Review

Recent Advances in Renal Cell Carcinoma Associated with Xp11.2 Translocations/*TFE* Gene Fusions

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Renal cell carcinoma associated with Xp11.2 translocations/*TFE* gene fusions (Xp11.2 RCC) has been classified as a distinct entity in the 2004 WHO classification of kidney tumors. Over the past seven years, aided by increased awareness, positive nuclear staining for *TFE*3, unique cytogenetic features, and modern molecular technology, more cases have been recognized as Xp11.2 RCC. This review summarizes the most recent advances in Xp11.2 RCC regarding to its clinical presentation, cytogenetic profile, histopathology, prognosis and treatment.
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Key Words: *renal cell carcinoma, Xp11.2 translocations/TFE gene fusions, clinical presentation, cytogenetic profile, histopathology, prognosis and treatment*

INTRODUCTION

Renal cell carcinoma associated with Xp11.2 translocations and *TFE3* fusions (Xp 11.2 RCC) was first reported by de Jong *et al*. in 1986.[1] However, it was only recognized as a distinct entity in 2004 WHO classification of kidney tumors.[2] These renal carcinomas are defined by several different translocations involving chromosome Xp11.2 and resulting in gene fusion/overexpression of transcription factor E3 (*TFE3*) gene. *TFE3* is located on chromosome Xp11.2 and belongs to the microphthalmia transcription factor (*MiTF*)/transcription factor E (*TFE*) family which also includes 3 other members: *MiTF*, transcription factgor EB (*TFEB*) and transcription factor EC (*TFEC*).[3-6] The *MiTF/TFE* family encodes basic helix-loop-helix-leucine zipper (bHLH-ZIP) transcriptional factors. In addition to regulating melanocytic differentiation, these transcriptional factors also play an important role in proliferation and survival.[7] Normally, the expression of *TFE3* is tightly controlled and routine imunohistochemical staining is not able to detect it. A common feature of Xp11.2 RCC is chromosome translocations resulting *TFE3* fusion with various partners and subsequently overexpression of TFE3 protein in tumor cells. The overexpressed TFE3 protein in Xp11.2 RCC is now detectable using a sensitive (97.5%) and specific (99.6%) polyclonal antibody to its C-terminal.

CLINICAL PRESENTATION

The profile of pediatric renal neoplasm is different from that of adult with RCC accounting for <3% of pediatric renal tumors[9-10] and >90% of adult renal tumors.[2] Xp11.2 RCC is estimated representing one-third of pediatric RCC[11] and <1% of adult RCC,[12] and affects patients ranging from 17-month-old[13] to 78-year-old with unknown gender preference in pediatric age group and a female predominance in adults.[14-17] The clinical presentation of Xp11.2 RCC is similar to other renal tumors. Pediatric and young adult patients are usually symptomatic at presentation and only a few cases are incidentally discovered during abdominal imaging. The most common symptom is hematuria, followed by abdominal mass, abdominal pain and weight loss. Rare atypical presentations in adult patients include a heavily calcified renal mass, outflow obstruction with persistent pyelonephphritis, renal cyst or nephrolithiasis.[2,15-18] The radiological findings of Xp11.2 RCC are not specific either.[19] However, in young patients, Xp11.2 RCC should be suspected if prominent lymph node metastases are present or the imaging findings are similar to those of papillary RCC.[20-22] In children, studies have indicated that previous chemotherapy may be a risk factor for developing Xp11.2 RCC. Approximately 10-15% of pediatric cases have a history of chemotherapy.[23-25] In adults, even though Xp11.2 RCC has been reported during pregnancy[26] or in association with hemodialysis,[27] no studies have been done to identify particular risk factors.

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CYTOGENETIC PROFILE

To date, eight *TFE3* fusion partners have been reported, including papillary renal cell carcinoma (*PRCC*),[15] alveolar soft part sarcoma locus (*ASPL*),[16,28] polypyrimidine tract-binding protein-associated splicing factor (*PSF*),[15] non-POU domain-containing octamer-binding (*NonO*),[15] clathrin heavy chain (*CLTC*)[15,29] and three unknown genes.[15,26,30] The most common translocations are *ASPL-TFE3*, *PRCC-TFE3* and *PSF-TFE3* fusions (**Table 1**).[18,24-25,31] Two other neoplasms that bear similar translocations are worth mentioning here. One is alveolar soft part sarcoma (ASPS). Both *ASPL-TFE3* RCC and ASPS harbor the same *ASPL-TFE3* fusion gene. However, the translocation is balanced in *ASPL-TFE3* RCC and is unbalanced in ASPS.[32] The other one is t(6;11)(p21;q12) translocated RCC [t(6:11) RCC] that bears *Alpha-TFEB* fusion gene with overexpression of *TFEB*. Since *TFE3* and *TFEB* are closely related members of *MiTF/TFE* transcriptional family, the clinical and histomorphologic features of t(6;11) RCC and Xp11.2 RCC overlap.[18] As a common transcriptional target of *TFE3* and *TFEB*, Cathepsin-K is overexpressed in both t(6;11) RCC and Xp11.2 RCC, but not in other types of RCCs.[33] The immunohistochemical character in distinguishing these two entities is positive nuclear staining for TFE3 in Xp11.2 RCC and for TFEB in t(6;11) RCC.[11,34] The major role of chimeric TFE3 fusion proteins in Xp11.2 RCC is transcriptional dysregulation. Tsuda *et al*[35] reported that *ASPL-TFE3*, *PSF-TFE3* and *NonO-TFE3* all bind to *MET* promoter. However, *ASPL-TFE3* induces a much stronger up-regulation of downstream MET receptor tyrosine kinase than *PSF-TFE3* or *NonO-TFE3* does. Evidence shows that the chimeric *PRCC-TFE3* and *NonO-TFE3* are more potent as transcription factors than wild type *TFE3*, while *PSF-TFE3* and *CLTC-TFE3* interfere with cell cycle control.[36]

Table 1. Translocations Identified in Xp11.2 RCC.

Fusion partner	**Chromosomal translocation**	**Gene fusion product**	**Frequency[31]**
PRCC[16]	t(X;1)(p11.2;q21)	*PRCC-TFE3*	78%
PSF[16]	t(X;1)(p11.2;p34)	*PSF-TFE3*	20%
ASPL[16,28]	t(X;17)(p11.2;q25)	*ASPL-TFE3*	Rare
NonO[16]	inv(X)(p11.2;q12)	*NonO-TFE3*	Rare
CLTC[16, 29]	t(X;17)(p11.2;q23)	*CLTC-TFE3*	Rare
Unknown[30]	t(X;10)(p11.2;q23)	Unknown-*TFE3*	Rare
Unknown[16]	t(X;3)(p11.2;q23)	Unknown-*TFE3*	Rare
Unknown[26]	t(X;19)(p11.2;q13.1)	Unknown-*TFE3*	Rare

HISTOPATHOLOGY

Grossly, Xp11.2 RCC is indistinguishable from conventional RCC.[17,28] The tumors are well circumscribed, but unencapsulated with tan-yellow, soft cut surfaces. Tumor size varies from 2.1 to 21 cm with mean size of 6.8 cm.[15] Areas with necrosis, hemorrhage, calcification and cystic changes may be present. Histologically, Xp11.2 RCC has nested or tubular to papillary growth patterns. Tumor cells have distinctive clear to eosinophilic, voluminous, granular cytoplasm and prominent cell borders. The nuclei are vesicular and have prominent nucleoli. Psammomatous calcification is also a common feature (**Figure 1**).[2,28,37] The morphology of Xp11.2 RCC with different gene fusion partners may vary slightly. For example, *ASPL-TFE3* RCC is associated with exuberant psammomatous calcification and such abundant cytoplasm that it was called ‘‘voluminous cell variant’’ of pediatric RCC before the translocation was identified. In contrast, the cytoplasm is less abundant and the psammoma bodies are fewer in *PRCC-TFE3* RCC. The histology variation might be explained by the heterogeneity of fusion partners of *TFE3*. Whether subtle morphologic differences exist in other Xp11.2 RCCs, such as *PSF–TFE3*, *NonO–TFE3*, *CLTC–TFE3* is curently not clear.[11] Because histologically Xp11.2 RCCs have clear cells with distinctive cell borders and grow in nested and/or tubular-papillary patterns, they may resemble conventional clear cell RCC (CCRCC), papillary RCC (PRCC), and clear cell papillary RCC (CCPRCC), a recently recognized new entity. In addition to the unique morphological features of each entities mentioned above, immunohistochemical markers are helpful in the differential diagnoses. Unlike other types of RCC, Xp11.2 RCC is negative or only focally postive for cytokeratins and epithelial membrane antigen (EMA). Vimentin is usually negative but may be weakly and focally positive. Nuclear staining of TFE3 is highly sensitive and specific for Xp11.2 RCC (**Figure 2**).[38] CD10 and alpha-methylacyl-coenzyme A racemase (AMACR) are also commonly positive in Xp11.2 RCC, but not specific.[39] In addition, recent studies by Argani *et al.*[14] showed that Xp11.2 RCCs rarely express c-kit; but they show high levels of phosphorylated S6, which is a mTOR pathway activation marker. In difficult cases with equivocal histology and immunhistochemical stainings, break-apart fluorescence in situ hybridization (FISH) assay and reverse transcriptase-polymerase chain reaction (RT-PCR) are useful confirmatory tests in the diagnosis of Xp11.2 RCC.[17,40-41] The immunohistochemical staining pattern for Xp11.2 RCC and other RCCs is summarized in **Table 2**.

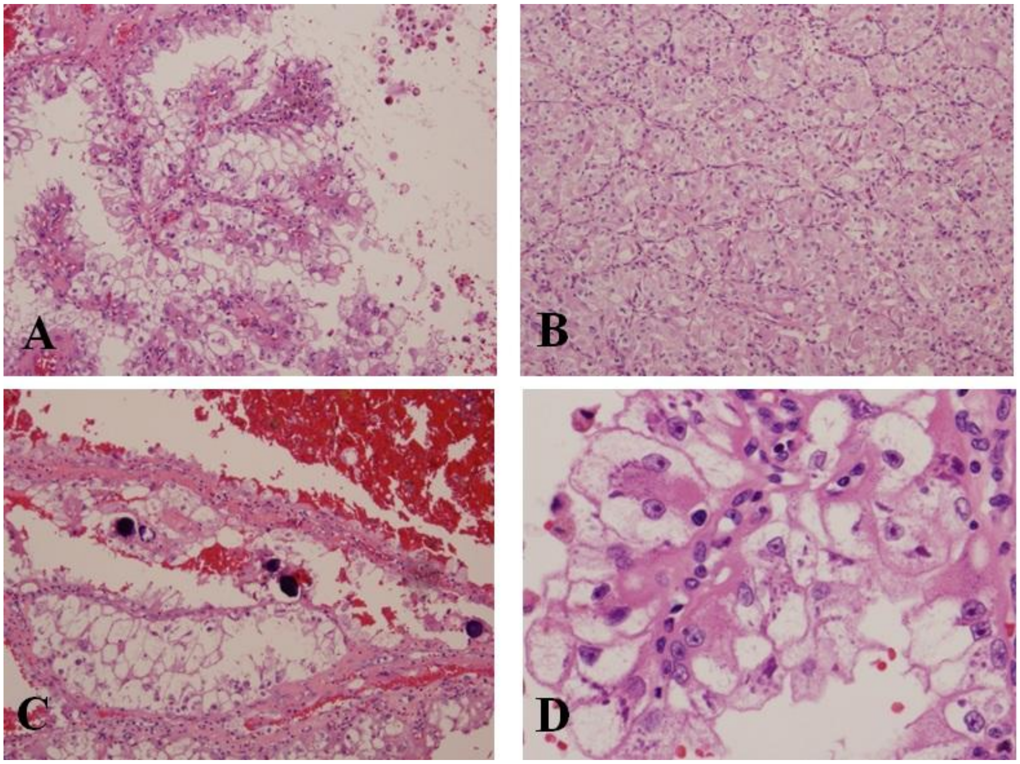

Figure 1. Characteristic microscopic features of Xp11.2 RCC. **A.** Papillary growth pattern with mixed clear/eosinophilic cells (H&E, x100); **B.** Nested growth pattern with mixed clear/eosinophilic cells (H&E, x100); **C.** Psammoma bodies are common (H&E, x100); **D.** Tumor cells have voluminous cytoplasm and distinct cell borders. Nuclei are vesicular and have prominent nucleoli (H&E, x400).

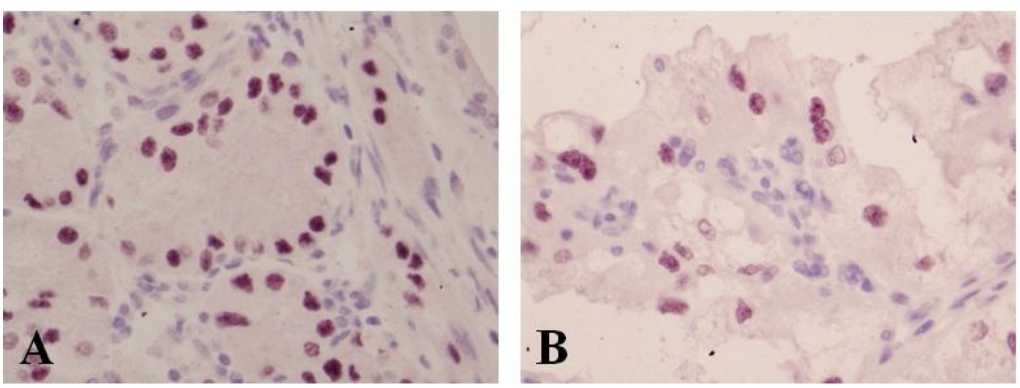

Figure 2. Positive nuclear staining for TFE3 in Xp11.2 RCC (x400). The nuclei of tumor cells are positive for TFE3 using an antibody against the C-terminal portion of the TFE3 in tubular/nested (**A**) and papillary (**B**) areas.

PROGNOSIS AND TREATMENT

Reports regarding the prognosis of Xp11.2 RCC in children and young adults are controversial. Initially, it was believed that the biological behavior of Xp11.2 RCC is indolent. In a study conducted by Ramphal *et al.*,[25] 13 pediatric patients diagnosed with stage I to IV Xp11.2 RCC underwent nephrectomy and resection of metastases with negative surgical margins. All but one patients were alive and tumor-free at last follow-up with an overall survival rates of 92% ± 7.4% at 5 years. However, recently, both prospective and retrospective studies have shown that Xp11.2 RCC is associated with significantly decreased disease-free survival and overall survival in this group of patients.[42-43] In adults, Xp11.2 RCC has a more aggressive clinical course with advanced stage at diagnosis, development of hematogenous metastases and rapid relapse.[15,17,44-45] The cancer-specific survival rate is significantly decreased in patients with Xp11.2 RCC than those with other types of RCCs.[45] The grim clinical outcome associated with Xp11.2 RCC warrants early detection, accurate diagnosis and close follow-up. The current management of Xp11.2 RCC is similar to conventional RCC. For localized Xp11.2 RCC including patients with positive regional lymph nodes, surgery is the treatment of choice.[20,46] For patients with hematogenous metastases, the current options are immunotherapy using cytokines, such as interleukin 2 (IL-2) and interferon alpha (IFNα) and multi-kinase inhibitors. Clinical studies have demonstrated certain efficacy of multi-kinase inhibitors, for example, sunitinib, sorafenib and mTOR/MET kinase inhibitor, in treating rapidly progressive metastatic Xp11.2 RCC in adult patients.[47-53] The optimal treatment approach for Xp11.2 RCC remains to be determined.

Table 2. The Immunostain Profiles of Xp11.2 RCC and its Close Mimickers.

	Xp11.2 RCC	**CCRCC**	**PRCC**	**CCPRCC**
TFE3	+	-	-	-
Cathepsin K	+	-	-	-
CK7	-	-	+	+
Vimentin	-	+	-	- or focal +
AMACR	+	-	+	-
CD10	+	+	+	- or focal +
CA9	-	+	-	+

SUMMARY

Xp11.2 RCC is a rare tumor affecting both pediatric and adult populations and is relatively common in children and adolescents. The clinical presentation is nonspecific and patients typically have a poor prognosis. In children, prior chemotherapy may predispose to developing Xp11.2 RCC. Eight *TFE3* fusion partners have been reported; however, the identities of three of them are unknown. The chimeric TFE3 fusion proteins contribute to tumorigenesis by dysregulating gene transcription and cell cycle. The characteristic histological pattern of Xp11.2 RCC is clear cells with voluminous cytoplasm arranged in nested and/or tubular-papillary architecture. Its immunohistochemical staining profile is unique, showing positive nuclear staining for TFE3 and Cathepsin-K and negative or focally weakly positive for cytokeratins. Modern molecular techniques of FISH and RT-PCR can confirm the diagnosis of Xp11.2 RCC. Surgery remains to be the treatment of choice for organ confined or cases with limited local metastasis. Newer therapeutic approach targeting the aberant *MiTF/TFE* transcriptional pathway, such as mTOR/MET inhibitors, may provide alternative treatment in the future.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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