Xp11.2 Translocation Renal Cell Carcinoma

Henry B. Armah, MD; Anil V. Parwani, MD, PhD

- Xp11.2 translocation renal cell carcinomas (RCCs), a recently recognized distinct subtype, are rare tumors predominantly reported in young patients. They comprise at least one-third of pediatric RCCs, and only few adult cases have been reported. They are characterized by various translocations involving chromosome Xp11.2, all resulting in gene fusions involving the transcription factor E3 (TFE3) gene. In recent years, at least 6 different Xp11.2 translocation RCCs have been identified and characterized at the molecular level. These include a distinctive RCC that bears a translocation with the identical chromosomal breakpoints (Xp11.2, 17q25) and identical resulting ASPL-TFE3 gene fusion as alveolar soft part sarcoma. They typically have papillary or nested architecture and are composed of cells with voluminous, clear, or eosinophilic cytoplasm. Their most distinctive immunohistochemical feature is nuclear labeling for TFE3 protein. Although only limited data are available so far, they are believed to be rather indolent, but there have been increasing, recent reports of an aggressive clinical course in adult cases. The consistent immunohistochemical staining for TFE3 in all RCC with unusual histology, regardless of patient age, is likely to expand the spectrum of Xp11.2 translocation RCC with respect to age, clinical behavior, and molecular abnormalities.


Xp11.2 translocation renal cell carcinomas (RCCs), a recently classified distinct subtype, are rare tumors that usually affect children and adolescents,1–5 with only a few reported adult cases to date.6–18 They result from gene fusions between the transcription factor E3 (TFE3) gene located on chromosome Xp11.2 and at least 6 various partners reported to date.1–18 To our knowledge, Tomlinson et al19 reported the first published pediatric case report of Xp11.2 translocation RCC in a 17-month-old child. It is estimated that approximately one-third of pediatric RCCs are Xp11.2 translocation RCCs,2–5 whereas conventional clear cell RCCs make up about 15% of RCCs in children.20,21 Unlike that found in children, conventional clear cell RCCs make up 70% of RCCs in adults and 53% in young adults,21 but the incidence of Xp11.2 translocation RCCs in these age groups is not known. Although only limited data are available thus far, to our knowledge, Xp11.2 translocation RCCs are believed to be rather indolent even when diagnosed at advanced stages,1–8 but there have been increasing, recent reports of an aggressive clinical course in adult cases.9–18

Xp11.2 translocation RCCs typically have nested or papillary architecture and are composed of cells with voluminous, clear, or eosinophilic cytoplasm.1–18 Translocations involving TFE3 induce overexpression of this protein and can be specifically identified by immunohistochemistry (IHC).7 Nuclear labeling for TFE3 is specific to Xp11.2 translocations.7 Argani et al7 reported that immunostaining of TFE3 is nuclear and should, in positive cases, be obvious at low-power magnification. A reliable interpretation requires the absence of cytoplasmic labeling of tumor cells and an absence of nuclear labeling in adjacent normal kidney. Diagnosis of Xp11.2 translocation RCCs, which remains underestimated in the absence of cytogenetic studies on fresh or frozen materials, is, therefore, now possible on archival paraffin blocks.7,16,18 With the advent of TFE3 IHC, archival cases for which frozen tissue is not available can now be confirmed to belong to this group of neoplasms by compatible histology. Indeed, frozen tumor for molecular analysis is not usually collected for most RCCs diagnosed in adults. This is in contrast to pediatric renal neoplasms, where frozen tissue collection and cytogenetics are emphasized as crucial to obtaining the correct diagnosis. Most adult RCCs are readily classified using routine histologic preparations. Although RCC in a child is uncommon and prompts consideration of distinctive entities, such as the Xp11.2 translocation RCC, RCC in adults is commonplace and has not prompted routine cytogenetic and molecular analysis in the past.

CLINICAL PRESENTATION

Clinically, Xp11.2 translocation RCCs usually present as an asymptomatic, painless renal mass, often identified accidentally during abdominal imaging.1–23 Two recent reports have suggested that a previous exposure to cytotoxic chemotherapy in childhood is a risk factor for developing Xp11.2 translocation RCC.22,23 Ramphal et al23 reported a case of ASPL-TFE3 translocation RCC, which developed 5 years after cytotoxic chemotherapy for ganglieneuroblastoma. Argani et al22 reported that approximately 10% to 15% of translocation RCCs were associated with previous exposure to cytotoxic chemotherapy in childhood and, therefore, suggested that translocation RCCs should be added to the list of chemotherapy-associated secondary neoplasms in children (along with acute leukemias, soft tissue sarcomas, and malignant gliomas).
no evidence of disease, 4 months after diagnosis. Multilocular cystic RCC-like features, who was alive, with (Figures 1 through 4). However, the Xp11.2 translocation RCCs reported the frequency of psammoma bodies as 50% and 62%, respectively. However, psammoma bodies are seen in papillary RCC. The usual absence of foamy macrophages, nuclear grooves, stromal inflammatory cells, and necrotic background in Xp11.2 translocation RCC may be useful in distinguishing them from papillary and conventional clear cell RCC.

**Immunohistochemical Features**

The most distinctive IHC feature of Xp11.2 translocation RCC, which is absent in conventional clear cell and papillary RCC, is a detectable nuclear staining for the chimeric (mutant) TFE3 protein (Figure 5). The antibody used recognizes the C-terminal portion of the TFE3 protein, which is retained in all TFE3 fusion proteins. Because native TFE3 is known to be expressed constitutively and ubiquitously, but is not detectable by IHC, in normal tissues, it is anticipated that all the different Xp11.2/TFE3 gene fusions consistently lead to the overexpression of TFE3 protein. Previous studies have reported specific IHC patterns that are suggestive of the diagnosis of Xp11.2 translocation RCC, in the absence of TFE3 IHC. Generally, the expression of cytokeratins (AE1/AE3, Cam 5.2, CK7, and epithelial membrane antigen [EMA]) and melanocytic markers (HMB-45 and Melan-A) were rare and weak, the expression of vimentin was variable and weak, and that of CD10 (Figure 6), E-cadherin (Figure 7), α-methylacyl coenzyme A racemase (Figure 8), and RCC antigen were common and strong in Xp11.2 translocation RCCs. The presence of extensive psammoma bodies, a feature that is rarely observed in conventional clear cell RCC, can occasionally be seen in papillary RCC. The usual absence of foamy macrophages, nuclear grooves, stromal inflammatory cells, and necrotic background in Xp11.2 translocation RCC may be useful in distinguishing them from papillary and conventional clear cell RCC.

**Gross Features**

Macroscopically, Xp11.2 translocation RCCs are usually tan-yellow, necrotic, and hemorrhagic and, therefore, may grossly mimic conventional clear cell RCC. Although, a cystic gross appearance is uncommon for Xp11.2 translocation RCCs, Suzigan et al recently reported a Xp11.2 translocation RCC in a 17-year-old adolescent girl with multicocular cystic RCC-like features, who was alive, with no evidence of disease, 4 months after diagnosis.

**Microscopic Features**

The most consistent histologic appearance of Xp11.2 translocation RCC is a carcinoma with mixed papillary and nested/alveolar architecture, composed of cells with clear and/or eosinophilic, granular, voluminous cytoplasm; discrete borders; vesicular chromatin; prominent nucleoli; and the presence of extensive psammoma bodies (Figures 1 through 4). However, the Xp11.2 translocation RCCs are morphologically heterogeneous. Argani and Ladanyi suggested that histologic variants of Xp11.2 translocation carcinomas were associated with specific chromosome translocation. The papillary renal cell carcinoma (PRCC)-TFE3 variant is generally composed of a mix of intermediate-sized, clear and eosinophilic cells (more often with a clear cell appearance), arranged in a predominantly nested pattern (either compact or alveolar), with small foci of a papillary pattern, and which shows few psammoma bodies; this is in contrast to the ASPL-TFE3 variant, which generally shows mixed pseudopapillary and nested pattern of voluminous clear or eosinophilic cells, and almost constant presence of extensive psammoma bodies. Two recent, large, original clinicopathologic studies of 28 cases and 31 cases of Xp11.2 translocation RCCs reported the frequency of psammoma bodies as 50% and 62%, respectively. However, psammoma bodies, a feature that is rarely observed in conventional clear cell RCC, can occasionally be seen in papillary RCC. The usual absence of foamy macrophages, nuclear grooves, stromal inflammatory cells, and necrotic background in Xp11.2 translocation RCC may be useful in distinguishing them from papillary and conventional clear cell RCC.
immunostaining as 100% and 82%, respectively. In the recent, largest (to our knowledge), original clinicopathologic study of 31 cases of Xp11.2 translocation RCCs, Camparo et al observed immunohistochemical expression of CD10, α-methylacyl coenzyme A racemase (p504s), Melan-A, E-cadherin, vimentin, HMB-45, EMA, AE1/AE3, and CK7 in 100%, 100%, 89%, 66%, 65%, 46%, 32%, 25%, and 17% of cases, respectively.

**Electron Microscopic Features**

Ultrastructurally, Xp11.2 translocation RCCs demonstrate abundant lipid droplets and glycogen, similar to that found in conventional clear cell RCC.13 Additionally, rare rhomboid granules or crystals, similar to that found in alveolar soft part sarcoma (ASPS), were also identified.13 Therefore, Xp11.2 translocation RCCs display the ultrastructural features of both conventional clear cell RCC and ASPS.

**Cytogenetic and Molecular Features**

Xp11.2 translocation RCCs result from gene fusions between the TFE3 gene located on chromosome Xp11.2 and at least 6 various partners reported to date.1-18 The molecular identity of 5 of these 6 gene fusion partners of TFE3 is known (83%), whereas the identity of the sixth, which is situated on chromosome 3, is not yet known.1-18 The 5 known gene fusion partners of TFE3 are PRCC, ASPL, polypyrimidine tract-binding protein–associated splicing factor (PSF), non-POU domain–containing octamer-binding (NONO; p54nrb), and clathrin heavy-chain (CLTC) genes, respectively, situated on chromosomes 1q21, 17q25, 1p34, Xq12, and 17q23 (Table 1).1-18 The t(X;17)(p11.2;q25) or ASPL-TFE3 translocation RCC and ASPS contain the identical ASPL-TFE3 fusion transcript; however, the t(X;17) translocation is consistently balanced (reciprocal) in the Xp11.2 translocation RCC and unbalanced in the ASPS.1 TFE3 is a member of the microphthalmia-associated transcription factor (MITF) family.24 Other members of this family include transcription factor EB (TFEB), transcription factor EC (TFEC), and MITF. Members of this family of proteins code for basic helix-loop-helix/leucine zipper (BHLH-LZ) transcription factors that bind to the consensus hexanucleotide E-box sequence CA[C/T]GTG, either as homodimers or heterodimers.24 Another subset of translocation RCCs are associated with a translocation t(6;11)(p21;q12) involving TFEB.25 Because TFE3 and TFEB translocation RCCs share clinical, morphologic, immunohistochemical, and molecular features, Argani and Ladanyi proposed to regroup these neoplasms under the

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Abbreviations: ASPL, alveolar soft part sarcoma locus; ASPS, alveolar soft part sarcoma; CLTC, clathrin heavy chain; NONO, non-POU domain-containing octamer-binding; PRCC, papillary renal cell carcinoma; PSF, polypyrimidine tract binding protein–associated splicing factor; RCC, renal cell carcinoma.
category Mitf/TFE family translocation carcinomas. Mitf and Tfe8 may be involved in regulating specific melanocyte differentiation genes. Although Tfe3 also has the ability to form heterodimers with Mitf, the ability to bind promoters necessary for the regulation of melanocyte differentiation seems to be hindered. This discrepancy between the binding ability of Tfe8 heterodimers compared with Tfe3 heterodimers may explain why Tfe8-associated RCCs express HMB-45 and Tfe3-associated RCCs do not.

Two mutually exclusive Aspl-Tfe3 gene fusions have been observed in RCCs, resulting in 2 distinct Aspl-Tfe3 fusion transcripts in which Aspl is fused to either exon 3 or exon 4 of the Tfe3 gene. The Aspl-Tfe3 fusion replaces the NH2-terminal portion of Tfe3 by Aspl sequences while retaining the Tfe3 DNA-binding region, activation domain, and nuclear localization signal. The Aspl-Tfe3 fusion protein functions as a stronger transactivator compared with native or wild-type Tfe3 at several promoters. The Aspl-Tfe3 fusion protein binds to the Met promoter and strongly activates it. Psf-Tfe3 and NonO-Tfe3 fusion proteins also bind to the Met promoter. Induction of Met promoter by Aspl-Tfe3 fusion protein results in strong Met autophosphorylation and activation of downstream signaling in the presence of hepatocyte growth factor (HGF). Papillary renal cell carcinoma is an ubiquitously expressed nuclear protein. The fusion of Tfe3 and Prcc results in 2 reciprocal in-frame fusion genes, Tfe3-Prcc and Prcc-Tfe3. The Prcc-Tfe3 fusion protein, which contains both the acidic activation domain and the C-terminal proline-rich activation domain of Tfe3, has been shown to be a more potent transcriptional activator than wild-type Tfe3. Unlike wild-type Psf or Pse, which are both nuclear proteins, Psf-Tfe3 fusion protein is targeted to the endosomal compartment. Although Psf-Tfe3 fusion protein appears to have no dominant effect on the nuclear localization of wild-type Psf, it sequesters Tfe3 and p53 in the extranuclear compartment, which leads to functionally null p53 and Tfe3 cells. The functional loss of p53 and/or Tfe3, most likely, contributes to the transformed phenotype through interference with cell cycle control.

Functionally, NonO is closely related to Psf, both of which are members of a family of Drosophila behavior and human splicing proteins. These proteins are thought to play an important role in the proper splicing of pre-messenger RNAs. The NonO-Tfe3 fusion protein, which contains both the acidic activation domain and the proline-rich activation domain of Tfe3, has been shown to be a more potent transcriptional activator than wild-type Tfe3. The Cltc-Tfe3 fusion protein retains the DNA-binding and C-terminal transactivation domains of Tfe3 but lacks the multimerization domain of Cltc. Clathrin is the major protein constituent of the coat that surrounds organelles to mediate selective protein transport. Recently, clathrin has also been found to stabilize fibers of the mitotic spindle and thus thought to play an important role in cell cycle control. Hence, the absence of clathrin at the mitotic spindle results in an increased frequency of misaligned chromosomes, which may lead to genetic instability and, ultimately, cancer.

**Differential Diagnosis**

Xp11.2 translocation RCC can occur in adults and may be aggressive cancers and, hence, require morphologic distinction from conventional clear cell and papillary RCCs. Although they may be uncommon on a percentage basis, given the vast predominance of RCCs in adults compared with children, adult Xp11.2 translocation RCC may well outnumber their pediatric counterparts. Accurate histopathologic diagnosis, supported by confirmatory Tfe3 IHC, should allow this subset of adult RCCs to be delineated so that their clinicopathologic features can be analyzed further. On routine hematoxylin and eosin sections, Xp11.2 translocation RCC may overlap significantly with conventional clear cell and papillary RCCs in adults. The formation of true papillae is rare in conventional clear cell RCC, although pseudopapillary areas arising from degeneration of acinar structures in conventional clear cell RCC may be difficult to distinguish from true papillae. Furthermore, conventional clear cell RCC seldom forms psammoma bodies, and so, when present, psammomatous calcifications are evidence in favor of an Xp11.2 translocation RCC. Although clear cells are uncommon in papillary RCC, clear cells may be seen in the areas of degeneration associated with hemosiderin deposition. Additionally, Xp11.2 translocation RCCs with prominent eosinophilic cytoplasm might be confused with type 2 papillary RCCs.

Additionally, whereas Xp11.2 translocation RCCs result from gene fusions between the Tfe3 gene located on chromosome Xp11.2 and at least 6 various partners reported to date, other specific genetic abnormalities have been described in the literature for the different types of renal cell tumors in its differential diagnosis. Most conventional clear cell RCCs have deletions in the short arm of chromosome 3 (3p−); papillary RCCs usually present with trisomies of chromosome 7 and 17 and/or loss of the Y chromosome (although the frequency of these alterations is lower in papillary type 2 tumors compared with type 1); chromophobe RCCs usually show losses of chromosomes 1, 2, 6, 10, 13, and 17; and oncocytomas usually present with monosomy 1, chromosome 19 aberrations or no aberrations.

**Current Treatment and Prognosis**

The optimal therapy for the Xp11.2 translocation RCCs remains to be determined. Some patients with Xp11.2 translocation RCC have received immunotherapy because, until recently, immunotherapy has been the only standard treatment for patients with advanced stage conventional clear cell RCC. However, recent gene expression profiling data suggest that Xp11.2 translocation RCCs may not respond to immunotherapy directed toward conventional clear cell RCCs. The gene expression profile of Xp11.2 translocation RCC was found to be closer to that of Asps, a sarcoma that is notoriously refractory to chemotherapy, than to that of conventional clear cell RCC. Hence, although Xp11.2 translocation RCC most probably arises in renal tubular epithelial precursors, like conventional clear cell RCC, their underlying biology may be driven by the Aspl-Tfe3 gene fusion shared with Asps. The Aspl-Tfe3 fusion protein common to Asps and the Xp11.2 translocation RCCs transactivates the Met promoter in vitro and, hence, increasing Met mRNA and protein expression. Finally, a Aspl-Tfe3 cell line exhibited diminished growth in response to either a selective inhibitor of the Met tyrosine kinase or RNA interference-mediated knockdown of Met in vitro. Hence, Met tyrosine kinase

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may be a potential novel therapeutic target in Xp11.2 translocation RCCs.

Xp11.2 translocation RCCs occur primarily, but not exclusively, in children and young adults and are believed to be rather indolent even when diagnosed at advanced stages.1–8 However, there have been increasing, recent reports of Xp11.2 translocation RCC with aggressive clinical course in patients aged 16 and older (Table 2).9–18 These recent reports emphasize that, although the tumor morphology in adult Xp11.2 translocation RCC was similar to that in children, most of these adult patients had an aggressive clinical course.9–18 Therefore, overall Xp11.2 translocation RCCs may be inherently more aggressive in adults than in children; however, the relatively short follow-up periods currently available and the potential bias inherent in nonconsecutive case series and case reports preclude a definitive statement. Additionally, there seems to be clinicopathologic heterogeneity even in adults, but the clinical and molecular basis for this heterogeneity remains to be elucidated.

References


