

Renal Cell Carcinoma Associated with Xp11.2 Translocation/Transcription Factor E3 (TFE3) Fusion

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Introduction

Renal cell carcinomas (RCC) associated with Xp11.2 translocations (Xp11.2 TRCCs) form a new and little known entity of the WHO 2004 classification [1-23]. de Jong et al. [1] and Tomlinson et al [2] first described Xp11 translocation as a previously unknown finding in the karyotype of two atypical renal masses presenting in infant males [13].

These neoplasms are defined by several translocations involving the transcription factor 3 (TFE3) gene that is located on chromosome Xp11.2, resulting in a gene fusion between TFE3 and at least 5 possible partners [3-7,16,18,21,23]. These include a distinctive RCC which bears a translocation with the identical chromosomal breakpoints (Xp11.2, 17q25) and identical resulting ASPL-TFE3 gene fusion as alveolar soft part sarcoma (ASPS), with the distinction that the t(X;17) translocation is cytogenetically balanced in these renal tumors [4]. The most commonly observed translocations are t(X;17)(p11.2;q25), t(X;1)(p11.2;p34), and t(X;1)(p11.2;q21), which lead to gene fusions of TFE3 with ASPL, PSE, and PRCC, respectively [3,15,16].

This review aims to highlight the helpful histologic, immunohistochemical, and cytogenetic features of this entity to enable correct diagnosis.

Incidence and Clinical Presentation

Xp11.2 TRCCs occur primarily, but not exclusively, in children and

young adults with a strong female predominance [3-5]. It is estimated that approximately one third of pediatric renal carcinomas are TFE3-related translocation carcinomas [3]. Recent studies have shown that adult Xp11 TRCC is more common than originally perceived, making up anywhere from 1.6% to 5% of adult RCCs [13].

Clinically, Xp11.2 TRCCs usually present as an asymptomatic, painless mass, often identified incidentally during abdominal imaging [3]. Cytotoxic chemotherapy may predispose to the development of Xp11.2 TRCC [8,20]. In this context, Argani et al. [8] reported that approximately 10% to 15% of Xp11.2 TRCC were associated with exposure to cytotoxic chemotherapy in childhood and, therefore, suggested that Xp11.2 TRCCs should be added to the list of chemotherapy-associated secondary neoplasms in children [3-8].

Gross Features

Macroscopically, Xp11.2 TRCCs are usually solid, tan-yellow, and may display hemorrhage and necrosis. The gross appearance may mimic conventional clear cell RCC. A multilocular cystic gross appearance is uncommon.

Microscopic Features

Microscopically, Xp11.2 TRCCs show papillary and/or nested architecture in a background of prominent capillary vasculature (Figures 1A and 1B) [1-23]. Areas with a solid growth pattern are rarely observed. The neoplastic cells are voluminous and polygonal, with clear and/or eosinophilic granular cytoplasm (Figure 1C). The nuclei are vesicular with prominent nucleoli. The stroma is desmoplastic and contains a variable amount of lymphocytes. Psammomatous calcifications and foci of stromal eosinophilic hyaline globules (Figure 1D) may be numerous and widespread. Satellite tumor nodules, multifocal necrosis and lymphovascular invasion are frequently observed.

Electron Microscopic Features

Ultrastructural examination demonstrates a distinctive combination of alveolar soft part sarcoma (ASPS)-like and conventional clear cell RCC epithelial features: well-formed rhomboid crystals, abundant electron-dense granules, well-formed cell junctions, intracellular glycogen and fat, well-formed glandular lumens with microvilli, and prominent basement membrane [4,19].

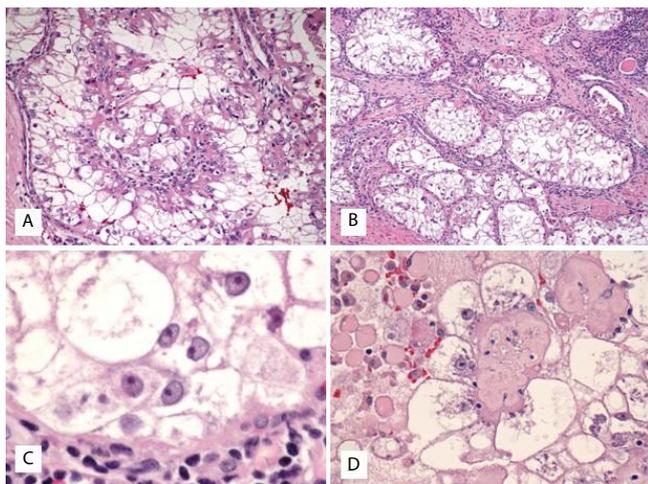


Figure 1: A: Translocation renal cell carcinoma. Note papillary architecture. Hematoxylin-eosin stain. 100x.

B: Translocation renal cell carcinoma. Note nested architecture. Hematoxylin-eosin stain. 100x.

C: Translocation renal cell carcinoma. Note voluminous clear cytoplasm, vesicular nuclei, and prominent nucleoli. Hematoxylin-eosin stain. 400x.

D: Translocation renal cell carcinoma. Note stromal nodular hyalinosis. Hematoxylin-eosin stain. 200x.

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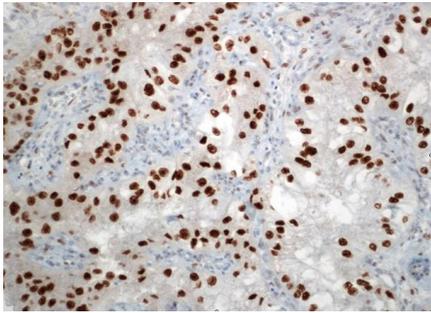


Figure 2: Translocation RCC. Note strong nuclear expression of TFE3. 200x.

Immunohistochemical Features

The most sensitive and specific immunohistochemical markers for these neoplasms bearing TFE3 gene fusion are TFE3 protein and cathepsin-K (Figure 2) [3,5,6,10,11,13-19,21-23]. Strong expression of CD10, RCC, E-cadherin, and alpha-methylacyl coenzyme A racemase (AMACR) is common. Vimentin is variably expressed, while expression of cytokeratins (AE1/AE3, Cam5.2, CK7), melanocytic markers (Melan-A, HMB-45), and EMA is rare and weak [3,10,19,21].

Cytogenetic and Molecular Features

In Xp11.2 TRCCs, the gene rearrangements result in the overexpression of several fusion proteins that contain the C-terminal portion of TFE3, a member of the microphthalmia-associated transcriptional factor family (MiTF). At least 5 known fusion gene partners, including ASPL on 17q25, PRCC on 1q21, PSF on 1q34, NonO on Xq12, and CLTC on 17q23, have been reported to date [15,16]. Furthermore, t(X;3)(p11;q23) and t(X;19)(p11.2;q13.1) have also been reported without a defined gene partner [23]. A closely related but rare variant of RCC harboring the t(6;11)(p21;q12) translocation involves the transcription factor EB (TFEB), also a member of the MiTF family [23]. Because TFE3 and TFEB translocation RCCs share clinical, histopathologic, immunohistochemical, and molecular features, Argani and Ladanyi proposed to reclassify these neoplasms under the category of "MiTF/TFE translocation carcinoma family" [7,23].

Differential Diagnosis

On routine hematoxylin-eosin sections, Xp11.2 TRCC requires morphologic distinction from renal neoplasms with clear cell cytology and papillary architecture: conventional clear cell RCC, papillary RCC, and clear cell papillary RCC (CCPRCC) [22]. The formations of true papillae, psammomatous calcifications and hyaline stromal nodules are rare in conventional clear cell RCC [3]. Furthermore, clear cell RCCs are typically negative for both CK 7 and AMACR, although both may be focally positive, especially in higher-grade tumors [22]. Cathepsin-K and TFE3, two markers of Xp11.2 TRCC, are consistently negative [22]. Clear cell RCCs have consistent genetic abnormalities. A deletion on the short arm of chromosome arm (del 3p), where the VHL gene resides, is present in most sporadic and familial tumors.

Xp11.2 TRCCs with prominent eosinophilic cytoplasm might be confused with type 2 papillary RCC [3,22]. Clear cell change and fine cytoplasmic granulations are typically seen in association with hemosiderin deposition and/or necrosis. The cytoplasmic clearing may reflect phagocytic activity of the renal carcinoma cells in these settings. [22]. The immunohistochemical profile of papillary RCC typically shows strong membranous positivity for CK7. Cathepsin-K

and TFE3 are both consistently negative. Cytogenetic studies show distinctive abnormalities unique to papillary RCC, including trisomy of chromosomes 7 and 17 along with loss of Y [22].

CCPRCC is a recently characterized, distinctive renal neoplasm, initially described in patients with end-stage renal disease, but is now known to arise in healthy kidneys as well [22,24]. CCPRCC can show a wide range of architectural features, including true papillary structures, branching tubules, and solid nests or ribbons. The neoplastic cells contain clear cytoplasm, small-to-intermediate size round or irregular nuclei, and inconspicuous nucleoli. The nuclei are typically polarized away from the basement membrane, creating a characteristic subnuclear vacuole similar to that seen in secretory endometrium. Pertinent negatives include lack of foamy histiocytes, psammomatous calcifications, or hemosiderin. CCPRCCs show a distinct immunoprofile not seen in conventional renal cell carcinomas [24]. The neoplastic cells are positive for CK7 and vimentin, and negative for RCC and AMACR [24]. Furthermore, no expression of cathepsin-K and TFE3 is observed in CCPRCC [22]. Cytogenetically, CCPRCC lacks typical abnormalities seen in either clear cell RCC or papillary RCC.

In conclusion, the diagnosis of an Xp11.2 TRCC is based on microscopic appearance, TFE3 immunostaining, and genetic analyses. TFE3 is a highly sensitive and specific immunohistochemical marker for screening tumors for the Xp11.2 translocation [15].

Biologic Behavior

Xp11.2 TRCCs occur primarily, but not exclusively, in children and young adults and are believed to be rather indolent, even when diagnosed at advanced stages. In contrast, the tumor tends to be more aggressive in adults with widespread systemic metastases. These patients have a poor clinical outcome [21]. Klatte et al [15] found a strong association between TFE3 expression and regional lymph node metastasis, which is generally accepted as a poor prognostic marker in the setting of metastatic RCC. Furthermore, ASPL-TFE3 gene fusion RCCs are more likely to present at an advanced stage in comparison with other TRCC [17]. The relatively short follow-up periods currently reported and the potential bias inherent in nonconsecutive case series and case reports preclude a definite statement as to the exact biologic behavior of this rare tumor.

Treatment

Because of the small number of TFE3 gene fusion-related renal tumors described in the literature, the impact of current treatment modalities remains to be uncertain [25]. The observed objective response rate and progression-free survival of targeted agents were similar to those reported for clear cell RCCs [26]. VEGFR-targeted therapies and mTOR inhibitors seem to be active in Xp11.2 TRCCs [26]. Sunitinib appears to be more effective than cytokine. Prospective randomized studies on novel targeted agents are needed to identify the optimal treatment strategy for this specific patient population [25].

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