Almonertinib-induced interstitial lung disease
A case report
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Abstract
Rationale: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have elicited favorable anti-tumor activity in non-small cell lung cancer especially the lung adenocarcinoma. Interstitial lung disease (ILD) is 1 of the fatal side effects of EGFR-TKIs. However, such type of side effect has not been observed in the follow-up during the treatment of the third-generation EGFR-TKI Almonertinib (also called HS-10296). Here, we first report an Almonertinib-induced ILD in an elderly female patient.

Patient concerns: A 70-year-old female diagnosed with “lung adenocarcinoma with intracranial metastasis” harboring a mutation of EGFR 19DEL was administered with Almonertinib 110mg orally as the first-line treatment. However, she presented with chest tightness, and shortness of breath, accompanying with paroxysmal dry cough 3 months after the initiation of Almonertinib.

Diagnoses: Extensive relevant examinations did not provide conclusive results and the chest computed tomography showed a diffuse ILD in bilateral pulmonary.

Interventions: The patient was diagnosed with Almonertinib-induced ILD in the absence of no other potential causes. She discontinued Almonertinib and was treated with oxygen uptake and methylprednisolone.

Outcomes: The whole symptoms were eliminated and the chest computed tomography showed ILD got remission after the prescription of methylprednisolone.

Lessons: Almonertinib has potential to cause the rare but severe interstitial lung disease. Clinicians should keep cautious of this when prescribing Almonertinib.

Abbreviations: CEA = carcino-embryonic antigen; CT = computed tomography; EGFR = epidermal growth factor receptor; HRCT = high-resolution chest computed tomography; IHC = immunohistochemistry; ILD = interstitial lung disease; LUAD = lung adenocarcinoma; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor.

Keywords: almonertinib, epidermal growth factor receptor-tyrosine kinase inhibitors, Interstitial lung disease, lung adenocarcinoma

1. Introduction

Non-small cell lung cancer (NSCLC) is the most common pathological type in lung cancer accounting for up to 85%.\textsuperscript{1,2} Epidermal growth factor receptor (EGFR) mutation is a confirmed oncogenic role in NSCLC among which the classic mutated forms of EGFR 19Del and EGFR 21L858R occupied approximately 80%.\textsuperscript{3,4} Previously, a list of crucial phase III trials have led to the administration of EGFR tyrosine kinase inhibitor (TKI) as the standard first-line treatment for advanced or metastatic EGFR-mutated NSCLC, in which the third-generation TKI Osimertinib was preferably recommended based on the outstanding results of clinical trial FLAURA.\textsuperscript{5,6} Almonertinib, a novel third-generation EGFR-TKI, was developed by Chinese pharmaceutical company. The phase I/II studies revealed Almonertinib’s robust anti-cancer activity in advanced and metastatic NSCLC patients harboring sensitive EGFR or T790M mutation and it was approved by National Medical Products Administration of China on March, 18, 2020 for pretreated NSCLC patients with EGFR T790M mutation positive.\textsuperscript{7} Interstitial lung disease (ILD) is a deadly adverse effect of EGFR-TKIs such as Gefitinib, Osimertinib, however, in Almonertinib this has not been observed up to now. Here we report a case of a patient diagnosed with “LUAD with intracranial metastasis” developing ILD during the application of Almonertinib. By sharing this case, we wish to remind clinicians to be cautious of this rare side effect.

2. Case presentation

A 70-year-old non-smoking female with chief complain of “continuous headache” was found an intracranial cancerous mass (44.7mm × 55.2mm) by intracranial magnetic resonance imaging on March, 12, 2020 (Fig. 1A-D). Then further workup
was completed showing multi-nodules in upper right lung by chest computed tomography (CT) (Fig. 1E-G) and chronic superficial gastritis and polypcolonic by gastrointestinal endoscopy. The positron emission tomography-computed tomography revealed the same cancerous intracranial mass (SUVmax = 10.9) and multiple nodules in upper right lung (with no abnormal SUVmax value). Tumor markers indicated the elevated serum carcino-embryonic antigen (CEA) at 1840.4 ng/ml (Fig. 2). Her past medical history included hypertension and type II diabetes which were under good control with regular drug administration. She underwent an "intracranial tumor resection operation" on March 30, 2020. The post-operative hematoxylin and eosin staining reported the metastatic adenocarcinoma, part of micropapillary adenocarcinoma with necrosis and calcification. The immunohistochemistry (IHC) staining revealed CKpan, CK7, CDX-2, EMA, TTF-1 and Napsin A were all positive, and GFAP, S-100, CK20, CA125, ER, PR and P16 were all negative, without a clear primary tissue but recommended to complete more examinations in lung and digestive system (Fig. 3). Meanwhile, genetic testing using intracranial cancer tissues recognized a mutation of EGFR 19DEL, programmed cell death ligand-1 < 1% by SP263 antibody, microsatellite stable, a level of 3.6 Mut/Mb in tumor mutation burden and murine double minute 2 amplification (7.33 times). Based on the medical history, gene alterations and IHC, a diagnosis of "intracranial metastasis from lung adenocarcinoma (LUAD)" was established and she was treated with Almonertinib 110mg orally once per day from April, 15, 2020.
However, on July, 30, she unexpectedly came to hospital with acute symptoms of chest tightness and shortness of breath, along with paroxysmal dry cough which she has suffered for a half month. Some relevant laboratory and imaging examinations were made (Table 1). The oxygen partial pressure and carbon dioxide partial pressure were 53.4 mmHg and 38.2 mmHg respectively and a level of 86.2% in saturation oxygen. The chest CT showed multiple high-density patches in bilateral pulmonary, symmetrically distributed beside the hilus of lung, which shaped a distinct contrast with that on June, 18, 2020 (Fig. 4A-F). The blood routine test showed $9.1 \times 10^9/L$ for white blood cell count and 5.6 mg/L for C-reactive protein, with 73.4% neutrophils and 6.6% eosinophils so the lung inflammation was not possible. At the same time, the virus testing results for human respiratory syncytial virus antibody, adenovirus antibody, herpes simplex virus IgM antibody, Epstein-Barr virus IgM antibody, Coxsackie virus IgM antibody, and Cytomegalovirus IgM antibody were negative. The serum CEA in Figure 2 was dramatically decreased to 10.6 ng/ml after the initiation of Almonertinib which was effective for cancer.

### Table 1

Demographic characteristics and laboratory and imaging findings of the patient on admission to hospital for ILD on July, 30, 2020.

| Demographic characteristics | 70 |
|----------------------------|----|
| Gender                     | Female |
| Smoking history            | No |
| Initial findings on admission to hospital on July, 30, 2020 | Hypertension, Type II diabetes |
| Past medical history       | Chest tightness, shortness of breath, and paroxysmal dry cough |
| Primary symptoms           | 15 |
| Days from the symptoms onset | 15 |

| Laboratory and imaging findings on admission to hospital on July, 30, 2020 |  |
|---------------------------------------------------------------------------|---|
| Carcino-embryonic antigen (ng/ml) (2020-07-27)                           | 10.6 |
| Potential of hydrogen                                                    | 7.432 |
| Oxygen partial pressure (mmHg)                                           | 53.4 |
| Carbon dioxide partial pressure (mmHg)                                   | 38.2 |
| Saturation oxygen (%)                                                    | 86.5 |
| Lactic acid (mmol/liter)                                                 | 1.9 |
| White blood cell count (10^9/liter)                                      | 9.1 |
| Neutrophils (%)                                                           | 73.4 |
| Eosinophils (%)                                                           | 6.6 |
| Lymphocytes (%)                                                           | 9 |
| Hemoglobin (g/liter)                                                     | 119 |
| Platelet count (10^9/liter)                                              | 222 |
| C-reactive protein (mg/liter)                                            | 5.6 |
| Erythrocyte sedimentation rate (mm/hour)                                 | 28 |
| B-type natriuretic peptide (ng/liter)                                    | 19.5 |
| Creatinine (umol/liter)                                                  | 47 |
| Albumin (g/liter)                                                        | 34.6 |
| Alanine aminotransferase (U/liter)                                       | 9 |
| Aspartate aminotransferase (U/liter)                                     | 18 |
| Creatine kinase (U/liter)                                                | 38 |
| High-sensitivity cardiac troponin I (ug/liter)                           | 0.003 |
| Prothrombin time (sec)                                                   | 11.2 |
| Activated partial-thromboplastin (sec)                                    | 30.7 |
| Fibrinogen (g/liter)                                                     | 4.82 |
| D-dimer (mg/liter)                                                       | 0.69 |
| Acid-fast bacilli in sputum for 3 times                                 | Negative |
| Multiple virus testing                                                   | Negative |
| 2019 Novel Coronavirus nucleic acid                                      | Negative |
| 2019 Novel Coronavirus IgG antibody                                     | Negative |
| 2019 Novel Coronavirus IgM antibody                                     | Negative |
| Antinuclear antibody                                                    | All negative |
| Anti-neutrophil cytoplasmic antibodies                                   | All negative |
| Cardiac ultrasonography                                                  | Ejection fraction value = 72.9%. Aortosclerosis. Mild bicuspid and tricuspid valve regurgitation. Left atrial enlargement (36mm). Pulmonary artery systolic blood pressure on the high side (34mmHg). Decreased left ventricular diastolic function (E/A ≈ 0.8) |
| Chest computed tomography                                               | Multiple high-density patches in bilateral pulmonary, symmetrically distributed beside the hilus of lung in a butterfly shape |

ILD = Interstitial lung disease.
control. Moreover, tests of antinuclear antibody and anti-neutrophil cytoplasmic antibodies for rheumatism and multiple times acid-fast bacilli of sputum were also negative. The B-type natriuretic peptide was 19.5ng/L and cardiac ultrasonography indicated a well-balanced cardiac function with 72.9% ejection fraction value.

After a multidisciplinary discussion, Almonertinib-induced ILD was considered in the absence of other potential causes so she stopped taking Almonertinib by our proposal. We prescribed her a dose micropump methylprednisolone of 40mg daily empirically, along with oxygen uptake and antibiotics. To prevent from side effects of methylprednisolone, we also administrated her pantoprazole (an acid-inhibitory drug) and Calcium pills. 7 days later, the whole symptoms resolved so a high-resolution chest CT (HRCT) was performed showing partial remission in ILD (Fig. 4G-I). Then from August, 10, the methylprednisolone was decreased to 30mg daily for 9 days. On August, 18, she discharged from hospital and transitioned to 20mg of oral prednisolone daily. On August, 31, 2020, we conducted a follow-up, she didn’t feel any uncomfortable. The blood routine testing, Liver and kidney function and electrolyte was within the normal range. The CEA decreased to 9.5ng/ml (Fig. 2). She also performed a HRCT showing the majority of ILD has been absorbed (Fig. 4J-L). Considering HRCT remained a little ILD sign which needed continuous treatment, meanwhile, the glucocorticoid should be decreased gradually instead of immediate stop, she switched to 8mg daily. Two months later we repeatedly advised her to take a chest CT but she strongly refused because she felt well and only did blood routine testing, Liver and kidney function, electrolyte testing which was normal. Then she continued with 8mg prednisolone. The total course of glucocorticoid treatment should be half a year. During the dosage change process, she developed Hypokalemia with 2.8mmol/L (the normal range was 3.5–5.5mmol/L) on August, 05, 2020, we prescribed her Potassium Chloride Sustained-Release Tablets 1g orally twice a day and a 15ml Potassium Intravenously. 3 days later the serum kalium returned to normal. This reminded us to monitor adverse effect closely.

3. Discussion
Since the third-generation EGFR-TKI was superior to the first/second-generation ones in center nervous system efficacy and appeared more sensitive to 19DEL than 21L858R mutation,[8] we prescribed her the Almonertinib. This patient without any pre-existing pneumonopathy presented with ILD 3 months after Almonertinib treatment. Before we concluded Almonertinib-induced ILD, we had excluded lung inflammation, virus infection, lung cancer progression, rheumatism, tuberculosisc and cardiac failure. The eosinophils accounted for 6.6% in all white blood cell count which ruled out an immune allergic reaction. Additionally, the drugs for treating past medical history diseases she has been taking for years have not been reported such side effect. Taken together, a diagnosis of Almonertinib-induced ILD was determined.

ILD is a sever event in patients treated with EGFR-TKIs. People with male gender, smoking habit and pneumopathy were more likely to confront with ILD.[9] It has been discovered that the occurrence time and rate of ILD varied in different TKIs. Previous studies found the occurrence rate of ILD in Gefitinib was the highest (2.6%-5.3%) among all the TKIs and often happens in an average of 15 days.[3,10] Compared with Gefitinib, Lux-lung 3 and Lux-lung 6 demonstrated ILD occurred lower (0.4%-1%) in about 35.5 days during the treatment of Afatinib.[5,11,12] The incidence for third-generation EGFR-TKI Osimertininb was 4% in around 3 months (79days) which was consistent with this case.[4,13] In the phase I/II study of Almonertinib, ILD has not been observed in the whole group probably due to the limited sample size and short-term follow-up.[6,7] However, this case report implied that it also has potential to cause ILD in spite of its rare incidence.
The subsequent anti-cancer therapy for patients after recovery from TKI-induced ILD still remains controversial currently. As this patient was in metastatic stage with potential relapse and poor prognosis, it was better to receive active treatment than just following up. Chemotherapy was not taken into account since EGFR-TKI was admittedly more effective than chemotherapy in LUAD with sensitive EGFR mutation. After reviewing some relevant literature and multidisciplinary discussion, we decided to choose Afatinib under the condition of informing the risk of ILD recurrence to patient and her families. As stated above, the incidence of Afatinib-related ILD in Lux-lung 3 and Lux-lung 6 was the lowest (0.4%-1%) among all the currently approved TKIs.[15,16] A recent study focusing on Afatinib without concurrent steroids as the following treatment for Osimertinib-induced ILD patients found it was safe with no ILD recurrence and effective with eminent objective response rate (75%) and disease control rate (100%).[14] Compared with the overall rate 4% of Osimertinib-induced ILD in the general population of both FLAURA and AURA studies,[4,15] the Japanese subgroup experienced a higher rate of 12.3% and 6.2% respectively,[16,17] which implied Asians were more susceptible to Osimertinib-induced ILD so this was outside our choice. It has been reported that NSCLC patients with EGFR mutation or Murine double minute 2 amplification were not sensitive to immune therapy and even would endure hyper-progressive disease,[18,19] so monotonous immunotherapy or the combination of immune and chemotherapy were not considered in this patient. Under these consideration, we plan to give priority to Afatinib with close monitoring.

Still, there is some limitation in this report. We’ve not got a lung tissue biopsy for pathological LUAD verification in this patient since it was difficult to conduct this, instead, we diagnosed with “metastatic intracranial adenocarcinoma from LUAD” empirically. The reasons for this diagnosis are listed as follows. First, the pathology of the intracranial cancer was adenocarcinoma and the CK (7), TTF1 and Napsin A were all positive in IHC. It has been long acknowledged that CK (7) positive refers to the epithelial-origin cancer especially the lung tissues.[20,21] The National Comprehensive Cancer Network and Pan-Asian European Society for Medical Oncology guidelines of NSCLC strongly recommended to ascertain LUAD by TTF-1 and Napsin A. [22,23] Moreover, EGFR 19DEL has been proved 1 of the most common mutated forms in LUAD.[24] Combining the medical history, IHC and genetic testing results, we concluded that the metastatic intracranial adenocarcinoma was derived from LUAD.

4. Conclusion

To our knowledge, this is the first to report the adverse effect of Almonertinib-induced ILD. We hope to make clinicians have a better comprehending of this drug and therefore keep it under good control. Notably, The phase III clinical trial for Almonertinib versus Gefitinib as the first-line treatment for advanced or metastatic NSCLC with EGFR mutation is ongoing, the efficacy as well as the side effects are both needed to be focused on.

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Author contributions

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