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Case report

A successful pembrolizumab treatment case of lung adenocarcinoma after becoming resistant to ALK-TKI treatment due to G1202R mutation

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ABSTRACT

Background: In current guidelines, the role of immune checkpoint inhibitors is not yet determined in the treatment strategy for NSCLC harboring ALK translocations.
Case: A 51-year-old woman with lung adenocarcinoma harboring ALK translocation was treated with alectinib until PD. After the second (CDDP/PEM) and third (crizotinib) line treatment, a second biopsy was performed, revealing PD-L1 tumor proportion score of 70–80% and G1202R mutation of ALK. Pembrolizumab was selected for the fourth line, leading to PR for more than 6 months.
Conclusions: While alectinib might induce resistance to ALK-TKI, it could increase PD-L1 positive cells to become sensitive to PD-1/PD-L1 inhibitors.

1. Introduction

The number of deaths reached 70,000 for lung cancer in Japan [1]. On the other hand, the progression of medical therapies is striking these days in the field of non-small cell lung cancer (NSCLC), including molecular targeted therapies for patients with driver gene mutations, e.g., epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. While molecular targeted therapies demonstrated a high response rate for patients with driver gene mutations, additional mutations have been known to cause resistance to the inhibitors.

In addition, immune checkpoint inhibitors were developed for precision medicine with the companion examination of programmed cell death-ligand 1 (PD-L1) tumor proportion rate. The position of the immune checkpoint inhibitors is not yet determined in the course of NSCLC management for patients with driver mutations. We report a case of lung adenocarcinoma for which anti-PD-1 antibody was effective

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after it became resistant to ALK-tyrosine kinase inhibitor (TKI) because of G1202R mutation.

2. Case

A 51-year-old woman visited her primary care physician with a cough and fever. She was referred to our hospital because of a mass at the right hilum on her chest X-ray (Fig. 1) and diagnosed with lung adenocarcinoma according to the biopsy specimens by bronchoscopy of the primary site. Clinical stage was determined as T3N3M1b (ADR) stage IV [2]. Gene mutation analysis indicated negative EGFR mutations and positive ALK translocation (FISH positive, ALK iScore 3 by iAEP immunohistochemistry). PD-L1 was not examined at the time. Past medical history and physical examination on the first visit was unremarkable.

First line treatment was initiated with alectinib. Two months after, the treatment effect was determined as partial response (PR) for the primary tumor, the metastasis of the lymph nodes, and the adrenal gland was determined with a computed tomography (CT) scan (Fig. 2). Five months later, the CT scan revealed regrowth of the metastasis of the lymph nodes and the adrenal gland. The relapse was so early for treatment with alectinib that we performed bronchoscopy to confirm the histopathology. The biopsy specimens from the entry of B6 demonstrated adenocarcinoma with ALK translocation similar to the first biopsy. Second line treatment, cisplatin+pemetrexed, was continued for 5 cycles until becoming a progressive disease (PD) due to regrowth of mediastinal lymph nodes. Because of the adverse effects of the cytotoxic chemotherapy, general malaise, anemia, and renal insufficiency, she opted for the rechallenge of ALK-TKI, crizotinib, for the third line. Crizotinib was discontinued after 1 month due to visual disturbance.

Before starting the third line treatment, a second biopsy was performed for the screening of PD-L1 and ALK-TKI resistant mutation. The specimen revealed a tumor proportion score (TPS) of 70–80% with PD-L1 staining by PD-L1 IHC 22C3 pharmDx KIT (Fig. 3) and ALK G1202R. The ALK G1202R gene mutation was analyzed using deep sequence by Miseq®

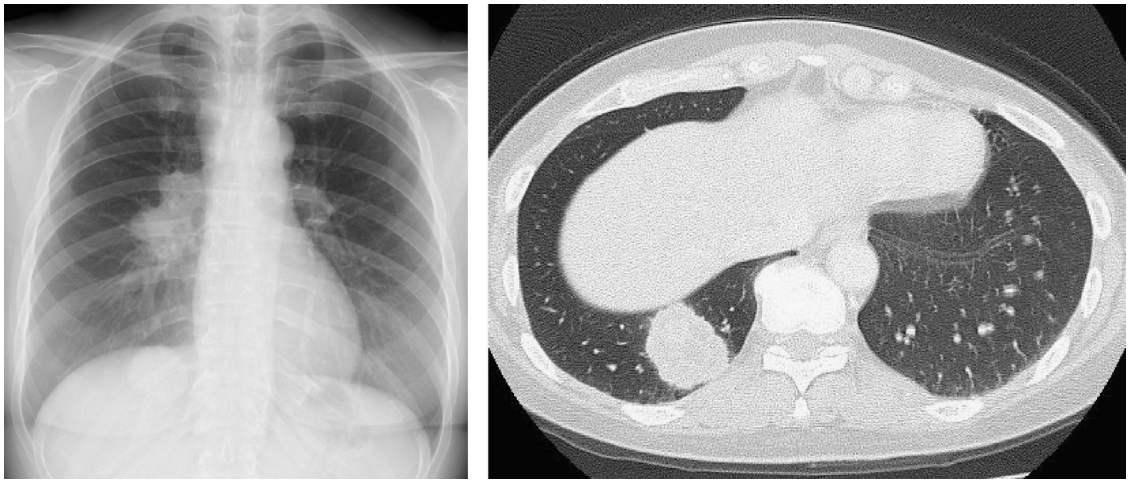

Fig. 1 – Left: A chest X-ray showed an abnormal shadow of a nodule in the right hilum and in the right lower field at the first visit to our hospital. right: Chest CT showed about a 4 cm nodular shadow in the right lower lobe at the same time.

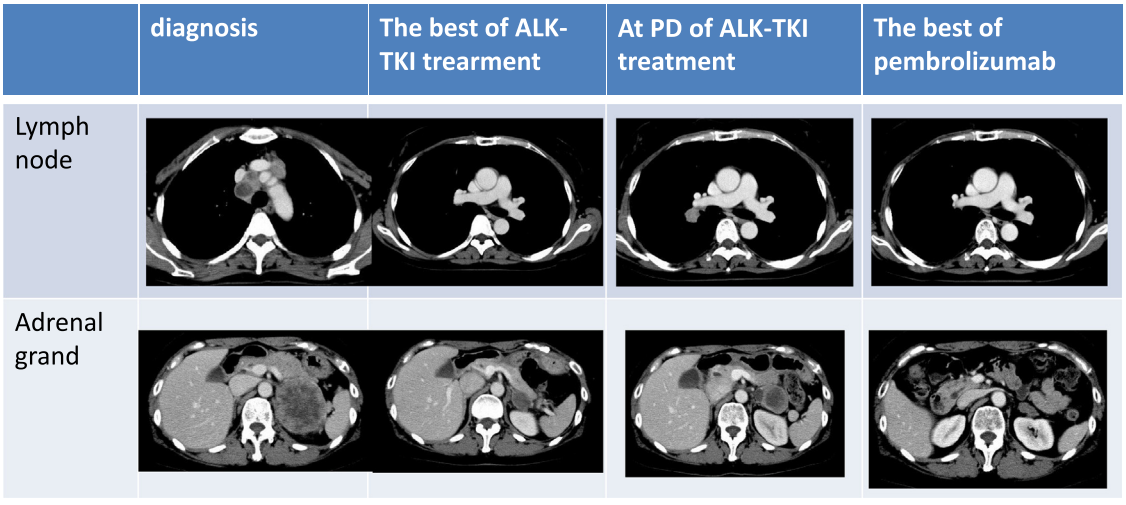

Fig. 2 – CT scans shows clinical course regarding the lymph node and adrenal gland. These are at the time of a diagnosis, the best of the ALK-TKI treatment, the PD of the ALK-TKI treatment, and the best of the pembrolizumab.