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Original Article

XP11.2 Translocation renal cell carcinoma: Clinical experience of Taipei Veterans General Hospital

Chia-Chen Hung [a], Chin-Chen Pan [b,d], Chih-Chieh Lin [a,c], Alex T.L. Lin [a,c], Kuang-Kuo Chen [a,c], Yen-Hwa Chang [a,c,*]

[a] *Division of Urology, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *Department of Urology, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[d] *Department of Pathology, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

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Abstract

Background: Xp11.2 translocation renal cell carcinoma (RCC), a recently recognized distinct subtype of RCC, is characterized by various translocations, all involving the TFE3 transcription factor gene. These rare cancers occur predominantly in children and young adults and comprise about one-third of pediatric RCCs. In the present study, we review the clinical course of Xp11.2 translocation renal cell carcinoma in our institution.

Methods: We identified eight cases with Xp11.2 translocation RCC between 2007 and 2010 from the pathological archives of the Taipei Veterans General Hospital. We retrospectively analyzed the patients' characteristics, clinical manifestations, and specific pathological features for definitive diagnosis, surgical and systemic treatment and clinical outcome of these rare cancers.

Results: Patients were aged 20 years to 49 years (mean age 28 years) with female predominance (6 females, 2 males). One patient presented with asymptomatic renal mass detected incidentally during abdominal sonography. Four patients complained of flank or abdominal pain, and the other three complained of gross hematuria at initial presentation. The mean tumor size was 9.2 cm (range, 4 cm−17 cm). Seven patients underwent radical nephrectomy for the primary tumor, while one presented with multiple metastases. All cases were confirmed by TFE3 immunohistochemistry, a sensitive and specific marker of tumors with TFE3 gene fusion, which showed positive nuclear staining. Three patients presented initially with metastatic diseases, and another three patients progressed to lung, liver and bone metastases at eight, seven and nine months postoperatively.

Conclusion: Although RT-PCR and DNA sequencing are the final diagnoses of the molecular identity of Xp11.2 translocation RCC, experienced pathologists could confirm the histologic diagnosis based on the distinctive morphologic features with positive TFE3 immunochemical nuclear stain. Surgical resection is the only treatment. The role of systemic therapy for local recurrence and metastasis remains to be determined.

Keywords: kidney; renal cell carcinoma; renal tumor; TFE3; Xp11.2 translocation

1. Introduction

Renal cell carcinomas (RCC) associated with Xp11.2 translocations were recently accepted in the 2004 WHO classification of renal tumors as a distinct entity. They are characterized by various translocations, all involving gene fusion with the transcription factor E3 (TFE3) gene at chromosome Xp11.2. The TFE3 gene is a member of the microphthalmia transcription factor (MiTF) family, which is a critical factor in melanocyte development. All family member proteins code for basic-helix-loop-helix leucine-zipper transcription factors that bind DNA as homodimers or heterodimers.[1,2] To date, at least six distinct recipient genes have been identified, of which, five are known. They are PRCC (papillary renal cell carcinoma), polypyrimidine

* Corresponding author. Dr. Yen-Hwa Chang, Division of Urology, Department of Surgery, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: yhchang@vghtpe.gov.tw (Y.-H. Chang).

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tract-binding protein-associated splicing factor (PSF), clathrin heavy-chain (CLTC), ASPL (alveolar soft part sarcoma locus) and non-POU domain-containing octamer-binding (NonO; p54nrb) genes, situated on chromosomes 1q21.2, 1p34, 17q23, 17q25 and Xq12, respectively. The molecular identity of the sixth gene, which is situated on chromosome 3, is not known yet.[3–5] The TFE3 fusion proteins function as strong transactivators compared to native TFE3. ASPL-TFE3–mediated direct transcriptional up-regulation of the MET receptor tyrosine kinase triggers dramatic activation of downstream signaling pathways and leads to cell proliferation, adhesion, cell motility, and invasion. Evidence supporting a similar role for other TFE3 fusion proteins is also provided.[6] To our knowledge, the first published case of Xp11.2 translocation RCC was a 17-month-old child, reported in 1991.[7] The incidence of translocation carcinoma has been estimated to be 20% to 54% of RCCs in children and young adults.[8–10] Although Xp11.2 translocation RCCs are less commonly reported in adults, Argani et al. have stated that adult Xp11 translocation RCCs may well outnumber their pediatric counterparts.[4] Xp11.2 translocation RCCs typically have nested or papillary architecture and are composed of cells with voluminous, clear, or eosinophilic cytoplasm mimicking clear cell and papillary renal carcinoma in histologic appearance. Translocations involving TFE3 induce overexpression of this protein and can be specifically identified by immunohistochemistry (IHC), using an antibody to the C-terminal portion of TFE3, which is demonstrated in all of the reported fusion products. Nuclear labeling for TFE3 protein by IHC is specific to Xp11.2 translocation RCC, but is not detectable in normal tissues or in other tumor types. IHC for nuclear TFE3 staining now allows confirmation of the diagnosis of Xp11 translocation RCC in archival tissues.[11] Although only limited data are available, Xp11.2 translocation RCCs are generally considered to be indolent, even when diagnosed at advanced stages. However, an aggressive clinical course in adult cases has recently been reported.[4]

2. Methods

A total of 8 cases of Xp11.2 translocation RCC, diagnosed between March 2007 and December 2010, were retrieved from the surgical pathological archives at our hospital. In this retrospective chart-review study, clinicopathologic data including patient characteristics, clinical manifestations, surgical techniques, pathologic findings and clinical outcomes were analyzed. The Fuhrman nuclear grading system, which uses a 4-point multiparametric scale based on nuclear features, size, shape, chromasia and nucleolar prominence, is used because of its simplicity and well-established prognostic role. Tumor sizes were evaluated by measuring the largest diameter of the tumor mass removed surgically or by CT image in one patient who did not receive the operation.

3. Results

The clinical data of the patients are shown in Table 1. There were 2 males and 6 females (male/female ratio of 0.33); mean age at presentation was 28 years (range 20 years to 49 years). Of the 8 cases, 3 (37.5%) presented with flank pain, 3 (37.5%) presented with gross hematuria, 1 (12.5%) presented with abdominal pain, and 1 was diagnosed incidentally. The tumor location was right-sided in 2 (25%) cases and left-sided in 6 (75%). No bilateral or multifocal disease was observed. The greatest dimension of the tumor ranged from 4 cm to 17 cm, with a mean tumor size of 9.2 cm. Seven (87.5%) patients underwent open radical nephrectomy for the primary tumor, of whom one received neck lymph node dissection and one underwent wedge resection of left upper lung (LUL) and lower lobes of lung (LLL) due to neck LN and lung metastases. All operations were performed by the open method. One patient (case no. 8) presented with advanced disease with extensive retroperitoneal and mediastinal lymphadenopathies, as well as multiple visceral metastases, which precluded primary tumor resection and metastasectomy due to his morbid condition.

Macroscopically, the tumors are tan-yellow in color and often with necrosis and hemorrhage, and therefore may grossly mimic clear-cell RCC. Microscopically, the tumors are composed of clear to eosinophilic cells arranged in nested, papillary or mixed architecture (Fig. 1). The Fuhrman grade was 2–3 in 3 cases and 3 in 4 cases. All tumor cells demonstrated nuclear labeling for TFE3 protein by IHC (Fig. 2). Five of 6 cases were positive for renal tubular marker CD10. All 4 tumors tested were negative for melanocytic

Table 1
Clinical data of patients.

No.	Age	Sex	Symptoms	Laterality	Size (cm)	TNM Stage	Fuhrman Grade
1	20	F	Abdominal pain	L	17	pT4 cN0M0 (Stage IV)[a]	3
2	34	M	Flank pain	L	12	pT2b cN0M0 (Stage II)	3
3	38	F	Incidental finding	L	5	pT3b cN1M0 (Stage III)[b]	2–3
4	39	F	Hematuria	L	10	pT2b cN0M0 (Stage II)	2–3
5	26	F	Flank pain	R	8	pT4 cN0M1 (Stage IV)[c]	3
6	20	F	Flank pain	R	4	pT1a cN0M0 (Stage I)	2–3
7	20	F	Hematuria	L	6.5	pT1b cN0M0 (Stage I)	3
8	22	F	Hematuria	L	11	cT4N1M1 (Stage IV)[a,b,c,d]	NA

NA = Not available.
[a] peritoneal invasion
[b] renal vein thrombus, neck LN invasion
[c] lung metastasis
[d] liver metastasis.

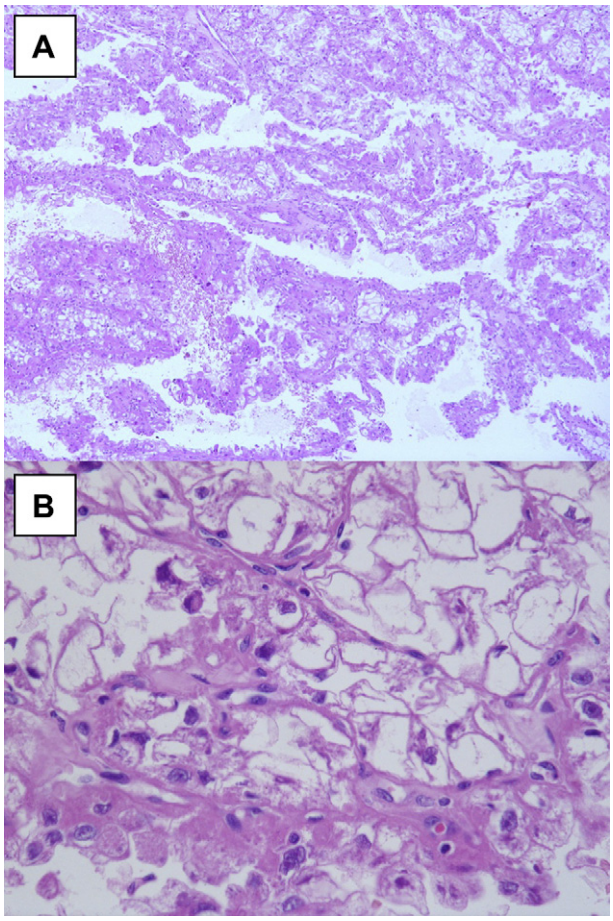

Fig. 1. (A) Compact papillary and nested architecture (hematoxylin-eosin, original magnification ×100); (B) voluminous clear to eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×400).

marker HMB45. RCC marker antigen was tested in 3 cases and positive in 2. Only the first of these cases was molecularly confirmed by RT-PCR to have a PRCC-TFE3 gene fusion (Fig. 3).

The pathology stage was T1a in 1 case, T1b in 1 case, T2 in 2 cases, T3b in 1 case and T4 in 2 cases. Four patients received adjuvant therapies including chemotherapy, targeted therapy, or immunotherapy. However, disease progression was noted in patients who presented with metastasis at diagnosis or after operation. Three patients are free from recurrence 24, 16 and 2 months after nephrectomy. The only patient (case no. 8) who rejected further management at initial diagnosis of left renal mass, developed multiple metastases (peritoneum, pleura, distant LN, liver, lung and bone) 3 years later. He received targeted therapy of temsirolimus (an inhibitor of mammalian target of rapamycin, mTOR) but he died 2 months following treatment due to advanced disease with respiratory failure.

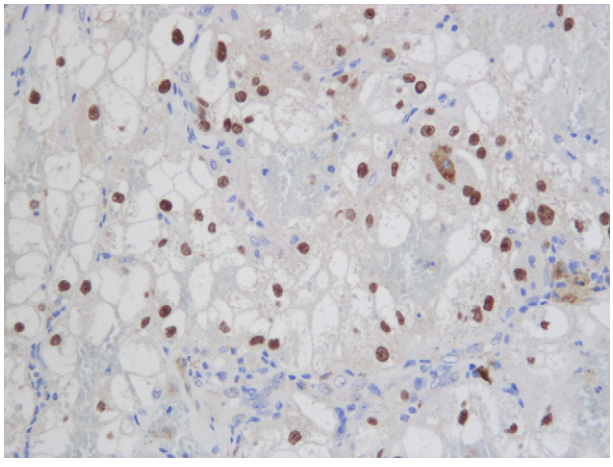

Fig. 2. IHC stain for TFE3 shows intense nuclear staining only in tumor cells (immunoperoxidase, original magnification ×400).

4. Discussion

Xp11.2 translocation RCCs are considered as pediatric carcinomas and show female predominance. In our cases, the mean age was 28 years and the male:female ratio 1:3, which were concordant with previous reports.

The mean tumor size in our series was 9.2 cm, which is larger than Patard's and Philippe's series (6.0∼6.8 cm).[12,13] The pT stage did not differ in our series compared with previous reports; 50% pT3/T4 in the former versus 48%–49% in the latter.[12,13] Renal translocation carcinoma tends to present with lymph node involvement at the time of diagnosis. It was reported in the literature that 50% of the cases had lymph node metastasis at diagnosis.[13] In our series, 37.5% (3/8) had lymph node invasion (N+) and/or distant metastasis (M+) at the time of diagnosis.

Morphologically, Xp11.2 translocation RCCs are composed of cells with abundant clear or pale cytoplasm with nested and/or papillary architecture on routine HE sections, which may overlap with clear-cell RCCs. However, the most distinct immunochemical feature of Xp11.2 translocation RCCs is a detectable nuclear staining for TFE3 protein, which may confirm the definitive diagnosis. Two recent studies of 28 cases[4] and 31 cases[14] of Xp11.2 translocation RCCs, reported the frequency of TFE3 immunostaining as 100% and 82%, respectively. In our series, all 8 cases presented with nuclear stain positive for TFE3. Other specific IHC patterns have been reported and are suggestive of the diagnosis of Xp11.2 translocation RCC in the absence of TFE3 IHC.[4,14–16] The expression of CD10, E-cadherin, α-methylacyl coenzyme A racemase and RCC antigen was common and strong, the expression of cytokeratins (AE1/AE3, Cam5.2, CK7 and epithelial membrane antigen [EMA]) and melanocytic markers (HMB-45 and Melan-A) was rare and weak, and that of vimentin was variable and weak in Xp11.2 translocation RCCs. In our series, CD10 was positive in 5/6 cases, HMB-45 was negative in 4/4 cases and EMA was negative in 1/1 case.

The only patient who did not receive nephrectomy (case no. 8) may represent the rapidly progressive nature of the cancer. He presented with intermittent gross hematuria at the age of 19 years and a faintly enhancing tumor of 5 cm diameter at the inter-polar region of the left kidney, with hemorrhage, was depicted by CT scan. Surgical intervention was recommended, but the patient rejected the option and took herbal medicine instead. Three years later, the patient came back with a huge

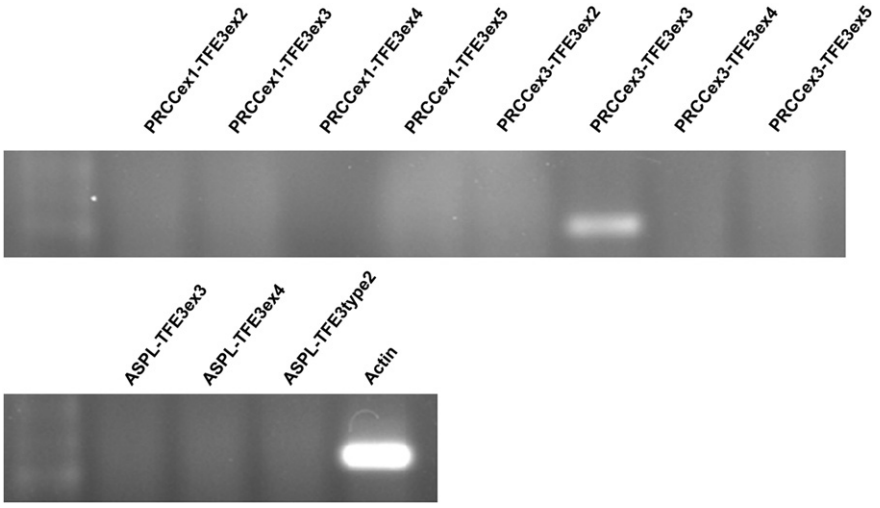

Fig. 3. RT-PCR in case 1 showed PRCC-TFE3 gene fusion.

left neck mass and distended abdomen. CT scan revealed a large left kidney tumor with multiple metastases, including lung, liver, bone and extensive lymph nodes. He had received prior interferon therapy based on his advanced disease. However, the patient developed rapid clinical deterioration in 2 months and was transferred to us for further management. Histological diagnosis of Xp11.2 translocation RCC was confirmed by needle biopsy of the left kidney tumor. Intra-abdominal carcinomatosis with marked ascites prohibited him from oral intake and medication. He was given mTOR inhibitors with weekly intravenous temsirolimus due to his high risk, and best supportive care. Regression of the neck masses and clinical improvement of symptoms were noted. The patient, however, died 2 months later due to advanced disease with respiratory failure. What makes this case unique, is the rapid progression of his cancer from a localized disease to terminal cancer in 3 years. It indicates that the natural history of Xp11.2 translocation RCC can be very aggressive if the primary tumor is left in place untreated. On the other hand, when the cancer is still organ-confined, such as in case no. 6 who was free of disease at 16 months following nephrectomy, complete resection of the primary tumor is the mainstay treatment. Also, metastasis (at diagnosis or after operation) seems to determine the prognosis. Optimal systemic therapy for Xp11.2 translocation RCCs remains to be determined. Two recent retrospective studies demonstrated an objective response to VEGF-targeted and/or mTOR inhibitor treatment.[17,18] Prospective studies are needed to confirm this retrospective observation, and further genetic and epigenetic studies are needed to prioritize the discovery of rational targets for the development of more effective therapies.

In conclusion, we report the clinical presentation, pathological features and outcomes of the recently diagnosed series of eight Xp11.2 translocation RCCs in our hospital. Immunochemical staining of TFE3 protein is the distinct feature of Xp11.2 translocation RCCs for histologic diagnosis; RT-PCR and DNA sequencing is the final diagnosis of the molecular identity. Surgical resection is the only choice of treatment. Clinical stage at diagnosis or after operation seems to determine the prognosis. The treatment response of systemic therapy (including targeted therapy) for local recurrence or metastasis needs more studies to confirm its efficacy.

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