Case Report

A "triple whammy" in adenocarcinoma lung

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ABSTRACT

Osimertinib (AZD9291), a third-generation epidermal growth factor receptor (EGFR)-tyrosine-kinase inhibitor (TKI), is useful in the treatment of non-small cell lung cancer who show resistance to first-generation EGFR-TKIs and harbor T790M mutation. Acquisition of resistance to osimertinib due to several mechanisms has been reported. We report the first case of an Indian patient with osimertinib resistance, due to C797S mutation. A 52-year-old nonsmoker man was detected to have metastatic lung adenocarcinoma (Stage IV) with EGFR exon 19 deletion and treated with erlotinib. After 12 months of response with erlotinib, he developed resistance because of the development of T790M mutation. He was started on osimertinib, with which he responded for 20 months. A follow-up positron emission tomography scan showed progressive disease. Subsequent liquid biopsy did not detect any mutation. However, rebiopsy of the lung lesion showed additional C797S mutation (in cis association with T790M). Hence, the patient was diagnosed to have "triple whammy," i.e., triple mutation of exon 19 deletion, T790M, and C797S mutations.

KEY WORDS: Non-small lung carcinoma, osimertinib resistance, triple mutation

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INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers. The prevalence of epidermal growth factor receptor (EGFR) mutations in NSCLC varies from 30% to 40% in Asians.[1] EGFR-tyrosine-kinase inhibitors (TKIs) have been established as a treatment of choice for EGFR mutations. However, resistance develops to EGFR-TKIs in about 60% of cases, commonly due to T790M mutation.[2]

Osimertinib/AZD9291 is a third-generation EGFR-TKI approved for use in T790M mutant NSCLC, with an overall response rate of about 60%, but acquired resistance to it occurs in about 10 months.[3,4] There are various mechanisms of acquired resistance to third-generation TKIs. We report a case of acquired resistance to osimertinib due to C797S mutation. To the best of our knowledge, it is the first case of osimertinib resistance to be reported in an Indian patient.

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CASE REPORT

A 52-year-old nonaddict man in November 2014 presented with complaints of cough and exertional dyspnea for 2 months. On examination, his vital parameters were normal. He had reduced breath sounds over the left basal regions on the respiratory system examination. The other system examinations were normal. Routine investigations showed hemoglobin of 15.3 g/dl, total leukocyte count of 7500/μL, blood sugar level of 89 mg/dl, and urea of 9 mg/dl. The chest radiograph showed left pleural effusion with bilateral nodular opacities [Figure 1]. The pleural fluid was exudative with the presence of malignant cells. The computed tomography (CT) of the chest showed mass in the left upper lobe with bilateral lung nodules and left pleural effusion [Figure 2a]. Transbronchial biopsy from the left upper lobe showed adenocarcinoma with the presence of exon 19 deletion in EGFR gene. Positron

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emission tomography (PET) scan [Figure 3a] and magnetic resonance imaging of the brain done for staging detected distant metastases in the brain and multiple vertebrae. His performance status was Stage 2 and TNM staging was Stage IV. He was started on erlotinib at a dose of 150 mg daily.

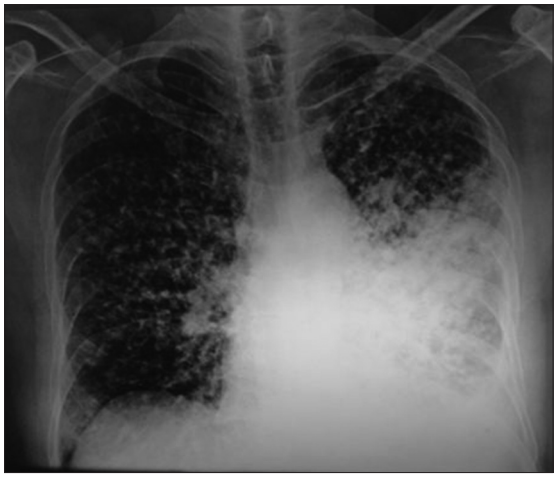

Figure 1: Chest radiograph in posteroanterior projection at initial presentation shows bilateral lung nodules with left-sided pleural effusion

He had good therapeutic response but developed acneiform lesions over the face, neck, and upper extremities. On continuing treatment, the rashes resolved. At the end of 6-month treatment with erlotinib, follow-up PET-CT showed partial response as per "response evaluation criteria in solid tumors" with resolution of lung and skeletal lesions, though pleural effusion remained unchanged [Figures 2b and 3b]. Pleurodesis was done for persistent left pleural effusion using bleomycin. Twelve-month posterlotinib treatment, imaging studies showed progressive disease with increase in lung nodules and new abdominal deposits arousing suspicion of erlotinib resistance [Figures 2c and 3c]. Repeat biopsy of the lung lesion detected the presence of T790M mutation in May 2016. He was then started on osimertinib 80 mg once daily. He had good clinical and radiological

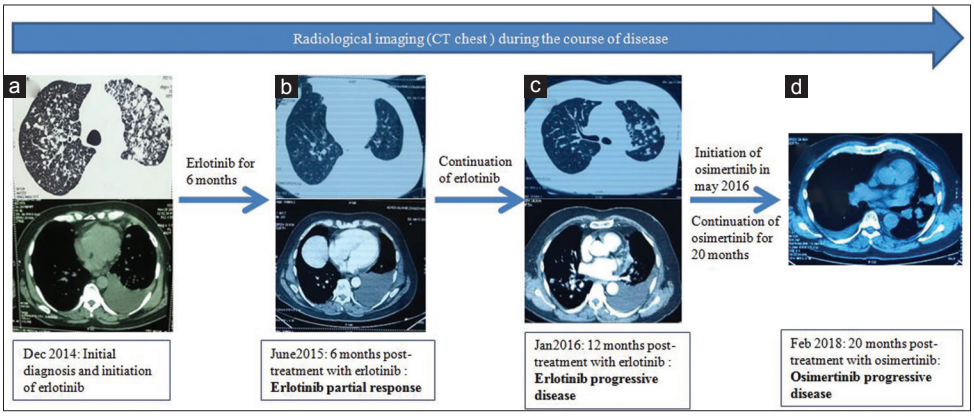

Figure 2: Medical course of the patient with follow-up computed tomography scan findings; (a) initial computed tomography scan during presentation and before start of erlotinib shows the presence of bilateral lung nodules with left pleural effusion; (b) computed tomography scan after 6 months of erlotinib treatment shows the resolution of lung nodules with persistence of left pleural effusion; (c) computed tomography scan after 12 months of erlotinib treatment shows the reappearance of lung nodules; (d) computed tomography scan after 20 months of osimertinib treatment shows the increase in lung lesions and new right-sided pleural effusion

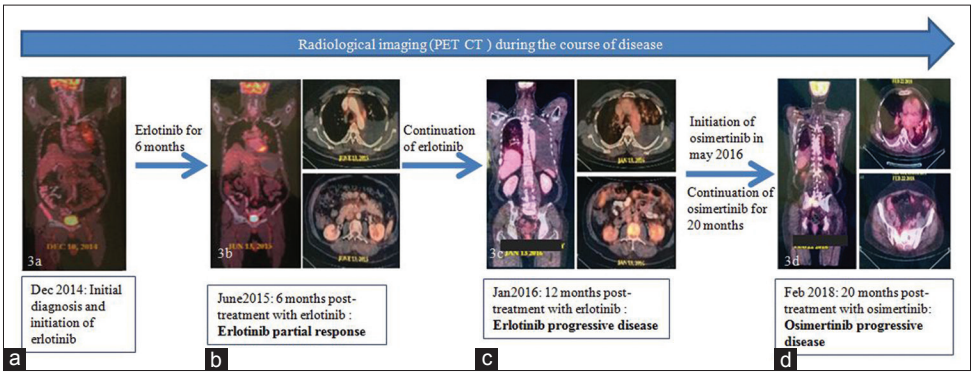

Figure 3: Medical course of the patient with follow-up positron emission tomography scan findings; (a) initial positron emission tomography scan during presentation and before start of erlotinib shows the presence of metabolically active lung lesions with left pleural effusion; (b) positron emission tomography scan after 6 months of erlotinib treatment shows the resolution of lung nodules with persistence of left pleural effusion; (c) positron emission tomography scan after 12 months of erlotinib treatment shows the reappearance of lung nodules with metastatic abdominal deposits; (d) computed tomography scan after 20 months of osimertinib treatment shows the increase in lung lesions and new right-sided pleural effusion with resolution of abdominal lesions

response for 20 months. The PET-CT done in February 2018 showed progressive disease with new lung lesions and right pleural effusion though abdominal lesions had resolved [Figures 2d and 3d]. Osimertinib resistance was suspected. Liquid biopsy was advised, which did not detect any mutation. Hence, a repeat tissue biopsy was performed, which confirmed the absence of histological transformation. The comprehensive tumor panel involving 170 genes by next-generation sequencing detected triple mutation of exon 19 deletion, T790M, and C797S mutations in EGFR gene. The C797S mutation was present in cis with T790M.

Table 1: Case reports of osimertinib resistance

Year	Author	Age/ sex	Country	Initial mutational analysis	Initial treatment	Detection of T790m mutation and start of osimertinib	Detection of Osimertinib resistance	Mechanism of resistance	Further treatment	Disease course
2018	Y Liu *et al*.[12]	67/M	China		Lobectomy, chemotherapy, gefitinib	13.5 months	17.7months	Different mechanisms in different lesions 1. L718V and Loss of T790M mutation 2. C797S mutation	Erlotinib, chest radiotherapy	
2018	R Minari *et al*.[13]	65/F	Italy	EGFR exon19 del	Osimertinib		18.9 months	BRAF V600E mutation and MET amplification: Acquired resistance to first line osimertinib		
2017	Y Liu *et al*.[14]	63/F	China		Gefitinib	23 months	2months	Heterogenous and multiple mechanisms, C-MET amplification	BPI-9016, crizotinib	Died
2017	SJ Klempner *et al*.[15]	69/F	USA, Asian patient	EGFR L858L mutation	Erlotinib	13 months	12 months	G796S mutation (in cis with T790M)	Chemotherapy, pembrolizumab and epacadostat	
2017	C Ricordel *et al*.[16]	57/M	France	EGFR exon19 del	Gefitinib	11 months	10 months	Transformation to large cell neuroendocrine carcinoma	Radiotherapy, osimertinib	
2017	S Arulananda *et al*.[17]	41/M	Australia, asian patient	EGFR exon19 del	Erlotinib	6 months	12months	Trans C797S mutation	Gefitinib, osimertinib	Died
2017	A Oztan *et al* [18]	47/M		EGFR exon19 del	Chemotherapy, bevaizumab, erlotinib	23 months	9months	G724S mutation	Chemotherapy	Died
2017	A Oztan *et al*.[18]	74/M		EGFR exon19 del	Chemotherapy, bevaizumab, erlotinib	7 years	8months	G724S mutation, Osimertinib started though insufficient tissue and no evidence of T790M mutation	Nivolumab	Died
2017	FH Knebel *et al*.[19]	53/M	Brazil	EGFR exon19 del	Chemotherapy, erlotinib	6months	7months	Multiple mechanisms including C797S mutation	Chemotherapy	Died
2017	SHI Ou *et al*.[20]	69/F	USA	EGFR L858R mutation	Brain radiotherapy, erlotinib	8months	5months	Multiple mechanisms including G796S/R mutation		
2017	D Zheng *et al*.[21]	56/F	China		Chemotherapy, gefitinib	13months	6.5 months	G796D mutation	Radiotherapy	
2016	K Chen *et al*.[22]	3 patients	China		Chemotherapy, gefitinib		6-11months	C797S mutation, L792F/Y/H		
2017	Ho CC *et al*.[23]	42/M	China	EGFR L858R mutation	Chemotherapy, radiotherapy, erlotinib	4 yrs	13months	BRAF V600E m		
2016	SHI Ou *et al*.[24]	73/F	USA	EGFR exon19 del	Erlotinib, chemotherapy, afatinib	24months	9months	MET amplification, loss of T790M	Chemotherapy, erlotinib, crizotinib and osimertinib	Died
2017	Lin Li *et al*.[25]	52/F	China	EGFR exon19 del	Surgery, chemotherapy, erlotinib	11months		Transformation to SCLC, osimertinib given though no T790M mutation	Chemotherapy	
2015	Yu H A[26]	60/F		EGFR exon19 del	Chemotherapy, erlotinib	15months	9months	C797S mutation		
2017	LE Raez *et al*.[27]	54/M	Florida	EGFR exon19 del	Brain radiotherapy, erlotinib	13 months	14months	C797S mutation	Nivolumab and ipilimumab	Died
2016	M Bersanelli *et al*.[28]	71/F	Italy	EGFR L858R mutation	Gefitinib, Chemotherapy	27 months	12months	L718Q mutation		

*The spaces left blank are due to incomplete data available in the respective cases

DISCUSSION

The first-generation EGFR-TKIs are recommended as the first-line treatment of advanced NSCLC harboring EGFR-sensitive mutations specifically exon 19 deletions and/or L858R mutation in exon 21. Although both gefitinib and erlotinib have shown similar effectiveness, erlotinib is associated with lower central nervous system recurrence rate compared with gefitinib in patients with brain metastases.[5] Hence, erlotinib was preferred in our patient.

Resistance develops to first-generation EGFR-TKIs after a median of 9–12 months of treatment in majority of the patients. T790M mutation is the most common mechanism occurring in 50%–60% of cases.[2,6] The second-generation EGFR-TKIs, i.e., afatinib, dacomitinib, and neratinib have demonstrated promising activity against T790M in preclinical models but have failed to overcome resistance in clinical patients due to dose-limiting toxicity.[7] Guidelines have recommended third-generation TKI osimertinib as standard single-drug therapy for patients with metastatic EGFR T790M mutation-positive NSCLC. Osimertinib received its first global approval by the US Food and Drug Administration in November 2015 based on the AURA trials which demonstrated an objective response rate of 61%–66% and a progression-free survival of 9.6–11 months in patients with T790M-positive NSCLC treated with osimertinib.[3,4,8] Similar results were found in AURA-3 trial too.[9] Our patient was started on osimertinib in May 2016. However, the patient developed resistance to osimertinib after 20 months.

A liquid biopsy was done for the patient initially. During the last few years, there is growing interest in liquid biopsy to assess the mutational status on circulating tumor DNA. It has a concordance rate of 60%–90% with those of tumor tissue but is limited by the relatively low sensitivity (60%–80%).[2,10] In clinical practice, liquid biopsy is now recommended as the first choice; the tumor biopsy is recommended only in the case of a negative result. In our case, the liquid biopsy was negative, so repeat tissue biopsy was performed.

The tissue biopsy showed resistance to osimertinib due to C797S mutation. The osimertinib resistance has been reported due to several mechanisms. The mechanisms can be EGFR dependent type or EGFR independent type. The EGFR dependent mechanisms are acquisition of new mutations (like C797S, G796D, G796S/R, L792F/Y/H, or C797G), amplification of exon 19 deletion or loss of T790 M mutation. The various EGFR independent mechanism are alternate kinase activation (MET and HER2), histological transformation, and phenotypic change such as epithelial-mesenchymal transition.[11] There can also be multiple heterogeneous mechanisms in a single patient. We searched PubMed regarding this resistance pattern with search words "osimertinib resistance." It yielded 24 citations for case reports or series. Most of these resistance cases have been described in trial condition. Only 20 clinical cases of acquired resistance to osimertinib have been reported independent of trial, details of which are shown in Table 1. It shows that majority of the patients are from China. The principle mechanism is EGFR C797S mutation seen in 9 patients, i.e., 45% of cases. Multiple mechanisms were seen in 4 patients. The patients developed resistance after a variable period of 2–18.9 months.[12-28] Osimertinib acts by covalently binding to the EGFR kinase-binding site C797, and acquired resistance to osimertinib occurs possibly by abolishing the covalent binding between osimertinib and C797 residue which was the mechanism in our case.[11] The patient thus had a triple mutation or "triple whammy" of EGFR exon 19 deletion/T790M/C797S mutations.

The recent National Comprehensive Cancer Network guidelines, version 4.2018, recommend switching over to chemotherapy in case of suspicion of osimertinib resistance, but no drugs have been approved for a specific mutation to date. The C797S mutation can vary in its management based on cis (both in the same allele) or trans (in different allele) association with T790M. If the association is in trans, the combination of first- and third-generation EGFR-TKIs might be helpful, whereas, if the association is in cis, then the patients are resistant to all three generations of EGFR-TKIs.[11] In our patient, it was cis type. The anti-EGFR monoclonal antibodies, such as panitumumab or cetuximab with brigatinib, a dual inhibitor of EGFR and ALK and EAI045, may be effective in our patient apart from chemotherapy.[11]

Thus, our patient who had a Stage IV lung cancer survived for 3.5 years and hoping for more with a good quality of life due to proper management with advancement in precision medicine.

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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