Clinical activity of crizotinib in lung adenocarcinoma harboring a *HLA_A-ROS1* rearrangement: A case report

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Abstract. The benefits of crizotinib therapy in patients with tyrosine receptor kinase ROS proto-oncogene 1 (*ROS1*)-rearranged non-small cell lung cancer (NSCLC) have been demonstrated. The present study reports a 47-year-old woman with lung adenocarcinoma harboring a rare *HLA_A-ROS1* rearrangement with clinical response to crizotinib. To the best of our knowledge there have been no reports of *HLA_A-ROS1*-rearranged lung cancer regarding clinical course and the efficacy of treatment with crizotinib. A good response to crizotinib therapy in the present case could be a reference for the treatment and prognosis of *ROS1*-rearranged NSCLC with the same fusion partner. The current report will remind oncologists and pulmonologists to consider the importance of accurate multigene panel assays for detecting driver oncogenes in treating patients with NSCLC.

Introduction

Targeted therapy is efficient for patients with advanced non-small cell lung cancer (NSCLC) with related gene mutations, highlighting the importance of actively searching for mutations. Tyrosine receptor kinase ROS proto-oncogene 1 (*ROS1*) rearrangements occur in 1-2% of patients with non-small cell lung cancer (NSCLC) (1). Crizotinib is a tyrosine kinase inhibitor (TKI) that targets the anaplastic lymphoma kinase gene (*ALK*) or *ROS1* kinase domain and is considered the standard of care for metastatic NSCLC who were positive for *ROS1* fusion gene. Although the frequency of *ROS1* rearrangements in lung cancers is low, the efficient determination of *ROS1* status in patients with NSCLC is critical for directing patient care. Here we report the case of a patient with NSCLC harboring a rare *HLA_A-ROS1* rearrangement, who showed a clinical response to crizotinib.

Case report

A 47-year-old Japanese woman with dyspnea for 2 months was referred to our hospital. She had no relevant history except for light smoking. Chest radiography analysis revealed a mass in the right upper lung field. Computed tomography (CT) analysis revealed a 7.0 cm mass in the right upper lobe with mediastinal invasion, contralateral mediastinal lymphadenopathy and a left adrenal gland tumor. Bronchoscopy analysis revealed a polypoid tumor at the orifice of the right upper lobe bronchus and a transbronchial biopsy was performed. Pathological examination showed primary lung adenocarcinoma with hepatoid cytology and signet cells (Fig. 1A and B). According to the 7th edition of TNM staging, the patient was classified as having stage IVB lung adenocarcinoma (T4aN3M1b). Mutation status was negative for *EGFR*, *ALK*, *BRAF*, and *ROS1*; the OncoGuide AmoyDx ROS1 gene fusion detection kit was used to detect ROS1 rearrangement. Programmed death-ligand 1 expression with a tumor proportion score of 5% was confirmed by immunohistochemistry analysis using 22C3 antibody. She was treated with radiation therapy for the primary lesion (50 Gy/20 Fr) as well as chemotherapy (carboplatin plus pemetrexed), which was followed by pemetrexed maintenance therapy. After 15 cycles of maintenance therapy, mediastinal lymphadenopathy was newly detected and pembrolizumab monotherapy was initiated as the second-line therapy. During the treatment, as the Oncomine CDx Target Test (Oncomine DxTT) was newly covered by insurance as a multigene panel assay for NSCLC in Japan, the residual specimen was subjected to Oncomine DxTT and *HLA_A-ROS1* rearrangement was detected. After 21 cycles of pembrolizumab monotherapy (Fig. 2), the CT

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Abbreviations: ALK, anaplastic lymphoma kinase gene; BRAF, V-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; CT, computed tomography; NSCLC, non-small cell lung cancer; Oncomine DxTT, Oncomine CDx Target Test; RET, rearranged during transfection; ROS1, tyrosine receptor kinase ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor

Key words: crizotinib, *HLA_A-ROS*1, Lung adenocarcinoma, multigene panel assay

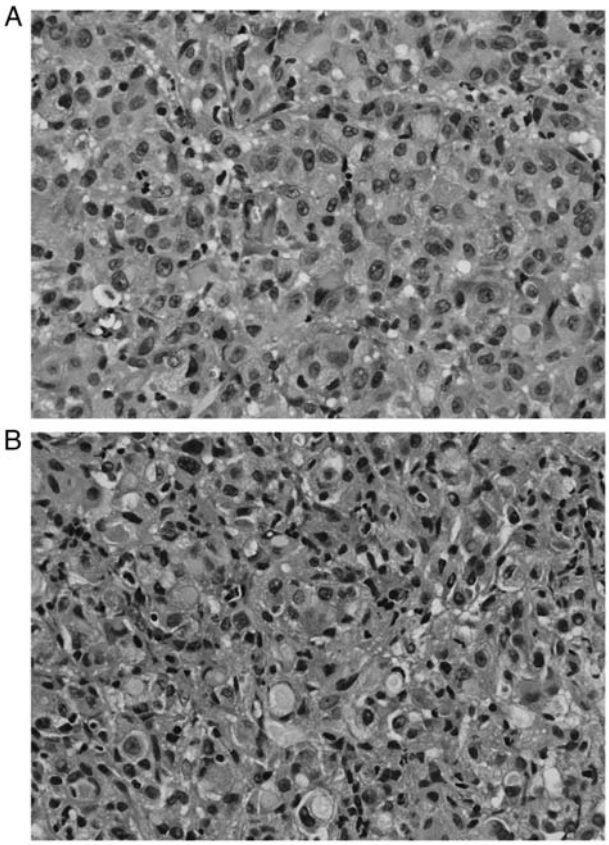

Figure 1. Pathological findings of bronchoscopic specimen. Pathological findings showed (A) hepatoid cytology and (B) signet-ring cells (hematoxylin and eosin stain; magnification, x400).

scan showed left supraclavicular lymphadenopathy (Fig. 3 A and B), and the patient was administered crizotinib therapy as the third-line therapy. She achieved a partial response as defined by the Response Evaluation Criteria in Solid Tumors version 1.1. Currently, cancer has been stable for over 16 months and patient follow up is ongoing (Fig. 3C and D).

Discussion

This is the first case report of a patient with lung adenocarcinoma harboring an *HLA_A-ROS1* rearrangement with a clinical course and response to crizotinib. To our knowledge, there is only one case report of *HLA_A-ROS1* rearrangement in melanoma (2). *HLA_A-ROS1* rearrangement was generated by the fusion of exon 34 of *ROS1* located on the long arm of chromosome 6 with exon 7 of *HLA_A* located on the short arm of chromosome 6 (Fig. 4). *ROS1*-rearranged NSCLC was majorly observed in young females with no or light smoking history (3). Currently, more than 34 *ROS1* fusion partner genes have been reported in NSCLC, including *CD74*, *SDC4*, *EZR*, and *SLC34A2* (4). In Japan we previously often used the OncoGuide AmoyDx ROS1 gene fusion detection kit to detect *ROS1* rearrangements including those in major partner genes (5,6); however, this single gene testing was unable to detect *HLA_A-ROS1* rearrangement. Pathologically, *ALK*- and *ROS1*-rearranged lung adenocarcinomas often show a solid growth pattern and possess hepatoid cells and signet ring cells (7). These pathological features are the indicators of *ALK* and *ROS1* rearrangement status in NSCLC. Hence, an additional multigene panel assay should be considered for patients suspected of carrying driver oncogenes based on patient background and pathological patterns even if single gene tests were negative.

Crizotinib is a potent TKI for *ALK*, *ROS1*, and mesenchymal-epithelial transition mutation-positive NSCLC. A previous study showed that crizotinib was associated with an overall response rate of 72% and a median progression-free survival of 19.3 months in advanced *ROS1*-rearranged NSCLC (8). The efficacy of crizotinib varies depending on *ROS1* fusion partner (9). A previous study showed that the patients carrying *non-CD74-ROS1* fusions could get better prognostic outcomes than those with *CD74-ROS1* fusions by crizotinib treatment (10). Hicks *et al* reported that a patient with lung adenocarcinoma harboring a rare *ZCCHC8-ROS1* fusion who responded to crizotinib showed progression-free survival of 7 months and total duration of treatment of 15 months (11). The dramatic response to crizotinib therapy in this case may be a reference for the treatment and prognosis for NSCLC with the same fusion partner.

In conclusion, this report describes a case of advanced lung adenocarcinoma harboring an *HLA_A-ROS1* rearrangement with a dramatic response to crizotinib therapy. The information presented in our report highlights to oncologists and pulmonologists the importance of accurate multigene panel assays in detecting driver oncogenes for treating patients with NSCLC.

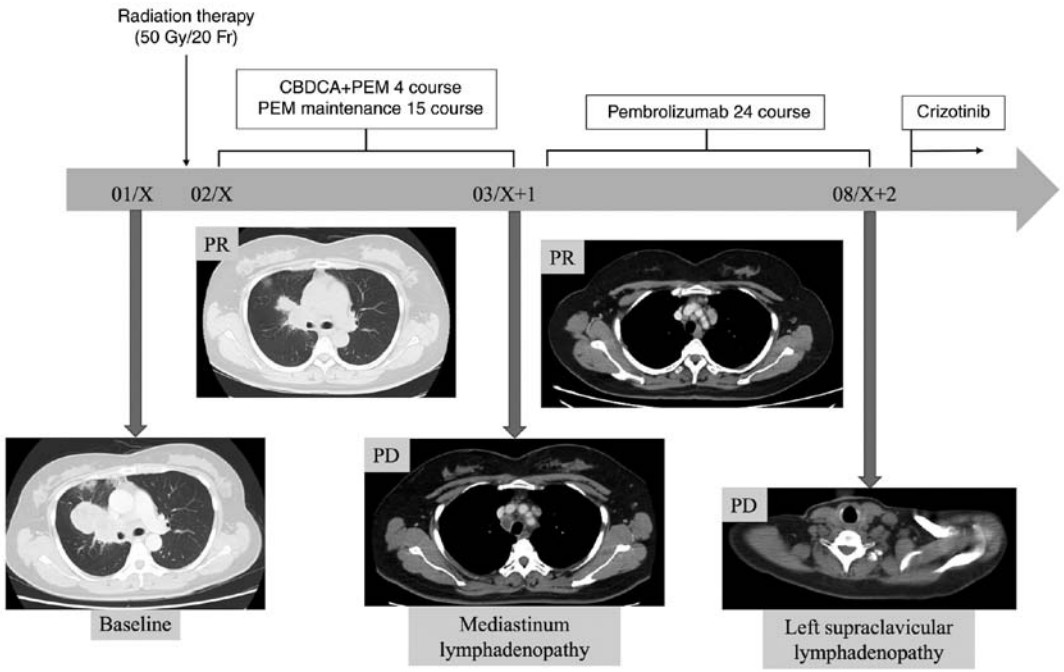

Figure 2. Treatment scheme and representative computed tomography scan images during treatment courses. CBDCA, carboplatin; PEM, pemetrexed; PR, partial response; PD, progressive disease.

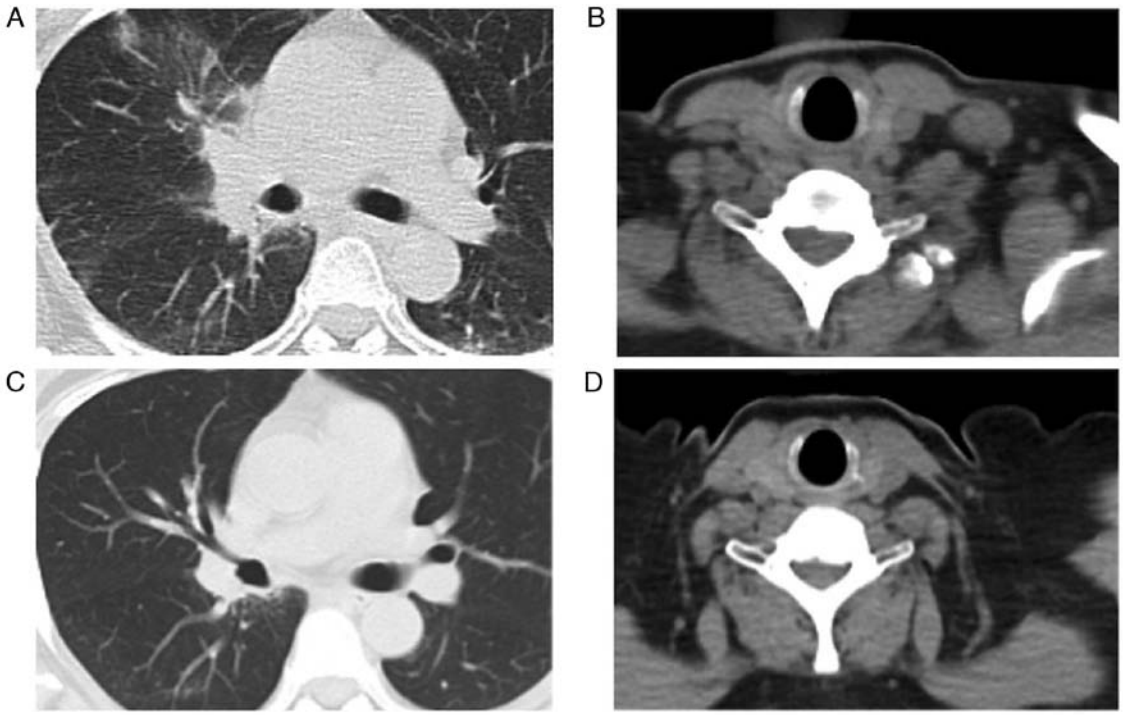

Figure 3. Thoracic imaging findings at the start of crizotinib therapy and 16 months after crizotinib therapy. Chest CT scan showed (A) primary lung tumor in right upper lobe and (B) left supraclavicular lymphadenopathy at the start of crizotinib therapy. Chest CT scan showed (C) shrinkage of tumor in the right upper lobe and (D) disappearance of left supraclavicular lymphadenopathy at 16 months after crizotinib therapy. CT, computed tomography.

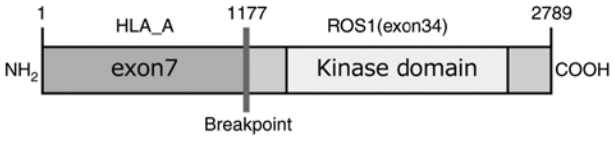

Figure 4. Predicted gene structure map. Transcript results of *HLA_A* exon 7 N-terminal coiled-coil domain fused to *ROS1* exon 34, which includes the *ROS1* kinase domain. ROS1, tyrosine receptor kinase ROS proto-oncogene 1.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RK analyzed and interpreted the patient lung cancer data and majorly contributed to writing the manuscript. MN interpreted the data and assisted in the preparation of the manuscript. HK, SH, MS and YH coordinated the clinics, performed the treatment, participated in the follow-up of the patients, obtained specimens and acquired data. MK, NT and HM made substantial contributions to conception and design and edited the manuscript. All authors read and approved the final manuscript. RK and MN confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was provided by the patient.

Patient consent for publication

The patient provided written informed consent for the publication of the data.

Competing interests

The authors declare that they have no competing interests.

References

1. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, Nardone J, Lee K, Reeves C, Li Y, *et al*: Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 131: 1190-1203, 2007.
2. Wiesner T, He J, Yelensky R, Esteve-Puig R, Botton T, Yeh I, Lipson D, Otto G, Brennan K, Murali R, *et al*: Kinase fusion are frequent in Splitz tumors and spitzoid melanomas. Nat Commun 5: 3116, 2014.
3. Shaw AT, Ou SHI, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, *et al*: Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371: 1963-1971, 2014.
4. Gendarme S, Bylicki O, Chouaid C and Guisier F: ROS-1 fusions in non-small-cell lung cancer: Evidence to date. Curr Oncol 29: 641-658, 2022.
5. Wu J, Lin Y, He X, Yang H, He P, Fu X, Li G and Gu X: Comparison of detection methods and follow-up study on the tyrosine kinase inhibitors therapy in non-small cell lung cancer patients with ROS1 fusion rearrangement. BMC Cancer 16: 599, 2016.
6. Ke W, Xu Z and Xue L: ROS1 gene rearrangement and clinicopathological characteristics in Chinese NSCLC patients. Int J Clin Exp Pathol 9: 5594-5599, 2016.
7. Zhao J, Zheng J, Kong M, Zhou J,Ding W and Zhou J: Advanced lung adenocarcinomas with ROS1-rearrangement frequently show hepatoid cell. Oncotarget 7: 74162-74170, 2016.
8. Shaw AT, Riety GJ, S, Bang YJ, Kim DW, Camidge DR, Solomon BJ, Varella-Garcia M, Iafrate AJ, Shapiro GI, Usari T, *et al*: Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): Updated results, including overall survival, from PROFILE 1001. Ann Oncol 30: 1121-1126, 2019.
9. Zhang Y, Zhang X, Zhang R, Xu Q, Yang H, Lizaso A, Xu C, Liu J, Wang W, Ou SHI, *et al*: Clinical and molecular factors that impact the efficacy of first-line crizotinib in ROS1-rearranged non-small-cell lung cancer: A large multicenter retrospective study. BMC Med 19: 206, 2021.
10. Li Z, Shen L, Ding D, Huang J, Zhang J, Chen Z and Lu S: Efficacy of crizotinib among different types of ROS1 fusion partners in patients with ROS1-rearranged non-small cell lung cancer. J Thorac Oncol 13: 987-995, 2018.
11. Hicks JK, Boyle T, Albacker LA, Madison R, Frampton G and Creelan BC: Clinical activity of crizotinib in lung adenocarcinoma harboring a rare ZCCHC8-ROS1 fusion. J Thorac Oncol 13: e148-e150, 2018.