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Case Report

Synergistic Occurrence of EGFR, ALK, and KRAS Gene Mutations in a Patient with Non-small Cell Lung Cancer (Adenocarcinoma)

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ABSTRACT

Lung cancer is a commonly diagnosed malignancy. Adenocarcinoma, a subgroup of non-small cell lung cancer, is the commonest form and presents in an advanced stage of the disease, leaving a limited treatment option. Response to the standard chemotherapy regimens is overall poor. We present a case of synergistic occurrence of triple gene mutations in a patient with well-differentiated adenocarcinoma lung treated at a tertiary cancer care center in North India.

Keywords: Non-small cell lung cancer, EGFR, ALK, KRAS

INTRODUCTION

Lung cancer is a commonly diagnosed malignancy, and it is one of the leading causes of death around the world, as well as in India.[1] It belongs to the "smart cancer" category involving numerous driver mutations in multiple genes with targeted therapies available for some genes. This has been chiefly possible due to the fact that the last two decades has been the era of molecular biology with the presence of simple aberrations in cancers such as chronic myeloid leukemia including breakpoint cluster region-Abelson murine leukemia (BCR-ABL) interactions, which can be targeted in contrast to other tumors where multiple molecular aberrations might occur. Despite having an oncogenic driver that can be targeted by molecular-targeted therapies, there might be failures, and recurrence may occur after response in the same tumor. Studies have shown that anaplastic lymphoma kinase (ALK) fusion gene is largely exclusive of epidermal growth factor receptor (EGFR) and Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations.[2] This case report presents a patient with the synergistic occurrence of EGFR, ALK, and KRAS gene mutations in a patient with well-differentiated adenocarcinoma lung treated at a tertiary cancer care center in North India.

CASE REPORT

A 56-year-old male presented to the hospital in January 2013 with complaints of cough, nodal swelling left neck, hoarseness of voice, and loss of appetite. Contrast enhanced computed tomography (CECT) thorax was suggestive of mediastinal lymph nodes with central low-density

areas with military nodules in bilateral lung and large nodular mass lesion in right lower lobe suggestive of tuberculous etiology with lesser possibility of a malignant neoplasm. He received anti-tubercular treatment (ATT) for a month with no relief. CECT neck was suggestive of left vocal cord palsy with <1 cm size bilateral upper jugular lymph nodes. Cervical lymph node biopsy performed exhibited metastatic adenocarcinoma. USG Whole Abdomen revealed a small hyper echoic lesion noted close to lower pole (size 20 × 21 mm) and involving the renal cortex. He was referred to our hospital for further management. Positron emission tomography-computed tomography (PET-CT) revealed metabolically active right lung mass with bilateral lung and lymph node involvement [Figure 1]. Slide review of the sections from cervical lymph node revealed metastatic papillary adenocarcinoma of lung origin. On immunohistochemistry (IHC), tumor cells were found to express cytokeratin (CK) 7, thyroid transcription factor (TTF)-1, and napsin and were negative for CK20. The final diagnosis made was adenocarcinoma lung – well differentiated.

The patient was administered Pemetrexed- and Cisplatin-based chemotherapy, which he tolerated well. In the meantime, EGFR mutational analysis was performed, and the tumor was found to have L858R mutation in exon 21. Re-evaluation after four cycles of chemotherapy with PET-CT showed good partial response to treatment with metabolically active residual disease. He was switched to tab Gefitinib and placed on regular follow-up [Figure 2]. Post six cycles of targeted therapy, reevaluation for response using PET-CT demonstrated residual disease in right upper deep cervical, right middle deep cervical, left lower paraesophageal, and bilateral hilar regions.

In the light of disease progression, multigene tumor profiling for 50 significant mutated genes was performed using next generation sequencing. The sample returned several genomic alterations in the patient's tumor sample namely ALK, EGFR, G protein subunit alpha Q (GNAQ), kinase insert domain receptor (KDR), KRAS, retinoblastoma transcriptional corepressor (RB) 1, SMAD family member (SMAD) 4 (2 alterations), and TP53 involving amino acid changes G1184E, L858R, T224N, Q472H, T50P, I680T, Q256L and V354L, Y88C, respectively. ALK on immunohistochemistry was, however, negative, and literature search revealed that this type of Alk rearrangement is not sensitive to crizotinib. Biopsy from cervical lymphadenopathy was suggestive of metastatic adenocarcinoma. On progression, he received Affatinib till March 2014. A PET-CT report in March 2014 showed metabolically active progressive lung and lymph nodal disease. Due to disease progression, he was planned and restarted on pemetrexed and cisplatin chemotherapy in April 2014 in view of his good response to this treatment earlier.

At this point of time, he was started on intercalated combination of chemotherapy and targeted therapy tab Erlotinb. Post three cycles of chemotherapy, PET-CT showed response to treatment in lung and lymph nodal disease. MRI pelvis showed focal altered signal intensity lesions in the left iliac bone and left femoral head. Possibility of metastatic disease with a differential of granulomatous disease was considered in the clinical context. PSA correlation was then suggested for altered signal in the prostate. He was then put on tab bicalutamide and triptorelin (a substitute for gonadotrophin releasing hormone, 11.6 mg). He further received three cycles of chemotherapy. An MRI brain showed

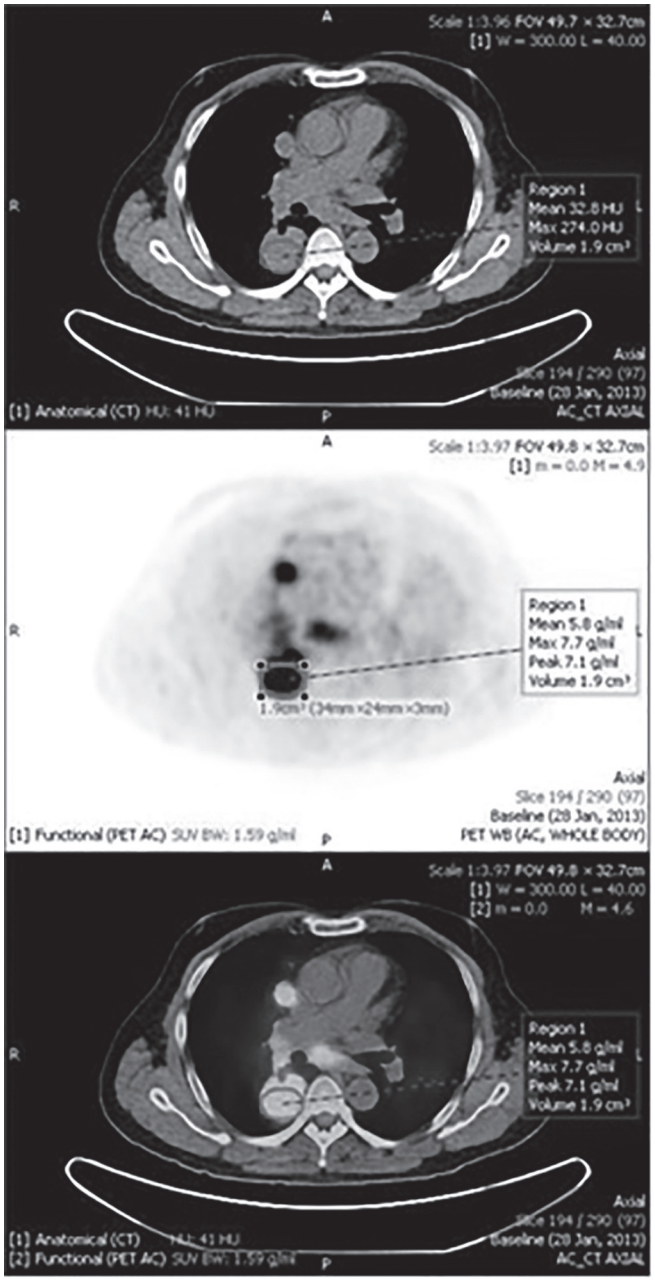

Figure 1: PET-CT images at presentation (January 2013). Metabolically active mass lesion in right lower lobe abutting the right paravertebral costal pleura.

few subcentimetric bilateral cerebral and left cerebellar enhancing lesions with perilesional edema suggestive of metastasis. The patient received palliative whole brain radiotherapy for brain metastasis and pemetrexed-based maintenance therapy. PET-CT again was suggestive of metabolically active progressive lymph nodal, lung, and bony disease. He was then started on second line docetaxel-based chemotherapy. Post third cycle, PET-CT showed stable disease with residual metabolically inactive lung and bone abnormalities with increasing right cervical lymphadenopathy, fine needle aspiration cytology (FNAC) was negative. He completed the fourth cycle of docetaxel-based chemotherapy in January 2015 and subsequently was not willing for further chemotherapy due to the poor tolerance to docetaxel. He was then started on tab Iressa 250 mg once a day and also received radiation to cervical lymph node in March 2015. PET-CT in May 2015 was suggestive of persistent right lung lower lobe lesion, lymph nodal, and bony abnormalities. His PSA level was 0.688 ng/ml on serology, which was suggestive of controlled prostatic disease. He noted a swelling in the right inguinal region and underwent WLE of inguinal growth. He received tab Iressa till July 2015. At this point of time, his PET-CT was suggestive of progressive disease. In view of his disease status, he was started on Nab Paclitaxel-based chemotherapy and was administered two cycles, which he tolerated well without any immediate morbidity till September 2015. He was not willing for further chemotherapy in view of generalized fatigue, weakness, asthma, asthenia, and weight loss and was put on best supportive care. He finally succumbed to his disease in October 2015. The time from diagnosis to death was 33 months.

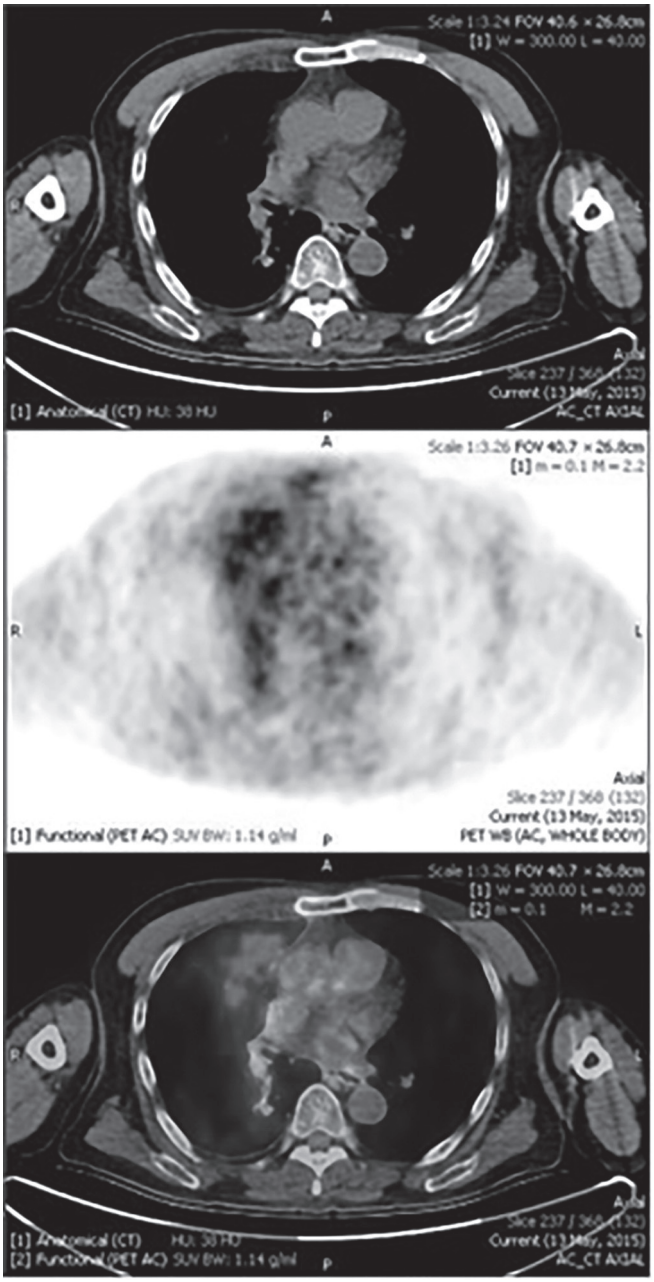

Figure 2: PET-CT images during follow-up (May 2015). Predominantly metabolically inactive lesion in right lung lower lobe superior segment with mild right basal pleural thickening.

DISCUSSION

Adenocarcinoma, a subgroup of NSCLC, is the commonest form and presents in an advanced stage of the disease leaving a limited treatment option. Response to the standard chemotherapy regimens is poor with short median survival.[3] Epidermal growth factor receptor (EGFR) is a transmembrane receptor protein kinase and has been associated with tumorigenesis in several malignancies including NSCLC. Receptor binding to the extracellular domain of EGFR causes protein kinase activation in the form of downstream signaling further leading to the growth, proliferation, and invasion of the cell.[4,5] Mutations in the EGFR gene are generally associated with adenocarcinoma histology of lung cancer, female sex, non-smokers, and Asian ethnicity. A recent study by Doval *et al.*[6] has shown the overall mutation frequency of EGFR as 25.9% in the lung cancer adenocarcinoma in the Indian population.

Non-small cell lung cancer is the largest subgroup of lung cancer harboring a majority of activating mutations in KRAS codon 12 and 13, p53, and EGFR.[7] The ALK fusion has been reported to be present in up to 11.6% of patients with NSCLC,[8] on the basis of the ethnic group studied and the screening method used for evaluation. It encodes a transmembrane receptor tyrosine kinase and aberrant ALK has been observed to act as an oncogene in many different cancers. EML4-ALK translocations tend to occur in younger patients and those with more advanced NSCLC while this association has not been observed for EGFR mutant NSCLC.

The variant allele frequencies of ALK, EGFR, and KRAS genes were 13.95%, 28.28%, and 5.51%, respectively. The ALK and

KRAS variants observed were novel and not reported so far. Sorting intolerant from tolerant algorithm was used for the prediction of effects of non-synonymous/missense variants. The results predicted whether an amino acid substitution affected the protein function based on sequence homology and the physical properties of amino acids. In case of ALK gene variant observed in this patient, the coding variant had 100% damaging effects while the same was not the case for KRAS gene coding variant.

Targeting the mutations has changed the overall treatment strategy for lung cancer and provides significant benefit to the patient. EGFR mutation screening is becoming a standard of care in the oncology clinical practice, and treatment with inhibitors showed efficacy and increase in the survival of patients with EGFR mutation positive lung cancer.

Interestingly, it has been suggested by various studies that ALK fusion gene is largely exclusive of EGFR and KRAS mutations.[2] The actual activation status of the two different receptors is important specially in the context of assessing the use of targeted therapies. ALK directed targeted therapy in the form of Crizotinib is an option; however, it could not be administered to the patient as the alteration identified was a missense mutation instead of gene arrangement, which was further validated by immunohistochemistry. Also, the patient had overall a very difficult disease, which could be due to the presence of various genetic alterations. In this perspective, lung cancers belong to the "smart cancers" category with a large number of mutations, which may be present as opposed to chronic myeloid leukemia, which is a relatively "dumb cancer" due to the presence of a single genetic alteration. Targeted therapy may be beneficial in the lung cancer patients but development of resistance remains a matter of concern. The persistence of multiple mutations and the development of multiple malignancies make the treatment process very cumbersome for the patients. The genetic trigger is switched on affecting various genes resulting in poor prognosis of patients. The presence of multiple malignancies only worsens the condition.

CONCLUSION

The present report brings to light the first case of the synergistic occurrence of EGFR, ALK, and KRAS gene mutations in a single patient. Genomic instability in such patient may also be responsible for multiple malignancies like the development of prostate cancer and *in situ* squamous cell carcinoma in this case. Deciding the course of treatment and the choice of therapy may pose a critical challenge to the physician in order to appropriately and adequately tackle the mutations in three potential tumor-driving genes in an individual patient.

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Conflicts of interest

There are no conflicts of interest.

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