Case Report

Concurrent epidermal growth factor receptor mutation and anaplastic lymphoma kinase translocation in non-small cell lung carcinoma: A therapeutic conundrum

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ABSTRACT

In non-small cell lung cancer (NSCLC), two key genetic alterations, epidermal growth factor receptor (EGFR) mutations, and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (ALK) rearrangements are commonly believed to be mutually exclusive. Studies have reported that concurrent EGFR/ALK co-mutation in NSCLC patients is rare, with a prevalence ranging from 0.1% to 1.6%. In this case report, we present the case of a 49-year-old female with stage IV lung adenocarcinoma with both EGFR mutation and ALK rearrangement. The patient received treatment with EGFR tyrosine kinase inhibitors, but the disease progressed and the patient succumbed to her disease. Our report also provides a comprehensive summary of the clinical and pathological features, as well as treatment strategies, for NSCLC patients with concurrent EGFR mutation and ALK rearrangement.

Key words: Anaplastic lymphoma kinase, Epidermal growth factor receptor, Tyrosine kinase inhibitors

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80–85% of cases [1]. In recent years, molecular genetic research on lung cancer has made remarkable progress, and the treatment of NSCLC has entered the era of targeted therapy. The most common driver gene mutation in NSCLC is epidermal growth factor receptor (EGFR), which is found in 45% of Asian patients and 20% of Caucasian patients with adenocarcinoma histology [2]. In individuals with sensitizing EGFR mutations, EGFR-tyrosine kinase inhibitors (TKIs) are suggested as first-line treatment. Anaplastic lymphoma kinase (ALK) rearrangement is less common than EGFR mutation, occurring in approximately 5% of NSCLC patients [3]. ALK-TKIs are indicated as first-line treatment for individuals with ALK rearrangement. Early studies showed that ALK positivity and EGFR mutation are mutually exclusive and cannot coexist. Although they are considered to be mutually exclusive, recent studies have shown that in some cases, although rarely, both EGFR mutation and ALK translocation can coexist [4].

Hence, the rationale of this case report is to discuss an approach to such a rare case and its management.

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CASE PRESENTATION

A 49-year-old, diabetic female (history of diabetes for 5 years; well controlled on oral hypoglycemic agents), non-smoker, with no family history of cancer, had chief complaints of right-sided chest pain, cough with mild hemoptysis, and significant weight loss over 2 years. The pain was deep-seated, gradually increasing in intensity with no radiation, not aggravated by any factors, and relieved by medications.

On auscultation, breath sounds were decreased on the right side of the chest. Vitals of the patient on presentation were blood pressure – 106/66 mmHg, SpO_2 – 95% on room air, pulse rate – 86/min, and respiratory rate – 17/min. The Eastern Cooperative Oncology Group performance status score was 2.

Her laboratory investigations revealed raised random blood sugar of 264 mg/dL (normal range <200 mg/dL), hemoglobin of 10.1 g/dL (normal range – 12–16 g/dL), total leukocyte count of 5.5 × 10^9/L (normal range – 4.5–11 × 10^9/L), platelet count – 3.7 × 10^9/L (normal range – 150–400 × 10^9/L), serum creatinine – 1.1 (normal range – 0.6–1.1 mg/dL), and total bilirubin of 0.8 (normal range – 0.3–1.2 mg/dL). Serum electrolytes were within normal limits. Sputum for acid–fast bacilli was negative.

Chest X-ray (CXR) posteroanterior (PA) view of the patient (Fig. 1) dated June 8th, 2023 showed a mass in the right upper lobe and costophrenic angle blunting on the right side. CXR

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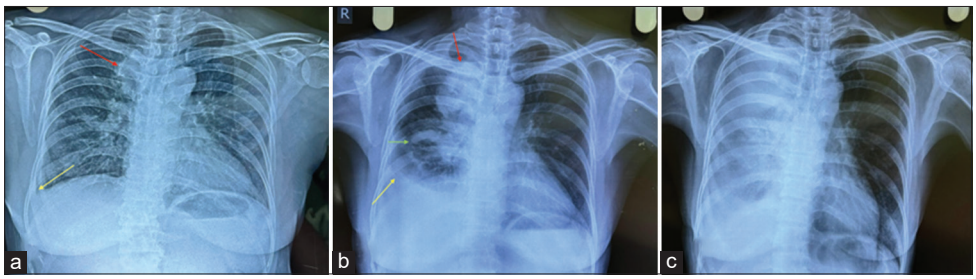

Figure 1: Chest X-ray posteroanterior view (a) Chest X-ray dated June 8th, 2023 showing a mass in right upper lobe (red arrow) and costophrenic angle blunting on right side (yellow arrow) (b) Chest X-ray dated March 22nd, 2024 showing right upper lobe mass (red arrow) which has increased in size with right lower lobe cavity (green arrow) with mild right-sided pleural effusion (yellow arrow) (c) Chest X-ray dated July 5th, 2024 showing complete right-sided lung collapse

dated March 22nd, 2024 revealed an increase in the size of the right upper lobe mass with the right lower lobe cavity with mild right-sided pleural effusion. CXR dated July 05th, 2024 indicated complete right-sided lung collapse with mediastinal shift toward the ipsilateral side.

Computed tomography (CT) thorax and abdomen (Fig. 2) showed a large heterogeneously enhancing mass lesion (11 × 7.5 × 5 cm) in the right upper lobe of the lung extending into the perihilar location. There was encasement of hilar vessels and upper and middle lobar bronchi with luminal narrowing. There was resultant collapse consolidation in the right upper and middle lobes. There was moderate loculated right-sided pleural effusion with diffuse pleural thickening and nodular pleural deposits. Prominent enlarged heterogeneously enhancing mediastinal lymph nodes were seen, larger measuring 22 × 16 mm in subcarinal location-suggestive of metastatic lymph nodes.

Cytology of the pleural fluid showed small clusters of atypical cells with a moderate amount of cytoplasm and round-to-oval hyperchromatic nuclei; background shows lymphocytes and few mesothelial cells, hence pleural fluid was positive for malignancy.

CT-guided trucut biopsy from the right lung lesion showed invasive adenocarcinoma (acinar predominant). Cells were arranged in cohesive sheets and acinar structures. They have moderate cytoplasm and round-to-oval nuclei with finely granular chromatin and prominent nucleoli (Fig. 3). Based on these findings, the patient was diagnosed with stage IVA right upper and middle lobe adenocarcinoma, T4N2M1a.

Further molecular screening using real-time polymerase chain reaction (PCR) revealed the presence of EGFR 21 exon mutation for both L858R and L861Q and echinoderm microtubule-associated protein-like 4- ALK (EML4-ALK) fusion. The test was conducted using the TRUPCR-IVD kit (real-time PCR method), and the detection instrument used was QuantStudio 5 by ThermoFisher Scientific (Fig. 4).

In view of the indolent nature of ALK-positive disease, therapy targeting EGFR was started. The patient was started on tablet gefitinib 250 mg once daily and the patient took this targeted therapy for 4 months. During the course of the treatment, the patient suffered from hepatotoxicity and hyperglycemia. After 4 months of treatment, the patient's chest pain worsened; CXR PA view showed right-sided lung collapse. Pulmonary medicine consultation and repeat imaging were advised but the patient was lost to follow-up. The patient succumbed to her disease 2 months after loss to follow-up.

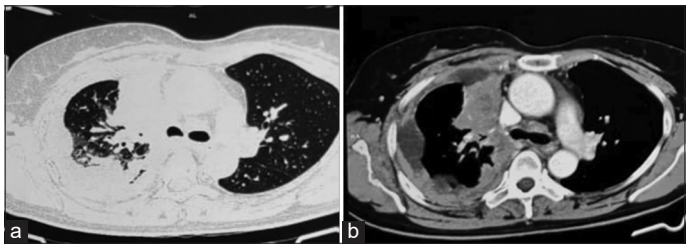

Figure 2: Sagittal view of computed tomography of the patient (a) Lung window (b) Mediastinal window

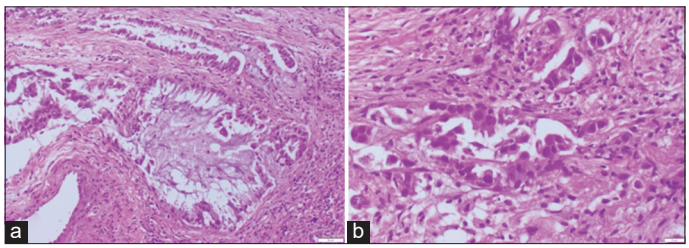

Figure 3: (a) Histopathology of adenocarcinoma lung; hematoxylin and eosin (H and E) staining, 10× (b) H and E, ×20

DISCUSSION

Although ALK rearrangements and EGFR mutations were previously reported to be mutually exclusive, several studies have shown that ALK fusions can occur concurrently with EGFR mutations [5]. Yang *et al*. reviewed 977 NSCLC surgical regimens and found that 1.3% of samples had both mutations [6]. The patients most likely to have both EGFR and ALK mutations tend to be young, non-smokers, with advanced disease at diagnosis, and adenocarcinoma classification of disease [7]. Although our patient is middle-aged, the rest of the description of this study matches our patient profile.

Two different hypotheses exist to explain the presence of dual-driver mutations. The first hypothesis is that genetic instabilities can cause genetic and phenotypic heterogeneity in the tumor, leading to different genetic alterations in different tumor cells rather than in a single clone of cells. The second hypothesis is that there can be activation of multiple oncogenic pathways due

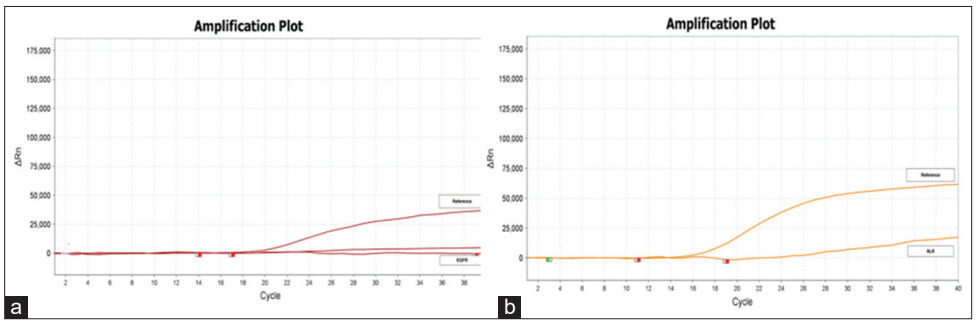

Figure 4: Amplification plot by real-time polymerase chain reaction for (a) epidermal growth factor receptor and (b) anaplastic lymphoma kinase

to alteration in a single clone of tumor cells [8].

Lou *et al*. reported that first-line EGFR-TKI treatment might be appropriate for patients with advanced NSCLC harboring concomitant EGFR mutation and EML4-ALK rearrangement, but other studies suggested that ALK inhibitors could be used first for dual-positive patients, particularly those with low abundance of EGFR mutants [9]. So far, there is no general consensus on the best treatment strategy for patients with EGFR/ALK co-alterations. Hence, we started our patient on EGFR-TKI in view of the indolent nature of ALK-positive disease. In a literature review of 100 cases by Lo Russo *et al*., the disease control rates using EGFR (n = 53) and ALK (n = 39) TKIs were 69.8% versus 79.5%, respectively, and overall response rates were 43.4% and 51.3%, respectively. About 22 patients in this review series received EGFR TKIs followed by ALK TKIs [10]. Our patient succumbed to the disease before we could switch the treatment. Liu *et al.* also reported that patients with co-occurring EGFR and *ALK* alterations treated with EGFR-directed oral TKIs had a significantly shorter progression-free survival (PFS) (6 months) compared to patients with non-EGFR/ALK co-alterations (15 months), p=0.046 [11].

Different response rates might be explained considering the intratumor heterogeneity of both genes, strictly related to gene mutation tumor burden. Therefore, the mutation tumor burden of each mutation could affect the targeted therapy response [12]. Variant allele frequency (VAF) is the percentage of a specific sequence reads (DNA variant) observed divided by the overall coverage at that locus. VAF acts as a surrogate to measure the proportion of variant DNA molecules carried in the tumor biopsy/specimen. In a study by Friedlaender *et al*., high allelic frequency was significantly associated with PFS but not overall survival [13]. It implies that therapy can be individualized based on VAF, especially when dual-driver mutations/heterogeneity exist depending on the mutation with high VAF. These hypotheses need to be validated in randomized control trials.

In patients with dual mutations, the mechanism of primary resistance to targeted therapies may be unique and is yet to be elucidated. At least one of the more recently discovered molecular drivers such as ROS 1, C-MET/RON, RET, or PIK3CA may play a role [14]. At this time, there is insufficient data to guide the selection of EGFR versus ALK inhibition as initial therapy, and both approaches remain justifiable.

CONCLUSION

We presented a case of a patient with both EGFR mutation and ALK rearrangement, who experienced clinical disease progression on EGFR-TKI. According to guidelines, as part of the initial diagnosis, EGFR, ALK, KRAS, and other gene mutations must be detected before treatment. Oncologists must take into account the presence of dual or multiple oncogenes when selecting the most suitable therapeutic strategies, which may include combination or sequential treatment methods. However, more research is required to gain a deeper understanding of therapeutic approaches in patients with both EGFR mutation and ALK rearrangement considering we have a scant number of studies for the same.

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