MED15-TFE3 Renal Cell Carcinoma: a Xp11 Translocation Renal Cell Carcinoma Subtype With Distinct Clinicopathological Features and Superior Prognosis

Weidong Gan (✉ gwd@nju.edu.cn)

Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School

Xiang Dong

Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School

Wei Guo

Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University

Peng Zhou

Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University

Jun Pan

Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School

Hongqian Guo

Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School

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Abstract

Background: MED15-TFE3 renal cell carcinoma is a rare subtype of the Xp11 translocation renal cell carcinoma. To data, only 14 cases of MED15-TFE3 renal cell carcinoma have been reported worldwide.

Methods: MED15-TFE3 gene fusion was identified in two cases of Xp11 translocation renal cell carcinoma by using RNA-sequencing. We reviewed and summarized the clinicopathological characteristics, imaging features and prognosis of the MED15-TFE3 renal cell carcinoma.

Results: Morphologically, MED15-TFE3 RCC have the typical cystic-solid (mostly cystic) structure. The tumor cells had round nuclei with inconspicuous nucleoli and abundant clear or eosinophilic cytoplasm. Psammoma bodies were randomly distributed within the stroma. Immunohistochemically, the typical TFE3 positive staining could be observed in both cases. The split red-green signal also revealed the positive results in fluorescence in situ hybridization (FISH) assay. Finally, RNA sequencing detected the existence of MED15-TFE3 gene fusion. One pediatric patient developed renal hilar lymph node metastasis before surgery. However, during the follow-up period, no disease recurrence and metastasis happened to both patients.

Conclusions: Different from the traditional Xp11 translocation RCC, MED15-TFE3 RCC may have the distinctive cystic-solid structure and superior prognosis. These findings enhanced our understanding of the heterogeneity in Xp11 translocation RCC.

Introduction

Xp11 translocation renal cell carcinoma (RCC) is classified as an independent subtype of RCC within the Microphthalmia-associated transcription factor (Mit) family translocation RCC in 2016 (1). The TFE3 gene located on chromosome Xp11.2, which could fuse with other genes by the chromosome translocation (2). ASPL-PRCC and SFPQ are the most common TFE3 fusion partners (3-5). In addition, various fusion genes have been reported, such as NONO, PARP14, CLTC, ARID1B, RBM10, LUC7L3, DVL2, KHSRP, KAT6B, NEAT1, GRIPAP1 and MED15 (6-10). The presence of different fusion partners contributes Xp11 translocation RCC to be a kind of highly heterogeneous tumor (11).

Morphologically, Xp11 translocation RCC is characterized by the papillary structure with clear or eosinophilic cytoplasm and psammoma bodies (3, 12). Immunohistochemically, the tumor cells poorly express epithelial markers. Conversely, the melanocytic marker may often be positively expressed in the tumor (13, 14). Clinically, the rare tumor occupies a large proportion of RCC in children. But adult patients have more aggressive clinical course and a poorer prognosis (11, 15, 16). Considering the heterogeneity in Xp11 translocation RCC, different genotypes of tumor may have various biological behaviors and clinical prognosis (14, 17, 18). We found not all Xp11 translocation RCCs have the same dismal prognosis. Here, we reported two cases of MED15-TFE3 RCC accompanied with the special morphologic feature and the indolent clinical course, and review the relevant literature to deepen the understanding of MED15-TFE3 RCC.

Methods

Immunohistochemistry

The tumor specimens were fixed with formalin (10% solution) and embedded in paraffin. The primary antibodies used in immunohistochemistry were listed below: TFE3 (ab179804, 1:250; Abcam), PAX8 (ab181054, 1:500; Abcam), (CK7) (OV-TL 12/30, 1:800; Dako), CAIX (ab108351, 1:150; Abcam), CD10 (ab951, 1:25; Abcam), Cathepsin K (3F9, 1:300; Abcam), CD117 (2E4, 1:1000; Dako), P504s (13H4, 1:200; Dako). The assessment of immunoreactivity was evaluated as described previously(19).

Fluorescence in situ hybridization

Four-μm-thick formalin-fixed, paraffin-embedded (FFPE) tissue sections were performed for Fluorescence in situ hybridization (FISH). The rearrangement of the TFE3 gene were detected by the dual-color break-apart TFE3 Probe (Anbiping company, Guangzhou, China). Detailed steps of FISH were presented in previous study (19). A minimum of 100 tumor nuclei were analyzed under the fluorescence

microscopy, and the split signal was defined as the distance >2 signal diameter. The positive FISH result was defined as more than 10% of tumor nuclei with split signal.

RNA Sequencing

RNeasy kit (QIAGEN) was performed for extracting the total RNA from the FFPE tissue sections. The high-throughput RNA-sequencing was carried out on the Illumina HiSeq™ 2000 (California, USA) by GloriousMed Technology (Beijing, China).

Results

Clinical characteristics

Patient 1. The patient was a 27-year-old female who found the renal tumors during the physical examination without any symptoms. The patient had no underlying disease and family history of tumors. Urinary computed tomography (CT) enhanced scan showed a cystic solid mass—predominantly cystic lesion, 6.8*5.2cm—at the right kidney. The solid part of the mass showed slightly circular enhancement during corticomedullary phase (Figure 1A-B). Robot-assisted laparoscopic partial nephrectomy was performed finally. According to the TNM staging, the tumor was in the stage of T1aN0M0. The patient recovered well postoperatively without any adjuvant therapy. No recurrence and metastasis were found during the 28 months follow-up.

Patient 2. The patient was a 16-year-old girl who visited to local hospital due to nausea and vomiting. The girl was firstly misdiagnosed with gastroenteritis and managed symptomatically. But the symptoms did not improve, so the patient further underwent abdominal ultrasound examination. Ultrasound image revealed inhomogeneous echogenicity, with the huge abdominal mass. Then the abdominal contrast CT scan was performed. The cystic solid lesion (16*15.5cm) contained a higher proportion of cystic component. And the solid component showed moderately enhanced in the corticomedullary phase. Besides the primary tumor, an enlarged lymph node was also observed at the right renal hilum (Figure 1C-D). Finally, the patient underwent open radical nephrectomy and lymphadenectomy in our hospital. The pathologic TNM staging was T2bN1M0. At follow-up 8 months after surgery, the girl exhibited no recurrence after surgery.

Pathological findings.

Microscopically, most parts of the tumor were cystic and solid structures were visible in some areas. The tumor cells arranged in cords or nests, containing abundant eosinophilic or clear cytoplasm. Psammoma bodies were randomly distributed within the stroma (Figure 2). CA-IX, CD10, CD117, CK7, Cathepsin K and P504s were negative in both MED15-TFE3 renal cell carcinomas. In contrast, the positive expression of TFE3 and PAX8 could be shown in both cases (Figure 3).

FISH assay had a higher accuracy in comparison to TFE3 immunohistochemical staining. Since males only had one X chromosome, a pair of separated (red and green) signal was considered as the positive FISH results. Due to one of the two X chromosomes happened to inactive in females, the positive results included a pair of separated (green and red) signals and a fused (yellow) signal. Both of our female cases had shown the feature (Figure 3). Considering the influence of section truncation, a single red or green single in males was also regarded as positive results. The same reasoning applied to female patients.

RNA Sequencing

In the study, RNA sequence was performed to identify the fusion transcripts. The fusion of TFE3 and MED15 was viewed by the Integrative Genomics Viewer (IGV, www.broadinstitute.org/igv) (Figure 4).

Discussion

Since the finding of PRCC as the first fusion partner in Xp11 translocation, various of partners have been reported in Xp11 translocation RCCs (4, 20). Available references indicated that the different molecular subtypes of Xp11 translocation RCC may

contribute to the different clinicopathological features (11, 14, 18, 19, 21, 22). For example, the ASPL-TFE3 RCCs may have the most typical morphologic structure of Xp11 translocation RCCs (22). Cathepsin K often observed positive expression in PRCC-TFE3 RCCs, while it was negative in ASPL-TFE3 and SFPQ-TFE3 RCCs (18). Compared with PRCC-TFE3 RCCs, ASPL-TFE3 RCCs tended to present with rapid progression and advanced stage (21).

As a part of the multiprotein mediator complex, MED15 is involved in RNA polymerase II-dependent transcription process. It has been reported that MED15 is an essential promoter of tumor initiation and progression in RCCs (23). The first case of MED15-TFE3 gene fusion was reported by Classe et al. (24). To data, only 14 cases of MED15-TFE3 RCC have been reported worldwide. Detailed clinicopathological information are summarized in Table 1. According to the available studies, MED15-TFE3 RCC are more common in young females (11/16,68.8%) with the average age at onset of 37.1 years, which is consistent with the report in the Xp11 translocation RCC (10, 25). Similarly, a majority of patients are asymptomatic, often incidentally observed during the physical examination. Although the prognosis of Xp11 translocation RCC remains controversial, most studies still consider that the tumor is an aggressive disease with a poor prognosis (10, 26, 27). Among the 194 Xp11 translocation RCC patients with complete follow-up information, nearly half of them (91 patients) had the aggressive behavior (10). However, Xp11 translocation RCC occurs more commonly in children and such RCCs have a better prognosis comparing to their adult counterparts (28-30). We report for the first time MED15-TFE3 gene fusion in pediatric patient with Xp11 translocation RCC. Meanwhile, the patient is the only one with lymph node metastasis within MED15-TFE3 RCCs. But, even pediatric patients with lymph node metastasis also have a more favorable prognosis than adult patients (15, 31). No recurrence or metastasis was revealed 8 months postoperatively in this patient, long-term follow-up is still required. In present studies of MED15-TFE3 RCC, the follow-up ranges from 8 to 180 months. All the patients were alive, except for one patient developed lung metastasis 15 years after the operation. In general, the prognosis of MED15-TFE3 RCC is excellent, which is different from the typical Xp11 translocation RCC. Combined with previous studies, we speculate that this type of fusion partner may have an excellent prognosis in Xp11 translocation RCC.

Table 1

The clinicopathological characteristics and prognosis of the MED15-TFE3 renal cell carcinoma.

Author	Age/Gender	Tumor size	Stage	Follow-up	Morphology	Immunohistochemistry					
						TFE3	PAX8	CK7	CA-IX	CD10	Cathepsin K
Classe et al	34/F	9.5	T2N0M0	NED (48m)	Mixed+cystic	+	N/A	N/A	N/A	N/A	N/A
Wang et al	42/M	1.5	T1N0M0	NED	Cystic	+	+	N/A	N/A	N/A	+
	41/M	9	T2N0M0	AWD (lung metastasis 15 years later)	Tubular& papillary& solid	+	+	N/A	N/A	N/A	+
	54/F	4	T1N0M0	NED	Cystic	+	+	N/A	N/A	N/A	+
	45/F	4.5	T1N0M0	NED	Cystic	+	+	N/A	N/A	N/A	+
	30/F	5	T1bN0M0	NED	Cystic, papillary, solid	+	+	N/A	N/A	N/A	+
Pei et al	22/F	2	T1N0M0	N/A	N/A	+	+	-	N/A	N/A	+
Ye et al	35/F	5	T1N0M0	NED	Mixed+cystic	-	+	+	+	+	-
Song et al	40/M	4	T1N0M0	NED (46m)	MCRN-LMP-like	+	+	-	-	+	N/A
	51/F	3.6	T1N0M0	NED (38m)	MCRN-LMP-like	+	+	-	-	-	N/A
	49/M	3	T1N0M0	NED (54m)	MCRN-LMP-like	+	+	-	-	-	N/A
	47/M	5.8	T1N0M0	NED (8m)	MCRN-LMP-like	+	+	-	-	-	N/A
	28/F	3.0	T1N0M0	NED (19m)	MCRN-LMP-like	+	+	-	-	-	N/A
	32/F	3.1	T1N0M0	NED (56m)	MCRN-LMP-like	+	+	-	-	+	N/A
Our study	27/F	6.8	T1N0M0	NED (28m)	Cystic	+	+	-	-	-	-
	17/F	16	T2N1M0	NED (4m)	Cystic	+	+	-	-	-	-
Note: M: male; F: female; m: months; NED: no evidence of disease; AWD: alive with disease; N/A: not available; +: positive; -: negative.											

On imaging, complex cystic component was common finding in Xp11 translocation RCCs (32, 33). The feature is particularly prominent in MED15-TFE3 RCCs (14, 34). Our cases also showed the mixed solid-cystic components (mainly cystic) on CT images. We reported a pediatric patient of MED15-TFE3 RCC with lymph node metastasis. The enlarged lymph node could be visualized before the preoperative CT. Considering the tendency of the Xp11 translocation RCC to happen to lymph node metastasis, the possibility of Xp11 translocation RCC should be considered for any RCC with enlarged lymph node in young patients. Two previous studies on CT imaging in MED15-TFE3 RCC also revealed the complex cystic mass (14, 34). For the MED15-TFE3 RCC, the mixed cystic-solid lesion on CT imaging may be the characteristic imaging feature.

Morphologically, most of MED15-TFE3 RCC have the extensively cystic structure, and a small part of them accompanied the fibrotic septa are similar to multilocular cystic renal neoplasm of low malignant potential. The tumor cells have round nuclei with inconspicuous nucleoli and abundant clear or eosinophilic cytoplasm. Psammoma bodies were frequently found in MED15-TFE3 RCC (14, 19, 24, 34). Interestingly, in the only previous case of MED15-TFE3 RCC with disease progression, it shows the tubular,

papillary and solid morphological structures, instead of the typical cystic-solid feature (19). We consider the simple structure of MED15-TFE3 RCC may associate with the favorable prognosis. Immunohistochemically, TFE3 showed varying degrees of positive expression in almost all MED15-TFE3 RCCs, except for one case was considered TFE3 negativity due to the weak nuclear staining (34). Like other studies about MED15-TFE3 RCC, PAX8 expression was positive in our cases. Interestingly, melanotic Xp11 neoplasm harboring the MED15-TFE3 fusion gene have been reported with negative expression for PAX8 and positive expression for Cathepsin K and HMB45 (19). Similar to previous studies about MED15-TFE3 RCC, we found that CK7 and CA-IX were frequently negative expression in tumor cells. Cathepsin K was regarded as the transcriptional target of the MiT family. The expression of Cathepsin K varies in different subtypes of Xp11 translocation RCCs, and has certain specificity. The marker is often positively expressed in PRCC-TFE3 RCC, while negatively in SFPQ-TFE3, ASPL-TFE3 and NONO-TFE3 RCC(35). Among all studies about MED15-TFE3 RCC, the positive and negative expression of Cathepsin K was observed in 6 and 3 cases (including our 2 cases), respectively. Hence, the expression of Cathepsin K in MED15-TFE3 RCC is uncertain, further reports with large sample size are needed. Cystic structure, psammoma body, and typical TFE3 positive staining may help to the diagnosis of MED15-TFE3 RCC.

However, it has been reported that the positive staining of TFE3 is not a specific manifestation of Xp11 translocation RCC, which can also be found in other types of RCCs (36). To confirm the existence of TFE3 translocation in our cases, TFE3 break-apart FISH assay was used. The assay was regarded as the golden standard for the diagnosis of Xp11 translocation RCC in recent years (10, 22). Distinct from the negative FISH result induced by intrachromosomal inversion, the MED15-TFE3 RCC show the typical positive FISH results in our cases. Considering the unusual morphological features and imaging findings of Xp11 translocation RCC in our cases, we carried out RNA sequencing to conclusively confirm the presence of MED15-TFE3 fusion gene.

Until now, there is no special drug for treating Xp11 translocation RCCs, and surgery remains the first choice for patients with early stage (10). Considering the aggressive behavior and poor prognosis in Xp11 translocation RCCs, radical nephrectomy was performed in most cases (21). No matter which surgical method is selected, the prognosis of patients with MED15-TFE3 RCC is excellent in current studies. In our previous study of Xp11 translocation RCC, we proven that nephron-sparing surgery should be taken into considering for the patient with cT1a tumor. However, for the patient with cT1b tumor, radical nephrectomy may be the priority choice of the surgery (28). This opinion may not be applicable in the patient with MED15-TFE3 RCC. Due to the excellent prognosis of patients, we speculate that nephron-sparing surgery could still be recommended as the preferred surgical method, even for patients with cT1b tumors.

The study had several limitations as well. Firstly, the small patient number limits the authenticity of our conclusions. Secondly, due to the high-throughput RNA-sequencing has not been routinely conducted in clinical work, most studies did not categorize Xp11 translocation RCCs according to the fusion partner. Therefore, the miss diagnosis of MED15-TFE3 RCC may limit the generalizability of conclusions.

Conclusion

In the study, we reported two cases of Xp11.2 translocation RCC with MED15-TFE3 gene fusion confirmed by RNA-sequencing. One of the cases was the first reported pediatric patient with renal hilar lymph node metastasis. MED15-TFE3 RCC is morphologically distinct from typical Xp11 translocation RCC, the represented cystic-solid structure is common shown in such tumor. Different from the poor prognosis of patients with traditional Xp11 translocation RCC, patients with MED15-TFE3 RCC tend to have an excellent prognosis. The distinctive features of MED15-TFE3 RCC deepen our understanding on heterogeneity of Xp11 translocation RCC.

Abbreviations

RCC: renal cell carcinoma; MiT: microphthalmia-associated transcription factor; FFPE: formalin-fixed paraffin-embedded; FISH: fluorescence in situ hybridization; CT: computer tomography

Declarations

Ethics approval and consent to participate

The research has been approved by the Ethics Committee of Nanjing Drum Tower Hospital. All participants signed written informed consent in the study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they had no competing interests.

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Authors' contributions

XD: writing, editing, conception. WG: data collection, assembly of the data. PZ: data collection. JP: editing. HG: conception, design. WG: design, supervision, review. All authors approved the final manuscript.

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Figures

Figure 1

CT images of patient 1 (A and B) and patient 2 (C and D). The mixed cystic-solid lesion at the lower pole of right kidney was shown in cross-sectional (A) and coronal (B) CT images. The giant cystic-solid lesion fills the right retroperitoneal space (C). The enlarged lymph node was observed at the right hilum (D).

Figure 2

Pathological findings in MED15-TFE3 RCCs. Typical cystic structures were shown in the tumor tissue (A). Tumor cells were round or oval in shape and arranged in cords or nests, containing abundant eosinophilic or clear cytoplasm (B-C). Obvious psammoma bodies were visible (D).

Figure 3

Typical pictures of IHC and FISH in MED15-TFE3 RCCs. Both cases showed the positive expression of TFE3 protein (A-B). The tumor cells were negative for Cathepsin K in both cases (C-D). A pair of separated (green and red) signals and a fused (yellow) signal could be detected by FISH assay in our cases (E-F).

Figure 4

RNA-sequencing results of the two patients. A fusion of TFE3 (donor end: chrX: 48893183) and MED15 (acceptor start: chr22: 20927885) was detected in patient 1 (A). A fusion of TFE3 (donor end: chrX: 48893141) and MED15 (acceptor start: chr22: 20927823) was detected in patient 2 (B).