

Fatal Interstitial Lung Disease Associated With Erlotinib: A Case Report and Review of Literature

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Abstract

Erlotinib is a human epidermal growth factor receptor / tyrosine kinase inhibitor (EGFR-TKI), which is effective as a first and second-line treatment for patients with advanced stage non-small cell lung cancer (NSCLC) with EGFR mutations. Erlotinib is considered to have a favorable safety profile, few cases of interstitial lung disease (ILD) related to erlotinib have been described. We report a case of a 58-year-old male with stage IV NSCLC treated with erlotinib who developed ILD and died on 55th day since commencing erlotinib. Respiratory symptoms during treatment with erlotinib should alert clinicians to rule out pulmonary toxicity, early erlotinib withdrawal is crucial.

Keywords: Drug-induced lung injury, Interstitial lung disease, Epidermal growth factor receptor tyrosine kinase inhibitor, Erlotinib, Non-small cell lung cancer

Introduction

Erlotinib is a reversible EGFR-TKI, which has been available for the treatment of patients with NSCLC since 2004 and has been included in NCCN guideline since 2010 as first-line treatment option for advanced NSCLC patients who harbor EGFR mutation [1]. From then on, erlotinib has opened up a new era of effective and relatively safe treatment of patients with advanced NSCLC [2,3]. Recently, the first case of erlotinib-induced ILD (eILD), diagnosed based on clinical and radiologic findings, was reported [4]. Herein, we report a case of a NSCLC patient treated with erlotinib who developed ILD and died.

Case Report

A 58-year-old male patient with complaint of sacrococcygeal pain for about 3 months was admitted to our hospital in 20th December, 2010. He had a history of cigarette smoking (1 pack/day for 35 years). Physical examination revealed normal vital signs except percussion pain in 2nd sacral vertebrae

(S2) level. Pelvic computed tomographic (CT) scan showed lytic lesion in the right side of S2 (Figure 1A). Chest CT scan found a nodule with lobulated and speculated margin in the superior segment of the left lower lobe (Figure 1B,1C). S2 punctured biopsy followed by excision of sacral neoplasms (Figure 1D-1G, Figure 2A,2B) revealed a diagnosis of metastasis non-small cell cancer, derived from lung. So the definite diagnosis was lung adenocarcinoma (T2aNxM1b; stage IV) without EGFR mutation or chromosomal rearrangements of anaplastic lymphoma kinase (ALK). He received cisplatin (75mg/m²) and pemetrexed (500 mg/m²) every 3 weeks as an initial anticancer treatment. After four cycles of chemotherapy, CT scan showed a stable disease condition (Figure 2C,2D), so 4 cycles of maintenance therapy of pemetrexed (500 mg/m²) every 3 weeks were given subsequently. But positron emission tomography-computed tomography (PET-CT) detection revealed extensive metastasis in the left pleura (Figure 3A,3B,3C) after the above therapy, and disease progression was documented. The patient was not eligible for any other chemotherapy due to his poor performance status (PS), and the treatment of choice remained EGFR-TKI (erlotinib, 150 mg once daily) in spite of his EGFR gene was wild, along with pleural fluid drainage. High-resolution CT (Figure 3D,3E) showed ground-glass opacities in both lungs,

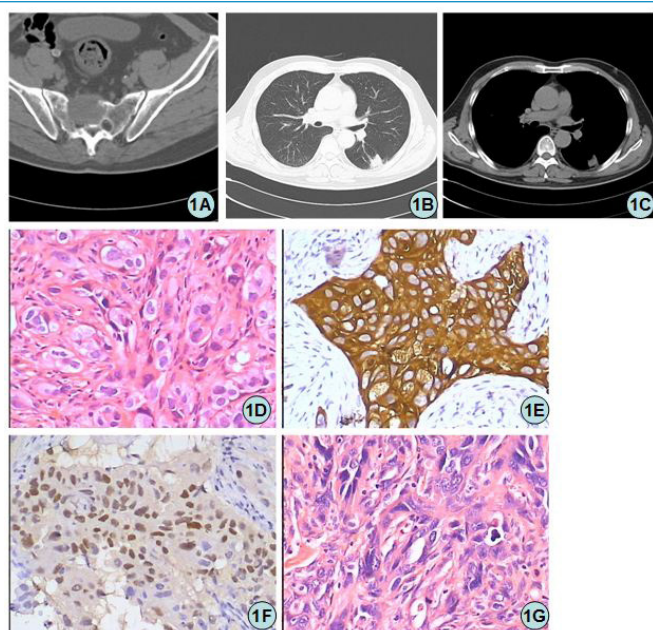


Figure 1:

Figure 1A: CT scan at the S2 level shows a lytic soft-tissue mass within the right side of the sacrum with erosion of the anterior cortex and extending into the right anterior sacral foramen. Figure 1B,1C: CT scan (lung window) obtained at the level of the left main bronchus reveals a nodule with lobulated and speculated margin in the superior segment of the left lower lobe. The nodule also can be seen in the mediastinal window. Figure 1D-1E: 1D HE staining of S2 punctured biopsy specimen in accordance with adenocarcinoma ($\times 40$); 1E CK7 positive ($\times 20$); 1F TTF-1 positive ($\times 20$); 1G HE staining of surgery biopsy specimen in accordance with adenocarcinoma ($\times 40$)

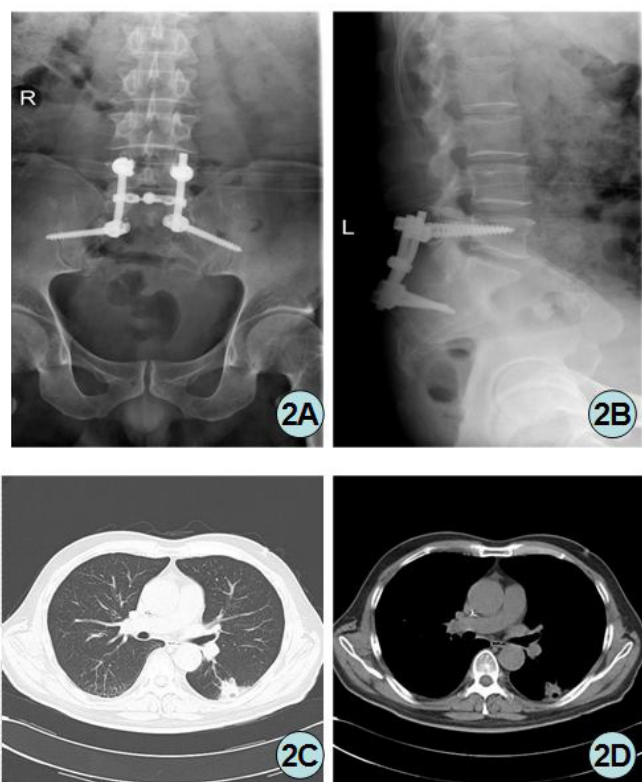


Figure 2

Figure 2A,2B: Anteroposterior and lateral radiographs show the changes after S2 metastatic tumor excision and lumbosacral spine stabilization applied rods and screws fixation. Figure 2C,2D: CT scan shows the nodule located in the left lower lobe slightly larger than before.

especially in the right side on 34th day since he received erlotinib. Because it appeared that the patient could not tolerate a bronchoscopy and transbronchial lung biopsy, eILD was impressed without a pathologic support. Immediate withdrawal of erlotinib and administration of methylprednisolone 2 mg/kg/d was prescribed for 5 days with dosage gradually reduction, along with supplemental oxygen, nebulisers and antibiotics. General conditions of the patient were deteriorated in the following days, as well as dyspnea and progressive respiratory failure developed. The patient died 3 weeks later (55 days after commencing erlotinib). No postmortem autopsy was obtained, due to his family request.

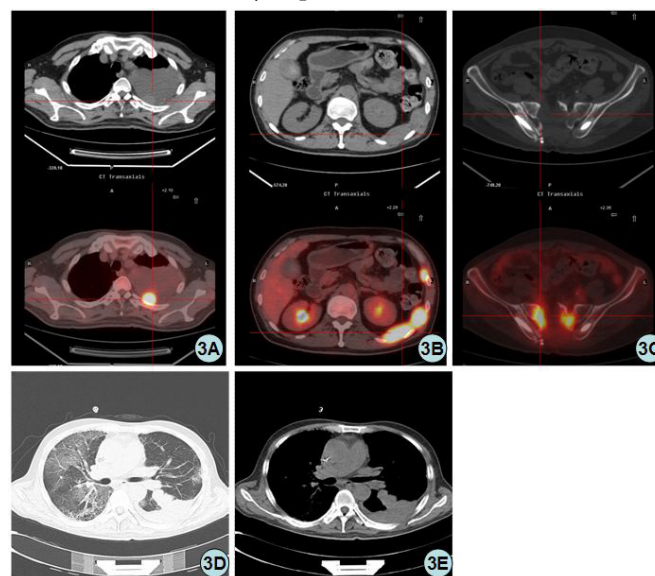


Figure 3

Figure 3A,3B: PET-CT shows multiple soft-tissue density nodules in the left pleura with intense hypermetabolism and massive pleural effusion, a finding highly suspicious for extensive metastasis in the left pleura. Figure 3C: PET-CT shows intense hypermetabolism in the periphery of metastatic tumor excision area in S2, which suggests local recurrence of metastatic tumor in S2. Figure 3D,3E: Chest CT reveals extensive bilateral ground-glass opacities especially in the right side after 34 days of erlotinib therapy. A persistent moderate left-sided pleural effusion is also noted.

Discussion

The most common adverse events related to erlotinib treatment are skin rash and diarrhea, while the most serious adverse event reported should be eILD. The incidence of eILD was about 0.2–6.5% in different studies, of which, the highest one lied in Asian, especially in the Japanese [5-11]. While the incidence of all-grade eILD in non-Asian countries was 0.9%. Similarly, treatment with erlotinib significantly increased the risk of developing high-grade ILD. Results indicated that the OR of eILD did not significantly associate with treatment duration of EGFR-TKIs [12]. The reason for this geographic difference is unclear, different genetic background in different population maybe partially explain the above difference [13]. The allele frequency of ABCG2C>A in Japanese (~30%) is higher than that in whites (~10%). This difference might be related to higher incidence of eILD events in Japanese patients (~5%) than in patients in the United States (~1%) [14].

eILD started from 5 days to >9 months (median 47 days) after initiating erlotinib therapy [15], and developed within 28

days after the start of treatment in most patients [16]. As to the patient in our report, the eILD was confirmed by HRCT and clinical symptoms 34 days after he received erlotinib, which in accordance with the report mentioned in the literature above. Of note, eILD was fatal in at least one third of these cases [17], the mortality is even higher near to 50% [18].

The exact mechanism of eILD has not been fully elucidated. A Japanese postmarketing surveillance study of erlotinib yielded four risk factors for the development or exacerbation of eILD: smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 to 4, concurrent or previous ILD, and concurrent or previous lung infection [8]. The amount of residual normal lung ($\leq 50\%$) was identified as risk factors for the development of eILD [16]. Relation between high plasma erlotinib concentrations and the development of eILD has been suggested [19,20]. The ABCB1 1236TT-2677TT-3435TT genotype was associated with higher plasma concentration and the risk of developing higher toxicity in patients treated with erlotinib [21]. Increased KL-6 serum level, which is a marker of type II pneumocyte injury, has been described in eILD [22]. EGFR inhibition by erlotinib may thus impair EGF-induced repair by pneumocytes [23]. Modulation of the metabolic pathway of erlotinib due to CYP1A and CYP3A may influence its toxicity [24]. The ATP-binding cassette subfamily G member 2 (ABCG2) 421C>A polymorphism can influence the apparent clearance of erlotinib in patients with NSCLC and may thus be the underlying cause of severe eILD [20]. There was a tendency for eILD to develop more readily when C3 levels were higher than the median and when C4A/C4B and APOA1 levels were lower than the median [11]. We could not detect erlotinib plasma concentration, KL-6, C3, C4A/C4B, APOA1 level, and ABCG2 polymorphism of the patient in our report, so we can not clarify the exact mechanism of eILD for him. The patient was a heavy smoker, which may have increased his risk of developing eILD.

Radiologic changes of eILD are nonspecific and seem to be similar to those of other drug-associated lung injury. The CT features of target agent-related ILDs can be classified into six categories: (1) diffuse alveolar damage or acute interstitial pneumonia, (2) bronchiolitis obliterans, (3) cryptogenic organizing pneumonia (COP) or COP-like pattern, (d) hypersensitivity pneumonitis, (5) interstitial pneumonia of either nonspecific interstitial pneumonia or usual interstitial pneumonia pattern, and (6) progressive disease of underlying ILD [25,26]. Erlotinib can cause Radiation Recall Pneumonitis after Palliative Definitive Radiotherapy [27]. The severity of eILD was classified as mild (abnormalities in $< 5\%$ of bilateral lobes), moderate (abnormalities in $5\%-20\%$ of bilateral lower lobes), or severe (abnormalities in $> 20\%$ of bilateral lower lobes) [16]. It is self-evident that the patient in our report belongs to the severe one.

eILD remains a poorly understood disease entity. The sparse data available comes mainly from case reports, retrospective trial analyses and postmarketing safety information, predominantly from Japanese patients.

Diagnosis of eILD is often difficult and is based on clinical, radiologic and, where available, pathologic observations. Ob-

taining histological samples is not always possible due to the poor health of the patients, and so the diagnosis is often one of exclusion. High suspicion is necessary in those patients under treatment with erlotinib who develop respiratory symptoms like dyspnea, cough or fever [3,28,29]. Diagnostic imaging is important primarily to provide an understanding of the baseline pulmonary status and radiographic pattern after onset, determining the severity and extent of the lesions, and assessing the treatment response [16]. In our report, the patient didn't have any hints of congestive heart failure, lung infection or lymphangitic carcinomatosis. His radiologic signs of ILD were apparent after 34 days of erlotinib treatment. We just thought that his respiratory symptoms, such as cough and dyspnea, were the result of pleural effusion. We should give him CT detection earlier, and find clues of ILD earlier.

There have been no randomized controlled or prospective trials to guide the management of eILD. Treatment of eILD is largely supportive, including supplemental oxygen and mechanical ventilation. Immediate discontinuation of the offending drug is recommended. Dose-reduction plays a limited role in preventing recurrence [30]. Systemic corticosteroids are usually prescribed when infection is ruled out, although no controlled trials have been conducted to evaluate their benefit [31,32]. Although resolution has been reported, many patients die of progressive respiratory failure [25]. As to the patient in our report, corticosteroids was ineffective, which was the same as the reported data [33].

Although several studies to date have reported on the predictive factors for eILD, it is currently difficult to prevent eILD. In conclusion, the incidence of eILD seems to be low, more cases could be expected with increasing number of patients receiving erlotinib. Clinicians should be aware of clinical and radiographic presentation of eILD. Erlotinib should be discontinued if the patient develops cough and dyspnea. Corticosteroids should be considered after the exclusion of infection, cardiogenic pulmonary edema, diffuse alveolar hemorrhage and lymphangitic carcinomatosis. Further research is needed to identify the risk factors and pathophysiology. This will guide patient selection for erlotinib therapy and help develop more effective treatment strategies [34].

Authors' Contribution

Ling-chuan Guo and Xi-ming Wang contributed equally to this work as co-first authors

Disclosure

The authors do not have any conflict of interest.

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