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Anaplastic lymphoma kinase rearrangement-associated renal cell carcinoma: Rare subset case report

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A B S T R A C T

Anaplastic lymphoma kinase rearrangement-associated renal cell carcinoma (ALK-RCC) is a rare subtype of renal cell carcinoma characterized by genetic rearrangements involving the ALK gene. Managing ALK-RCC is challenging due to its rarity and limited treatment options. Targeted therapies directed at the ALK gene have shown promise.

ALK-RCC is a rare subtype of renal cell carcinoma with unique clinical and pathological features. ALK inhibitors may hold promise as a targeted therapy for ALK-RCC. Further research is needed to understand the behavior of ALK-RCC and develop effective treatment strategies.

1. Introduction

Anaplastic lymphoma kinase rearrangement-associated renal cell carcinoma (ALK-RCC) is a rare and distinct subtype of renal cell carcinoma characterized by genetic rearrangements involving the anaplastic lymphoma kinase (ALK) gene. Moreover, ALK-RCC represents a unique molecular entity within the spectrum of renal malignancies in relation to its clinical and pathological features.[1]

Due to the rarity of ALK-RCC, its management creates significant challenges such as lack of treatment options and established guidelines. However, targeted therapies directed against ALK gene have shown potential in ALK-positive malignancies. Further research in development of specialized approaches for ALK-RCC management is needed to explore the efficacy of these treatments.[2]

We present a case report of ALK-RCC in a 61-year-old male patient presenting with progressive weight loss over five months. A computed tomography (CT) scan without contrast which revealed a left exophytic lower pole renal mass measuring 2 cm. Furthermore, the patient underwent laparoscopic partial nephrectomy. The histopathology diagnosis was consistent with and showed ALK-rearranged renal cell carcinoma.

2. Case presentation

A 61-year-old Saudi male with a history of diabetes and hypertension presented with a sole complaint of progressive weight loss for 5 months. Physical examination was unremarkable. A computed tomography (CT) scan with contrast of the urinary system was performed. It revealed a left exophytic lower pole solid and enhancing renal mass with central necrosis measuring 2*1.6 cm with no extensions to the left renal vein or surrounding lymph nodes. A CT chest was performed and showed no signs of lung metastasis. Laboratory findings indicated a Creatinine level of 68. Subsequently, the patient underwent a laparoscopic partial nephrectomy. The postoperative course was uneventful, and the patient was discharged from the hospital on the third postoperative day.

The histopathological findings revealed findings consistent with ALK-rearranged renal cell carcinoma exhibiting unifocal tumor focality. The tumor size was 1.5 cm encapsulated by fibrofatty tissue and entailed calcified cut surfaces. It was abutting the surgical margin but grossly away from the fibrofatty tissue by 1.0 cm. It extended into the perinephric fat but did not have sarcomatoid or rhabdoid features. There was no tumor necrosis, lymphovascular invasion, or lymph nodes submitted. It corresponded to histologic grade 3 (WHO/ISUP). In accordance with the American Joint Committee on Cancer (AJCC, 8th edition, 2017) pathologic staging, the tumor was categorized as pT3aN0Mx

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stage.

Microscopic examination revealed findings of solid sheets of eosinophilic polygonal cells with abundant eosinophilic cytoplasm, intracytoplasmic vacuolization, and prominent nucleoli. The tumor was encompassed by a dense lymphoplasmacytic infiltrate and included extensive fibrosis with calcification.

Immunohistochemical analysis showed tumor cells were positive for TFE3 (Fig. 1), ALK (Fig. 2), and SMA. They were negative for all other stains, including PAX8 (Fig. 3), CKAE1/AE3, EMA (Fig. 4), CK7, CK20, CK8/18 CAM5.2, RCC, CD10 (Fig. 5), HMB45, MelanA, synaptophysin, chromogranin, S100, CD34, CD31, FLI-1, desmin, CD117, CD68, CD45, Inhibin, AMAOR, and N-1.

The tumor cells confirmed the presence of ALK gene rearrangement or fusion partner gene

through molecular analysis by FISH, indicating ALK activation.

Post-surgery, the patient showed recovery without requiring adjuvant therapy. The patient was followed up every 3 months and regularly went through serial thoracic and abdominal CT scans that did not reveal any evidence of tumor progression after 3 and 6 months of surgery.

3. Discussion

Anaplastic lymphoma kinase rearrangement-associated renal cell carcinoma (ALK-RCC) is an extremely rare tumor representing less than 1 % of all kidney neoplasms.[3] Debelenko et al. first described ALK-RCC in 2011.[1] Although ALK-RCC is currently considered an "emerging/-provisional" type of renal cell carcinoma, in the 2016 World Health Organization classification,[4] the Genitourinary Pathology Society proposed categorizing ALK-RCC as a "novel entity" based on a substantial amount of growing research.[5]

ALK is a receptor protein kinase that serves an important role in the nervous system's development. It is encoded by the ALK gene located on the 2p23 chromosome.[6] ALK rearrangements with other fusion partners have been described in various malignancies, such as anaplastic large-cell lymphoma (ALCL), non-small cell lung cancer (NSCLC), anaplastic thyroid carcinoma, and others.[7] The spectrum of differential diagnosis of ALK rearrangement-associated RCC is broad, and includes papillary RCC, RMC, collecting duct carcinoma, MiTF family translocation RCC (specifically, Xp11.2 translocation RCC and TFEB translocation RCC), mucinous tubular and spindle cell carcinoma (MTSC), and thyroid-like follicular carcinoma of the kidney.[8]

ALK rearrangement-associated RCCs include a number of morphological characteristics and gene fusion types. Two primary histological types are known. The first type, which is more common in children with sickle-cell trait, presents with giant polygonal tumor cells, eosinophilic vacuolated cytoplasm, and prominent nuclei in solid sheets and nest structures. Lymphocytes may be present in varying proportions. Immunohistochemically, no specific immunophenotype is noted. Additionally, the first type may involve vinculin-ALK fusion. The second type, lacking VCL-ALK fusion, is clinically and morphologically variable, often occurring in adults with architectural features similar to Papillary RCC, characterized by cells with clear to eosinophilic cytoplasm.[9,10]

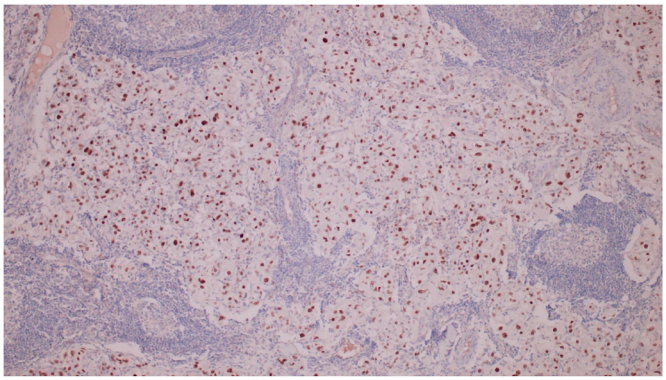

Fig. 1. TFE3

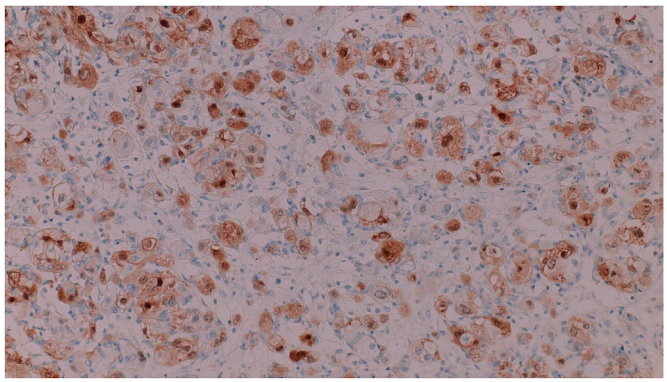

Fig. 2. ALK

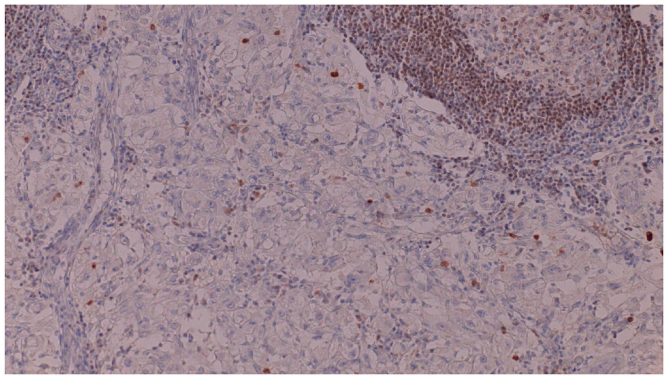

Fig. 3. PAX8

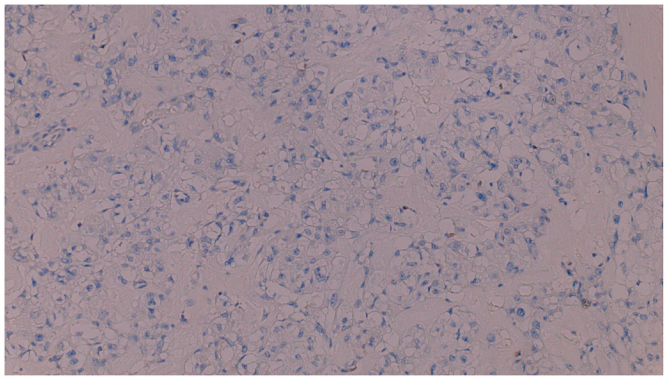

Fig. 4. EMA

Patients with VCL-ALK fusion are of African-American race and characterized by having sickle cell trait.[1] Conversely, patients with non-VCL-ALK fusion lack sickle cell trait and are predominantly observed among patients from East Asia.[11]

Patients with ALK-RCC had a median age of 44 years (range: 30–85 years). The most commonly experienced initial symptoms in these patients were a palpable mass (40 %), respiratory symptoms (40 %), back pain (20 %), hematuria (20 %), and weight loss (20 %). It was noted that only one patient (20 %) was exhibiting no symptoms at the time of diagnosis. All patients were affected by advanced RCC. Sites that were frequently metastasized to were lungs (80 %), lymph nodes (60 %), bones (20 %), brain (20 %), and thyroid (20 %).[2]

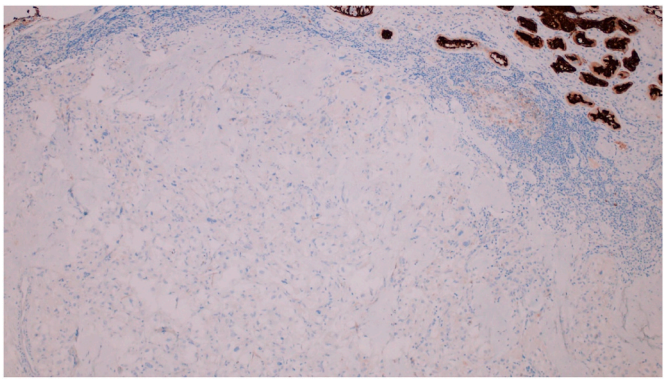

Fig. 5. CD10

Ultrasound sonography demonstrates a hypoechoic mass generally located in the renal medulla. A routine computed tomography scan reveals the presence of an isodense mass. A contrast computed tomography scan shows a slightly enhancing or heterogeneous enhancing mass.[12] Radical nephrectomy should be performed in patients with early stage cancer or without distant metastasis. Lymph node resection is selected for patients with metastasis to regional or distant lymph nodes.[1] No patient who underwent partial nephrectomy as management was found in the literature.

The identification of ALK gene translocation in RCC promises a beneficial molecular targeted therapy of ALK inhibitor, crizotinib, for patients with advanced stage.[13] Crizotinib was the initial ALK inhibitor drug to receive approval for the treatment of metastatic Non-small cell lung cancer.[14] Subsequently, second-generation ALK-I; alectinib, brigatinib, and ceritinib, and, recently, a third-generation ALK-i (lorlatinib) have been introduced in the same clinical setting. The effectiveness of all these drugs has demonstrated significant efficacy in patients affected by ALK-positive advanced NSCLC, thereby revolutionizing the treatment options available for this specific subgroup of patients.[14]

In recent years, the potential of Crizotinib in the field of renal cell carcinoma (RCC) treatment has also been investigated, primarily due to its ability to inhibit the mitogen-activated protein kinase (MET).[15]

Lannantuono et al. performed a systematic review on adult metastatic ALK-RCC patients treated with ALK-i. In this study, it was observed that alectinib was administered to 80 % of patients, while crizotinib was given to 20 % of patients as ALK inhibitors. Regarding the assessment of ALK inhibitor activity, 80 % of patients achieved a radiological “partial response”, indicating a reduction in tumor size, while 20 % of patients had a “stable disease”, meaning no significant change in tumor size. None of the patients experienced disease progression during ALK-i treatment. The average progression-free survival (PFS) for patients receiving ALK-i was 4.8 months, with a range of 3–9 months.

The study concluded a favorable activity of first and second generation ALK-i in pretreated ALK-RCC patients in terms of either radiological response or performance status improvement.[2] The management of ALK-RCC poses significant challenges due to limited treatment options and the lack of established guidelines. However, targeted therapies directed against ALK, such as ALK inhibitors, have shown promising results in other ALK-positive malignancies, raising the possibility of novel treatment strategies for ALK-RCC in the near future.[16]

4. Conclusion

This case report highlights the clinical and pathological features of ALK-RCC, an extremely rare subtype of renal cell carcinoma. The diagnosis of ALK-RCC was confirmed through histopathological examination, immunohistochemistry, and molecular analysis. The rarity of ALK-RCC presents challenges in understanding its clinical behavior and optimal management.

ALK inhibitor therapy might be of great benifit in managing patients with advanced stage of ALK-RCC in the near future. Further research and case reports are needed to improve our knowledge and guide therapeutic interventions for this unique renal malignancy.

Ethical approval (IRB approval)

Approved by the Institution Review Board of Scientific Research Center, Prince Sultan Military Medical City (E−2339).

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CRediT authorship contribution statement

Hamad S. AlAkrash: Investigation, Supervision, Visualization. **Hisham M. Ghabbani:** Writing – original draft, Writing – review & editing. **Faisal A. AlSaleh:** Writing – original draft, Writing – review & editing. **Rashad M. Nassar:** Writing – original draft, Writing – review & editing. **Almaha A. AlHumaidan:** Writing – review & editing. **Abdullateef M. AlHasan:** Validation, Visualization. **Abdullah M. AlMosa:** Validation, Visualization. **Abdulaziz A. AlBluwi:** Supervision. **Hossam S. Eltholoth:** Supervision, Validation. **Nagoud M. Ali:** Investigation. **Ahmed Y. AlZahrani:** Supervision.

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