Drug-induced interstitial lung disease caused by gefitinib in the treatment of non-small cell lung cancer: A case report

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Abstract. Gefitinib, a first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), is widely used in treating non-small cell lung cancer (NSCLC) with EGFR mutations. Although effective, gefitinib is associated with rare but life-threatening interstitial lung disease (ILD). In the present study, a 68-year-old male with stage IIIB lung adenocarcinoma was reported, who developed acute interstitial pneumonia 20 days after initiating gefitinib therapy. The patient presented with high fever (41˚C), dyspnea and hypoxemia. Chest CT revealed bilateral diffuse interstitial infiltrates and pleural effusion. After excluding infectious and cardiac etiologies, gefitinib-induced ILD was diagnosed. Immediate discontinuation of gefitinib, combined with high-dose glucocorticoids (methylprednisolone 80 mg/day) and oxygen therapy, led to clinical improvement. However, ILD recurred upon rechallenge with the original gefitinib dose. This case highlights the importance of early recognition and prompt management of EGFR-TKI-related ILD. The challenges of rechallenging EGFR-TKIs post-recovery was further discussed and the need for personalized risk-benefit assessments was emphasized.

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of cases (1,2). Early diagnosis of NSCLC involves the detection of tumor markers, CT scans and biopsies. Although biopsy is the 'gold standard', it is invasive and may cause pain and infection. In recent years, liquid biopsy has proven to be a non-invasive method for early screening in which circulating tumor cells, circulating tumor DNA and exosomes in the blood are detected (3). The treatment methods for NSCLC include surgery, radiotherapy, chemotherapy, molecular targeted therapy and immunotherapy.

Driver gene mutations are frequently detected in patients with advanced NSCLC. The epidermal growth factor receptor (EGFR) gene is the gene with the highest mutation rate in Asian patients with NSCLC, and EGFR signal transduction plays a notable role in tumorigenesis. EGFR-tyrosine kinase inhibitors (TKIs) such as gefitinib are therefore an important treatment method for patients with advanced NSCLC harboring EGFR sensitive mutations (4-6). While EGFR-TKIs can improve the survival of patients with advanced NSCLC, their use is complicated by adverse effects that range from mild dermatological reactions to rare but fatal drug-induced interstitial lung disease (ILD).

There is no single, absolute standard for the diagnosis of ILD caused by EGFR-TKIs, but the following elements form a basis: (i) New or worsening respiratory symptoms or hypoxia; (ii) new radiographical findings via high-resolution computed tomography (HRCT) consistent with ILD; and (iii) temporal association with gefitinib initiation and the exclusion of other likely causes (7,8). Gefitinib-induced ILD, with a reported incidence of 1-5%, typically manifests within 4 weeks of treatment initiation and carries a mortality rate exceeding 30% (9,10). The clinical presentation and course of EGFR-TKI-induced ILD can vary widely. Early diagnosis and intervention are critical. However, clinical overlap with tumor progression or infection complicates the management of this disease. In the present study, a case of gefitinib-induced ILD was presented. Unlike typical EGFR-TKI-induced ILD, the patient manifested acute high fever as the initial symptom-a rare feature not commonly reported in the literature. Furthermore, rapid recurrence of severe ILD within 24 h of gefitinib rechallenge provides unequivocal evidence of causality and highlights the peril of re-exposure. These characteristics amplify the novelty of the current report and emphasize the diagnostic challenges, therapeutic strategies and considerations for rechallenging EGFR-TKIs.

Case presentation

A 68-year-old male patient with a 15-year smoking history and hypertension presented with a paroxysmal cough in

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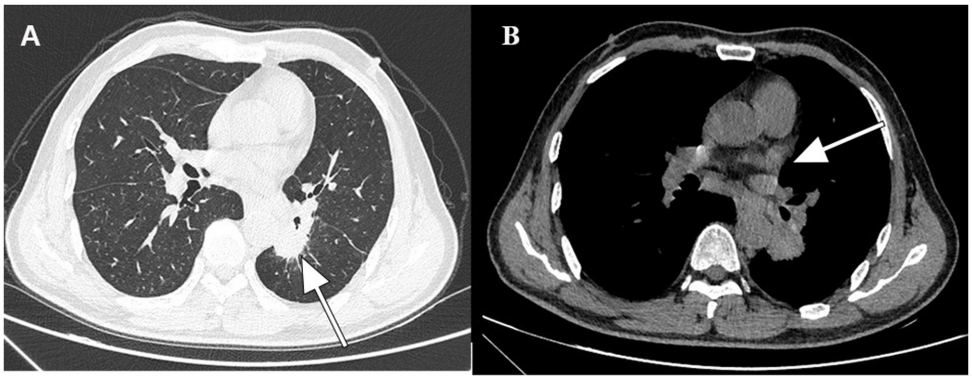

Figure 1. Chest CT scans of gefitinib-induced interstitial lung disease before treatment. CT scan parameters: 120 kV, 131 mAs, slice thickness: 2.5 mm. (A) The white arrow indicates a mass in the left lower lobe of the lung. (B) The white arrow indicates enlarged mediastinal lymph nodes. CT, computed tomography.

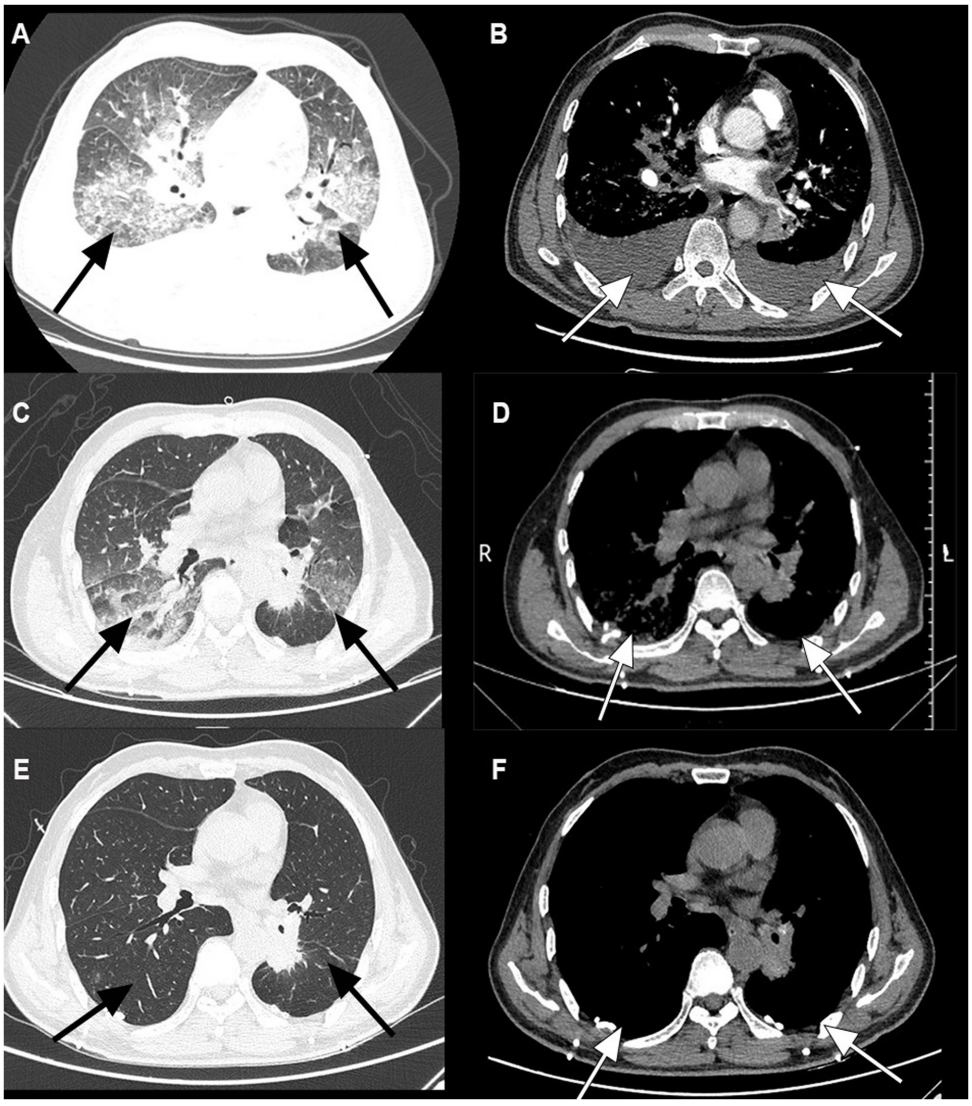

Figure 2. Chest CT scans of gefitinib-induced interstitial lung disease comparison between before and after treatment. The black arrow indicates diffuse ground-glass opacities in both lungs, and the white arrow indicates pleural effusion. CT scan parameters: 120 kV, 131 mAs, slice thickness: 2.5 mm. Contrast agent: Iodixanol. (A and B) The chest CT showing bilateral diffuse ground-glass opacities (involving >50% lung fields), with bilateral pleural effusion before treatment. (C and D) The repeat chest CT showing residual ground-glass opacities (<30% lung involvement) and pleural effusion after therapy. (E and F) CT showing almost completely resolved ground-glass opacities (<10% lung involvement) and pleural effusion after therapy. CT, computed tomography.

August 2021. The patient had no other chronic comorbidities, including chronic obstructive pulmonary disease, autoimmune disorders or other conditions affecting respiratory function or drug metabolism. Chest CT revealed a left lower lobe mass

and mediastinal lymphadenopathy (Fig. 1A and B). A subsequent biopsy indicated lung adenocarcinoma. Whole-body CT examination further revealed mediastinal and left hilar lymph node metastasis. Therefore, lung adenocarcinoma (cT2N3M0, stage IIIB) was diagnosed. Considering the difficulty of complete surgical resection, the patient was finally diagnosed with unresectable locally advanced NSCLC. Subsequent pathological gene detection indicated an EGFR exon 19 deletion. After one cycle of chemotherapy with pemetrexed (500 mg/m^2, with a total dose of 900 mg) and carboplatin (AUC=5, with a dose of 600 mg), gefitinib (250 mg/day) was initiated in late September 2021 due to severe bone marrow suppression, which necessitated the discontinuation of chemotherapy.

A total of 20 days post-gefitinib initiation, the patient developed a fever (41˚C) and progressive dyspnea. On October 17, the patient further developed wheezing, palpitations and shortness of breath, with a blood oxygen saturation of only 80%. Arterial blood gas analysis showed a PaO_2 of 43 mmHg and a $PaCO_2$ of 28 mmHg. Physical examination revealed tachypnea with bilateral fine crackles audible over the lower lung fields. A repeat chest CT showed extensive diffuse disease in both lungs, with interstitial disease and bilateral pleural effusion (Fig. 2A and B). Since the pulmonary inflammation had progressed rapidly and the patient had developed type I respiratory failure, the patient was transferred to the ICU for further treatment. The patient underwent a series of tests for infection, including blood, urine and sputum cultures as well as respiratory virus, fungal and tuberculosis testing. The results of the laboratory tests and virus indicators were negative, suggesting a low possibility of bacterial or viral pneumonia. In addition, a cardiac cause was ruled out following cardiac ultrasonography. Therefore, ILD caused by gefitinib was highly suspected. Immediate methylprednisolone therapy was commenced, gefitinib administration was halted, an oxygen mask (oxygen flow rate of 5 l/min) was used, and thoracentesis and catheter drainage were performed. The patient was treated with intravenous methylprednisolone 80 mg daily for 1 week, followed by 40 mg daily for 1 week, which was then transitioned to oral prednisone and tapered as follows: 30 mg daily for 1 week, 20 mg daily for 1 week, 10 mg daily for 1 week and finally 5 mg daily for 2 weeks before discontinuation. No additional tapering strategies were used. The total duration of corticosteroid therapy was 7 weeks. After 6 days of treatment, the condition of the patient notably improved, spontaneous breathing was stable, PaO_2 increased to 98% and reexamination by chest CT showed that the inflammation was relieved (Fig. 2C and D). The patient was considered stable, discharged and the steroid administration was tapered weekly as described. The patient returned to the hospital after 4 weeks and follow-up chest CT showed that the inflammation had been controlled (Fig. 2E and F).

After steroid withdrawal for 1 month, gefitinib was restarted at 250 mg/day due to disease progression. Within 2 weeks, ILD had recurred, prompting the permanent discontinuation of gefitinib.

Discussion

Gefitinib-induced ILD poses significant diagnostic challenges due to its non-specific clinical presentation, which often overlaps with infectious pneumonia, tumor progression or cardiogenic pulmonary edema (1,11). In the present case, the patient's acute onset of fever, hypoxemia and bilateral ground-glass opacities on CT raised the suspicion of ILD, but rigorous exclusion of alternative etiologies was required. Notably, while dyspnea and cough are the most common presenting symptoms, often accompanied by hypoxemia and radiographical evidence of diffuse lung injury, the initial manifestation of a high-grade fever observed in the present patient is uncommon. Large-scale studies and literature reviews of EGFR-TKI-related ILD consistently report that high fever over 40˚C is an uncommon symptom compared with respiratory symptoms (12,13). When fever does occur, it is often low-grade or moderate. However, in the present case, the absence of microbial pathogens in the cultures and the indication of normal cardiac function by echocardiography strengthened the diagnosis of drug-induced injury. The absence of specific early symptoms transforms ILD into a 'silent threat', necessitating proactive surveillance. HRCT remains the cornerstone for evaluating ILD as it reliably highlights characteristic patterns such as diffuse alveolar damage and interstitial thickening (14). Periodic HRCT in high-risk populations is essential for early detection, enabling timely intervention before irreversible fibrosis occurs. While balancing risks and costs, HRCT use can significantly improve diagnostic accuracy and patient outcomes. Future advances in biomarker detection may refine this approach, but HRCT remains indispensable today.

While ILD is a recognized adverse effect of EGFR-TKIs, its incidence and severity vary significantly between generations (15). First-generation TKIs such as gefitinib carry a substantially higher risk of ILD compared with third-generation TKIs such as osimertinib. This difference is attributed to the greater selectivity of osimertinib for mutant EGFR over wild-type EGFR, potentially reducing off-target effects in the lung parenchyma (16). Additionally, the severity and incidence of ILD induced by gefitinib may differ from the ILD induced by other EGFR-TKIs. Among the reported cases of ILD caused by gefitinib, the majority occurred within 4 weeks of administration (17). In the POLARSTAR study, 58.5% of the ILD cases also developed within 4 weeks of erlotinib treatment, while osimertinib-induced ILD is more likely to be delayed (median time: 3-6 months) (13,18,19).

The pathogenesis of EGFR-TKI-related ILD remains incompletely understood, but emerging evidence implicates both direct epithelial toxicity and immune-mediated mechanisms. For instance, gefitinib inhibits heat shock protein 70 (HSP70), a molecular chaperone critical for mitigating oxidative stress and repairing alveolar epithelial damage (20). Preclinical studies have demonstrated that HSP70 downregulation exacerbates pulmonary fibrosis, a finding consistent with the rapid progression of ILD observed in the present patient (21,22). Additionally, gefitinib upregulates interleukin-6, a pro-inflammatory cytokine linked to acute lung injury (23). The temporal association between drug initiation and symptom onset (20 days) in the present case aligns with the proposed immunological mechanisms, where cytokine storms precipitate diffuse alveolar damage (24). These findings highlight the dual role of EGFR-TKIs in targeting oncogenic signaling pathways while inadvertently disrupting pulmonary homeostasis.

The immediate discontinuation of gefitinib and the initiation of glucocorticoids are pivotal to reversing ILD progression (15,25,26). In the present study, the patient received methylprednisolone at 80 mg/day, a moderate-dose regimen that achieved rapid clinical improvement. This aligns with studies advocating for early, aggressive steroid therapy to suppress immune hyperactivation (13,27). However, the optimal dosing remains a contentious topic; severe cases may require pulse therapy (such as methylprednisolone 1 g/day for 3 days) to control fulminant inflammation (26,28). The marked radiological resolution in the present case underscores the importance of timely intervention. Nonetheless, steroid tapering must be gradual to prevent relapse as abrupt withdrawal may exacerbate subclinical inflammation (29).

Reintroducing EGFR-TKIs after ILD recovery remains a clinical dilemma (30). While EGFR-TKIs can often be successfully reintroduced at the same or reduced dose after the resolution of mild/moderate ILD with appropriate management, same-dose gefitinib rechallenge carries a significant and well-documented risk of rapid, frequently fatal, ILD recurrence. A study suggests that switching to third-generation agents (such as osimertinib) or dose reduction may mitigate recurrence risk (31). In the present study, after re-administering gefitinib in response to strong patient demand, ILD rapidly recurred, highlighting the unpredictability of this approach. Notably, pre-existing risk factors, such as smoking history and male sex, likely heightened the susceptibility to recurrent injury (32). Current guidelines recommend permanent discontinuation of the culprit EGFR-TKI, with alternative therapies considered for disease control (33). In select cases, cautious rechallenge combined with steroid or with acetylcysteine prophylaxis may be attempted, but this requires meticulous monitoring (13).

In conclusion, gefitinib-induced ILD is rare but with high mortality, and the exact pathogenesis remains unclear, which needs further exploration in the future. Patients with NSCLC with high risk factors for ILD should be monitored. Once ILD occurs, it is necessary to stop the EGFR-TKI in time and give effective treatment. Further research is needed to elucidate biomarkers predictive of ILD risk, such as serum IL-6 levels or HSP70 expression, which could guide personalized therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JL conceptualized the study, developed methodology and wrote the original draft. BQ and ZPW contributed to data acquisition and analysis, and were involved in writing, reviewing and editing the manuscript. JL and BQ confirm the authenticity of all the raw data. YPS visualized data and supervised the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication, which included the acquisition of clinical data and associated images.

Competing interests

The authors declare that they have no competing interests.

References

1. Balata H, Fong KM, Hendriks LE, Lam S, Ostroff JS, Peled N, Wu N and Aggarwal C: Prevention and early detection for NSCLC: Advances in thoracic oncology 2018. J Thorac Oncol 14: 1513-1527, 2019.
2. Hendriks LEL, Remon J, Faivre-Finn C, Garassino MC, Heymach JV, Kerr KM, Tan DSW, Veronesi G and Reck M: Non-small-cell lung cancer. Nat Rev Dis Primers 10: 71, 2024.
3. Shan L, Qiao Y, Ma L, Zhang X, Chen C, Xu X, Li D, Qiu S, Xue X, Yu Y, *et al*: AuNPs/CNC nanocomposite with A 'Dual Dispersion' Effect for LDI-TOF MS analysis of intact proteins in NSCLC serum exosomes. Adv Sci (Weinh) 11: e2307360, 2024.
4. Herbst RS, Morgensztern D and Boshoff C: The biology and management of non-small cell lung cancer. Nature 553: 446-454, 2018.
5. Shi Y, Wu L, Ji Y, Chen G, Li B, Bi M, Yang R, Miao L, Zhang G, Gao H, *et al*: Efficacy and safety of limertinib versus gefitinib as first-line treatment for locally advanced or metastatic non-small-cell lung cancer with EGFR-sensitising mutation: A randomised, double-blind, double-dummy, phase 3 trial. Lancet Respir Med 13: 677-686, 2025.
6. Gibson AJW, D'Silva A, Elegbede AA, Tudor RA, Dean ML, Bebb DG and Hao D: Impact of Asian ethnicity on outcome in metastatic EGFR-mutant non-small cell lung cancer. Asia Pac J Clin Oncol 15: 343-352, 2019.
7. Velimirovic M, Brignola M, Chheng E, Smith M and Hassan KA: Management of pulmonary toxicities associated with systemic therapy in non-small cell lung cancer. Curr Treat Options Oncol 25: 1297-1311, 2024.
8. Conte P, Ascierto PA, Patelli G, Danesi R, Vanzulli A, Sandomenico F, Tarsia P, Cattelan A, Comes A, De Laurentiis M, *et al*: Drug-induced interstitial lung disease during cancer therapies: Expert opinion on diagnosis and treatment. ESMO Open 7: 100404, 2022.
9. Hotta K, Kiura K, Takigawa N, Yoshioka H, Harita S, Kuyama S, Yonei T, Fujiwara K, Maeda T, Aoe K, *et al*: Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese Patients with non-small cell lung cancer: The Okayama lung cancer study group experience. J Thorac Oncol 5: 179-184, 2010.
10. Riely GJ, Wood DE, Ettinger DS, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, *et al*: Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 22: 249-274, 2024.
11. Beom SH, Kim DW, Sim SH, Keam B, Park JH, Lee JO, Kim TM, Lee SH and Heo DS: Gefitinib-induced interstitial lung disease in Korean lung cancer patients. Cancer Res Treat 48: 88-97, 2016.
12. Matsuno O: Drug-induced interstitial lung disease: Mechanisms and best diagnostic approaches. Respir Res 13: 39, 2012.
13. Ohmori T, Yamaoka T, Ando K, Kusumoto S, Kishino Y, Manabe R and Sagara H: Molecular and clinical features of EGFR-TKI-associated lung injury. Int J Mol Sci 22: 792, 2021.

14. Park SC, Tan J, Wang X, Lederman D, Leader JK, Kim SH and Zheng B: Computer-aided detection of early interstitial lung diseases using low-dose CT images. Phys Med Biol 56: 1139-1153, 2011.
15. Miyagahara T, Fujimori N, Ueda K, Takamatsu Y, Matsumoto K, Teramatsu K, Takaoka T, Suehiro Y, Shimokawa Y, Omori K, *et al*: Incidence and appropriate management of drug-induced interstitial lung disease in Japanese patients with unresectable pancreatic cancer: A multicenter retrospective study. Asia Pac J Clin Oncol 19: 533-541, 2023.
16. Le T and Gerber DE: Newer-generation EGFR inhibitors in lung cancer: How are they best used? Cancers (Basel) 11: 336, 2019.
17. Kawata T, Higashimori M, Itoh Y, Tomkinson H, Johnson MG, Tang W, Nyberg F, Jiang H and Tanigawara Y: Gefitinib exposure and occurrence of interstitial lung disease in Japanese patients with non-small-cell lung cancer. Cancer Chemother Pharmacol 83: 849-858, 2019.
18. Taronna G, Leonetti A, Gustavo Dall'Olio F, Rizzo A, Parisi C, Buti S, Bordi P, Brocchi S, Golfieri R, Ardizzoni A, *et al*: Transient asymptomatic pulmonary opacities and interstitial lung disease in EGFR-mutated non-small cell lung cancer treated with osimertinib. Tumori 108: 592-599, 2022.
19. Gemma A, Kudoh S, Ando M, Ohe Y, Nakagawa K, Johkoh T, Yamazaki N, Arakawa H, Inoue Y, Ebina M, *et al*: Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10708 Japanese patients with non-small-cell lung cancer. Cancer Sci 105: 1584-1590, 2014.
20. Zhang X, Zhang X, Huang W and Ge X: The role of heat shock proteins in the regulation of fibrotic diseases. Biomed Pharmacother 135: 111067, 2021.
21. Namba T, Tanaka K, Hoshino T, Azuma A and Mizushima T: Suppression of expression of heat shock protein 70 by gefitinib and its contribution to pulmonary fibrosis. PLoS One 6: e27296, 2011.
22. Tanguy J, Pommerolle L, Garrido C, Kolb M, Bonniaud P, Goirand F and Bellaye PS: Extracellular heat shock proteins as therapeutic targets and biomarkers in fibrosing interstitial lung diseases. Int J Mol Sci 22: 9316, 2021.
23. Ishiguro Y, Ishiguro H and Miyamoto H: Epidermal growth factor receptor tyrosine kinase inhibition up-regulates interleukin-6 in cancer cells and induces subsequent development of interstitial pneumonia. Oncotarget 4: 550-559, 2013.
24. Fujita K, Hirose T, Kusumoto S, Sugiyama T, Shirai T, Nakashima M, Akiyama Y and Sasaki Y: High exposure to erlotinib and severe drug-induced interstitial lung disease in patients with non-small-cell lung cancer. Lung Cancer 86: 113-114, 2014.
25. Akamatsu H, Inoue A, Mitsudomi T, Kobayashi K, Nakagawa K, Mori K, Nukiwa T, Nakanishi Y and Yamamoto N: Interstitial lung disease associated with gefitinib in Japanese patients with EGFR-mutated non-small-cell lung cancer: Combined analysis of two Phase III trials (NEJ 002 and WJTOG 3405). Jpn J Clin Oncol 43: 664-668, 2013.
26. Fontes ESM, Campainha S, Marques ID, Dinis R, Inácio JR, Mendes JJ, Luís R, Ferreira AM, Racha-Pacheco R, Rolo R, *et al*: Diagnosis and management of drug-induced interstitial lung disease in the context of anti-cancer therapy: A multidisciplinary viewpoint by portuguese experts. Clin Drug Investig 44: 801-810, 2024.
27. Kuo LC, Lin PC, Wang KF, Yuan MK and Chang SC: Successful treatment of gefitinib-induced acute interstitial pneumonitis with high-dose corticosteroid: A case report and literature review. Med Oncol 28: 79-82, 2011.
28. Lin X, Guo H, Zhao W, Li M, Lin G, Chu Q, Chen E, Chen L, Chen R, Chu T, *et al*: Expert consensus on cancer treatment-related lung injury. J Thorac Dis 17: 1844-1875, 2025.
29. Zhang X, Li H, Zhu M and Zhang Y: Re-administration of gefitinib following diffuse interstitial lung disease in a patient with advanced lung adenocarcinoma: A case report and review of the literature. Oncol Lett 9: 2419-2421, 2015.
30. Nishioka N, Imai H, Endo M, Notsu A, Doshita K, Igawa S, Yokouchi H, Ninomiya T, Tokito T, Soda S, *et al*: Real-world data on subsequent therapy for first-line osimertinib-induced pneumonitis: Safety of EGFR-TKI rechallenge (Osi-risk Study TORG-TG2101). Target Oncol 19: 423-433, 2024.
31. Kiriu T, Tamura D, Tachihara M, Sekiya R, Hazama D, Katsurada M, Nakata K, Nagano T, Yamamoto M, Kamiryo H, *et al*: Successful osimertinib rechallenge with steroid therapy after osimertinib-induced interstitial lung disease. Intern Med 57: 91-95, 2018.
32. Shibaki R, Ozawa Y, Noguchi S, Murakami Y, Takase E, Azuma Y, Maebeya M, Sugimoto T, Hayata A, Hayakawa T, *et al*: Impact of pre-existing interstitial lung abnormal shadow on lung injury development and severity in patients of non-small cell lung cancer treated with osimertinib. Cancer Med 11: 3743-3750, 2022.
33. Endo M, Johkoh T, Kimura K and Yamamoto N: Imaging of gefitinib-related interstitial lung disease: Multi-institutional analysis by the West Japan thoracic oncology group. Lung Cancer 52: 135-140, 2006.