CASE REPORT

ALK-rearranged squamous cell carcinoma of the lung

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Abstract

Background: ALK rearrangement is a very rare subset of squamous cell carcinoma (SCC) and one of the clinical features in patients is lack of data. Here, we report eight patients diagnosed with SCC of the lung harboring ALK rearrangement.

Methods: We collected primary NSCLC samples at the Beijing Chest Hospital between January 2012 and December 2018 for Ventana (D5F3) immunohistochemical detection. Among the 148 patients diagnosed ALK-rearranged non small cell lung cancer (NSCLC), only eight cases were SCC. We collected patients' information from electronic patent records (EPRs).

Results: The eight cases of SCC were diagnosed by immunohistochemistry (IHC). Two were given crizotinib as second-line therapy. One patient had stable disease (SD) and progression-free survival (PFS) of six months. The other patient had progressive disease (PD) but PFS was only one month. The side effects were tolerable. This report identified 31 cases of ALK rearrangement in SCC patients from a literature search (including the eight patients in this study). These fusion genes are often seen in a younger age group (mean age: 55.6 years) and non-smokers (18/31, 58.1%). A total of 20 cases received an ALK inhibitor as first- or second-line treatment which included 11 with a partial response (PR), four with SD, and five with PD. The DCR and ORR was 75.0% (15/20) and 55.0% (11/20), respectively. The median duration time of therapy was 6.4 ± 4.4 months.

Conclusions: Patients with ALK-rearranged SCC obtained clinical benefit from ALK-inhibitor therapy, especially those who were non-smokers and whose tumors had been identified by IHC+/FISH+.

KEYWORDS: ALK inhibitor drug, ALK rearrangement, immunotherapy, PDL1, squamous cell carcinoma

INTRODUCTION

Lung cancer has among the highest morbidity and mortality of all cancer types, and is responsible for the highest rate of cancer-related mortality worldwide. Primary lung cancer is mainly divided into two pathological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which mainly include adenocarcinoma (ADC), squamous cell cancer (SCC) and other subtypes. Treatment methods for lung cancer mainly include surgical resection, chemotherapy and molecular targeted therapy.

Numerous oncogenic driver mutations have been identified in patients with NSCLC. Echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase rearrangement fusion genes (EML4-ALK) have been previously identified in approximately 5% of NSCLC patients, a population that consists mostly of adenocarcinoma patients. These fusion genes are often seen in a younger age group of never or light ex-smokers. Patients with SCC who harbor the ALK rearrangement are extremely rare (only 1%).

Targeted treatment of metastatic ALK-rearranged non-small cell lung cancer with ALK inhibitors leads to higher response rates and improves progression-free survival (PFS) relative to conventional chemotherapy regimens.

However, only limited data on ALK rearrangement in SCC are available and we seldom have the opportunity to...
see those patients in daily clinical practice. Here, in this study, we report eight cases with ALK-positive SCC together with a review of the literature.

METHODS

Clinical data collection

We collected primary NSCLC samples at the Beijing Chest Hospital between January 2012 and December 2018 for Ventana (D5F3) immunohistochemical detection. Among the 148 patients with pathologically diagnosed ALK-rearranged NSCLC, overexpression of ALK protein occurred in eight patients with SCC, as confirmed by immunohistochemistry (IHC).

Treatment response evaluation and follow-up

Patient treatment information was obtained from electronic patient records (EPRs). The tumor response in patients who received standard chemotherapy was assessed every two cycles. In the patients who received an ALK inhibitor, the tumor response in this group was assessed after the first cycle (every 28-day cycle) of treatment and subsequently after every two cycles. Tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. During follow-up, CT scans of the thorax and enhanced MRI of the brain were used to assess the disease. Responses to treatment were reported as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Regular IHC and Ventana IHC analysis

Immunohistochemistry analysis

There were five surgically resected samples and eight biopsy samples assessed by immunohistochemistry analysis including P40, P63, cytokeratin 5/6, CK7, thyroid transcription factor 1 (TTF-1), and napsin-A. IHC revealed that the tumor cells showed diffuse staining and were positive for P40, P63, CK5/6, CK7, but were completely negative for thyroid transcription factor-1 (TTF-1) and napsin-A. Although few cells (less than 5% of all) showed adenomatous differentiation, most had typical characteristics of SCC. Based on these findings, the results confirmed the histological type was SCC.

ALK immunohistochemistry analysis

Sections of formalin-fixed and paraffin-embedded (FFPE) tissue 4 μm thick were stained with the Ventana ALK (D5F3) rabbit monoclonal primary antibody, together with rabbit monoclonal negative control immunoglobulin, Optiview DAB IHC detection kit, and an Optiview amplification kit on a Ventana BenchMark ULTRA stainer (Ventana Medical Systems). This procedure was performed according to the manufacturer’s instructions.

Immunoreactivity was evaluated as positive when the tumor (any percentage of positive tumor cells) showed intense granular cytoplasmic staining. The test results were evaluated using light microscopy. A binary method of interpretation was used as follows: strong granular cytoplasmic staining (any percentage) in the tumor cells was scored EML4-ALK (+); otherwise, and they were scored EML4-ALK (−).

Statistical analysis

The association between ALK rearrangement status and clinicopathological data was assessed using SPSS software, version 17.0 (SPSS, Chicago, IL, USA), and survival analysis was performed using Fisher’s exact test and the Kaplan–Meier test. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Clinicopathological features of ALK-rearranged SCC (TABLE 1)

Two of the eight cases in this study were female and six were male. Five of eight patients with ALK-rearranged SCC were ex- or current smokers. Pathological staging was I–IV and included one patient (stage I), one patient (stage II), three patients (stage III) and three patients (stage IV), respectively.

SCC was confirmed by typical histopathological features. All eight cases were positive for CK5/6, CK7, p63 and/or p40 expression, negative for TTF-1 and napsin A. Ventana IHC (D5F3) confirmed the presence of ALK in all cases.

Five patients received surgery. Three of five cases (Cases 3, 6 and 8) received adjunctive chemotherapy and no recurrence was observed after regular follow-up. Intrapulmonary metastasis recurred 14 months after surgery in Case 5 and the patient abandoned further treatment. There was a recurrence in Case 7 with local metastasis 25 months after surgery who subsequently received radiotherapy. Then, 10 months later, the patient suffered from intrapulmonary and bone metastasis and received first-line chemotherapy with a combination of four cycles of gemcitabine and carboplatin to which there was no treatment response. The patient refused a further course of treatment for economic reasons.

Three patients had advanced NSCLC. Case 2 was a male aged 76 years. He was unable to afford the high cost of targeted therapy, and only accepted one cycle of chemotherapy before refusing subsequent treatment. The other two patients with ALK-rearranged SCC had previously undergone standard chemotherapy. Two patients were treated...
with crizotinib and then switched regimens when they were diagnosed with PD during chemotherapy. One received a SD response; unfortunately, the second patient underwent crizotinib for only one month’s duration and then died as a result of cancer progression.

Case 1: An ALK inhibitor benefit

A 54-year-old woman with no previous history of smoking was clinically diagnosed with NSCLC (cT2N2M1b, stage IV). A histopathological analysis of biopsied tumor tissue revealed SCC. IHC confirmed positivity for p40 and p63, negativity for TTF-1 and napsin-A (FIGURE 1); ALK protein was overexpressed which was confirmed via IHC ALK rearrangement. The patient received first-line chemotherapy with four cycles of a combination of gemcitabine and carboplatin which did not suppress rapid tumor growth. The chemotherapy regimen was interrupted and replaced; the patient accepted crizotinib as second-line treatment and showed SD but relapsed after six months.

Case 2: An ALK inhibitor nonresponder

Case 2 was a 35-year-old woman who was a non-smoker. She was clinically diagnosed with NSCLC (cT4N3M1b, stage IV). IHC analysis of biopsied tumor tissue revealed positive CK7 and negative TTF-1 and napsin-A immunoreactivity, confirming a diagnosis of SCC (FIGURE 2). Carboplatin plus taxol was administered as first-line chemotherapy. However, this regimen was discontinued following disease progression. Rebiopsy was performed and confirmed a diagnosis of SCC and IHC ALK rearrangement. The patient accepted crizotinib as second-line treatment but there was no response and she subsequently died of disease after one month.

**TABLE 1** Clinical details of patients

| Age (y) | Sex | Method of diagnosis and type of tissue sample | ALK detection | Stage | Smoking history pack-year | Prior treatment | ALK inhibitor | Efficacy | PFS (m) |
|---------|-----|---------------------------------------------|---------------|-------|--------------------------|----------------|---------------|----------|--------|
| Case 1  | 54  | F                                            | IHC           | IV    | Non-smoker               | PDC            | Crizotinib   | SD       | 6.0    |
| Case 2  | 76  | M                                            | IHC           | IV    | Smoker                   | PDC            | None         | None     | None   |
| Case 3  | 53  | M                                            | IHC, IIIa     |       | Smoker                   | Adjunctive PDC | None         | None     | None   |
| Case 4  | 35  | F                                            | IHC           | IV    | Non-smoker               | PDC            | Crizotinib   | PD       | 1.0(Dead) |
| Case 5  | 64  | M                                            | IHC, II       |       | Smoker                   | None           | None         | None     | None   |
| Case 6  | 64  | M                                            | IHC, IIIa     |       | Smoker                   | Adjunctive PDC | None         | None     | None   |
| Case 7  | 63  | M                                            | IHC           | I     | Non-smoker               | PDC            | None         | None     | None   |
| Case 8  | 64  | M                                            | IHC, IIIa     |       | Smoker                   | Adjunctive PDC | None         | None     | None   |

Abbreviations: F, female; FISH, fluorescence in situ hybridization; M, male; m, months; PD, progressive; PDC, platinum-doublet chemotherapy; PFS, progression-free survival; PR, partial response; RT-PCR, reverse transcription polymerase chain reaction; SD, stable disease; y, year.

**FIGURE 1** Immunobiological characteristics of case 1. Immunohistochemical analysis of lung cancer tissue. (a) Hematoxylin and eosin staining (200×); (b) ALK Ventana (DF53, 200×), (c) positive staining for CK56 (200×), (d) positive staining for P40(200×), (e) negative staining for TTF-1 (200×), (f) positive staining for CK7(200×), (g) Naspin-A (200×), (h) positive staining for P63 (200×)
Descriptive analysis and qualitative synthesis

We identified 31 cases of ALK rearrangement in SCC patients from a literature search (TABLE 2). In this study, a total of 31 cases were included which includes the eight patients. There was a prevalence of female (15 females, 16 male), and never smoker patients (18 never smokers, 12 smokers). The average age of patients was 55.6 ± 13.3. The mean age of female patients was 49.6, younger than 61.1 of male. The pathological staging was I + II, III and IV in three (9.6%), 10 (32.3%; IIIA eight, IIIB two) and 18 (58.1%) patients, respectively. There were eight surgically resected samples and 31 biopsies. A total of 13 (41.9%) cases were recorded as focal positive and 18 (58.1%) cases with advanced disease. In 31 cases of SCC, 10 were identified as ALK-positive only by Ventana IHC (D5F3), one case was by NGS, 20 cases were diagnosed as ALK-positive by Ventana IHC (D5F3) and FISH, two cases were IHC (−)/FISH (+), two cases were IHC (+)/FISH (−), and 16 cases were IHC (+)/FISH (+).

Eight patients underwent tumor resection. Five received postoperative adjunctive chemotherapy and attended regular check-ups for postoperative recurrence. After regular follow-up appointments, two patients were found to have recurrent disease. One accepted crizotinib, resulting in SD of nine months duration, the other patient accepted alectinib. This patient was considered to have obtained a PR with nine months.

Three patients diagnosed with stage III SCC underwent radiation therapy. After regular check-ups, one patient was confirmed to have recurrent disease, and underwent treatment with crizotinib. This patient was considered to have obtained a PR with nine months.

This report includes all patients who were treated with at least one type of ALK-TKI therapy and some patients had more than one treatment with different kinds of TKI. All the treatments administered for each lines of therapy were analyzed. A total of 20 patients received at least one ALK-TKI (20 cases evaluable lines of treatment). There were 13 patients with ALK-rearranged SCC who had previously undergone standard chemotherapy for SCC prior to treatment with crizotinib and switched regimens when ALK rearrangement was detected, when they had been diagnosed with progressive disease (PD) during chemotherapy (three cases received more than one kind of ALK-TKI). Seven patients were treated as first-line administration (one case was PR for three months without further information) (Table 3).

Seven patients who smoked accepted ALK treatment (two received alectinib, five received crizotinib). A total of 13 non-smokers accepted ALK treatment (four received alectinib and nine received crizotinib). The objective response rate (ORR) was 28.6% (2/7) and 69.2% (9/13), respectively ($p = 0.16$). The disease control rate (DCR) was 57.6% and 69.2% (9/13), respectively ($p = 0.28$). The duration of treatment was almost 1.2 months longer than in smokers (smokers 5.6 ± 2.2 vs. 6.8 ± 3.6 months; $p = 0.752$). Therefore, smokers with ALK SCC who responded to crizotinib/alectinib showed a shorter duration time of treatment and worse response than non-smokers.

In 20 cases confirmed to be ALK-positive by IHC and FISH, 15 cases received an AKI-inhibitor. There was one SD case in four patients assayed by IHC (+)/FISH (−) or IHC (−)/FISH (+). There were eight PR cases, two SD cases, and one PD case, out of a total of 11 patients, both IHC (+)/FISH (+). The DCR was 90.1% (10/11) and 25.0% (1/4), respectively ($p = 0.01$). Four patients in which ALK rearrangement was assayed by IHC (−)/FISH (+) or IHC (+)/FISH (−) did not respond to crizotinib, and the duration time of treatment decreased sharply from one to four months ($p = 0.001$).
| Author                  | Age (years) | Sex | Method of diagnosis and/or type of tissue sampled | ALK detection | Stage | Smoking history (pack-year) | Prior treatment | ALK inhibitor | Efficacy | Duration of treatment (months) |
|-------------------------|-------------|-----|-------------------------------------------------|---------------|-------|---------------------------|----------------|---------------|----------|-----------------------------|
| 1. Kinh et al. 2013     | 36          | F   | Bronchial biopsy of the cervical lymph node      | IHC+, FISH+   | IV    | Non-smoker                | None           | None          | None     | None                        |
| 2. Ochi et al. 2013     | 45          | F   | Bronchial biopsy of cervical lymph node          | IHC−, FISH+   | IV    | Smoker                    | None           | None          | None     | None                        |
| 3. Alrifai et al. 2013  | 69          | M   | Bronchial biopsy of cervical lymph node          | IHC+, FISH+   | IIa   | Smoker                    | Radiation      | None          | None     | None                        |
| 4. Wang et al. 2014     | 55          | F   | Bronchial biopsy of primary lesion               | IHC+, FISH+   | IV    | Non-smoker                | PDC            | Crizotinib    | PR       | 5.8                         |
| 5. Mikes et al. 2015    | 36          | M   | Bronchial biopsy of primary lesion               | IHC+, FISH+, RT-PCR | IV    | Non-smoker                | None           | Crizotinib    | PR       | 3.0 (PR maintain)           |
| 6. Zhang et al. 2015    | 55          | F   | Bronchial biopsy of primary lesion               | IHC+          | IV    | Non-smoker                | PDC            | Crizotinib    | PR       | 6                            |
| 7. Takanashi et al. 2015| 60          | M   | Bronchial biopsy of primary lesion               | IHC+, FISH+, RT-PCR+ | II   | Smoker                    | Adjuvant       | None          | None     | None                        |
| 8. Vergne et al. 2016   | 58          | F   | Bronchial biopsy of primary lesion               | IHC+, FISH+   | IV    | Non-smoker                | None           | Crizotinib    | PR       | 7.1                         |
| 9. Tamiya et al. 2015   | 78          | M   | Bronchial biopsy of primary lesion               | IHC+, FISH+   | IV    | Smoker                    | None           | Alectinib     | PD       | 1.5                         |
| 10. Wang et al. 2016    | 37          | F   | Bronchial biopsy of primary lesion               | IHC+          | IIb  | Non-smoker                | Radiation, PDC | Crizotinib    | PR       | 9                            |
| 11. Yamamoto et al. 2016| 76          | M   | Bronchial biopsy of primary lesion               | IHC−, FISH+   | IIIa | Non-smoker                | Radiation      | None          | None     | None                        |
| 12. Mamesaya et al. 2017| 52          | F   | Bronchial biopsy of primary lesion               | IHC+, FISH+   | IV    | Non-smoker                | PDC            | Alectinib     | PR       | 11                           |
| 13. Bolzachini et al. 2017| 51        | M   | Biopsy of primary lesion, surgery               | IHC+, FISH+   | IIIa | Non-smoker                | PDC            | Crizotinib, Alectinib | PR | 14                 |
| 14. Li et al. 2017     | 45          | F   | Biopsy of primary lesion                         | IHC+, FISH+, NGS | IV   | Non-smoker                | None           | Crizotinib, Alectinib | PR | 9                           |
| 15. Sagawa et al. 2018  | 73          | M   | Bronchial biopsy                                | IHC+, FISH+   | IV    | Non-smoker                | None           | Alectinib     | PR       | >9                          |
| 16. Huang et al. 2018   | 50          | F   | Lung biopsy                                     | NGS+           | IV    | Smoker                    | PDC            | Crizotinib, Alectinib | PR/PR (QT prolong) | >4 |
| 17. Watanabe et al. 2018| 65          | F   | Bronchial biopsy                                | IHC−, FISH+   | IV    | Smoker                    | PDC            | Crizotinib, Alectinib | PD | 2/1                        |
| Case 2                  | 36          | M   | Bronchial biopsy                                | IHC+, FISH+   | IIb  | Smoker                    | PDC            | Crizotinib, Alectinib | PR    | 12/5                        |
| Case 3                  | 62          | M   | Bronchial biopsy                                | IHC−, FISH+   | IV    | Smoker                    | PDC            | Crizotinib     | PD       | 1                            |
| 18. Wang et al. 2019    | 63          | M   | Bronchial biopsy                                | IHC+, FISH−, NGS+ | IV   | Smoker                    | None           | Crizotinib, SD   | 3        | (Continues)                 |
The EML4-ALK fusion gene is one of the most important molecular alterations in NSCLC, but is extremely rarely expressed in SCC. In our center, IHC analysis includes p40, P63, cytokeratin (CK) 5/6 and CK7, thyroid transcription factor-1 (TTF-1) and napsin-A. To confirm the diagnosis of SCC requires TTF-1 and napsin-A completely negative and other indicators positive. In our report IHC findings were strongly suggestive that the tumors were SCC.

Caliò et al. reported that ALK rearrangements may be found in pure lung squamous cell carcinomas and the frequency was 2.5% (one of 40 cases) in biopsy samples. The ALK-positive rate depends on tissue size and has been found to be higher in surgical specimens in comparison to smaller biopsy specimens. It has been confirmed that the whole specimen obtained surgically showed typical morphohistology of SCC, and contained no other histological type. Furthermore, heterogeneous expression of ALK-protein was seen throughout the entire area of the tumor. There was a possibility that the tumor was not pure SCC. Occasionally, the histological type of the small amount of specimen obtained via TBB was difficult to determine in subsequent IHC and molecular analyses.

In our report, five patients were surgically diagnosed with eight diagnosed via small biopsy specimens. The majority of the 31 cases in our study were diagnosed using small biopsy specimens. Fusion genes are often seen in a younger age group (mean age: 55.6 years old) and female group (15/31), especially non-smokers.

The recommended methods for detection of ALK rearrangement include Ventana IHC (D5F3), in-situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR). Previous studies have found that ALK-positive with SCC is 1%, as detected by IHC/FISH or PCR. Because of the low frequency in squamous lung cancer, ALK fusion gene testing is not routinely recommended in the National Comprehensive Cancer Network guideline for the treatment of NSCLC. The China Food and Drug Administration (CFDA) granted full approval for crizotinib in the treatment of patients with ALK-positive NSCLC on January 22, 2013 and Ventana IHC (D5F3) has been approved by the CFDA as an aid in identifying patients who are eligible for treatment with crizotinib. Until now, the updated CAP/IASLC/AMP molecular testing guideline for lung cancer recommended IHC as an equivalent alternative to FISH for ALK testing, since Ventana IHC (D5F3) is the most convenient and inexpensive method for ALK rearrangement, therapeutic decisions based on IHC results are clearly reasonable.

ALK-inhibitor (crizotinib/alectinib) is much more effective than chemotherapy for ADC with harbored the ALK rearrangement. In advanced NSCLC, the disease control rate is 60% and median progression-free survival of response is 4–10 months for first-line combination chemotherapy. The disease control rate (DCR) decreases 20%–40% for second-line chemotherapy and median duration of response is

| Author     | Age (years) | Sex | Smoking history (pack-year) | Stage | ALK detection | Prior treatment | ALK inhibition | Duration of treatment (months) | Efficacy | Prior treatment | ALK inhibitor | Efficacy | Duration of treatment (months) |
|------------|-------------|-----|----------------------------|-------|---------------|----------------|---------------|-------------------------------|----------|----------------|---------------|----------|-------------------------------|
| Case 2     | 32          | F   | Non-smoker                 | IV    | IHC+, FISH-, NGS+ | None           | Crizotinib     | 4                              | PD       | None           | Crizotinib     | PD       |                                |
| Case 3     | 53          | F   | Non-smoker                 | IIIA  | IHC+, FISH-, NGS+ | PDC            | Crizotinib     | 9                              | SD       | None           | Crizotinib     | SD       |                                |
| Case 4     | 73          | F   | Smoker                      | IV    | IHC+, FISH-, NGS+ | PDC            | Crizotinib     | 10                             | SD       | None           | Crizotinib     | SD       |                                |

**Table 2** (Continued)
In conclusion, because of the increasing number of reported cases of ALK SCC, this presents an opportunity to allow doctors to define specific guidelines. Molecular characteristics of lung cancer have underlined the pathogenic and therapeutic importance of specific genes involved in tumor growth. This report highlights the importance of searching for driver mutations in patients with SCC. ALK-targeted therapy could be an effective treatment option. Non-smoker status and IHC (+)/FISH (+) may be predictive factors in those patients. It is therefore strongly recommended to choose various methods to identify ALK-positive patients.

| Abbreviations: DCR, disease control rate; N, member; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. |
|-----------------|-----|-----|-----|-----|-----|-----|
|                | Npts | NPR | NSD | NPD | ORR (CR + PR%) | DCR (CR + PR + SD%) | Duration time of treatment Mean (month) |
| Total patients  | 20   | 11  | 4   | 5   | 55.0%          | 75.0%                | 6.4 ± 4.4                          |
| First-line treatment | 7   | 4   | 1   | 2   | 57.1%          | 71.4%                | 4.5 ± 2.9                          |
| Second-line treatment | 13  | 7   | 3   | 3   | 53.8%          | 76.9%                | 7.4 ± 4.8                          |
| Smoker          | 7    | 2   | 2   | 3   | 28.6%          | 57.6%                | 5.6 ± 3.2                          |
| Non-smoker      | 13   | 9   | 3   | 1   | 69.2%          | 92.3%                | 6.8 ± 3.6                          |
| IHC +/FISH +    | 11   | 8   | 2   | 1   | 72.3%          | 90.1%                | 8.8 ± 4.4                          |
| IHC or FISH +   | 4    | 0   | 1   | 3   | 25.0%          |                     | 2.8 ± 1.2                          |

TABLE 3 Qualitative synthesis of reported best response
advised that ALK inhibitor drug treatment could be one of the preferred approaches in cases of non-smoker patients with ALK SCC.

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