Rare MYH9-ROS1 Fusion Gene-Positive Lung Adenocarcinoma Showing Response to Entrectinib Treatment: A Case Study

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Abstract
The c-ros oncogene 1 (ROS1) fusion gene is a rare genomic alteration detected in nearly 1–2% of lung adenocarcinomas. The major partner genes of ROS1 include CD74, SDC4, and EZR. Here, we report a case of MYH9-ROS1 fusion gene-positive lung adenocarcinoma, a rare ROS1 fusion gene. The patient was a woman in her 40s who was diagnosed with advanced primary lung adenocarcinoma after a thorough examination. Initial genetic testing conducted using mediastinal lymph node biopsy specimens collected by endobronchial ultrasound-guided transbronchial needle aspiration revealed no driver gene mutations, including the ROS1 fusion gene. The patient was treated with four courses of immunochemotherapy. As the disease worsened, another genetic test was conducted using FoundationOne® CDx, and the MYH9-ROS1 fusion gene was detected. Multiple lung metastases disappeared after the administration of entrectinib; the response persisted up to a year. Adverse events of rash, dysgeusia, and peripheral edema were observed, and the patient required temporary drug interruption; however, we were able to continue entrectinib following a short-term drug interruption. This is the first report on the effectiveness of entrectinib against lung adenocarcinoma with the rare MYH9-ROS1 fusion gene.
Introduction

The c-ros oncogene 1 (ROS1) fusion gene is a rare genomic alteration detected in 1–2% of lung adenocarcinomas [1]; the major ROS1 fusion partner genes include CD74, SDC4, and EZR [2]. Two drugs, crizotinib and entrectinib, have proven to be effective against ROS1 fusion gene-positive nonsmall-cell lung cancer [3, 4]. The MYH9 gene encodes the heavy chain of nonmuscle myosin IIA, a cytoplasmic myosin that plays a role in processes requiring the generation of intracellular chemomechanical force and translocation of the actin cytoskeleton; MYH9 variants are associated with cancer [5]. MYH9 is a rare fusion partner of ROS1 [6]; however, the efficacy of drugs against this fusion is not well understood. In addition, because this fusion gene is rare, several conventional tests fail to detect it. Here, we report a case in which the MYH9-ROS1 fusion gene initially went undetected but was later detected using FoundationOne® CDx, a hybrid-capture-based diagnostic method, and the patient responded well to treatment with entrectinib.

Case Presentation

A woman in her 40s visited Respiratory Medicine of Toyama Prefectural Central Hospital because of abnormal shadows on a chest radiograph. The patient had no history of smoking, no significant medical history, and no family history of cancer. She complained of lower abdominal pain; a chest radiograph was ordered as part of the examination. The X-ray revealed left pleural effusion and enhanced left hilar shadowing. Lung cancer was suspected upon examination, and metastases were found in the lungs, colon, systemic bone, lymph nodes, pleura, and peritoneum. Endobronchial ultrasound-guided transbronchial needle aspiration was performed on the mediastinal lymph nodes, and thyroid transcription factor 1 (TTF-1)-positive adenocarcinoma tissue was collected. An Oncomine™ Dx Target Test (Thermo Fisher Scientific, Waltham, MA, USA) was performed on the adenocarcinoma tissue sample, and no driver gene abnormalities were detected. The patient was then started on immunochemotherapy with carboplatin, paclitaxel, bevacizumab, and atezolizumab. The disease progressed to a stable disease at the end of two courses but exhibited worsened multiple lung metastases and a bladder tumor at the end of four courses. We performed a transurethral resection of the bladder tumor and histologically diagnosed it as bladder metastasis of the lung adenocarcinoma (shown in Fig. 1). The tumor specimen was tested using FoundationOne® CDx (Foundation Medicine, Cambridge, MA, USA) and was found to be positive for the MYH9-ROS1 fusion gene. Subsequently, the patient was prescribed entrectinib 600 mg/day, which resulted in a significant change; a week later, computed tomography revealed shrinkage of multiple lung metastases and the bladder tumor. The patient required temporary drug interruption for a week because of the appearance of a generalized erythema; her condition improved, and the disease did not relapse after restarting entrectinib. The cancerous lesions throughout the body disappeared after restarting entrectinib, resulting in a complete response; this effect was sustained for a year (shown in Fig. 2). The entire course of this patient is shown in Figure 3.

Discussion/Conclusion

Herein, we report a case of a rare MYH9-ROS1 fusion gene-positive lung adenocarcinoma. The ROS1 fusion gene is a rare genomic alteration detected in 1–2% of lung adenocarcinomas [1]. The efficacy and safety of entrectinib for ROS1 fusion-positive nonsmall-cell lung cancer have already been demonstrated in the STARTREK trial; however, the trial did not include
MYH9-ROS1 fusion [4]. We report that a patient with MYH9-ROS1 fusion gene-positive lung adenocarcinoma was treated with entrectinib and responded well to the treatment.

MYH9 is a rare partner of the ROS1 fusion gene and occurs in approximately 1% of ROS1 fusion cases [6, 7]. MYH9 has also been reported as a rare fusion partner for other genes such as ALK, RET, and NTRK [8–10]. When the patient’s adenocarcinoma sample tested negative for driver mutations, we started treatment with cytotoxic anticancer agents and immune checkpoint inhibitors; however, the response was unsatisfactory. We then used FoundationOne® CDx, a hybrid-capture-based technology, which detected the MYH9-ROS1 fusion gene. As MYH9 is a rare gene fusion partner, it is undetectable by amplicon methods such as Oncomine™ owing to a lack of coverage [11]. In Japan, the AmoyDx® ROS1 fusion test kit is also available for detecting the ROS1 fusion gene; however, it does not detect the MYH9-ROS1 fusion gene [12]. Due to the limitations of these methods, detection of the MYH9-ROS1 fusion gene was possible using FoundationOne® CDx in our case, as the hybrid-capture method was capable of detecting unknown or rare fusion partners.
The patient experienced multiple side effects after starting entrectinib treatment, including the appearance of a skin rash. The patient was initially administered an immune checkpoint inhibitor when the fusion gene was not detected, followed by entrectinib treatment. Response to immune checkpoint inhibitors in a case of MYH9-ROS1 fusion gene-positive nonsmall-cell lung cancer has been reported before [13]; however, atezolizumab had no effect in our case. Moreover, severe adverse events such as skin rashes have been reported with the use of tyrosine kinase inhibitors, such as alectinib and vemurafenib, after immune checkpoint inhibitors [14, 15]. We postulate that treatment with entrectinib post-immunochemotherapy had a similar effect in our patient and should be used cautiously.

In conclusion, we successfully identified a case of lung adenocarcinoma with the MYH9-ROS1 fusion gene as the driver mutation, using FoundationOne® CDx. As demonstrated in this report, the use of hybrid-capture-based next-generation sequencing methods can be advantageous over conventional tests for the detection of unknown or rare fusion genes. To the best of our knowledge, this is the first report on the use of entrectinib for the treatment of MYH9-ROS1 rare fusion gene-positive lung adenocarcinoma. The patient showed a good treatment response, and entrectinib could be an effective therapy for lung adenocarcinoma with this rare fusion gene.

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Statement of Ethics

This study protocol was reviewed and approved by Toyama Prefectural Central Hospital, Ethics Committee, approval number 62-19. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.
Conflict of Interest Statement

Takeshi Tsuda received an honorarium from Chugai Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to declare.

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Author Contributions

Takeshi Tsuda, Naoki Takata, Takahiro Hirai, Yasuaki Masaki, and Hirokazu Taniguchi treated the patients. Shin Ishizawa performed histopathological analysis. Hirokazu Taniguchi overviewed this study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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