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Review

Review of renal carcinoma with t(6;11)(p21;q12) with focus on clinical and pathobiological aspects

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Summary. Recently, a new category of MiTF/TFE family translocation carcinomas of the kidney has been proposed. This category includes Xp11.2 renal cell carcinoma (RCC) and the t(6;11) RCC. These tumors share clinical, morphological, immunohistochemical and molecular genetic features. In this article, we review t(6;11) RCC. This tumor predominantly affects children and young adults. Macroscopically, the tumor generally forms a well circumscribed mass. Satellite nodules may be observed. Histologically, the tumor comprises large cells and small cells surrounded by basement membrane material. Immunohistochemically, tumor cells show nuclear immunolabeling for TFEB and usually express Cathepsin-K in the cytoplasm. Karyotyping detects the rearrangement between chromosome 6p21 and chromosome 11q12. *Alpha-TFEB* fusion can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybridization (FISH). Most cases affecting children and young adults seem to be indolent, but some adult cases have presented with metastasis or caused death. As previously reported cases remain limited to date, further examination in a large scale study will be needed in order to elucidate clinical behavior and molecular characteristics.

Key words: Renal carcinoma with t(6;11)(p21;q12), TFEB, Cathepsin-K

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Introduction

A subset of renal cell carcinoma (RCC) mainly affecting children and young adults has been designated as RCC associated with Xp11.2 translocations/*TFE3* gene fusions (Xp11.2 RCC) (Armah and Parwani, 2010; Ross and Argani, 2010; Kuroda et al., 2012). This neoplastic entity has been integrated into the latest World Health Organization Classification (Argani and Ladanyi, 2004). Another subset of renal neoplasms having t(6;11) translocations was described in 1996 by Dijkhuizen et al. in abstract form, but this neoplasm would not be further described and is thought to be clear cell RCC. The distinctive morphologic, immunohistochemical, ultrastructural, and cytogenetic features of this neoplasm were first described in 2001 by Argani et al. The characteristic gene fusion was first identified in 2003 (Davis et al., 2003; Kuiper et al., 2003). Argani and Ladanyi (2003, 2005, 2006) proposed the term "MiTF/TFE family translocation carcinoma" unifying t(6;11) RCC and Xp11.2 RCC, as both TFEB and TFE3 are members of the MiTF/TFE family of transcription factors, and t(6;11) RCC and Xp11.2 RCC share clinical, morphologic, immunohistochemical and molecular features. In this article, we review the topic of renal carcinoma with t(6;11)(p21;q12), with focus on clinical and pathobiological aspects.

Clinical characteristics

This neoplasm is extremely rare and accounts for 0.02 % of all renal carcinomas and seems to be less frequent than Xp11.2 RCC (Geller et al., 2008; Hora et

al., 2009; Zhong et al., 2012). Twenty seven cases have been reported to date (Inamura et al., 2012; Petersson et al., 2012). The patients may present with hematuria, abdominal pain or an abdominal mass (Argani et al., 2001; Campero et al., 2008; Zhong et al., 2012). The tumor may be also incidentally found (Argani et al., 2005). The age of patients ranges from 6 to 57 years with a median of 23 years. There is a slight female predominance. The tumor size ranges from 1.0 to 20cm with a median of 6.5cm (Inamura et al., 2012). Two cases which arose after the patients had received cytotoxic chemotherapy in childhood have been reported (Argani et al., 2006). Imaging analyses, including computed tomography scan and magnetic resonance imaging, may detect the main tumor and surrounding small daughter lesions.

Pathological findings

Macroscopic findings

The tumors are generally well circumscribed and satellite nodules around the main tumor are often observed (Argani et al., 2005; Ishihara et al., 2011). The cut surface shows tan-brown to yellow in color (Argani et al., 2005; Ishihara et al., 2011; Petersson et al., 2012; Zhong et al, 2012). Focal cystic change, hemorrhage or necrosis may be present (Petersson et al., 2012; Zhong et al., 2012).

Microscopic findings

Histologically, the tumor consists of large cells with clear to eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli, and small cells resembling lymphocytes with a narrow cytoplasmic rim. The nuclei possess dense chromatin and small or inconspicuous nucleoli (Argani et al., 2001; Pecciarini et al., 2007; Hora et al., 2009; Suárez-Vilela et al., 2011; Inamura et al., 2012; Petersson et al., 2012) (Fig. 1A). Papillary growth is also seen (Davis et al., 2003; Argani et al., 2005; Pecciarini et al., 2007; Inamura et al., 2012). The arrangement of the small neoplastic cells around a round core of basement membrane material results in the formation of rosette-like structures (Hora et al., 2009; Petersson et al., 2012) (Fig. 1B). The biphasic cell population (large and small cells) is an important diagnostic clue (Argani et al., 2001, 2005; Ishihara et al., 2011; Petersson et al., 2012). However, the small cell component may be inconspicuous and its absence has been reported (Campero et al., 2008; Zhong et al., 2012). Cell borders are generally distinct (Argani et al., 2005). Some tumors may contain melanin pigment in the cytoplasm (Ishihara et al., 2011) and psammoma bodies may be observed (Argani et al., 2005; Ishihara et al., 2011; Suárez-Vilela et al., 2011; Inamura et al., 2012). Entrapped renal tubules may be observed at the peripheral area of the tumor (Argani et al., 2001).

Histochemical findings

The clear cells frequently contain abundant cytoplasmic glycogen and hence show a positive reaction to periodic acid-Schiff (PAS) with granular pattern in the cytoplasm, and these granules are digested with diastase treatment. Hale's colloidal iron may weakly and focally stain the cytoplasm of some tumors (Inamura et al., 2012). The basement membrane material in the center of the rosette-like structures is positive for PAS both before and after diastase treatment and is also

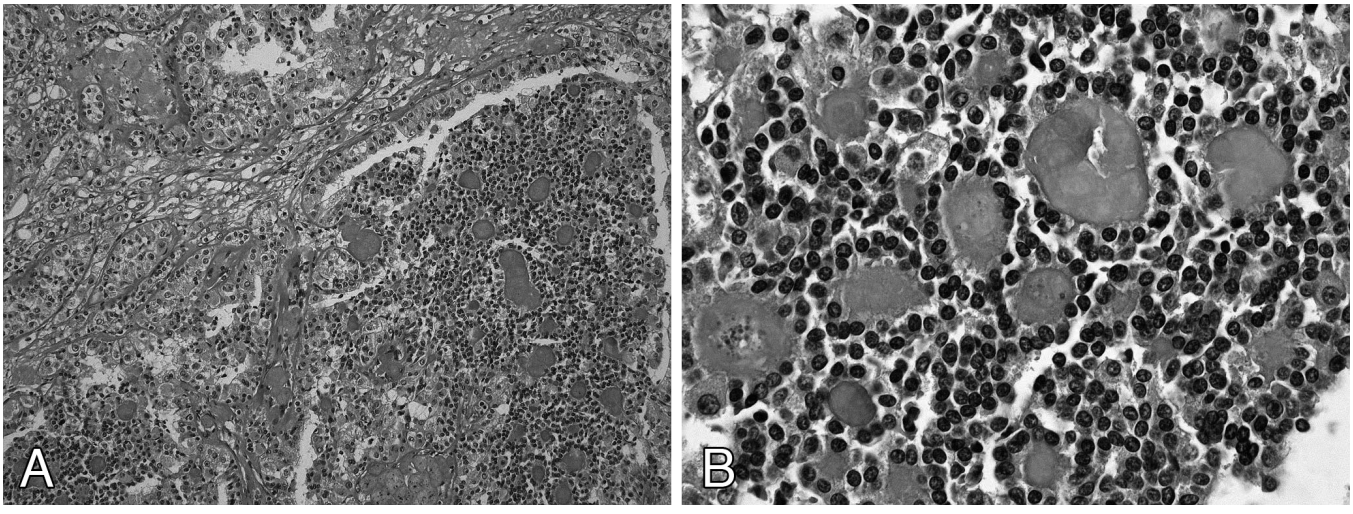

Fig. 1. Microscopic findings of renal carcinoma with t(6;11)(p21;q12). **A.** The tumor comprises large tumor cells with vesicular chromatin and small neoplastic cells with dense chromatin. **B.** Basement membrane material surrounded by small neoplastic cells gives rise to the appearance of rosette-like structures.

positive for methenamine silver stain (Argani et al., 2001).

Immunohistochemical findings

Diffuse nuclear immunoreactivity for TFEB is a critical diagnostic marker for t(6;11) translocation RCCs. Immunoreactivity for TFEB is highly sensitive and specific for this tumor, as exemplified by Argani et al who could not demonstrate any staining for TFEB in any of the 1089 other tumors, including Xp11.2 RCCs (Argani et al., 2005). The nuclear immunoreactivity should be evident at low-power magnification (x4, objective), with more than moderate positivity (2+) in order to be considered positive (Argani et al., 2005) (Fig. 2A). It is important to note that for TFEB immunohistochemisty, excessive antigen retrieval, the use of highly-concentrated antibody, and excessive signal amplification could lead to false-positive results (Argani et al., 2005). TFE3 is consistently negative in this tumor (Martignoni et al., 2009). Cathepsin-K is generally positive for the MiTF/TFE family of renal translocation carcinomas, including this tumor and Xp11.2 RCC, but negative for other types of renal carcinoma (Martignoni et al, 2009; Inamura et al, 2012) (Fig. 2B). In most cases focal immunoreactivity for melanocytic markers, including melanosome-associated antigen (detected by HMB45) and Melan A is present (Argani et al., 2001, 2005; Pecciarini et al., 2007; Campero et al., 2008; Petersson et al., 2012). Some tumors are negative or focally positive for epithelial markers, including cytokeratin and epithelial membrane antigen (EMA), but other cases may be positive for these markers (Argani et al., 2001, 2005; Campero et al., 2008; Ishihara et al., 2011; Suárez-Vilela et al., 2011). Most tumors are negative for MiTF (Martignoni et al., 2009), although focal positivity has been reported (Argani et al., 2005; Petersson et al., 2012). In addition, CD10, alpha-Methylacyl CoA racemase (AMACR) and E-cadherin are expressed in most cases (Campero et al., 2008; Inamura et al., 2012; Petersson et al., 2012).

Ultrastructural findings

Electron microscopic examination of tumor cells has revealed that the eosinophilic tumor cells contain abundant mitochondria, whereas the clear cells harbour abundant cytoplasmic glycogen and apical neutral lipid droplets (Argani et al., 2001; Davis et al., 2003). Additionally, abundant Golgi complexes and rough endoplasmic reticulum are present in the cytoplasm (Argani et al., 2001; Petersson et al., 2012). Also, there are the rosette-like structures composed of small neoplastic cells surrounding basement membrane material ultrastructurally (Argani et al., 2001). Cell junctions, junctional complexes and rudimentary microvilli may occasionally be observed (Argani et al., 2001; Davis et al., 2003; Zhan et al., 2010). No definitive melanosomes or premelanosomes have been identified (Davis et al., 2003; Petersson et al., 2012). Reduplicated basement membrane material forming large pools have been observed in the stroma (Petersson et al., 2012).

Molecular genetic findings

Genetically, this tumor is characterized by the fusion of the 5' portion of the *Alpha* gene mapped at 11q12 with the *TFEB* gene located at 6p21 (Davis et al., 2003). Karyotyping detects the rearrangement between chromosome 6p21 and chromosome 11q12 (Argani et al., 2001; Davis et al., 2003; Pecciarini et al., 2007;

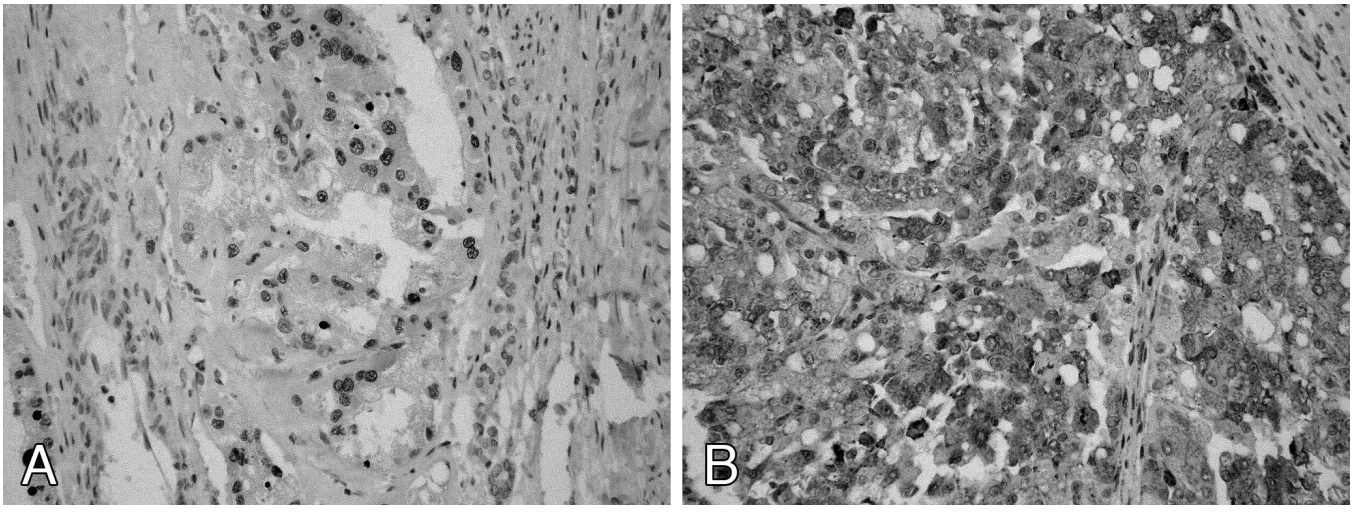

Fig. 2. Immunohistochemical results of renal carcinoma with t(6;11)(p21;q12). **A.** Many tumor cells show nuclear immunolabeling for TFEB. **B.** Cathepsin-K is expressed in the cytoplasm of neoplastic cells.

Geller et al., 2008; Malouf et al., 2011; Inamura et al., 2012; Petersson et al., 2012). The *Alpha-TFEB* fusion can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) or fluorescence *in situ* hybridization (FISH) (Davis et al., 2003; Argani et al., 2005; Pecciarini et al., 2007; Zhan et al., 2010). The diagnostic *TFEB* break-apart FISH assay for paraffin-embedded material has recently been reported (Argani et al., 2012a,b). The *Alpha-TFEB* fusion point seems to vary from case to case (Davis et al., 2003; Kuiper et al., 2003; Zhan et al., 2010; Inamura et al., 2012). As *Alpha* is an intronless gene and lacks splice signals, Argani et al. (2005) consider that the molecular detection of DNA PCR may be a robust alternative to RT-PCR. No loss of heterozygosity of chromosome 3p, *VHL* mutation or *VHL* methylation for mutation or epigenetic alteration related to clear cell RCC has been detected (Petersson et al., 2012). *ASPL-TFE3* fusion transcript was detected in one tumor (Petersson et al., 2012). In array comparative genomic hybridization assay, losses of part of chromosome 1 and chromosome 22 were found in one analyzed tumor (Petersson, et al., 2012).

Differential diagnosis

Pathologists need to distinguish t(6;11) translocation carcinoma from Xp11.2 RCC, clear cell RCC, papillary RCC, chromophobe RCC, clear cell papillary RCC and epithelioid angiomyolipoma (eAML) which may appear similar at the morphological level. However, most of the immunohistochemical features are distinct from this neoplasm. In the group of Xp11.2 RCCs, individual cases may resemble the t(6,11)(p21; q12) tumor and at times both tumors may be indistinguishable from each other. Particularly, *PSF-TFE3* RCC may show the biphasic pattern of large and small cells surrounding hyaline material (Argani and Ladanyi, 2003). In addition, *PRCC-TFE3* RCC and *ASPL-TFE3* RCC may contain a component of small cells in some cases (Campero et al., 2008). In such cases, including both TFEB and TFE3 is crucial to arrive at the correct diagnosis (Argani et al., 2007; Kuroda et al., 2012). The comparison of Xp11.2 RCC and this tumor is summarized in Table 1. It is also worth noting that clear cell RCC, papillary RCC, chromophobe RCC and clear cell papillary RCC may display areas which resemble the morphological and immunohistochemical features of t(6;11) RCCs (Kuroda et al., 2003a,b; Inamura et al., 2012; Petersson et al., 2012). In such instances the age of the patient, presence of stromal change, including basement membrane material and significant (intensity and extension) nuclear immunoreactivity for TFEB, positivity for Cathepsin-K and melanocytic markers are important features to take into account for accurate diagnosis. The distinction of this tumor from eAML is particularly important because melanocytic markers are frequently expressed, and epithelial markers are frequently only weakly expressed or negative for t(6;11) carcinomas (and completely negative in eAML) (Argani et al., 2005; Inamura et al., 2012). Moreover, eAML often contain areas of perivascular hyalinization which may be reminiscent of the basement membrane material observed in t(6;11) RCC and both tumors frequently express Cathepsin-K (Martignoni et al., 2012). The distinction of eAML from t(6;11) carcinomas is facilitated by identifying whether the patient has any clinical signs of the tuberous complex, presence of multiplicity of lesions and of course the immunohistochemical application of TFEB. Interestingly, two renal oncocytomas with a similar t(6;11)(p21;q13) have previously been reported, but the *Alpha-TFEB* gene fusion was not detected in these tumors (Jhang et al., 2004; Medendorp et al., 2007). However, these tumors seem to be quite different from each other morphologically (Kuroda et al., 2003c).

Suggestive origin

Based on the ultrastructural identification of rudimentary microvili, it has been suggested the t(6;11) carcinoma (like Xp11.2 RCC, renal carcinoma) originate from the proximal tubules of the nephron (Argani et al., 2005; Medendrop et al., 2007).

Therapy

Both total nephrectomy and nephron-sparing surgery has been performed for t(6;11) RCC. The latter of course requires technical feasibility, which includes the skill of the surgeon and the size of the tumor. Reportedly, the number of cases with metastasis is limited. In one such case the patient was treated by interferon, sunitinib malate therapy (vascular endothelial growth factor inhibitor) and temsirolimus (a mammalian target of rapamycin inhibitor). Sunitinib malate therapy resulted in a partial response in this patient (Ishihara et al., 2011).

Table 1. Comparison of Xp11.2 RCC and RCC with t(6;11).

	Xp11.2 RCC	RCC with t(6;11)
Patient age	children, young adults	children, young adults
Chromosomal translocation	t(x;17)(p11.2;q25) t(X;1)(p11.2;q21) t(X;1)(p11.2;p34) inv(X)(p11;q12) t(X;17)(p11.2;q23)	t(6;11)(p21;q12)
Gene fusion	*ASPL-TFE3* *PRCC-TFE3* *PSF-TFE3* *NonO-TFE3* *CLTC-TFE3*	*Alpha-TFEB*
Immunohistochemistry TFE3 (nucleus) TFEB(nucleus) Cathepsin K (cytoplasm)	 ++~+++ -~+ 60% +	 -~+ ++~+++ 100% +

Prognosis

Most cases affecting children and young adults seem to be rather indolent (Argani et al., 2005; Geller et al., 2008; Hora et al., 2009; Petersson et al., 2012), but recurrence occurs in 17% of patients (Inamura et al., 2012). Some adult cases have presented with metastasis or pursued an aggressive clinical course causing death (Pecciaarini et al, 2007; Campero et al., 2008; Martignoni et al, 2009; Ishihara et al., 2011; Inamura et al., 2012)

Future perspectives

As previously reported cases are limited, the true biological behavior of this tumor remains to be established. Apart from surgery, there is no standard therapeutic strategy for this tumor at present. Accordingly, further investigation in a large scale study will be necessary in order to elucidate the clinical behavior of t(6;11) RCC and establish a gold standard of treatment. As the breakpoint of *Alpha-TFEB* fusion may be diverse, the search for the relationship between fusion points and the response of chemotherapy or the prognosis may supply the important information for the clinical aspect. We agree with Argani's proposal of the term "MiTF/TFE family translocation carcinoma" unifying t(6;11) RCC and Xp11.2 RCC, as both TFEB and TFE3 are members of the MiTF/TFE family of transcription factors, and t(6;11) RCC and Xp11.2 RCC share clinical, morphologic, immunohistochemical and molecular features.

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