Xp11.2 translocation renal cell carcinoma (RCC) is a newly identified category of RCC described in the 2004 WHO Classification of Kidney Tumors. Although the incidence of this disease is rare, it accounts for one third of pediatric RCCs. It is different from other RCCs in clinical manifestations, histopathologic features, biological behaviour and prognosis. At present, Xp11.2 translocation RCC has seldom been reported. This review analyzed recent researches on Xp11.2 translocation RCC, described its classification and summarized the characteristics of epidemiology, clinical manifestations, histopathology, diagnosis, treatment and prognosis.

In 2004, the World Health Organization updated the pathohistologic classification of renal cell carcinoma (RCC), and Xp11.2 translocation RCC was accepted as a distinctive entity. Now there are only a few reports about Xp11.2 translocation RCC in China. This review described the classification, diagnosis and treatment of Xp11.2 translocation RCC.

Xp11.2 translocation RCC is characterized by various translocations including chromosome Xp11.2, all resulting in fusion of genes including the TFE3 transcriptional factor gene. In recent years, several types of Xp11.2 translocation RCC have been identified (Table 1). It is interesting that the ASPL-TFE3 fusion gene was first discovered in alveolar soft part sarcoma (ASPS). Thereafter it was detected in some RCC patients. The chromosomal breakpoints of these two genes are both located in Xp11.2 and 17q25, and identically resulting ASPS-TFE3 gene fusion. But they have different phenotypes. The t(X;17) translocation is unbalanced in ASPS [der(17)t(X;17)(p11.2;q25)]; whereas the t(X;17) translocation is balanced in ASPS-TFE3 RCC [t(X;17)(p11.2;q25)].

TFE3 is one of four members of the MiT transcriptional factor family. The other members are MITF, TFEB and TFC. These MiT members share perfect homology in their DNA binding domains and bind a common DNA motif. TFEB also has been found to be involved in chromosomal translocation in some RCC patients. This subset of RCC harbors t(6;11)(q21;q13) that results Alpha-TFEB gene fusion.5

**Epidemiology**

Xp11.2 translocation RCC is rare, and mostly occur in children and young adults, with no gender predominance being reported. Currently, the incidence of this disease can not be accurately estimated. As reported abroad, about one third of pediatric RCCs are Xp11.2 translocation RCCs. The incidence of adult Xp11.2 translocation RCC has not yet been identified. However, according to current data, the percentage of patients with Xp11.2 translocation RCC among the entire population of adult RCC patients is relatively low. Argani et al. reported that no TFE3 protein was detected in 86 adult RCC patients. Xiao et al. also reported that only 2 (0.9%) of 229 Chinese RCC patients were confirmed to be Xp11.2 translocation RCC.

Xp11.2 translocation RCC maybe associate with history of chemotherapy. Ramphal et al. had reported seven Xp11.2 translocation RCC patients among a series of pediatric RCC patients, and one (14%) of them had received chemotherapy for abdominal ganglioneuroblastoma five years before diagnosis of RCC. As reported by Argani et al. among 39 chromosome translocation RCC (included Xp11.2 translocation RCC and Alpha-TFEB RCC) patients confirmed in Johns Hopkins Hospital, six had history of chemotherapy, and the intervals between chemotherapy and the diagnosis of RCC ranged from 4 to 13 years.

**Clinical manifestation**

Gross hematuria is the most common symptom of Xp11.2 translocation RCC. However, the classic triad of RCC (hematuria, flank pain, and a palpable abdominal mass) is rare in Xp11.2 translocation RCCs; extrarenal symptoms also are uncommon. There is no association between Xp11.2 translocation RCC and von Hippel-Lindau (VHL) syndrome. No Xp11.2 translocation RCC combined VHL syndrome has been reported. The imaging feature of Xp11.2 translocation RCC is similar with that of conventional RCC (clear cell carcinomas).11 It is difficult to distinguish them from each other by radiology. The tumor of Xp11.2 translocation RCC is frequently calcified. Even there was one report that a patient was initially thought to have renal calculus because of the tumor’s pelvic location and calcified appearance and received extracorporeal shockwave...
Histiopathology

Xp11.2 translocation RCC resembles conventional RCC on gross examination, most commonly being tan-yellow, and often necrotic and hemorrhagic. The most distinctive histopathologic appearance of Xp11.2 translocation RCC is papillary structure comprised of clear cells, or nested architecture composed of cells with granular eosinophilic cytoplasm. It is difficult to distinguish Xp11.2 translocation RCC from conventional RCC by regular HE staining.

Different types of Xp11.2 translocation RCC have different histopathologic features. ASPL-TFE3 RCC is characterized by cells with voluminous, clear or eosinophilic cytoplasm, loose intercellular connection, vesicular nuclear chromatin, and prominent nucleoli; psammoma bodies are common and sometimes extensive, often arising within characteristic hyaline nodules. PRCC-TFE3 RCC is generally featured with less cytoplasm, fewer psammoma bodies and hyaline nodules, and more compact nested architecture; and are typically surrounded by calcified fibrous pseudocapsule. The histopathologic features of other types of Xp11.2 translocation RCC have yet to be clearly defined.

Xp11.2 translocation RCC is frequently negative or only weakly positive for epithelial markers like cytokeratin, Vimentin and epithelial membrane antigen (EMA), but it always express renal cell carcinoma marker antigen and CD10.

Biological Behavior

Now we still know little about biological behavior of Xp11.2 translocation RCC. According to available reports, Xp11.2 translocation RCC seems to be more aggressive than conventional RCC. Argani et al. reported that 16 of 28 patients with Xp11.2 translocation RCC were presented at stage III or stage IV (AJCC 2003), and lymph node metastasis was identified in 11 of 13 patients with evaluable lymph nodes.

Different types of Xp11.2 translocation RCC have different biological behaviors. ASPL-TFE3 RCCs commonly present at advanced stage at diagnosis; almost all patients have lymph node metastases at diagnosis no matter what size of primary mass is. Argani et al. reported that seven of eight ASPL-TFE3 RCC were presented at stage III or stage IV (AJCC 2003) at diagnosis, and lymph node metastasis was identified in five of six patients with evaluable lymph nodes. PRCC-TFE3 RCC seems to be less invasive. Argani et al. reported that among ten patients with evaluable PRCC-TFE3 RCC, three presented at stage I, two at stage II, four at stage III, and one at stage IV; only one of the four patients who received hilar lymph node dissection had lymph node metastasis. The biological behaviors of the other types of Xp11.2 translocation RCC need to be definitively defined.

Diagnosis

Detecting TFE3 protein in cell nuclei by immunohistochemistry is the most important assay for distinguishing Xp11.2 translocation RCC from other types of RCC, with sensitivity of 97.5% and specificity of 99.6%. In addition, we can detect the mRNA expression of TFE3 fusion gene by reverse transcription-polymerase chain reaction (RT-PCR). TFE3 gene exists widely in normal tissues and other neoplasms, but it is undetectable because its expression is tightly regulated and its half-life is short. The mechanism of TFE3 protein positive in Xp11.2 translocation RCC is unclear. The most possible mechanism is that the fusion gene promotes overexpression of TFE3 protein by producing a strong promotor.

After a tumor is diagnosed as Xp11.2 translocation RCC, we can distinguish the type of fusion gene and the phenotype of the translocated chromosome by further cyogenetic or molecular analysis.

Treatment

The optimal therapy for Xp11.2 translocation RCC remains to be determined. Now, surgical dissection is the main treatment for Xp11.2 translocation RCC, like conventional RCC. Even if the patient is diagnosed with local lymph node metastasis, we should still perform aggressive operation. Geller et al. reported that the overall survival rate (72.4%) of 58 pediatric RCC patients with local lymph node metastasis but no distant metastasis was nearly triple that of adult patients with similar presentation. Because Xp11.2 translocation RCCs account about one third of pediatric RCCs, and local lymph node metastasis is common in Xp11.2 translocation RCCs, we suppose that Xp11.2 translocation RCC with local lymph node metastasis and no distant metastasis has a relatively favorable prognosis.

Xp11.2 translocation RCC does not respond to adjuvant therapies like immunotherapy, radiotherapy and chemotherapy. Whereas, it had been reported that the response rate of metastatic RCC (excluding Xp11.2 translocation RCC) to interferon-α (IFN-α) and interleukin-2 (IL-2) used alone or in combination was 11–20%. Recent gene expression profiling data may help to explain why Xp11.2 translocation RCC may not respond to adjuvant therapy which is effective for conventional RCC. By microarray profiling, the gene expression profile of Xp11.2 translocation RCC was found to be more similar with that of ASPS, a sarcoma which is refractory to chemotherapy, than with that of conventional RCC. Though Xp11.2 translocation RCC likely arises from renal tubular epithelial precursors like conventional RCC does, its underlying biological behaviors may be driven by ASPL-TFE3 fusion gene which is shared with ASPS.

Perhaps we can find a new treatment option aimed at chromosome translocation. Recently, gene expression profiling studies for ASPL-TFE3 RCC have suggested a novel therapeutic target. At RNA level, ASPS has been shown to overexpress the gene for MET receptor tyrosine kinase as other translocation-associated sarcomas do. In vitro, ASPL-TFE3 fusion protein, exists in both ASPS and Xp11.2 translocation RCC, transactivates MET gene promoter, increasing MET mRNA expression. High level of MET protein can
be detected by immunohistochemistry and Western blot. In vitro, the growth of an ASPL-TFE3 cell line could be diminished in response to either a selective inhibitor of MET tyrosine kinase or RNA interference-mediated knockdown of MET. Hence, MET tyrosine kinase is a potential therapeutic target of ASPL-TFE3 RCC.

**Prognosis**

The prognosis of Xp11.2 translocation RCC remains unknown. According to available reports, the clinical course of Xp11.2 translocation RCC appears to be indolent. Take the series of ASPL-TFE3 RCC mentioned before for example, although most patients were in advanced stage at diagnosis, many of them survived for a long time with or without tumor after treatment (for example, one patient at stage pT4N1Mx survived for over 10 years with tumor, and one at stage pT3aN1M0 survived for over 7 years without tumor).

**Summary**

Now we still know little about Xp11.2 translocation RCC. With limited cases and short follow up, we have not comprehended its features of clinical manifestation, pathology and biological behaviors. The effect and mechanism of Xp11.2 translocation and the fusion gene on the emerging and developing of this disease are still unknown. With the clinicians paying more attention to this kind of RCC and more widely use of detection assay, more and more Xp11.2 translocation RCCs will be confirmed, and we will know it more comprehensive.

**References**


