A case of ROS1-rearranged lung adenocarcinoma with osteoblastic bone metastasis

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A B S T R A C T

A 53-year-old woman was referred to our hospital for detailed examination of abnormal chest shadows recognized on CT imaging. Transbronchial lung biopsy of a right S6 nodular shadow led to a diagnosis of lung adenocarcinoma. FDG-PET-CT showed FDG accumulation in the Th11 and L2 vertebral bodies and osteoblastic bone lesions. Since osteoblastic bone metastasis in lung cancer is extremely rare, CT-guided bone biopsy was performed. The tumor was diagnosed as ROS1-rearranged lung adenocarcinoma, for which crizotinib was administered, which led to improvement of both the primary and metastatic lesions. We report here a rare case of ROS1-rearranged lung adenocarcinoma with osteoblastic bone metastasis of lung cancer.

1. Introduction

Most bone metastasis of lung cancer generally have osteolytic changes, with osteogenic changes being a result of their therapeutic responses. Additionally, it is extremely rare for osteoblastic bone metastasis to be observed at the first visit, which has been reported in only a few cases in patients of lung cancer [1–3].

We report a case of ROS1-rearranged lung adenocarcinoma with an osteoblastic metastatic tumor diagnosed by bone biopsy at the first visit, which improved with crizotinib administration.

2. Case report

A 53-year-old Japanese woman was referred to our hospital in November 20XX for detailed examination of abnormal chest shadows on computed tomography (CT) scan.

She had mild right back pain for one month before her visit.

She had a family history of laryngeal cancer in her father. Her medical history was unremarkable, and she had no smoking history.

Physical examination on admission revealed a blood pressure of 128/74 mmHg, pulse rate of 78 beats per minute, temperature of 36.2 °C, and percutaneous oxygen saturation of 98% on room air. Her neck was supple. Her cardiovascular examination was normal and breath sounds were clear. Her neurological examination was completely normal and no skin lesions were observed.

Laboratory findings (Table 1) showed an elevated level of serum C-reactive protein (1.04 mg/dL). Her serum levels of electrolytes, creatinine, blood urea nitrogen and tumor markers were normal.

Chest CT showed an irregularly shaped nodule 24 mm in maximum diameter in the S9 region, consolidation in the S6 region of the right lung, and osteoblastic bone lesions in Th11 and L2 (Fig. 1).

Fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT) scan demonstrated strong FDG uptake in the primary lung lesion (maximal standard uptake value (SUVmax = 6.64)) and mild FDG uptake in the Th11 and L2 vertebral lesions (SUVmax = 3.13, 2.54) (Fig. 2). There was no significant accumulation in the area of consolidation in the right lower lobe (SUVmax = 1.64) (Fig. 3). Transbronchial lung biopsy of the nodular shadow in the S9 segment of the right lung

Table 1

Laboratory data on admission.

Hematology		Serology	
WBC	7350/μL	CRP	1.04 mg/dl
Neut	64.8%	KL-6	220 U/mL
Lym	23.8%	AN-A	(−)
Eos	4.4%		
RBC	$441 \times 10^4/μL$		
Ht	39.7%	Tumor markers	
Hb	13.3 g/dl	CEA	0.7 ng/mL
PLT	$29.3 \times 10^4/μL$	SCC	0.6 ng/mL
		CYFRA	<1 ng/mL
Biochemistry		Pro-GRP	55 pg/mL
AST	11 U/L		
ALT	11 U/L		
ALP	229 U/L		
LDH	133 U/L		
BUN	13 mg/dL		
CRE	0.5 mg/dL		
Alb	4 g/dl		
Ca	9.2 mg/dL		
Na	142 mEq/L		
K	4 mEq/L		
Cl	105 mEq/L		

was performed. Histological examination of the lung revealed invasive adenocarcinoma (Fig. 4). Both epidermal growth factor receptor (EGFR) gene and anaplastic lymphoma kinase (ALK) mutations of the tumor were negative, and programmed cell death ligand-1(PD-L1) protein immunostaining (22C3) of the tumor showed a tumor proportion score (TPS) of 60%.

PET-CT showed mild FDG accumulation in the Th11 and L2 vertebral bodies and osteoblastic bone lesions, indicating the extremely rare finding of bone metastasis of lung cancer at the first visit.

CT-guided bone biopsy of the Th11 osteoblastic lesions was additionally performed. Histological examination of the bone lesions (Fig. 5) showed metastasis of tumor cells between the trabecular bones in the bone sclerosis area. Immunohistologically, the cancer cells were confirmed to be positive for *anti*-cytokeratin (CK) antibodies (AE1/AE3) and thyroid transcription factor-1 (TTF-1), leading to a diagnosis of metastasis of lung adenocarcinoma. Interestingly, the right lung

infiltrative shadow observed on chest CT at admission underwent spontaneous remission. According to the imaging findings and clinical course, organizing pneumonia was diagnosed. No brain metastases were detected on brain enhanced MRI. The clinical tumor stage was determined as cT1cN1M1b cStage IVa, and pembrolizumab was administered as primary treatment.

While being treated with pembrolizumab, although, there was no significant increase in her primary tumor, her bone metastasis grew. Due to her lung tumor having ROS1-rearrangement, we decided to switch her to crizotinib (250 mg every 12 hours). This led to significant reduction in both her primary and bone metastasis. (Fig. 6). Crizotinib administration is still ongoing without any serious side effects.

3. Discussion

Osteoblastic bone lesions may be common in prostate cancer [4], but is extremely rare at the initial diagnosis of lung cancer.[1]The incidence of osteoblastic bone metastasis of lung cancer varies from 1.2% to 25% according to autopsy reports [5–7]. This wide variation in reported incidence is thought to be because there are no clear standard criteria to differentiate between osteoblastic and osteolytic bone metastases. In addition, the majority of autopsy cases might have had osteogenesis as part of the therapeutic response, which would result in osteoblastic lesions in bone metastasis.

However, no previous report has shown the frequency of lung cancer presenting with osteoblastic bone metastasis at the first visit.

Reportedly, tumor cells can disrupt normal bone remodeling, leading to osteolytic bone metastasis if osteoclasts predominate, and osteoblastic bone metastasis if osteoblastic bone formation predominates [4]. Garfield et al. reported that bronchoalveolar carcinoma might develop more osteoblastic bone metastases than normal lung cancer [8].

In slow-growing tumors, such as well-differentiated adenocarcinoma, bone formation by normal bone tissue, occurring as a protective response, predominates over bone destruction caused by the tumor, which might result in osteoblastic bone metastasis. Not all osteoblastic bone lesions are caused directly by slow-growing tumor. In prostate cancer, it is thought that osteoblastic lesions formation occurs due to production of insulin-like growth factor (IGF) [9], fibroblast growth factor (TGF-β) [10], transforming growth factor β (TGF-β) [10], bone
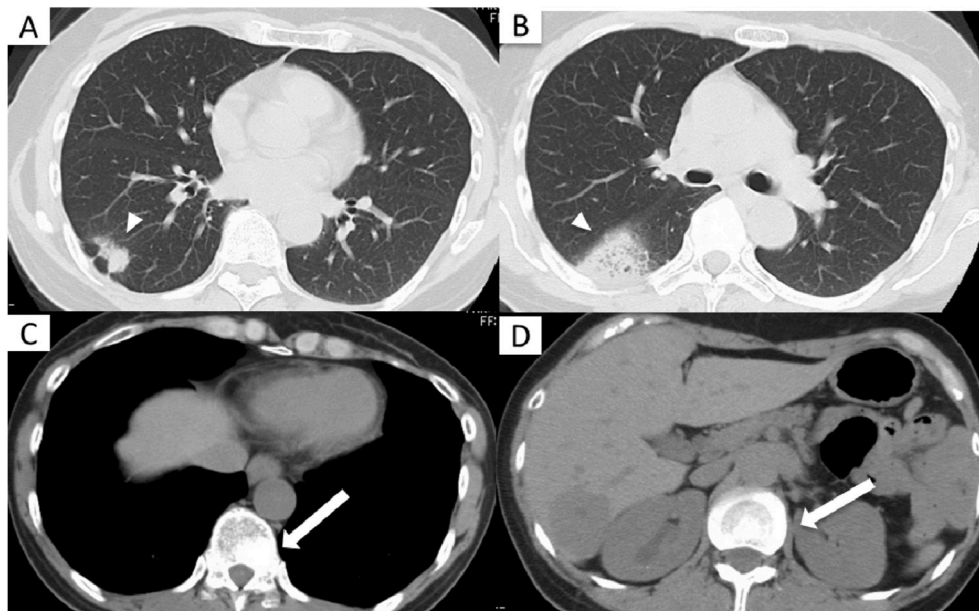
Fig. 1. Chest CT on admission

Chest CT showed an irregularly shaped nodule 24 mm in maximum diameter in the S9 region and consolidation in the S6 region of the right lung (arrowheads) (A, B: lung windows), along with osteoblastic bone lesions in Th11 and L2 (arrow) (C, D: soft-tissue windows).
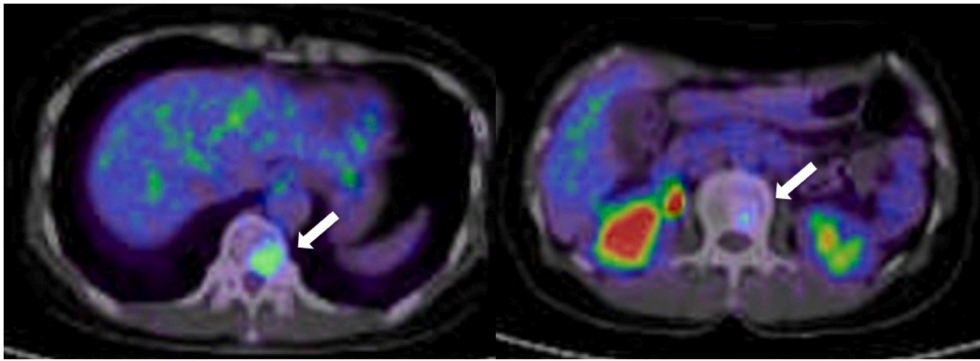
Fig. 2. FDG-PET/CT of lung lesions
Fluorodeoxyglucose was concentrated in the primary lung lesions (*arrow*).
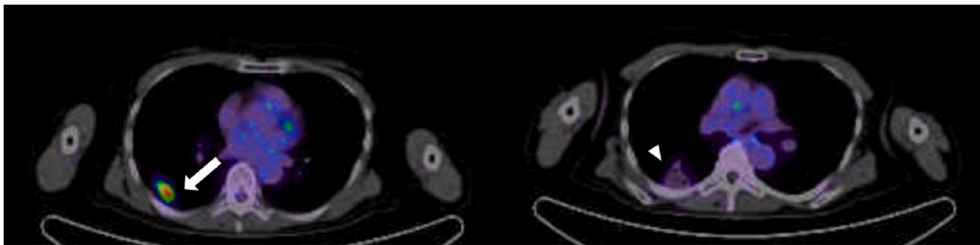There was no significant accumulation in the area of consolidation in the right lower lobe (*arrowheads*).

Fig. 3. FDG-PET/CT of the metastatic vertebral lesions of lung cancer
Fluorodeoxyglucose was mildly concentrated in the Th11 and L2 vertebral lesions (*arrows*).
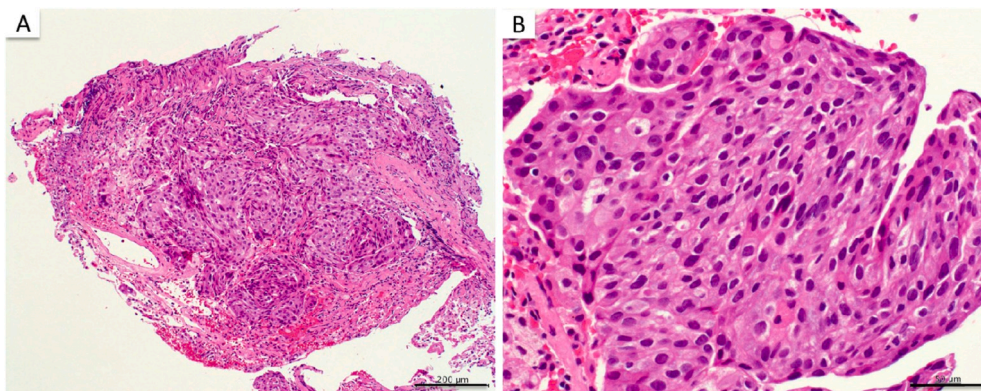

Fig. 4. Histological examination of the lung
Tumor cells showed invasive growth with a partial glandular arrangement in the right S9 segment [(A): Hematoxylin and eosin (H&E) staining, bar: 200 μm], [(B): H&E staining, bar: 50 μm].

morphogenetic protein (BMP), endothelin (ET)-1[11], and platelet-derived growth factor (PDGF) [12,13]. In lung cancer, excessive VEGF production from the tumor cells have been implicated in promoting osteoblastic lesions [14]. Although, the mechanism for osteoblastic formation in lung cancer is not fully understood, it may be due to a combination of tumor growth and osteoblastic promoting factors. Furthermore, the present case was found to have both ROS1-rearrangement and a high TPS score due to PD-L1 expression. The frequency of PD-L1 expression in non-small cell lung cancers with a driver mutation is equivocal.

It has been reported that EGFR gene and ALK fusion gene mutation are occasionally seen in lung adenocarcinoma, resulting in a TPS score of 50% or more, which means that EGFR gene and ALK fusion gene mutation and PD-L1 expression are not mutually exclusive [15].

There are reports that ROS1 and PD-L1 expression are mutually

exclusive [16]. On the other hand, Jongmin et al. reported that high PD-L1 expression frequently overlaps with ROS1 rearrangement [17]. No consensus has been reached regarding PD-L1 expression and driver mutations in lung adenocarcinoma.

To the best of our knowledge, this is the first case report of ROS1-rearranged lung cancer with osteoblastic bone metastasis. It remains uncertain whether or not ROS1-rearranged lung cancer is more likely to cause osteoblastic bone metastases than normal lung cancer.

In future, we wish to clarify the bone metastasis pattern and its correlation with PD-L1 expression in ROS1-rearranged lung cancer by evaluating a larger number of similar cases.

In conclusion, we report a case of ROS-1 rearranged lung adenocarcinoma with osteoblastic bone metastasis. The association between ROS-1 rearrangement and osteoblastic bone metastasis is still uncertain. Further studies and bone tissue biopsies in patients with lung cancer
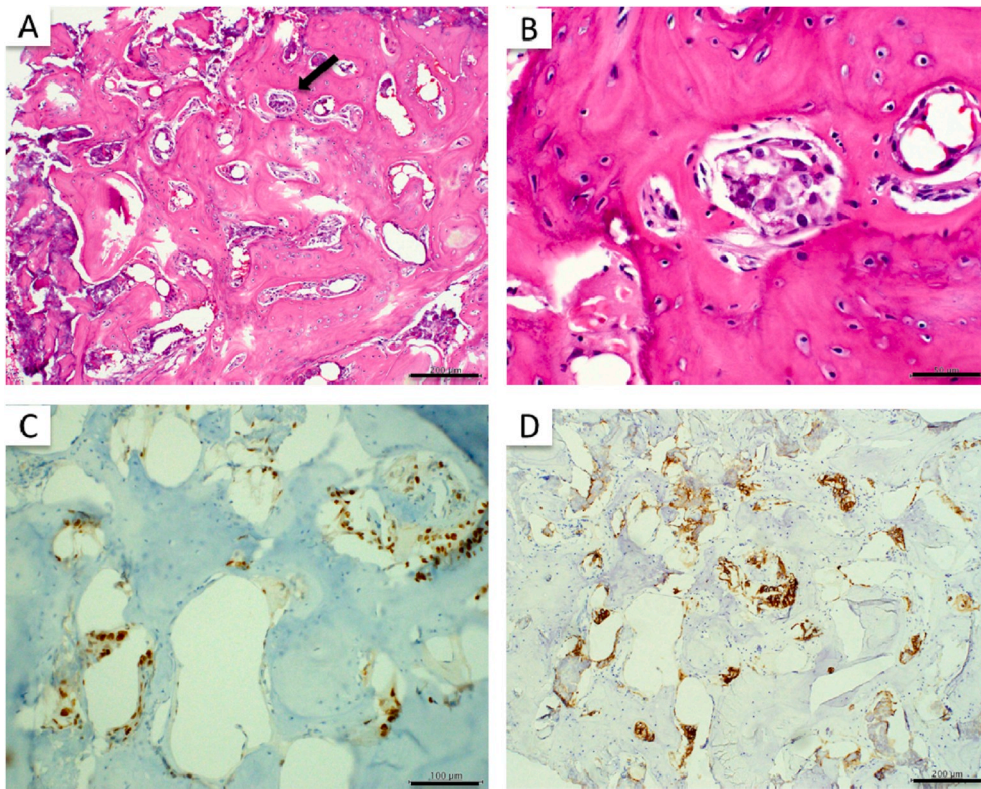
Fig. 5. Histological examination of the metastatic bone tumor.

Tumor cells were observed between the trabecular bones in the bone sclerosis area (*arrows*)

Immunohistochemical analysis showed that the tumor cells were positive for TTF-1 and CK7. [(A): H&E staining, bar: 200 μm], [(B): H&E staining, bar: 50 μm], [(C): TTF-1 staining, bar: 100 μm], [(D): CD7 staining, bar: 200 μm].
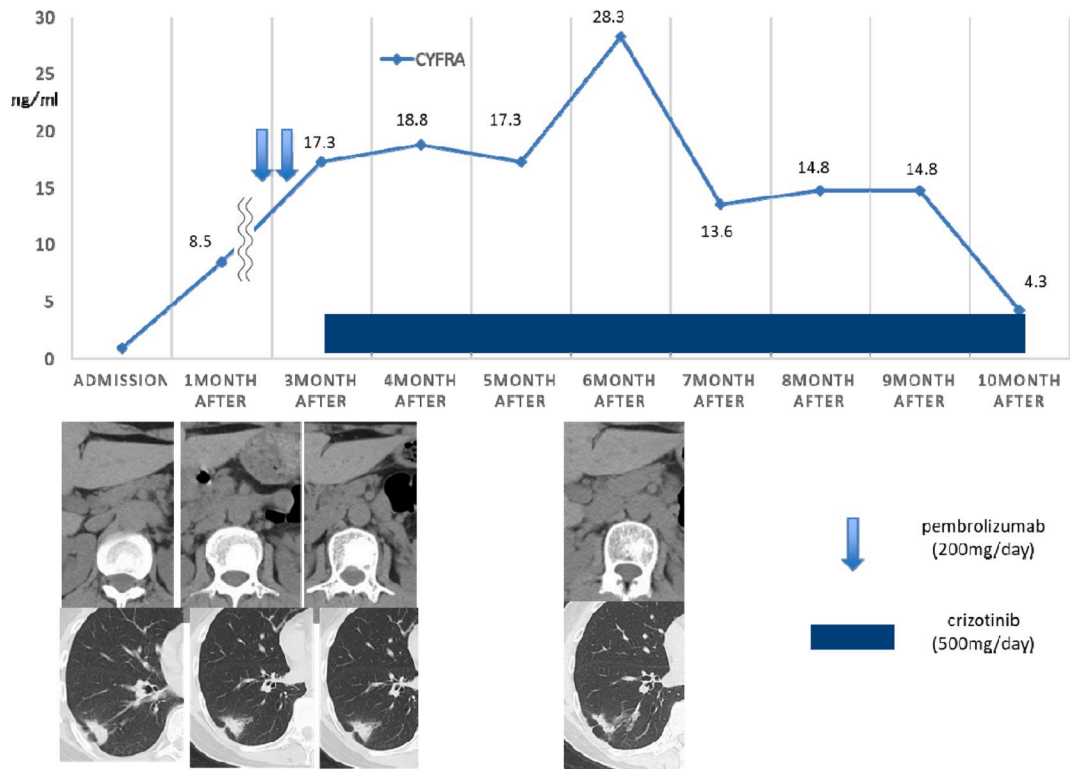

Fig. 6. Patient's clinical course

The clinical course, laboratory data, radiological findings and treatment of the present case.

with tumor driver mutation are critically important to identify this phenomenon.

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