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Case Report: Afatinib Monotherapy for Double-Primary Locally Advanced Non-Small Cell Lung Cancer Exon-21 L861q Mutation with History of Colorectal Cancer

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Abstract

Introduction: Uncommon mutation exon-21 L861Q is a rare type Non-Small Cell Lung Cancer (NSCLC). Despite the limited data regarding this type of mutation, Afatinib as one of the oral tyrosine kinase inhibitors (TKI) shows good anti-tumor activity.

Clinical Features: A 50-year-old woman with a history of post-operative colorectal cancer (2014) without undergoing chemotherapy and radiotherapy; came in October 2020 with severe dyspnea due to massive pleural effusion with a right lower lung bulky mass. Histopathology in 2014 was a low-grade adenocarcinoma colorectal cancer, while the biopsy of the right lung mass in 2020 was a mucinous adenocarcinoma, ALK-negative, TPS 1.75, and exon-21 L861Q mutation.

Intervention and Outcomes: The patient underwent thorax drainage to evacuate pleural effusion fluid. Through multidisciplinary discussions, the patient was recommended to take the oral drug TKI Afatinib 40 mg QD in January 2021. On the 2nd week of taking Afatinib, the patient complained of painful swallowing, mouth sores, sore tongue, and joint pain throughout the body; confirmed to be the side effects of the drug. Complaints diminished with supporting drugs, however, did not resolve completely. CT scan in April 2021 showed a significant reduction in lung mass. Due to severe side effects and drastic weight loss, the Afatinib dose was reduced to 20 mg QD. Radiotherapy was incorporated in her treatment session with IMRT to cover the whole tumor.

Discussion: Determining the best treatment to treat the patient was initially difficult due to the raising doubt regarding the correlation between the current lung cancer with her previous history of colorectal cancer. Treating the newer lung mass as primary cancer was obviously different rather than treating lung metastatic colorectal cancer. This issue could then be resolved by incorporating more thorough NGS examination. With the finding of exon-21 L861Q mutation in this patient, Afatinib monotherapy is considered the therapy of choice.

Keywords:

lung cancer, colorectal cancer, uncommon mutation, NSCLC, exon 21, L861Q, Afatinib.

Introduction

Tyrosine kinase inhibitors (TKI) have become standard therapy in lung cancer patients with Epidermal Growth Factor Receptors (EGFR) mutations. Currently, there are three generations of TKI, the first generation is EGFR-reversible TKIs, gefitinib and erlotinib; second-generation is EGFR-irreversible TKIs, dacomitinib and afatinib; and the third generation which is also EGFR-irreversible TKI, osimertinib. Most clinical research data showed encouraging results of administering TKI to approximately 45% of all non-small cell lung cancer (NSCLC) patients, particularly those with EGFR mutations such as exon-19 deletion and L858R mutation.1,2 About 20% of NSCLC patients are presenting uncommon mutations such as, exon-20 insertion; G719X, L861Q, S768I mutations, and exon-19 insertion; which were predominantly excluded in larger studies, however, data from various smaller studies have shown that Afatinib, a second-generation EGFR TKI; actually provides promising results.[1–3]

The occurrence of two primary cancers encountered in one patient has been reported frequently in case reports or case series due to their limited data collection. The phenomenon is suspected heavily

related to genetic disturbances or mutations; allowing these individuals to be more susceptible to certain cancers in any period of their lifetime. EGFR mutations are closely related to the incidence of malignancies in brain (glioblastoma), head and neck, pancreatic, colorectal, lung, kidney and bladder. Likewise, BRCA-1 and BRCA-2 mutations are closely related to the incidence of breast, ovarian, thyroid, pancreatic, prostate and liver cancer1. In colorectal cancer, however, though the incidence is increasing, EGFR mutations are not very common.[1,4]

Nowadays, mutational gene mapping with Next Generation Sequencing (NGS) is being incorporated since the beginning and becoming the new standard of diagnostic tool. The gene mutation profile can accurately guide the clinicians in determining the best treatment for the patient.[5,6]

Afatinib is a second-generation TKI that irreversibly binds to EGFR, thereby inhibiting homo- or hetero-dimer signals from the ErbB receptors family. As the result of this inhibition, cancer cells proliferation permanently halted, losing their ability to repopulate, only living up to their age limit of cells which ranges from 250-400 days. However, cancer stem cells could become dormant or in apparent death, which could be activated after some time. This should be taken into account to provide long-term monitoring of patients to anticipate cancer recurrences.[1]

For NSCLC patients with commojn mutation of exon-19 deletion and exon-21 mutations; Afatinib is the first line recommended therapy as par to conventional chemotherapy, which significantly increases Progression-Free Survival (PFS) and Overall Survival (OS). Likewise, in uncommon mutation NSLSC, Afatinib still shows promising results and lower toxicities compared to conventional chemotherapy.[4–7]

Clinical Presentation

Mrs. E, 50 year-old female, presenting complaints with severe dyspnea for more than 2 weeks, accompanied by chest pain laterally on the right, and cough sometimes accompanied by blood. On physical examination, the frequency of breathing was fast and shallow; on auscultation, breathing sounds were not identified in the middle to lower segments of the right lung. Liver is palpable but difficult to define as hepatomegaly or an encroaching right lung mass. Patient had worsening breathlessness when lying down, and she preferred semi-sitting position that unable her to be examined with CT scan.

Patient had a history of colorectal cancer and had surgery in 2014, which was 6 years before this term of admittance. The patient did not continue her colon cancer treatment with radiotherapy or chemotherapy, due to her anxiety towards the side effects of therapy.

She started her treatment with immediate installation of thorax-drain to evacuate the effusion that caused respiratory distress. The fluid from her pleural effusion was haemorrhagic, with fluid cytology results confirmed to be malignant cells. On this occasion, a tissue biopsy was performed by the thoracic surgeon, using the core-biopsy method. Three days after drainage, her breathing pattern was improving and she was able to lie down. She underwent Thorax CT-Scan with contrast, revealing a bulky mass in the lower right lung (Figure 1).

The histopathology of the lung mass was reported three days later, confirmed to be a mucinous

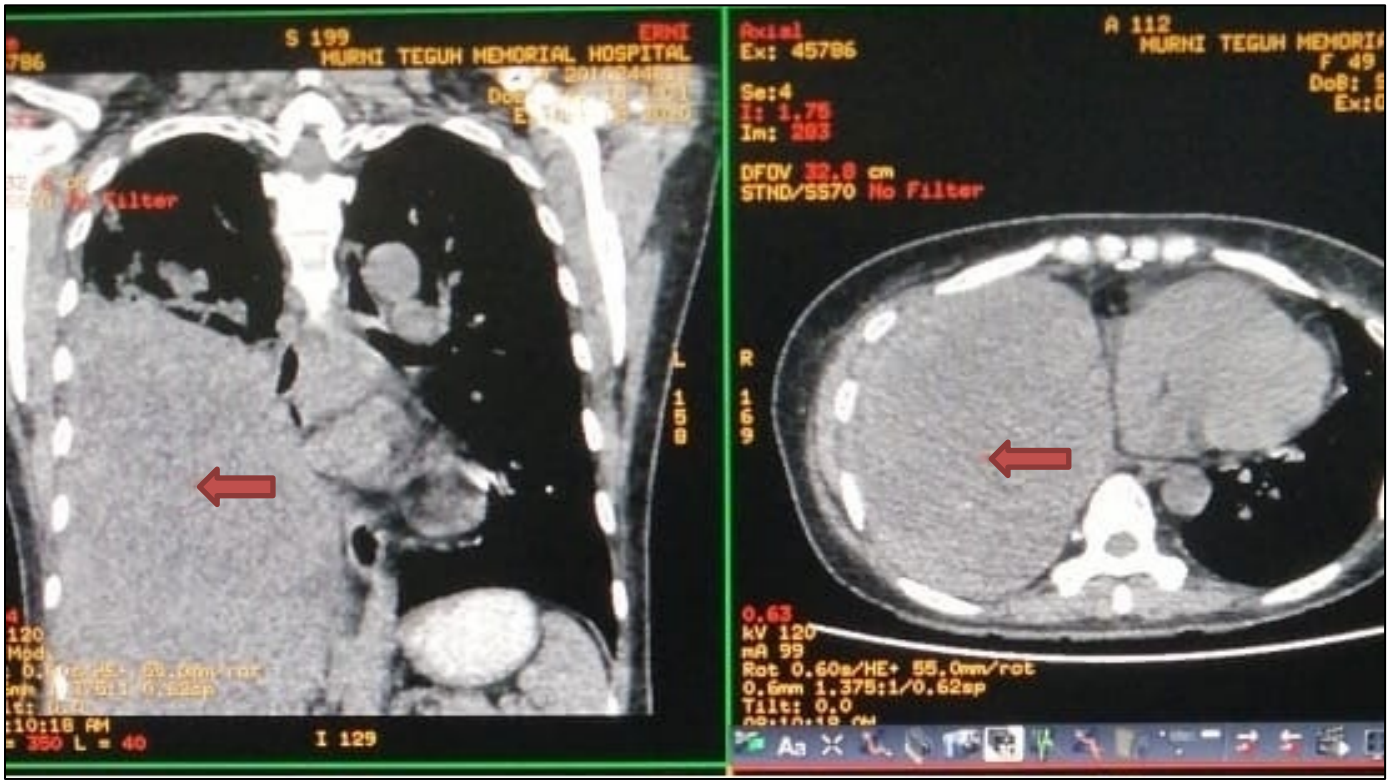

Figure 1. The first chest CT-Scan shows a large right lung mass.

adenocarcinoma of the lung. Examination with NGS concluded to be ALK-negative, PDL1 with TPS Score 1.75, and an exon-21 with L861Q mutation was detected. There was no metastatic lesion in other part of the body.

Intervention and Results

With the finding of the exon 21 L861Q mutation, the patient was recommended to start taking continuous oral TKI Afatinib 40 mg once daily; taken as a whole and not to be crushed by any means, before meal. According to the multidisciplinary discussion, she was originally planned to undergo radiotherapy, but due to the location of the mass at the bottom of the right lung, which was closely attached to the liver, radiotherapy was postponed. She was discharged, and she routinely came for wound care and blood tests to anticipate drug side effects.

On the second week of observation, she began to complain about painful swallowing, mouth sores, tongue sores and progressive joint pain throughout the body; confirmed as the adverse effect of Afatinib. Furthermore, she complained of not being able to rest or do activities; itching skin rashes appeared and loss of appetite. She was prescribed oral medication Lansoprazole 30 mg qd, Celecoxib 100 mg bid, Loratadine 10 mg qd, Megesterol acetate 800 mg qd and Betamethasone topical cream. Complaints did not completely disappear but reduced to the level of tolerable without dose adjustment.

In April 2021, a Thorax CT-Scan with contrast was repeated. There was a remarkable impression of a significant reduction in lung mass (Figure 2). Though, she still complained of the same side effects, with a very significant weight loss from 46 kg at the start of therapy to 38 kg. Nutritional counseling was carried out to maintain and increase her body weight, however, monitoring in the next three months, her body weight still did not increase, so the clinician decided to reduce the dose of Afatinib to 20 mg qd. She was then referred to Department of Radiation Oncology, to start her Radiotherapy session, to cover the bulky lung tumor up-to 60 Gy in 30 fractions using Intensity-Modulated Radiotherapy (IMRT) with Elekta Versa HD. The patient was immobilized using a thermoplastic mask placed on the thorax. The free breathing technique was employed due to inability to hold the breath effectively. Spirometry was not conducted before and after radiation treatment due to dyspnea during the treatment. The radiation planning evaluation was; PTV V95% = 100%, PTV V107% = 0%, Heart Dmean 29,41 Gy, Lung Left V20= 40%.

Discussion

Tailoring the best treatment for a patient with special attention in this setting is always advisable to be discussed in a multidisciplinary team. The main problem at the time of patient admission was to ascertain whether the right lung bulky mass arises as a metastasis from her previous colorectal cancer; or on the contrary, was a second primary cancer, considering the timespan between the two occurrences was approximately 6 years. In addition, the histopathological finding ofthe colorectal cancer in year 2014 was not comprehended with immunohistochemistry staining or genetic mapping. As she was previously treated abroad, re-examination of paraffin block was obviously difficult. Thus, clinicians were unable to compare the genetic profiling of her previous colorectal cancer cells with the newer finding of her lung cancer cells she recently had.

Taking into account as per her latest data: a) only one solitary lesion was found in her right lung without any involvement of other organs; b) the time

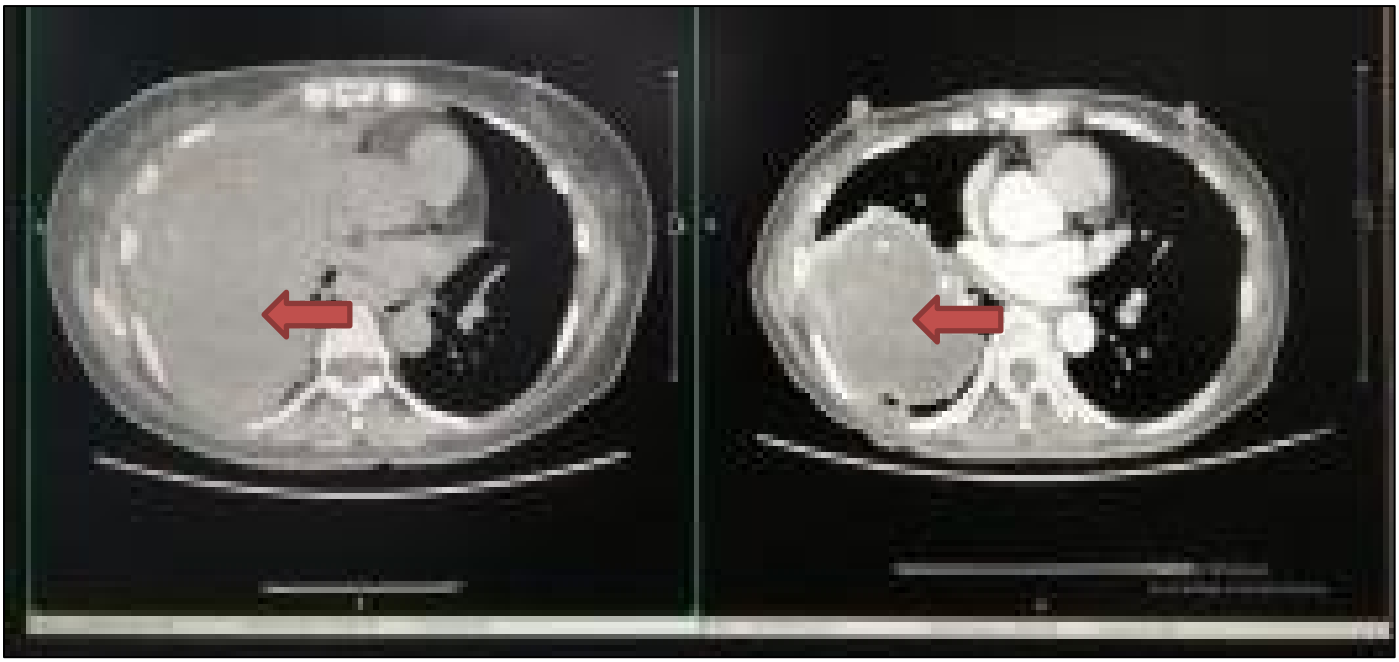

Figure 2. Comparison of chest CT scan of lung masses before (left) and 3 months after (right) consumption of Afatinib.

interval between the two cancers occurrence, which was 6 years adrift; c) colorectal cancer population is less likely to detect EGFR mutations; the clinicians decided to treat the patient as a primary lung cancer case, instead of lung metastatic colorectal cancer. This decision is crucial in determining the treatment regimen to be administered to achieve better outcome.

According to a report from the American Association for Cancer Research (AACR) through the GENIE Project, which collaborates with various international institutions to collect massive data; the exon-21 L861Q mutation was found in 0.14% of all cancer cases, including lung adenocarcinoma, brain anaplastic astrocytoma, colorectal adenocarcinoma and clear cell kidney cancer.[8] These precious data is becoming the basis for the clinician's consideration of prescribing oral Afatinib, in conjunction with other various publications showing a promising response of Afatinib to the exon-21 L861Q mutation, and especially in this patient whom had double primary of lung cancer and previous colorectal cancer.[5–7]

Afatinib monotherapy is quite effective in the treatment of various cases, especially NSCLC and other type of cancers. Combination of Afatinib with a MEK-inhibitor Selumetinib has been tested in phase I colorectal cancer, and NSCLC with KRAS mutations, obtaining quite promising results but higher toxicity profile was found to be very challenging either.[9]

Conclusion

A comprehensive examination and adequate comparative data are needed to be able to determine which best treatment is recommended for this case of double-primary cancer. The correlation between previous colorectal cancer with the newer lung cancer could be traced retrospectively by identifying the genetic mutations. With the recent development of NGS, these genetic mutation profiles could be detected sooner, without compromising the high accuracy.

Afatinib as monotherapy is quite effective in treating NSCLC with exon-21 L861Q mutations. The main obstacle experienced by our patient, is that the side effects of the drug are quite severe while consuming a dose of 40 mg qd. Dose reduction is inevitable, being down to 20 mg qd to ensure continuity of her treatment. However, the aim of this patient's treatment was considered to be a palliative setting, mainly to improve the patient's quality of life.

The main obstacle for clinicians and patients is that only limited data and publications are available for double primary cases. Other issues are, Afatinib itself is not vastly available, not covered by National Health Insurance, and the price of the drug is still very expensive.

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