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Successful treatment with afatinib following the failure of osimertinib rechallenge with osimertinib-induced interstitial lung disease: A case report

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ABSTRACT

Herein, we report the case of an 84-year-old woman with epidermal growth factor receptor (*EGFR*) mutation exon 19 deletion postoperative recurrent lung adenocarcinoma. Osimertinib was administered as a first-line treatment; however, she was urgently admitted to our hospital due to dyspnea on the 46th day. Chest computed tomography revealed bilateral diffuse ground-glass opacities (GGOs) suggestive of grade 3 osimertinib-induced interstitial lung disease (ILD). After discontinuation of osimertinib in combination with short-term corticosteroid therapy, widespread GGOs were promptly resolved. As the disease gradually deteriorated after discontinuation of osimertinib, we administered osimertinib (80 mg every other day) followed by careful observation. However, bilateral GGOs re-appeared on the 15th day, and the diagnosis of osimertinib-induced ILD was established. After the improvement in ILD following corticosteroid therapy, afatinib was administered as salvage therapy, resulting in desirable control of lung cancer without any relapse of ILD. Our results indicate that afatinib would be a promising alternative treatment option even in patients who develop osimertinib-induced ILD and experience failure of osimertinib rechallenge.

1. Introduction

Despite the dramatic effect of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) on *EGFR*-mutant non-small cell lung cancer (NSCLC), interstitial lung disease (ILD) rarely occurs as a serious and sometimes fatal adverse effect of EGFR-TKIs. Osimertinib is a third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and *EGFR* T790M resistance mutations [1]. Osimertinib is recommended as a first-line treatment because the median progression-free survival is significantly longer than that of first-generation EGFR-TKIs, including gefitinib and erlotinib [2]. However, ILD occurs as an adverse effect of osimertinib with a frequency of 2%–4% [2–5]. In addition, a higher frequency of ILD has been reported for osimertinib compared with first- and second-generation EGFR-TKIs among Japanese patients [6,7]. When drug-induced ILD develops, it generally requires cessation of the causative drug [8,9]. However, the preferred treatment strategy for these patients remains unclear. Here, we report a case of an *EGFR* mutation-positive NSCLC patient who developed first-line osimertinib-induced ILD who experienced failure of osimertinib rechallenge but was safely treated with afatinib.

2. Case presentation

An 84-year-old woman with p-staged 1A lung adenocarcinoma experienced relapse 8 years after complete surgical resection. Chest computed tomography (CT) revealed a nodular shadow and pleural effusion in the left lung (Fig. 1A). The carcinoembryonic antigen (CEA) level dramatically increased to 869.2 ng/mL. As the molecular analysis of surgical specimens confirmed that the tumor harbored *EGFR* exon 19 deletion, 80 mg of osimertinib was administered daily as first-line therapy after left pleural effusion drainage. One month after the initiation of osimertinib, CEA levels significantly decreased to 104.2 ng/mL. However, she was urgently admitted to our hospital due to dyspnea on the 46th day. Her oxygen saturation by pulse oximetry dropped from 95% to 80% measured on room air, and she required 2 L/min oxygen therapy via a nasal cannula. Although CEA levels decreased to 41.3 ng/

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mL, the level of Krebs von den Lungen-6 (KL-6) was high at 717 U/mL, and the chest CT revealed diffuse ground-glass opacities (GGOs) in both lungs (Fig. 1B). We suspected that the patient developed grade 3 osimertinib-induced ILD. However, congestive heart failure could not be completely ruled out because of edema of her lower extremities despite normal echocardiography. Therefore, osimertinib was discontinued, followed by the initiation of corticosteroid pulse therapy and diuretics. Five days later, GGOs on CT imaging and edema of the lower extremities improved; therefore, we discontinued corticosteroid therapy (Fig. 1C). On the 54th day following the discontinuation of osimertinib, CEA levels significantly increased to 357.3 ng/mL, and left pleural effusion had increased. Therefore, we carefully re-administered 80 mg of osimertinib every other day. However, 15 days later, she developed dyspnea again without edema of the lower extremities, and chest CT also revealed diffuse bilateral GGOs (Fig. 1D). Based on the clinical course, the diagnosis of osimertinib-induced ILD was confirmed. The ILD pattern on CT was considered to be uniform faint infiltration pattern. After withdrawing osimertinib, corticosteroid pulse therapy was initiated. Subsequently, her symptoms and x-ray images promptly improved, and the dose of prednisolone was tapered to 5 mg daily. As the patient was aged

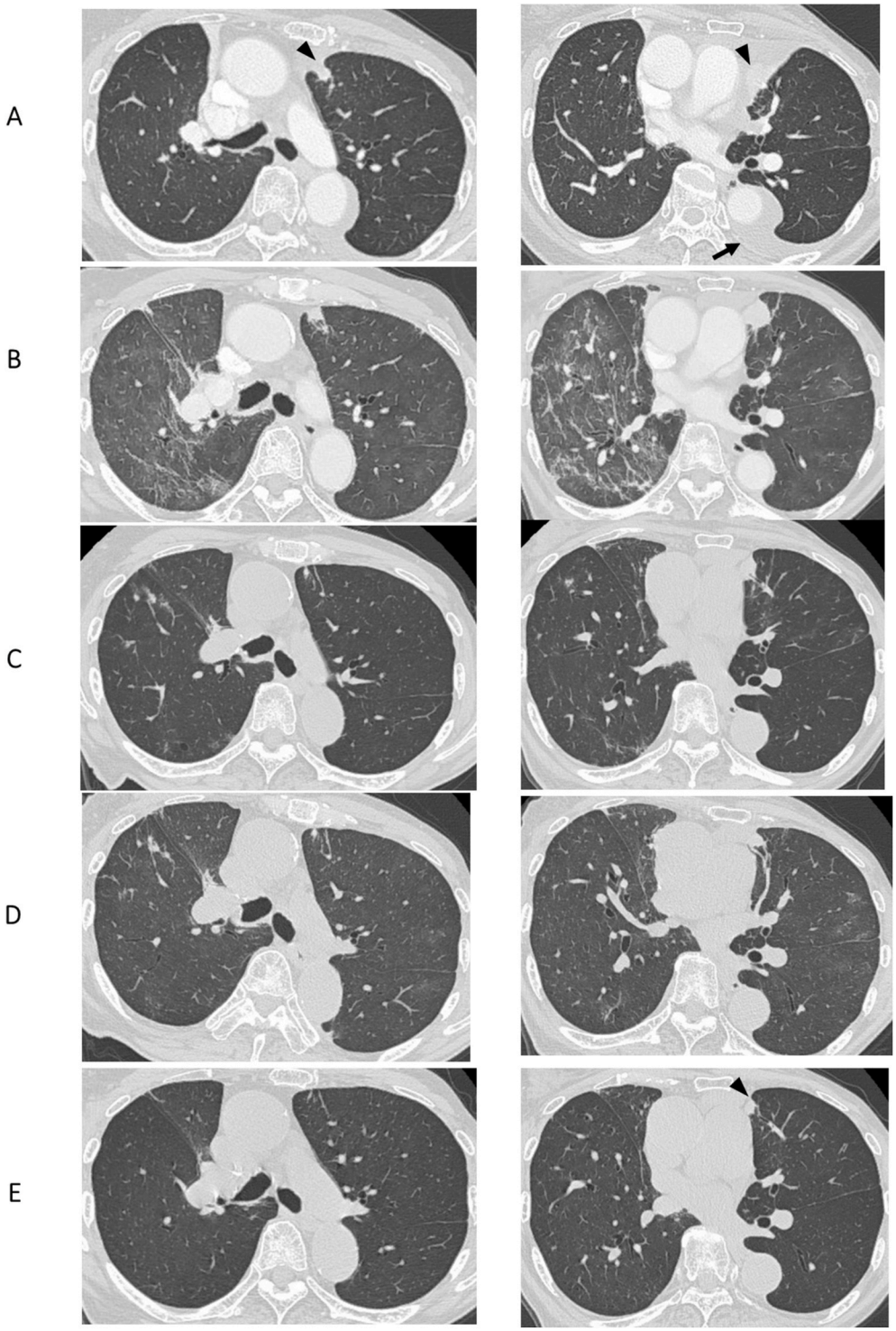

Fig. 1. (A) Chest computed tomography (CT) on lung cancer recurrence. Chest CT revealing a nodular shadow (arrowhead) and pleural effusion in the left lung (arrow). (B) Osimertinib-induced interstitial lung disease (ILD), on the 46th day after the initiation of osimertinib. Chest CT revealing diffuse ground-glass opacities in both lungs. Left pleural effusion decreased. (C) Chest CT 2 weeks after osimertinib-induced ILD developed. Chest CT revealing improvement in the diffuse ground-glass opacities in both lungs. (D) Osimertinib-induced ILD on the 15th day after re-administration of osimertinib. Chest CT revealing diffuse ground-glass opacities in both lungs. (E) Chest CT 2 months after the initiation of afatinib. Chest CT revealing a decrease in the size of the left nodular shadow (arrowhead) without ILD relapse.

enough to be intolerant to cytotoxic chemotherapy, 20 mg of afatinib was administered daily starting on the 30th day following the discontinuation of osimertinib. On the 77th day after initiating afatinib treatment, CEA levels dramatically decreased to 17.9 ng/mL, and chest CT revealed a decrease in the size of the left nodular shadow (Fig. 1E), and the only adverse event was a mild rash. Prednisolone was finally discontinued, and she was treated with afatinib over 13 months without any relapse of ILD.

3. Discussion

Herein, we report the case of a patient who developed grade 3 osimertinib-induced ILD with failure of osimertinib rechallenge but was safely treated with afatinib. In the Japanese subset analysis of the FLAURA study, the frequency of ILD was higher for osimertinib (12.3%) than gefitinib (1.8%). However, the frequency of grade ≥3 ILD was the same in both groups [6]. In clinical practice, it is challenging to manage patients who develop severe osimertinib-induced ILD. Some reports have revealed the successful treatment of osimertinib rechallenge with concomitant corticosteroids in patients developing osimertinib-induced ILD [10–15]. On the other hand, there are limited reports on osimertinib rechallenge without concomitant corticosteroids. Despite reports of successful osimertinib rechallenge after grade 1 osimertinib-induced ILD without concomitant corticosteroids [15], it is unclear whether osimertinib rechallenge without concomitant corticosteroids can be a treatment option for osimertinib-induced ILD ≥ grade 2. However, in the present case, ILD rapidly relapsed 15 days after osimertinib rechallenge without concomitant corticosteroids. Thus, the present case indicates that osimertinib rechallenge without concomitant corticosteroids should be avoided in patients developing grade 3 ILD.

In the present case, afatinib was administered as salvage therapy, resulting in desirable control of lung cancer without any relapse of ILD. To date, there have been several case reports of successful treatment with erlotinib after gefitinib-induced ILD, and it is known that patients who develop ILD with one EGFR-TKI may be safely treated by switching to another EGFR-TKI [16–18]. In relation to this, successful treatment with afatinib after osimertinib-induced ILD has been reported, with eight cases reported to date [15,19,20]. Taking these reports together with the present case, afatinib may be an important treatment option in patients with osimertinib-induced ILD.

As for ILD pattern, chest CT in the present case showed bilateral diffuse GGO. To date, there was a report on ILD pattern of CT which comprised of organizing pneumonia pattern, faint infiltration pattern and diffuse alveolar damage pattern [21]. The CT pattern in the present case was considered to be uniform faint infiltration pattern, which is a common finding. However, the relationship with ILD pattern and ILD recurrence is still unclear [21].

In conclusion, the present case indicates that osimertinib rechallenge without concomitant corticosteroids should be avoided in patients with *EGFR*-mutant NSCLC who develop severe osimertinib-induced ILD. In addition, afatinib is an important treatment option for these patients. Further accumulation of case reports is required to validate our results.

Declaration of competing interest

Sekine A reports personal fees from Nippon Boehringer Ingelheim and AstraZeneca. Ikeda S reports grants and personal fees from Chugai Pharmaceutical, during the conduct of the study; grants and personal fees from AstraZeneca and Nippon Boehringer Ingelheim. Baba received personal fees from AstraZeneca K·K., and Nippon Boehringer Ingelheim. Ogura T reports personal fees from Nippon Boehringer Ingelheim.

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