Rapidly progressive squamous cell lung cancer with *MET* exon 14 skipping mutation metastasized to atypical bone sites – a case report

Rychle progredující spinocelulární karcinom plic se skipping mutací *MET* exonu 14 metastazoval do atypických míst v kostech – kazuistika

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Summary

Background: The mesenchymal-epithelial transition factor (MET) exon 14 skipping mutation has recently emerged as a driver gene in non-small cell lung cancer (NSCLC) in clinical practice. Clinical trials of several MET inhibitors have shown the effectiveness of MET inhibitors in NSCLC patients with *MET* exon 14 skipping mutation. To the best of our knowledge, however, there was no patient with sole *MET* exon 14 skipping mutation who progressed rapidly and had a poor prognosis. ***Case:*** A 61-year-old man presented with pain in the dorsum of the left foot and in the left elbow. Chest CT revealed a mass in the right lower lobe of the lung, and FDG-PET showed metastases in the ribs, thoracic vertebra, left elbow, and left metacarpal bone. Corrected calcium level was elevated up to 14.1 mg/dL. The histopathology of the transbronchial biopsy specimen was morphologically consistent with squamous cell carcinoma. *MET* exon 14 skipping mutation was positive in Oncomine Dx Target Test Multi-CDx system. Within a few weeks of admission, the patient's respiratory condition rapidly deteriorated carcinomatous lymphangiosis and died of acute respiratory failure one month after admission. In this patient, bone metastases to atypical sites and hypercalcemia were also observed. ***Conclusion:*** Chest physicians should be noted that there might be rapidly progressive fatal patients among those with *MET* exon 14 skipping mutations.

Keywords

rapid progression – squamous cell lung cancer – *MET* exon 14 skipping mutation – bone metastasis – hypercalcemia

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Souhrn

Východiska: Skipping mutace exonu 14 faktoru mezenchymálně-epiteliální tranzice (MET) byla v klinické praxi nedávno označena jako stěžejní gen u nemalobuněčného karcinomu plic (non-small cell lung cancer – NSCLC). V klinických studiích několika inhibitorů MET byla prokázána jejich účinnost u pacientů s NSCLC se skipping mutací *MET* exonu 14. Pokud je nám ale známo, v těchto studiích nebyl žádný pacient s jedinou skipping mutací *MET* exonu 14, který by rychle progredoval a měl špatnou prognózu. ***Případ:*** Muž ve věku 61 let si stěžoval na bolesti v dorsu levé nohy a v levém lokti. CT hrudníku odhalila masu v pravém dolním laloku plic a FDG-PET prokázala metastázy v žebrech, hrudní páteři, levém lokti a levé metakarpální kosti. Korigovaná hladina vápníku byla zvýšena až na 14,1 mg/dl. Histopatologie vzorků transbronchiální biopsie morfologicky odpovídala spinoceulárnímu karcinomu. Skipping mutace *MET* exonu 14 byla v systému Oncomine Dx Target Test Multi-CDx pozitivní. Během několika málo týdnů po přijetí pacientův stav dýchacího traktu rapidně zhoršil karcinomatózní lymfangiózu a za měsíc od přijetí do nemocnice pacient zemřel na akutní respirační selhání. U tohoto pacienta byly také zjištěny metastázy do netypických míst a hyperkalcemie. ***Závěr:*** Pulmologové by měli mít na paměti, že mezi pacienty se skipping mutacemi *MET* exonu 14 mohou být rychle progredující pacienti s fatálním vývojem onemocnění.

Klíčová slova

rychlá progrese – spinocelulární karcinóm plic – skipping mutace *MET* exonu 14 – kostní metastázy – hyperkalcemie

Introduction

Treatment of advanced non-small cell lung cancer (NSCLC) has dramatically improved due to development of driver gene targeted tyrosine kinase inhibitors (TKIs) [1]. As one of the treatable driver mutations in NSCLC patients, the mesenchymal-epithelial transition factor (MET) exon 14 skipping mutation has recently emerged in clinical practice [2,3]. Clinical trials of several MET inhibitors have shown the effectiveness of MET inhibitors in NSCLC patients with *MET* exon 14 skipping mutation [4,5]. NSCLC patients with *MET* exon 14 skip gene are known to have a higher median age and a higher proportion of patients with a history of smoking than those in NSCLC patients with other driver genes [4,5]. Very recently, rapid progressed case in a NSCLC patient with both *MET* exon 14 skipping mutation and epidermal growth factor receptor (EGFR) exon 20 insertion was reported [6]. It was unclear which driver gene was more involved in the rapid progression of this patient. To the best of our knowledge, however, there was no patient with sole *MET* exon 14 skipping mutation who progressed rapidly and had a poor prognosis. In this patient, we found metastasis to atypical bone sites and hypercalcemia. We show herein a case with a *MET* exon 14 skipping mutation-positive NSCLC patient with pain due to bone metastases in elbow and dorsum of the foot as the first symptom. He had rapid deterioration in a month and had unfortunate outcome. In this driver gene positive patients, there might be patients who progress rapidly. Physicians should be aware of these rare patients.

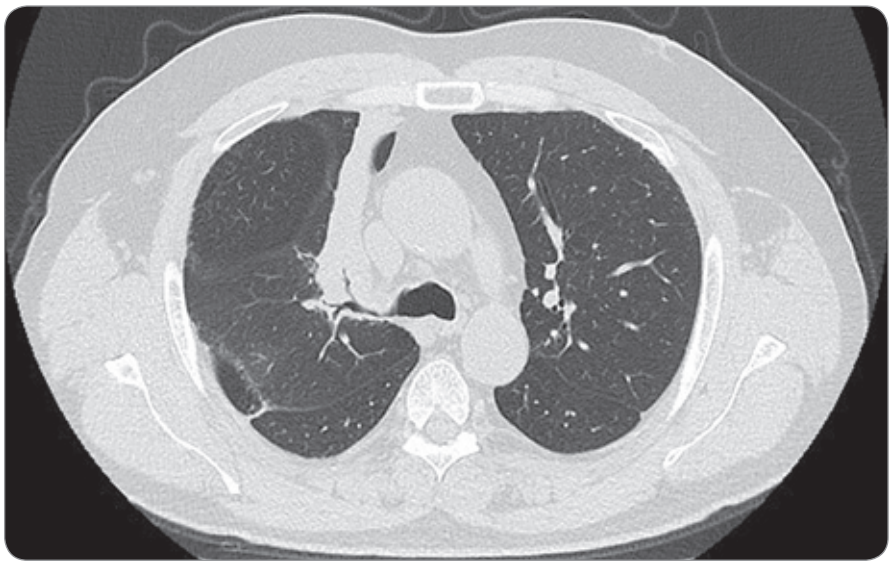

Fig. 1. Chest CT at the time of admission revealed a mass and atelectasis in the right upper lobe of the lung (arrows).

Case report

A 61-year-old man presented with pain in the dorsum of the left foot and in the left elbow. The patient had smoking history with 39 pack-year, but he had no asbestos exposure. Physical examination was unremarkable and his performance status (PS; Eastern Cooperative Oncology Group) at admission was 1. Chest CT revealed a mass and atelectasis in the right upper lobe of the lung (Fig. 1), and FDG-PET showed metastases in the ribs, thoracic vertebra, left elbow, and left metacarpal bone (Fig. 2). Albumin-corrected calcium level was elevated up to 14.1mg/dL. The histopathology of the transbronchial biopsy specimen obtained from the right lower lobe was morphologically consistent with squamous cell carcinoma. The EGFR gene mutation, *ALK* fusion gene, *ROS1* fusion gene, and *BRAF* gene mutation were all negative. But *MET* exon 14 skipping mutation was positive in Oncomine Dx Target Test Multi-CDx system. His clinical stage was T4N2M1c stage IVB. Since the pain in the left foot and elbow was strong, oxycodon was administered. In addition, treatment of hypercalcemia was started with zoledronic acid, saline infusion, and diuretics. Within a few

weeks of admission, the patient's general condition rapidly deteriorated to PS of 3. In addition, decreased permeability of both lung fields in chest radiograph, which was due to deterioration of carcinomatous lymphangiosis, and rapid exacerbation of respiratory condition appeared. The patient was unable to receive MET inhibitor treatment due to the rapid deterioration of his general condition but also negative result of Archer MET, a test used for companion diagnostics. He died of acute respiratory failure one month after admission. Autopsy was not permitted.

Discussion

In some driver genes of NSCLC, there are drugs that act specifically on their respective molecular target sites [7]. Patients treated with such drugs often have a long term of response. However, not all the patients who received TKI responded, and some patients did not [8,9]. In EGFR mutation and *ALK* fusion gene, patients with rapid progression despite administration of specific drugs have been reported [10,11]. On the other hand, there have been reports of lung cancer patients who rapidly worsened and died even though their condition were not poor at the first reference [12,13]. However, most of them were patients with negative driver genes or those with uncommon histopathological malignancies [12,13]. In our patient, *MET* exon 14 skipping mutation was positive in Oncomine Dx Target Test Multi-CDx system. But Archer MET, a test used for companion diagnostics, was negative. Therefore, specific TKI could not be administered. Due to the progression of respiratory failure, which is thought to be due to the progression of cancerous lymphangiopathy of the lung, only supportive therapies had to be performed.

In our patient, hypercalcemia was observed, and it was possible to be a functioning tumor. It is well known that lung cancer patients with paraneoplastic syndrome including hypercalcemia have poor prognosis [14–18]. Most of the histological types of lung cancer presenting with hypercalcemia have been squamous cell lung cancer [15], which was the same histopathological type as confirmed in our patient. Hypercalcemia in lung cancer patients has also been reported in those with bone metastases in various sites, and this hypercalcemia has been often observed in patients with lung adenocarcinoma [19,20]. In our patient, metastases were present in two ribs, forearms, and metatarsals, and it was possible that hypercalcemia was related to bone metastases [21]. Measurement of parathyroid hormone-related peptide was not performed, but if it was, it was highly possible that a meaningful value might be obtained.

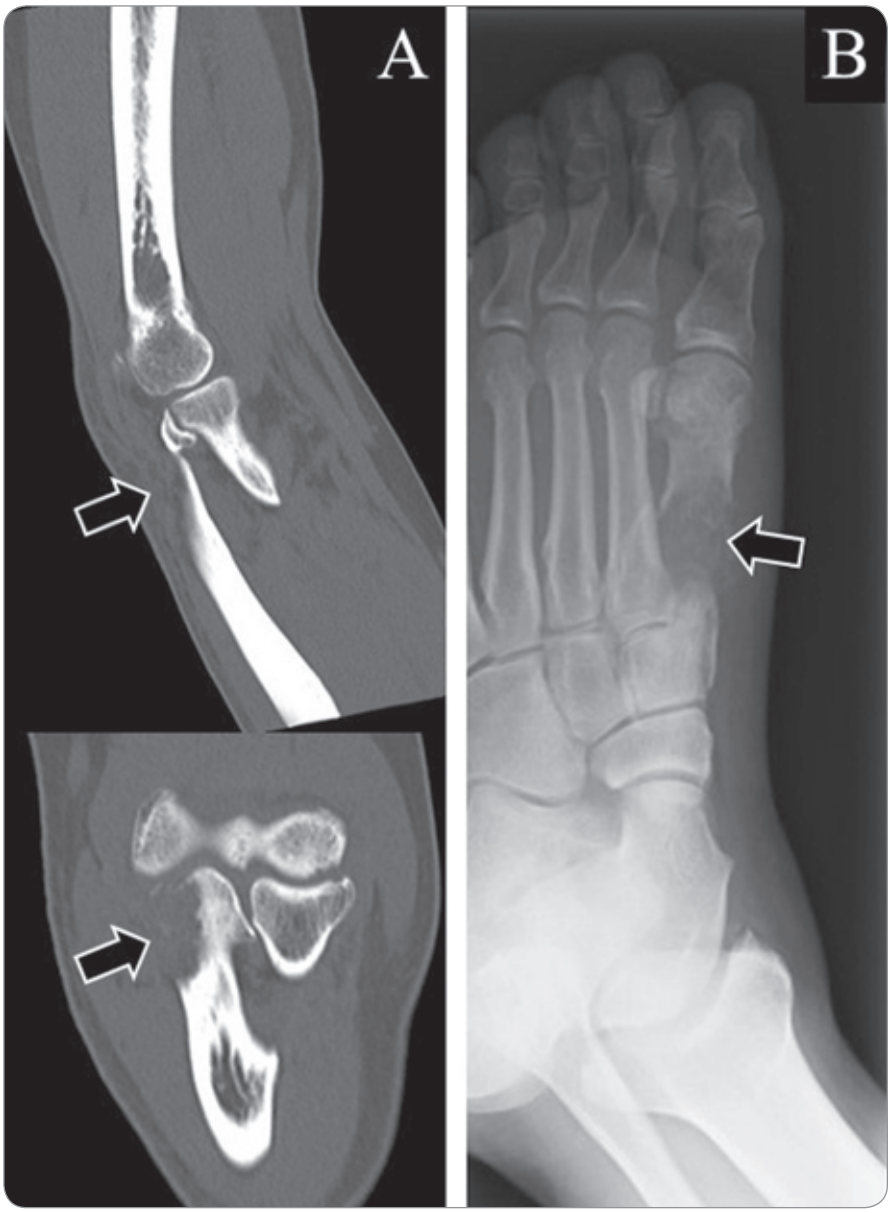

Fig. 2. CT scan showed an osteolytic change (arrows) in radius (A) and left metatarsal bone (B) due to bone metastasis.

Bone metastasis frequently develops in bones near the primary lesion in relation to blood flow. Therefore, NSCLC patients metastasize to the vertebrae and rib, but rarely metastasize to the metacarpal bone and elbow [23–25]. Patients with systemic dissemination might develop bone metastases away from the primary site throughout the body [26]. Our patient developed bone metastases to atypical sites, but as he had no metastases to other organs, therefore, he was evaluated not to be in a dissemination state. In patient with *MET* exon 14 skipping mutation, bone metastasis in such

uncommon bone sites might occur in patients without dissemination.

Very recently, Jiao et al reported a case of a 33-year-old NSCLC patient with *MET* exon 14 skipping mutation, who also harbored a somatic EGFR exon 20 insertion. They reported that the overall survival of this patient was 9 months [6]. This patient had bone metastases, but the metastatic sites were T8 and T12 vertebral bones. The patient had no paraneoplastic syndrome including hypercalcemia. At present, exon 20 insertion is one of the types of EGFR mutated NSCLC that is difficult to treat and is associated with a poor prognosis [27]. Therefore, it was quite possible that EGFR exon 20 insertion was involved in the poor prognosis of this patient. Our patient was negative for EGFR mutation and other driver genes. There was such a difference between the patient reported by Jiao et al and ours. However, the presence of their patient and ours might suggest the possibility of rapid progression in some patients with *MET* exon 14 skipping mutation.

Conclusion

NSCLC patients with *MET* exon 14 skipping mutations might include patients with rapid progression as observed in our patient. Such aggressive progression might associate with bone metastases to atypical sites and hypercalcemia. Chest physicians should be noted that there might be rapid progressive fatal patients among those with *MET* exon 14 skipping mutations. It is desired that effective treatments would be established for these patients with poor prognosis.

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Authors' contributions

NK and SH designed the study, NK, HS, KY, SY, and SH collected the data. NK, KY and SH prepared the manuscript. All authors approved the final version of the article.

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