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Ceritinib-Induced Organising Pneumonitis

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Abstract

Even though tyrosine kinase inhibitors (TKI) improve survival in non-small cell lung cancer (NSCLC), it is related to the risk of drug-induced pneumonitis. Whilst little is known regarding TKI-induced pneumonitis, adverse reactions carry a significant mortality rate and impact the available treatment options. Here, we present a case of an elderly gentleman diagnosed with metastatic ALK-positive NSCLC, who initially experienced ceritinib-induced skin vasculitis and subsequently developed acute respiratory distress syndrome upon being re-challenged with ceritinib. The patient's clinical and radiological condition showed improvement after initiating intravenous methylprednisolone and discontinuing the targeted therapy. Ceritinib-associated pneumonitis represents a rare form of pulmonary toxicity, emphasising the importance of early identification and intervention to mitigate mortality risk.

Subject Areas

Respiratory Medicine

Keywords

Ceritinib, Pneumonitis, Acute Respiratory Distress Syndrome, Corticosteroids

1. Introduction

The prognosis for non-small cell lung cancer (NSCLC) patients with molecular

mutations has significantly improved due to the development of tyrosine kinase inhibitor (TKI) targeted therapies. The anaplastic lymphoma kinase (ALK) fusion gene occurs in approximately 3% to 7% of NSCLC cases [1]. The first approved TKI for treating ALK-rearranged NSCLC was crizotinib. However, for patients with advanced ALK-rearranged NSCLC or those who experienced disease progression during crizotinib treatment, the second-generation highly selective ALK-TKI drugs, alectinib and ceritinib, have proven effective [2].

Molecular targeting agents have increased the recognition of drug-related pneumonitis. However, only a limited number of studies and case reports on ALK-related pneumonitis have been published, and the clinical course and risk factors of ALK-related pneumonitis still need to be clarified [3]-[5]. While ceritinib-related interstitial pneumonitis is rare, it has been reported in approximately 1.1% of cases of treatment [2]. In clinical trials investigating crizotinib-induced ILD among 1397 cases, 34 patients (2.4%) experienced any grade ILD, 13 (0.9%) developed grade 3 or 4 ILD, and 7 (0.5%) resulted in death [6]. There have also been reports of successful rechallenge therapy with either crizotinib or alectinib following the onset of ALK-TKI-induced ILD [7]. Here, we present a case where acute interstitial pneumonitis, accompanied by acute respiratory distress syndrome (ARDS), required mechanical ventilation after the patient was re-challenged with ceritinib.

2. Case Report

An elderly man was referred to our respiratory team due to worsening his respiratory distress, necessitating ventilator support. He is a known advanced poorly differentiated adenocarcinoma of the lungs and was taking ceritinib at a daily dose of 450 mg. Approximately six weeks after starting ceritinib, he developed vasculitis in his lower limbs, which led to the discontinuation of the medication. The patient declined a skin lesion biopsy. He was given a short course of dexamethasone for the vasculitis.

After three weeks following the resolution of the lower limb vasculitis, ceritinib was re-challenged. However, three days into resuming the medication, the patient experienced breathlessness and required supplemental oxygen at a rate of 3 L/min via nasal prongs. A chest radiograph revealed opacities in the upper right lung zone (**Figure 1(A)**), and treatment with intravenous piperacillin-tazobactam was initiated to address hospital-acquired pneumonia. The patient's condition deteriorated within 48 hours of ceritinib reintroduction, necessitating mechanical ventilation. Subsequent chest radiography showed widespread alveolar opacities (**Figure 1(B)**), resulting in a PF ratio of 95, indicative of ARDS.

Due to the patient's high ventilator requirements, bronchoscopy and bronchoalveolar lavage could not be performed. Laboratory results indicated a white cell count of 14×10^9/L, 12 mg/dl C-reactive protein, and 3 ng/ml procalcitonin. Testing for MTB gene Xpert DNA in tracheal aspirate yielded negative results. A provisional diagnosis of ceritinib-induced acute interstitial pneumonitis

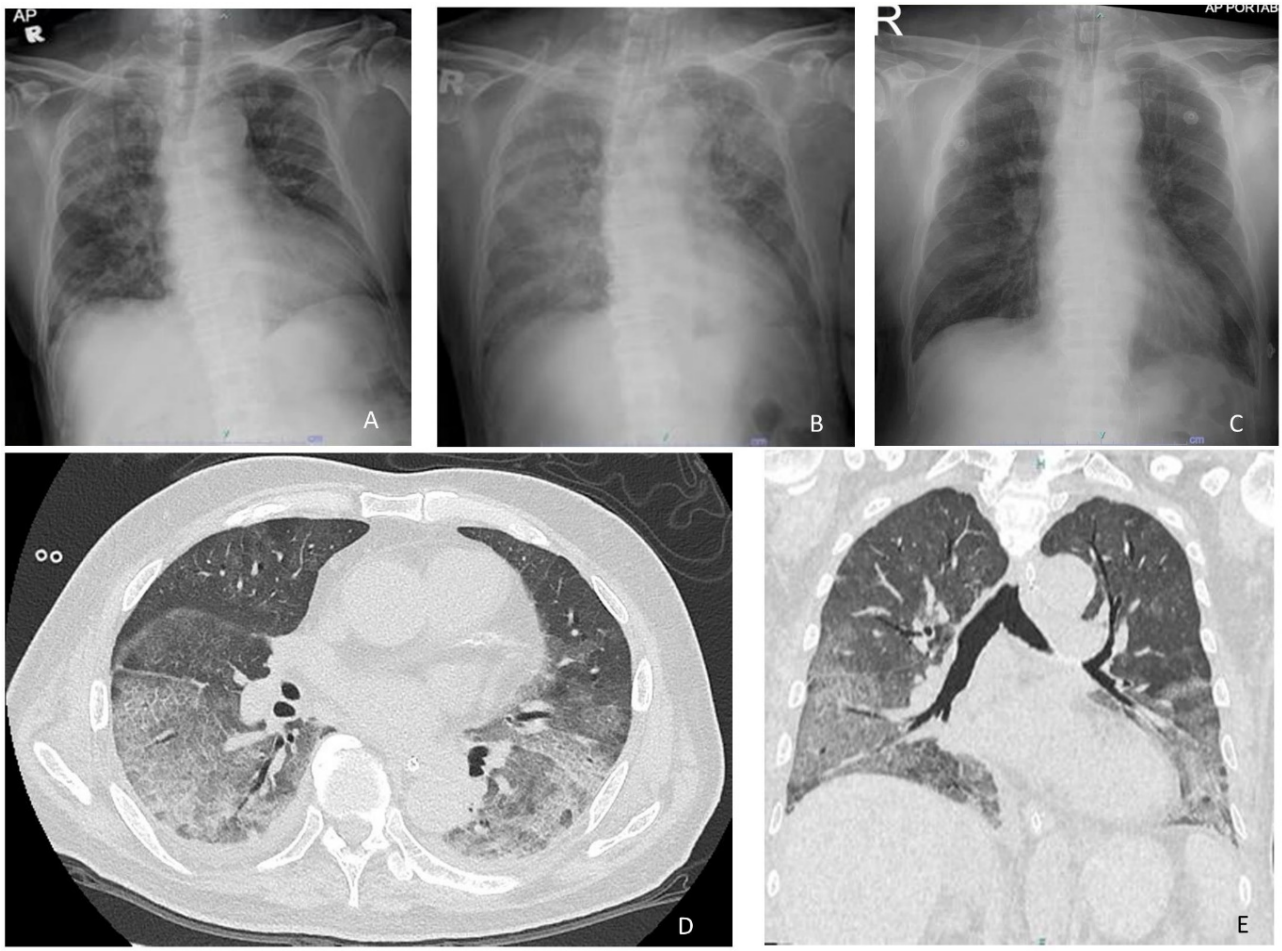

Figure 1. (A) Chest radiograph showing right upper zone air space opacities. (B) Chest radiograph showing diffuse alveolar opacities. (C) Chest radiograph 48 hours after methylprednisolone showing remarkable improvement of the alveolar opacities. (D & E) High resolution computed tomograph of the thorax showing diffuse ground glass opacities with interlobar septal thickening.

entertains and empirically covers pneumocystis jirovesi pneumonia. Intravenous methylprednisolone (MTP) at 2 mg/kg and IV Bactrim were administered. After 24 hours of treatment, the patient's need for oxygen significantly decreased. A repeated chest radiograph 24 hours after initiating the IV MTP revealed improved diffuse air alveolar opacities (**Figure 1(C)**). A high-resolution computed tomography scan of the thorax was performed once ventilator support had stabilised, showing diffuse ground glass opacities, a "crazy paving" pattern, and an "arcade-like" signs consistent with an organising pattern (**Figure 1(D)** and **Figure 1(E)**). Subsequent tracheal aspirate Pneumocystis jirovecii DNA was detected with a cycle threshold value of 31.25. The tracheal aspirate for Mycobacterium tuberculosis PCR (XPert MTB/RIF) and Aspergillus antigen (ELISA), bacterial and fungal cultures were negative.

After over one week of ventilator support, the patient developed new air space opacities on the right midzone. Ventilator-associated pneumonia was suspected, leading to an escalation of antibiotics to the carbapenem group. However, cultures from bronchoalveolar lavage did not reveal the presence of bacteria, acid-fast

bacilli, or fungi. A transbronchial lung biopsy could not be performed due to concerns about high ventilator pressures and the risk of pneumothorax. A blood culture later identified Candida tropicalis, prompting the initiation of IV Anidulafungin.

The patient's condition gradually improved, reflected in lower oxygen requirements and adjustments to ventilator settings. MTP dosage was gradually reduced to 1 mg/kg for five days, followed by a transition to prednisolone at a dose of 0.5 mg/kg, with weekly tapering of 5 mg. Serial chest radiographs revealed progressive improvement in air space opacities. By the third week of mechanical ventilation, the patient underwent a tracheostomy due to difficulties with weaning and prolonged ventilation. Oxygen support was successfully transitioned to a venturi mask, and the patient received pulmonary rehabilitation in the general ward.

3. Discussion

Drug-induced interstitial lung disease (ILD) accounts for about 1% of TKI-treated NSCLC [8]. A meta-analysis of 18 trials involving ALK-TKI monotherapy and advanced NSCLC revealed an overall incidence of pneumonitis at 2.14% for all grades, 1.33% for high-grade pneumonitis (grade 3 or above), and 0.22% for grade 5 pneumonitis [9]. Notably, Japanese cohorts exhibited higher rates of ALK-TKI pneumonitis across all grades [9]. Furthermore, a systematic review indicated that patients receiving prior chemotherapy were more susceptible to developing all-grade pneumonitis than those receiving first-line ALK-TKI treatment. [10] Among the TKIs, Brigatinib is most frequently associated with pneumonitis, with reported rates ranging from 4% to 9.1%, while Lorlatinib has the lowest incidence of both all-grade and high-grade pneumonitis [10] [11].

Chest CT (thin-section CT; section thickness of 2.0 - 2.5 mm or less) should be performed when there is a positive temporal relationship between drug exposure and symptom onset to evaluate the pattern and progression of pulmonary abnormalities in DRP. DRP exhibits diverse and non-specific CT patterns, including diffuse alveolar damage, eosinophilic pneumonitis, hypersensitivity pneumonitis, organising pneumonia, and nonspecific interstitial pneumonia [12]. The CT pattern of DRP is also frequently associated with various types of histopathologic manifestations [13]. Therefore, CT plays a crucial role in the early diagnosis and monitoring of drug-related interstitial pneumonitis, as it can also help rule out other possible causes of the patient's symptoms. In our case, we observed the organising pattern on CT during the rechallenge of ceritinib.

Bronchoscopy with bronchoalveolar lavage (BAL) is performed to rule out infection, alveolar haemorrhage, or lymphangitic spread. Although the BAL fluid-derived differential cell count is often non-specific, it may offer diagnostic clues (e.g., eosinophilia) for DRP. The BAL differential white cell count typically shows a distinctive "mixed pattern" with increased lymphocytes (20% - 40%), neutrophils (approximately 10%), and eosinophils (about 5%), along with some plasma cells or mast cells. The lymphocyte CD4/CD8 ratio is decreased [14]. The decision

to perform lung biopsy in patients suspected of having DRP depends on the severity of lung involvement, a benefit-risk analysis, and consideration of alternative diagnoses. The histopathologic patterns observed in lung biopsies are not specific and can be seen with other causes, such as tumour infiltration and infections. In our patient's case, immediate bronchoscopic and histopathological evaluation was not pursued due to clinical instability and the risk of hypoxia. However, the rapid weaning of ventilator requirement and improvement in chest radiography after discontinuing ceritinib and corticosteroid therapy suggest a probable diagnosis of DRP. Moreover, acute bilateral ground glass opacities on chest imaging, consistent with exudative oedema and hyaline membrane formation, are characteristic of ALK-TKI-related pneumonitis.

The mortality rate for ALK-related interstitial pneumonitis is approximately 10%, but most patients respond well to steroids, leading to symptom resolution within days or weeks [15]. In cases of severe or progressive grade 2 or 3 pneumonitis (according to Common Terminology Criteria for Adverse Events), discontinuing the suspected drug is advisable, especially when DRP is considered a possible or likely cause. Glucocorticoids are frequently prescribed to aid in resolving lung injury, especially in severe cases, as determined by symptoms, gas exchange derangements, and radiologic abnormalities. The pneumonitis may be related to the dose and usage of ALK-TKI, and dose adjustment may control the occurrence of pneumonitis [16]. Regarding retreatment with ALK-TKI and the associated risks of pneumonitis upon restarting therapy, current guidelines lack sufficient evidence and specific recommendations.

Despite the benefits of TKI treatment in terms of progression-free and overall survival for molecular mutated NSCLC patients, it is crucial to be vigilant about DRP. Distinguishing pure pneumonitis from superimposed infection can be challenging. Various approaches such as procalcitonin levels, CT imaging, molecular testing, and assessing the temporal relation of drug exposure can be helpful to aid in this differentiation. If respiratory symptoms arise after initiating TKI treatment, a thorough clinical and lung function evaluation should be conducted. In cases of severe TKI-related acute interstitial pneumonitis, immediate discontinuation of TKI treatment is recommended. In our patient's case, mechanical ventilation, early initiation of corticosteroid therapy, and treating the superimposed infection played a crucial role in stabilising this life-threatening situation.

Authors' Contribution Statement

The work conducted and presented in this manuscript has not been published or submitted for publication in another journal. All authors named in the manuscript have made substantial contribution each to qualify for authorship according to BIMJ authorship criteria and have approved of the content of the manuscript. We have disclosed all financial support for our work and other potential conflicts of interests.

Ethics Statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

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