsequently, surgical treatment was performed, and the planned surgical modalities were left inferior lobectomy. Thoracoscopic exploration showed that the left hilum of the lung showed dense fibrotic changes, the lower lobe trachea and pulmonary veins could not be separated by thoracoscopy. So the patient was converted to thoracotomy for left pneumonectomy. After opening the pericardium, the upper and lower pulmonary veins were removed and excised in the pericardium. The para-arch and subcarinal lymph nodes were fibrosed and fused and had reasonably clear boundaries with the surrounding tissue (*Figure 4*). Postoperative pathology showed foam cells, multinucleated giant cells, and scattered atypical cells in the whole lobe of the left lung, consistent with the changes after treatment of adenocarcinoma. There was no lymph node metastasis. Pathological results showed that the patient had achieved pathologic complete response (pCR).

The patient continued to take alectinib after discharge and has been followed up for more than one year. She has returned to her normal daily life. *Table 1* shows the pulmonary function re-examination findings, and *Figure 5* shows the CT re-examination findings. The carcinoembryonic antigen concentration decreased to 2.22 ng/mL. No wheezing occurred during light physical labor, and the dyspnea was relieved.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the only currently approved type of targeted adjuvant therapy for NSCLC (4). The breakthrough results of the EVAN study, which explored erlotinib versus vinorelbine plus cisplatin as adjuvant therapy for EGFR-positive stage IIIA NSCLC, showed a significantly better 5-year overall survival rate with erlotinib than with chemotherapy (84.8% *vs.* 51.1%). Patients in the chemotherapy arm either reached the end point or were censored at the end of the follow-up; thus, the 5-year disease-free survival could not be calculated, the disease-free survival curve in the erlotinib group remained superior to that in the chemotherapy group throughout the trial, consistent with the overall survival curve (5). Osimertinib also achieved a breakthrough in the ADAURA study (6,7), becoming the first EGFR-TKI to receive an indication for adjuvant therapy. This reflects the efficacy of osimertinib regardless of previous chemotherapy. For evaluation of neoadjuvant therapy, the NeoADAURA study is currently ongoing; however, the phase III data are not yet available (8).

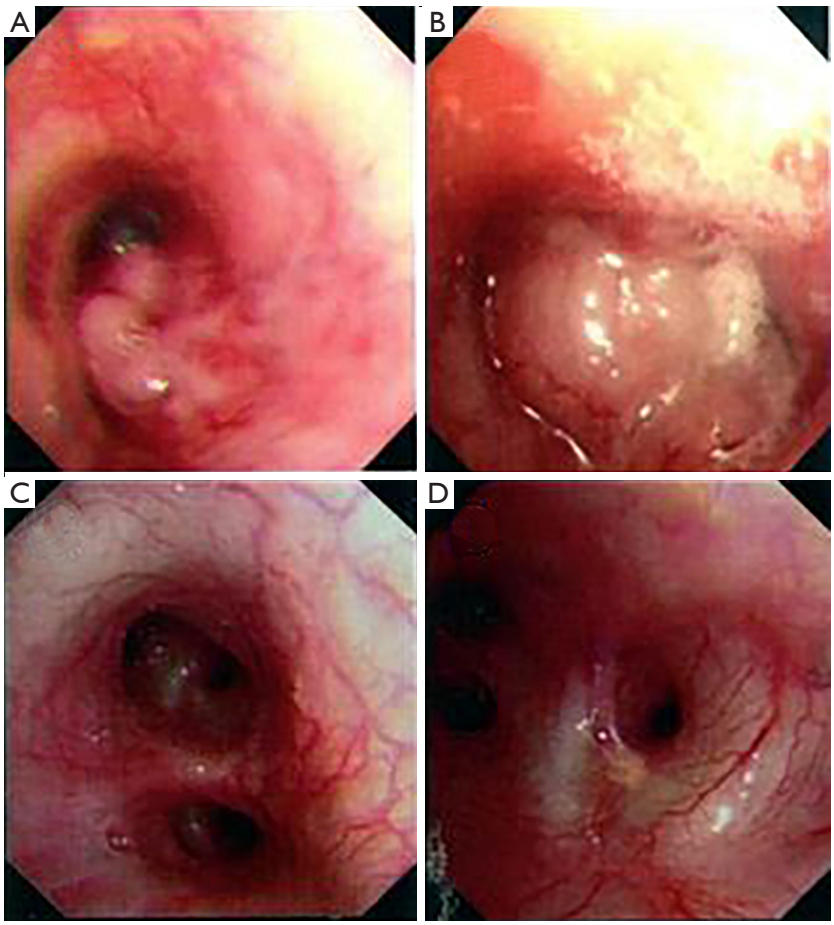

Figure 3 Bronchoscopy. Before targeted therapy, bronchoscopy revealed stenosis of the left main bronchus, and the bronchus was completely occluded by an endobronchial tumor in the left lingual segment and left lower lobe of the lung (A,B). After treatment, the opening of the left main bronchus was more patent than before treatment, the ridge between the upper and lower lobules was sharp, and the mucosa was congested and edematous (C). The mucosa of the anterior segment of the ascending branch of the upper lobe was hyperemic and edematous, and the orifice of the tongue was narrowed (D).

ALK rearrangement is a poor prognostic factor for patients with resectable NSCLC. In a previous study, ALK-fusion was detected in 29 (3.7%) of 764 patients with resectable stage I to III NSCLC, and ALK rearrangement was associated with a poor prognosis in patients with resectable NSCLC compared with other driver mutations (9). For these ALK-positive patients, the fusion rate is low and the prognosis is poor. However, based on the large number of patients with lung cancer, approximately 75,000 patients are diagnosed with ALK-positive NSCLC each year, and mature perioperative data are not available (10-13). The ALK-positive population has also been excluded from clinical trials of neoadjuvant or adjuvant therapy with immune checkpoint inhibitors for lung cancer (14,15). There are no controlled clinical studies to support the advantage of TKI treatment in patients with ALK-positive NSCLC.

Alectinib has been reported in several cases as neoadjuvant therapy for lung cancer. Yue *et al.* (16) reported a clinically successful case of alectinib in stage IIIB ALK-positive NSCLC downgrading to ypT1aN0M0 IB. Gu *et al.* (17) also reported a similar case of ALK-positive NSCLC with stage IIIB reduced to stage T1aN0M0, IA after treatment with alectinib. Lococo *et al.* (18) demonstrated the safety and feasibility of salvage surgery after treatment of advanced lung adenocarcinoma with alectinib in 10 cases. In this case, two and a half months after the patient received adjuvant alectinib, radiologic

and pathological evidence of a substantially reduced tumor was obtained without any adverse events. The TNM stage was reduced from cT4N2M0, IIIb to ycT2aN0M0, IB. Clearly, the therapeutic efficacy of alectinib is obvious. In the ALEX study, the median progression-free survival of patients with advanced lung cancer treated with alectinib reached 34.8 months, and the 5-year overall survival was 62.5% (19). However, this patient chose surgical treatment in pursuit of long-term survival. Longer follow-up is needed to determine whether patients benefit from the surgery.

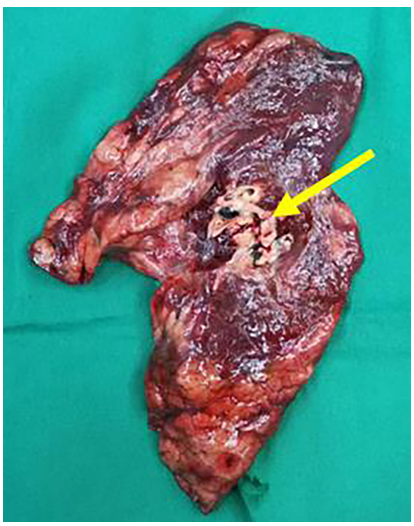

Figure 4 Surgical removal of left lung tissue. The arrow shows fibrotic tumor tissue between the upper and lower lobes of the left lung.

This case demonstrates that alectinib is feasible and has a good safety profile as a neoadjuvant therapy for ALK-positive NSCLC. However, there are still some unanswered questions, such as whether this patient should continue to use alectinib despite achieving pCR and how long the postoperative adjuvant therapy should be continued. According to the ADAURA study, osimertinib requires 3 years of oral administration after surgery for EGFR-positive NSCLC patients. But patients with advanced ALK-positive NSCLC have longer progression-free survival and overall survival. Does this necessitate longer adjuvant therapy after surgery? And with alectinib's effective neoadjuvant therapy, was is really necessary to perform pneumonectomy or lobectomy or stereotactic body radiotherapy? These questions still need to be answered by controlled clinical studies or other studies with large sample sizes.

Conclusions

Alectinib is a potent second-generation ALK-TKI. In this case, two and a half months after the patient received

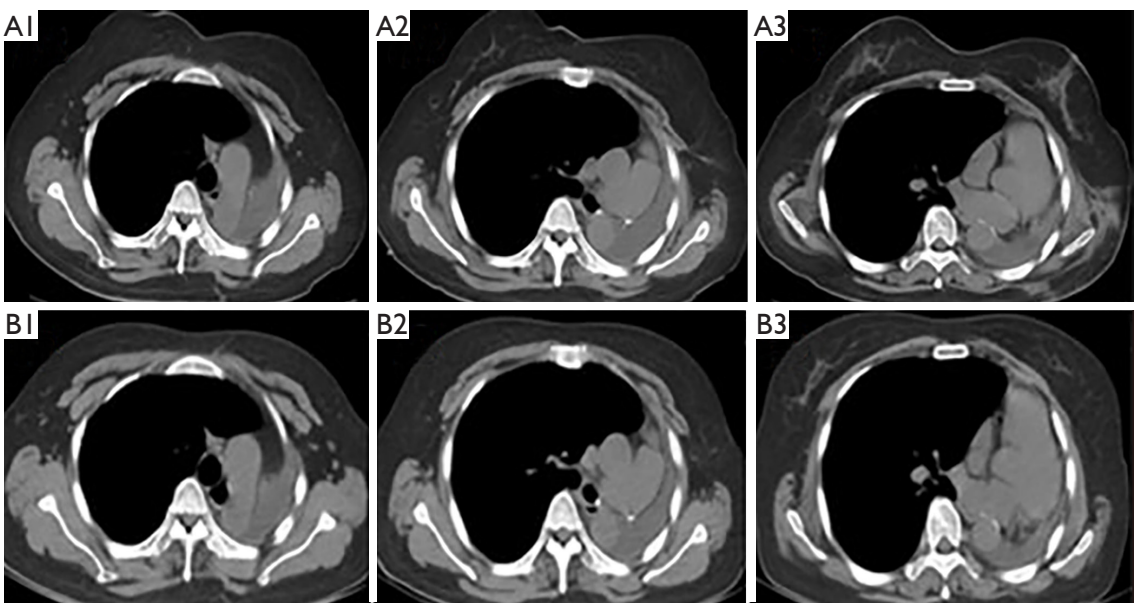

Figure 5 Chest CT after surgery. (A1, A2, and A3) are half a year after surgery; (B1, B2, and B3) are one year after surgery. CT, computed tomography.

adjuvant alectinib, radiologic and pathological evidence of a substantially reduced tumor was obtained without any adverse events. This case demonstrates that alectinib is feasible and has a good safety profile as a neoadjuvant therapy for ALK-positive NSCLC. It can be very effective downstaging and made the definitive treatment possible. Whether patients continued to use alectinib after neoadjuvant therapy; if patients continue to receive alectinib after surgery, the most reasonable duration of treatment and whether patients can achieve long-term remission or cure still need further investigation.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-111/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-111/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-111/coif). 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 this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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