The preliminary experiences of translocation renal cell carcinoma and literature review

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Received 5 August 2013; accepted 7 January 2014
Available online 17 April 2014

Abstract Xp11.2 translocation renal cell carcinoma (RCC) is rare and predominantly found in children and young adults. Because of the property of overexpressed transcription factor E3 (TFE3) fusion protein, immunohistochemical (IHC) staining with TFE3 antibody makes an excellent diagnostic tool. This study analyzed preliminary experiences of eight Xp11.2 translocation RCCs in our institution between 2007 and 2012. In four males and four females with a mean age of 28.4 years. Xp11.2 translocation RCCs were diagnosed. TFE3 IHC stain was positive in all tumor specimens. As the initial presentation, four patients suffered from abdominal pain, three cases had gross hematuria, and one case had hemoptysis caused by existing lung metastasis. The tumor was located in the right kidney (75%) with mean diameter of 5.85 ± 2.64 cm. Three cases (38%, 3/8) presented with lymph node metastasis at the time of diagnosis. In five cases (63%, 5/8), the initial diagnosis was Stage III and IV. Treatment included open surgery (one partial nephrectomy and five radical nephrectomies), cryoablation, immunotherapy, and target therapy. The mean follow-up time was 32 months. One patient died after 23.4 months of follow-up. The application of TFE3 IHC stain will improve the diagnostic accuracy for detecting XP11.2 translocation renal cell carcinoma. Surgery or cryoablation both had excellent prognosis in early stages. Although the disease is believed to be indolent, an increasingly aggressive clinical course should be kept in mind, especially for children and young adults.

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Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Renal translocation carcinomas of the kidney were first described as aggressive tumors in the pediatric literature [1]. The renal cell carcinoma (RCC) associated with Xp11.2 translocation / transcription factor E3 (TFE3) gene fusion was delineated as a distinct entity in the 2004 World Health Organization renal tumor classification [2]. Large reports have shown that overall incidence of Xp11.2 translocation RCCs is low (0.9%) and predominantly occurring in children and young adults younger than 40 years of age, accounting for about one-third of pediatric RCCs [3–5]. In contrast, conventional clear cell RCCs make up about 15% of RCCs in children, 53% in young adults, and 70% in adults [2,6]. However, there are few large case series reporting this new entity; thus, the clinical manifestations, biological behavior, histopathological features, and prognosis are still poorly understood. Because only a few cases have been described in Taiwan, we share our preliminary experiences and literature review in the Xp11.2 translocation RCCs as follows, by: (1) determining the incidence of RCCs associated with the Xp11.2 translocation and TFE3 expression in our institute; (2) characterizing its clinical behavior and survival; and (3) discussing possible treatment and outcome [7].

Materials and methods

With Institutional Review Board approval for retrospective chart review between 2007 and 2012, there were eight cases in which Xp11.2 translocation RCCs were diagnosed within 754 unilateral, sporadic RCC cases at our institution. Further immunohistochemical (IHC) studies with TFE3 staining were performed on tumors found in younger patients and/or showed microscopic features suspicious of Xp11.2 translocation RCC. The score of TFE3 IHC stain was from 0 to 3+ as previously described [8]. A tumor scored as positive was subdivided into moderate (2+) and strong (3+), based on the staining intensity. Weak to equivocal (1+) nuclear staining in combination with no (0) staining was considered negative for TFE3 expression [8].

The surgical indication is according to the European Association of Urology (EAU) guidelines, in which partial nephrectomy for tumors smaller than 7 cm, cryoablation for tumors smaller than 7 cm, and radical nephrectomy for tumors larger than 7 cm are suggested. General history, initial presentation of disease, imaging studies (contrast-enhanced computed tomography, magnetic resonance imaging), and characteristics of the tumor (location, size) were all recorded [9–13]. The histopathological characteristics (tumor stage, Fuhrman nuclear grade, and score of TFE3 IHC stain), treatment methods (surgery, immunotherapy or target therapy), and clinical outcome were analyzed.

Results

The incidence of Xp11.2 translocation RCC was approximately 1.06% in our series. There were four males and four females with mean age 28 ± 9.3 years without systemic disease. Demographic and clinical characteristics of the patients are summarized in Table 1. The chief complaints included abdominal pain in four cases, gross hematuria in three cases, and hemoptysis in one case. The tumors were located over the right kidney in six cases (75%) and on the left side in two cases (25%). The mean diameter of the tumors was 5.8 ± 2.6 cm and the mean volume was 80 ± 71 mL. Three cases (37.5%) were found to have lymph node metastasis at the time of diagnosis. Two and one cases were at early Stages I and II, respectively. In five cases (63%, 5/8), the diagnosis of advanced Stages III and IV was made at the time of presentation. Treatments and clinical outcomes are recorded in Table 2. Four cases underwent open surgery (one partial nephrectomy because the diameter of the tumor was smaller than 7 cm and the technique feasible, and four radical nephrectomies because the tumor was larger than 7 cm or difficult resection because the tumor was located near the renal hilum) and three patients received retroperitoneoscopic cryoablation. In the cryotherapy group, an initial diagnosis of benign tumors by biopsies performed twice was made in one case (case No. 4). Finally, radical nephrectomy was done with the definite diagnosis of Xp11.2 translocation RCC because of tumor progression in size. Case No. 7 chose retroperitoneoscopic cryoablation because of a small renal tumor (T1a) and a rapid recovery was needed for the patient to attend the university entrance examination; she has been cancer-free after 11.6 months of follow-up. One case (No. 6) with initial presentation of a small renal mass with lung metastasis was undergoing salvage cryoablation for cytoreductive therapy before further immunotherapy with interleukin-2 (IL-2), and has maintained a stable disease condition after 15.5 months. The average follow-up period after treatment was 29.7 ± 20 months (range, 11.6–70.2 months). One patient (case No. 2, initial T3aN1) with retroperitoneal and Virchow lymph node metastasis underwent cytoreductive nephrectomy and immunotherapy ( interferon-α) with a sequence of target therapies (sunitinib, sorafenib, temsirolimus). However, she expired after 23.4 months of follow-up with a progression-free survival time of 14.3 months. The remaining seven cases were still alive, even though two developed recurrence in the lymph nodes and one was stable with lung metastasis.

Because of the limited follow-up period and small case numbers, there were no significant differences among cancer characteristics and disease-free survival [age <30, >30], p = 0.655; sex , p = 0.317; BMI <20, 20–25, ≥25, p = 0.779; largest diameter <4, 4–7, 7–10, p = 0.607; stage, p = 0.801; and treatment method (open method, cryotherapy), p = 0.655].

Microscopically, Xp11.2 translocation RCCs showed tumor cells arranged in papillary and nested architecture with voluminous clear to eosinophilic cytoplasm (Fig. 1). TFE3 IHC stain was performed in all eight cases and all revealed positive nuclear labeling. The score of TFE3 IHC stain was 2+ in three tumors and 3+ in the remaining five tumors. The tumors categorized by Fuhrman grade revealed Grade 2 in two cases, Grade 3 in four cases, and Grade 4 in two cases (Table 1).
Discussion

The Xp11.2 translocation RCC, an uncommon renal carcinoma arising in children and young adults, was categorized as a new entity in the 2004 World Health Organization classification of renal tumors. There are TFE3 gene fusions with PRCC, ASPSCR-1 and PSF at t(X;1)(p11.2;q21), t(X;17)(p11.2;q25) and t(X;1)(p11.2;p34), respectively [14,15]. Because of the property of over-expressed TFE3 fusion protein, IHC staining with TFE3 antibody makes a useful auxiliary diagnostic tool to differentiate other subtypes of RCC morphologically overlapping with translocation RCC [2,4,8,16]. The microscopic features, including papillary or nested (alveolar, compact) or mixed architecture, voluminous eosinophilic to clear cytoplasm, presence of calcification and hyalinization, and high Fuhrman nuclear grade, may mimic clear cell or papillary RCC [4,8].

However, there is one report indicating occasional false-positive or false-negative staining results of TFE3 may hinder accurate diagnosis [17]. Therefore, another diagnostic approach, such as cathepsin-K IHC stain, TFE3 break-apart fluorescence in situ hybridization (FISH) assay and reverse transcription polymerase chain reaction (RT-PCR), might serve as additional utilities for cases with histological features of translocation RCC but with negative or equivocal TFE3 immunostaining [17–21].

Adult Xp11.2 translocation RCCs account only for an incidence of 1.6–5% in all renal neoplasms, but RCCs in pediatric/young adult (younger than 45 years) had 15% Xp11.2 translocation RCC in proportion [16,22]. Many adult RCCs do not receive routine TFE3 IHC stains, and are misclassified as other subtype of RCCs. The real incidence of adult Xp11.2 translocation RCCs may be underestimated. Cryopreservation of tumor samples will help in further cytogenetic analysis, RT-PCR, or FISH if it is positive for TFE3 stain. Most adult Xp11.2 translocation RCCs also had poor prognosis with initial metastasis or early metastasis [23,24]. In our study, in all patients the diagnosis was made at a younger age (mean 28 years old). Series have reported mean tumor size ranging from 6.8 to 9.2 cm in the largest diameter, which is larger than the 5.8 cm in our series [4,23,25].

The radiological characteristics determine subtype of RCCs with the degree of enhancement, enhancement pattern, and the contents of the tumor, such as calcification, fat, necrosis, or hemorrhage. The translocation RCCs have higher attenuating lesions (>40 HU) on unenhanced computed tomography scan that suggest a tumor with high cellularity and heterogeneous low attenuating necrotic or hemorrhagic foci [26]. Because of 73% translocation of RCC having thick, fibrous capsules, the gradual enhancement pattern on three-phase contrast-enhanced scans found the peripheral rim of these tumors to be a fibrotic capsule [27]. Because of the resemblance to papillary RCCs histopathologically and radiologically, the preoperative diagnosis of Xp11 translocation carcinoma remains a challenge.

The classic triad of renal cancer (abdominal mass, pain, and hematuria) appeared as the initial symptoms at the time of diagnosis; in four of eight cases (50%) it presented as abdominal pain or flank pain and three in eight cases...
(37.5%) as hematuria. Several studies for Xp11 translocation RCCs are summarized in Table 3. In five of eight cases (62.5%), the diagnosis of advanced Stage III/IV was made in our series, which is comparable with other series [35–73.7%] [4,23,28,29]. Translocation RCC often involves lymph nodes at the time of diagnosis. Three of eight cases (38%) had lymph node involvement at the time of diagnosis in our series, which is compatible with 35.5–43.4% in other series [4,23,28,30]. The average rate of cancer-specific death was 19.87% (7.1–31.6%) during an average follow-up period of 33.14 months (range, 11–61.6 months) [4,7,16,23,28,29].

Different subtypes of RCCs present different gene factors and clinical behaviors as presented in Table 4 [31]. Most clear cell RCCs have deletions in the short arm of chromosome 3 (3p−); papillary RCCs are usually found to have trisomy of chromosomes 7 and 17 and/or loss of the Y chromosome; chromophobe RCCs usually present loss of chromosomes 1, 2, 6, 10, 13, and 17 [32]. A study enrolling 75 cases also found 65% of patients with non—translocation-associated RCC were low stage (Stages I/II), whereas 65% of patients with Xp11.2 translocation RCC were high stage (Stages III/IV) [33]. In general, Xp11.2 translocation RCC presents at a higher initial cancer stage (35–73.7%) with strong trends of regional lymph node involvement or metastases (24.8–85%) and females predominate, compared to other subtype RCCs [2,4,5,33].

In our series, one patient (case No. 6) with multiple lung metastases at the beginning of diagnosis received retroperitoneoscopic cryoablation and immunotherapy with high-dose IL-2 (600,000 IU/kg) that produced stationary lung nodules after 15.5 months of follow-up. Nishida et al. reported cryoablation of metastatic bone lesion could reduce lung metastasis [34]. The immune response after cryoablation may play an important role in the treatment of RCCs. However, the optimal therapy for metastatic Xp11.2 translocation RCCs remains uncertain. Targeted therapy with vascular endothelial growth factor (VEGF) inhibitors such as sunitinib and sorafenib, or the inhibitor of mammalian target of rapamycin (mTOR) kinase such as temsirolimus and everolimus, have been reported to produce effective results for metastatic lesions [35–38]. In this series, we had only one case receiving serial sunitinib, sorafenib, and temsirolimus and the progression-free

### Table 2: Treatment and prognosis of Xp11.2 translocation renal cell carcinoma.

<table>
<thead>
<tr>
<th>Case</th>
<th>Operative method</th>
<th>Immunotherapy</th>
<th>Target therapy</th>
<th>Overall survival (mo)</th>
<th>Progression-free survival (mo)</th>
<th>Recurrent site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Radical nephrectomy with lymphadenectomy</td>
<td>None</td>
<td>none</td>
<td>70.2a</td>
<td>70.2a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Radical nephrectomy with lymphadenectomy</td>
<td>Interferon-α</td>
<td>Sutent → Nexavar → Temsirolium</td>
<td>23.4</td>
<td>14.3</td>
<td>Lymph node</td>
</tr>
<tr>
<td>3</td>
<td>Radical nephrectomy with lymphadenectomy</td>
<td>None</td>
<td>none</td>
<td>46.0a</td>
<td>46.0a</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Biopsies two times and then radical nephrectomy</td>
<td>Interleukin-2</td>
<td>none</td>
<td>34.4a</td>
<td>32.8</td>
<td>Lymph node</td>
</tr>
<tr>
<td>5</td>
<td>Partial nephrectomy</td>
<td>None</td>
<td>Interferon-α</td>
<td>24.5a</td>
<td>24.5a</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Retroperitoneoscopic renal cryoablation with 1 probe</td>
<td>None</td>
<td>Interleukin-2</td>
<td>15.5a</td>
<td>15.5a</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Retroperitoneoscopic renal cryoablation with 3 probes</td>
<td>None</td>
<td>none</td>
<td>11.6a</td>
<td>11.6a</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Radical nephrectomy with lymphadenectomy</td>
<td>None</td>
<td>none</td>
<td>12.0a</td>
<td>12.0a</td>
<td></td>
</tr>
</tbody>
</table>

a Still surviving in 32-mo average follow-up period.

Figure 1. (A) Hematoxylin-eosin stain showing compact papillary and nested architecture with voluminous clear to eosinophilic cytoplasm (magnification ×250). (B) Nuclear strong labeling for immunohistochemical TFE3 stain (magnification ×250).
### Table 3  Comparison for characteristics of Xp11 translocation RCC [4,7,16,23,28,29].

<table>
<thead>
<tr>
<th>Literature review</th>
<th>Case</th>
<th>Average age (y)</th>
<th>Sex (M:F)</th>
<th>Size (cm)</th>
<th>Stage</th>
<th>Surgical treatment</th>
<th>Medical treatment</th>
<th>Median follow-up (mo)</th>
<th>Progression-free survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This series</td>
<td>8</td>
<td>28.4</td>
<td>1:1</td>
<td>5.8 (3–9.6)</td>
<td>I/II:37%, III/IV:63%</td>
<td>RN:4, PN:1, Cryo:3</td>
<td>Targeted therapy: 1, Immunotherapy: 3</td>
<td>29.7 (11–70)</td>
<td>28.4 ± 21</td>
</tr>
<tr>
<td>Malouf et al.</td>
<td>54</td>
<td>24 (1–64)</td>
<td>1:1.4</td>
<td>—</td>
<td>I/II:65%, III/IV:35%</td>
<td>RN + PN:36</td>
<td>—</td>
<td>19.2 (1–58)</td>
<td>2–9 mo in 7 cases</td>
</tr>
<tr>
<td>Camparo et al.</td>
<td>31</td>
<td>24.6</td>
<td>1:1.38</td>
<td>6.9 (2.5–20)</td>
<td>I/II:58%, III/IV:42%</td>
<td>RN:26, PN:4</td>
<td>—</td>
<td>29.5 (5–92)</td>
<td>26.3 (3–36)</td>
</tr>
<tr>
<td>Argani et al.</td>
<td>28</td>
<td>37.3 (22–78)</td>
<td>1:3.66</td>
<td>6.8 (2.1–21)</td>
<td>I/II:42.9%, III/IV:57.1%</td>
<td>PN:2</td>
<td>Immunotherapy: 1, Targeted therapy, or immunotherapy: 4</td>
<td>11 (3–72)</td>
<td>1,1,6 y in 3 cases</td>
</tr>
<tr>
<td>Rao et al.</td>
<td>19</td>
<td>14.2 (7–24)</td>
<td>1:1.4</td>
<td>—</td>
<td>I/II:26.3%, III/IV:73.7%</td>
<td>RN:18, PN:1</td>
<td>—</td>
<td>47.86 (13–79)</td>
<td>—</td>
</tr>
<tr>
<td>Hung et al.</td>
<td>8</td>
<td>28 (20–49)</td>
<td>1:3</td>
<td>9.2 (4–17)</td>
<td>I/II:50%, III/IV:50%</td>
<td>RN:7</td>
<td>—</td>
<td>61.6 (9–132)</td>
<td>—</td>
</tr>
<tr>
<td>Komai et al.</td>
<td>7</td>
<td>42 (15–59)</td>
<td>1:0.75</td>
<td>8.3 (2–16)</td>
<td>I/II:57%, III/IV:43%</td>
<td>RN + PN:7</td>
<td>—</td>
<td>14 (2–24)</td>
<td>—</td>
</tr>
</tbody>
</table>

Cryo = cryoablation; PN = partial nephrectomy; RN = radical nephrectomy; (—) = unknown data.

### Table 4  Comparison with other subtypes of renal cell carcinomas [4,7,16,23,28,29,31].

<table>
<thead>
<tr>
<th>Renal cell carcinoma subtype</th>
<th>Incidence</th>
<th>Average age (y)</th>
<th>Sex (M:F)</th>
<th>Initial diagnosis of advanced stage (III/IV)</th>
<th>Initial lymph node metastasis</th>
<th>Genetic factor</th>
<th>Inherited syndromes</th>
<th>Inherited gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>70–80%</td>
<td>61.4</td>
<td>1.61:1</td>
<td>24.5%</td>
<td>4.5%</td>
<td>−3p, +5q22, −6q, −8p, −9p, −14q</td>
<td>Von Hippel-Lindau (VHL)</td>
<td>VHL (3p25-26)</td>
</tr>
<tr>
<td>Papillary</td>
<td>10–15%</td>
<td>63.1</td>
<td>2.55:1</td>
<td>19.1%</td>
<td>6.4%</td>
<td>+3q, +7, +8, +12, +16, +17, +20, −Y, trisomy 7 &amp; 17</td>
<td>Papillary type 1 / type 2</td>
<td>c-MET (7q34) / FH (1q42-43)</td>
</tr>
<tr>
<td>Chromophobich</td>
<td>3–5%</td>
<td>60.8</td>
<td>1.32:1</td>
<td>11.3%</td>
<td>0.5%</td>
<td>−1, −2, −6, −10, −13, −17, −21</td>
<td>Birt-Hogg-Dube (BHD)</td>
<td>BHD (17p11.2)</td>
</tr>
<tr>
<td>Xp11.2 translocation</td>
<td>1%</td>
<td>26.6</td>
<td>1:1.84</td>
<td>47.7%</td>
<td>35.5–43.4%</td>
<td>t(X;1)(p11.2;q21), t(X;17)(p11.2;q25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
survival was only 4, 3, and 4 months, respectively. In comparison with the published results of 5–11-month progression-free survival of targeted therapy in metastatic renal cell carcinoma [39–42], we did not find effective results in this case. Immunotherapy was reported to have poor effect with a combination of interferon-α and IL-2 for three cases of adult Xp11.2 translocation RCCs [16]. In our series, however, three cases received immunotherapy (2 IL-2 and 1 interferon-α) where two cases had progression-free survival less than 3 months because of lymph node recurrence, and one initial case of lung metastasis remains as stable disease after 15.5 months of follow-up.

The Fuhrman grading system was first introduced in 1982 for the grading schema of RCC based on the morphology [43]. The grading system is determined on nuclear characteristics and has been proven to be a powerful prognostic predictor for RCC [43–45]. One report indicated that in TFE3-positive RCCs the diagnosis of a high Fuhrman grade (III/IV) was made in 87.5% of cases and the 5-year cancer-specific survival was low (15.6%) [25]. In our study, six cases (75%) also showed higher Fuhrman grade (III/IV). There was no significant statistical correlation between patient survival, either overall or cancer-specific, and Fuhrman grade ($p = 2.286$, $e = 0.233$) or score of TFE3 IHC stain ($p = 0.326$, $e = 0.255$) in our study; however, because of the limited case number and relatively short follow-up period in the current series, the exact relationship between patient survival, TFE3 IHC stain, and Fuhrman grade may need further investigation.

In conclusion, although the incidence is rare, the diagnosis of an Xp11.2 TRCC is based on histological appearance, TFE3 IHC study, and genetic analyses. TFE3 is a highly sensitive and specific immunohistochemical marker for screening suspicious tumors for the Xp11.2 translocation RCC in children and young adults. Because of higher tumor stage and more lymph node involvement than nonselective RCC, Xp11.2 translocation RCC with advanced stage has a poor prognosis even if aggressive surgical intervention is performed and no optimal medical therapy is administered for metastasis. Traditional open surgery and minimally invasive cryotherapy both have a good prognosis in early stages. Before international multicenter studies including larger numbers of cases are designed to confirm current outcomes, optimal treatment strategies for this rare Xp11.2 translocation RCC cannot be determined. Early detection and complete surgery still remain the standard of care. We herein present our preliminary experiences for this new and rare entity of renal cell carcinoma in Taiwan.

References


