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*Case Report*

# A rare case of Exon 19 deletion transforming to Exon 20 insertion in a case of adenocarcinoma of lung

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## ABSTRACT

Epidermal growth factor receptor (EGFR) gene mutations play an important role in the presentation, prognosis, and management of non-small cell lung cancer (NSCLC) patients. Several clinical studies claimed the incidence of EGFR Exon 20 insertion mutations in NSCLC and have similar clinical characteristics to those with common EGFR mutations but poorer prognosis. Insertion mutations within the Exon 20 of the EGFR gene are typically located after the C-helix of the tyrosine kinase to result in the domain of EGFR and have been reported to increase the kinase activity of the protein. This eventually leads to the ligand-independent activation of several downstream pathways such as mitogen activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (Pi3K)-(mTOR) mammalian target of rapamycin pathways, which are involved in several cellular processes such as cell proliferation, metastasis, and migration while preventing apoptosis. Thus, EGFR exon insertion mutations are gain of function mutations. Specific EGFR and frame-in insertions occur in 3–7% of NSCLC and are known to predict primary resistance to treatment with all clinically available EGFR-tyrosine kinase inhibitors (TKIs). Many clinical and preclinical studies have reported significant antitumor activity with various first and second-generation EGFR TKIs such as Erlotinib, Gefitinib, and Afatinib and have led to prolonged survival in EGFR mutated patients, as compared to wild-type EGFR tumors with chemotherapy. In addition, third-generation EGFR TKIs, such as Osimertinib, have shown encouraging results in metastatic NSCLC patients harboring EGFR mutations including EGFR, p. Thr790Met-mutations, that have shown to confer resistance to first and second-generation EGFR TKIs and who have progressed on prior TKI therapy. Drugs such as Afatinib, Dacomitinib, Erlotinib, Gefitinib, and Osimertinib have already gained FDA approval for use in EGFR-mutated metastatic NSCLC patients. Here, we report the case of a 47-year-old man who is a non-smoker with an EGFR Exon 19 positive NSCLC treated with Gefitinib developed an EGFR Exon 20 insertion positive brain metastasis initiated on Afatinib as the targeted therapy and responded well to the treatment.

**Keywords:** Epidermal growth factor receptor, Gefitinib, Afatinib, exon19 deletion, exon 20 insertion, Non-small cell lung carcinoma

## INTRODUCTION

Carcinoma of the lung is having the highest rate of mortality among all cancers.[1] It is classified into two major categories: Small cell lung carcinoma (SCLC) occurring in 15% of the cases and non-SCLC occurring in the rest of the 85% of cases. The most common two pathological variants are adenocarcinoma and squamous cell carcinoma. Overall 5-year overall survival rate (OS) ranges from 4% to 7% despite the multiple antitumor therapies.[1] Epidermal growth factor receptor mutation (EGFR) plays a crucial role in the management of non-SCLC.[2] Treatment of choice ranges from first-generation tyrosine kinase inhibitors (TKIs) including Gefitinib and Erlotinib to second-generation TKI inhibitors (Afatinib).[2] First-line treatment with an EGFR TKI improves outcomes compared with standard platinum-based chemotherapy. Among the EGFR TKIs, Erlotinib and Gefitinib are the

preferred frontline agent.[3] Tumors with programmed death-ligand 1 (PD-L1) expression of 50% or higher pembrolizumab or atezolizumab monotherapy demonstrated improvement in OS compared with doublet chemotherapy.[4] Patients with PD-L1 expression <50%, a combination of doublet chemotherapy with concurrent pembrolizumab is preferred.[4] The cisplatin-based regimen is better than a carboplatin-based regimen or the non-platinum regimens are the preferred chemotherapy regimen if considered.[5] Non-squamous non-small cell lung cancer (NSCLC) and if the programmed death ligand expression is <50% the preferred regimen will be a combination of pemetrexed, carboplatin, or cisplatin, and pembrolizumab.[5] EGFR p. T790M exon 20-point mutation is the most common resistance mutation among the patients treated with first and second-generation TKIs.[2] Osimertinib is a third-generation TKIs introduced for the treatment of these kinds of resistance mutations.[2] The most common resistance mutation is an *EGFR* Exon 20 p.C797S point mutation.[2] In a recent genetic analysis in a 40-year-old male, a non-smoker patient diagnosed with a case of non-small cell adeno lung carcinoma positive for EGFR Exon 19 deletion mutation treated with Gefitinib for 22 months. In our case, during the treatment period, he developed holocranial headache and evaluation revealed metastatic lesions in the brain. Excision specimen was send for histopathological examination, came out as metastatic adenocarcinoma of lung. The gene core somatic 161 gene panel of the lesion was suggestive of the development of a new mutation (EGFR Exon 20 insertion) which was negative on the primary tumor. He was initiated on second-generation TKI Afatinib and responded well to the treatment. Here, we aim to describe and discuss this case in the landscape of the literature data.

## CASE REPORT

A 47-year-old male patient, a known case of rheumatic heart disease, moderate aortic regurgitation, and subclinical hypothyroidism, was incidentally detected to have an 11 × 7 mm solitary pulmonary nodule in the left lower lobe during the routine medical examination. He was asymptomatic at the time of the diagnosis. The lesion increased in size over the next three years; hence, he was evaluated further. The whole-body PET scan showed 1.4 × 1.4 × 1.9 cm, well-defined nodular opacity with the central cavitation present in the superior segment of the left lower lobe of the lung, and mediastinal/Hilar lymph nodes on the right upper paratracheal/subcarinal lymph nodes were present. He underwent computed tomography (CT) guided biopsy of the lung mass and the histopathological study was inconclusive. Bronchoscopy revealed a normal TBNA and the subcarinal biopsy done was inconclusive. As the multiple attempts to establish the tissue diagnosis by minimally invasive techniques failed, he underwent video assisted throracoscopic surgery-assisted wedge resection of the pulmonary nodule. The histopathological examination of the resected specimen revealed well-differentiated adenocarcinoma with free margins from the tumor, lymph nodes along the pulmonary ligament, and pulmonary vein was also free from the tumor deposits. The stage of the tumor was identified as pT1N0M0.

At this stage of the disease course, he did not merit adjuvant chemo/radiation therapy. He was advised for total lobectomy, which he denied. A follow-up whole-body positron emission tomography (PET) scan 2 years later revealed a subcarinal lymph node mass. Endobronchial a guided transbronchial needle aspiration showed non-small cell carcinoma favoring adenocarcinoma. He underwent image guided radiation therapy with 5706 Grey/32# along with weekly paclitaxel and carboplatin for a total of 6 weeks. Repeat PET CT scan done after 3 months revealed a decrease in size, number, and metabolic activity of the preexisting mediastinal and hilar lymph nodes, mildly fluorodeoxyglucose (FDG) avid pleural fibrotic and fibro nodular opacity in the right lungs (involving the superior segment of the right lower lobe adjacent to the body of the DV6. Given the images and consideration of the fact that the radiation part was anterior and there are minimal non-FDG avid fibrotic opacities anteriorly, the new findings of FDG avid patchy consolidation along with fibrotic opacities merited the consideration of disease progression. After considering the findings, he was started on palliative chemotherapy with pemetrexed and cisplatin. Post three cycles of the chemotherapy repeat PET CT revealed a decrease in the number and metabolic activity of mediastinal and hilar lymph nodes (partial metabolic reduction). His chemotherapy was continued and he completed a total of four cycles. Meanwhile, his tumor block was sent to NGS panel for druggable targets and was found to have positivity for the activating mutation of Exon 19 deletion and negative for anaplastic lymphoma kinase d5F3 translocation, G719S/G719A/G19C, S768I insertion mutations, T790M, L858R, L861Q, and ROS1D4D6 with an H value of 70%. PDL1 IHC was detected to have 2% of the tumor cell proportion score. The patient was started on targeted therapy with Gefitinib. Repeat PET CT after 6 months showed partial response. He was continued with the Gefitinib treatment. He reported back after 1 year with acute onset of holocranial headache which was not relieved with the medications. His magnetic resonance imaging (MRI) brain was done suggestive of a large lesion involving the right parietal and temporal lobe with signal characteristics and mass effect suggestive of the metastatic lesion of the brain. PET CT scan showed no other FDG avid lesions elsewhere in the body. He underwent right parieto-occipital craniotomy and excision of the space-occupying the lesion, followed by whole-brain radiotherapy. Histopathology was suggestive of metastatic adenocarcinoma of the lung with dural invasion. Immunohistochemistry was positive for thyroid transcription factor 1, Napsin A, and CK7. Tissue NGS showed positivity for EGFR, p. Asn

771_His773du p (exon 20 insertions), and was negative for Exon 19 deletion or T790 M mutation, which was positive previously in the primary malignancy. PDL1 was found to be 5%. His blood samples were tested for EGFR mutations (Exon 19, 21, and 20 deletions, T790M, and L858R) and the results were negative. His targeted therapy changed to Afatinib from Gefitinib. Repeat MRI brain after 3 months of the surgery showed post-operative status with residual cavity showing significant reduction in the cavity size with no other significant change. He improved after the targeted therapy with Afatinib. He became asymptomatic and tolerated the therapy. He was kept on close follow-up and Afatinib was continued. CEMRI after 6 months of Afatinib revealed a significant increase in a residual cavity in the right parietal lobe extending to the right occipital lobe noted as compared to the previous scan. There was a significant increase in perilesional edema compared to the previous scan, causing a mass effect in the form of effacement of adjacent sulcal spaces and chinking of the right lateral ventricles with a midline shift of 13 mm to the left side and causing right-sided uncal herniation. PET CT showed no other abnormal FDG avid lesion detected in the scanned region of the body. He underwent repeat craniotomy and gross total excision of the tumor. The tumor histopathology examination, immune histo chemistry, and next generation sequencing showed metastatic adenocarcinoma of lung with Exon 20 insertion (p. Asn 771_His773du p). PDL1 by IHC on 22C3 Dako showed tumor proportion score of 55. Hence, he was planned to be started on immunotherapy.

## DISCUSSION

The EGFR protein encoded by the EGFR gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. The protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to the epidermal growth factor. The EGFR ligand interaction induces receptor dimerization and tyrosine autophosphorylation which leads to activation which leads to activation of the downstream signaling pathways that ultimately result in cell proliferation. Neoplastic cells can develop several resistance mechanisms. The resistance mutation first described is a point mutation of p.C797S in *EGFR* Exon 20.[1] In this reported case, the patient's primary tumor was having a deletion mutation in the Exon 19 and was initiated on Gefitinib, later developed Exon 20 insertion positive lesion in the brain which also responded well to the second-generation TKI. Ham *et al*. reported two cases of lung carcinoma having two different mutations following treatment. In the reported case by Ham *et al*., there was a transition from adenocarcinoma to small cell carcinoma following Osimertinib treatment, with concomitant loss of the p. T790M mutation.[6] It is not uncommon that within a single tumor specimen, two or more cells may harbor different EGFR mutation. In a study by Hata *et al*., Exon 20 (T790M) and L858R were found in 3 of 318 (0.9%) *EGFR* mutation-positive patients before exposure of the tumor by EGFR-TKIs. Previously, it was believed that Exon 20 mutation was a second hit mutation that, in turn, leads to leading to resistance to many of the EGFR-TKIs.[7] In a study conducted by Toyooka *et al*., it was found that two (2 of 397, 0.5%) NSCLC patients who had never smoked had two concurrent *EGFR* mutations. In their reported study, one mutation was found to be Exon 20 (T790M) and the another was L858R before the treatment with EGFR-TKIs.[8] In Asian patients, EGFR double activating mutations were previously detected.[9] The most common double-activating mutations were Exon 19 and Exon 21.[9] Gefitinib is the first-line EGFR receptor blocker approved for the treatment of the NSCLC. The mutations within specific regions of the EGFR tyrosine kinase are the principle of the targeted therapy with EGFR-TKIs in cases of NSCLC.[10] Afatinib is a second-generation TKI active on Exon 19 EGFR mutations. Leu858Arg EGFR mutated patients showed resistance to treatment with Afatinib in many clinical scenarios. Leu858Arg EGFR is distinct from the Exon19 EGFR mutations. Due to this feature, Afatinib showed resistance to Leu858Arg EGFR mutations.[11] Poziotinib is an orally bioavailable EGFR inhibitor. It is quinazoline based and irreversible with potential anticancer activity. It inhibits EGFR (human epidermal growth factor receptor 1 or epidermal growth factor receptor family 1), human epidermal growth factor receptor 2, human epidermal growth factor receptor 4, and EGFR mutants. Osimertinib is a third-generation mutant selective inhibitor. Osimertinib blocks EGFR inhibitors including the T790M EGFR mutations. FDA approved Osimertinib in EGFR, p. Thr790M positive metastatic NSCLC patients. AURA3 trial is a clinical trial that confirmed the benefit of Osimertinib in EGFR, p. Thr790M mutated NSCLC. Amivantamab is an EGFR-MET-specific antibody. It binds to the extracellular domain of the receptor and bypassing the development of resistance at the TKI binding site. Amivantamab showed longer and better antineoplastic action in patients with *EGFR* Exon 20 insertion mutations after a course of platinum-based chemotherapy.[12] Mobocertinib (TAK-788) is an irreversible EGFR TKI. Mobocertinib potentially and selectively inhibits activating *EGFR* Exon 20 insertion mutations. Preclinical data support the efficacy of Mobocertinib in patients with *EGFR* Exon 20 insertion mutation harboring NSCLC.[13] As a single agent pembrolizumab is the standard therapy in patients with ≥50% PD-L1 expression. At present, combination with pembrolizumab or atezolizumab with a platinum-based agent is the first-line treatment regardless of PD-L1 expression in case of both squamous and non-squamous NSCLC. First-line single agent immune checkpoint inhibitor showed limited activity in EGFR mutated NSCLC. The combination of immunotherapy and targeted agents raised

safety concerns in case of both ALK and EGFR positive NSCLC cases. A tezolizumab in combination with platinum-based chemotherapy and bevacizumab is a treatment option in EGFR mutated or ALK positive NSCLC cases before first-line TKIs.[14] Our findings are following the data and suggest that two different types of the EGFR mutation can coexist in same patients with NSCLC (Here, two mutations presented sequentially and exclusively). In conclusion, *EGFR* Exon 20 insertions are rare. To the best of our knowledge, appearance of metachronous Exon 20 insertion in a known case of Exon 19 deletion is not reported in the literature. Gefitinib has different efficacy according to the type of complex *EGFR* mutations.

## CONCLUSION

Development of the new resistance mechanisms by the neoplastic cells are challenging now a days. Most common are point mutations of exon 20. Exon 20 insertions also described rarely in some cases those having other mutations initially. Recent third generation tyrosine kinase inhibitors are helpful in treatment of such cases to some extend.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

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