CASE REPORT

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Dual ALK/ROS1 Positivity in Lung Adenocarcinoma: A Case of Complete Response to Lorlatinib

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ABSTRACT

Objective: Anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 (ROS1) rearrangements are unique, mutually exclusive mutations that drive non-small cell lung cancer. Concurrent immunohistochemical positivity for both markers is exceedingly rare and may lead to diagnostic and therapeutic uncertainty, particularly when molecular confirmation is lacking.

Case Presentation: A 54-year-old woman presented with a solitary brain metastasis and underwent surgical resection, followed by whole-brain radiotherapy with a focal boost. Histopathology confirmed metastatic lung adenocarcinoma. Baseline staging with positron emission tomography-computed tomography (PET-CT) demonstrated a 20×19- mm hypermetabolic lingular lung nodule, mediastinal lymphadenopathy, and multiple sclerotic bone lesions. Immunohistochemistry of the tumor showed strong ALK (D5F3) and ROS1 (D4D6) expression, whereas deoxyribonucleic acid-based next-generation sequencing did not detect actionable rearrangements. Based on the immunophenotype, lorlatinib was initiated as first-line therapy. Serial PET-CT and brain magnetic resonance imaging demonstrated complete metabolic and radiologic remission of both intracranial and systemic disease, which has been sustained for nine months.

Conclusion: This case illustrates a rare discordance between immunohistochemical and molecular findings. In this individual patient, treatment with lorlatinib coincided with sustained systemic and intracranial disease control. These observations should be interpreted cautiously, but may provide practical insights for similar complex clinical scenarios.

Keywords: Lung adenocarcinoma; ALK; ROS1; lorlatinib

INTRODUCTION

Ranked as the second most commonly diagnosed cancer globally, lung cancer follows prostate cancer in men and breast cancer in women, and remains the top cause of cancer-related fatalities.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases. The identification of tumor-specific changes in cancer-related oncogenes, along with the introduction of techniques such as genetic sequencing, has enhanced our understanding of the etiopathogenesis of the disease and facilitated the development of targeted treatments.[2]

NSCLC is a prime example of precision oncology. Mutations in anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 (ROS1) rearrangements characterize unique oncogenic pathways that are susceptible to targeting with tyrosine kinase inhibitors (TKIs), such as crizotinib and lorlatinib.[3] Although these alterations are relatively rare, appearing in approximately 4% and 2% of lung adenocarcinomas, respectively, they define clinically significant molecular subgroups with important therapeutic consequences.[4,5]

ALK and ROS1 are often grouped together as key oncogenic drivers in lung cancer because of their similar evolutionary origins, structural likeness, and comparable activation processes through gene rearrangements.[6] The first targeted agent, crizotinib,[7] was initially developed as a MET inhibitor but later demonstrated remarkable clinical efficacy in ALK- and ROS1-positive tumors. Because resistance to crizotinib

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inevitably develops, second-generation inhibitors—ceritinib, alectinib (which lacks anti-ROS1 activity), and brigatinib—have been introduced and have significantly improved patient survival. More recently, lorlatinib has been developed as the most thorough and selective inhibitor in the ALK/ROS1 inhibitor category.[8] Preclinical studies have demonstrated that lorlatinib exhibits highly targeted activity against these two tyrosine kinases and effectively reduces off-target toxicity. At the same time, it maintains a wide range of effectiveness against secondary resistance mutations and achieves remarkable penetration through the blood-brain barrier.[9]

The Ventana immunohistochemistry (IHC) platform has been approved by the United States (US) Food and Drug Administration for the detection of ALK and ROS1 expression. However, the US National Comprehensive Cancer Network guidelines recommend fluorescence *in situ* hybridization (FISH) as the "gold standard" method for NSCLC.[10]

These rearrangements are mutually exclusive and represent distinct molecular events in tumor development.[11] Nonetheless, there have been infrequent accounts of ALK and ROS1 proteins being co-expressed through IHC without the presence of dual fusion events in molecular testing.[4,6] Such discrepancies might result from antibody cross-reactivity, variations within the tumor itself, or fusion partners that remain undetected by current sequencing methods because of their low threshold.[6] In this report, we present a rare case of a patient with metastatic lung adenocarcinoma who exhibited both ALK and ROS1 positivity, yet showed negative results on next-generation sequencing (NGS) and experienced an extended complete response (CR) to lorlatinib.

CASE PRESENTATION

A 54-year-old woman with no history of smoking presented with progressive headaches and visual disturbances. Magnetic resonance imaging (MRI) of the brain revealed multiple contrast-enhancing intracranial lesions, including a dominant left parietal mass that prompted surgical resection at Ordu University Training and Research Hospital. Histopathological analysis revealed an adenocarcinoma, indicating metastatic cancer originating in the lungs (OEAH-B24-13161).

Staging positron emission tomography-computed tomography (PET-CT) demonstrated a 20×19 mm hypermetabolic nodule in the lingular segment of the left upper lobe, which was considered the primary lung lesion. Mildly fluorodeoxyglucose (FDG)-avid subaortic and left hilar lymph nodes were also present, with the largest measuring approximately 2 cm. In addition, several skeletal sites—including the humeral heads, scapula, T11 and L1 vertebrae, and the left femoral head—showed low-grade FDG uptake (standardized uptake value: 3,3) consistent with suspected bone metastases.

Immunohistochemical analysis was performed on formalin-fixed paraffin-embedded tumor tissue using the Ventana platform. The tumor showed diffuse, strong (3+) cytoplasmic staining for TTF-1 and napsin A, supporting a pulmonary origin. Both ALK (clone D5F3) and ROS1 (clone D4D6) demonstrated diffuse, strong cytoplasmic positivity in the majority of tumor cells (>80%), with appropriate internal positive controls.

Molecular profiling was conducted using a deoxyribonucleic acid (DNA)-based targeted NGS panel covering common actionable alterations, including rearrangements of ALK and ROS1, and alterations in *EGFR, KRAS, BRAF, MET, RET*, and *NTRK*. No gene fusions or pathogenic mutations were detected. The estimated tumor cellularity was approximately 40%.

Additional orthogonal confirmation using ribonucleic acid (RNA)-based fusion assays or FISH could not be performed because of limited residual tissue. Although re-biopsy was discussed, the patient preferred to avoid additional invasive procedures. This should be acknowledged as a limitation of this case.

Based on the strong and diffuse ALK and ROS1 immunoreactivity and the overall clinicoradiologic profile, first-line systemic therapy with lorlatinib (100 mg once daily) was initiated, together with denosumab for bone protection.

Prior to systemic therapy, the patient had undergone surgical resection of the brain metastasis, followed by whole-brain radiotherapy (30 Gy in 10 fractions), with a focal boost to metastatic nodules (up to 38 Gy).

Treatment response was prospectively monitored every three months using contrast-enhanced brain MRI and whole-body FDG PET-CT. Baseline target lesions included the pulmonary nodule in the lingular segment of the left upper lobe (20×19 mm), subaortic and left hilar lymph nodes, and multiple metabolically active skeletal lesions (humeral heads, scapula, thoracolumbar vertebrae, and left femoral head).

At the first evaluation (3 months), PET-CT demonstrated complete metabolic resolution of all extracranial lesions, while brain MRI showed no residual or recurrent enhancing intracranial disease. Serial imaging at 6 and 9 months confirmed a sustained complete radiologic and metabolic response without evidence of progression.

The treatment was well tolerated, with only grade 1 hyperlipidemia and no grade ≥3 adverse events. Written informed consent was obtained from the patient for the

publication of this case report and any accompanying clinical information and images.

DISCUSSION

This case describes an uncommon diagnostic and therapeutic scenario: concurrent ALK and ROS1 positivity by IHC in a metastatic lung adenocarcinoma despite negative DNA-based NGS, followed by a sustained clinical response to lorlatinib. Although ALK and ROS1 rearrangements are typically considered mutually exclusive driver events, discordant results between protein expression and molecular testing have occasionally been reported.

IHC remains a practical and widely used screening method for both ALK and ROS1. However, interpretation can be challenging. False-positive staining may occur due to antibody cross-reactivity, background mucin, or non-specific cytoplasmic staining, whereas false negatives may result from low protein expression or technical factors. For this reason, current guidelines recommend confirmatory testing with molecular techniques when results are unexpected or clinically discordant.[12,13]

Discordance between IHC and DNA-based NGS is increasingly recognized. DNA panels may fail to detect complex or rare fusion partners, intronic breakpoints, or low-abundance transcripts. Several studies have shown that RNA-based fusion assays can identify rearrangements missed by DNA sequencing and may provide higher sensitivity for gene fusion detection.[14] A recent study by Ilié et al.[15] found that RNA-based NGS outperformed both IHC and FISH in identifying ALK rearrangements, effectively clarifying numerous cases previously deemed negative by DNA-based methods. In this scenario, our case showing double ALK/ROS1 immunopositivity responding to lorlatinib despite negative NGS findings highlights the potential for biologically significant but latent fusions or protein-level activation that may not be detectable by standard DNA-NGS methods. Therefore, negative DNA-based results do not definitively rule out biologically relevant oncogenic activation.

In routine clinical practice, when strong and diffuse IHC positivity is observed but DNA-based testing is negative, additional steps are often considered. These include reassessment of tumor cellularity, repeat sampling when feasible, FISH, or RNA-based fusion analysis. In the present case, orthogonal testing could not be performed due to limited residual tissue and the patient's preference to avoid further invasive procedures, which represents a limitation of this report.[16]

Despite the absence of molecular confirmation, our patient experienced a durable systemic and intracranial response to lorlatinib. Lorlatinib is known for its potent activity against both ALK and ROS1 alterations, and for its excellent central nervous system (CNS) penetration.[9] While a single case cannot establish predictive value, this observation suggests that strong protein-level expression may, in selected situations, still reflect a therapeutically relevant target.[17]

Lorlatinib is a multitargeted TKI that effectively penetrates the brain and demonstrates strong activity against ALK and ROS1 rearrangements, including those with resistance mutations.[18,19] In this scenario, the effectiveness of the drug, even without detectable fusion, reinforces the idea that activation at the protein level, rather than just gene rearrangement, can initiate oncogenesis.

The sustained response lasting over nine months (CR) aligns with the results of the CROWN and PROFILE 1014 studies, highlighting lorlatinib's effectiveness in managing both CNS-dominant and systemic conditions.[9]

Dual ALK/ROS1 expression remains exceedingly rare, with only a limited number of cases described in the literature. Reported outcomes have been heterogeneous, and standardized management strategies are lacking.[15-17] Our findings should therefore be interpreted cautiously, but they may contribute to the growing recognition that multimodal diagnostic approaches—integrating histology, IHC, molecular testing, and clinical behavior—are essential for individualized treatment decisions.

CONCLUSION

Although dual ALK and ROS1 positivity in lung adenocarcinoma is rare, this case illustrates the potential clinical relevance of discordant immunohistochemical and molecular findings. In this patient, lorlatinib was associated with sustained systemic and intracranial disease control despite the absence of molecularly confirmed gene fusions. These observations should be interpreted cautiously, but may provide practical insights for managing similar complex clinical scenarios.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying clinical information and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., Concept: A.T., Design: A.T., Data Collection or Processing: A.T., Analysis or Interpretation: N.Ö., Literature Search: N.Ö., Writing: N.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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