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N. Thumallapally
Northwell Health, nthumalla1@northwell.edu

S. Parylo
Northwell Health, sparylo@northwell.edu

A. Vennepureddy
Northwell Health, avennepure@northwell.edu

U. Ibrahim
Northwell Health, UIBRAHIM@northwell.edu

A. Sokoloff
Zucker School of Medicine at Hofstra/Northwell, asokoloff@northwell.edu

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Case Report

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Synchronous Presence of *EGFR*, *ALK* Driver Mutations Along With PD L1 Overexpression in a Resected Early Stage Non-Small Cell Lung Cancer: A Case Report and Review of Literature

Nishitha Thumallapally[a, c], Sara Parylo[b], Adarsh Vennepureddy[a], Uroosa Ibrahim[a], Alisa Sokoloff[a]

Abstract

Treatment of lung cancer has been revolutionized with development of drugs that target key driver mutations and immune checkpoints. Until recently, it was believed that these driver mutations are mutually exclusive. However, few reports have emerged citing the presence of both mutations either synchronously or metachronously. We describe a case report of lung adenocarcinoma harboring two driver mutations in the same tumor cells as well as exhibiting high PDL1 expression. We further discuss the possible association of these driver mutations with PDL1 expression.

Keywords: Lung cancer; Driver mutations; PDL1 expression

Introduction

Lung cancer is broadly classified as small cell and non-small cell origin. Non-small cell lung cancer (NSCLC) is further classified as adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. Until the early 2000s, the standard of care for NSCLC included surgery, radiation, and platinum-based chemotherapy. However, prognosis remained poor with metastasis; treatment centered around platinum-based chemotherapy offered a 5% survival at 5 years [1]. Patients with the same stage of disease at diagnosis who received the same therapy were noted to have widely variable responses, which led to molecular research of additional factors impacting survival [2]. Such molecular research has revealed that 64% of lung adenocarcinomas have driver gene alterations [3] including epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and gene rearrangement in echinoderm microtubule-associated protein-like anaplastic large cell lymphoma kinase (ALK).

Until recently, it was considered that these driver mutations are mutually exclusive. However, this view has recently been challenged, due to the emergence of findings supporting the coexistence of these two genes in the same tumor cells [2, 3].

Here in, we describe another case of synchronous presence of *EGFR*, *ALK* mutation in same tumor tissue along with over expression of PD L1.

Case Report

A 77-year-old male was diagnosed with stage IB NSCLC in 2014. He had 3.5 × 2.5 × 2 cm poorly differentiated adenocarcinoma in right lower lobe. He underwent right upper lobectomy and five regional lymph nodes that were removed were negative for tumor. Patient was a former smoker with 15 pack-year history and stopped smoking 20 years ago. Two years after undergoing surgery, chest computed tomography (CT) scan showed two new solid nodules measuring 7 mm and 9 mm respectively in the left lower lobe of lung. Six months later, repeat CT scan revealed that the previously described left lower lobe lung nodules had coalesced into a single lobulated lesion measuring 2 × 1.5 cm. Due to rapid increase in size of nodule, PET scan was warranted. It showed FDG avid 2.2 × 1.7 cm lesion in left lower lobe (max SUV 14.6). Furthermore, CT-guided biopsy of the nodule was positive for malignancy with histology favoring adenocarcinoma. Robotic assisted wedge resection of the nodule was performed. It demonstrated a 2 × 2cm poorly differentiated adenocarcinoma of the lung with negative margins. Upon mutation profiling, the tumor harbored *EGFR* (Exon 21 L858R) mutation. Furthermore, on fluorescence *in situ* hybridization (FISH) assay, *ALK* translocation was detected. Immunohistochemistry (IHC) revealed high PD L-1 expression (90%).

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[a]Department of Hematology/Oncology, Staten Island University Hospital, Northwell Health, NY, USA
[b]Department of Medicine, Staten Island University Hospital, Northwell Health, NY, USA
[c]Corresponding Author: Nishitha Thumallapally, 475 Seaview Avenue, Staten Island, NY 10305, USA. Email: nishithareddy99@gmail.com

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Adjuvant chemotherapy with four cycles of cisplatin and pemetrexed was recommended as tumor exhibited high risk features such as poor differentiation and no lymph node dissection was attempted.

Discussion

NSCLC is the leading cause of cancer-related death worldwide. With help of precision medicine, treatment of NSCLC is more individualized than ever before. The approval of gefitinib in the early 2000s, which was a first- generation tyrosine kinase inhibitor (TKI), represented the beginning of NSCLC treatment with molecularly targeted therapy. Certain subsets of patients were discovered to have high response rates to gefitinib, which led to additional research and the discovery of *EGFR* activating mutations. Further research down the line led to the identification of *ALK* translocations followed by development of therapy targeting inhibitory checkpoint molecules, which bind to ligands often expressed by NSCLC cells. Programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1) represent the most well-researched targets. PD-1 inactivates T cells upon binding to PD-L1 or PD-L2, which are often expressed by NSCLC cells [4]. PD-1 antibody blockade increases effector T cell function and decreases levels of tumor-promoting cytokines [5].

EGFR and *ALK* mutations had previously been widely considered mutually exclusive [6, 7]. In recent years, the exclusivity of *EGFR* and *ALK* mutations has been challenged. Table 1 [2, 6-19] summarizes all the cases in the literature describing the concomitant presence of the *EGFR* and *ALK* mutations. Yang et al reviewed 977 NSCLC surgical regimens and found that 1.3% of samples had both mutations [8]. Lee at al analyzed 6,637 NSCLC cases and found four cases of concomitant *EGFR* and *ALK* translocation [20]. The patients most likely to have both *EGFR* and *ALK* mutations tend to be young, non-smokers, with advanced disease at diagnosis, and adenocarcinoma classification of disease [9]. In a meta-analysis by Yang et al, also found that PD-L1 overexpression had a statistically significant association with the *KRAS* mutation, which our patient was not found to have [21].

Akbay et al used murine models to demonstrate that mutant EGFR expression in bronchial epithelial cells induced PD-L1, and NSCLC cell lines with activated EGFR exposed to EGFR inhibitors subsequently reduced PD-L1 expression. This potentially suggests that EGFR signaling remodels the tumor environment and connects EGFR inhibitor treatment response to PD-L1 inhibition [5]. These results are supported by a later study by Azuma et al suggesting that PD-L1 expression is increased with the increased EGFR signaling caused by activating *EGFR* mutations. In surgically resected NSCLC, high PD-L1 was associated with *EGFR* mutations and was an independent negative prognostic factor. In multivariate analysis, EGFR and adenocarcinoma were associated with increased PD-L1 expression independent of other factors [22]. However, it is important to note that evidence of a connection between PD-1/PD-L1 and EGFR expression is far from universally accepted. For example, Zhang et al used immunohistochemistry analysis of 143 surgically resected lung adenocarcinoma specimens to conclude that there is no statistically significant relationship between PD-L1 and EGFR expression in lung adenocarcinoma [23].

Tang et al built upon the previously mentioned findings and examined the association between *EGFR* mutation and PD-L1 expression in 170 Chinese patients with advanced NSCLC [24]. The objective was to determine if patients treated with TKIs for *EGFR* mutations had any correlations between PD-L1 expression and prognosis. PD-L1 was overexpressed in 65.9% of samples, and positive PD-L1 was associated with *EGFR* mutations. However, there was no significant correlation between PD-L1 and the curative effect of TKIs for *EGFR* mutations.

The introduction of TKIs for *EGFR* mutations and anti-PD-L1/PD-1 therapy has posed the question about whether EGFR TKIs are more efficacious than anti-PD-L1/PD-1 therapies or whether the reverse is true. In addition, there are questions of whether *EGFR* mutations themselves or their treatment with TKIs predispose patients to PD-L1 overexpression or whether *EGFR* mutations and PD-L1 expression are directly or indirectly linked to each other.

Role of EGFR TKI and anti PD-1/PD-L1 therapies in the adjuvant setting of NSCLC

Zhong et al studied the effectiveness of gefitinib compared to chemotherapy in the adjuvant setting in patients with *EGFR* mutant, completely resected stage II-IIIA NSCLC. This was a randomized, open label, phase III trial done in China (ADJUVANT Trial) [25]. A total of 222 patients were randomized, 111 to gefitinib and 111 to vinorelbine plus cisplatin. Gefitinib was administered as 250 mg once daily for 24 months and chemotherapy was administered as intravenous vinorelbine (25 mg/m^2 on days 1 and 8) plus intravenous cisplatin (75 mg/m^2 on day 1) every 3 weeks for four cycles. Median follow-up was 36.5 months. Median disease-free survival was significantly longer with gefitinib (28.7 months (95% CI: 24.9 - 32.5)) than with vinorelbine plus cisplatin (18.0 months (13.6 - 22.3); hazard ratio (HR) 0.60, 95% CI 0.42 - 0.87; P = 0.0054). Based on the superior disease-free survival, reduced toxicity, and improved quality of life, adjuvant gefitinib could be a potential treatment option compared with adjuvant chemotherapy in these patients. However, the duration of benefit with gefitinib after 24 months might be limited and overall survival data are not yet mature.

Data supporting the use of adjuvant EGFR TKIs were reported in two retrospective analyses and two prospective trials RADIANT, SELECT respectively [26-29]. All these trials showed encouraging improvements in survival for patients with *EGFR* mutant stage I-III NSCLC who received adjuvant EGFR TKIs compared to patients who did not. Collectively, these results suggest that patients with *EGFR*-mutant, stage IB-IIIA resected NSCLC might benefit from adjuvant EGFR TKIs treatment. However, there were differences in the selection and staging of the patients, timing of administration of TKI whether as maintenance following adjuvant chemotherapy or

Table 1. Summary of Previously Reported Patient Characteristics and Treatment Outcomes of NSCLC With Concomitant *EGFR* Mutation and *ALK* Fusion [2, 6-19]

Author	Patients	Age	Sex/ethinicity	Smoking status	*EGFR* mutation	First line	Best response	Second line	Best response	Third line	Best response
Thumallapally et al [2]	1	72	M/C	Heavy	L861Q exon21	Crizotinib	NR	ND			
Chiari et al [13]	1	67	F/C	Never	L858R exon 21	Carbo/Pem	SD	Gefitinib/ erlotinib/ afatinib	PR/PD	Crizotinib	PR
Chen et al [11]	1	56	F/A	Heavy	Del exon 19	Cis/Gem	Toxicity	Erlotinib	SD	Crizotinib	CR
Miyanaga et al [14]	1	55	F/A	Never	Del exon 19	Cis/Pem	SD	Gefitinib/ erlotinib	PD	Crizotinib	SD
									SD		
Tanaka et al [15]	1	39	M/A	Light	Del exon 19	Cis/Doc	SD	PEM	PR	Erlotinib	PD
Tiseo et al[9]	1	48	M/C	Never	Del exon 19	Cis/Gem	PR	Erlotinib	PD		
Popat et al [10]	1	65	F/C	Never	Del exon 19	Carbo/ vinorelbine	PR	Erlotinib	CR		
Santelmo et al [7]	1	52	F/ C	Heavy	Del exon 19	Gefitinib	PR	ND			
Zhao et al [16]	1	48	F/A	Never	L858R exon 21	Erlotinib	SD	Crizotinib	SD		
Rossing et al [17]	1	61	M/C	Never	L858R exon 21	Carboplatin/ vinorelbine/Beva	PR	Crizotinib	PR	PEM	PD
Lee et al [6]	1	73	M/Asian	Former	Del exon 19	Gefitinib	PD	Crizotinib	PR		
Jurgens et al [18]	1	69	M/C	Light smoker	exon 21 L 861	Gefitinib	PD	Carbo/Pem/ Beva	PR	Pem	PD
Sasaki et al [19]	2	NR	Asian	NR	Del exon 19 (2)	Erlotinib (2)	PR (2)	ND			
Yang et al [8]	11	Median age 59	Female (8)/ male (3)/Asian	Never (11)	Del exon 19 (6)	Gefitinib (3)	PR (3)	Crizotinib(2)	PR(1), S D(1)		
					L858R exon 21 (4)	Erlotinib (5)	PR (4), PD (1)	Crizotinib(1)	PD(1)		
					Exon 20 (1)	Afatinib (2)	PR (1), SD (1)	Crizotinib (1)	PR(1)		
Sweiss et al [12]	3	37	Male (2)/ female (1)	Never smoker (2)	Exon 23 polymorphism	Carbo/Beva/Pac	PR	Erlotinib/ Beva	PD	Crizotinib	SD
		57		Heavy smoker (1)	Exon 19 Del (1)	Erlotinib	PR	Crizotinib	PD	Erlotinib	PD
		52			L858R (1)	Crizotinib	PD	Carbo/Pem	PD		
Thumallapally et al (current patient)	1	77	M/C	Light	L858R exon21	Cis/pem	SD	ND			

AC: adenocarcinoma; A: Asian; Beva: Bevacizumab; C: Caucasian; Carbo: carboplatin; Cis: cisplatin; CR: complete remission; Doc: docetaxel; Gem: gemcitabine; Heavy smoker: more than 1 pack a day; Light smoker: less than 1 pack a day; ND: not done; NR: not reported; Pts: patients; PD: progressive disease; PR: partial response; Pac: paclitaxel; Pem: pemetrexed; SC: squamous carcinoma; SD: stable disease; TKI: tyrosine kinase inhibitor.

Table 2. Adjuvant Targeted Therapy in Resected NSCLC [25, 28-30]

Zhong et al [25] (ADJUVANT trial)	Phase III	Resected stage II-IIIA *EGFR* mutant NSCLC	N = 222	Gefitinib vs. cisplatin plus vinorelbine	Median PFS was 28.7 months with gefitinib and 18 months with cisplatin plus vinorelbine.
Kelly et al [28] (RADIANT trial)	Phase III	Resected stage Ib-IIIA NSCLC. Tumors expressed EGFR protein by IHC or FISH	N = 973	Erlotinib vs. placebo	Median PFS was 50.7 months with erlotinib and 48.2 months with placebo.
Pennell et al [29] (SELECT trial)	Single arm Phase II	Resected stage IA-IIIA *EGFR* mutant NSCLC	N = 100	Erlotinib 150 mg/ day for 2 years after adjuvant chemotherapy	Two-year DFS was 90%. Median time to recurrence after stopping erlotinib was 12 months.
Goss et al [30] (NCIC CTG BR19 trial)	Phase III	Resected stage IB-IIIA NSCLC	N = 503	Gefitinb 250 mg daily or placebo after adjuvant chemotherapy	Median DFS and OS were similar in both the groups.
ALCHEMIST (NCT02193282)	Randomized phase III	Resected stage IB-IIIA *EGFR* mutant NSCLC	N = 450 estimation	Adjuvant erlotinib vs. placebo	Currently ongoing
ADAURA (NCT02511106)	Randomized phase III	Resected stage IB-IIIA *EGFR* mutant NSCLC	N = 700 estimation	Adjuvant AZD9291 vs. placebo	Currently ongoing

PFS: progression-free survival; DFS: disease-free survival; OS: overall survival.

upfront TKI administration without adjuvant chemotherapy in the above mentioned clinical trials.

Data from the ongoing ALCHEMIST (NCT02193282) and ADAURA (NCT02511106) trials could help to identify if EGFR TKIs do provide an overall survival benefit in the adjuvant setting. At this point of time, EGFR TKI administration in the adjuvant setting is not FDA approved. However it might get FDA approval once the ALCHEMIST and ADAURA trials show overall survival benefit. These trials are summarized in Table 2 [25, 28-30].

Phase III currently ongoing randomized trials testing immune checkpoint inhibitors in early lung cancer could have the potential to represent the next step in the effort to develop predictive markers in this setting (Table 3) [31, 32].

PEARLS is an international, triple-blinded, placebo-controlled randomized phase III trial [31]. This study will prospectively investigate the benefit of adjuvant pembrolizumab 200 mg every 3 weeks for a maximum of 18 doses versus placebo in pathological stage IB (T ≥ 4 cm)-IIIA, after completion of radical surgery with or without standard adjuvant chemotherapy. A total of 1,380 eligible patients will be randomized, approximately 690 patients in each treatment arm, with DFS as primary end-point.

ANVIL is a phase III trial evaluating nivolumab (a humanized IgG4 anti-PD-1 monoclonal antibody) 3 mg/kg every 2 weeks for a maximum of 12 doses versus placebo in pathological stage IB (T ≥ 4 cm)-IIIA with DFS and OS as primary end-points after proper adjuvant chemotherapy.

BR31 and NCT02486718 are phase III trial testing, respectively, durvalumab 10 mg/kg every 2 weeks and atezolizumab (both anti-PD-L1 monoclonal antibodies) 1,200 mg every 3 weeks for 16 cycles, in the same setting of patients and stages, having as primary end-point DFS in PD-L1positive patients in BR31 trial and DFS in overall population in NCT02486718 [32, 33].

The results of the aforementioned studies will provide important guidance. A literature review reveals no clearly defined protocol for treating NSCLC cases of *EGFR* and *ALK* mutations with PD-L1 overexpression. Specifically reviewing simultaneous *EGFR* and *ALK* mutations reveals discussions of responses to treatment of EGFR alone, ALK alone, or progression in response to treatment of a single mutation. In response

Table 3. Adjuvant Immunotherapy Trials in NSCLC [31, 32]

PEARLS trial [31] (NCT02504372)	Randomized phase III	Resected stage IB-IIIA NSCLC	N = 1,380	Pembrolizumab 200 mg IV every 3 weeks for 1 year vs. placebo after standard adjuvant treatment	Currently ongoing
ANVIL trial [32] NCT02595944	Randomized phase III	Resected stage IB-IIIA NSCLC	N = 714	Nivolumab every 2 weeks for 1 year vs. observation after standard adjuvant treatment	Currently ongoing
NCT02273375	Randomized phase III	Resected stage IB-IIIA NSCLC	N = 1,360	MEDI4736 IV infusion for 12 months vs. placebo infusion after standard adjuvant treatment	Currently ongoing
NCT02486718	Randomized phase III	Resected stage IB-IIIA NSCLC	N = 1,127	Atezolizumab IV infusion Q3 weeks for 16 cycles vs. observation after standard platinum based chemotherapy	Currently ongoing

to the cases of progression after single mutation treatment, the other mutation was treated or traditional chemotherapy was initiated [10-12]. Adding the question of concomitant PDL-1 overexpression further complicates the issue, as per the prior discussion.

Our patient was not given treatment targeting EGFR, ALK, or PD-L1. Given the high-risk tumor features, despite being at early TNM stage at diagnosis, the patient was treated with cisplatin and pemetrexed, an older, more studied NSCLC treatment regimen. With the documentation of additional cases of EGR, ALK, and PDL-1 expression in NSCLC, clinicians may be able to develop treatment protocols for these patients.

Conflict of Interest

The authors fully declare there is no financial or other conflict of interest.

Declarations

Informed consent has been obtained from the patient.

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