Case Report

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Renal cell carcinoma associated with Xp11.2 translocation/transcription factor E3 gene fusion: an adult case report and literature review

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Abstract

Renal cell carcinoma (RCC) associated with Xp11.2 translocation/transcription factor E3 (*TFE3*) gene fusion is a rare and independent subtype of RCC included in the classification of MiT (microphthalmia-associated transcriptional factor) family translocation RCC. Herein, we report an adult case of Xp11.2 translocation RCC, and review the relevant literature to improve our understanding of the pathogenesis, epidemiology, clinical manifestations, diagnosis, differential diagnosis, treatment, and other aspects of the disease.

Keywords

Xp11.2/TFE3 associated renal cell carcinoma, TFE3+, immunohistochemical staining, chromosomal rearrangement, fluorescence in situ hybridization, prognosis

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Introduction

Renal cell carcinoma (RCC) associated with Xp11.2 translocation/TFE3 gene fusion is a rare and independent subtype of RCC, with high malignant potential. In 2016, this type of RCC was included in the

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new category of MiT (microphthalmia-associated transcriptional factor) family translocation RCC.[1–4] The origin of the name of this disease reflects the fact that it is characterized by fusions involving the *TFE3* gene, located on chromosome Xp11.2, which leads to overexpression of the TFE3 protein in the nucleus of cancer cells.[5] Clinical studies have shown that the incidence of TFE3-related RCC is very low in adults, accounting for about 0.9% to 4% of cases of kidney cancer,[1,6–8] and the incidence ranges from 15% to 75% of cases of kidney cancer in children and adolescents.[1,9] Because of the rarity of this disease in adults, our understanding of its pathogenesis and treatment is incomplete.

This case report presents an adult patient with TFE3-related RCC who underwent left retroperitoneal laparoscopic partial nephrectomy. The pathologic diagnosis demonstrated MiT family translocation RCC:Xp11.2/TFE3-related RCC. We also review the relevant literature to supplement our understanding of the clinical features, pathologic findings, diagnosis, and differential diagnosis for this distinctive RCC.

Case Report

A 38-year-old male patient was admitted to the Urology Center of the First Hospital of Jilin University, (Changchun, Jilin, China) because of a left renal mass found incidentally on magnetic resonance imaging (MRI) 25 days before admission. His medical history was significant for a 12-year history of chronic hepatitis C, for which he received standard medical treatment, including 1 year of interferon therapy. Therapy was discontinued once the patient's serum glutamic pyruvic transaminase and glutamic-oxaloacetic transaminase indicators normalized. At follow-up, 25 days before the current presentation and hospitalization, the patient underwent routine physical examination in his local hospital. Bilateral kidney evaluation on MRI plus third-phase enhancement showed round abnormalities in the middle inferior region of the left kidney. The size of renal mass was 2.4 cm × 1.8 cm, and the boundaries of the tumor were clearly defined; the lesion was slightly strengthened in contrast enhancement. Where no further detail was observed in the enhancement phase, small circular structures with multiple long T1 and long T2 signals were seen bilaterally. The patient was then referred to our hospital.

After hospital admission, computed tomography (CT) of the urinary system (Figure 1) revealed a mass of slightly elevated density in the middle of the left kidney (CT value of about 50 Hounsfield units (HU)). Several small, cystic, low-density, liquid shadows in the left kidney and a nodule shadow in the lower pole of the left kidney were visualized as well. No renal hilar lymphadenopathy was seen on CT imaging, and no distant metastases were found by general imaging examination. Based on these results, a clinical diagnosis was made of left renal cancer, stage I (cT1aN0M0), according to the American Joint Committee on Cancer staging

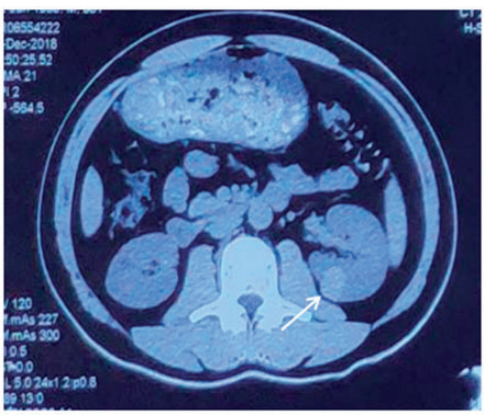

Figure 1. Unenhanced axial computed tomography on admission revealed a middle and lower left renal mass (white arrow) as a shadow of slightly high density.

guidelines (7th edition). Left retroperitoneal partial nephrectomy by laparoscopy was performed. During the operation, a 2-cm tumor protruding 1 cm from the surface of the left renal parenchyma was seen in the middle of the kidney. The left renal mass and surrounding tissues were removed successfully. The patient recovered well after surgery and had minimal blood drainage. The patient was discharged home after the drainage tube was removed on postoperative day 4. During the follow-up period, more than 1 year after discharge, the patient remained disease free without recurrence.

Postoperative pathology images are shown in Figure 2. Grossly, the tumor section, gray white and light brown with solid and soft texture, was about 2.2 cm × 2 cm × 0.5 cm, and the tumor was confined to the renal capsule. Microscopic evaluation with hematoxylin and eosin stain showed the tumor cells with clear or eosinophilic cytoplasm and obvious nucleoli, formed as a papillary structure. No infiltration of cancer cells was detected in the vessels, nerves, or peripheral cutting edges. Left MiT family translocation RCC:Xp11.2 translocation/TFE3 gene fusion RCC was diagnosed, with nuclear grade 3, according to the 2016 World Health Organization (WHO)/International Society of Urological Pathology (ISUP) classification, and pTNM:T1a by the 2017 American Joint Committee on Cancer guidelines (8th edition). Immunohistochemical features are shown in Figure 3, with positive staining for TFE3, vimentin, CD10, P504S, PAX8, CK-pan (scattered) and negative staining for CK7 and carbonic anhydrase IX. Results of TFE3 break-apart fluorescence in situ hybridization (FISH) assay on paraffin-embedded tissue are shown in Figure 4, demonstrating the split in red and green signals that indicates the *TFE3* gene rearrangement.

This case report was an individual retrospective study; thus, approval by the ethics committee was not required. Oral informed consent was obtained from the patient.

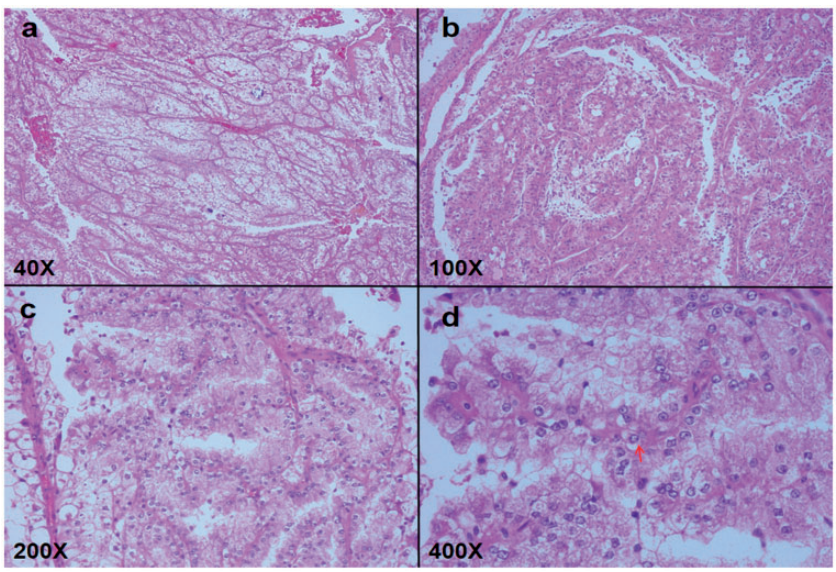

Figure 2. Pathologic views showing clear or eosinophilic cytoplasm of tumor cells, obvious nucleoli (red arrow), and papillary structures formed from tumor cells.

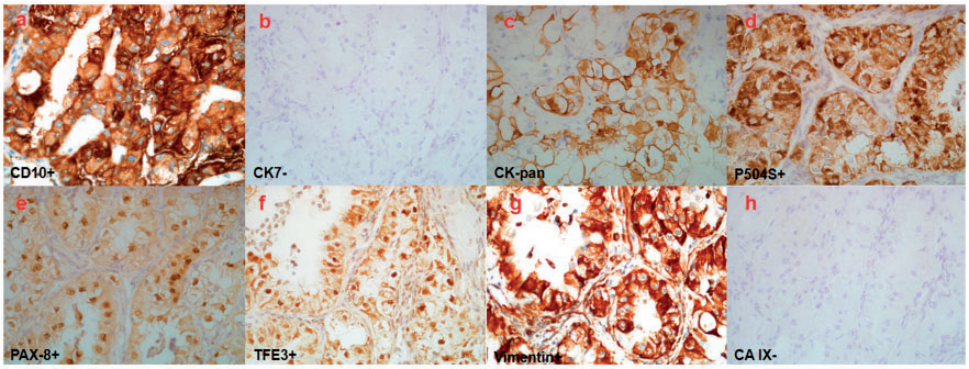

Figure 3. Representative immunohistochemical (IHC) images (a–f) of sections from the renal mass. Transcription factor E3 (TFE3), CD10, P504S, PAX8, vimentin, and cytokeratin (CK) were highly expressed, whereas CK7 and carbonic anhydrase IX (CA IX) were not expressed (400× magnification).

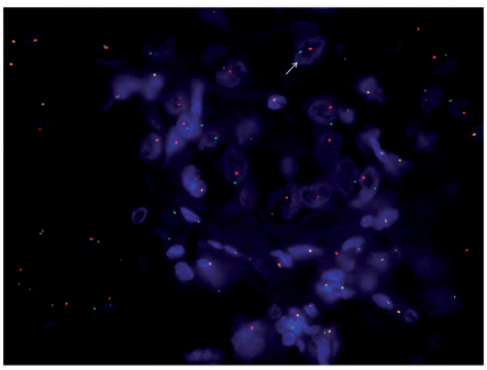

Figure 4. Transcription factor E3 (TFE3) fluorescence in situ hybridization (FISH) assay on paraffin-embedded tissue showing the split red and green signals (white arrow) indicating *TFE3* gene rearrangement (1000× magnification).

Discussion

The initial report by Tomlinson et al. of RCC being associated with Xp11.2 translocation/TFE3 gene fusion was in a 17-month-old child.[10] Since then, both adult and adolescent cases have been found worldwide. This genetic disease is caused by increased TFE3 expression as a result of translocation of the *TFE3* gene on chromosome Xp11.2,[1] and it is associated with cytotoxic chemotherapy in pediatric patients.[11] Table 1 shows currently identified translocations and fused genes that involve *TFE3*; the number of such gene fusions will increase as in-depth study of this disease proceeds. Clinically, the most common types of gene fusions are the first three: t(X;1)(p11.2;q21.2), with the *PRCC* gene; t(X;17)(p11.2;q25) with the *ASPL* gene (also called *ASPSCR1*); and t(X;1)(p11.2;p34) with the *SFPQ* gene (also called *PSF*).[1] It is worth noting that the same *ASPL-TFE3* fusion gene is involved in alveolar soft part sarcoma, which may be related to an imbalance of the translocation mechanism.[12,13] The translocation mechanism of TFE3 fusion is heterogeneous, which explains the diverse cytology and pathology of the disease.[1]

Clinical features

The symptoms of Xp11.2/TFE3-associated RCC are the same as those of clear cell renal carcinoma (ccRCC) and papillary RCC (PRCC), including hematuria, painless abdominal mass, and lumbago on the affected side.[1,5] However, approximately one-third of the cases of this genetic disease are asymptomatic. For example, in the adult case reported here, the tumor was discovered incidentally by MRI during physical examination. Clinical studies have

Table 1. Translocations resulting in gene fusion in Xp11.2 translocation renal cell carcinoma.

Chromosome translocation	Gene fusion	Reference
t(X;1)(p11.2;q21.2)	*PRCC-TFE3*	Argani et al., 2002[14]
t(X;17)(p11.2;q25)	*ASPL* (*ASPSCR1*)-*TFE3*	Rakheja et al., 2005[15]
t(X;1)(p11.2;p34)	*SFPQ* (*PSF*)-*TFE3*	Haudebourg et al., 2010[16]
t(X;17)(p11.2;q23)	*CLTC-TFE3*	Argani et al., 2003[17]
t(X;3)(p11.2;q21)	*PARP14-TFE3*	Huang et al., 2015[18]
t(X;10)(p11.2;q23)	Unknown	Caliò et al., 2019[1]
t(X;17)(p11.2;q21.33)	*LUC7L3-TFE3*	Malouf et al., 2014[19]
t(X;19)(p11.2;q13.3)	*KHSRP-TFE3*	Malouf et al., 2014[19]
t(X;17)(p11.2;p13)	*DVL2-TFE3*	Argani et al., 2016[20]
t(X;22)(p11.2;q11.21)	*MED15-TFE3*	Wang et al., 2018[21]
t(X;6)(p11.2;q25.3)	*ARID1B-TFE3*	Antic et al., 2017[22]
t(X;5)(p11.2;q31.2)	*MATR3-TFE3*	Wang et al., 2018[21]
t(X;1 (p11.2;p31.1)	*FUBP1-TFE3*	Wang et al., 2018[21]
t(X;11)(p11.2;q13.1)	*NEAT1-TFE3*	Pei et al., 2019[23]
t(X;10)(p11.2;q22.2)	*KAT6B-TFE3*	Pei et al., 2019[23]
inv(X)(p11.2;q12)	*NONO* (p54nrb)-*TFE3*	Clark et al., 1997[24]
inv(X)(p11.2;p11.3)	*RBM10-TFE3*	Argani et al., 2017[25]
inv(X)(p11.23;p11.23)	*GRIPAP1-TFE3*	Classe et al., 2017[26]

ASPSCR1, alveolar soft part sarcoma chromosome region, candidate 1; *SFPQ*, splicing factor proline- and glutamine-rich protein; *PSF*, PTB-Associated splicing factor; *PTB*, polypyrimidine tract binding protein; *CLTC*, clathrin heavy chain; *PARP14*, poly(ADP-ribose) polymerase family member 14; *LUC7L3*, LUC7 like 3 pre-mRNA splicing factor; *KHSRP*, KH-type splicing regulatory protein; *DVL2*, disheveled segment polarity protein 2; *MED15*, mediator complex subunit 15; *ARID1B*, AT-rich interaction domain 1B; *MATR3*, matrin 3; *FUBP1*, far upstream element binding protein 1; *NEAT1*, nuclear paraspeckle assembly transcript 1; *KAT6B*, K (lysine) acetyltransferase 6B; *NONO*, non-POU domain containing octamer binding; *RBM10*, RNA binding motif protein 10; *GRIPAP1*, GRIP associated protein 1; *GRIP*, glutamate receptor interacting protein 1.

shown that the incidence of Xp11.2/TFE3-related RCC is very low in adults, accounting for only 0.9% to 4% of kidney cancer cases,[1,6–8] and from 15% to 75% of pediatric kidney cancer cases.[1,9] Its prevalence in adults might be underestimated because of the morphologic overlap with the more common adult RCC subtype.[1,27] Tumors in children and adolescent patients tend to be less aggressive and thus have a more favorable prognosis. Although our case was a young man, this tumor type occurs more often in women. According to retrospective studies, the incidence of Xp11.2/TFE3-related RCC has a female-to-male ratio of 1.6–3.6:1. Although it is more common in children and adolescents, the sex difference is not evident in pediatric patients.[1,28]

Pathologic features

Pathologic features are critical to the diagnosis of Xp11.2 translocation RCC. Grossly, the tumor usually presents as a unilateral isolated mass, with tan-yellow or brownish-yellow cut surfaces, sometimes accompanied by hemorrhage, necrosis, or occasionally an unusual cystic structure.[28] Microscopically, Xp11.2/TFE3-related RCC has a unique structural feature; namely, clearly demarcated papillary and nest-like structures composed of epithelial cells. The cells contain transparent to eosinophilic cytoplasm, obvious nucleoli, and psammoma bodies. Some solid, nested, trabecular, and microcystic pattern structures have been reported in the literature, and these structural variations may be

associated with the different chromosomal translocations involved.[8,29] Xp11.2/TFE3-related RCC usually has the following immunohistochemical characteristics: PAX8+, vimentin+, P504S+, CK7−, carbonic anhydrase IX−, and CD10+. Positive immunostaining of the TFE3 protein was initially the gold standard diagnostic test for this type of hereditary RCC, with conventional ccRCC and PRCC being negative for TFE3.[2,7,28,30] However, diagnosis is now confirmed by the more accurate gene karyotype detection and FISH analysis based on paraffin-embedded sections or formalin-fixed tissue.

FISH analysis

Because of common false-positive or false-negative results in TFE3 immunostaining, the diagnosis of the *TFE3* gene rearrangement by FISH is now the gold standard for Xp11 translocation RCC.[31] A dual-color, break-apart FISH assay has been widely used to recognize the chromosomal translocations involving the *TFE3* gene.[32,33] This assay can detect gene translocations quickly and accurately, and it can be applied in paraffin-embedded tissue sections.[1,34] The typical break-apart signals of *TFE3* gene translocation are shown as a pair of split red and green signals in the nucleus, whereas the normal result on FISH is a fused hybridization signal.[33] However, recent studies have found that FISH assays can show false-negative or subtle positive results in some cases, caused by intrachromosomal inversions involving *TFE3*. The proximity of the genes involved in the *TFE3* rearrangement explains these equivocal results, especially rearrangements involving *NONO*, *GRIPAP1*, *RBMX*, and *RBM10*.[33,35] Therefore, RNA sequencing or other molecular techniques may be needed to confirm equivocal cases.[19]

Differential diagnosis

In the differential diagnosis with other types of RCC, Xp11.2/TFE3-related RCCs have more variability in clinical manifestations because of the heterogeneity of their tissue structure, especially in children and adolescents.[27] In some cases, because it is difficult to distinguish PRCC from ccRCC by clinical features, it is important to use multiple immunohistochemical markers in combination with pathologic findings. For example, Xp11.2/TFE3-related RCC and ccRCC can be identified by CK7, CD10, and carbonic anhydrase IX. Cathepsin K is a relatively reliable immunohistochemical marker for Xp11.2/TFE3-related RCC, being expressed in 47% of those patients with this disease.[1] CD10 is expressed in almost all TFE3 tumors and ccRCC, and although carbonic anhydrase IX is positive in conventional ccRCC (TFE3−, cathepsin K−, CD10+, carbonic anhydrase IX+), it is almost never expressed in Xp11.2 translocation RCC (TFE3+, cathepsin K+, CD10+, carbonic anhydrase IX−).[1,36] In addition, RCC associated with Xp11.2 translocation/TFE3 gene fusions can be differentiated from PRCC by alpha-methylacyl COA racemase (AMACR) and CK7. AMACR tends to be positive in RCC with *TFE3* gene fusions and PRCC, and CK7 is negative in RCC with *TFE3* gene fusions but positive in PRCC (TFE3−, AMACR+, CK7+).[1] In contrast, Xp11.2/TFE3-related RCC has a more distinctive papillary and nest-like structure with well-circumscribed boundaries, as well as a large number of clear to eosinophilic cancer cells with gritty bodies.[5,27,36] All of these characteristics help differentiate RCC with *TFE3* gene fusions from common types of RCC.

In the differential diagnosis of other rare renal masses, immunohistochemistry and copy number assessment can assist with the clinical diagnosis. The differential diagnosis of mixed epithelial stromal tumor of the

kidney has characteristic immunohistochemical results: positive for PAX8, PAX2, and CK7 in epithelial cells, and positive for smooth muscle actin, CD10, and estrogen and progesterone receptors in the stromal component.[31,37,38] Mucinous tubular and spindle cell carcinoma is associated with multiple genetic alterations. Copy number assessment is a useful method in differential diagnosis, commonly showing multiple chromosomal losses involving chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22, and without gains of chromosomes 7 and 17.[31,39] This tumor also demonstrates that CK7 is usually positive in immunohistochemical staining. Fumarate hydratase-deficient RCC is another rare renal neoplasm, and it can be identified by negative immunostaining for fumarate hydratase.[31]

Prognosis and treatment

The prognosis of Xp11.2 translocation RCC is highly variable, from being less aggressive in children and adolescents[1,5,27] to exhibiting rapidly aggressive behavior in adults.[8,40] Previous cases have shown that patients with Xp11.2 translocation RCC usually have poor prognosis after lymph node metastasis.[7,41,42] Overall, compared with other types of RCC, TFE3-associated RCC is more malignant than PRCC and roughly equivalent to ccRCC.[8,27] Because the number of previously reported cases is not large, a greater understanding of the prognosis of this disease is needed.

Treatment of Xp11.2 translocation RCC is not yet optimal. Surgery remains the main treatment for patients without distant metastasis, which is the same treatment as for ccRCC, because this disease is diagnosed by postoperative pathology in most cases. In general, for a localized MiT family RCC, surgery is the only curative treatment, with the goal of clear margins to improve oncological outcomes. Nephron-sparing surgery should be considered in case of cT1 neoplasms because renal tumors can be completely removed along the pseudocapsule, which permits negative surgical margins to be obtained.[3,43,44] For patients with metastatic Xp11.2 translocation RCC, adjuvant therapies such as targeted therapy and immunotherapy are being tested. Recent studies have shown that vascular endothelial growth factor receptor-targeted agents and mammalian target of rapamycin inhibitors have positive effects in the treatment of metastatic TFE3 RCC.[45–49] Other targeted agents and immune checkpoint inhibitors are currently being tested and developed.[50–52] In general, because of the small sample sizes to date and the unclear mechanisms of disease, the best therapeutic methods combining immunotherapy and targeted therapy have not yet been fully determined.

Conclusions

Overall, the incidence of Xp11.2 translocation RCC is relatively low, especially in adults, and the clinical features and underlying mechanisms of the disease have not been fully clarified. We share an adult case here, which may help urologists understand the disease better. This case report and literature review may provide a better understanding of this rare renal cancer, and contribute to developing a more favorable treatment that will improve the long-term survival rate for patients. Based on current research trends, targeted therapy may improve tumor-free survival and quality of life of patients with Xp11.2-associated RCC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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