Concomitant expression of exon 19 mutation epidermal growth factor receptor and anaplastic lymphoma kinase gene rearrangement in metastatic adenocarcinoma lung responsive to crizotinib

Sir,

Epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements usually are mutually exclusive and such occurrence are extremely rare in adenocarcinoma lung.

ALK rearrangements correlate with specific clinical and pathological features and may cause potential resistance to anti-EGFR tyrosine-kinase inhibitors (TKIs). Use of EGFR-TKIs gefitinib or erlotinib and ALK-TKI crizotinib in a concomitant lung adenocarcinoma has shown mixed results with few progressing and few responding. Patients housing both mutations have shown an objective response and increased sensitivity to ALK-TKI alone but can also be sensitive to both targeted therapies, thus suggesting a variable dependence on EGFR and ALK oncogenes. Patients with double mutations have a higher incidence of brain metastases and also renal dissemination as seen in our case, indicating their aggressive nature.

A 36-year-old male, nonsmoker presented with nonproductive cough, weight loss, and headache with vomiting. Magnetic resonance imaging (MRI) brain showed multiple intracranial metastatic lesions. Computed tomography (CT) scan chest showed irregularly marginated 5.8 cm × 4.9 cm × 5.9 cm lesion involving the posteromedial basal segments of the right lower lobe (RLL), biopsy from which showed adenocarcinoma histology with immunohistochemistry (IHC) positive for cytokeratin-7 (CK7), thyroid transcription factor-1 while negative for P63. Whole-body positron emission tomography (WB-PET) scan showed mass lesion RLL with a standard uptake value (SUV) of 16.45. Multiple skeletal lesions were seen involving whole spine, right scapula, sternum, ribs, and pelvic bones with SUV of 10.0–15.99. The left kidney showed a hypermetabolic focus of SUV 13.19 suggestive of metastasis. Evaluation for EGFR with real-time polymerase chain reaction assay was positive for exon 19 deletion mutation. IHC for ALK stained positive which was further confirmed with fluorescent in situ hybridization.

He was diagnosed with metastatic adenocarcinoma lung with concomitant EGFR and ALK positivity. The patient was treated with palliative whole-body radiation therapy to a dose of 30 Gy/10 fractions for his brain metastasis and then started on oral crizotinib 250 mg twice/day monthly schedule. Response assessment after 3 months with CT scan and WB-PET showed a significant reduction in size and metabolic activity of lung and skeletal lesions. He was continued on monthly crizotinib with WB-PET after 12 months showed near complete morphological and metabolic resolution of the lung, skeletal, and kidney lesions.

The advent of molecular characteristics in non-small cell lung cancer (NSCLC) like mutations in exons 18–21 of tyrosine kinase EGFR has made possible the precise treatment with EGFR-TKIs such as gefitinib, erlotinib, and afatinib. Rearrangement of ALK with echinoderm microtubule-associated protein-like-4 oncogene on the chromosome-2 short arm in approximately 3%–7% NSCLC adenocarcinoma cases specific for ALK-TKIs such as crizotinib and ceritinib. EGFR mutations have been known to predominate in well-differentiated adenocarcinomas.

Figure 1: (a) Image-guided biopsy from the lung mass showing adenocarcinoma histology (H and E, ×100). (b) Immunohistochemistry staining positive for thyroid transcription factor-1 (×100). (c) Immunohistochemistry staining positive for cytokeratin-7 (×100). (d) Real-time polymerase chain reaction showing epidermal growth factor receptor mutation at exon 19. (e) Immunohistochemistry staining positive for anaplastic lymphoma kinase (×100). (f) Tumor cells staining positive for echinoderm microtubule-associated protein-like-4-anaplastic lymphoma kinase translocation by fluorescent in situ hybridization method.
ALK in poorly differentiated adenocarcinomas\textsuperscript{15,16} in young Asian nonsmokers.\textsuperscript{4} However, around 100 cases of concomitant presence have been reported in the world\textsuperscript{14} and only one case in India.\textsuperscript{4} Regarding such coexistence, few have described it to be about 1%,\textsuperscript{2} 1.3%,\textsuperscript{17} 1.6%,\textsuperscript{1} and even 0.3%.\textsuperscript{11} With around 100 such concomitant cases reported in the world,\textsuperscript{14} Kamath et al.\textsuperscript{4} have reported the only case in India, while we report the second case in an upfront metastatic patient. Kamath et al.\textsuperscript{4} used gefitinib 250 mg/day, however, the disease progressed after 3 months. The patient was upfront metastatic which prompted the use of crizotinib 250 mg twice/day. The patient showed a dramatic response with near complete metabolic resolution of the primary lung mass, skeletal lesions, and renal metastasis over a period of 9 months after starting crizotinib. Exhaustive review of Indian\textsuperscript{4,15,18} and world literature\textsuperscript{19} revealed no similar case has shown such an excellent therapeutic response to crizotinib in a widely disseminated state.

EGFR mutations have been reported as a resistance mechanism with ALK translocations treated with ALK-TKIs\textsuperscript{20} while concomitant ALK rearrangements an acquired resistance mechanism for EGFR-TKIs.\textsuperscript{21} EGFR-TKIs such as gefitinib\textsuperscript{4} and erlotinib\textsuperscript{3,5-8} and ALK-TKI crizotinib\textsuperscript{9,10} have shown mixed results. Few patients progressed\textsuperscript{4,6-9} while few responded.\textsuperscript{5,8,10} In double-mutated cases, ALK-TKIs have been found to more effective than EGFR-TKIs\textsuperscript{11,12,14} but can also be sensitive to both targeted therapies, thus suggesting a variable dependence on EGFR and ALK oncogenes.\textsuperscript{13} Double-positive patients are resistant to EGFR-TKIs and sensitive to ALK-TKIs; therefore, these patients may be treated with first-line ALK-inhibitors than with first-line EGFR-inhibitors.\textsuperscript{14,11} Newer generation TKIs have also been reported to be of relevant intracranial efficacy.\textsuperscript{22} Clinical trials testing the safety and efficacy of co-inhibition of both ALK and EGFR could be an interesting preposition in the near future.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.
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