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CASE REPORT

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A case of multiple primary lung adenocarcinoma with a CD74-NRG1 fusion protein and HER2 mutation benefit from combined target therapy

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Abstract

Neuregulin 1 (NRG1) gene fusion is a rare oncogenic driver gene in multiple tumor types, leading to the activation of the epidermal growth factor receptor (ErbB)-mediated pathway. Therefore, afatinib, a pan-ErbB family inhibitor, may be a therapeutic candidate for NRG1 fusion-driven tumors. In this case, we report a multiple primary lung adenocarcinoma patient harboring the CD74-NRG1 fusion, epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (ERBB2) mutation simultaneously. The patient received afatinib and pyrotinib combination therapy and showed a significant treatment response with a progression-free survival of 5 months. Our case further supports the use of targeted therapy for NRG1 fusion-positive non-small-cell lung cancer.

KEYWORDS
afatinib, lung adenocarcinoma, NRG1 gene fusion, pyrotinib, targeted therapy

INTRODUCTION

Personalized targeted therapy has significantly improved the survival of non-small-cell lung cancer (NSCLC).[1] Identifying novel oncogenic drivers can improve the standard of care for treatment of NSCLC. Neuregulin 1 (NRG1) gene fusions have been well established as an emerging oncogenic driver gene in recent years. NRG1 contains an epidermal growth factor (EGF)-like domain, which combines with human tyrosine kinases of the ErbB/human epidermal growth factor receptor (HER) receptor family, especially ErbB3 and ErbB4, resulting in heterodimerization (ErbB3/HER2 or ErbB3/ErbB4, or ErbB4/HER2) and activation of ErbB-mediated downstream signaling pathways.[2]

NRG1 gene fusions have been found in several tumor types, such as NSCLC, colorectal cancer (CRC), cholangiocarcinoma, pancreatic cancer, and pancreatic ductal adenocarcinoma (PDAC).[3,4] In a published report, NRG1 fusions in NSCLC have been described more frequently in the invasive mucinous adenocarcinoma subtype.[3] The prevalence of NRG1 fusion in lung cancer is relatively low compared with other common driver gene mutations.[5] In a study, NRG1 fusions were found in 25 of 9592 NSCLC cases (0.26%).[3] The most common NRG1 fusion partners in lung cancer were CD74 and SDC4.[3]

Afatinib, a first-line treatment option for patients with metastatic EGFR-mutated NSCLC, is an oral, irreversible tyrosine kinase inhibitor that inhibits ErbB signaling. Afatinib irreversibly binds to EGFR (ErbB1), HER2 (ErbB2), and ErbB4, and blocks transphosphorylation of ErbB3,[6] making it a treatment option for patients with NRG1 fusion-driven tumors. Afatinib has demonstrated activity in preclinical tumor models with NRG1 fusions.[7,8] Many published case reports have described responses to afatinib in patients with solid tumors harboring NRG1 fusions.[9–11] However, there is limited clinical evidence on treatment effects of EGFR targeted therapies such as afatinib in NRG1 fusion-positive

lung cancer due to the relatively low frequency of NRG1 fusions.

In this article, we present a Chinese patient with multiple primary lung adenocarcinoma harboring NRG1 fusion. Our case supports the use of targeted therapy for NRG1 fusion-positive NSCLC, adding to existing available data regarding the potential of afatinib as targeted therapy in this setting.

CASE PRESENTATION

A 62-year-old female, never-smoker, had multiple nodules (right upper lobe and left lower lobe of the lung) detected in a routine chest CT screening in November 2020. The positron emission tomography-computerized tomography (PET-CT) suggested that a solid nodule (2.2×2.1 cm) and a ground-glass nodule (1.5×1.5 cm) in the right upper lobe of the lung, the FDG metabolism was high in the solid nodule while normal in the ground-glass nodule, both of which were assumed to be malignant lesions. A ground-glass hilar mass (3.1×3.2 cm) in the left lower lobe of the lung with elevated FDG metabolism was also assumed to be malignant.

The patient underwent video-assisted thoracoscopic (VATS) right upper lobectomy with mediastinal lymph node dissection from November 2020. The postoperative pathology showed invasive adenocarcinoma with a papillary (60%), acinar (30%), and micropapillary pattern (10%) in specimen A, the tumor size was 2.5×2.2×2 cm and Spread Through Air Spaces (STAS) was observed. In specimen B, the pathology showed invasive adenocarcinoma with acinar (70%) and mural-type (30%), the tumor size was 2.5×2×2 cm with 2/5 lymph nodes metastatic (the paratracheal and tracheobronchial regions)

The results of genetic testing are shown in Table 1. The postoperative genetic profile indicated CD74-NRG1 fusion (allele frequency 21.85%), ATM exon 32 frameshift mutation (p.Q1620fs) and PD-L1 expression<1% in specimen A, while EGFR exon 21 p.L858R mutation (10.27%) and PD-L1 expression 1% in specimen B. The genetic testing of the paratracheal metastatic lymph nodes indicated ERBB2 exon 20 insertion mutations (p.Y772_A775dup) (allele frequency 0.53%), CD74-NRG1 fusion (allele frequency 6.06%), ATM exon 32 frameshift mutation (p.Q1620fs) (allele frequency 6.22%), MTOR exon 3 missense mutation (p.S56N) (allele frequency 56.62%), and PD-L1 expression<1%. The genetic testing of the tracheobronchial metastatic lymph nodes indicated ERBB2 exon 20 insertion mutations (p.Y772_A775dup) (allele frequency 3.89%), NF1 exon 17 nonsense mutation (p.628*) (allele frequency 7.12%), and 1% ≤ PD-L1 expression<50%. The patient received two cycles of pemetrexed and carboplatin from January 2021 to February 2021. The patient stopped the adjuvant chemotherapy and had an examination and treatment for the left nodule because she was worried about the lesion in the left lung.

The needle biopsy of the left lower lobe lesion showed adenocarcinoma, PD-L1 expression was negative, and the genetic testing indicated ERBB2 exon 20 insertion mutations (p.Y772_A775dup) (allele frequency 14.21%) and an NF1 exon 17 nonsense mutation (p.628*) (allele frequency 17.47%). The patient underwent Cyberknife treatment of the left lower lobe lesion in June 2021.

The chest CT showed a lesion in the left lower lobe of the lung and left pleural effusion in August 2021, and the patient received a diagnostic thoracentesis. The cytopathology indicated that cancer cells were found in pleural fluid, which confirmed the pleural metastasis. The patient was therefore diagnosed as stage IV lung adenocarcinoma. However, the remaining pleural effusion was inadequate for gene detection. This patient rapidly progressed after pemetrexed-based adjuvant therapy. EGFR mutation was found only in the primary lesion. Then she received treatment according to IMpower130. She was treated with atezolizumab plus albumin-bound paclitaxel and carboplatin for two cycles from August 2021 to September 2021. Neck-thoraco-abdominal CT showed the tumor was stable (Figure 1b), but brain magnetic resonance imaging (MRI) suggested multiple brain metastasis in October 2021. The genetic testing of peripheral blood did not reveal EGFR, ALK, KRAS, BRAF, ROS1, RET, NTRK1, ERBB2 or Met gene mutation.

TABLE 1 Results of genetic testing

Region	Pathology	Genetic testing	PD-L1 expression
Nodule of right upper lobe (specimen A)	Adenocarcinoma	CD74-NRG1 fusion ATM exon 32 frameshift mutation (p.Q1620fs)	<1%
Nodule of right upper lobe (specimen B)	Adenocarcinoma	EGFR exon 21 p.L858R mutation	1%
Left lower lobe lesion	Adenocarcinoma	ERBB2 exon 20 insertion mutations (p.Y772_A775dup) NF1 exon 17 nonsense mutation (p.628*)	Negative
Paratracheal lymph nodes	Metastatic adenocarcinoma	ERBB2 exon 20 insertion mutations (p.Y772_A775dup) CD74-NRG1 fusion ATM exon 32 frameshift mutation (p.Q1620fs) MTOR exon 3 missense mutation (p.S56N)	<1%
Tracheobronchial lymph nodes	Metastatic adenocarcinoma	ERBB2 exon 20 insertion mutations (p.Y772_A775dup) NF1 exon 17 nonsense mutation(p.628*)	1% ≤ PD-L1 < 50%

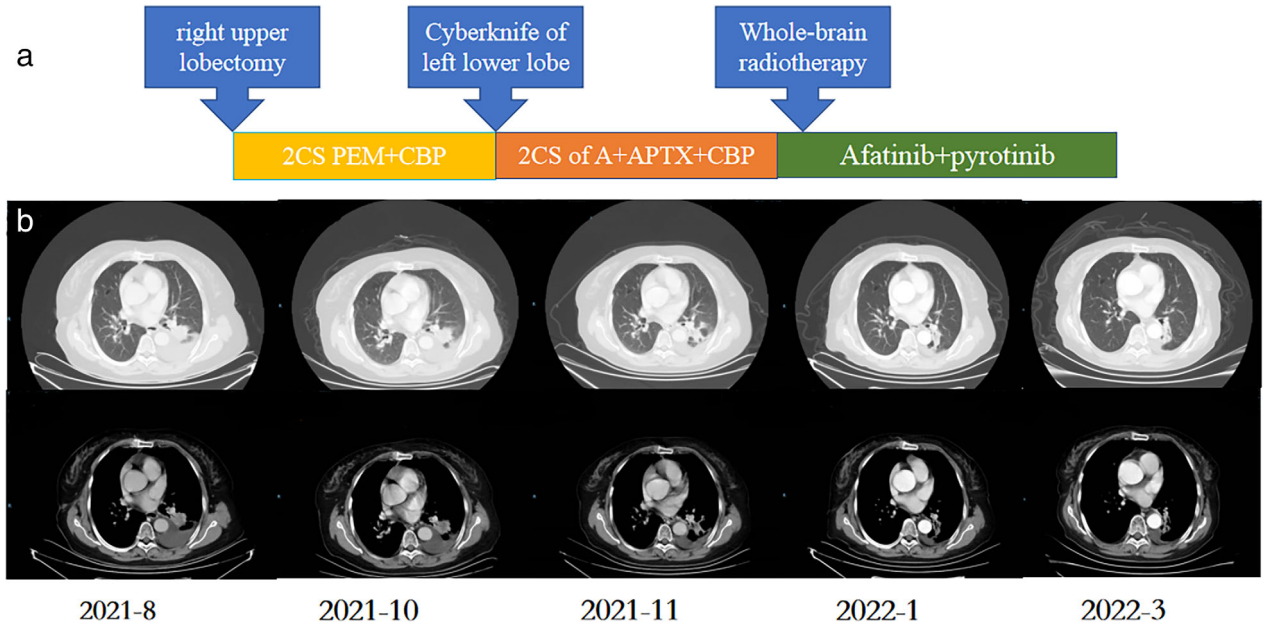

FIGURE 1 (a) Treatment time line. CS, cycles; PEM, pemetrexed; CBP, carboplatin; A, atezolizumab; APTX, albumin-bound paclitaxel. (b) Computerized tomography (CT) at baseline before the start of chemoimmunotherapy (August 2021). CT at baseline before the start of targeted therapy (October 2021). CT at week 4 after targeted therapy (November 2021). CT at week 12 after afatinib therapy (March 2022)

The patient was subsequently treated with a combined regimen of afatinib (30 mg/day) and pyrotinib (an irreversible pan-HER inhibitor) (320 mg/day) from October 2021. She was also treated with whole-brain radiotherapy (95% PTV-Brain 40 Gy/2 Gy/20 f) for brain metastasis from November 2021 to December 2021. The patient experienced grade 2 diarrhea (CTCAE 5.0) since receiving targeted therapy. The lesion of the left lower lobe showed shrinking on neck-thoraco-abdominal CT with a decrease of left pleural effusion in January 2022. The patient still had a partial response (PR) according to RECIST 1.1 (Response Evaluation Criteria In Solid Tumors) until the latest follow-up (Figure 1b).

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

DISCUSSION

NRG1 fusions are uncommon genomic events. Currently, there are no approved targeted therapies for NRG1 fusion driven tumors. Targeting this tumor with afatinib is an approach with a clear molecular rationale. Mechanistically, CD74-NRG1 gene fusion leads to overactivation of ERBB2 and ERBB3,[12] leading to multiple effects such as growth, proliferation, decreased apoptosis, cellular migration, and angiogenesis. Theoretically, a matched targeted therapy could be afatinib, an irreversible pan-ErbB family inhibitor that inhibits the signaling from all homodimers and heterodimers formed by ERBB receptor family members. In the present study, we reported an unusual case of a female patient with lung adenocarcinoma harboring NRG1 gene fusions combined with HER2 mutation. Our report showed afatinib has a relatively good effect on the pulmonary lesion of this case, and our case further supported the use of targeted therapy in a patient with positive NRG1 fusion. In addition, tumor cells expressing NRG1 have been shown to be responsive to EGFR, HER2, and HER3 inhibitors in human tumor models in the preclinical setting,[13,14] including lapatinib and afatinib,[13] with afatinib reported as being the most effective.[15] Individual case reports or small series have noted clinical benefit with afatinib in patients harboring NRG1 fusion mutation.[9–11,16] Cheema et al. reported a case of invasive mucinous pulmonary adenocarcinoma with CD74-NRG1 fusion in which the patient benefited from afatinib with PR and a progression-free survival (PFS) of 6.5 months.[11] Gay et al. described two patients with stage IV lung adenocarcinoma. The first patient with SLC3A2-NRG1 fusion achieved PR and a durable responses to afatinib of 12 months. The second patient, harboring CD74-NRG1 fusion, was diagnosed with mucinous adenocarcinoma, and achieved PR and a durable response to afatinib for 10 months as well.[10] Wu et al. reported a lung adenocarcinoma patient harboring CD74-NRG1 fusion who received afatinib as first-line treatment and showed a significant treatment response with a PFS of 8 months.[5] Jones et al. describe two patients with advanced cancers refractory to standard therapies. Both patients were treated with afatinib. Case 1 was a lung adenocarcinoma patient with SDC4-NRG1 gene fusion in whom PR was achieved and maintained for 12 months. Case 2 was a cholangiocarcinoma patient with ATP1B1-NRG1 gene fusion, who also achieved PR and maintained a response for 8 months.[16] Cadranel et al. reported six cases, including five lung cancer

patients with CD74-NRG1 or SDC4-NRG1 fusion and one colorectal cancer patient with POMK-NRG1 fusion. The best response with afatinib was stable disease (SD) in two patients (duration up to 16 months) and PR of >18 months in three patients, including one with ongoing PR after 27 months.[9]

Response to an ERBB3 monoclonal antibody, GSR2849330, has also been reported.[8] Recently, combining erlotinib, an EGFR tyrosine kinase inhibitor, and lumretuzumab, an ERBB3 monoclonal antibody, was also shown to be effective in two patients with lung invasive mucinous adenocarcinoma (IMA) NRG1-positive.[17] Moreover, developments in bispecific antibody technology may be important to patients with NRG1 fusion. Schram et al. investigated zenocutuzumab (Zeno, MCLA-128), a HER2 × HER3 bispecific antibody, and found it can inhibit HER3 and AKT phosphorylation, induce expression of apoptosis markers, and inhibit growth. Three patients with chemotherapy-resistant NRG1 fusion-positive metastatic cancer who were treated with Zeno achieved rapid symptomatic and radiographic responses.[18]

The results of the eNRGy1 Global Multicenter Registry were published recently. This is the largest retrospective study evaluating the clinicopathologic features and prognosis of lung cancer patients harboring NRG1 rearrangements, providing useful information regarding testing methods and responses to convectional therapies as well as afatinib. NRG1 gene fusions were more common in never-smokers (57%), nonmetastatic patients (71%), and the IMA subtype (57%). In addition, patients harboring NRG1 rearrangements tended to exhibit low response rates and short PFS when treated with platinum-based or taxane-based post-platinumdoublet chemotherapy. Moreover, NRG1 fusion-positive lung cancers derived limited benefit from chemo-immunotherapy or immunotherapy alone. The activity of targeted therapy with afatinib (ORR 25% and PFS 2.8 months) was also modest, regardless of fusion partner.[19]

Moreover, EGFR mutation and HER2 mutation were also present in this patient in this case. It is well known that afatinib is a dual nonreversible tyrosine kinase inhibitor of EGFR and HER2. Afatinib downregulated the phosphorylation of EGFR and HER2 as well as their downstream signaling, and induced an antiproliferative effect through G1 arrest and apoptotic cell death in HER2-altered NSCLC cells and a xenograft mouse model of HER2-altered lung cancer cells.[20] Based on these experimental principles, the therapeutic effect of patients with HER2-mutated NSCLC treated with afatinib has been promising, with a few clinical studies and case reports having been reported.[21–24] This might be one of the reasons why this patient was treated with afatinib and benefited from it.

Finally, the patient in our report was treated with pyrotinib at the same time because of HER2 mutation. Pyrotinib is an oral, irreversible, pan-ErbB tyrosine kinase inhibitor against HER1, HER2, and HER4. In a prospective, multicenter, open-label, single-arm, phase II study, pyrotinib showed promising antitumor activity and an acceptable safety profile in chemotherapy-treated patients with HER2-mutant NSCLC.[25]

This patient in this case had a multiple primary lung adenocarcinoma, with three primary lesions showing different genetic characteristics. Interestingly, in the metastatic lymph nodes, we can see the gene mutation from two of the primary tumors at the same time. The evaluation and progression of the multiple primary tumor is complex and needed dynamic monitoring. For this patient, the use of a combination of afatinib and pyrotinib showed a significant treatment response, which indicates that the combination strategy can be feasible for this kind of primary multi-mutation-driven lung cancer. This case also suggests that NRG1 fusions represent a novel potential target in solid tumor types that warrants further study. Wider, prospective clinical trials of NRG1 fusions, with centralized testing, are warranted to assess the efficacy of afatinib in NGR1 fusion-positive patients.

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DECLARATION OF COMPETING INTERESTS

The authors have no competing interests to declare that are relevant to the content of this article.

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