Case Report: Clinical complete response of advanced renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion by treated by camrelizumab and axitinib: A rare case report

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Renal cell carcinoma (RCC) associated with Xp11.2 translocation/TFE3 gene fusions is a rare subtype of renal tumor. This entity predominantly occurs in juveniles, but rarely in adults. Xp11.2 translocation RCC (tRCC) patients with lymph node or organ metastasis are associated with poor prognosis, and the strategy remains controversial. Herein, we presented our experience with the diagnosis and treatment of an adult case of Xp11.2 tRCC. In our clinical practice, a 32-year-old male manifested fever and right flank paroxysmal blunt pain, and computed tomography showed an inhomogeneous mass, 6 cm in diameter, in the right kidney. Then right partial nephrectomy (PN) and renal hilar lymph node dissection by laparoscopic surgery were performed. Pathology revealed that the tumor cells were positive for TFE3 immunohistologically and positive for TFE3 break-apart fluorescence in situ hybridization assay. A splice site mutation c.1544-1G>T of protein tyrosine phosphatase receptor delta (PTPRD) was detected by next-generation sequencing and weak PTPRD expression was confirmed in tumor tissues compared to tumor periphery. This patient was diagnosed with stage III RCC and received immune checkpoint inhibitor (camrelizumab) in combination with tyrosine kinase inhibitor (axitinib) treatment for 1 year. He achieved a clinical complete response with no sign of recurrence or metastasis.

PTPRD mutation might be a favorable indicator for Xp11.2 tRCC patients managed by PN and followed by the adjuvant therapy of immune checkpoint inhibitor and tyrosine kinase inhibitor.

KEYWORDS
immunotherapy, PD-1, tyrosine kinase inhibitor, Xp11.2 translocation renal cell carcinoma, PTPRD-mutation
Introduction

Xp11.2 translocation renal cell carcinoma (tRCC) is generally a pediatric renal cell carcinoma (RCC), accounting for 20%–40%, while relatively rare in adult RCC, only 1%–1.6% (Bruder et al., 2004; Kmetec and Jeruc, 2014). Xp11.2 tRCC was officially recognized as a distinct entity in 2004 and had been reported as being more aggressive and having a poorer prognosis compared with conventional RCC (Bruder et al., 2004; Qiu et al., 2010). This entity of RCC is generally characterized by a range of translocations on chromosome Xp11.2 leading to a gene fusion between TFE3 and at least six possible partners (Klatte et al., 2012; Sun et al., 2021a). The diagnosis of Xp11.2 tRCC is based on some immunohistochemical markers, such as TFE3, and fluorescent in situ hybridization (FISH) rather than histological characteristics and imaging examination (Calio et al., 2019). Although several studies revealed genomic and transcriptomic characteristics of this entity of RCC, the optimal strategy for Xp11.2 tRCC remains controversial. With its aggressive biological behavior and local invasion tendency in adults, Xp11.2 tRCC tends to present with lymphatic and distant metastasis at diagnosis. To date, there is not yet a consensus regarding therapy (Calio et al., 2019). Surgical resection achieved favorable outcomes for early disease (He et al., 2015; Liu et al., 2016). However, adult patients at the advanced stage had worse outcomes even with postoperative adjuvant monotherapy (He et al., 2015; Liu et al., 2016). We herein report a rare case with Xp11.2 tRCC treated with partial nephrectomy (PN) and followed by camrelizumab in combination with axitinib, with 18 month follow-up.

Case presentation

The patient was a 32-year-old man who manifested fever and right flank paroxysmal blunt pain. No other special clinical symptom was identified. Computed tomography (CT) showed an inhomogeneous mass, 6 cm in diameter, in the right kidney, and multiple lymph nodes enlargements were found adjacent to inferior vena cava and abdominal aorta (Figures 1A,B) and no evidence of distant organ metastasis. The patient had no past medical history of malignancy. Glomerular filtration rate (GFR) of the right kidney was 49 ml/min/1.73 m², and 68 ml/min/
Representative images of the postoperative pathological features of the analyzed tumors. (A) HE (hematoxylin and eosin) staining of tumor sample, 200x. (B) HE staining of metastatic hilar lymph nodes sample, 200x. (C) Tumor cells display TFE3 nuclear positive. (D) TFE3 break-apart probe assay identified split signals, 1,000x. (E) Ki67 expression. (F) PAX-8 expression. (G) CD10 expression. (H) CD117 expression. (I) CA9 expression. (J) HMB45 expression (Images E-J have a magnification at 200x).
1.73 m² on the left, which showed decreased kidney function on the right side (Webster et al., 2017). As there were no contraindications to surgery, the patient then underwent right PN and scavenging of enlarged lymph nodes by laparoscopic surgery on 9 Oct 2020. Intraoperatively, a well-circumscribed solid mass, 6 cm in diameter, was identified in the upper part of the right kidney and multiple hilar and inferior vena cava lymph nodes were scavenged (Figure 1C). The cut surface of the tumor was gray-white or gray-yellow with a large area of necrosis (Figure 1D).

Postoperative pathological examination revealed that the case was considered to be Xp11.2 translocation/TFE3 gene fusions associated with RCC, with a size of 6 × 5.5 × 5 cm³, and the right renal hilar lymph node was confirmed with metastases (Figures 2A,B). The tumor observed was in pT1bN1M0, stage III according to AJCC Cancer Staging Manual, presenting WHO/ISUP Grade 3 of nuclear grade. Immunohistochemistry (IHC) results revealed positive for TFE3, almost the entire neoplastic cell nuclei stained positive with moderate (2+) to strong (3+) staining intensity (Figure 2C). FISH results showed a separated red and green signal in most nuclei of the tumor cells, which indicated the rearrangement of the TFE3 gene (Figure 2D). Immunohistochemical staining showed positive for Ki67 (15%), PAX-8, and CD10 (Figures 2E–G), and negative for CD117, CA9, and HMB45 (Figures 2H–J).

Next, we performed genomic profiling with a multi-gene next-generation sequencing (NGS) panel (Onco Panscan™, Genetron Health) to identify any genetic alterations that might be relevant to the prognosis of this tumor. A splice site mutation c.1544-1G>T of protein tyrosine phosphatase receptor delta (PTPRD) was detected, which is localized in the splice acceptor site of intron 21 of the PTPRD gene. Sequencing results are presented in Figure 3A. We suppose this PTPRD c.1544-1G>T variant could probably impair PTPRD splicing and cause premature termination of protein transcription. And then, we performed IHC of anti-PTPRD by using a tumor sample. Weak PTPRD expression was confirmed in the tumor sample (Figure 3B, upper part) compared to the tumor periphery (Figure 3B, lower part). Previous studies have reported that the inactivation of PTPRD can promote angiogenesis and metastasis and is associated with a high malignant phenotype (Solomon et al., 2008; Bae et al., 2019). Then, we could predict the aggressive behavior of this tumor. Therefore, we decided to perform postoperative adjuvant therapy to treat the remaining enlarged lymph node adjacent to the abdominal aorta and to prevent the progression of the tumor.

Regarding the results from several clinical studies, combination immunotherapy with target therapy is superior to monotherapy in the treatment of advanced renal cancer. KEYNOTE-426, a phase 3 clinical trial, showed superior efficacy of immune checkpoint inhibitor (pembrolizumab) plus tyrosine kinase inhibitor (axitinib) over sunitinib monotherapy in treatment-naïve, advanced renal cell carcinoma (Rini et al., 2019; Powles et al., 2020; Qu et al., 2021). Then, after 2 weeks of surgery, the patient was given a

![FIGURE 3](https://example.com/figure3.png)

**FIGURE 3**

NGS-based identification of PTPRD mutation and PTPRD expression of the analyzed tumors. (A) NGS-based identification of the c.1544-1G>T mutation. (B) PTPRD expression in tumor sample (upper part) and tumor periphery (lower part), 200x.
novel anti-PD-1 antibody (camrelizumab, 200 mg) intravenously once every 3 weeks, 16 cycles for about 1 year plus axitinib (5 mg) orally twice daily for 1 year. Mild adverse events (grade 1–2) were only observed in the 1st–2nd cycle of treatment, which includes periodontitis, abdominal distension, and mild to moderate diarrhea. During the rest cycles of the treatment, no other treatment-related adverse events were observed. The patient underwent periodic follow-up examinations, including laboratory tests and CT every 3 months. PET-CT was performed on the 12th month postoperatively, which indicated neither lymph node enlargement adjacent to the aorta nor remote organ metastases (Figures 4A,B), indicating a clinical complete response. Until now, the patient is currently alive without recurrence or metastasis 18 months after surgery and the GFR of the right kidney was 39 ml/min/1.73 m², 58 ml/min/1.73 m² on the left, which showed most preservation of kidney function. This patient is still on further follow-up without medication.

**Discussion**

Xp11.2 tRCC typically affects children, with a one-third incidence in juveniles and 1%–1.6% incidence in adults (Bruder et al., 2004; Sukov et al., 2012; Kmetec and Jeruc, 2014). Xp11.2 tRCC in adult patients may be associated with advanced stages, large tumors, and may present with metastatic disease with poor prognosis (Qiu et al., 2010; Qu et al., 2016). As Xp11.2 tRCC has no specific macroscopic appearance, and clinically most tumors resemble clear cell RCC (Armah and Parwani, 2010). Unlike pediatric RCC, cytogenetics is not routinely performed for adult RCC due to the relatively lower incidence rate, which results in most misdiagnoses as conventional RCC. The diagnosis of Xp11.2 tRCC relies on morphological features, IHC findings, and molecular pathological analysis (Calio et al., 2019). TFE3-IHC has the advantages of rapid diagnosis, economy, and high sensitivity in diagnosing Xp11.2 tRCC. Thus, TFE3-IHC can be performed proactively as a screening test, and FISH can be performed as a verification test. Hirobe et al. suggested that the combination of TFE3-IHC and FISH is an effective method to diagnose Xp11.2 tRCC, which can improve specificity and potentially eliminate false positives resulting from overstaining (Hirobe et al., 2016). In this case, the results of positive immunostaining of TFE3 and positive TFE3 break-apart FISH assay, as well as positive CD10 and negative CD7, CD117, led to the ultimate diagnosis of Xp11.2-TFE3 tRCC (Calio et al., 2019).

**PTPRD** mutation was detected by NGS and reduced PTPRD expression was confirmed in tumor cells in this study. PTPRD belong to the protein tyrosine phosphatases family and function as a tumor suppressor in human cancers (Zhao et al., 2015). Cox et al. provided the first evidence that PTPRD was identified as a frequent target of deletion in human cancers (Cox et al., 2005). Subsequent studies further showed somatic mutations of **PTPRD** were identified in colorectal cancer, lung cancer, glioblastoma, and melanoma (Sjoblom et al., 2006; Weir et al., 2007; Solomon et al., 2008; Veeriah et al., 2009). Inactivation of **PTPRD** was linked to malignancy in glioma and melanoma (Solomon et al., 2008; Ortiz et al., 2014). Deleterious mutations of **PTPRD** are associated with bad prognosis in lung cancer patients (Sun et al., 2021a). Furthermore, with regard to protein expression, reduced PTPRD expression was found in tumor tissue in several cancers including renal cancer which was associated with a bad prognosis (Li et al., 2011; Bae et al., 2019). On the contrary, overexpression of PTPRD suppressed colon cancer cell migration, suggesting that gain of PTPRD could suppress tumor metastasis (Veeriah et al., 2009).
The evidence seen is consistent with the notion that PTPRD normally functions as a tumor suppressor. Our case found a splice site mutation c.1544-1G>T of PTPRD, which probably impairs PTPRD splicing and causes premature termination of protein transcription. And then reduced PTPRD expression was displayed in the tumor sample compared to the tumor periphery (Figure 3B). Based on the aforementioned evidence, we assumed this case may associate with a poor prognosis.

Current treatment for Xp11.2 tRCC is still controversial. The treatment recommended for Xp11.2 tRCC is mostly based on small retrospective studies and similar to conventional RCC. Surgical intervention plays an important role and is currently focusing on organ preservation; however, this is based upon tumor localization and institutional experience (He et al., 2015; Calio et al., 2019). Adult patients at an advanced stage had poorer outcomes even with postoperative adjuvant monotherapy (He et al., 2015; Liu et al., 2016). Choueiri et al. reported that only three patients (20%) could achieve a partial response when treated with anti-angiogenesis targeted therapy, which appeared to demonstrate some efficacy for adult patients with metastatic Xp11.2 RCC (Choueiri et al., 2010). Immune checkpoint inhibitors (ICI) represent a novel class of drugs used in metastatic RCC, however, experience in advanced Xp11.2 tRCC is limited. Clark et al. reported that patients with tRCC patients showed better outcomes when treated with ICI than those treated with anti-angiogenesis therapy (Clark et al., 2019). In a retrospective analysis by Boilèве et al., the median PFS for tRCC patient.

Data availability statement

The original contributions presented in the study are included in the article supplementary materials, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed earlier have contributed sufficiently to be included as authors. All of the authors had full access to the data for this study and take full responsibility for the integrity of the data. JZ and DX conceived and designed the study. JD, CF, and DX performed the surgery. JX was responsible for the pathological diagnosis. KD and NC were responsible for NGS detection and assembly of data. JZ and KD drafted the manuscript. All of the authors revised the article critically, gave
final approval of submission, and agreed to be accountable for all aspects of the work.

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Conflict of interest

Author KD and NC were employed by Hangzhou Jichenjunchuang Medical Laboratory Co., Ltd.

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