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Short Communication

Kidney: Renal cell carcinomas with MiT family translocation

Pedram Argani

Department of Pathology, The Johns Hopkins Hospital, Baltimore MD (PA) pargani@jhmi.edu

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Abstract

Review on Renal cell carcinomas with MiT family translocations, with data on clinics, and the genes involved.

Keywords
Renal cell carcinoma; MiT family; NONO; TFE3; SFPQ; PRCC; CLTC; ASPSCR1; MALAT1; TFEB chromosome X; chromosome 1; chromosome 6; chromosome 17.

Clinics and pathology

Disease

Xp11 translocation renal cell carcinomas (RCCs) harbor gene fusions involving TFE3 transcription factor. The t(6;11) RCCs harbor a specific MALAT1 (Alpha)-TFEB gene fusion. TFEB and TFE3 belong to the same MiT subfamily of transcription factors (MiT for microphthalmia-TFE). Because of similarities at the clinical, morphologic, immunohistochemical, and genetic levels, the Xp11 translocation RCCs and t(6;11) RCCs are currently grouped together under the category of MiT family translocation renal cell carcinoma.

Epidemiology

Xp11 translocation RCC are the most common RCC in children, and comprises approximately 1% of adult RCC. There are only approximately 50 reported cases of t(6;11) RCC, median age is 31 years. Both RCC have been associated with prior exposure to cytotoxic chemotherapy.

Clinics

These form masses in the kidney. Xp11 translocation RCC are frequently calcified on imaging.

Pathology

Xp11 translocation RCC most commonly feature papillary architecture and epithelioid clear cells, with abundant psammoma bodies. Xp11 translocation RCCs can also present with unusual morphology mimicking other types of RCCs. Xp11 translocation RCCs can show solid or nested growth with clear to granular eosinophilic cytoplasm mimicking clear cell RCC, multilocular cystic RCC-like features, anaplastic/pleomorphic giant cells, tubular growth reminiscent of collecting duct carcinoma, well-developed fascicles of spindled neoplastic cells with bland nuclei in focal myxoid stroma mimicking mucinous tubular and spindle cell carcinoma, sarcomatoid change, oncocytic areas mimicking oncocytoma, oncocytic spindled areas resembling epithelioid angiomyolipoma, trabecular patterns mimicking carcinoid tumor, and colonization of renal pelvic urothelium mimicking urothelial carcinoma.

The t(6;11) RCC typically demonstrates a distinctive biphasic morphology, comprising larger epithelioid cells and small cells clustered around basement membrane material. The larger epithelioid cells may have clear to eosinophilic cytoplasm, and their nested architecture is similar to that of clear cell RCC. The smaller cells clustered around basement membrane material resemble the Call-Exner bodies of adult granulosa cell tumor.

These neoplasms typically do not show prominent cytologic atypia or mitotic activity. While these

lesions appear well delineated grossly, microscopically they characteristically entrap single native renal tubules at their periphery. Over time and with greater experience a broad range of morphologic appearances have been found in the t(6;11) RCC.
Some of the illustrated morphologic appearances in genetically-confirmed cases include extensive hyalinization (both nodular mass-forming hyalinization and diffuse pericellular hyalinization), papillary architecture mimicking papillary RCC, clear cell morphology with an absence of smaller cells mimicking clear cell RCC, oncocytoma like morphology, oncocytic papillary morphology, cystic dilatation of entrapped renal tubules leading to a grossly cystic appearance, tubulocystic carcinoma-like morphology, and higher grade nested architecture which raises the broad differential diagnosis of high grade unclassified RCC.

Treatment

Surgical excision.

Cytogenetics

Cytogenetics Morphological

See Table 1.

Result of the chromosomal anomaly

Fusion Protein

Description

Xp11 translocation renal cell carcinomas (RCCs) demonstrate fusion of the TFE3 transcription factor gene with one of multiple reported genes including ASPSCR1 (ASPL), PRCC, NONO (p54nrb), SFPQ (PSF), and, lastly, CLTCin the t(X;17)(p11.2;q23) Table 1). The two most common Xp11 translocation RCCs are those bearing the t(X;1)(p11.2;q21) which fuses the PRCC and TFE3 genes and the t(X;17)(p11.2;q25)which fuses the ASPSCR1 and TFE3 genes. The ASPSCR1/TFE3 gene fusion is the same gene fusion found in alveolar soft part sarcoma (ASPS), a rare pediatric neoplasm of uncertain histogenesis.

Neoplasm	Fusion	Age Range (years)	Translocation
ASPS	*ASPSCR1/TFE3*	1-71	der(17)(X;17)(p11.2q25)
RCC	*ASPSCR1/TFE3*	1-75	t(X;17)(p11.2;q25)
RCC	*PRCC/TFE3*	2-69	t(X;1)(p11.2;q21)
RCC	*SFPQ/TFE3*	3-68	t(X;1)(p11.2;p34)
RCC	*NONO/TFE3*	29-51	inv(X)(p11.2q12)
RCC	*CLTC/TFE3*	14	t(X;17)(p11.2;q23)
RCC	*PARP14/TFE3*	32	t(X;3)(p11.2;q23)
RCC	*DVL2/TFE3*	73	t(X;17)(p11;p13)
RCC	*LUC7L3/TFE3*		t(X;17)(p11;q21)
RCC	*RBM10/TFE3*	32	inv(X)(p11.2p11.23)
RCC	*KHSRP/TFE3*		t(X;19)(p11.2;p13)
Xp11 PEComa	*SFPQ/TFE3, NONO/TFE3 and others*	9-55	t(X;1)(p11.2;p34), inv(X)(p11.2q12) and others
Melanotic Xp11 Translocation Cancer	*SFPQ/TFE3 and likely others*	11-55	t(X;1)(p11.2;q34) and likely others
Subset of Epithelioid Hemangioendothelioma	*YAP1/TFE3*	14-50	t(X;11)(p11.2;q13)
RCC	*MALAT1(Alpha)-TFEB*	3-68	t(6;11)(p21;q12)
RCC	*CLTC/TFEB*		t(6;17)(p21;q23)
RCC	*KHDRBS2/TFEB*		inv(6)(p21q11)
RCC	*COL21/TFEB*		inv(6)(p21p12)
RCC	*TFEB/CADM2*		t(3;6)(p12;p21)

Table 1. TFE3 or TFEB Gene Fusions ASPS= Alveolar soft part sarcoma, RCC= Renal cell carcinoma, PEComa= Perivascular epithelioid cell tumor

Other common translocations are the inv (X)(p11.2q12) which fuses the NONO (p54nrb) and TFE3 genes; the t(X;1)(p11.2;p34) which fuses the SFPQ (PSF) and TFE3 genes. Although native TFE3 transcription factor protein is ubiquitously expressed, its normal levels are generally undetectable by immunohistochemistry. However, the TFE3 gene fusion partners in the Xp11 translocation RCC contribute strong promoters leading to overexpression of the fusion protein and strong nuclear labeling for TFE3 by immunohistochemistry.

The t(6;11)(p21;q12) translocation fuses the gene for transcription factor EB (TFEB) with MALAT1 (Alpha), an untranslated gene of unknown function, resulting in overexpression of native TFEB. Along these lines, the t(6;11) RCCs (also known as Alpha-TFEB RCCs) demonstrate specific nuclear labeling for TFEB protein by immunohistochemistry, whereas TFEB protein is not detected by immunohistochemistry in other neoplasms and normal tissues.

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