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Case Report

Successful osimertinib rechallenge without concomitant corticosteroids after osimertinib-induced pneumonitis

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ABSTRACT

A 60-year-old woman was diagnosed with cT4N3M1c stage IVB lung adenocarcinoma with epidermal growth factor receptor mutation of exon19 deletion. After one month of treatment with osimertinib, a cough and diffuse ground glass opacities were observed in the bilateral lung field. Based on the clinical course and the exclusion of other etiologies, osimertinib-induced pneumonitis was diagnosed. The shadows resolved after osimertinib was discontinued. However, brain metastasis and leptomeningeal metastasis developed 20 months later; therefore, osimertinib was re-administered without concomitant corticosteroids. The pulmonary lesion and leptomeningeal metastasis were successfully treated without recurrence of drug-induced pneumonitis for eight months.

1. Introduction

Osimertinib is a highly effective drug for treating epidermal growth factor receptor (EGFR) mutant lung adenocarcinoma. However, several studies have indicated that osimertinib causes drug-induced pneumonitis more frequently than first or second-generation EGFR-tyrosine kinase inhibitor (TKI)s, especially in the Japanese subset [1–6]. In addition, another report showed that drug-induced pneumonitis induced by osimertinib had a lower mortality rate than first-generation EGFR-TKI [7]. Although there have been some case reports of osimertinib re-administration in combination with corticosteroids after drug-induced pneumonitis, there have been few reports of successful re-administration of osimertinib without concomitant corticosteroids [8,9]. Furthermore, there is a lack of knowledge regarding the detailed discussion of cases in which osimertinib was re-administered without concomitant corticosteroids.

We herein describe and discuss a case of successful osimertinib rechallenge without concomitant corticosteroids after osimertinib-induced pneumonitis.

2. Case presentation

A 60-year-old woman was referred to our hospital due to bilateral multiple nodular shadows at her annual physical examination. She had no previous medical history. She had no history of smoking or dust inhalation either. Computed tomography (CT) showed a mass shadow in the right posterior inferior segment of the lung, bilateral multiple nodular shadows and mediastinal lymphadenopathy. A transbronchial biopsy of the lung tumor and endobronchial ultrasound-transbronchial needle aspiration of mediastinal lymph nodes confirmed adenocarcinoma with EGFR mutation of exon19 deletion. Positron emission tomography-CT showed mediastinal

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lymph node metastases and multiple bone metastases. Brain magnetic resonance imaging revealed enhanced multiple nodules in the brain. She was therefore diagnosed with cT4N3M1c stage IVB lung adenocarcinoma. Treatment with osimertinib was started after gamma knife radiosurgery, but one month later, she became aware of a dry cough. Her oxygen saturation, measured by pulse oximetry, was 96 % on room air and her body temperature was 35.9 ˚C. Physical examination revealed no fine crackles on chest auscultation. Chest X-ray showed a diminished mass shadow in the right pulmonary hilum and bilateral ground glass opacities in the lower lung field. CT confirmed shrinkage of the primary and metastatic site of the lung cancer and also revealed diffuse ground-glass opacities with interlobular septal thickening in the lower lobes dominant (Fig. 1A–F). Blood tests showed elevated serum levels of Krebs von den Lungen-6 (1130 U/L) and surfactant protein D (176 ng/mL). The serum levels of N-terminal prohormone of brain natriuretic peptide (302 pg/mL), β-D-glucan (5.0 pg/ml) and CMV-C7HRP (negative) did not elevate. Bronchoalveolar lavage (BAL) fluid analysis revealed a cell count of 0.61 × 10^5/ml, with cell differential of 51 % macrophages, 10.4 % lymphocytes, 34.2 % neutrophils, 3.4 % eosinophils and a CD4/CD8 ratio of 0.97. No microorganisms (including Pneumocystis DNA PCR) were detected on the BAL fluid culture. Transbronchial lung biopsy specimens showed alveolitis, infiltration of lymphocyte and eosinophil, the proliferation of type 2 alveolar epithelial cells and fibrin deposition (Fig. 2). Based on the clinical course and the exclusion of other etiologies, we diagnosed the patient with grade 2 osimertinib-induced pneumonitis. Since respiratory failure was not evident, osimertinib was discontinued without corticosteroids. The patient's symptoms and ground-glass opacities improved within one month.

After a combination chemotherapy of carboplatin, pemetrexed and pembrolizumab as second-line therapy and seven courses of pemetrexed and pembrolizumab as maintenance therapy, the disease progressed. Seven courses of docetaxel plus ramucirumab were administered as third-line therapy and erlotinib as fourth-line therapy, but drug fever appeared. After two courses of S-1 administered as fifth-line therapy, brain metastases and leptomeningeal metastasis developed. Rapid desensitization with erlotinib was conducted

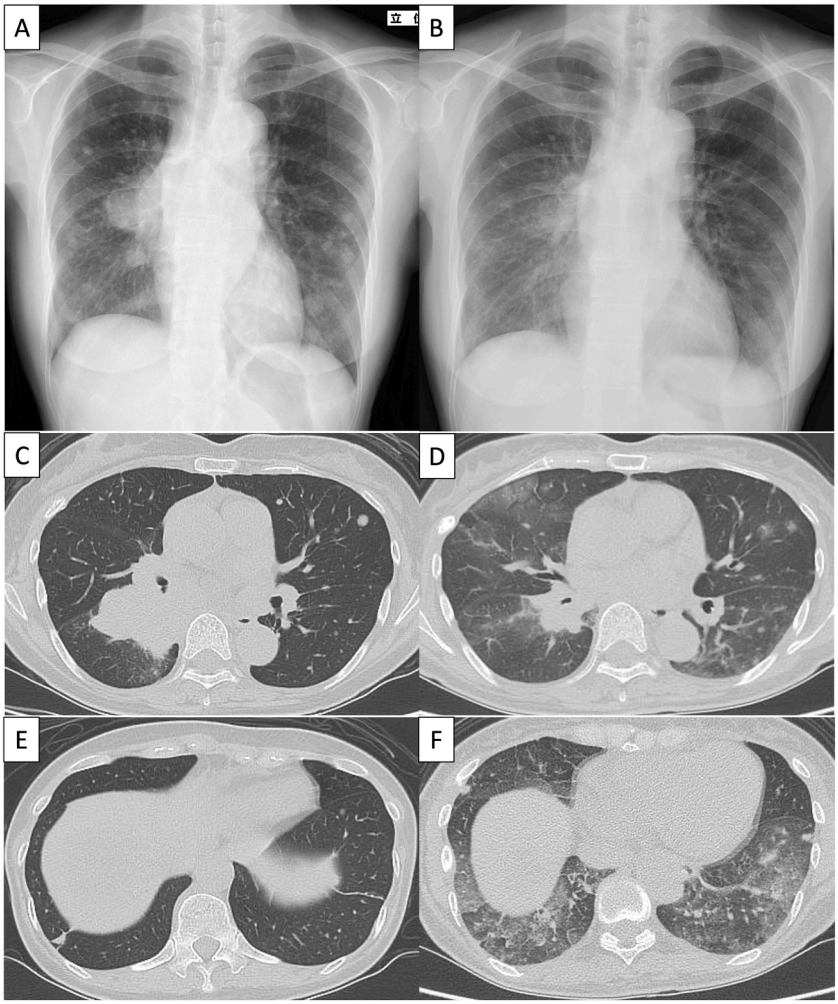

Fig. 1. A chest radiograph showing a mass shadow in the right pulmonary hilum and multiple nodular shadows predominantly in both lower lung fields on initial examination (A) These shadows became smaller one month of treatment with osimertinib and ground-glass opacities appeared in the bilateral lower lung fields (B). Computed tomography of the chest confirms shrinkage of the primary and metastatic sites of cancer. It also reveals the presence of diffuse ground-glass opacities with interlobular septal thickening in the lower lobes dominant one month after the administration of osimertinib (C–F).

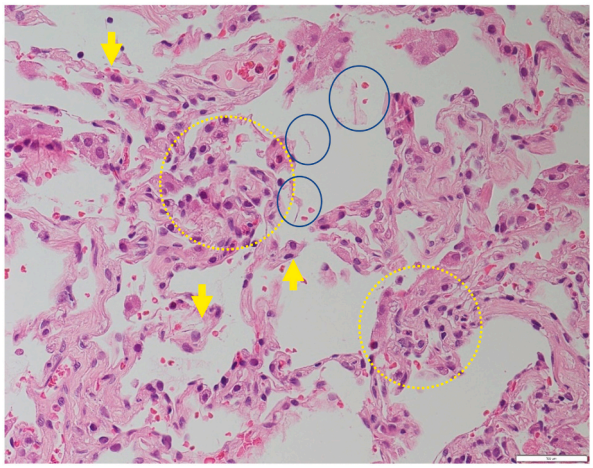

Fig. 2. A transbronchial lung biopsy specimen shows alveolitis, infiltration of lymphocyte and eosinophil (yellow dot circle), the proliferation of type 2 alveolar epithelial cells (yellow arrow) and fibrin deposition (blue circle) (Hematoxylin and Eosin staining, × 200).

and 150 mg of erlotinib was administered again. One month later, pulmonary metastases increased. Twenty months after the first osimertinib therapy, osimertinib was re-administered as seventh-line therapy without concomitant corticosteroids with sufficient patient informed consent since there were few other effective treatment options considering the penetration to the brain. The pulmonary metastases were improved (Fig. 3A–D). Brain and leptomeningeal metastases did not worsen and remained no symptom for eight months.

3. Discussion

Several studies have indicated that osimertinib causes drug-induced pneumonitis more frequently than first or second-generation EGFR-TKIs, especially in the Japanese subset: the incidence of drug-induced pneumonitis was 3.5–4.3 % for first-generation gefitinib and erlotinib and 4.4 % for second-generation afatinib compared to 4.8–18.0 % for third-generation osimertinib [1–6]. On the other hand, Noonan et al. reported transient asymptomatic abnormal pulmonary opacities (TAPO) had occurred during osimertinib treatment [10]. Since the clinical course of TAPO differs from that of drug-induced pneumonitis, it has been reported that withdrawal of osimertinib is unnecessary [11]. In the present case, we diagnosed the patient with grade 2 drug-induced pneumonitis, not TAPO, because of the presence of symptoms and the findings of alveolitis in the histopathology.

Drug-induced pneumonitis with first-generation EGFR-TKIs is characterized by a diffuse alveolar damage pattern [12], and a high mortality rate (31.6–35.7 %) has been reported [2,13]. Therefore, patients with a history of interstitial lung disease (ILD) have been excluded from clinical trials to evaluate the efficacy and safety of EGFR-TKIs. Re-administration of EGFR-TKI after drug-induced

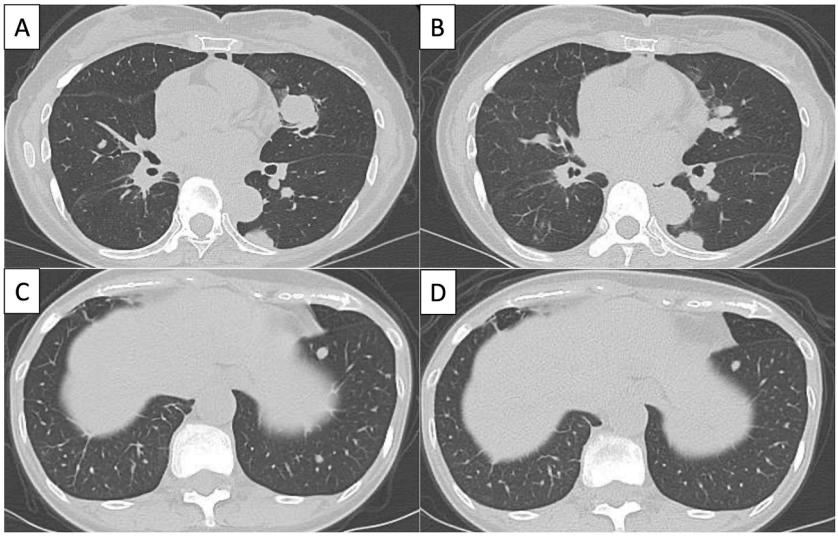

Fig. 3. Computed tomography of the chest confirms shrinkage of the primary and metastatic site of the lung cancer and revealed no evidence of diffuse ground-glass opacities after the rechallenge of osimertinib (A–D).

pneumonitis is also usually not conducted. On the other hand, the reported mortality rate of osimertinib-induced pneumonitis is 11.8 %, which is lower than that of first- or second-generation TKIs [7]. Under those backgrounds, there are some reports of patients who receive osimertinib in combination with corticosteroids after osimertinib-induced pneumonitis [8,9,14–16]. On the other hand, two case reports of osimertinib re-administered without corticosteroids resulted in a relapse of ILD [17,18].

Unlike previous reports, drug-induced pneumonitis did not recur despite the absence of a concomitant corticosteroid in this case. The first possible reason may be that a long time had passed between the onset of drug-induced pneumonitis and the re-administration of the drug. A second possible reason is that the rapid desensitization of erlotinib, also an EFGR-TKI, due to erlotinib-induced drug fever may have had a protective effect against relapse of drug-induced pneumonitis. Rapid desensitization with EGFR-TKI has been reported as useful for EGFR-TKI-induced severe rashes [19]. Moreover, a case of successful desensitization after drug-induced pneumonitis with isoniazid, an antituberculosis drug, was reported [20].

4. Conclusion

We experienced a successful osimertinib rechallenge without concomitant corticosteroids after the rapid desensitization of EGFR-TKI. Patients who did not require corticosteroids for the treatment of previous osimertinib-induced pneumonitis and for whom a long time has passed since the onset of osimertinib-induced pneumonitis may be possible to be re-administered osimertinib without concomitant corticosteroids.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We obtained informed consent from the patient described in this manuscript.

References

[1] Y. Ohe, F. Imamura, N. Nogami, I. Okamoto, T. Kurata, T. Kato, S. Sugawara, S.S. Ramalingam, H. Uchida, R. Hodge, S.L. Vowler, A. Walding, K. Nakagawa, Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset, Jpn. J. Clin. Oncol. 49 (1) (2019) 29–36.

[2] A. Gemma, S. Kudoh, M. Ando, Y. Ohe, K. Nakagawa, T. Johkoh, N. Yamazaki, H. Arakawa, Y. Inoue, M. Ebina, M. Kusumoto, K. Kuwano, F. Sakai, H. Taniguchi, Y. Fukuda, A. Seki, T. Ishii, M. Fukuoka, Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer, Cancer Sci. 105 (12) (2014) 1584–1590.

[3] M. Ando, I. Okamoto, N. Yamamoto, K. Takeda, K. Tamura, T. Seto, Y. Ariyoshi, M. Fukuoka, Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib, J. Clin. Oncol. 24 (16) (2006) 2549–2556.

[4] T. Hirashima, M. Satouchi, T. Hida, M. Nishio, T. Kato, H. Sakai, F. Imamura, K. Kiura, I. Okamoto, K. Kasahara, H. Uchida, S.L. Vowler, T. Mitsudomi, Osimertinib for Japanese patients with T790M-positive advanced non-small-cell lung cancer: a pooled subgroup analysis, Cancer Sci. 110 (9) (2019) 2884–2893.

[5] H. Akamatsu, N. Katakami, I. Okamoto, T. Kato, Y.H. Kim, F. Imamura, M. Shinkai, R.A. Hodge, H. Uchida, T. Hida, Osimertinib in Japanese patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial, Cancer Sci. 109 (6) (2018) 1930–1938.

[6] Y. Sato, H. Sumikawa, R. Shibaki, T. Morimoto, Y. Sakata, Y. Oya, M. Tamiya, H. Suzuki, H. Matsumoto, T. Yokoi, K. Hashimoto, H. Kobe, A. Hino, M. Inaba, Y. Tsukita, H. Ikeda, D. Arai, H. Maruyama, S. Hara, S. Tsumura, S. Sakata, D. Fujimoto, Drug-related pneumonitis induced by osimertinib as first-line treatment for epidermal growth factor receptor mutation-positive non-small cell lung cancer: a real-world setting, Chest 162 (5) (2022) 1188–1198.

[7] T.J.R. Society, The JRS Guidelines for the Management of Drug-Induced Lung Disease, second ed., Medical review, Tokyo, 2018.

[8] H. Kodama, K. Wakuda, M. Yabe, N. Nishioka, E. Miyawaki, T. Miyawaki, N. Mamesaya, T. Kawamura, H. Kobayashi, S. Omori, A. Ono, H. Kenmotsu, T. Naito, H. Murakami, M. Endo, T. Takahashi, Retrospective analysis of osimertinib re-challenge after osimertinib-induced interstitial lung disease in patients with EGFR-mutant non-small cell lung carcinoma, Invest. N. Drugs 39 (2) (2021) 571–577.

[9] M. Imaji, D. Fujimoto, Y. Sato, Y. Sakata, Y. Oya, M. Tamiya, H. Suzuki, H. Ikeda, T. Kijima, H. Matsumoto, M. Kanazu, A. Hino, M. Inaba, Y. Tsukita, D. Arai, H. Maruyama, S. Hara, S. Tsumura, H. Kobe, H. Sumikawa, S. Sakata, N. Yamamoto, Safety and efficacy of osimertinib rechallenge or continuation after pneumonitis: a multicentre retrospective cohort study, Eur. J. Cancer 179 (2023) 15–24.

[10] S.A. Noonan, P.B. Sachs, D.R. Camidge, Transient asymptomatic pulmonary opacities occurring during osimertinib treatment, J. Thorac. Oncol. 11 (12) (2016) 2253–2258.

[11] H. Lee, H.Y. Lee, J.M. Sun, S.H. Lee, Y. Kim, S.E. Park, J.S. Ahn, K. Park, M.J. Ahn, Transient asymptomatic pulmonary opacities during osimertinib treatment and its clinical implication, J. Thorac. Oncol. 13 (8) (2018) 1106–1112.

[12] K. Kashiwabara, H. Semba, S. Fujii, S. Tsumura, Outcome in advanced non-small cell lung cancer patients with successful rechallenge after recovery from epidermal growth factor receptor tyrosine kinase inhibitor-induced interstitial lung disease, Cancer Chemother. Pharmacol. 79 (4) (2017) 705–710.

[13] S. Kudoh, H. Kato, Y. Nishiwaki, M. Fukuoka, K. Nakata, Y. Ichinose, M. Tsuboi, S. Yokota, K. Nakagawa, M. Suga, G. Japan Thoracic Radiology, H. Jiang, Y. Itoh, A. Armour, C. Watkins, T. Higenbottam, F. Nyberg, Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study, Am. J. Respir. Crit. Care Med. 177 (12) (2008) 1348–1357.

[14] I.K. Matsuo T, S. Takashima, M. Atari, S. Watanabe, Y. Minamiya, Successful Osimertinib Rechallenge after Osimertinib-Induced Interstitial Lung Disease in a Patient with Postoperative Recurrence of Lung Cancer, vol. 59, Japanese Journal of Lung Cancer, 2019, p. 6.

[15] E. Miyauchi, M. Ichinose, A. Inoue, Successful osimertinib rechallenge in a patient with T790M-mutant non-small cell lung cancer after osimertinib-induced interstitial lung disease, J. Thorac. Oncol. 12 (5) (2017) e59–e61.

[16] T. Kiriu, D. Tamura, M. Tachihara, R. Sekiya, D. Hazama, M. Katsurada, K. Nakata, T. Nagano, M. Yamamoto, H. Kamiryo, K. Kobayashi, Y. Nishimura, Successful osimertinib rechallenge with steroid therapy after osimertinib-induced interstitial lung disease, Intern. Med. 57 (1) (2018) 91–95.

[17] M. Nagasaka, S.M. Gadgeel, Retreatment with osimertinib following pneumonitis, Clin. Lung Cancer 19 (1) (2018) e53–e55.

[18] Y. Sato, A. Sekine, E. Hagiwara, M. Sato, T. Yamaya, M. Asaoka, K. Higa, S. Ikeda, T. Baba, S. Komatsu, T. Iwasawa, T. Ogura, Successful treatment with afatinib following the failure of osimertinib rechallenge with osimertinib-induced interstitial lung disease: a case report, Respir Med Case Rep 33 (2021) 101450.

[19] M. Nagase, N. Ohshima, M. Kawashima, M. Ohgiya, M. Ikeda, Y. Morio, A. Tamura, Usefulness of rapid desensitization therapy for severe rash caused by molecularly targeted drugs used in the treatment of non-small-cell lung cancer, Intern. Med. 59 (24) (2020) 3201–3205.
[20] Y.M. Nishizawa Y, C. Yamamorii, A. Tagamii, M. Fujimura, S. Nakao, A case of successful desensitization therapy for lsoniazid-induced pneumonitis, Nihon Kokyuki Gakkai Zasshi 42 (7) (2004) 6.