Review paper

Review of *TFEB*-amplified renal cell carcinoma with focus on clinical and pathobiological aspects

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The disease entity of *TFEB*-amplified renal cell carcinoma (RCC) has been recently established. In this article, we review such cases. Clinically, the age of patients ranged from 28 to 83 years with a mean age of 62.8 years. The size of the tumor ranged from 1.9 to 19.5 cm with a mean size of 8.7 cm. The tumor demonstrated a variety of architectural patterns such as solid, alveolar, papillary, pseudopapillary, nested or tubular. The International Society of Urological Pathology (ISUP) grade usually corresponds to grade 3 or 4. Cytomorphology shows eosinophilic, clear, amphophilic or even oncocytic cytoplasm. Necrosis can be frequently observed. Neoplastic cells with *TFEB*-amplified RCC show diffuse or patchy positivity for *TFEB*. Fluorescence in situ hybridization frequently show the amplification of more than 10 or 20 copies of the *TFEB* gene. Most *TFEB*-amplified RCCs behave in an aggressive fashion. Metastasis frequently occurs. In conclusion, this tumor seems to be characterized by occurrence in older patients, frequent necrosis, papillary/pseudopapillary growth pattern, high-grade nuclear grade, *TFEB* gene amplification, and aggressive clinical behavior. In order to clarify whether this tumor is a distinct entity from previously described renal tumors or not, a further examination in a large scale study will be required in the future.

Key words: *TFEB*-amplified, renal cell carcinoma, pathology, review.

Introduction

Peckova *et al.* first described a case of *TFEB*-amplified renal cell carcinoma (RCC) in 2014 [1]. Since then, approximately 42 cases with such features have been reported [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. To date, there seems to be a difference in the clinicopathological aspect between *TFEB*-translocation RCC and *TFEB*-amplified RCC. In this article, we review *TFEB*-amplified RCC with a special reference to clinical and pathobiological aspects.

Clinical characteristics

The 42 patients consisted of 24 males and 18 females [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

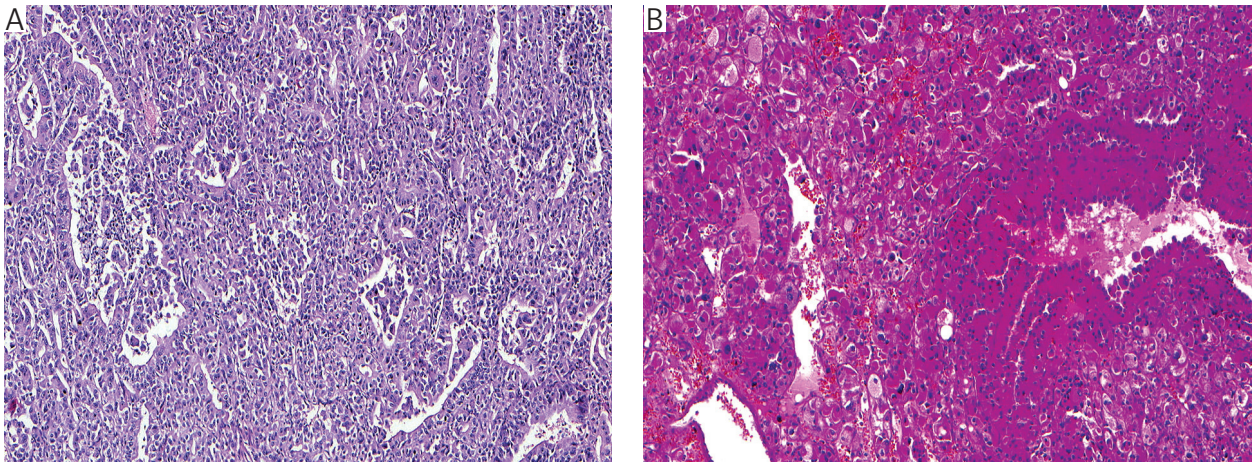

Fig. 1. A) Microscopic findings of *TFEB*-amplified renal cell carcinoma (RCC). Neoplastic cells with clear to eosinophilic cytoplasm proliferate with solid and papillary growth patterns. B) The cytoplasmic eosinophilia is prominent

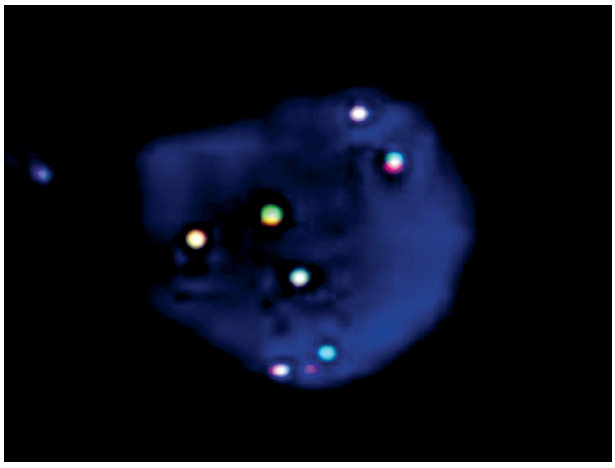

Fig. 2. Fluorescence *in situ* hybridization findings of *TFEB* gene in *TFEB*-amplified RCC. The amplification as well as translocation of *TFEB* gene is demonstrated

The age of patients ranged from 28 to 83 years with a mean age of 62.8 years [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

Pathological findings

Macroscopic findings

The tumor size was available in 41 cases. The size of the tumor ranged from 1.9 to 19.5 cm with a mean size of 8.7 cm [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. Tumor thrombosis was identified in four cases [3, 8].

Microscopic findings

The tumor demonstrated a variety of architectural patterns such as solid, alveolar, papillary, pseudopapillary, nested or tubular (Fig. 1A). ISUP grade usually corresponds to grade 3 or 4 [1, 3, 4, 8, 11]. Cytomorphology shows eosinophilic, clear, amphophilic or even oncocytic cytoplasm [2, 8, 14]. Cytoplasmic eosinophilia seems to be more frequent in *TFEB*-amplified RCC than *TFEB*-translocation RCC (Fig. 1B) [14]. The biphasic growth pattern consisting of large and small neoplastic cells is characteristic of *TFEB*-translocation RCC, but this pattern seems to be less frequent in *TFEB*-amplified RCC [14]. Rarely, cases with grade 2 have been reported [11, 14]. Necrosis can be frequently observed [1, 3, 5, 8]. Hemorrhage may be observed in some cases. Sarcomatoid change has been reported [14].

Immunohistochemical findings

Neoplastic cells with *TFEB*-amplified RCC show diffuse or patchy positivity for TFEB. However, some tumors may be completely negative or show lower level expression than *TFEB*-translocation RCC [14]. TFE3 is negative in most cases. Most tumors are diffusely or patchily positive for melan-A. The positivity for cathepsin-K is various.

Molecular genetic findings

Fluorescence *in situ* hybridization (FISH) frequently shows amplification of more than 10 or 20 copies of the *TFEB* gene (Fig. 1). However, cases with low-amplification of the *TFEB* gene have also been described. This tumor may be associated with translocation of the *TFEB* gene in some cases or not in other cases. Namely, RCC with immunohistochemical positivity of TFEB protein is divided into three categories, namely RCC with translocation of the *TFEB* gene, RCC with amplification of the *TFEB* gene, and RCC with translocation as well as amplification of the *TFEB* gene. Co-amplification of the *VEGFRA* gene located in the chromosome region 6p21.1 has been described in most cases [5, 7, 11, 12, 14].

Co-amplification of the *RUNX2* gene or *CCND3* gene has also been described [11, 14]. Chromosomal abnormalities have been identified in eight cases [4, 8]. Using array comparative genomic hybridization method, gains of chromosome 6p or chromosome 2q were observed in six and four cases, respectively [4, 8]. Loss of chromosome 3p has been identified in seven cases [4, 8]. Gain of chromosome 7 or chromosome 17 has been described [4]. Among them, seven tumors involved the *VHL* gene locus [4, 8]. Point mutation of the *TP53* or *CDKN2A* gene has been reported in *TFEB*-amplified RCC [8].

Differential diagnosis

The original diagnosis includes various histologic subtypes such as clear cell RCC, papillary RCC, translocation RCC, unclassified RCC or RCC with sarcomatoid change [8]. Accordingly, these diseases should be distinguished from *TFEB*-amplified RCC. The distinction from epithelioid angiomyolipoma is also important [2]. Pathologists need to note that some molecular genetic studies such as loss of chromosome 3p or gain of chromosome 7 or 17 may not be available in the distinction from clear cell RCC or papillary RCC [4].

Therapy

As co-amplification of the *VEGFRA* gene has been frequently reported in *TFEB*-amplified RCC, VEGF may become a therapeutic target [5, 7, 11, 12]. Radiation therapy has been tried previously [2].

Prognosis

Most *TFEB*-amplified RCCs behave in an aggressive fashion [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. The 5-year survival rate is estimated to be 48% [11]. Metastasis frequently occurs in this tumor. Metastatic sites include lung, heart, bone, liver and colon [2, 8, 9].

Future perspectives

TFEB-amplified RCC seems to be characterized by papillary/pseudopapillary architecture, frequent necrosis, high nuclear grade and aggressive clinical behavior with frequent distant metastasis. The copy number of *TFEB* gene amplification in previously reported *TFEB*-amplified RCCs has varied from case to case. Therefore, whether the copy number of the *TFEB* gene has a significant impact on prognosis of *TFEB*-amplified RCC or not requires further examination.

The authors declare no conflict of interest.

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