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CASE REPORT

Interstitial lung disease associated with capmatinib therapy in a patient with non-small cell lung cancer harboring a skipping mutation of *MET* exon 14

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Abstract

Capmatinib is a MET tyrosine kinase inhibitor (TKI) that has recently been approved for the treatment of advanced non–small cell lung cancer (NSCLC) positive for skipping mutations of *MET* exon 14 (*MET*ex14). Drug-induced interstitial lung disease (ILD) is a relatively rare, but potentially serious, side effect of TKIs administered for lung cancer treatment. Here we report a case of capmatinib-induced ILD in a patient with NSCLC harboring a *MET*ex14 skipping mutation. Capmatinib should be immediately discontinued if ILD is suspected, and treatment with corticosteroid should be considered.

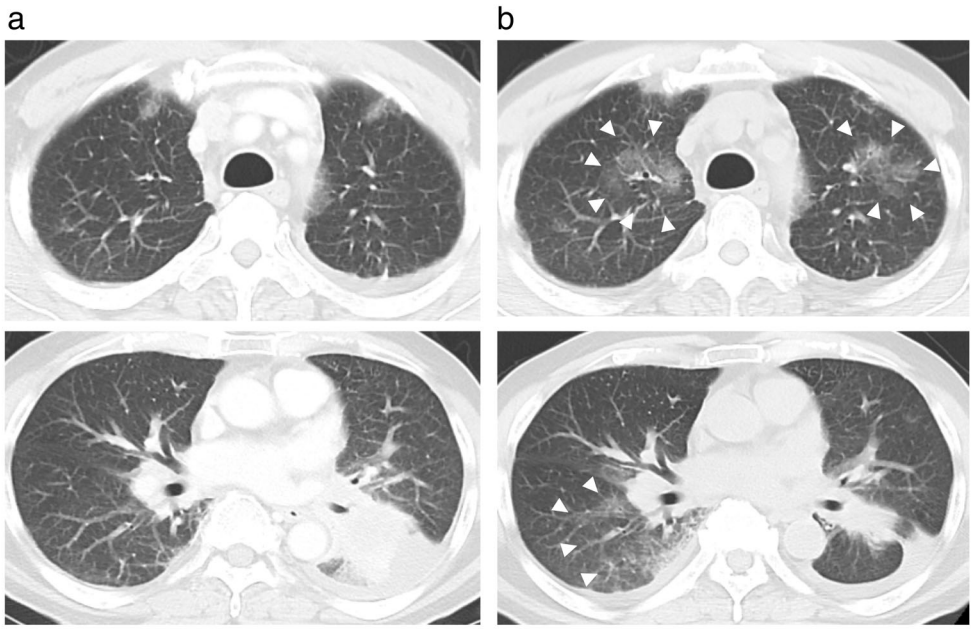
Introduction

Identification of biologically significant genetic alterations that lead to activation of oncogenes in cancer has the potential to provide therapeutic opportunities. Molecularly targeted therapy for lung adenocarcinoma harboring skipping mutations of *MET*ex14 has recently been introduced into clinical practice.[1] Two MET TKIs—capmatinib and tepotinib—have thus been approved for the treatment of advanced NSCLC in patients confirmed to be positive for such mutations.[2,3] *MET*ex14 alterations were initially identified in small cell lung cancer and NSCLC in 2003 and 2005, respectively.[4] Genetic alterations of *MET*ex14 have been detected in 4.3% of lung adenocarcinomas and in 3.0% of squamous cell lung cancers.[5] These alterations are targetable driver mutations similar to alterations of *EGFR* and *ALK*,[6] given that lung adenocarcinomas harboring *MET*ex14 alterations show a substantial clinical response to MET inhibition.[7,8] Drug-induced ILD is a relatively rare but potentially serious side effect of TKIs administered for lung cancer treatment.[9] Here, we report a case of capmatinib-induced ILD in a patient with NSCLC harboring a *MET*ex14 skipping mutation.

Case report

A 68-year-old male former smoker (50 pack years) of Japanese descent was diagnosed with stage IV lung adenocarcinoma (cT3N3M1c) with multiple pleural disseminations as well as a positive intra-abdominal lymph node. He was taking amlodipine besilate as a routine medication, and there was no clinically apparent ILD at baseline. Analysis of biopsied tumor tissue with an Applied Biosystems 7500 real-time PCR system revealed a *MET*ex14 skipping mutation. Given the lack of an approved MET-targeted therapy, the patient participated in cohort 5b (treatment-naïve) of a phase 2 trial, GEOMETRY mono-1, and capmatinib was administered orally at a dose of 400 mg twice daily. After treatment for 29 days, he was admitted to our hospital with fever and dyspnea. His oxygen saturation was 90% on room air. No findings such as edema or jugular vein

distention were noted. Laboratory tests revealed a B-type natriuretic peptide level of 56.0 pg/mL (normal range; 0–20 pg/mL) and KL-6 level of 531 U/mL (normal range; <500 U/mL). Sputum culture was negative. Chest computed tomography (CT) revealed extensive right consolidation with multiple ground-glass opacities (GGOs) throughout both lungs, despite shrinkage of the primary lung lesion in the left lower lobe (Fig 1a,b). Capmatinib treatment was immediately discontinued, and empirical treatment with piperacillin and tazobactam was administered. After antibiotic treatment for four days, his fever remained and CT revealed progression of the GGOs in both upper lobes. We performed bronchoscopy to identify the underlying etiology of the pneumonitis, and cellular analysis of bronchoalveolar lavage fluid revealed a lymphocytic cellular pattern (Fig 1c). Hematoxylin-eosin staining of a specimen of the right lung revealed mild infiltration of small round inflammatory cells and neutrophils, suggestive of alveolitis (Fig 1d). On the basis of these clinical features, we made a diagnosis of capmatinib-induced ILD of grade 3. We initiated prednisolone treatment at a dose of 60 mg daily. The patient experienced gradual clinical



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Category	Cell counts (%)
Alveolar macrophages	60
Neutrophils	2
Lymphocytes	37
Eosinophils	1

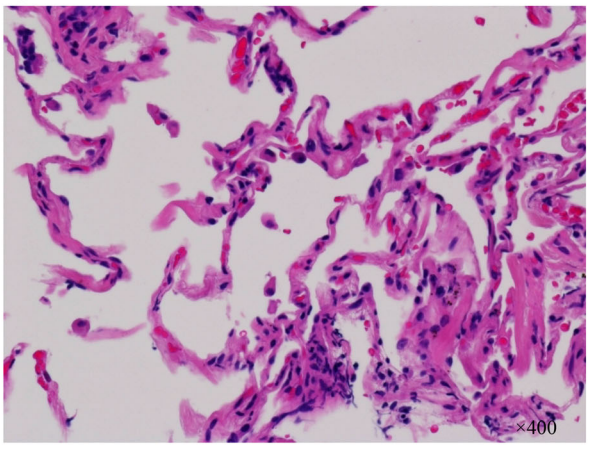

Figure 1 Computed tomography (CT) scan and histological findings indicative of capmatinib-induced ILD. (**a**) CT scan showing the primary lung lesion in the left lower lobe before capmatinib treatment. (**b**) CT scan at 31 days after the initiation of capmatinib treatment showing extensive right consolidation with multiple ground-glass opacities (GGOs) throughout both lungs (arrowheads), despite shrinkage of the primary lung lesion. (**c**) Cellular analysis of bronchoalveolar lavage fluid at 33 days after capmatinib initiation. (**d**) Hematoxylin-eosin staining of a specimen of the right lung revealed mild infiltration of small round inflammatory cells and neutrophils at 33 days after capmatinib initiation.

improvement and was discharged on treatment with prednisolone at 20 mg/day for one month.

Discussion

Capmatinib was approved by the U.S. Food and Drug Administration in May 2020 and by the Ministry of Health, Labor, and Welfare of Japan in June 2020 for the treatment of advanced NSCLC positive for *MET*ex14 skipping mutations.[2] Indeed, increasing evidence supports the use of MET-TKIs in patients with NSCLC harboring such mutations.[1] The increasing application of next-generation sequencing (NGS) to tumor and blood samples has resulted in the relatively frequent identification of *MET*ex14 mutations in individuals with NSCLC.[10–12] These mutations appear to be more frequent in older adults, with age also being a risk factor for ILD.[9,13] As far as we are aware, our report is the first to provide CT and histological evidence for capmatinib-associated ILD as the first line treatment. Another case of capmatinib-induced pneumonitis in a patient who had received prior pembrolizumab treatment has already reported.[14] Recent studies have implicated signaling by hepatocyte growth factor and its receptor (MET) in inhibition of tissue fibrosis. It remains unclear whether MET-TKIs influence such an antifibrotic role, with the mechanism underlying the pulmonary toxicity of MET-TKIs remaining incompletely understood.[15] In a clinical trial of tepotinib, a TKI in the same class as capmatinib, the development of ILD led to permanent drug discontinuation in two patients (1.3%).[3] A recent retrospective review of 1669 patients who received crizotinib, a multikinase TKI that targets MET, in four clinical trials (PROFILE 1001, 1005, 1007, and 1014) reported an overall incidence of ILD of 1.2%, although the incidence was higher at 3.7% in Japanese patients.[16] A higher incidence of drug-induced lung injury has been noted in Japan than in other countries.[9,17] Treatment with corticosteroid should be considered for this condition as appropriate.[9] Although the patient in this report developed steroid-sensitive ILD, it remains possible that MET-TKIs may induce severe acute ILD. Physicians should thus recognize that capmatinib has the potential to cause acute interstitial pneumonia in some patients. The present case highlights the need to identify risk factors and the underlying etiology of ILD in order to develop effective strategies for monitoring of this condition in patients treated with MET-TKIs.

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Disclosure

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