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Histologic transformation of *ALK*-rearranged adenocarcinoma to squamous cell carcinoma after treatment with *ALK* inhibitor

Sehhoon Park[a], Joungho Han[b], Jong-Mu Sun[a,*]

[a] Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[b] Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

Anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC) treated with *ALK* tyrosine kinase inhibitor (TKI) eventually acquires resistance to the treatment. However, our current knowledge regarding the resistance mechanisms is based on non-synonymous mutation and amplification in *ALK*, with the reasons still unknown for nearly half of all such cases. Other than genomic alteration as a resistance mechanism, up to 10% of NSCLC with activating epithelial growth factor receptor (*EGFR*) mutation showed resistance to *EGFR* TKI through histologic transformation. Although limited in number, there are cases showing transformed samples retaining the initial genomic alteration, which support lineage transition as a novel resistance mechanism. In this report, we described the first case of squamous cell carcinoma (SCC) transformation from adenocarcinoma (ADC) in NSCLC with *ALK* rearrangement after treatment with *ALK* TKI.

1. Case presentation

A 52-year-old, female never-smoker presented with a right middle lobe mass, identified during a routine health screening. Initial chest CT showed a single 3.0-cm nodule confined to the lung, without invasion of the heart and with no other metastatic sites. Curative video-assisted thoracoscopic right middle lobectomy and mediastinal lymph node dissection were performed.

The surgical specimen was a 3.0-cm × 2.5-cm adenocarcinoma (ADC) with moderate differentiation, without lymph node involvement, pT1cN0M0 (by American Joint Committee on Cancer 8th edition of the TNM classification). *ALK* rearrangement was confirmed by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Eleven months after the surgery, recurrence in the pleura and lymph nodes was observed. Based on the positive *ALK* rearrangement result, the patient underwent crizotinib treatment for 20.7 months by participating in the PROFILE 1014 study. After a partial response to crizotinib, the disease progressed in the right lung. The patient was then enrolled in the NP28673 (alectinib) clinical trial and demonstrated a partial response for 39.7 months. At the time of alectinib resistance, a second bronchoscopic biopsy was taken from the right upper lobe. The squamous cell carcinoma (SCC) histology was identified from the alectinib-resistant sample, with *ALK*-positive, p63-positive, and TTF-1-negative results found through IHC (Fig. 1). As a subsequent treatment, the patient received TPX-0005-01, which showed no clinical effect. After the TPX-0005-01 failure, cytotoxic chemotherapy was applied in a sequence of pemetrexed/cisplatin induction therapy, followed by pemetrexed maintenance, which showed a partial response for 8.9 months. The patient is currently undergoing gemcitabine monotherapy as treatment.

2. Discussion

To the best of our knowledge, this is the first clinical case with target sequencing data to show squamous cell transformation from *ALK*-rearranged ADC after treatment with an *ALK* tyrosine kinase inhibitor (TKI). Previously, histologic transformation was considered a consequence of treatment-induced selection pressure, in which a pre-existing SCC at the time of diagnosis would exhibit tumor dominance after elimination of the ADC. However, increasing evidence shows that transformed SCCs retain the same genomic alteration that was shown in the ADC. This finding supports the hypothesis of lineage transition during the TKI treatment. Interestingly, these reports were mainly in *EGFR*-mutated patients treated with an *EGFR* TKI [1–3]. Although the underlying mechanisms remain unclear, there is early evidence to support the idea that histologic transformation could be the result of genomic evolution in a specific pathway under treatment pressure. As a representative case, there was a report of *PIK3CA* mutation acquisition

* Corresponding author at: Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea.
E-mail address: jongmu.sun@skku.edu (J.-M. Sun).

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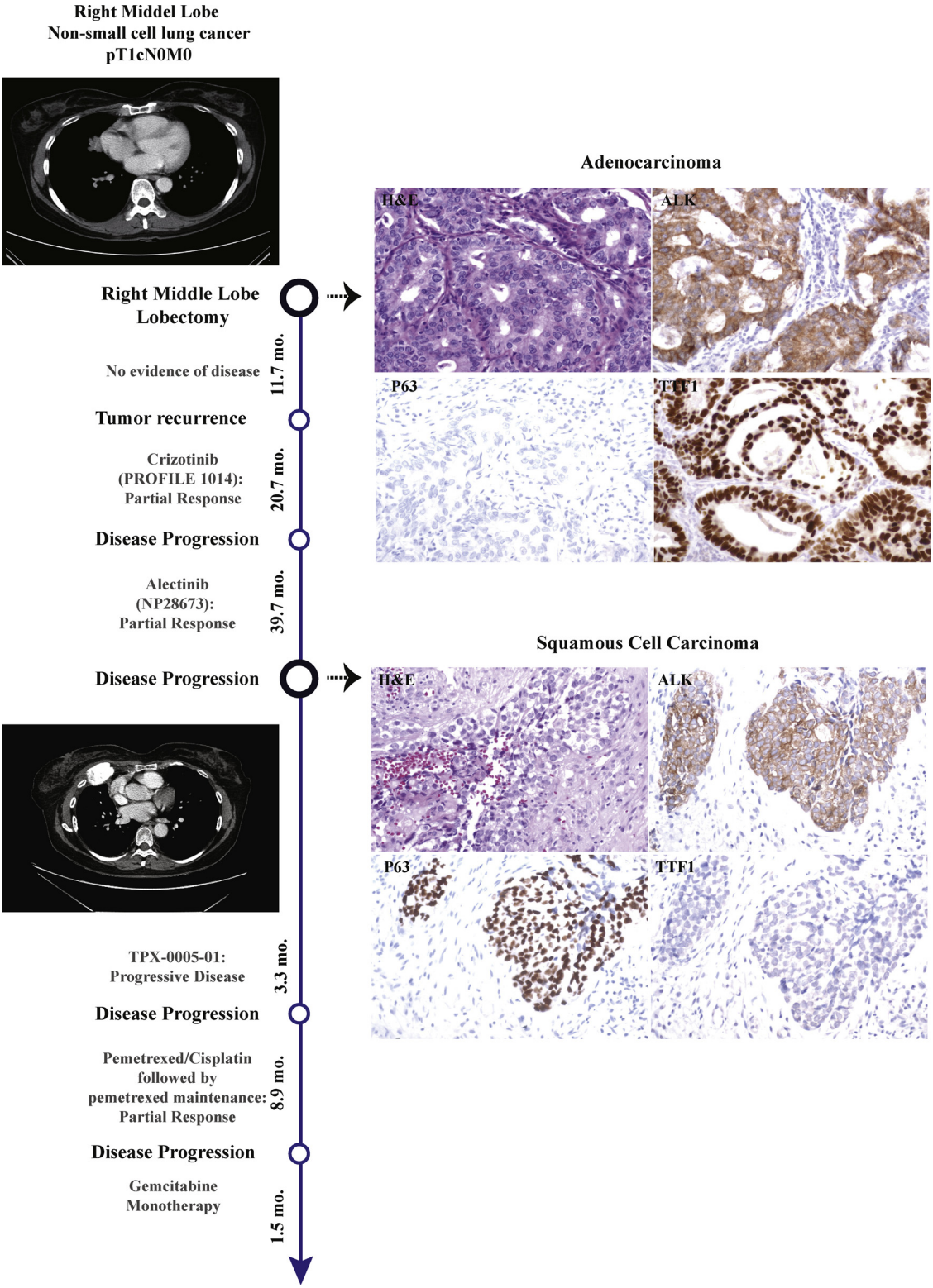

Fig. 1. Treatment history and pathology with immunohistochemistry (IHC) of the patient. IHC revealed that the baseline adenocarcinoma (ADC) sample was TTF-1-positive, while the transformed squamous cell carcinoma (SCC) was p63 positive. The baseline CT scan image and the image at the time point of SCC transformation were shown.

in a patient with a transformed SCC [4]. In the preclinical mouse mode, an *LKB1*- and *PTEN*-inactivated mouse was observed to show a transformation from ADC to SCC, which is also related to the *PI3K* pathway [5–8].

In our case, we conducted deep target gene sequencing (381 genes) of the ADC sample and the transformed SCC sample [3]. Both samples had an *EML4-ALK* variant 2 rearrangement. In addition, initial non-synonymous mutations in *BARD1*, *NOTCH4*, and *PTCH1* were also observed in the transformed SCC. As aforementioned, this finding provides clinical evidence of histologic transformation resulting from

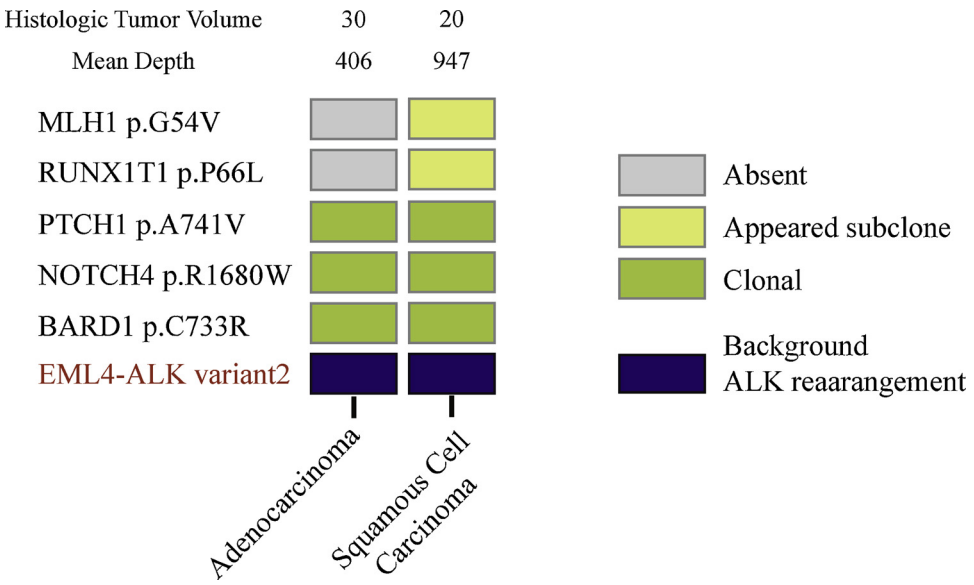

Fig. 2. The transformed sample maintained the initial *EML4-ALK* variant 2 rearrangement. Acquired mutations were observed in MLH1 and RUNX1T1. Tumor volume was calculated based on the total proportion of the tumor component in an entire cell observed on a slide, which was manually calculated by the pathologist. Mean depth was calculated based on the average number of reads per gene included in the target panel.

lineage transformation of tumor cells harboring an *EML4-ALK* rearrangement after treatment with *ALK* TKIs. However, our results were somewhat different than those of a previous report, which found that only *RUNX1T1* p.P66 L and *MLH1* p.G54 V were acquired in the transformed SCC; these had little relationship with the PI3K pathway. The interpretation of this finding must be further elucidated through future studies (Fig. 2 and Supplementary Table 1).

From a clinician's perspective, whether the transformed tumor would exhibit the characteristics of ADC or SCC was an important issue in determining subsequent cytotoxic chemotherapy. After discussion among the internal tumor board, we applied a pemetrexed and cisplatin treatment, followed by pemetrexed maintenance based on the initial ADC histology. A partial response has lasted for 8.9 months. This is comparably longer than the outcomes reported in a clinical trial conducted with ADC histology (PFS 6.9 months) [9]. This observation indicates that underlying characteristics of the transformed SCC could be similar to those of the ADC, despite having the morphology of an SCC. After undergoing progression to the pemetrexed treatment, the patient is currently under treatment with gemcitabine monotherapy (response not evaluated).

As aforementioned, the resistance mechanism in *ALK*-rearranged NSCLC treated with *ALK* TKIs is mostly based on underlying genomic alteration, with the mechanism unknown for nearly half of the population [10]. Based on our observations, the histologic transformation from ADC to SCC appears to be a novel resistance mechanism to *ALK* TKI.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.027.

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