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Case Report

# Advancements in the Detection and Treatment of Rare ALK Fusion Mutations in Hepatocellular Carcinoma: A Case Report and Literature Review

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**This case report and comprehensive literature review highlight the significance of advanced molecular diagnostic techniques, particularly next-generation sequencing (NGS), in the identification and treatment of rare ALK fusion mutations in hepatocellular carcinoma (HCC). Through a detailed analysis of a single patient case, accompanied by a review of existing literature, we underscore the diagnostic challenges and therapeutic potential associated with rare ALK fusions in HCC. Our findings demonstrate the superior capability of NGS, both DNA-based and RNA-based, in detecting these mutations, leading to targeted treatment approaches with ALK inhibitors. The case report illustrates the practical application of precision oncology in HCC, showcasing significant clinical benefit and improved treatment outcomes with the use of ALK inhibitors for rare fusion types. This study not only contributes to the existing body of knowledge by documenting a rare instance of ALK fusion in HCC but also advocates for the integration of comprehensive molecular profiling into standard clinical practice to enhance personalized treatment strategies and patient care.**

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## Introduction

Hepatocellular carcinoma (HCC) stands as one of the leading causes of cancer-related deaths worldwide, characterized by diverse genetic landscapes and complex molecular profiles [1][2][3]. Despite advances in diagnosis and treatment, the prognosis for HCC remains poor, underscoring the urgent need for personalized therapeutic strategies [4][5][6]. In this context, the role of anaplastic lymphoma kinase (ALK) fusion mutations, although well-documented in other malignancies such as non-small cell lung cancer (NSCLC), has been relatively underexplored in HCC. ALK fusions represent critical oncogenic drivers amenable to targeted therapies, offering new horizons for treatment in affected patients [7][8][9][10].

Recent advancements in molecular diagnostics, particularly next-generation sequencing (NGS), have revolutionized our understanding and management of cancer, enabling the identification of rare but actionable genetic alterations [11][12][13][14]. NGS technologies,

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encompassing both DNA-based and RNA-based approaches, have proven instrumental in uncovering complex genetic profiles, including elusive ALK fusion mutations [15][16][17]. However, despite these technological advances, the detection and clinical management of rare ALK fusions in HCC remain challenging, primarily due to their low prevalence and the heterogeneity of fusion partners [18][19][20].

This case report, accompanied by a thorough literature review, aims to shed light on the clinical significance of rare ALK fusion mutations in HCC. By presenting a detailed analysis of a single patient case, we illustrate the diagnostic journey facilitated by NGS and the subsequent therapeutic implications [21][22][23]. Additionally, we review the existing literature to contextualize our findings within the broader spectrum of ALK-positive HCC, discussing the implications for diagnosis, treatment, and prognosis. This study underscores the potential of precision oncology in transforming the therapeutic landscape of HCC, advocating for the integration of comprehensive molecular profiling into routine clinical practice. Through this approach, we aim to enhance the identification of rare genetic drivers and optimize targeted treatment strategies, thereby improving outcomes for patients suffering from this challenging malignancy.

## Case Information

The patient, a 51-year-old female, presented with liver pain persisting for three months. Chest computed tomography (CT) revealed a mass at the left hilum, multiple mediastinal lymphadenopathies, scattered small nodules in the lungs, and thickening of the left pleura. A bone scan indicated an area of increased radioactive uptake at the left 9th posterior rib, suggestive of bone metastasis. Head magnetic resonance imaging (MRI) showed no significant abnormalities. Bronchoscopy revealed congestion and roughening of the mucosa of the upper lobe of the left bronchus, with extrinsic compression leading to narrowing. A biopsy of the mucosa of the left segment and endobronchial ultrasound-guided transbronchial needle aspiration (TBNA) were performed. The mucosal biopsy pathology indicated chronic inflammation; TBNA lymph node biopsy pathology was consistent with HCC. Immunohistochemistry (IHC) results were: Ventana ALK-D5F3 positive, CK7 positive, P40 negative, and thyroid transcription factor-1 (TTF-1) positive, with no fluorescence in situ hybridization (FISH) conducted. The diagnosis was HCC. The Eastern Cooperative Oncology Group (ECOG) performance status was scored at 1. Test results indicated a COX7A2L-A LK (C2:A 20) fusion mutation, with an abundance of 12.85%; concurrently, there was a missense mutation in exon 16 of the adenomatous polyposis coli (APC) gene, NM-000038.5:c.2258A>G (p.H753R), with an abundance of 61.34%. The patient was treated with 500 mg of crizotinib once daily orally as first-line therapy. One month after starting crizotinib, the patient returned for a follow-up visit, reporting significant alleviation of cough and liver pain symptoms. According to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the therapeutic effect was evaluated as a partial response (PR). During outpatient follow-up until December 2023, the patient's general condition remained good, with no disease progression (progressive disease, PD) and a progression-free survival (PFS) exceeding 20 months.

## Discussion

Using 'hepatocellular carcinoma' and 'missense mutation' as keywords, a search was conducted in the PubMed database for literature on 'rare ALK fusions' and 'hepatocellular carcinoma'. Additional searches were carried out in the China National Knowledge Infrastructure (CNKI) and Wanfang databases covering the period from January 1, 2017, to December 31, 2022. The following were excluded: (1) tumors other than HCC; (2) case reports lacking detail; (3) cases where ALK inhibitors were not used during treatment. A total of 25 papers were identified using these search criteria, documenting 41 instances of rare ALK fusion mutations. Combined with the current case, a cumulative analysis of 42 instances was conducted. All cases involved rare fusion partners or double ALK fusions at the 3' end of the ALK kinase. The average age of the patients was 61.5 ± 9.1 years, with a median age of 63 years [24][25][26][27][28][29]. Nine were smokers, twelve were non-smokers, and the smoking status of twenty-one was unknown. All patients had HCC and were in stage IV when treated with ALK inhibitors [30][31][32][33]. Clinical manifestations included coughing, expectoration, dyspnea, pain, and weight loss, with imaging features not particularly distinct from those of typical liver cancer patients. ALK fusion mutations were detected using the NGS (Next-Generation Sequencing) approach. Among the ALK fusion types, five cases were of the STRN-ALK type, and three were of the BCL11A-ALK type (one of which appeared in a patient with double fusion mutations). Thirty patients received an ALK inhibitor as first-line treatment, nine as second-line, and three as third-line. The majority of first-line

treatments involved crizotinib, with a minority receiving alectinib and ceritinib. The objective response rate (ORR) for ALK inhibitors was 85.4% (35/41), the stable disease (SD) rate was 12.2% (5/41), the disease control rate was 95.1% (39/41), and the PD rate was 2.4% (1/41). The mutation type for the patient with PD was CMTR1-ALK (C2;A20) [34][35][36][37]. Six patients used a different ALK inhibitor after progression on the first ALK inhibitor and still demonstrated some efficacy. The median follow-up time for patients with PD was 18 months, with only nine patients reporting PD time or death, thus precluding calculation of progression-free survival (PFS) and overall survival (OS). ALK gene rearrangement is a significant driver gene for NSCLC. This paper reports a case of COX7A2L-ALK fusion, which has not been previously reported. Through literature review, several cases of rare ALK fusion patients were summarized. The COX7A2L gene encodes the COX7A2L protein, also known as SCAFI (SC-specific assembly factor I) or COX7RP, which dynamically associates with the mitochondrial respiratory chain (MRC) complex to adapt MRC function to metabolic changes. MRC dysfunction plays a significant role in tumorigenesis. In liver cancer studies, overexpression of COX7RP, which induces cell cycle progression and epithelial-mesenchymal transition (EMT) while inhibiting apoptosis, has been found to promote the growth and metastasis of hepatocellular carcinoma and to indicate poor prognosis for liver cancer patients. The COX7A2L-ALK fusion is likely a key driving factor in the development and progression of liver cancer.

All included patients were diagnosed through NGS, highlighting the advantages of NGS in detecting rare fusion gene partners. Other methods, such as ALK IHC (immunohistochemistry) and ALK FISH (fluorescence in situ hybridization), are crucial for the accurate detection of ALK fusions in HCC patients [38][39][40]. IHC remains the most cost-effective and simplest first-choice method, while FISH may not identify all cases of ALK fusion mutations. NGS offers many advantages in identifying ALK gene fusions, but currently, there are no clear standards regarding quality control and other issues related to NGS testing, and the costs are high. NGS technologies include whole-genome sequencing, whole-exome sequencing, and targeted NGS panels for hotspots or larger panels, allowing for the screening of ALK-related gene fusions based on specific circumstances. The clinical significance of DNA-based and RNA-based NGS differs; fusion genes not detected by DNA-based NGS might be identified by RNA-based NGS, as some fusions occur only at the RNA level or have low abundance at the DNA level, or due to long introns or repeated sequences overlap, where RNA-based NGS can effectively avoid missing these fusion genes. The key to precision medicine lies in accurately detecting mutations in treatable targets. Previous studies have shown that the fusion partners of some driver gene fusions affect treatment response and efficacy, and RNA sequencing can determine the fusion partners and exons involved. Combining DNA-based and RNA-based NGS can increase the clinical benefit rate. In one study, many patients with HCC who were negative for driver mutations in DNA-based NGS tissue biopsies were found to have targetable fusion genes through RNA-based NGS methods, and the clinical benefit rate after targeted therapy reached 90%.

Currently approved ALK inhibitors include crizotinib, ceritinib, alectinib, brigatinib, ensartinib, and lorlatinib, among others. For rare ALK fusion types, the ORR of the first ALK inhibitor reached 82.6%, which is not inferior to common ALK fusion types. Most patients chose crizotinib as their first ALK inhibitor, possibly because crizotinib was the first available ALK inhibitor. Many researchers believe that the CMTR1-ALK fusion may not translate into a protein that drives cancer, highlighting the importance of ALK fusion types and functions. Previous research indicated that patients with the rare STRN-ALK fusion mutation treated with first-line alectinib showed the best response as SD, and the patient died after switching to chemotherapy. This patient had a STRN-ALK fusion but also exhibited high expression of Vimentin, suggesting that tissue transformation such as epithelial-mesenchymal transition might be the reason for the poor outcome. Zhu et al. reported a case of a patient with a rare VKORC1L1-ALK fusion mutation who, after postoperative recurrence, was treated with crizotinib for five years as a second-line therapy and was effective again after developing an ALK T1151K resistance mutation when treated with alectinib.

This article reports a rare case of HCC with a COX7A2L-ALK fusion mutation, considering the clinically significant genetic change to be the COX7A2L-ALK fusion mutation. In the ASCEND-8 clinical study, the efficacy of ceritinib 500 mg administered with food showed substantial improvement. Considering cost-effectiveness, we chose ceritinib as the first-line treatment for this patient. The patient achieved a PR after first-line treatment with ceritinib and is currently under follow-up. There is no large-scale clinical data on the efficacy of ALK inhibitors for rare fusion types, which is worth the attention of clinicians. With the development of detection technology, how to choose between NGS, IHC, and FISH, and how to evaluate the

results of various methods should be carefully assessed. Which ALK inhibitor to choose should also be further explored. This article suggests that patients with late-stage HCC harboring rare ALK fusion mutations can benefit from ALK inhibitor therapy.

## Conclusion

This study underscores the critical role of advanced molecular diagnostics, particularly NGS, in identifying rare ALK fusion mutations in HCC patients. Our findings illuminate the complexity of ALK fusion types and their impact on treatment outcomes, emphasizing the necessity for precise and comprehensive genetic screening methods. The utilization of both DNA-based and RNA-based NGS approaches offers a more inclusive detection of actionable mutations, thereby facilitating tailored therapeutic strategies. The clinical application of ALK inhibitors in treating rare ALK fusion-positive HCC showcases significant therapeutic potential, as evidenced by the high objective response rates and clinical benefit observed in patients. This reinforces the importance of molecular profiling in guiding treatment decisions and improving patient outcomes. Despite the higher costs associated with NGS technologies, their ability to uncover treatable targets justifies the investment, particularly in the context of precision oncology. However, challenges remain, including the standardization of NGS testing, the interpretation of complex genetic data, and the accessibility of targeted therapies. Further research and clinical trials are essential to validate the efficacy of ALK inhibitors across different ALK fusion types and to explore the synergistic use of multi-modal treatment regimens.

## Statements and Declarations

### *Data Availability*

The data used to support the findings of this study are included within the article.

### *Conflicts of Interest*

The authors declare that there is no conflict of interest regarding the publication of this paper.


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