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Case Report

First-Line ALK-Directed Therapy in Metastatic Renal Cell Carcinoma

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Abstract

ALK rearrangement in renal cell carcinoma represents a rare molecular subtype in these entities. Only a few cases have been reported to receive ALK-directed therapy in a later-line metastatic setting. We report the case of a 23-year-old male patient with pulmonary metastatic RCC harboring an ALK rearrangement. The initial histological sample obtained from a kidney biopsy revealed a VCL-ALK fusion. Subsequently, the patient received first-line therapy with alectinib, a highly selective ALK inhibitor. Following near-complete remission of multiple pulmonary nodules, as well as a partial response of the retroperitoneal lymph nodes and the primary tumor, a cytoreductive nephrectomy was performed. The patient remains on ALK-directed maintenance therapy and has achieved a complete remission. To the best of our knowledge, this is the first published case worldwide using an ALK inhibitor first-line in metastatic RCC.

Keywords: Renal cell carcinoma; ALK rearrangement; ALK inhibitor

Introduction

Clear cell renal cell carcinoma (ccRCC) accounts for approximately two percent of global cancer-related deaths. [1] Since the introduction of novel therapies in the metastatic setting, such as multi-tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (CPIs), mortality rates have significantly decreased. Nevertheless, certain rare molecular subtypes may benefit from alternative treatment approaches.

Renal cell carcinomas associated with anaplastic lymphoma kinase (ALK) gene rearrangements (ALK-RCC) are rare, with an incidence of less than 1% among all RCCs. [2] On a molecular level, ALK rearrangements display broad genomic heterogeneity. One such variant involves a fusion with the vinculin (VCL) gene. To our knowledge, this specific rearrangement has been described in only five patients with RCC to date. [3-6] Four of these patients were children with hereditary sickle cell disease, and one was a middle-aged woman without sickle cell disease [3-6].

ALK-rearranged tumors are well known in non-small cell lung cancer (NSCLC), for which highly effective ALK-directed targeted therapies are established. In contrast, only five published cases have reported the use of ALK-directed therapy in patients with ALK-RCC following prior systemic treatment. [7-9] All of these patients demonstrated significant clinical benefit from ALK inhibition, with 80% achieving a partial response [7].

In this case report, we present a patient with metastatic VCL–ALK rearranged RCC who received alectinib as first-line systemic therapy.

Case Report

The 23-year old male patient suffered from respiratory symptoms and weight loss of 4 kilograms in 6 months. He had undergone an external computed tomography (CT) of the thoracic-abdominal region. The findings showed an 8x6 cm lesion on the right kidney with thrombosis of the right renal vein, a retroperitoneal lymphadenopathy and disseminated pulmonary lesions in both lungs (Figure 1). A cranial CT showed no signs of cerebral lesions. Subsequently, the patient was administered to the urological department.

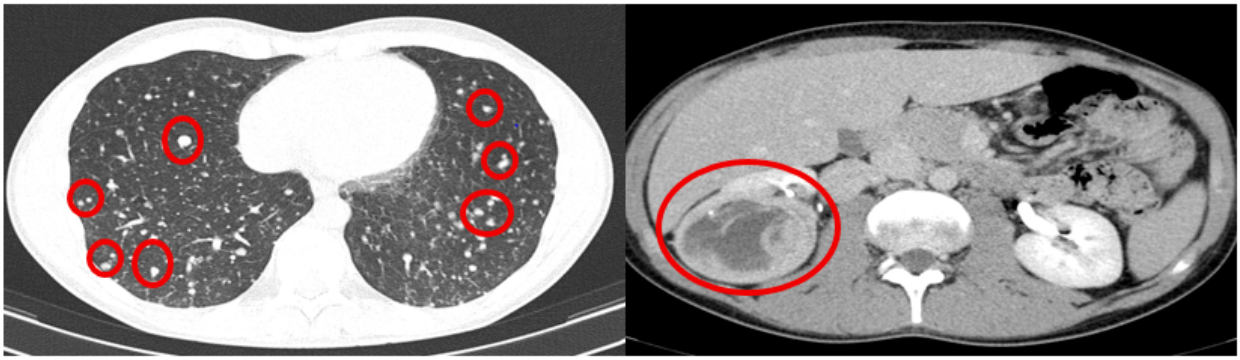

Figure 1: Initial CT scan in December 2023.

Note: Showing the primary tumor and disseminated pulmonary metastases.

A biopsy of the kidney lesion was performed. The histological staining showed invasive pseudo-solid cellblocks with an eosinophilic cytoplasm and 1-2 multiple-row cores (Figure 2).

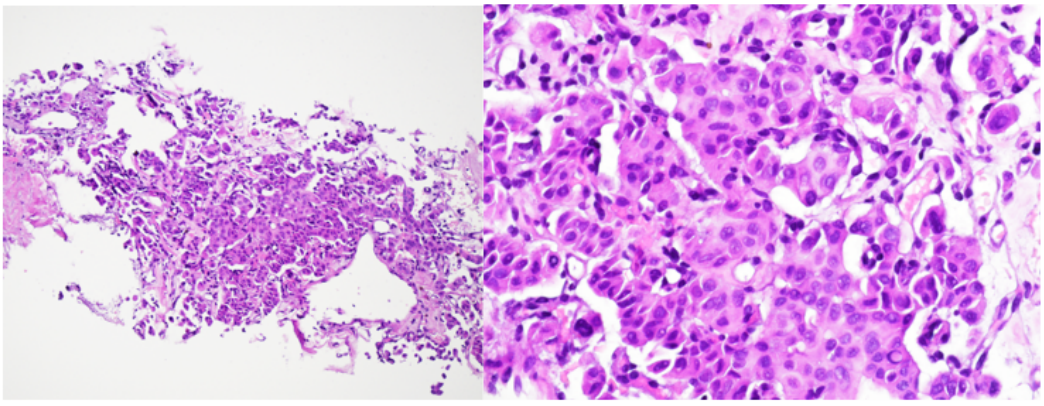

Figure 2: Haemoxylin and eosin staining.

The immunohistological stains showed the following profile: AE1/AE3+, PAX8+, CA IX-, CK7+, GATA3+, OCT2/3+, 34ßE12-, racemase-, TTF-1- (Figure 3).

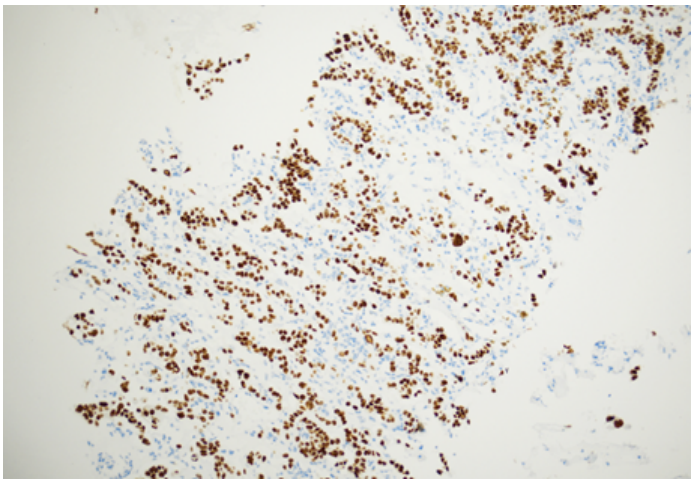

Figure 3: PAX 8 staining.

With a VENTANA PD-L1 (SP263) Assay, a combined-positive-score (CPS) of over 50 was detected. Due to the inconclusive immunohistological pattern a next-generation-sequencing (NGS) panel was performed, in which a VCL-ALK fusion was detected. In addition, a fluorescence in situ hybridization (FISH) was conducted, which confirmed the suspected VCL-ALK fusion (Figure 4).

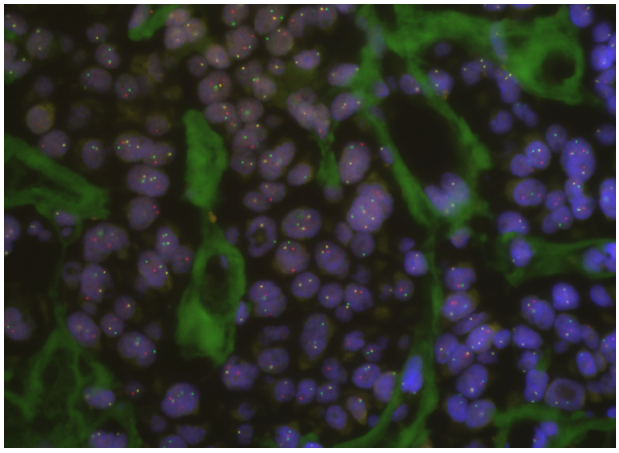

Figure 4: FISH probe.

Note: Positive for VCL-ALK fusion.

Subsequently, the patient was transferred to the oncological department for systemic therapy. In the multidisciplinary tumor conference an off-label 1st line therapy with alectinib, a highly selective ALK inhibitor, was decided. Therapy started in February 2024 with 600mg twice daily orally.

Follow-up CT scans every three months between April and September showed an impressive response with a significant reduction of the primary tumor, the retroperitoneal lymph nodes and the pulmonary metastases (Figure 5).

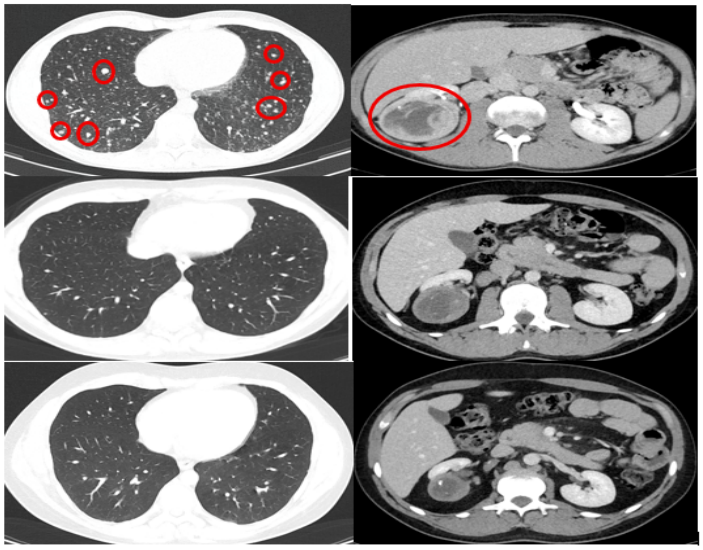

Figure 5: Initial CT scan in December 2023 and following CT's in April and September 2024.

In previous reports an association between VCL-ALK rearranged RCC's and sickle cell anaemia was described. Therefore, a haemoglobin electrophoresis was performed. [4] This showed regular haemoglobin fractions.

Due to near complete remission of the pulmonary nodules as well as regression of the primary tumor and of the retroperitoneal lymph nodes, a cytoreductive nephrectomy was performed 11 months after the start of alectinib. Histologically a massive regression with a broad fibrotic zone was observed, resulting in a TNM-classification of ypT3a, V0, L0, Nx.

Although no data on RCC and adjuvant ALK inhibition exist, given the clinical experience with ALK mutated NSCLC's, the patient was put on alectinib maintenance therapy.

Throughout the therapy, the patient presented himself in a good condition with no relevant side effects except slightly elevated transaminases, equivalent to a Common Terminology Criteria for Adverse Events (CTCAE) of 1. The last follow-up CT scan was performed in March 2026, in which an ongoing complete remission is noted.

Discussion

ALK rearrangements have been identified across several oncological entities, most notably in lymphomas and non–small cell lung cancer (NSCLC). Approximately 5% of NSCLCs harbor ALK rearrangements, with EML4-ALK fusions accounting for around 90% of these cases. [10] Targeting the ALK fusion protein has demonstrated significant anti-tumor efficacy, with objective response rates of 74% versus 45% when comparing crizotinib to standard-of-care chemotherapy in first-line NSCLC treatment. [11] After a median follow-up of 46 months, the median overall survival (OS) had not yet been reached. [11] Since then, several next-generation ALK inhibitors have been developed, including alectinib, which has shown superior efficacy over crizotinib in terms of progression-free survival (PFS) [12,13].

The VCL-ALK fusion is an even rarer event compared with the EML4-ALK fusion observed in NSCLC. It has been reported in only a few cases of renal cell carcinoma, high-grade glioma, epithelioid fibrous histiocytoma, and myofibroblastic tumors. [12] Since its first identification in RCC in 2010, ALK-VCL rearrangement has been described in only four patients with RCC. [3-6] Nonetheless, ALK–VCL RCCs have been included in the updated 2024 WHO classification of renal neoplasms [14].

For this rare RCC subtype, no specific treatment recommendations are currently available in the ESMO guidelines. [15] Previously published case reports have predominantly described pediatric patients with sickle cell disease. In contrast, our patient was an adult male without any evidence of hereditary comorbidities.

To the best of our knowledge, only five patients with ALK-rearranged RCC have received ALK-directed therapy to date. [7-9] All were treated with either alectinib or crizotinib in later treatment lines. Therefore, initiating ALK-directed therapy as first-line systemic treatment represents a novel approach with promising results. In our case, a complete remission of pulmonary metastases was achieved after 11 months of therapy, followed by cytoreductive nephrectomy, without relevant adverse events.

Author contributions

TR is the main author of this case report. NBD is the main case manager and is a main contributer to this case report. LK and HW are contributers to this case report. MM, CE and ML performed the histological and molecular-pathological examamination. MoL and KCDM performed the kidney biopsy. PR and HM were advisors for the medical treatment.

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Data availability

All data generated or analysed during this study are included in this published article.

Competing Interests

Tädcke R:

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