Int J Clin Exp Pathol 2017;10(8):8773-8776
www.ijcep.com /ISSN:1936-2625/IJCEP0060064

Case Report

t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma: a case report and review of literature

Jing Ma*, Yingmei Wang*, Yixiong Liu, Peifeng Li

*Department of Pathology, Xijing Hospital and School of Basic Medicine, Fourth Military Medical University, Xi'an, China. *Equal contributors.*

Received June 22, 2017; Accepted June 26, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma is a recently recognized renal cell carcinoma caused by the formation of Alpha-TFEB fusion genes. Herein, we have reported a rare case. A 20-year-old female patient presented with a mass measuring 4.1 cm × 3.3 cm in left kidney, and radical left nephrectomy was performed. Then the patient underwent unmarkable prognosis without recurrence or metastasis in the 18-month follow-up. Microscopic findings showed the tumor mainly composed of medium and large epithelioid cells with the structures of solid nesting and pseudopapillary. The tumor cells showed well-circumscribed, abundant eosinophilic cytoplasm and obvious small nucleoli. Furthermore, multifocal hemosiderin deposition and focal osseous metaplasia were observed. The tumor cells were positive for E-cadherin and focally positive for HMB45, Melan-A, AE1/AE3, Vimentin, RCC and CK19. FISH analysis for TFEB break-apart probe revealed a break-apart signal pattern meaning TFEB gene rearrangement. t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma is a rare tumor that mostly occurs in young adults with a beneficial prognosis. Diagnosis is usually performed according to the age of the patients, the pathologic morphology and immunophenotype. Positive TFEB expression in neoplastic cell nuclei can be regarded as sensitive and specific diagnostic event for this type of tumor. TFEB gene break-apart and rearrangement in FISH test is crucial to the diagnosis of the disease.

Keywords: Renal cell carcinoma, TFEB gene, FISH, chromosome translocation

Introduction

t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma (referred to as TFEB renal cell carcinoma) is a recently recognized low potential malignant renal cell carcinoma caused by the formation of Alpha-TFEB fusion genes which is composed of a non-protein-encoding gene Alpha located in chromosome 11 and TFEB gene located in chromosome 6 [1]. This tumor frequently occurs in adolescents. In general, TFEB renal cell carcinoma is composed of large and small tumor cells with either nesting or acinous arrangement. Characteristic structures of "pseudorosettes" can be formed by the small cells in some cases. In this study, a case of t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma was reported to summarize its clinicopathologic features.

Case report

The 20-year-old girl presented with an occasional tumor in left kidney for 4 days. Abdominal ultrasonography indicated an irregular echo mass measuring 4.1 cm × 3.3 cm on the upper part of her left kidney. Low echoes with regular shapes were observed in the center of the mass, and a patched echo enhancement was detected around them. CDFI results indicated a weak blood flow signal. CT examination indicated a solid lesion in the superior part of the left kidney, and reinforcement was detected in the enhancement scan. Blood routine examination and routine urine test results were normal. The patient had no urinary tract irritation symptoms, such as frequent urination, urgent urination, dysuria, and dysuria. She did not exhibit gross hematuria, foamy urine, and pyuria and experience pain in her bilateral waist and stomach. Urine volume had no obvious change. Radical left nephrectomy was performed for the patient under general anesthesia. No special treatment was administered after surgery. During the 18 month follow-up visit, no tumor recurrence or metastasis was detected.

Gross findings: The excised left kidney was approximately 12.5 cm × 7 cm × 6 cm. A spheri-

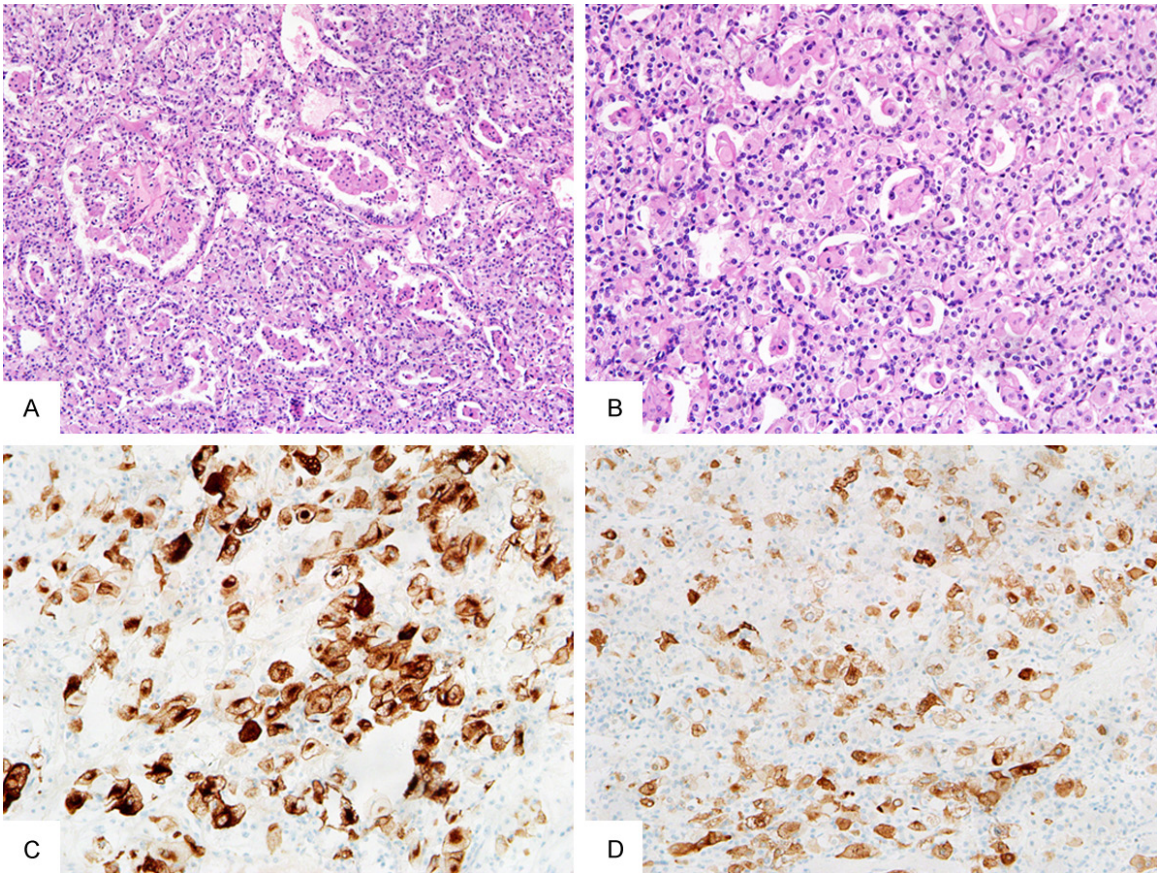

Figure 1. The histomorphological and immunohistochemical features of TFEB renal cell carcinoma. (A) The medium and large epithelioid tumor cells showed solid nesting arrangement, and pseudopapillary structures were found in local area (HE, × 100). (B) Tumor cells have clear boundaries with abundant cytoplasms and obvious nucleoli (HE, × 200). The tumor cells showed focal expression of HMB-45 (C) and Melan-A (D) (IHC, × 200).

cal tumor was found in the upper part of the left kidney and had an approximate size of 4 cm × 4 cm × 3.5 cm. The section of the tumor was colorful and solid with moderate texture and obvious envelops. The tumor was close to the renal capsule and pelvis.

Microscopic findings: The tumor was mainly composed of medium and large epithelioid cells, which lacks small cells with little cytoplasm. The cellular arrangement was solid nesting or acinous, and pseudopapillary structures were also observed in local region (**Figure 1A**). The tumor cells were polygonal, oval, or short fusiform with clear boundaries. The cytoplasm was plentiful with acidophilia. The nucleus was oval or short fusiform with abundant chromatin and evident small nucleolus (**Figure 1B**). Multinuclear tumor cells with two or three nuclei were observed. The mitotic figure of the tumor cell was difficult to detect. Multifocal hemosiderin deposition was found in the tumor, and partial pink substance deposition and ossification were also observed. The peripheral fibrous capsule of the tumor was complete with around plentiful dilated blood vessels.

Ventana BenchMark XT system was used for the immunohistochemical staining of the tumor tissues. The tumor cells manifested the diffuse expression of E-cadherin, and focal positive reaction for HMB45 (**Figure 1C**), Melan-A (**Figure 1D**), AE1/AE3, Vimentin, RCC, and CK19. P504S expression was weakly positive in the partial area, and CD10 and CD117 expression levels were scattered. CD34 staining showed abundant vascular net in the tumor. Meanwhile, all the results of S-100, EMA, Desmin, Cam5.2, TFE3, and CK7 were negative, and Ki-67 staining showed that the tumor proliferation index was around 8%.

FISH test: A TFEB gene break-apart probe was purchased from USA Empire Genomics Com-

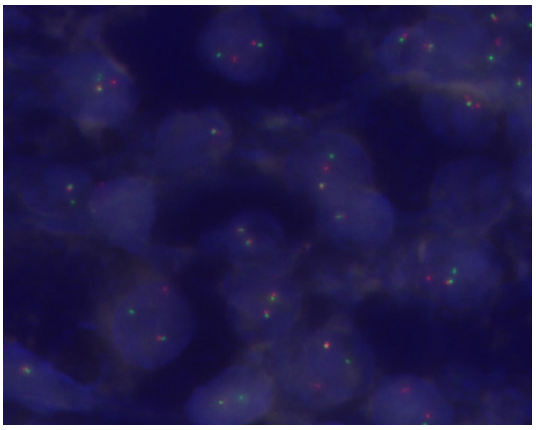

Figure 2. Abnormal TFEB break-apart signals in tumor cells were observed (green signals means the centromere side of TFEB gene and orange signals means the telomere side of TFEB gene; FISH, high magnification).

pany. The TFEB gene was marked with green fluorescence on the side of centromere and orange fluorescence on the side of the telomere. Two orange-green fusion signals were observed in normal cells, which presented contiguous orange-green or yellow signal points. When the distance between the orange and green signals exceeded the size of one fusion signal, it was regarded as orange and green signal break-apart. One normal fusion signal and a pair of abnormal orange-green break-apart signals were found in the tumor cells of this case (**Figure 2**).

The final pathological diagnosis was t(6;11)(p21;q12)/TFEB gene fusion-associated renal cell carcinoma.

Discussion

TFEB renal cell carcinoma is an unusual fusion gene-associated renal cell carcinoma. Argani et al. were the first to report this case in 2001 [2]. However, this term was not officially recognized in the Vancouver kidney tumor classification by the International Society of Urological Pathology until 2013 [3]. As a subtype of MiFT-associated renal cell carcinoma, the Alpha and TFEB genes fuse together in the tumor, thus upregulating TFEB expression and causing the abnormal expression of melanocyte markers, which becomes a key characteristic of TFEB renal cell carcinoma. This type of carcinoma frequently occurs in teenagers and young children, although it can occur in adults as well. The age ranges from 3-year to 77-year with an average age of 30.33-year, which is significantly younger than that of usual clear cell and papillary renal cell carcinomas. The clinical symptoms are similar to those of usual renal carcinomas and typically include gross hematuria, waist pain, and abdominal mass [4]. Special symptom and physical sign may not be observed until physical examination. Imaging findings have no obvious distinction from those of clear cell carcinomas of kidney. The tumor has a size from 1.0 cm to 20 cm, and its average diameter is around 6.5 cm. In the present study, the patient is a young female who had a small renal mass that was accidentally detected during physical examination.

TFEB renal cell carcinoma shares the similar gross appearance with common kidney carcinoma, and the tumor has a clear boundary and complete envelope. The section is brown and has a soft texture and may be accompanied by focal cystic degeneration, hemorrhage, or necrosis [4]. Microscopically, the tumor cells are composed of large and small epithelioid cells with nesting or acinous arrangement. The large cells have abundant clear or eosinophilic cytoplasm and vesicular nuclei with obvious nucleoli [4]. The small cells have a close arrangement, and the nuclei contain abundant nuclear chromatins with small or inconspicuous nucleoli. The small cells are often clustered in the center of the acinus, which can arrange around the basilar membrane tissues with glassy degeneration and forms special structure of “pseudorosettes” or “Call-Exner bodies” [5]. Therefore, the component of small cells is usually the “indicative clue” for diagnosis of this disease. However, this component may be inconspicuous or absent in some cases, just like in this case. Both tumor cells have inconspicuous atypia, and the mitotic figures are very rare. Extensive glassy degeneration, papillary structures, and structures of other tumors, such as clear cell carcinoma, papillary renal cell carcinoma, and acidophilic adenoma, can be found in some cases. A lot of fine vessels can be observed in the mesenchymal stroma. In the current case, the tumor lacks the component of small cells and its morphology is similar to that of a clear cell carcinoma. However, motley and irregular acinous structure and deposition of pink substance and ossification in local areas indicated the possibility of special type of renal carcinoma.

TFEB renal cell carcinoma is of a unique immunophenotype. Its most significant difference from other types of renal cell carcinoma is the diffused or focal expression of melanocyte markers, particularly HMB-45 and Melan-A, without S-100 expression. Positive cathepsin K expression is another key feature of TFEB renal cell carcinoma [1]. Furthermore, the tumor may show the expression of kidney tubule transcription factor PAX8 and local various expression of RCC, CD10, Vimentin, Cam5.2, and cytokeratin. EMA and TFE3 are typically negative [6]. The important immunohistochemical manifestation which is different from other kidney carcinomas and normal renal tissue, is that the nuclei of this tumor are positive for TFEB antibody, which is caused by the Alpha-TFEB gene fusion. Therefore, the presence of positive TFEB in the cell nuclei of tumor cells can be regarded as a sensitive and specific diagnostic event for this kind of tumor. Furthermore, TFEB gene break-apart probe test is a more sensitive testing method than immunohistochemistry and can be used to paraffin-embedded tumor tissues. In the present case, the immunohistochemical expression of tumor confirmed to the characteristics of TFEB renal cell carcinoma, and one orange-green break-apart signal in the tumor cell indicating rearrangement of TFEB gene, was determined in the FISH test.

Most manifestations of TFEB renal cell carcinoma are inertia medical course with good prognosis. However, tumor metastasis can occur in some patients and even cause their deaths [4]. Therefore, long-term follow-up is of great importance. Moreover, no standard for the prediction of the biological behavior of this tumor is currently available, although Kvetoslava et al. believed that invasive TFEB renal cell carcinoma can likely occur in old people [7], and that large gross tumor volume, insufficient small cell component, visible necrosis, and TFEB gene amplification might be the predictive factors for tumor invasiveness [7]. In the present case, the patient is young and the small tumor has no apparent necrosis. TFEB gene amplification was not detected in FISH test. Thus, this case is considered as low potential malignant renal cell carcinoma. However, with regard to morphology, the tumor tissues lack the component of small cells and thus close follow-up is necessary.

Acknowledgements

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure of conflict of interest

None.

Address correspondence to: Peifeng Li, Department of Pathology, Xijing Hospital and School of Basic Medicine, Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China. E-mail: lipeifeng00@hotmail.com

References

[1] Yan FC, Shi F, Zhou Q, Gao Y, Zhang JX, Chang H. t(6;11)(p21;q12) transcription factor EB (TFEB) gene fusion associated renal cell carcinoma. J Diag Pathol 2015; 22: 1007-8096.

[2] Argani P, Hawkins A, Griffin CA, Goldstein JD, Haas M, Beckwith JB, Mankinen CB and Perlman EJ. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol 2001; 158: 2089-2096.

[3] Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, Hes O, Moch H, Montironi R, Tickoo SK, Zhou M and Argani P. The international society of urological pathology (ISUP) vancouver classification of renal neoplasia. Am J Surg Pathol 2013; 37: 1469-1489.

[4] Rao Q, Zhou XJ. Molecular genetics of pediatric renal cell carcinoma. J Med Postgra 2012; 25: 967-970.

[5] Xia QY, Shi SS, Shen Q, Wei X, Wang X, Ma HH, Lu ZF, Zhou XJ, Rao Q. Renal cell carcinoma with t(6;11)(p21.2;q13)/MALAT1-TFEB fusion: a clinical and pathological analysis. Chin J Pathol 2015; 44: 895-899.

[6] Smith NE, Illei PB, Allaf M, Gonzalez N, Morris K, Hicks J, Demarzo A, Reuter VE, Amin MB, Epstein JI, Netto GJ and Argani P. t(6;11) renal cell carcinoma (RCC): expanded immunohistochemical profile emphasizing novel RCC markers and report of 10 new genetically confirmed cases. Am J Surg Pathol 2014; 38: 604-614.

[7] Peckova K, Vanecek T, Martinek P, Spagnolo D, Kuroda N, Brunelli M, Vranic S, Djuricic S, Rotterova P, Daum O, Kokoskova B, Vesela P, Pivovarcikova K, Bauleth K, Dubova M, Kalusova K, Hora M, Michal M and Hes O. Aggressive and nonaggressive translocation t(6;11) renal cell carcinoma: comparative study of 6 cases and review of the literature. Ann Diagn Pathol 2014; 18: 351-357.