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Co-occurrence of interstitial lung disease and pulmonary embolism as adverse events of adjuvant osimertinib treatment for *EGFR* mutant non-small cell lung cancer: a case report

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Abstract

Background Postoperative osimertinib for *EGFR* mutant non-small cell lung cancer has become the standard of care. However, its adverse events in clinical practice remain unclear. We report a case of interstitial lung disease and pulmonary embolism occurring simultaneously as adverse events during adjuvant osimertinib treatment.

Case presentation A 74-year-old woman, diagnosed with left lower lobe lung adenocarcinoma harboring an *EGFR* mutation, underwent a left lower lobectomy with lymph node dissection. During adjuvant osimertinib therapy, the patient developed respiratory distress with hypoxia, leading to the diagnosis of interstitial lung disease. Despite immediate steroid therapy, respiratory distress persisted, the patient developed leg edema. She was diagnosed with deep vein thrombosis and pulmonary embolism via contrast-enhanced computed tomography scan. Following treatment with steroid and anticoagulation, her clinical symptoms improved rapidly, and she showed no recurrence of interstitial lung disease, pulmonary embolism, or lung cancer over the following nine months.

Conclusions We encountered a case of interstitial lung disease and pulmonary embolism occurring simultaneously as adverse events during adjuvant osimertinib treatment. In patients with osimertinib-induced interstitial lung disease, particularly when respiratory symptoms show poor improvement with steroid treatment, the possibility of pulmonary embolism complications should be suspected.

Keywords Osimertinib, Lung cancer, Interstitial lung disease, Pulmonary embolism

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Background

Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is increasingly used as adjuvant chemotherapy for *EGFR*-mutant non-small cell lung cancer (NSCLC) due to its proven efficacy [1]. However, limited data is available on the adverse events (AEs) associated with osimertinib, particularly in the adjuvant setting in clinical practice. Here, we report a case of a patient who developed interstitial lung disease (ILD) accompanied by pulmonary embolism (PE) simultaneously during adjuvant osimertinib treatment.

Case presentation

A 74-year-old non-smoking woman was diagnosed with a left lower lobe lung adenocarcinoma harboring an *EGFR* exon 19 deletion mutation, and underwent a left lower lobectomy with systematic lymph node dissection. Postoperative pathological staging was pT2aN2M0 and pStage IIIA according to the UICC 8th edition. The patient received four courses of adjuvant chemotherapy with cisplatin and vinorelbine, following osimertinib (80 mg/day). After 49 days of osimertinib treatment, the patient developed respiratory distress with hypoxia; percutaneous oxygen saturation was 85% on room air with exertion. Blood tests revealed elevated levels of Krebs von den Lungen-6 (KL-6; 746 U/ml) and surfactant proteins D (SP-D; 497 pg/ml), alongside significantly increased D-dimer levels (62 μg/ml). A plain chest computed tomography (CT) scan showed diffuse ground-glass opacities in both lungs (Fig. 1). Based on these findings, the patient was diagnosed with ILD. Osimertinib treatment was discontinued, and methylprednisolone (1 mg/kg/day) was initiated immediately. Despite steroid therapy, respiratory distress persisted, the patient developed leg edema. A blood test performed four days after the diagnosis of ILD showed a further increase in D-dimer levels (78 μg/mL), prompting contrast-enhanced CT. It revealed thromboses in the main trunk of the right pulmonary artery and the right femoral vein (Fig. 2). She was subsequently diagnosed with deep vein thrombosis (DVT) and PE. Anticoagulation therapy with apixaban (20 mg/day) was initiated, resulting in rapid improvement of clinical symptoms and CT findings (Fig. 3). Steroid therapy was tapered and discontinued six weeks after initiation. Over the following nine months, the patient showed no recurrence of ILD, PE, or NSCLC.

Discussion and conclusions

Osimertinib selectively and irreversibly binds to and inhibits EGFR proteins harboring driver mutations and the T790M resistance mutation, while sparing wild-type EGFR [2]. In the FLAURA study, advanced-stage *EGFR*-mutant NSCLC patients treated with osimertinib had more favorable progression-free survival and overall survival compared to patients treated with first-generation EGFR-TKIs [3, 4]. Notably, fewer patients in the osimertinib group experienced grade three or higher AEs compared to the first-generation EGFR-TKI group (34% vs. 45%). Furthermore, the ADAURA trial demonstrated the efficacy of adjuvant osimertinib treatment in resectable *EGFR*-mutant NSCLC patients [1]. Based on these results, osimertinib has become the standard of care as adjuvant treatment, in addition to being used

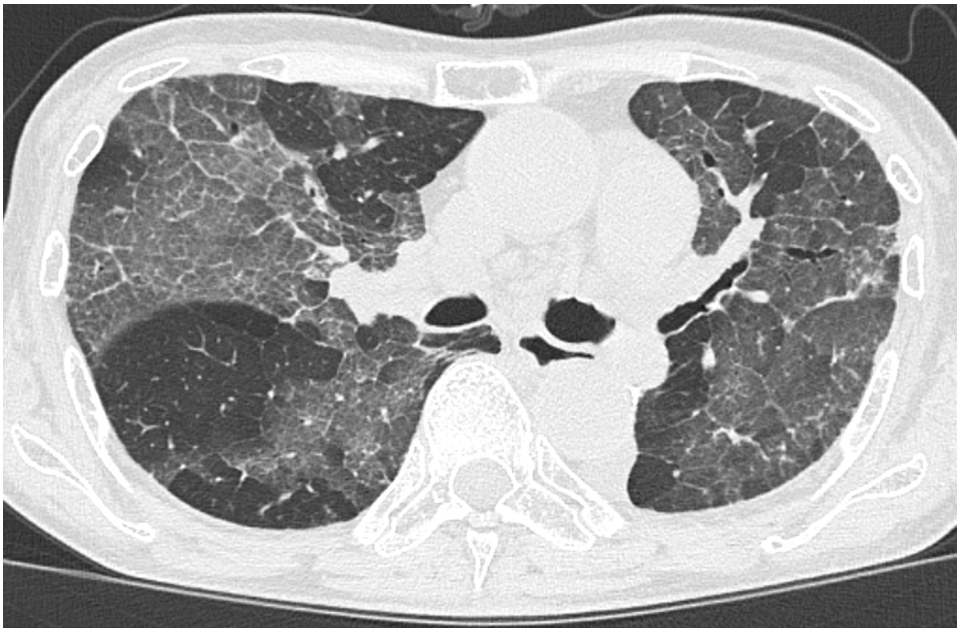

Fig. 1 Chest computed tomography scan showing the diffuse ground-glass opacities in both lungs

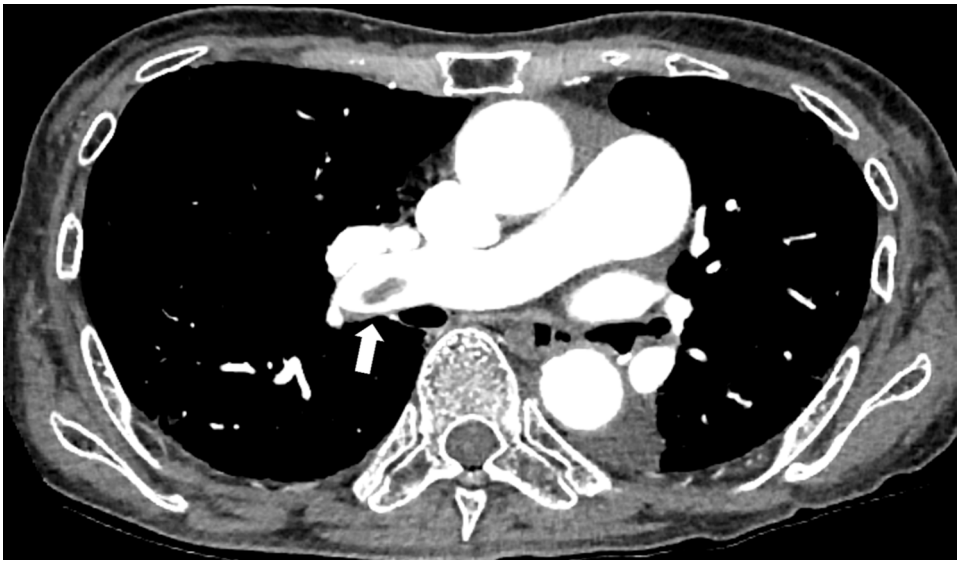

Fig. 2 Contrast-enhanced chest computed tomography scan showing thrombosis in the right pulmonary artery (arrowhead)

for advanced-stage NSCLC patients harboring *EGFR* mutation.

EGFR plays an essential role in epithelial maintenance, and EGFR-TKIs are thought to impair epithelial cell growth and migration while altering cytokine expression, leading to the recruitment of inflammatory cells and consequent tissue injury [5]. Therefore, EGFR-TKIs, including osimertinib, sometimes cause serious AEs. In the ADAURA study, the major AEs of osimertinib were diarrhea (46%), paronychia (25%), and dry skin (23%)[1]. These AEs are thought to be caused by epithelial injury by osimertinib. ILD is also recognized as a serious AE that often leads to the discontinuation of EGFR-TKI treatment, and was reported in 3% of patients treated with osimertinib in the ADAURA study [1]. It is thought that EGFR-TKIs may induce ILD through neutrophil infiltration and production of inflammatory cytokines in lung tissue [5].

Venous thromboembolism (VTE), including PE, has been reported as a rare AE of osimertinib [6]. Previous cases of VTE during osimertinib treatment have primarily involved patients with advanced disease, whereas our report concerns a patient in the postoperative adjuvant setting. In NSCLC, advanced disease has been identified as an independent predictor of VTE, with a four-fold increased risk in patients with metastatic disease compared to those with localized tumors [7]. While VTE in advanced disease may be driven by the aggressiveness of cancer cells, our patient had no radiographic evidence of residual disease. Although the detailed mechanism of osimertinib-induced VTE remains unclear, EGFR-TKIs have been implicated in vascular endothelial dysfunction and platelet activation, which may underlie the thrombotic events observed [8, 9].

In our case, although the relationship between ILD and PE is unclear, osimertinib treatment may have caused inflammation in the lung tissue, with the resulting injury potentially contributing to the development of both ILD and PE. Alternatively, respiratory symptoms caused by ILD may have prolonged the patient's bed rest, leading to the development of DVT in her legs. Thrombus formation could have been accelerated by a combination of these factors. Another possibility is that steroids administered for ILD treatment purposes may have contributed to thrombus formation. However, this hypothesis is unlikely, as elevated D-dimer levels were detected prior to steroid administration.

Diagnosing PE is generally challenging due to its nonspecific signs and symptoms. In this case, diagnosing PE was particularly difficult because the patient also had ILD, which complicated the interpretation of respiratory symptoms. Patients with interstitial pneumonia may have elevated D-dimer levels without radiographically detectable thrombosis, likely due to subclinical coagulation activation and endothelial injury [10]. Initially, we considered this possibility in our case in relation to the development of drug-induced ILD. We suspected DVT/PE due to the presence of leg edema and further elevated D-dimer levels, which led to the appropriate diagnosis via contrast-enhanced CT and successful treatment with anticoagulants in addition to steroids. Both ILD and PE are serious AEs caused by osimertinib, and this is the first report simultaneous complications in postoperative adjuvant setting to the best of our knowledge.

In conclusion, we encountered a case of ILD and PE occurring simultaneously as AEs during adjuvant osimertinib treatment. In patients with osimertinib-induced ILD, particularly when respiratory symptoms show poor

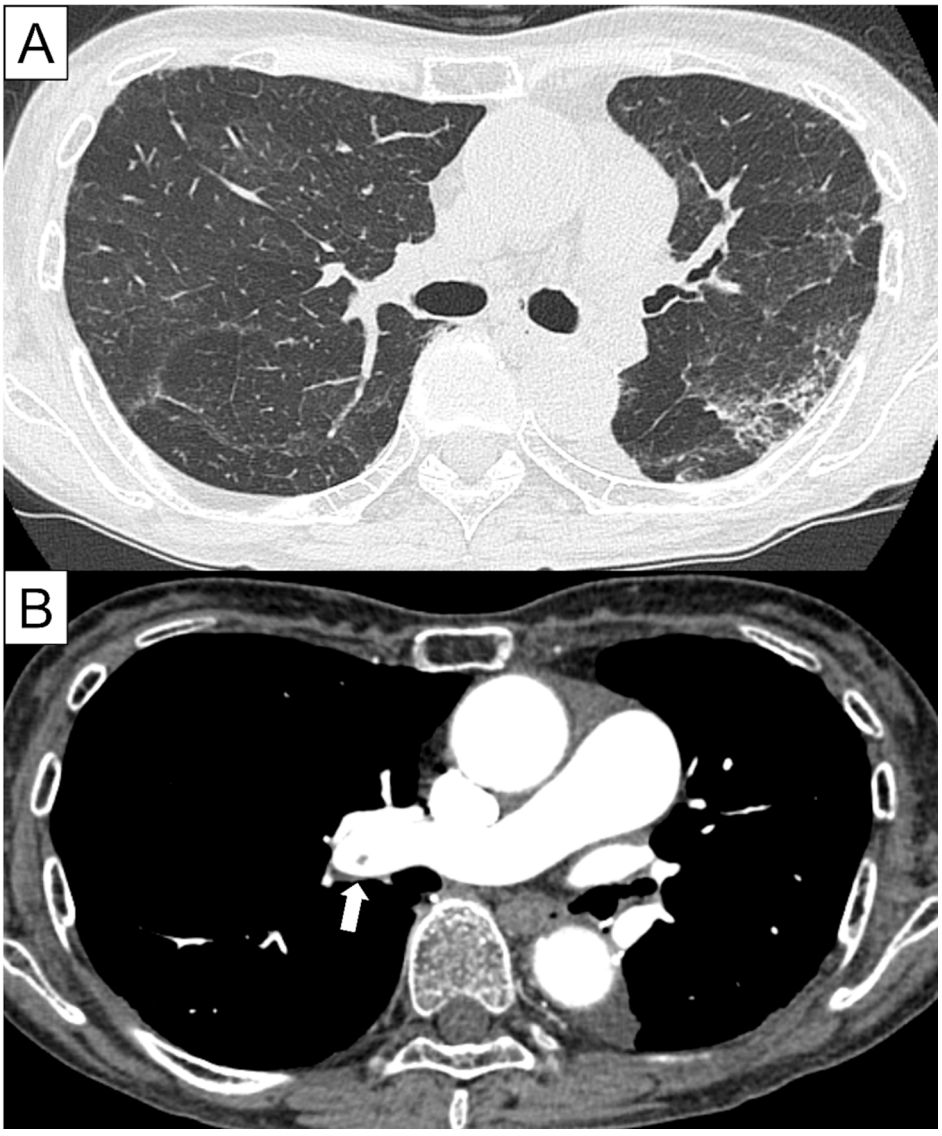

Fig. 3 Contrast-enhanced chest computed tomography scan taken 11 days after treatment with steroids and anticoagulation. The computed tomography scan showed significant improvement of (**A**) diffuse ground-glass opacities and (**B**) pulmonary thrombosis in the main trunk of the right pulmonary artery

improvement with steroid treatment, the possibility of PE complications should be suspected.

Abbreviations

EGFR	Epidermal growth factor receptor
TKI	Tyrosine kinase inhibitor
NSCLC	Non-small cell lung cancer
AEs	Adverse events
ILD	Interstitial lung disease
PE	Pulmonary embolism
KL-6	Krebs von den lungen-6
SP-D	Surfactant proteins D
CT	Computed tomography
DVT	Deep vein thrombosis
VTE	Venous thromboembolism

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Author contributions
K.M, K.Sh and S.To participated in the conception, design and analysis of this case report and drafted the manuscript. S.F, T.S, K.I, S.Ta, K.Su, M.O and S.S participated in the clinical treatment and helped to draft the manuscript. All the authors read and approved the final manuscript.

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Data availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent (approved by the institutional review board of Okayama University Hospital) was obtained from the patient for the publication of this case report and any accompanying images.

Consent for publication
Obtained.

Competing interests
The authors declare no competing interests.

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