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Case Report

Case Series: EGFR and ROS-1 Co-Occurrence in Advanced Non–Small Cell Lung Cancer

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ABSTRACT

Non–small cell lung cancer (NSCLC) is a heterogeneous disease with diverse molecular alterations. Two of the most common genetic abnormalities found in advanced NSCLC are mutations in the epidermal growth factor receptor (*EGFR*) and rearrangements in the ROS proto-oncogene 1 (*ROS-1*). Although these two alterations are typically mutually exclusive, there have been reports of their co-occurrence in a small subset of NSCLC patients. The discovery of this comutation has recently become apparent due to the increased use of more sensitive whole genome sequencing. We share our experience with two cases of coexisting *EGFR* and *ROS-1* alterations. The first case is a 60-year-old man diagnosed with advanced adenocarcinoma of the lung with metastasis to bone and left adrenal gland. The second case is a 49-year-old woman diagnosed with stage IV lung adenocarcinoma with metastasis to the contralateral lung and diffuse abdominal lymphadenopathy. The first case was treated with osimertinib, and currently has had a stable disease on this medication for more than 3 years. The second case had a short interval of stable disease on osimertinib; then she developed progressive disease with poor response to anti–ROS-1 therapy. We believe patients with advanced NSCLC may have a higher incidence of coalterations, especially in the areas of the world with higher *EGFR* mutations and in the era of higher usage of whole genome sequencing. The presence of comutations will allow for a good long-term response to anti-EGFR therapy. This highlights the importance of the use of next-generation sequencing whenever possible and considers variant allele frequency as a factor in directing the therapy. There are many other unanswered questions, such as the best treatment sequencing or even the combined targeted therapy approach. This case series may add some information to the current literature.

Keywords: EGFR, ROS-1, co-occurrence, advanced lung adenocarcinoma

INTRODUCTION

Lung cancer in the population of Saudi Arabia is still uncommon, with a 3.4% incidence of all newly diagnosed cases in 2020.[1] It is the seventh most common cancer among Saudi nationals and the fifth most common cancer among males. The national incidence of an epidermal growth factor receptor (*EGFR*) mutation in lung cancer patients is around 28.7%,[2] which is more common than the incidence in the Western population. The use of EGFR tyrosine kinase inhibitors (TKIs) has greatly improved the survival and quality of life of patients with non–small cell lung cancer (NSCLC) and with *EGFR* mutations. However, many patients exhibit de novo or primary/early resistance. The development of comprehensive genomic profiling has led to the discovery of various mutations and coexisting genetic alterations, and many studies have revealed that concurrent genetic alterations may play an important role in the response and resistance of *EGFR*-mutant NSCLC to EGFR-TKIs. Therefore, a better understanding of specific concurrent gene alterations and their impact on EGFR-TKI treatment efficacy is necessary to optimize clinical outcomes.[3]

The coexistence of an *EGFR* driver mutation with other driver alterations like ROS proto-oncogene 1 (*ROS-1*) rearrangement, *KRAS* mutation, *BRAF* mutation, and *ALK* rearrangement is rare globally, and there is no clear consensus on approaching such conditions due to the rarity.[4–6] To our knowledge, no cases of this coalteration have been reported in our country and the Gulf region. We share our experience managing two cases with *EGFR* and *ROS-1* coalterations. One of these cases has been on anti-EGFR therapy for more than 3 years with excellent partial response.

This study obtained permission from the institutional review board of King Abdullah International Medical Research Center, Riyadh, Saudi Arabia. The approval

Table 1. Lung cancer next-generation sequencing (NGS) panel result (Case 1)

NGS Summary Case 1		
Positive	3	Clinically significant variants
	8	Therapies with potential clinical benefit
	1	Therapies associated with resistance
Disease-relevant genes with no reportable alterations identified		
ALK	*BRAF*	*ERBB2*
MET	*NRAS*	*P1K3C.A*
RET	*MAP2K1*	*KRAS*
Disease-relevant mutations not detected in this patient		
EGFR T790M N	Not detected in 4511 NGS reads	
EGFR exon 19 deletion	Not detected in 3255 NGS reads	
EGFR C797S	Not detected in 4542 NGS reads	

Actionable genomic mutations

Genomic findings detected	**Allelic fraction**	**Therapies in lung adenocarcinoma**	**Approved therapies in other indications**	**Therapies associated with resistance**
SLC34A2-ROS1 fusion exon 13- exon 32 Pathogenic Tier 1A	Supported by 22,381 NGS reads	Ceritinib, crizotinib, lorlatinib	—	EGFR tyrosine kinase Inhibitor
EGFR c.2573T>G (p.L858R) Pathogenic Tier 1A	29% (of 2787 reads)	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib	—	—
RAF1 c.770C>T (p.S257L) Tier 2C				
BRAF c.1787G>A (p.G596D) Tier 2C				

number is IRB/0678/24. Verbal consent was collected from the subjects and documented in the charts.

CASE 1

A 60-year-old man, married, with a 20-pack-year history of smoking, was diagnosed with stage IV adenocarcinoma of the right lung on February 20, 2020. His disease was metastatic at presentation to rib bones and the left adrenal gland; he had an excellent performance status (ECOG performance status 0). His past medical history was consistent with hypertension, chronic kidney disease, and hypothyroidism on replacement therapy. His family history was unremarkable. Owing to the lack of genome sequencing in his primary medical facility, he started on a systemic therapy combination consisting of carboplatin, paclitaxel, and bevacizumab. After two cycles, he presented with an acute abdomen and was found to have a lactate dehydrogenase of 347 (125–220 U/L) and CO2 of 20 (23–31 mmol/L). His computed tomography (CT) of the abdomen, taken on March 20, 2020 (at presentation), revealed signs of free intra-abdominal air and large bowel perforation. Treatment was interrupted due to intestinal perforation related to bevacizumab. He underwent surgical exploration with colonic resection and intra-abdominal washing. Upon patient review in our center, his solid tumors next-generation sequencing (NGS) tissue panel (52 genes) was done and revealed EGFR c.2573T>G (p.L858R) with an allelic fraction of 29% (of 2787 reads) and SLC32A2-ROS1 fusion (exon13-exon 32) with an allelic fraction of 22,381 NGS reads (Table 1). After the thoracic oncology multidisciplinary tumor board discussion, the patient started on osimertinib 80 mg oral daily in early May 2020. The first CT assessment on June 23, 2020 (about 2 months of osimertinib therapy), showed partial response in the right lung primary mass and the left adrenal lesion. His treatment has continued up to now; during this period, he received 42 months of osimertinib and did 14 CT scan evaluations, all of which showed disease stability. No grade 3 or 4 toxicities were observed.

CASE 2

A 49-year-old married woman who never smoked, with a history of uterine fibroid, a post myomectomy in 2015, and an endometrial polypectomy in 2021, is presented in Case 2. In July 2022, she was diagnosed with stage IV lung adenocarcinoma of the left side with metastasis to the contralateral lung, peritoneum, and retroperitoneal abdominal lymph nodes. She was symptomatic with dyspnea and abdominal pain as well. Her ECOG performance status at diagnosis was one. Owing to unexpected delays in NGS panel results and in light of her severe symptoms, the decision was made to proceed with carboplatin and pemetrexed. She received one cycle of chemotherapy. The solid tumors NGS tissue panel (52 genes) results came after cycle one and revealed multiple mutations, RAF1 c.770C>T (p.S257L), SLC34A2-ROS1 fusion with an allelic fraction of 43638 NGS reads, BRAF c.1787G>A (p.G596D), and EGFR c.2156G>T (p.G719V) (Table 2). The baseline echocardiogram was normal. The thoracic oncology multidisciplinary meeting recommended starting her on osimertinib 80 mg orally daily. She tolerated the treatment very well, with no reportable toxicity. The first CT scan assessment (after 2 months of osimertinib therapy) showed partial treatment response in the mediastinal and hilar lymph nodes with stable disease in the primary tumor site. The second CT scan assessment in early December 2022 revealed disease

Table 2. Lung cancer next-generation sequencing (NGS) panel result (Case 2)

NGS Summary Case 2				
Positive		4	Clinically significant variants	
		8	Therapies with potential clinical benefit	
		0	Therapies associated with resistance	
Actionable genomic mutations				
Genomic findings detected	**Allelic fraction**	**Therapies in lung adenocarcinoma**	**Approved therapies in other indications**	**Therapies associated with resistance**
EGFR c.2156G>T (p.G719V) Pathogenic Tier 1A	8.40% (of 2000 reads)	Dacomitinib, erlotinib, gefitinib, osimertinib	—	—
SLC34A2-ROS1 fusion Pathogenic Tier 1A	Supported by 43,638 NGS reads	Certinib, crizotinib, entrectinib, lorlatinib	—	—

progression in the mediastinal lymph nodes, mild disease progression of the primary tumor, and worsening in the size of the abdominal lymph nodes. Moreover, she was admitted as a case of pericardial effusion, which was thought to be an osimertinib adverse event. After cardiac condition stabilization, she started on crizotinib with short clinical stability for approximately 6 weeks. Unfortunately, her clinical condition deteriorated and had further progression on imaging. Her performance could not allow for systemic chemotherapy, and she passed away on January 24, 2023.

DISCUSSION

EGFR mutation is a recognized biomarker alteration in advanced NSCLC. It accounts for 15% to 30%. In some areas of the world, the incidence of *EGFR* reaches up to 50%.[7] The incidence of *EGFR* mutation in the Middle East and North Africa is higher than that of the Western population, with reported incidences of 21% to 28%.[8] Clinical evidence revealed that treatment with EGFR-TKIs is associated with better treatment response, progression-free survival, and overall survival compared with chemotherapy for advanced NSCLC in the first-line setting in patients harboring *EGFR* mutation. Furthermore, third-generation EGFR-TKIs are superior to the first- and second-generation EGFR-TKIs in terms of response rate, progression-free survival, overall survival, and intracranial disease control rate.[9] The majority of patients with the *EGFR* mutation have a mutation in exon 19 (deletion) or exon 21 L858R (point mutation). There are many other uncommon *EGFR* mutations, such as G719X in exon 18, L861Q in exon 21, and S768I in exon 20.[10]

ROS-1 rearrangement is a well-known molecular subtype of advanced non-squamous NSCLC, which accounts for around 1% to 2%. They are frequently seen in a younger age woman with adenocarcinoma. *ROS-1* rearrangement generally has no overlap with other oncogenic driver mutations. In both cases, an NGS-based gene panel test was used, which consists of hotspot mutations in 35 genes and gene fusions in 23 genes using formalin-fixed, paraffin-embedded tissue. This method appears superior to other traditional testing methods like immunohistochemistry and fluorescence in situ hybridization in the era of precision medicine.

In the first case, EGFR exon 21 L858R mutation was detected, which is the second most common mutation after exon 19 deletion and results in high sensitivity to EGFR-TKIs.[11] Our second case harbors an uncommon EGFR exon 18 mutation p.G719V, part of point mutations resulting from the substitution of glycine at position 719 with other genes like alanine (*G719A*), cysteine (*G719C*), and serine (*G719S*). Like G719X in exon 18, L861Q in exon 21, and S768I in exon 20, all had modest responses to EGFR-TKI therapy as well.[10]

Currently, there are more than 20 *ROS-1* fusion partners, including CD74, EZR, FIG1, CCD6, KDELR2, LRI3, SDC4, SLC34A2, TPM3 and TPD52L1. The most common rearrangement is CD 74, which accounts for 40% to 45%; however, another common fusion partner is SLC34A2-ROS-1, which accounts for 12%.[12] Treatment options include crizotinib, *ALK*, and MET inhibitors.[13] Lorlatinib, a third-generation *ALK* inhibitor, is also an effective therapy, especially in patients who are progressing on crizotinib.[14] Entrectinib, a *TRK* inhibitor, is an effective treatment option in first-line settings, especially in patients harboring brain metastasis.[15] Our reported two cases harbor SLC34A2-ROS-1 fusion; this fusion is responsive to crizotinib.[16]

Comutations of the *EGFR* and *ROS-1* rearrangement are extremely uncommon. Detection of comutations becomes more evident because of the use of higher-sensitive methods of detecting these mutations, such as NGS. The comutation may consist of a major driver mutation and minor coexisting mutation (subclonal with low variant allele frequency) that coexist with no clear clinical significance. In a retrospective analysis of 421 patients with an *EGFR* mutation, the rate of *ALK* and *ROS-1* fusion genes was 3.1% using reverse transcriptase–polymerase chain reaction; in this retrospective analysis, patients with concomitant *ALK* and *ROS-1* treated with EGFR-TKI had shorter progression-free survival compared with those without concomitant mutations; however, no difference in overall survival. Patients treated with *ROS-1* inhibitors had a median progression-free survival of 6 months only.[5] Wiesweg et al.[6] reported concomitant oncogenic driver mutation in the *EGFR* domain in 6 of 25 ROS-1–positive patients, 5 of whom had responded to anti-EGFR therapy.

Lambros et al.[17] reported 10 patients with *ROS1* rearrangements and concomitant *EGFR* mutations treated with first-line EGFR-TKIs. Their responses include six partial responses (PR), two stable diseases (SDs), and two progressive diseases (PDs). Second-line crizotinib therapy was used in four patients upon disease progression on EGFR-TKI therapy, with two PR, one SD, and one PD observed.[17]

Our two cases of *EGFR* and *ROS-1* rearrangements coexistence have adenocarcinoma histology, both patients were under 65 years old, and both have the common clinical characteristics of *EGFR* and *ROS-1* rearrangements. Nonetheless, no unique clinical features that can clinically help to anticipate this genetic coexistence.

There is no consensus on how to sequence the treatment of such conditions; this is expected due to the rarity of this situation. Few factors can contribute to the decision-making in this regard, like the prevalence of the mutations and the NGS-reported variant allele frequency. Higher variant allele frequency may help in choosing the first-line therapy needs to be offered. Owing to the higher prevalence of the *EGFR* mutation in our population and lack of variant allele frequency data, we treated our two cases with anti–EGFR-TKIs. The first case had one of the commonest *EGFR* mutations and showed excellent progression-free survival with very long overall survival; however, the second case showed only stable disease lasting approximately 6 months only. The explanation of poor treatment response in the second case is possibly related to the presence of an uncommon *EGFR* mutation known to be less responsive to anti-EGFR therapy. The other reason is the coexistence of *BRAF* mutation, which is known to have less systemic treatment response, and finally, the higher *ROS*-1 variant allelic fraction reads. The question that remains is what the subsequent therapy is upon disease progression. Generally, sequencing of second-line targeted therapy can be considered carefully in patients with diffuse and mild progression; however, switching to systemic chemotherapy should be considered in case of rapidly progressive disease. Our second case received crizotinib because she was not fit for systemic chemotherapy. She responded shortly to crizotinib, which is likely in consensus with the general belief and understanding of poor treatment outcomes in patients whose genetic profiling has more than one alteration.[18]

In conclusion, the incidence of concomitant *EGFR* and *ROS-1* alterations in patients with advanced, non-squamous NSCLC may be higher than expected, and this encourages the conduct of NGS in a study with enough patients to reveal a more accurate frequency of this concomitant alteration. The presence of another driver alteration, like *ROS-1* with the *EGFR* mutation, still allows patients to respond well to anti-EGFR therapy. The decision to use a first-line treatment targeting one mutation over another needs more clinical research as well as identification of factors that help in the clinical decisions, like variant allele frequency. The use of anti-EGFR and ROS-1 combination therapy in the first-line setting treatment is still an open area for exploration and cannot be recommended currently due to the lack of supportive evidence. Healthcare professionals should be vigilant about this presentation, and close observation is required.

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