Case Report

Novel *LZTR1* germline mutation as a mechanism of resistance to osimertinib in *EGFR*-mutated lung adenocarcinoma: a case report

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Background: Tyrosine kinase inhibitors (TKIs) are now the standard of care first-line therapy for epidermal growth factor receptor (*EGFR*)-mutated advanced non-small cell lung cancer (NSCLC) patients. Despite positive outcomes in most patients, with extended progression-free survival (PFS), a small population of patients respond poorly to these drugs. Complex genetic and non-genetic resistance mechanisms may be the drivers of disease in cancer, but further research is required to identify these mechanisms in the clinic. Germline molecular testing alongside broad-panel somatic next-generation sequencing (NGS) has allowed for detection of resistance mutations in *EGFR*-mutated NSCLC patients that may be linked with poor response on TKIs.

Case Description: Here, we present a case of an NSCLC patient harboring an *EGFR* somatic mutation and a concomitant leucine-zipper-like transcriptional regulator-1 (*LZTR1*) germline mutation. The patient experienced rapid disease progression on first-line EGFR TKI, osimertinib-chemotherapy, combination therapy with a PFS of only 4 months as compared to the median PFS of 27.9 months in the FLAURA2 study.

Conclusions: This case report indicates that identification of germline resistance mutations such as *LZTR1* may be associated with poor response to EGFR TKIs. Furthermore, further characterization of these resistance mutations beyond somatic mutations can aid in development of future therapeutic options, which currently do not exist. It is recommended that germline testing be performed as part of the initial patient workup, if available.

Keywords: Lung adenocarcinoma; germline testing; next-generation sequencing (NGS); targeted therapy; case report

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Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States with approximately 340 deaths per day, almost 2.5 times more than colorectal cancer (1). Globally, depending on region, between 12.8% and 49.1% of patients with non-small cell lung cancer (NSCLC) harbor an epidermal growth factor receptor (*EGFR*) gene mutation (2). Although EGFR tyrosine kinase inhibitors (TKIs) provide significant clinical benefit to these patients, resistance eventually occurs via genetic and nongenetic mechanisms (3). There are few known *de novo* EGFR TKI resistance mechanisms. Here we present a patient with initial stage IIIA (T1b cN2 M0) adenocarcinoma of the lung, with confirmed *EGFR* exon 19 mutation (c.2236–2250del) with potential resistance to TKIs due to her leucine-zipper-like transcriptional regulator-1 (*LZTR1*) c.1653C>G variant. While *LZTR1* mutations have been associated with EGFR resistance preclinically, to our knowledge, this is the first report of a patient with an *LZTR1* germline mutation who had rapid progression on EGFR TKI. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-723/rc).

Case presentation

A 52-year-old female former smoker with a past medical history of hypertension, autoimmune glomerulonephritis, and asthma, presented to urgent care with hemoptysis. A chest computed tomography (CT) showed a spiculated opacity measuring 1.1 cm × 1.1 cm in right middle lobe (RML) of the lung, in addition to a large right subcarinal lymph node measuring 2.6 cm × 1.7 cm, and a right hilar lymph node measuring 1.7 cm × 0.9 cm. Subsequent positron emission tomography (PET)-CT showed a hypermetabolic 1.1 cm RML nodule measuring up to 2.4 standardized uptake value (SUV), a poorly visualized right hilar lymph node with hypermetabolic activity measuring 7.2 SUV, and a 1.3 cm subcarinal lymph node with an SUV of 10 SUV. A magnetic resonance imaging (MRI) of the brain showed no evidence of intracranial metastatic disease. Of note, mediastinal staging was not done at the time of initial diagnosis. She was diagnosed with stage IIIA (T1b cN2 M0) adenocarcinoma of the lung (*Figure 1*). She reported a 10-pack-year smoking history and quit approximately 15 years prior to the diagnosis. Tumor analysis via clinical commercial Clinical Laboratory Improvement Amendments (CLIA)-certified next-generation sequencing (NGS) test was pursued as part of standard of care, identifying an *EGFR* exon 19 deletion (c.2236–2250del; p.E746_A70del), CCNE1 amplification, LZTR1 (c.1653C>G; p.Y551*), PIK3CA (c.3140A>G; p.H1047R), RB1 (c.2330del; p.777Lfs*33), TP53 (c.278del; p.L93Rfs*30), tumor mutational burden (TMB) (low), microsatellite instability (MSI) (stable), programmed death-ligand 1 (PD-L1) 22C3 0% (*Table 1*). No family history of cancer was reported. She was treated with concurrent radiation therapy for a total of 6,000 cGy in 30 fractions, with weekly cisplatin (30 mg) and etoposide (50 mg), completing six cycles. She then transferred care to City of Hope. All procedures performed in this study were in accordance with the ethical standards of the City of Hope Institutional Review Board and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Restaging scans showed resolution of the subcarinal and right hilar adenopathy with a decrease in the right lower lobe pulmonary nodule. She elected to participate in a Precision Medicine Study at City of Hope which includes germline genetic testing via commercial CLIA-certified test revealing a pathogenic *LZTR1* mutation (c.1653C>G; p.Y551*) (*Table 1*). Given prior radiation treatment, surgical resection was not pursued. Considering

Highlight box

Key findings

- This is the first report of a clinical germline leucine-zipper-like transcriptional regulator-1 (*LZTR1*) mutation in an epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) patient and had rapid disease progression on osimertinib-chemotherapy combination therapy.

What is known and what is new?

- Tyrosine kinase inhibitors (TKIs) are the standard of care first-line therapy for *EGFR*-mutated advanced NSCLC patients. However, a subset of patients respond poorly to these TKIs.
- Concurrent germline mutations may be one mechanism in which these tumors bypass the effectiveness of EGFR TKIs in NSCLC.

What is the implication, and what should change now?

- An *LZTR1* germline mutation may act as a potential negative biomarker of TKI therapy in actionable *EGFR*-mutated NSCLC.
- The use of germline mutation testing in advanced NSCLC beyond somatic mutation testing may help better understand the TKI-resistant subset of patients.

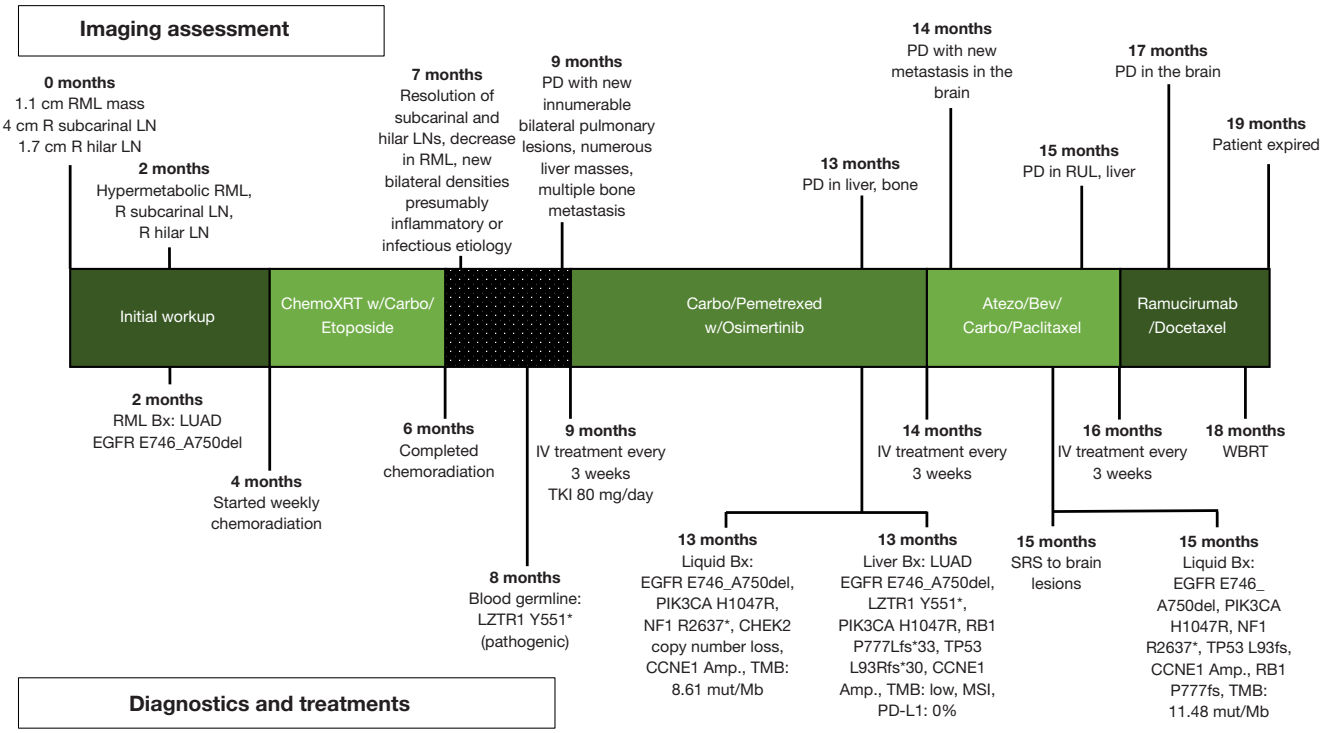

Figure 1 Patient's clinical timeline. RML, right middle lobe; R, right; LN, lymph node; Bx, biopsy; LUAD, lung adenocarcinoma; EGFR, epidermal growth factor receptor; ChemoXRT, chemoradiation therapy; w, with; Carbo, carboplatin; LZTR1, leucine-zipper-like transcriptional regulator-1; PD, progressive disease; IV, intravenous; TKI, tyrosine kinase inhibitor; Amp., amplification; TMB, tumor mutation burden; Mut/Mb, mutations per megabase; MSI, microsatellite instability; PD-L1, programmed death-ligand 1; Atezo, atezolizumab; Bev, bevacizumab; SRS, stereotactic radiosurgery; RUL, right upper lobe; WBRT, whole-brain radiation therapy.

the actionable *EGFR* mutation and her history of autoimmune glomerulonephritis, maintenance therapy with osimertinib, an EGFR TKI, was planned in lieu of single agent immunotherapy. Prior to initiating adjuvant osimertinib, an additional CT of the chest showed diseased progression evidenced by multiple hepatic and bony lesions. Given the disease progression, systemic therapy with carboplatin [area under the curve (AUC) 5], pemetrexed (500 mg/m^2) every 3 weeks, and osimertinib (80 mg daily) was initiated. Restaging PET-CT and MRI of the abdomen, following four cycles of carboplatin and pemetrexed, showed an increase in the size and number of liver lesions. A liver biopsy was performed and demonstrated the lesion was consistent with poorly differentiated carcinoma and metastatic pulmonary adenocarcinoma. Tumor profiling of the liver lesion was also obtained, which showed the pathogenic germline *LZTR1* variant at an allele frequency of 68% and the previously noted *EGFR* exon 19 deletion at a frequency of 24%. Consequently, treatment was escalated to carboplatin (AUC 5), paclitaxel (175 mg/m^2), bevacizumab (15 mg/kg), and atezolizumab (1,200 mg) every 3 weeks. Despite aggressive treatment with carboplatin, paclitaxel, bevacizumab, and atezolizumab, she continued to progress with disease metastasis to the brain, lung, and liver. She was treated with stereotactic radiosurgery (SRS) to the brain lesion and switched her systemic treatment to ramucirumab (10 mg/kg) plus docetaxel (37.5 mg/m^2, dose reduced by 50% for drug-drug interaction with concomitant medication posaconazole) every 3 weeks. Multiple new brain lesions were noted and whole brain radiotherapy was initiated upon progression. The patient and family transitioned to comfort care. Shortly after the transition, the patient deceased.

Discussion

In the precision oncology approach, the implications of germline pathogenic variants continue to extend beyond its traditional role in early cancer detection and risk reducing

Table 1 Patient detailed molecular testing patient genomic profile

NGS panel type	Genomic alteration detected	Allele/cfDNA frequency	Predicted effect
Liquid NGS germline results: 155 genes panel	LZTR1 (c.1653C>G; p.Y551*)	Heterozygous	Pathogenic
	MLH3 (c.4268G>A; p.R1423H)	Heterozygous	VUS
Liquid NGS test one results: 83 genes (clinically relevant exons) panel	EGFR (p.E746_A750del)	25.8%	Pathogenic
	PIK3CA (p.H1047R)	17.8%	Pathogenic
	NF1 (p.R2637*)	0.7%	Pathogenic
	CHEK2 (copy number loss)	Detected	Pathogenic
	CCNE1 (amplification)	High (+++)	Pathogenic
	ESR1 (p.A505P)	9.0%	VUS
	NF1 (p.N2383S)	1.1%	VUS
	TMB (8.61 Mut/Mb)	N/A	–
	MSI-high (not detected)	N/A	–
Tissue NGS test results: 523 full gene (entire exon) and 165 RNA-seq fusion panel	CCNE1 (amplification)	N/A	Pathogenic
	EGFR (c.2236_2250del; p.E746_A750del)	24%	Pathogenic
	LZTR1 (c.1653C>G; p.Y551*)	68%	Pathogenic
	PIK3CA (c.3140A>G; p.H1047R)	17%	Pathogenic
	RB1 (c.2330del; p.P777Lfs*33)	50%	Pathogenic
	TP53 (c.278del; p.L93Rfs*30)	44%	Pathogenic
	TMB (low)	N/A	–
	MSI (stable)	N/A	–
	PD-L1 22C3 (no expression; 0%)	N/A	–
Liquid NGS test two results: 83 genes (clinically relevant exons) panel	EGFR (p.E746_A750del)	8.3%	Pathogenic
	PIK3CA (p.H1047R)	7.2%	Pathogenic
	NF1 (p.R2637*)	0.3%	Pathogenic
	TP53 (p.L93fs)	9.4%	Pathogenic
	CCNE1 (amplification)	Medium (++)	Pathogenic
	RB1 (p.P777fs)	12.9%	Pathogenic
	ESR1 (p.A505P)	3.0%	VUS
	NF1 (p.N2383S)	1.7%	VUS
	MTOR (p.R2505*)	0.3%	VUS
	PIK3CA (p.L551L)	0.1%	SYN
	TMB (11.48 Mut/Mb)	N/A	–
	MSI-high (not detected)	N/A	–

NGS, next-generation sequencing; cfDNA, cell-free DNA; LZTR1, leucine-zipper-like transcriptional regulator-1; EGFR, epidermal growth factor receptor; TMB, tumor mutational burden; Mut/Mb, mutations per megabase; N/A, not applicable; MSI, microsatellite instability; RNA-seq, RNA-sequencing; PD-L1, programmed death-ligand 1; VUS, variant of uncertain significance; SYN, synonymous mutation.

options. Germline pathogenic variants are reported to cause an earlier age at cancer diagnosis and our patient was diagnosed at an earlier age of 52 years old (4). Preliminary evidence also shows that germline molecular testing guidelines need to be expanded as germline mutations have been detected in lung cancer patients without smoking history or family history of cancer (4,5). A case report of a young lung cancer patient with maternally inherited *BRCA2* germline variant showed efficacy of olaparib in combination with pembrolizumab (6). More recently, a phase II study investigating the role of germline mutations in advanced solid tumors showed efficacy of *BRCA1/2* inhibitor olaparib (7). Taken together, this suggests that germline mutation variants are more common in lung cancer than previously thought and may be a potential avenue for future therapeutic targets.

Somatic mutations in *LZTR1* gene mutations have been reported in various cancers including glioblastoma, hepatocellular, esophagogastric, and colorectal cancers. Proposed as a tumor suppressor gene, *LZTR1* gene encodes leucine zipper-like transcription regulator 1 protein containing Kelch-BTB-BACK domains. LZTR1 protein functions as a substrate adaptor of CUL3 (8). Kelch domain is required for substrate recognition while the BTB-BACK domain interacts with CUL3. The role of LZTR1 and its target substrates in human cancers is not clearly understood. It is thought to be involved in ubiquitination and degradation of endogenous KRAS and mitogen-activated protein kinase (MAPK) pathway activation (9). LZTR1 has been shown to function as a "RAS killer protein" and recent preclinical studies showed that *LZTR1* may regulate the growth and invasion of lung cancer cells through RAS/MAPK signaling (9-12).

Recently, Ko *et al.* [2023] uncovered two oncogenic receptor tyrosine kinase (RTK), EGFR and AXL as novel protein substrates of LZTR1 using multiple unbiased proteomics screens (13). Ubiquitination by LZTR1 led to lysosomal mediated degradation of EGFR and AXL proteins and signaling downregulation. The presence of somatic and germline mutations of *LZTR1*-mutant tumors was shown to cause EGFR and AXL accumulation and deregulated signaling, which may mediate TKI resistance. The study demonstrated that EGFR and AXL accumulated at significantly higher levels in schwannomas from individuals with germline mutations of *LZTR1* compared to those with sporadic schwannomas and *SMARCB1*-related schwannomas. By analyzing transcriptomic profiles from RNA-sequencing (RNA-seq) data of schwannoma patients with *LZTR1* and those without *LZTR1*, the study also found that EGF-dependent RTK activation and RTK activities are significantly higher in *LZTR1* mutation group. Through *in vitro* and *in vivo* experiments, the group revealed that when treated with a single RTK inhibitor, the persistent activity of EGFR or AXL is sufficient to sustain survival and growth of *LZTR1*-mutated cells. Hence, it was proposed that co-inhibition of both EGFR and AXL would provide a more effective treatment opportunity in reducing tumor growth and improving survival compared with single-drug treatments in *LZTR1* mutant tumors. In our patient, an *LZTR1* pathogenic mutation Y551* was detected prior to initiation of osimertinib-chemotherapy combination treatment and the patient rapidly progressed within 4 months as compared to progression-free survival (PFS) 27.9 months in FLAURA2 study (14). While evidence of *LZTR1* germline mutation resistance remains scarce the detection of a pathogenic germline mutation suggests that it may have affected this patient's rapid progression. However, impact due to the interaction between chemotherapy and osimertinib or other resistance mechanisms cannot be fully excluded.

Conclusions

In *EGFR*-mutated NSCLC patients, the presence of a concurrent germline *LZTR1* mutation may indicate resistance and serve as a potential negative biomarker for predicting efficacy of osimertinib. This study was limited as it is a single EGFR patient report with a concomitant *LZTR1* germline mutation. While *EGFR* mutations are common in lung cancer germline mutation testing is not performed on all patients and it is difficult to ascertain the frequency of this co-mutation in all patients. Nevertheless, our findings are concordant with the literature regarding a possible EGFR-LZTR1 resistance relationship. Future preclinical and clinical studies are required to determine the mechanism of resistance and concomitant therapeutic options, as suggested by Ko *et al.* (13).

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-723/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-723/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the City of Hope Institutional Review Board and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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