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Xp11.2 translocation renal neoplasm with features of *TFE3* rearrangement associated renal cell carcinoma and Xp11 translocation renal mesenchymal tumor with melanocytic differentiation harboring *NONO-TFE3* fusion gene

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ABSTRACT

Xp11.2 translocation/*TFE3* rearrangement-associated renal cell carcinoma (RCC) and Xp11 translocation renal mesenchymal tumor are distinct tumor entity. To broaden the spectrum of Xp11 neoplasms, we investigated a novel tumor exhibiting morphologies overlapping Xp11.2 translocation/*TFE3* rearrangement-associated RCC and the mesenchymal counterpart with melanocytic differentiation by immunohistochemistry, fluorescence in situ hybridization (FISH) and RNA sequencing, as well as literature review. Histologically, the tumor was composed of three different types of tumor cells, including a large proportion of clear cells, small round cells, and a few spindle cells, presenting a relatively clear border in the majority area. The nuclei of all tumor cells showed extensively and strong positive expressions of *TFE3*. Whereas, the clear cells positively expressed the RCC-related markers including PAX8, RCC marker and CD10, and negatively expressed HMB45; On the contrary, the small round cells and spindle cells positively expressed melanocytic marker HMB45, and negatively expressed PAX8, RCC marker and CD10. The ki67 index was higher in the small round cells and spindle cells than that in the clear cells. FISH revealed the rearrangement of TFE3 gene in all the three types of cells. The *NONO-TFE3* fusion gene was detected in all tumor cells by RNA sequencing. This unique Xp11 translocation-associated neoplasm might represent a distinct entity overlapping Xp11 translocation RCC and the mesenchymal counterpart with melanocytic differentiation, broadening the spectrum of Xp11 neoplasms. The patient died of tumor recurrence and lung metastasis after seven months after the surgery suggesting those tumors have an unfavorable prognosis.

1. Introduction

Xp11.2 translocation/ *TFE3* rearrangement-associated renal cell carcinoma (RCC) was a relatively uncommon renal carcinoma, which was first categorized into MiT family translocation renal cell carcinoma as a unique entity in 2004 WHO [1]. Xp11.2 translocation RCC comprises approximately 40% of pediatric RCC but less than 4% of adult RCC. *TFE3* gene, located on chromosome Xp11.2, is one member of the micropathalima-associated transcription factor family with the other three members *TFEB*, *TFEC*, and *MiTF*. Besides, Xp11.2 translocation/ *TFE3* rearrangement could be detected in some mesenchymal tumors including TFE3 rearrangement-associated perivascular epithelioid cell tumor (PEComa), Xp11 neoplasm with melanocytic differentiation, and alveolar soft part sarcoma [2–9]. Xp11 translocation RCC and the corresponding mesenchymal neoplasms are distinct entities due to their different morphologies, immunophenotypes and clinical characteristics. Herein, we investigated a rare Xp11.2 translocation tumor which contained both epithelial and mesenchymal elements displaying features of RCC and mesenchymal tumor with melanocytic differentiation, which had not been reported in the literature up till now. We aimed to provide new insight into the Xp11.2 translocation/*TFE3* rearrangement-associated tumor and broaden the spectrum of this relatively rare tumor.

2. Materials and methods

2.1. Materials

A rare case exhibiting different morphologies including Xp11.2

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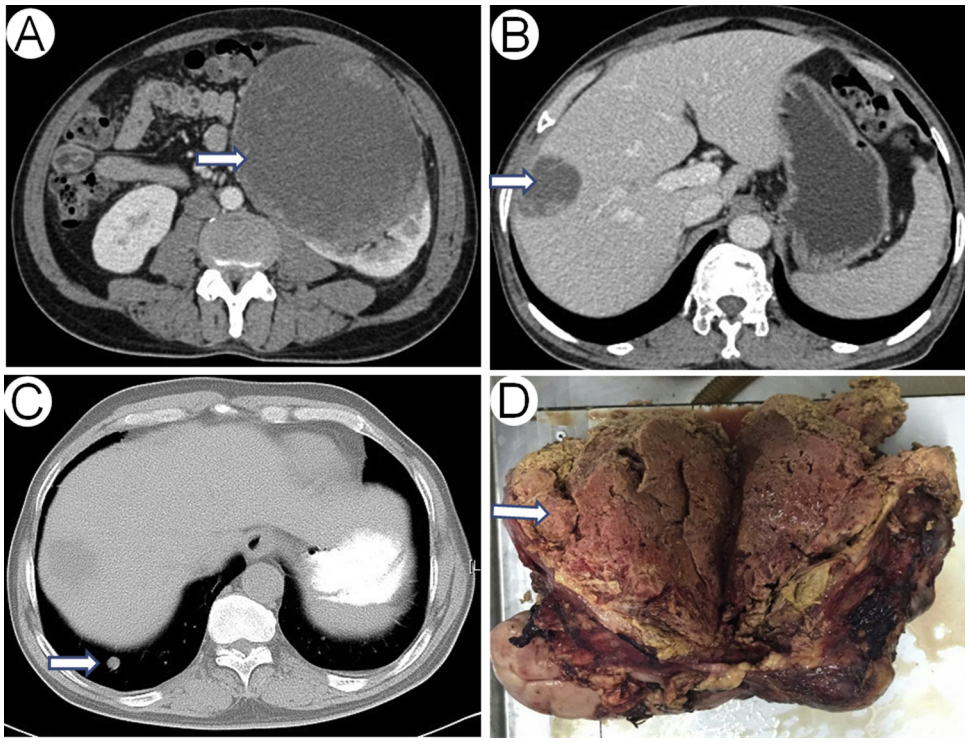

Fig. 1. The computed tomography and gross features of the tumor. A: Computed tomography showed an inhomogeneous mass (15 × 14 cm) in the left kidney. A plenty of retroperitoneal lymph nodes were enlarged. B: Multiple masses were found in the liver. C: A tumor metastatic nodule was identified in the lung after seven months of the surgery. D: Grossly, a tumor of 15 cm in diameter was identified in the upper polar of the left kidney. The cut surface of the tumor was gray-white or gray-yellow with a large area of necrosis.

translocation/*TFE3* rearrangement-associated RCC and the mesenchymal counterpart with melanocytic differentiation was observed under microscope after *H*&*E* staining. The clinicopathological data was collected accompanied with literature review.

2.2. Immunohistochemistry (IHC)

A set of 4 μm-thick sections cut from 4% neutral formalin-fixed, paraffin-embedded block of tumor tissues was used for IHC study. The sections were immunostained with the antibodies against TFE3 (Cellmarque, MRQ-37), PAX8 (Ventana, MRQ-50), RCC marker (Ventana, PN-15), CD10 (Ventana, SP67), alpha-methylacylCoA racemase (AMACR) (Ventana, polyclonal), Melanoma (Ventana, HMB45), vimentin (Ventana, V9), CAIX (Ventana, polyclonal), TFEB (Abcam, polyclonal), Melan A (Ventana, A103), Cathepsin K (Maixin, polyclonal), cytokeratin (CKpan) (Ventana, AE1/AE3), Low Molecular Cytokeratin (Zhongshan, CAM5.2), epithelial membrane antigen (EMA) (Ventana, E29), cytokeratin-7 (CK7) (Ventana, SP52), Ksp-cadherin (Maixin, MRQ-33), E-cadherin (Maixin,4A2C7), CD117 (Ventana, 9.7), P53 (Ventana, DO-7), SMA (Ventana, 1A4), LCA (Ventana, RP2/18), ALK (Ventana, D5F3), CD56 (Maixin,123C3.D5), CgA (Maixin, SP12), synaptophysin (syn, Ventana, MRQ-40), CD99 (Maixin, 013), Fli1 (Maixin, G146-22), Myogenin (Maixin, F5D), and Ki67 (Ventana, 30-9). All IHC assays were performed on the Roche BenchMark XT fully automatic IHC/ISH instrument using ultraViewTM DAB detection kit (Ventana, Arizona, America) with optimized protocols, except TFE3, for which a manual method was applied using an overnight incubation according to the literature [10]. Positive and negative controls were used in this study.

2.3. Fluorescence in situ hybridization (FISH)

Two different paraffin-embedded blocks picking from 30 blocks, one of which was merely composed of clear tumor cells, and the other was only consisted of small round cells and spindle cells, were chosen to detect the *TFE3* gene in different types of cells by FISH. Two 4 μm-thick sections were hybridized with a dual-color break-apart *TFE3* probe, a homebrew dual color break-apart probe (donated by Professor Qiu Rao, Nanjing Jinling Hospital) was used following the instruction of the kit [11]. FISH patterns were established by assessing 200 interphase tumor cells. Rearrangement of *TFE3* gene was considered present if > 50% of nuclei showed FISH signal patterns of separated 1 red, 1 green and/or 1 fused signals (1R1G1F), or separated 2 red and 2 green singles (2R2G), indicating the split of the TFE3 gene based on the instruction of the probe kit as well as the established standard in the literature [11].

2.4. RNA sequencing

RNA sequencing was applied to screen the fusion gene with *TFE3* using the same paraffin-embedded blocks as those used in FISH analysis. Total RNA was extracted after xylene deparaffinization using the RNeasy formalin-fixed paraffin-embedded kit (QIAGEN). Ribosomal RNA was depleted using RNase H followed by library preparation using the KAPA Stranded RNA-seq Kit (KAPA Biosystems). Library concentration was examined using a KAPA Library Quantification Kit (KAPA Biosystems), and the library quality was accessed using an Agilent High Sensitivity DNA kit and Bioanalyzer 2100 (Agilent Technologies). RNA sequencing was performed on Illumina HiSeq next-generation sequencing (NGS) platforms (Illumina). Three tools, including Fusion-Catcher (version 0.99.4e), Factera and Socrates (https:// github.com/ jibsch/ Socrates) were applied for the detection of any potential fusion gene with TFE3 from RNA-sequencing data. The results were manually reviewed on the Integrative Genomics Viewer [12].

3. Results

3.1. Clinical manifestations

The patient was a 57-year-old man who presented fever with the left flank paroxysmal blunt pain without any cause three months ago. No other special clinical symptom was identified. Computed tomography showed an inhomogeneous mass (15 × 14 cm) in the left kidney (Fig. 1A). A plenty of retroperitoneal lymph nodes were enlarged. In

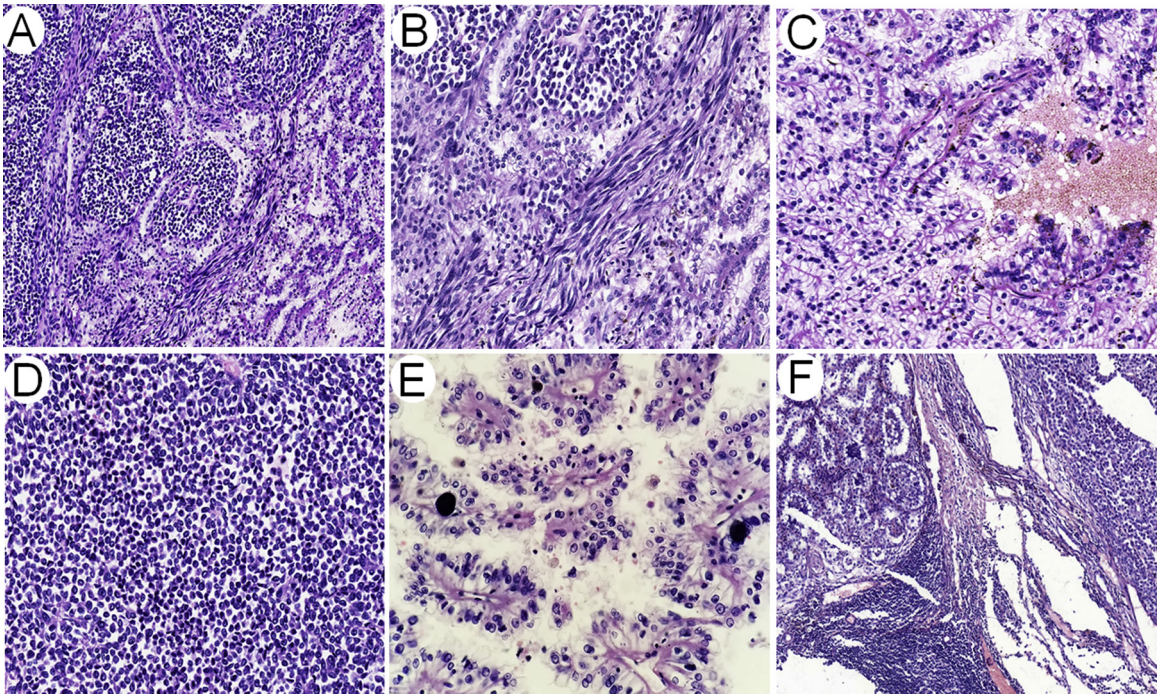

Fig. 2. The histological features of the tumor. A: Histologically, the tumor was composed of three different types of tumor cells, including the clear cells, small round cells and some spindle-shaped fibroblast-like cells. The three cellular components seemed to present a relatively clear border, and focally interpenetrated. (*H&E* × 100). B: The highlight of the morphologies and distributions of the three types of cells (H&E × 200). C: The clear cells had clear cytoplasm, round nucleus arranging in glandular, tubular, cystic or papillary structures. The nuclei were of WHO/ISUP Grade 2 and most lined towards the lumen and far away from the basal membrane. D: The small round cells had rare cytoplasm and round, deep staining nuclei arranging in solid sheets mimicking sarcoma. (H&E × 200) E: A few psammoma bodies focally scattered in the stroma of the clear cells. (H&E × 400) F: The tumor cells, including clear cells, small round cells and spindle cells metastasized to lymph nodes. (H&E × 100).

addition, multiple masses were found in the liver, suggesting that the tumor had metastasized to the retroperitoneal lymph nodes and liver (Fig. 1B). The patient had no past medical history of malignancy. Then he underwent left-radical nephrectomy and scavenging of regional lymph nodes by laparoscopic surgery. Unfortunately, the patient died of tumor recurrence and lung metastasis of the tumor (Fig. 1C) after seven months after the surgery.

3.2. Pathology examinations

Grossly, a large tumor of 15 cm in diameter was identified in the upper polar of the left kidney. The renal capsule, mucous membrane of renal pelvis and renal portal vein were all involved. The cut surface of the tumor was gray-white or gray-yellow with a large area of necrosis (Fig. 1D).

Histologically, the tumor was composed of three different types of tumor cells presenting totally distinct morphologies including the clear cells, small round cells and spindle cells (Figs. 2A, B and 3 A). The clear cells accounting for 45% of the tumor had vacuole cytoplasm, round nuclei and homogeneous chromatin, arranging in glandular, tubular, cystic or papillary structures. The nuclei were of WHO/ISUP Grade 2, which most lined towards the lumen and far away from the basal membrane, mimicking the pattern of secretory endometrium or clear cell papillary RCC (Fig. 2C). The small round cells took up a large proportion (about 50%) of the tumor presenting rare cytoplasm, round and deep staining nuclei, which arranged in solid sheets mimicking sarcoma (Fig. 2D). A few spindle-shaped fibroblast-like cells arranged in fascicular clusters which made up approximately 5% of the tumor. A small amount of psammomatous calcifications focally scattered in the stroma of the clear cells (Fig. 2E). The boundaries between the three types of tumor cells were clear, and the cells focally interpenetrated. Focal necrosis mainly occurred in small round cells. A plenty of tumor thrombi were detected in the vessels of the stroma. In addition, the tumor cells, including clear cells, small round and spindle cells metastasized to 4 lymph nodes among the 13 dissected ones (Fig. 2F).

3.3. Immunohistochemical results

The three types of tumor cells without exception showed extensive and strong positivity for TFE3 (Fig. 3B). However, PAX8 (Fig. 3C), RCC marker (Fig. 3D), CD10, p504 s, HMB45 and Ki67 displayed different expression panels in the three types of cells. The clear cells positively expressed some immunomarkers related to RCC including PAX8, RCC marker, CD10 and p504 s, while negatively expressed melanocytic marker HMB45, which was partially consistent with the immunophenotype of RCC. On the contrary, the small round cells and spindle cells positively expressed melanocytic marker HMB45 (Fig. 3E), while negatively expressed the RCC related markers such as PAX8, RCC marker, CD10 and p504 s, consistent with the panel of Xp11 translocation-associated mesenchymal neoplasm with melanocytic differentiation. Notably, the ki67 index differed greatly between the clear cells (about 4%), small round cells and spindle cells (about 60%). (Fig. 3F) (Table 1).

3.4. Genetic analysis

TFE3 gene was detected by FISH in clear cells, small round cells and spindle cells, separately. FISH results showed a separated red and green signal in the most nuclei of the clear cells, small round cells and spindle cells, which indicated the rearrangement of *TFE3* gene in all the three types of cells (Fig. 4A, B). Then RNA sequencing results revealed the identical gene rearrangement containing the fusion of *TFE3* (exon 6) and *NONO* (exon 7) in the three different cellular elements (Fig. 4C, D).

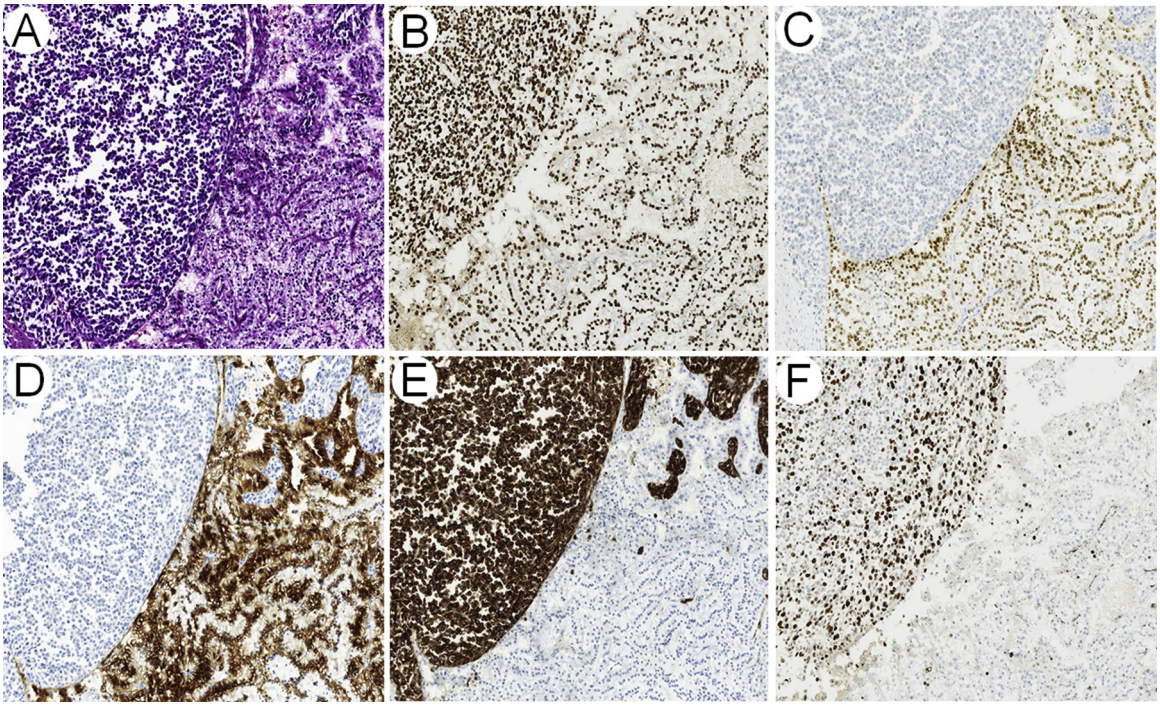

Fig. 3. The histological features and immunophenotypes of different cellular elements. A: The *H&E* staining clearly outlined the clear cells and small round cells; B: The immunohistochemical results showed that the nuclei of all tumor cells presented extensively and strong positive expressions of TFE3; C: PAX8 was positively expressed in the clear cells, but negatively expressed in the small round cells; D: The clear cells exhibited positive immunoreactivity for RCC marker, but the small round cells displayed negative immunoreactivity for RCC marker; E: The small round cells positively expressed melanocytic marker HMB45, but the clear cells negatively expressed HMB45; F: The ki67 index was higher in the small round cells than that in the clear cells. (The expression panel of the spindle cells is identical to the small round cells. That was not shown here.) (100×).

Table 1
The immunophenotypes of the clear cells, small round cells and spindle cells.

	Clear cells	Small round cells and spindle cells
TFE3	strong +	strong +
PAX8	strong +	-
RCC marker	strong +	-
CD10	strong +	-
P504s	strong +	-
HMB45	-	strong +
Vimentin	-	focal +
CAIX	-	-
TFEB	-	-
MelanA	-	-
CathepsinK	-	-
Ckpan	focal +	-
CAM5.2	focal +	-
EMA	-	-
CK7	-	-
Ksp-cad	-	-
E-cad	-	-
CD117	-	-
P53	-	-
SMA	-	-
LCA	-	-
ALK	-	-
CD56	-	-
CgA	-	-
Syn	-	-
CD99	-	-
Fli1	-	-
Myogenin	-	-
Ki67	4%	60%

3.5. Pathology diagnosis

Xp11.2 translocation renal neoplasm with features of *TFE3* rearrangement associated renal cell carcinoma and Xp11 translocation renal mesenchymal tumor with melanocytic differentiation harboring *NONO-TFE3* fusion gene.

4. Discussion

An increasing number of Xp11 translocation-associated neoplasms, including Xp11 translocation RCCs and the mesenchymal counterparts such as *TFE3* rearrangement-associated perivascular epithelioid cell tumor (PEComa), Xp11 neoplasm with melanocytic differentiation, and alveolar soft part sarcoma have been gradually identified. Xp11 translocation-associated neoplasms harbor fusion genes involving four members (*TFE3*, *TFEB*, *TFEC* and *MiTF*) of the MiT family of transcription factors. The MiT family genes contain similar DNA binding domains, which could combine certain DNA with specific structure, and modulate the expressions of multiple related genes and proteins, and then facilitate the tumorigenesis. *TFE3* gene could fuse with one of multiple reported genes including *NONO*, *ASPL*, *PRCC*, *PSF*, *CLTC*, *SFPQ*, *LUC7L3*, *KHSRP*, *PARP14*, *DVL2*, *RBM10*, *MED15*, *GRIPAP1*, and a plenty of unidentified genes [13,14], which lead to the over expression of *TFE3* protein to promote the tumorigenesis and result in various tumors with distinct morphologies and clinical characteristics.

The impact of individual fusion variant on specific clinicopathologic features of Xp11 translocation-associated neoplasms just have been recently reported [14]. Morphologically, a wide spectrum could be seen in Xp11 translocation RCCs, presenting alveolar, nested or papillary architecture, with clear or eosinophilic cytoplasm, prominent nucleoli or psammoma bodies, sometimes like the morphologies of clear cell RCC, papillary RCC, and collecting duct carcinoma and spindle cell [15]. Immunohistochemically, Xp11 translocation RCCs consistently express TFE3, PAX8, PAX2, RCC marker and CD10, like most clear cell RCC and papillary RCC [16]. Different from the common RCC, epithelial markers such as cytokeratin and epithelial membrane antigen

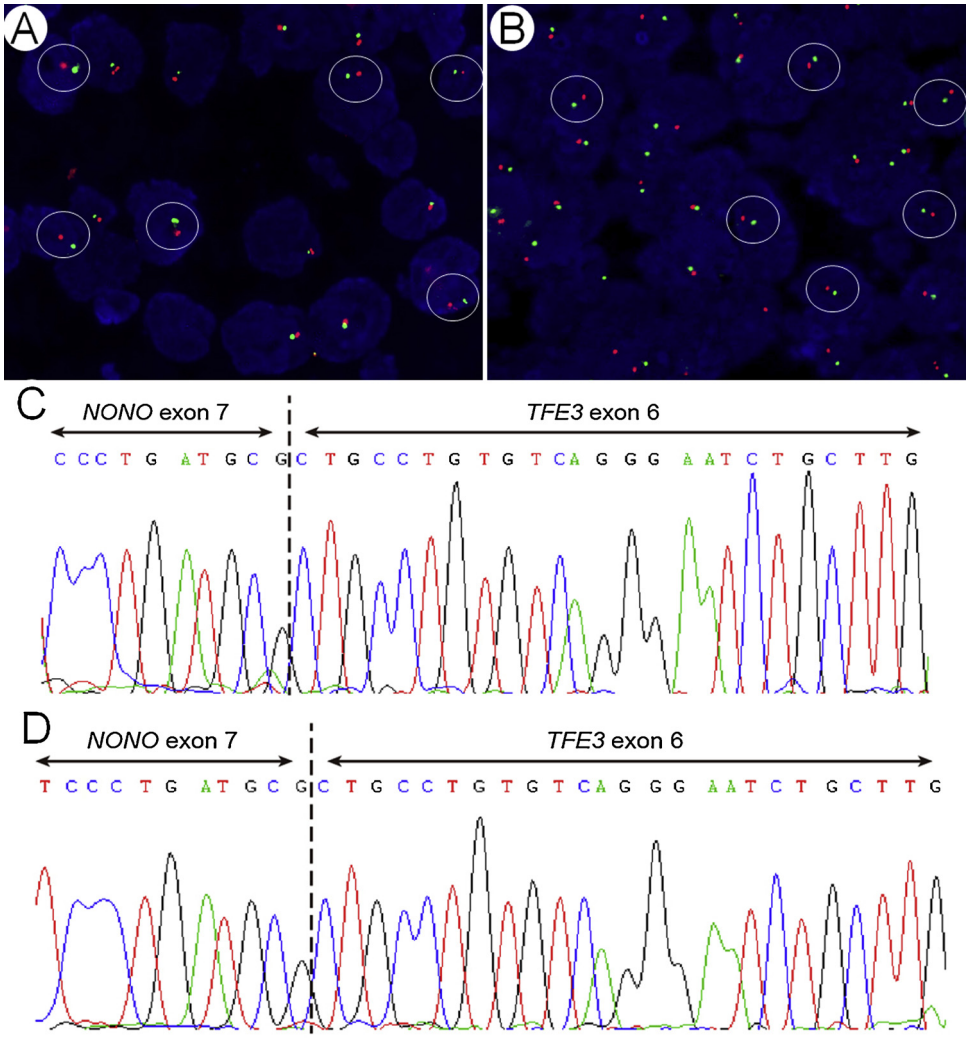

Fig. 4. FISH and RNA sequencing results. FISH analysis showed a separated red and green signal in the most nuclei of the clear cells (A), the small round cells and spindle cells (B), which revealed the rearrangement of TFE3 gene in all the three cellular elements. RNA sequencing results revealed the same fusion gene fused by NONO (exon 7) and TFE3 (exon 6) in the clear cells (C), as well as in the small round cells and spindle cells (D).

(EMA) are typically unexpressed, and vimentin might not be positive. Xp11 translocation-associated mesenchymal neoplasms, such as *TFE3* rearrangement-associated PEComa, Xp11 neoplasm with melanocytic differentiation, and alveolar soft part sarcoma mainly display nested or sheet structures separated by delicate vascular networks and are mostly composed of epithelioid cells containing clear or granular eosinophilic cytoplasm, well differentiated spindle cells or fat component, round or oval nuclei containing small nucleoli, and melanin pigments in some cases. Immunohistochemically, the mesenchymal neoplasms often exhibit positive immunoreactivity for TFE3, HMB45, Melan-A and Cathepsin K, whereas the other immunomarkers including RCC related markers (PAX8, PAX2, RCC Marker and CD10), and epithelial markers (CKpan and EMA) are nonreactive to these tumors [15].

In the present case, the clear tumor cells have round nuclei and homogeneous chromatin, arranging in glandular, tubular, cystic or papillary structure, with most nuclei lining towards the lumen and far away from the basal membrane, mimicking the pattern of secretory endometrium or clear cell papillary RCC. The clear cells positively expressed PAX8, RCC marker, CD10 and p504 s, and negatively expressed melanocytic marker HMB45, which is partially consistent with the morphology and immunophenotype of clear cell RCC. However, the clear cells showed the growth pattern of secretory endometrium or clear cell papillary RCC, and negative immunoreactivity to Vimentin, both of which were different from usual clear cell RCCs. Moreover, usual RCCs rarely metastasize to lymph nodes, and preoperative metastasis to lymph nodes is suspicious of Xp11.2 RCC. Except for the clear cells, there were a variety of small round cells with rare cytoplasm and round, deep staining nuclei, which arranged in solid sheets mimicking sarcoma. Besides, there were a small amount of spindle-shaped fibroblast-like cells arranging in fascicular clusters among the clear cells and small round cells. Interestingly, both the small round cells and spindle cells presented negative expressions of PAX8, RCC marker, CD10 and p504 s, but positive expression of HMB45, and the latter was a reliable immunomarker for melanocytic differentiation. It is notable, the three kinds of tumor cells could not be categorized into the same tumor entity based on the entirely different morphologies and immunophenotypes. FISH results showed the rearrangement of *TFE3* gene in all the three types of cells, and RNA sequencing identified the identical *NONO-TFE3* fusion gene in all the three cellular elements. Despite the different morphologies, the basic pathogenesis of them might be in common because they all presented similar gene rearrangement and fusion. Based on the identical fusion gene but distinct morphologies and immunophenotypes, the diagnosis of Xp11.2 translocation renal neoplasm with features of *TFE3* rearrangement associated renal cell carcinoma and Xp11 translocation renal mesenchymal tumor with melanocytic differentiation harboring *NONO-TFE3* fusion gene might be appropriate [17]. Other tumors, such as clear cell RCC with sarcomatous differentiation, primitive neuroectodermal tumor (PNET), neuroendocrine

neoplasm or rhabdosarcoma should be considered as the differential diagnosis. Immunohistochemistry could facilitate the differential diagnosis. The sarcomatous elements in the clear cell RCC with sarcomatous differentiation frequently expressed CA IX, CD10 and PAX8 without the expression of HMB45 [18]. The negative expressions of CD99, Fli1, CD56, synaptophysin, chromogranin and myogenin could help to exclude the diagnosis of PNET, neuroendocrine neoplasm or rhabdosarcoma, even though there were some overlaps in the morphology of those tumors with the present case. Especially, we for the first time reported the small round cell tumor with *TFE3* rearrangement harboring *NONO-TFE3* fusion gene, different from previously depicted small round cell tumors, which included PNET, neuroendocrine neoplasm, rhabdosarcoma and small cell lymphoma. It is difficult to differentiate them based on the morphology due to the similar uniform small round cells. However, the specific immunostaining panels could be useful to distinguish them.

It is interesting that the epithelial and mesenchymal elements appeared simultaneously in the tumor. This unique morphology had not been reported in the literature up till now. The most common fusion genes in melanotic Xp11 translocation renal cell carcinoma, Xp11 neoplasm with melanocytic differentiation, *TFE3* rearrangement-associated PEComa were *SFPQ-TFE3*, *NONO-TFE3* and *DVL2-TFE3* [19]. *NONO-TFE3* fusion gene appearing in the present case indicated that epithelial and mesenchymal tumors might occur simultaneously in Xp11 translocation-associated neoplasm harboring *NONO-TFE3* fusion gene. Argani et al concluded five cases NONO-TFE3 RCC and one case NONO-TFE3 PEComa with Melanin Pigment. Morphologically, four of five cases NONO-TFE3 RCC demonstrated psammomatous calcifications and a pattern with sub-nuclear vacuoles mimicking clear cell papillary RCC [3], both of which could also be obviously observed in our case. By immunohistochemistry, all five cases were immunoreactive for PAX8 and CA IX, but none expressed cathepsin K, similar to our cases. In addition, in Argani's report, the morphology of NONO-TFE3 PEComa was a nested epithelioid neoplasm, with clear granular eosinophilic cytoplasm and abundant melanin pigment, being positive for cathepsin K, but not for PAX8. However, in our case, the mesenchymal elements were not immunoreactive for cathepsin K. It was really MiTF-TFE family transcription factors regulated cathepsin K expression, and tumors which expressed MiTF, frequently exhibited cathepsin K labeling. However, depending on the cellular context, the presence of MiTF-TFE family transcription factors alone might not be sufficient to induce cathepsin K expression [20]. As far as our case is concerned, the special cellular context including both epithelial and mesenchymal elements and distinct genetic background might be related to the negative expression of Cathepsin K.

Since the three cellular elements showed similar gene alterations, the underlying mechanisms why they presented different morphologies remained unknown. To further elucidate the mechanisms, we detected some immunomarkers related to epithelial and mesenchymal transformation of tumor cells. Whereas, the clear cells, small round cells and spindle cells all presented negative expressions of EMA and E-cadherin, which indicating that the concurrent appearance of the epithelial and mesenchymal morphologies might not be due to the epithelial and mesenchymal transformation. The concurrent epithelial and mesenchymal elements possibly arise from the same multipotential tumor stem cells but differentiated towards distinct directions. Another speculation was that they might be independent tumors coming from distinct orientations and just occurred concurrently in the same tumor. However, the underlying mechanisms needed further investigation.

It was reported the overall outcome of Xp11 translocation RCC was like clear cell RCC, but it was significantly better than that of the mesenchymal counterpart, the latter frequently experiencing recurrence and metastases or death of tumor [2,21]. In the present case, the patient died of tumor metastasis after seven months after the surgery, probably suggesting an unfavorable prognosis of those tumors. Therefore, it was necessary to distinguish these two kinds of elements, especially when they occurred simultaneously in the kidney.

In conclusion, we described an unusual case of Xp11.2 translocation renal neoplasm with features of *TFE3* rearrangement associated renal cell carcinoma and Xp11 translocation renal mesenchymal tumor with melanocytic differentiation harboring *NONO-TFE3* fusion gene. Given the different morphologies, immunophenotypes and prognostic features, our study manifested that Xp11 translocation RCC was distinct from the corresponding mesenchymal neoplasm despite the identical *NONO-TFE3* fusion gene. This unique Xp11 translocation-associated neoplasm might represent a distinct entity, which overlaps Xp11 translocation RCC and the mesenchymal counterpart, broadening the spectrum of Xp11 translocation-associated neoplasm and improving the recognition of these tumors.

Author contributions

Wenjuan Yu designed the research study and wrote the paper. Yuewei Wang performed some research studies. Qiu Rao carried out the molecular study. Yanxia Jiang analyzed the pictures and data. Wei Zhang collected the clinicopathological data and performed some research studies. Yujun Li contributed essential reagents and tools.

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