Case Report
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Characteristics of Renal Cell Carcinoma Harboring *TPM3-ALK* Fusion

Chang Gok Woo[1,2], Seok Jung Yun[3,4], Seung-Myoung Son[1,2], Young Hyun Lim[2], and Ok-Jun Lee[1,2]

Departments of [1]Pathology and [3]Urology, Chungbuk National University Hospital, Cheongju;
Departments of [2]Pathology and [4]Urology, Chungbuk National University College of Medicine, Cheongju, Korea.

The World Health Organization 2016 edition assigned anaplastic lymphoma kinase (*ALK*) rearrangement-associated renal cell carcinoma (ALK-RCC) as an emerging renal tumor entity. Identifying ALK-RCC is important because ALK inhibitors have been shown to be effective in treatment. Here, we report the case of a 14-year-old young man with ALK-RCC. Computed tomography revealed a well-demarcated 5.3-cm enhancing mass at the upper pole of the left kidney. There was no further history or symptoms of the sickle-cell trait. The patient underwent left radical nephrectomy. Pathologically, the mass was diagnosed as an unclassified RCC. Targeted next-generation sequencing identified a *TPM3-ALK* fusion gene. The present report and literature review demonstrate that TPM3-ALK RCC may be associated with distinct clinicopathological features. Microscopically, the tumors showed diffuse growth and tubulocystic changes with inflammatory cell infiltration. Tumor cells were dis-cohesive and epithelioid with abundant eosinophilic cytoplasm and cytoplasmic vacuoles. If morphological features and TFE3 expression are present in adolescent and young patients, molecular tests for *ALK* translocation should be performed. This awareness is critically important, because *ALK* rearrangement confers sensitivity to ALK inhibitors.

Key Words: Anaplastic lymphoma kinase, TPM3 protein, gene rearrangement, renal cell carcinoma, ALK inhibitors

INTRODUCTION

Anaplastic lymphoma kinase (ALK) is a membrane-associated receptor tyrosine kinase that belongs to insulin receptor superfamily.[1] *ALK* rearrangement is oncogenic, activating cellular signaling pathways by dimerization via the specific structures of fusion partners.[2] Genetic alteration in *ALK* has been identified in various tumors. Recently, the World Health Organization designated *ALK* rearrangement-associated renal cell carcinoma (ALK-RCC) as a new/emerging renal tumor entity.[3] Identifying ALK-RCC is important because ALK inhibitors have been shown to be effective in treating this tumor. Notwithstanding, ALK-RCC is rare, and few studies have described its clinicopathological features.[4-7] To date, 28 cases of ALK-RCC have been reported, and six partner genes have been confirmed.[3,8-11] Here, we present a case of RCC with *TPM3-ALK* fusion and review its clinicopathological characteristics.

CASE REPORT

A 14-year-old male individual presented with gross hematuria. Abdominal computed tomography revealed a 5.3×4.5-cm, well-demarcated, solid cystic mass at the upper pole of the left kidney (Fig. 1A). There was no further history, and laboratory tests were unremarkable. Hemoglobin electrophoresis showed normal RBCs. The patient underwent left radical nephrectomy, revealing stage III (pT1bN1) disease. The postoperative course was uneventful, and he was discharged without any complications. There was no further treatment after the operation, and no recurrence was observed during the 4-month follow-up period.

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Corresponding author: Ok-Jun Lee, MD, PhD, Department of Pathology, Chungbuk National University College of Medicine, Chungdae-ro 1, Seowon-gu, Cheongju 28644, Korea.
Tel: 82-43-269-6276, Fax: 82-43-269-6276, E-mail: md5218@naver.com

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Pathological and molecular findings

Grossly, the mass involved the renal medulla and cortex (Fig. 1B). Microscopically, the tumor showed diffuse growth, focal tubulocystic changes, and multifocal inflammatory cell infiltration, similar to renal medullary carcinoma (RMC) (Fig. 2A and B). The infiltrated inflammatory cells were mainly lymphocytes. The tumor cells were dis-cohesive and epithelioid with abundant eosinophilic cytoplasm and cytoplasmic vacuoles. Although most nuclei were round-to-oval, some nuclei were multinucleated and pleomorphic (ISUP grade 4). Mitosis was observed in two to three cells per 10 high-powered fields (Ki-67 index, 10%). Abundant background mucin and intracytoplasmic mucin were frequently seen. Coagulative necrosis was also found. The tumor cells showed diffuse positivity for pan-cytokeratin in immunohistochemistry, and INI1 expression was preserved. In addition, the tumor was positive for PAX8, CD10, and vimentin. Immunoreactivity for TFE3, but without genuine *TFE3* rearrangement, was observed. We performed targeted next-generation sequencing. Library preparation was performed using the Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific, Waltham, MA, USA), and the products were sequenced on the Ion S5 System (Thermo Fisher Scientific). Sequencing data analysis was performed using Ion Reporter 5.4. Next-generation sequencing identified a *TPM3-ALK* fusion gene between exon 7 of *TPM3* and exon 20 of *ALK*. The tumor showed membranous and cytoplasmic ALK expression (anti-ALK antibody, D5F3, Ventana, Tucson, AZ, USA) in tumor cells (Fig. 2C).

This study adhered to the guidelines established by the Declaration of Helsinki and was approved by the Institutional Review Board of Chungbuk National University Hospital (Cheongju, Korea, IRB No: 2019-09-018). Informed consent was obtained from the patient's parents.

DISCUSSION

The recognition of *ALK* alterations in neoplasms is important, because of the potential benefit of ALK inhibitors. However, screening for *ALK* rearrangement in RCC is not routinely performed in view of cost-effectiveness.[12] Previous studies have reported that this tumor is found in <1% of RCCs and in 3.8% of pediatric and young adults with RCC.[5,13] Attempts have been

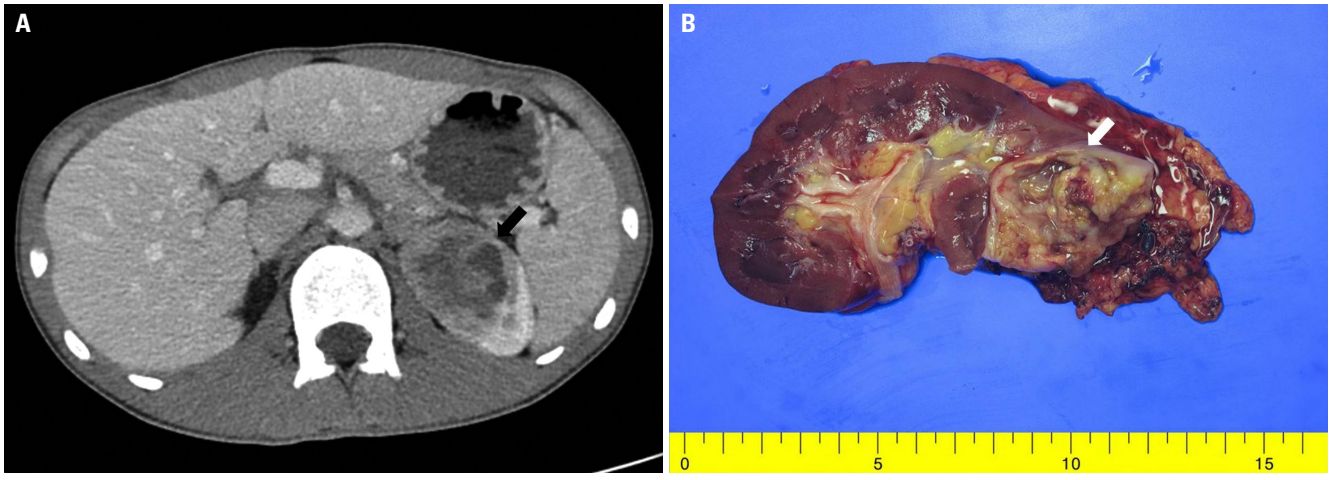

Fig. 1. Gross findings of *ALK* rearrangement-associated renal cell carcinoma. (A) A well-demarcated, solid cystic mass (arrow) at the upper pole of the left kidney is observed on abdominal computed tomography. (B) The mass (arrow) is yellow-to-grey, involving the renal medulla and cortex.

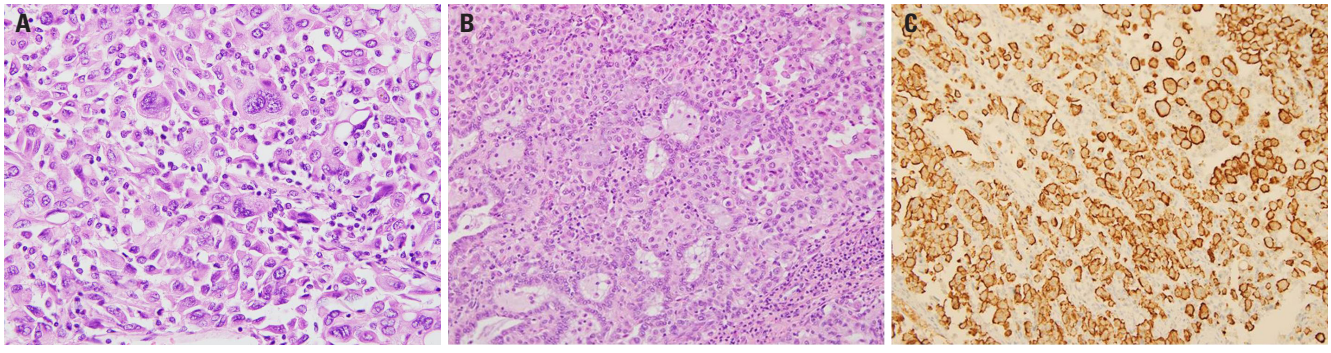

Fig. 2. Microscopic findings of *ALK* rearrangement-associated renal cell carcinoma. (A) The tumor cells are dis-cohesive and epithelioid with abundant eosinophilic cytoplasm, cytoplasmic vacuoles, and intracytoplasmic mucin. Some tumor cells have extreme nuclear pleomorphism and multinucleated giant cells (H&E, ×400). (B) The tumor shows diffuse growth and focal tubulocystic changes (H&E, ×200). (C) Membranous and cytoplasmic ALK expression was confirmed by immunohistochemistry (×200).

Table 1. Clinicopathological Characteristics of Patients in the Literature with *TPM3-ALK* Renal Cell Carcinoma

Case	Study	Age (yr)	Sex	Symptoms	Sickle cell trait	Size (cm)	Borders	Growth pattern	Tumor cells	Inflammatory infiltrate
1	Tao, et al.[9]	16	M	NA	No	4.5	Well-circumscribed, pseudocapsular	Solid and focal tubular	Polygonal-to-spindle shapes with abundant eosinophilic cytoplasm and intracytoplasmic lumina	Lymphoplasmacytic inflammatory infiltrate
2	Tao, et al.[9]	16	F	NA	No	7.0	Well-circumscribed, pseudocapsular	Solid and focal tubular	Polygonal-to-spindle shapes with abundant eosinophilic cytoplasm and intracytoplasmic lumina	Lymphoplasmacytic inflammatory infiltrate
3	Tao, et al.[9]	14	M	NA	No	3.7	Well-circumscribed, pseudocapsular	Solid and focal tubular	Polygonal-to-spindle shapes with abundant eosinophilic cytoplasm and intracytoplasmic lumina	Lymphoplasmacytic inflammatory infiltrate
4	Bodokh, et al.[10]	36	F	Pyelonephritis	No	4.0	Expansive borders	Solid, papillary, tubular, and cribriform	Cuboidal cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, and mucin	Infiltration of numerous foamy macrophages
5	Shin, et al.[15]	12	F	Fatigue, pallor, and abdominal pain	No	6.0	Well-circumscribed	Solid and nests	Large and anaplastic cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, and mucin	Prominent lymphocytic infiltrate
6	Thorner, et al.[11]	49	M	No	No	6.4	Well-circumscribed	Solid, acinar, and cord-like	Giant, spindle, and polygonal cells with eosinophilic cytoplasm and intracytoplasmic mucin	Many lymphocytes in the stroma
7	Armstrong, et al.[14]	55	F	No	No	3.1	Well-circumscribed	Solid and cystic changes	Irregular cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, and mucins	Lymphocytes and eosinophils
8	This case	14	M	Gross hematuria	No	5.3	Well-circumscribed	Solid, nest, tubular, and cystic changes	Giant, irregular, and polygonal cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, and mucins	Lymphoplasmacytic inflammatory infiltrate

Case	Necrosis	Mitosis (Ki-67)	ISUP grade	Diagnosis	Fusion	ALK	TFE3	Stage	Follow up
1	NA	NA	4	NA	Exon 8 of TPM3 Exon 20 of ALK	No*	Diffuse	pT3aNxM0	NA
2	NA	NA	4	NA	Exon 8 of TPM3 Exon 20 of ALK	Yes	Diffuse	pT3aN1M0	NA
3	NA	NA	3	NA	Exon 8 of TPM3 Exon 20 of ALK	Yes	Diffuse	pT1aN1M0	NA
4	Present	Scant (<1%)	-	Unclassified	Exon 8 of TPM3 Exon 20 of ALK	Yes	NA	pT1aN0M0	Alive (2 years) No progression
5	Present	Present	-	NA	NA	Yes	Diffuse	NA	Regional recurrence after a year
6	NA	Many	4	Unclassified	NA	Yes	Diffuse	pT1bN1M0	Alive (2 years) No progression
7	Present	NA	4	NA	NA	Yes	Positive	T1aNxM0	Alive (8 months) No progression
8	Present	2–3/10 HPF (10%)	4	Unclassified	Exon 7 of TPM3 Exon 20 of ALK	Yes	Focal	pT1bN1M0	Alive (4 months) No progression

NA, not available; ALK, anaplastic lymphoma kinase; HPF, high-power fields.
*Poor antigen retrieval; false negativity.

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made to establish the characteristics of this tumor; however, its rarity and the variety of histologic features depending on fusion partners make it difficult. Various partner genes (*VCL*, *TPM3*, *EML4*, *HOOK1*, *STRN*, and *RAD51AP2*) have been reported, along with various clinicopathological findings. Of these genes, *VCL-ALK* RCC was described in children with the sickle-cell trait. *TPM3* has been primarily reported as a partner in ALK-RCC. The coiled-coil structure of TMP3 induces dimerization of the fusion protein and promotes ALK activation. Including the present case, eight cases of *TPM3-ALK* RCC have been reported. We investigated the clinicopathological characteristics of this subtype (Table 1). *TPM3-ALK* RCCs have been detected in five teenagers and three young-to-middle aged adults. Men and women have been affected equally, although the number of patients is too small to seek any meaning. Symptoms of the disease resulted from mass effects and hemorrhage in two patients. No patients had the sickle-cell trait. All tumors were well-circumscribed and measured 3.1 cm to 7.0 cm (mean, 5.0 cm). Histologically, all cases demonstrated solid growth patterns, and the majority of cases (75%, 6/8) had tubular architectures. The tumor cells had polygonal and pleomorphic cells with abundant eosinophilic cytoplasm and cytoplasmic vacuoles. Some cases (62.5%, 5/8) showed intracytoplasmic mucin, reminiscent of ALK-positive lung cancer. The nuclei presented with high ISUP grade (3 or 4). Intratumoral inflammatory infiltrates, coagulative necrosis, and high proliferative activity were also noticed in most cases. These pathological features were similar to RMC; however, all cases expressed INI-1 and had no clinical findings of RMC. The pathological diagnosis was made in three cases as unclassified RCC. All *TPM3-ALK* RCCs had exons 20 through 29 of *ALK*, in which the entire tyrosine kinase domain was included. Two fusion points within the *TPM3* gene have been identified (exon 7 and exon 8), and all had a coiled-coil structure for dimerization of the fusion protein. This tumor showed typical ALK expression and TFE3 immuno-positivity in all cases, not related to *TFE3* rearrangement. The expression of TFE3 in *TPM3-ALK* RCC remains unknown. The majority of patients were stage pT1, and half had lymph node metastasis (pN1) at diagnosis. An in vitro study showed that *TPM3-ALK* fusion conferred higher metastatic capacity than other fusion proteins.[14] Although the majority of patients lived uneventfully, a young woman experienced relapse at 1 year after surgery. She was treated with an ALK inhibitor, showing good outcomes.[11] Considering lymph node metastasis at diagnosis in half of the cases, increased metastatic potential in in vitro study, and the aggressive clinical behavior in other tumors with *TPM3-ALK* fusion, *TPM3-ALK* RCC may be aggressive.[15] However, clinical data are insufficient to predict a prognosis.

The present case and literature review suggest that *TPM3-ALK* RCC may be associated with distinct clinicopathological features. Tests for the detection of *ALK* translocation are far from routinely performed in all cases. If the morphological features mentioned above are present and TFE3 expression is found in adolescent and young patients, molecular tests for *ALK* translocation should be performed. This awareness is crucially important, because *ALK* rearrangement confers sensitivity to ALK inhibitors.

AUTHOR CONTRIBUTIONS

Conceptualization: Chang Gok Woo and Ok-Jun Lee. Data curation: Seok Jung Yun. Formal analysis: Chang Gok Woo, Seung-Myoung Son, and Young Hyun Lim. Investigation: Chang Gok Woo, Seung-Myoung Son, and Young Hyun Lim. Methodology: Chang Gok Woo, Seung-Myoung Son, and Young Hyun Lim. Project administration: Seung-Myoung Son and Young Hyun Lim. Resources: Seok Jung Yun. Software: Chang Gok Woo. Supervision: Chang Gok Woo and Ok-Jun Lee. Validation: Chang Gok Woo and Ok-Jun Lee. Visualization: Chang Gok Woo and Ok-Jun Lee. Writing—original draft: Chang Gok Woo and Ok-Jun Lee. Writing—review & editing: Chang Gok Woo and Ok-Jun Lee. Approval of final manuscript: all authors.

ORCID iDs

Chang Gok Woo https://orcid.org/0000-0002-9131-3779
Seok Jung Yun https://orcid.org/0000-0001-7737-4746
Seung-Myoung Son https://orcid.org/0000-0002-1646-4649
Young Hyun Lim https://orcid.org/0000-0002-4044-5245
Ok-Jun Lee https://orcid.org/0000-0003-2065-3597

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