

Case report

Acute interstitial lung disease in a patient with anaplastic lymphoma kinase-positive non-small-cell lung cancer after crizotinib therapy

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Crizotinib, an orally active multi-targeted small-molecule anaplastic lymphoma kinase (ALK) inhibitor, is an effective treatment modality for advanced ALK-positive non-small-cell lung cancer (NSCLC). Most drug-related adverse events are mild to moderate; however, some patients may develop acute interstitial lung disease (ILD) which is sometimes fatal. We present a case of crizotinib-associated ILD in a 47-year-old woman treated with crizotinib for metastatic adenocarcinoma of the lung. The patient presented with acute breathlessness and hypoxaemia in the second month of crizotinib therapy; radiological and histopathological work-up was suggestive of acute interstitial pneumonia. The patient improved clinically with corticosteroid therapy and was successfully re-challenged with crizotinib. In conclusion, while treating NSCLC patients with crizotinib, it is important to promptly investigate and treat any new-onset respiratory symptoms, as the latter could represent an adverse effect related to therapy. Prompt discontinuation of the offending drug and initiation of corticosteroid therapy may prevent adverse outcomes.

INTRODUCTION

Anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) is a heterogeneous molecular subtype of NSCLC with aberrantly activated ALK kinase in at least 27 ALK-fusion variants identified [1, 2]. Crizotinib is a multi-targeted small-molecule ALK inhibitor approved for the treatment of advanced ALK-positive NSCLC in August 2011 [3, 4].

CASE PRESENTATION

A 47-year-old Indian woman, who was a non-smoker, presented with severe upper interscapular back pain since 1 month. Radiological evaluation revealed a right upper lobe lung mass with T5 and T9 vertebral body metastasis. Percutaneous lung biopsy of the lung lesion was suggestive of moderately differentiated adenocarcinoma. Thus, she was diagnosed with Stage IV bronchogenic carcinoma with contralateral pulmonary and bony metastasis. The tumour was negative for epidermal growth factor receptor (EGFR) mutation.

Fluorescence *in situ* hybridisation analysis with break-apart probes for the ALK gene revealed the presence of an ALK rearrangement. The patient received palliative radiotherapy to symptomatic T5 and T9 spine metastases followed by oral crizotinib (250 mg/day) with intravenous zoledronic acid. After 2 months of crizotinib therapy, the patient presented with acute onset of nocturnal cough, worsening dyspnoea, resting hypoxaemia and bilateral basal end-inspiratory crackles on respiratory system examination. There was no history of fever. Sputum tests for an infective aetiology and serology for atypical pathogens were negative. High-resolution computed tomography (HRCT) of the thorax showed new-onset bilateral ground-glass opacities and fibrosis, despite obvious shrinkage of the primary tumour lesions and regression of mediastinal lymph nodes (Fig. 1). Bronchoscopy with broncho-alveolar lavage (BAL) and transbronchial lung biopsy (TBLB) was performed. BAL fluid was negative for malignant cells and infective aetiology (bacteria, fungal elements and acid fast bacilli) and histopathology of the TBLB sample revealed interstitial inflammation and fibrosis suggestive of acute interstitial pneumonitis. Thus,



Figure 1: High-resolution CT scan images showing bilateral ground-glass opacities with interstitial inflammation with fibrosis.

the exclusion of infection and malignancy indicated that crizotinib therapy was the most likely attributable cause for severe interstitial lung disease (ILD) in this patient. Crizotinib treatment was immediately discontinued and oral corticosteroid therapy (prednisolone at 0.5 mg/kg) was initiated and gradually tapered over 8 weeks. The patient showed progressive symptomatic and clinical improvement after initiation of steroid therapy with complete resolution of symptoms and signs on follow-up at 8 weeks. As the patient refused conventional chemotherapy on follow-up, she was successfully re-challenged with crizotinib under steroid cover. The patient had a partial response to re-treatment without further worsening of the ILD.

DISCUSSION

Drug-induced ILD has been reported with EGFR tyrosine kinase inhibitors with male gender, smoking history and coincidence of interstitial pneumonia as independent risk factors [5]. Severe, life-threatening or fatal ILD/pneumonitis can also occur in patients treated with crizotinib. Across all clinical trials ($n = 1225$), 31 crizotinib-treated patients (2.5%) had any grade ILD, 11 patients (0.9%) had Grade 3/4 and 6 patients (0.5%) had fatal ILD. These cases generally occurred within 2 months after the initiation of treatment [6]. As far as we are aware, our patient is the one among the few reported cases of histologically documented crizotinib-associated ILD and the second case of successful crizotinib retreatment after crizotinib-induced ILD [7–10]. Although crizotinib is generally well tolerated, physicians should be aware of the possibility of a pulmonary toxicity manifesting as ILD and thus a high index of suspicion for ILD should be entertained especially if there is new onset of respiratory symptoms that are not suggestive of an infectious aetiology.

CONSENT

Written informed consent was obtained from the patient's family for publishing this case report and accompanying images.

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AUTHORS' CONTRIBUTIONS

All authors have revised the manuscript critically and gave the final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

None declared.

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