Case report

A case of synchronous multiple primary lung adenocarcinomas harboring epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement successfully treated with combination of osimertinib and alectinib

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ABSTRACT

Synchronous multiple primary lung cancers (SMPLC) should be distinguished from intrapulmonary metastasis to define the optimal treatment approach. Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements are typically mutually exclusive and the co-existence of both mutations is relatively rare. Herein, we report a case of SMPLC harboring each EGFR mutation and ALK rearrangement successfully treated with combination of osimertinib and alectinib. A combination of EGFR- and ALK-tyrosine kinase inhibitors could be an effective and tolerable therapeutic option for SMPLC with EGFR mutations and ALK rearrangement.

1. Introduction

Lung cancers are one of the leading causes of cancer-related death. Lung adenocarcinoma is the most common subtype of lung cancer. Comprehensive genomic profiles and cancer signaling pathways in lung adenocarcinoma have been recently clarified [1]. Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements are one of major oncogenic drivers in lung adenocarcinoma. These mutations were thought to be mutually exclusive [2,3]. However, cases with concomitance of EGFR mutations and ALK rearrangements have recently been reported [4,5].

In recent years, the incidence of synchronous multiple primary lung cancers (SMPLC) has been increasing, ranging from 0.2% to 8% of all non-small cell lung cancer (NSCLC) cases [6]. Careful pathohistological diagnosis is very important because the distinction between SMPLC and intrapulmonary metastasis implies different therapeutic approaches [7,8]. Molecular genetic analysis in different lesions could help to optimise therapeutic strategies in SMPLC [9]. We herein report a case of SMPLC, harboring both EGFR mutation and ALK rearrangement. The patient was successfully treated with a combination of osimertinib and alectinib.

2. Case report

A 74 years-old non-smoker woman was referred to our hospital for multiple lung nodules in July 2018. Chest computed tomography (CT) revealed mediastinal lymphadenopathy, right slight pleural effusion and four opacities, including a 32-mm solid mass in the left lower lobe (LLL), a 21-mm mixed ground glass nodule (GGN) in the right lower lobe (RLL), a 18-mm GGN in the left upper lobe (LUL) and a 9-mm GGN in the right upper lobe (RUL) (Fig. 1 A and B). The level of serum carcinoembryonic antigen (CEA) was not elevated. Subsequently, transbronchial biopsy was performed for the LLL mass. Pathological examination revealed poorly differentiated adenocarcinoma (Fig. 2 A). Immunohistochemistry and fluorescence in situ hybridization identified ALK rearrangement without EGFR mutation (Fig. 2 B). The RLL lesion was considered as intrapulmonary metastasis of adenocarcinoma. The lesions in LUL and RUL were considered as two synchronous primary lung cancers.
Thereafter, the patient received full-dose alectinib (300 mg twice daily) and a CT scan confirmed the good partial response of the LLL mass and lymphadenopathy. However, other lesions in the RLL, RUL, and LUL did not respond to alectinib. The patient remained in remission under treatment with alectinib for 15 months; nevertheless, the level of serum CEA was elevated, followed by the enlargement of the RLL mass and the

Fig. 1. Summary of chest computed tomography findings. At initial diagnosis (A, B), at 15 months after administration of alectinib (C, D) and after 7 months of combination therapy with alectinib and osimertinib (E, F). A 32-mm solid mass in the LLL (A) and a 21-mm mixed ground glass nodule in the RLL (B) were detected at initial diagnosis. After treatment with alectinib, the LLL mass was shrunk (C), the RLL mass was enlarged, and the pleural effusion was increased (D). Combination therapy with alectinib and osimertinib resulted in shrinkage of the RLL mass and decrease in the right pleural effusion (F). LLL, left lower lobe; RLL, right lower lobe.

Fig. 2. Pathological examinations of hematoxyline and eosin staining (A, C) and immunohistochemical detection of ALK fusion oncprotein (B, D). (A, B) The mass in the left lower lobe showed poorly differentiated adenocarcinoma stained for ALK. (C, D) The cell block sample from the right pleural effusion with adenocarcinoma showed non-mucinous adenocarcinoma. The cells showed no staining for ALK. Scale bars: 50 μm in inserts. ALK, anaplastic lymphoma kinase.
increase in right pleural effusion (Fig. 1C and D). The cell block specimen of the right pleural effusion showed adenocarcinoma harboring an EGFR exon 19 deletion without ALK rearrangement (Fig. 2C and D).

In November 2019, a treatment with full-dose osimertinib (80 mg daily) plus alectinib was initiated. Following administration of osimertinib, a CT scan showed obvious shrinkage of the RLL mass and reduction in right pleural effusion with decreased serum CEA level (from 83.9 to 3.5 ng · dl⁻¹). This combination therapy has been continued for >15 months, with good partial response for both lung cancers and absence of any adverse effects (Fig. 1E and F).

3. Discussion

Recent advances in diagnostic technologies, including high-resolution CT, have resulted in an increasing incidence of multiple lung cancers [6]. For multiple lung cancers, the distinction between SMPLC and intrapulmonary metastasis is required to provide optimal treatment [7,8]. However, owing to the morphologic and immunohistochemical similarities of these malignancies, this distinction can be challenging [9]. A definition of SMPLC has been proposed by the International Association for the Study of Lung Cancer [10,11]. Comprehensive histological assessment is a powerful tool for the diagnosis of SMPLC, and separate biopsies for different lung masses should be recommended in patients suspected with SMPLC [10,12,13]. If only small biopsies are available, molecular profiling may help to distinguish SMPLC from intrapulmonary metastases [10].

Comprehensive molecular profiling in lung adenocarcinoma has been recently clarified [1]. EGFR mutations and ALK rearrangements are one of major driver oncogene mutations in lung adenocarcinoma [1,2,14–17]. Although they have been considered mutually exclusive [2,3], co-existence of both gene alterations in a single primary tumor occurs in approximately 1–2% of patients with NSCLCs [4,5]. On the other hand, only one case of SMPLC, with both EGFR mutation and ALK rearrangement, has been reported thus far [18]. The report revealed that EGFR-positive adenocarcinoma and ALK-positive adenocarcinoma showed different microscopic appearances (i.e., lepidic versus papillary, respectively) in surgically resected specimens. In our case, the LLL mass and the RLL mass showed similar histology, although different radiographic findings were found between the two lesions.

Osimertinib is an effective third-generation EGFR-Tyrosine kinase inhibitor for the treatment of patients with EGFR mutation-positive NSCLCs [19]. Alectinib is also a preferred first-line treatment option for advanced ALK rearrangement-positive NSCLCs [20]. However, a treatment dilemma occurs when a patient has single primary lung cancer with co-alterations or SMPLC with EGFR mutation and ALK rearrangement. In these cases, single-agent targeted therapy for either of the genetic alterations alone does not result in sufficient clinical benefit, and the optimal treatment strategy remains unclear [5,21,22]. Recent studies revealed that a combination tyrosine kinase inhibitor therapy could be effective and tolerable in patients with co-occurring different genetic alterations [22–24]. Schrock et al. administered a combination therapy of full-dose alectinib and osimertinib to a patient with lung adenocarcinoma harboring EGFR L858R mutation and acquired ALK fusion [22]. This combination therapy was effective and tolerable with limited adverse effects (grade 1 myalgia and grade 2 elevation of creatinine phosphokinase). Batra et al. also reported this combination therapy was effective with no significant toxicity for a patient with lung adenocarcinoma harboring EGFR deletion 19 mutation and acquired ALK fusion [25]. In the current case, the patient was responded to a concurrent combination treatment with osimertinib and alectinib for the progression of EGFR-positive lung lesions during treatment of ALK-positive lung lesions with alectinib. SMPLC and right pleural effusion were diminished by the combination therapy, and the disease has been controlled for >15 months without adverse effects.

To our knowledge, this is the first clinical report showing that a combination therapy of full-dose osimertinib plus alectinib could result in good efficacy in a patient with SMPLC harboring EGFR mutation and ALK rearrangement, along with an acceptable safety profile. This combination treatment can be tolerable and effective against SMPLC consisting of each EGFR-mutant and ALK-mutant NSCLCs. Furthermore, we emphasize the need for intensive molecular evaluation of multiple lesions when dealing with SMPLC cases with heterogeneous responses to treatment.

4. Conclusion

A combination of osimertinib and alectinib could be an effective and tolerable therapeutic option for SMPLC with EGFR mutations and ALK rearrangement.

Statement of ethics

Written informed consent was obtained from the patient.

Author contributions

Y. I. was involved in the care of the patient, obtained consent from the patient, wrote the first draft of the case report, and had responsibility for the final draft of the case report; Y. J. and O. M. were involved in the care of the patient and contributed to critical revision of the manuscript; Y. O. and S. E. participated in the care of the patient and the manuscript revisions.

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Declaration of competing interest

The authors declare no conflicts of interest.

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