ROS1-rearranged high-PD-L1-expressing lung adenocarcinoma manifesting as mediastinal tumor: A case report

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Abstract. ROS proto-oncogene 1 receptor tyrosine kinase (ROS1)-rearranged lung cancer is rare and comprises only 1% of lung adenocarcinoma cases. It has recently been reported to have good response to crizotinib, a tyrosine kinase inhibitor of anaplastic lymphoma kinase. Driver oncogene mutations with approved therapies seldom coexist with a high expression of Programmed death-ligand 1 (PD-L1). The present case report describes a rare case of ROS1 rearrangement with high-PD-L1-expressing occult lung adenocarcinoma. A 32-year-old woman presented with chest pain and a prolonged cough. Chest computed tomography (CT) revealed a 57x36-mm tumor in the mediastinum, with no tumors detected in other regions. Positron emission tomography (PET)-CT showed a strong fluorodeoxyglucose accumulation in the tumor (SUVmax 13.2). Mediastinal tumor resection was completely resected using a video-assisted thoracic surgery approach. Pathological examination showed the tumor cells were positive for thyroid transcription factor 1, Napsin-A, ROS1, and PD-L1 (tumor proportion score >99%). ROS1 rearrangement was confirmed by fluorescence *in situ* hybridization. The mediastinal tumor was diagnosed as mediastinal lymph node metastasis of ROS1-rearranged PD-L1 high-expression undifferentiated lung adenocarcinoma (pathological stage 3, TxN2M0). Two months after the operation, the CT scan showed multiple mediastinum lymph nodes metastases with rapid tumor growth. The patient achieved a complete response after three cycles of S-1 plus cisplatin with concurrent radiotherapy 60 Gy/30 Fr.

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Introduction

The c-ros oncogene 1 (ROS1)-rearranged lung cancer is rare and comprises only 1 to 2% of patients with non-small cell lung cancer (NSCLC), and there were approximately 15,000 new patients with NSCLC each year considered to be driven by ROS1 rearrangement (1). The ROS1-rearranged lung cancer was recently reported to have good response to crizotinib, a tyrosine kinase inhibitor of anaplastic lymphoma kinase (2,3).

Case report

A 32-year-old woman presented with chest pain and a prolonged cough. She had a smoking history of 2.5 pack years. Chest computed tomography (CT) revealed a 57x36-mm tumor in the mediastinum, with no tumors detected in other regions (Fig. 1A). Positron emission tomography (PET)-CT showed a strong fluorodeoxyglucose (FDG) accumulation in the tumor (SUVmax 13.2) (Fig. 1B). Mediastinal tumor resection was planned by a video-assisted thoracic surgery approach. No signs of macroscopic tumor invasion to the right lung or superior vena cava were noted during surgery (Fig. 1C). The tumor was completely resected. Pathological examinations revealed the tumor to be 53x37 mm (Fig. 1D), and H&E staining of the tumor cells showed a solid, alveolar pattern of proliferation (Fig. 1E). Immunohistochemistry revealed the tumor cells as positive for TTF-1, Napsin-A, ROS1, and PD-L1 and negative for Thyroglobulin and EML4-ALK (Fig. 2). The tumor proportion score (TPS) of PD-L1 was >99% using the clone 22C3 pharmDx kit (Agilent Technologies, Inc., Santa Clara, CA, USA) (Fig. 2). ROS1 rearrangement was confirmed by fluorescence *in situ* hybridization (Fig. 2). The mediastinal tumor was diagnosed as mediastinal lymph node metastasis of ROS1-rearranged PD-L1 high-expression undifferentiated lung adenocarcinoma (pathological stage 3, TxN2M0). Two months after the operation, CT showed multiple mediastinum lymph nodes metastases with rapid tumor growth. The patient achieved a complete response after three cycles of S-1 plus cisplatin with concurrent radiotherapy 60 Gy/30 Fr (Fig. 3).

Discussion

The mediastinal tumor in the present case was diagnosed as lymph node metastasis of lung cancer, despite no tumor

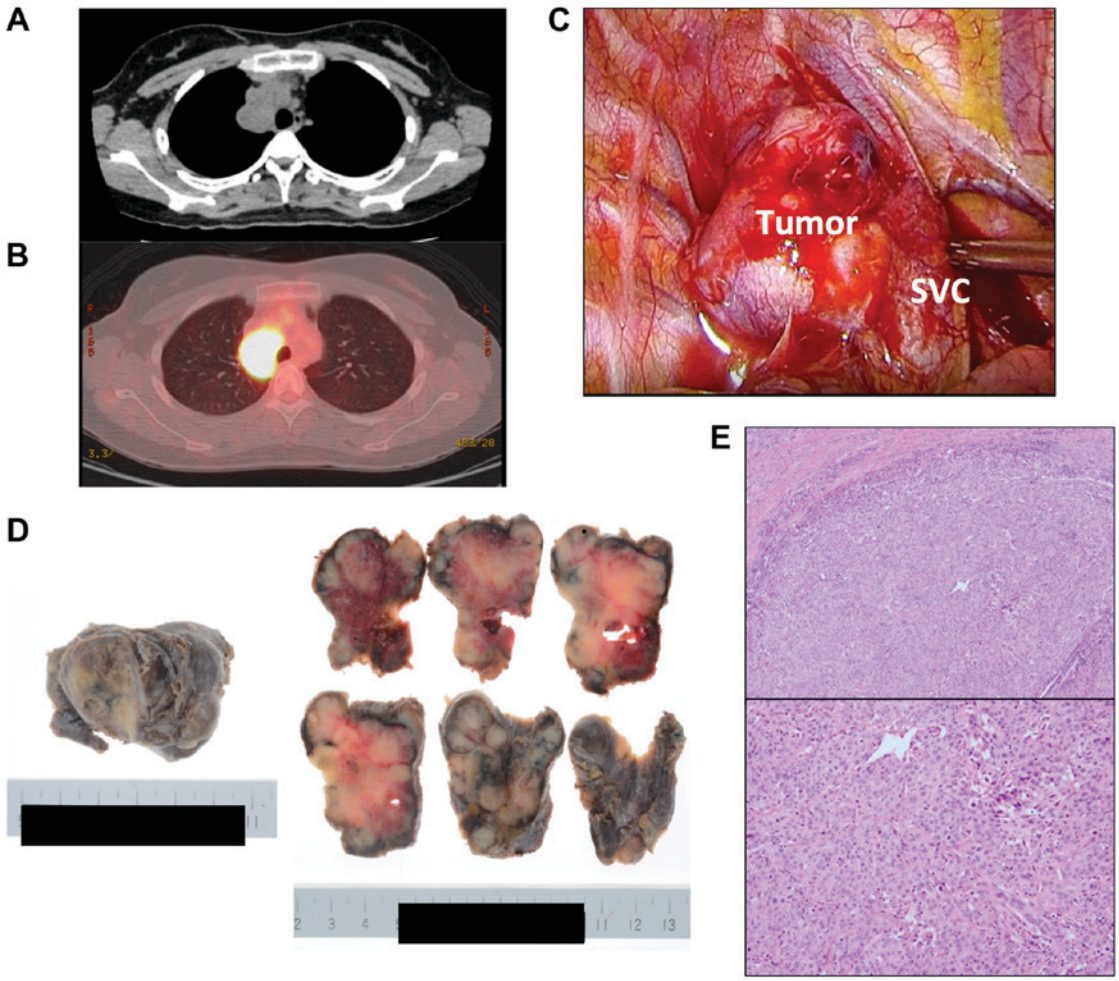

Figure 1. (A) CT showed a 57x36-mm tumor in the mediastinum. (B) PET-CT showed a strong accumulation of FDG in the tumor (SUVmax 12.7). The accumulation of FDG in the right 7th costal bone was also detected. (C) Intraoperative findings. There were no signs of tumor invasion to the lung, bronchus, SVC, or azygos vein. (D) Macroscopic pictures of the resected tumor. (E) H&E staining of the tumor (magnification upper panel, x40, lower panel, x100). CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose; H&E, hematoxylin and eosin; SVC, superior vena cava.

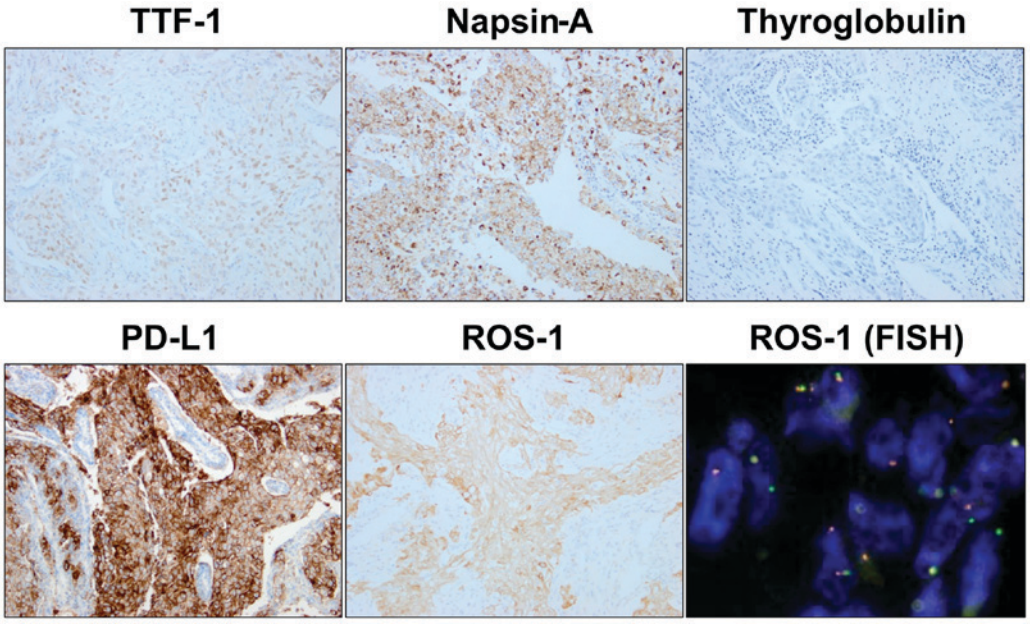

Figure 2. An immunohistochemistry analysis (magnification, x100) and FISH testing of ROS1 of the resected tumor. The tumor was positive for TTF-1, Napsin-A, ROS1, and PD-L1 and negative for Thyroglobulin. FISH shows the 3' (red) and 5' (green) regions of the ROS1 gene, separated by rearrangement. In this tumor, separated red and green fluorescence was detected. FISH, fluorescence *in situ* hybridization; ROS1, ROS proto-oncogene 1 receptor tyrosine kinas; PD-L1, Programmed death-ligand 1.

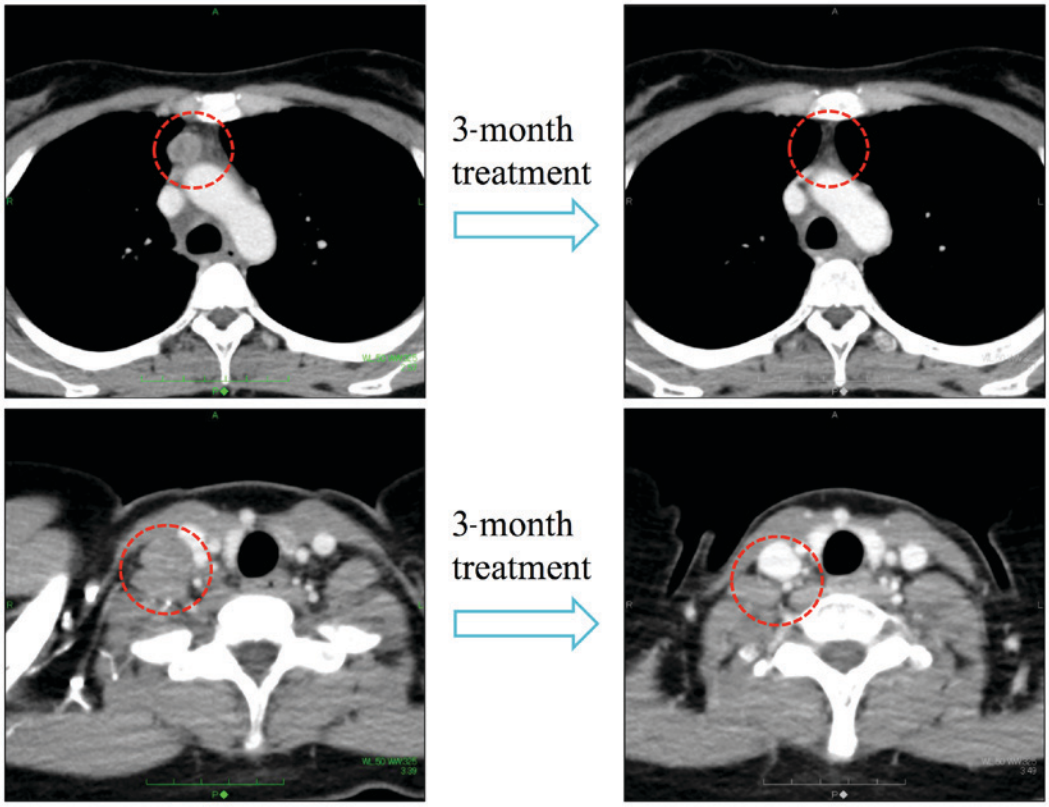

Figure 3. The efficacy of concurrent chemoradiotherapy for the recurrent lesion. The patient achieved a CR after three cycles of S-1 plus cisplatin with concurrent radiotherapy 60 Gy/30 Fr. The red circles indicate lymph node metastatic lesions.

being evident in the lung fields on CT or PET-CT. This type of lung cancer is known as occult lung cancer and is rare (4). Immunohistochemistry was helpful for diagnosing the origin of this tumor. The tumor was positive for TTF-1 and Napsin-A, and negative for thyroglobulin which was useful for distinguishing a lung origin from a thyroid origin. Based on these findings, the tumor was diagnosed as lung adenocarcinoma.

ROS1-rearranged lung cancer is rare and comprises only 1% of lung adenocarcinoma, which was recently reported to have good response to crizotinib, a tyrosine kinase inhibitor of anaplastic lymphoma kinase (2,3). A high expression of PD-L1 predicts a good response to immune checkpoint inhibitor monotherapy with pembrolizumab (5,6). Some 24.9-30.2% of advanced non-small cell lung cancer (NSCLC) had a TPS of PD-L1 of ≥50% (7). Driver oncogene mutations with approved therapies seldom coexist with a high expression of PD-L1, with a reported frequency of only 6% (7). The combination of ROS1 rearrangement and a high expression of PD-L1 is therefore considered very rare.

We chose the S-1 plus cisplatin with concurrent radiotherapy regimen for the recurrent lesion as the patient refused others due to hair loss. This regimen was reported to be effective for locally advanced non-small cell lung cancer with mild toxicities (8,9). Although the patient achieved a CR after this treatment, careful follow-up is needed. If the tumors recur, crizotinib or pembrolizumab are definitive treatment options (2).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HO and YT collaborated in the conception of the present study. KU, NS, TD and DH collected the data and prepared the pictures presented in the figures. MT, YT and YM critically revised the manuscript and were involved in data interpretation. All authors contributed to writing the manuscript and approved the final version.

Ethics approval and consent to participate

Written informed consent was obtained from the patients.

Patient consent for publication

Written informed consent was obtained from the patients for the publication of any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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