

REVIEW PAPER

A REVIEW OF ALK-REARRANGED RENAL CELL CARCINOMAS WITH A FOCUS ON CLINICAL AND PATHOBIOLOGICAL ASPECTSNAOTO KURODA¹, EMIKO SUGAWARA², HIRONORI KUSANO³, YOSHIKI YUBA⁴, KENJI YORITA¹, KENGO TAKEUCHI⁵¹Department of Diagnostic Pathology, Kochi Red Cross Hospital, Kochi, Japan²Devison of Diagnostic Pathology, Tokyo Medical and Dental University Hospital, Tokyo, Japan³Department of Pathology, Kurume University School of Medicine, Kurume, Japan⁴Department of Pathology, Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan⁵Pathology Project for Molecular Targets, The Cancer Institute, Japanese Foundation of Cancer Research, Tokyo, Japan

ALK-rearranged renal cell carcinoma (ALK-RCC) has been recently proposed and incorporated into the recent World Health Organisation Classification of renal tumours as a provisional entity. In this article, we review ALK-RCC with a focus on clinical and pathobiological aspects. Seventeen cases have been described to date. ALK-RCC accounts for less than 1% of all renal tumours. The age of patients ranges from 6 to 61 years with a mean age of 29.6 years. Grossly, the tumour forms were ill-demarcated or well demarcated solid mass in the renal medulla. Histologically, RCC with *VCL-ALK* translocation resembles renal medullary carcinoma and mucinous cribriform pattern, signet-ring cell pattern and solid rhabdoid pattern are often observed in RCC with non-*VCL-ALK* fusion. Immunohistochemically, ALK protein diffusely expresses and TFE3 is often expressed. *ALK* gene can fuse to *VCL*, *TPM3*, *EML4*, *HOOK1* or *STRN* gene. A break-apart fluorescence *in situ* hybridisation study is clinically available for the practice of definite diagnosis. ALK inhibitor therapy will provide great benefit for patients with advanced stage of ALK-RCC in the near future.

Key words: ALK, renal cell carcinoma, pathology, review.

Introduction

Renal cell carcinoma (RCC) with translocation of chromosome 2p23 was first described by Yoshida *et al.* in 1986 [1]. To date, the rearrangement of *ALK* gene has been reported in various tumours including anaplastic large cell lymphoma [2], diffuse large B-cell lymphoma [3], inflammatory myofibroblastic tumour [4], and non-small cell lung carcinoma [5], thyroid carcinoma [6, 7], and ciliated mucinodular papillary tumour of the lung [8, 9]. Subsequently, RCC with rearrangement of *ALK* gene was described for the first time by Debelenko *et al.* in 2011 [10]. To date, 17 cases with *ALK*-rearranged renal cell carcinoma (ALK-RCC)

have been reported [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. In the International Society of Urologic Pathology in 2013 [23] and the World Health Organization Classification Tumours of the Urinary System and Male Genital Organs in 2016 [24], ALK-RCC has been incorporated into the histological classification of renal tumours as a provisional entity. In this article, we review this tumour with a focus on clinical and pathobiological aspects.

Epidemiology

ALK-RCC accounts for < 1% of all renal neoplasm [12, 13, 15]. Patients with *VCL-ALK* fusion

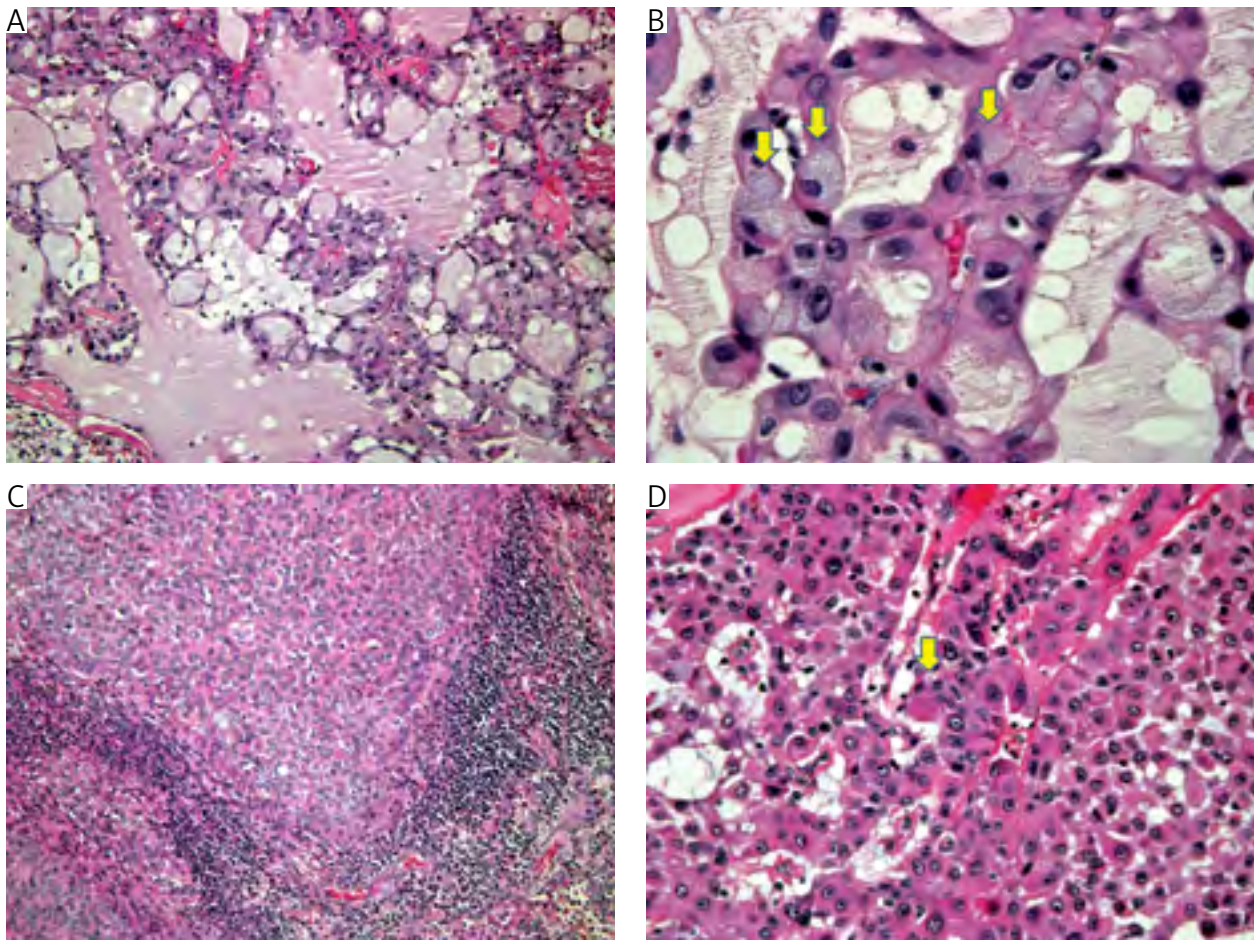


Fig. 1. Microscopic findings. A) Mucinous cribriform pattern. B) Signet-ring cells (arrows). C) Solid growth pattern. D) Rhabdoid cells (arrow)

have sickle cell trait and are of African-American race [10, 11, 16]. By contrast, patients with *non-VCL-ALK* fusion do not show sickle cell trait and frequently occur in patients in East Asia [12, 15, 21]. The information about age and sex was available in 16 of 17 patients. The age of patients ranged from 6 to 61 years with a mean age of 29.6 years [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. Patients consisted of 10 males and 6 females [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21].

Clinical symptoms

Patients with ALK-RCC generally present with flank, abdominal, or periumbilical pain, gross or haematuria [10, 11, 16, 18, 19, 20, 21]. Some tumours are incidentally discovered by medical check-up [12, 15, 21].

Imaging findings

Ultrasound sonography demonstrates a hypoechoic mass generally located in the renal medulla [10, 20]. A simple computed tomography scan shows

an isodense mass [12]. A contrast computed tomography scan shows a slightly enhancing or heterogeneous enhancing mass [11, 21].

Pathological findings

Macroscopic findings

Grossly, ill-demarcated or well demarcated solid tumour is observed in the renal medulla [10, 16, 17]. Cystic change or haemorrhage may be present [15, 18], but pseudocapsule is absent [21]. The cut surface of the tumour shows a tan to brown or white to grey-white colour [17, 18, 19, 21].

Microscopic findings

Renal cell carcinoma with *VCL-ALK* translocation resembles renal medullary carcinoma and consists of polygonal or spindle cells with abundant eosinophilic cytoplasm, vacuolisation and frequent intracytoplasmic lumina, vesicular nuclei, and lymphoplasmacytic infiltrate [11, 16, 23, 24, 25, 26]. Mucinous cribriform pattern (Fig. 1A), signet-ring cell pattern (Fig. 1B), solid growth (Fig. 1C), and rhabdoid fea-

tures (Fig. 1D) are often observed in RCC with non-*VCL-ALK* fusion [12, 21, 27, 28]. Morphologically, some tumours may resemble Xp11.2 RCC with papillary growth of clear to eosinophilic cells [13].

Immunohistochemical findings

ALK protein expresses diffusely in the cytoplasm of tumour cells [10, 11, 12] (Fig. 2). Neoplastic cells are generally positive for AE1/AE3, cytokeratin CAM5.2, epithelial membrane antigen, cytokeratin 7, vimentin, PAX2, and PAX8 but negative for Melanosome-related antigen (HMB45), Melan A, RCC Ma, and Cathepsin K [10, 12, 15, 16, 17, 20, 21]. The expression of CD10 and AMACR varies [10, 12, 15, 20, 21]. TFE3 is often expressed in the nuclei of tumour cells [10, 17, 18, 20]. The expression of INI1 is retained [16, 17, 18, 19, 20], but losses in some tumours [10]. Ki-67 index is generally low [10, 16].

Ultrastructural findings

Tumour cells show bundles of tonofilaments, intercellular junctions, intracytoplasmic lumina lined by microvilli and lipofuscin-like lysosomal structures [11, 17].

Molecular genetic findings

The definite diagnosis of ALK-RCC is possible using a break-apart FISH probe [12, 13, 15, 16, 17, 18, 19, 20, 21] (Fig. 3). The rearrangement of *ALK* gene should be considered present when split signals show more than 15% of total tumour cells [13, 21]. The previously reported fusion partners to *ALK* gene include *VCL* [10, 11, 16, 17], *TPM3* [12, 17, 20], *EML4* [12], *HOOK1* [18], and *STRN* gene [21]. The translocation of *TFE3* gene is not observed, despite TFE3 protein expression in some tumours [12, 14, 20].

Differential diagnosis

ALK-RCC should be distinguished from renal medullary carcinoma (RMC), collecting duct carcinoma (CDC), yolk sac tumour, mucinous tubular and spindle cell carcinoma (MTSCC), papillary RCC, Xp11.2 RCC, RCC with t(6;11), succinate dehydrogenase (SDH)-deficient RCC, and metastatic cancer. Renal medullary carcinoma generally occurs in African-American patients with sickle cell trait. Histologically, RMC may resemble ALK-RCC, particularly RCC with *VCL-ALK* fusion, but loss of INI1 is observed [23, 24, 29]. CDC is characterised by medullary location, predominant tubular growth, stromal desmoplasia, and absence of urothelial carcinoma [23, 24, 30]. Yolk sac tumour consists of endothelial-like cells and possesses hyaline globule-like structures showing positivity for PAS stain with diastase treatment. MTSCC is composed of tubular

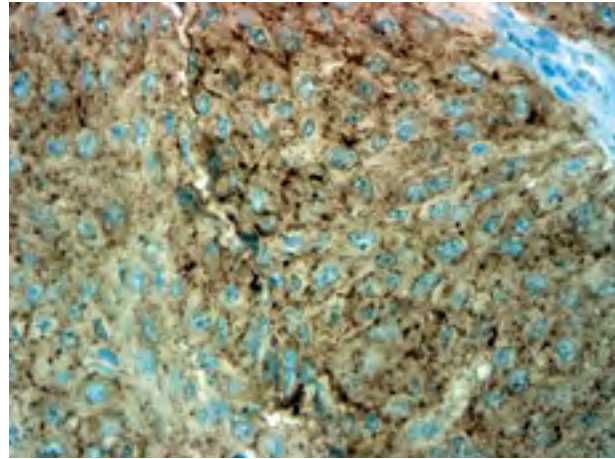


Fig. 2. Immunohistochemical finding. The cytoplasm of neoplastic cells shows diffuse reactivity for ALK protein

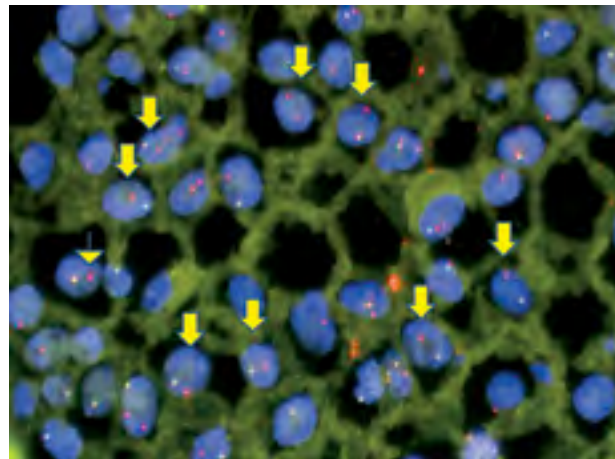


Fig. 3. A break apart fluorescence *in situ* hybridisation finding of *ALK* gene. Split signals are seen (arrows). Orange and green signals show 3' and 5' sites, respectively

structures with frequent elongation and anastomosis and spindle cells with stromal mucin deposition [23, 24, 31]. The distinction from papillary RCC is very important because ALK-RCC often show a papillary configuration. However, ALK-RCC seems to contain more abundant stromal mucin than papillary RCC. Because psammoma bodies and foamy macrophages are observed in both tumours, these findings are not diagnostic clues [32]. Xp11.2 RCC consists of voluminous tumour cells with clear to eosinophilic cytoplasm with hyaline nodules and psammoma bodies in the stroma [23, 24, 33]. Some Xp11.2 RCCs may mimic ALK-RCC, and ALK-RCC can express TFE3 immunohistochemically. Therefore, general evaluation including immunohistochemistry of both TFE3 and ALK proteins and FISH analysis of *TFE3* and *ALK* genes is necessary. RCCs with t(6;11) histologically show two cell patterns of large and small neoplastic cells with pseudorosettes that small cells surround around basement membrane [34]. SDH-deficient

RCC histologically consists of cuboidal cells with eosinophilic cytoplasm, vacuolisation, flocculent intracytoplasmic inclusion, and indistinct cell border [35]. Finally, exclusion from metastatic cancer arising in another organ is required. Particularly, the distinction of ALK-RCC from renal metastasis of *ALK*-rearranged lung adenocarcinoma is very important [36].

Therapy

Radical nephrectomy or nephroureterectomy should be performed in patients with early stage cancer or without distant metastasis [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. Lymph node resection is selected for patients with metastasis to regional or distant lymph nodes [10, 11, 17, 20, 21]. No patient who underwent partial nephrectomy was present previously. The identification of *ALK* gene translocation in RCC promises a beneficial molecular targeted therapy of ALK inhibitor, crizotinib, for patients with advanced stage [11]. There is no report on clinical trials of axitinib in ALK-RCC regarding metastatic renal cell carcinoma [37].

Prognosis

No recurrence or distant metastasis was observed in RCC with *VCL-ALK* translocation to date [10]. Renal cell carcinoma with *non-VCL-ALK* fusion may pursue an aggressive clinical course [13, 14, 21], but some cases behaved in a favourable clinical fashion [12]. However, the number of previously reported cases is too low to accurately evaluate the clinical behaviour of ALK-RCC. Patients with advanced stage of ALK-RCC may benefit from ALK inhibitor therapy in the near future.

Future perspectives

We firmly believe that ALK-RCC is a distinct tumour entity because of its hopeful molecular targeted therapy, namely ALK inhibitor, for *ALK* gene. Accordingly, this tumour should be absolutely incorporated into the next WHO classification of renal tumour. In order to accomplish this, a large-scale study with focus on pathological characteristics and therapeutic response to ALK inhibitor is needed. A case of RCC with *ALK* increased copy number showing histological features of ALK-RCC has been reported [38]. To ascertain whether this tumour can apply as an ALK inhibitor or not will require further examination. A vascular pattern characteristic of ALK-RCC may be found in the future [39].

This study was approved by the Ethical Committee (no. 144) of Kochi Red Cross Hospital and was partly supported

by Grant-in-Aid from Life Fund of Kochi Shimbun and Kochi Broadcast 2012.

The authors declare no conflicts of interest.

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