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CASE REPORT

Renal Cell Carcinoma with t(X;17)(p11.2;q25) in a 5-year-old Taiwanese Boy. A Case Report and Review of the Literature

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Introduction

The classification of adult renal cell carcinomas (RCCs) is well established and is mainly based on histopathologic features and genetic abnormalities [1]. In comparison, pediatric RCCs are more difficult to classify. In the past few years, it has become evident that a great majority of pediatric RCCs belong to the newly-recognized family of Xp11 translocation RCCs [2, 3]. These tumors are genetically characterized by different chromosome translocations, resulting in gene fusions between Xp11.2 and TFE3 transcription factor genes [2]. At least 5 genetic variants have been identified, including t(X;1)(p11.2;q21) translocation with PRCC-TFE3 fusion [4], t(X;1)(p11.2;p34) translocation with PSF-TFE3 fusion [5], inv(X)(p11;q12) translocation with *NonO* ($p54^{nrb}$)-TFE3 fusion [5], t(X;17)(p11.2;q25) translocation with ASPL-TFE3 fusion [6],and t(X;17)(p11.2;q23) with CLTC-TFE3 fusion [7]. Additionally, a subset of epithelioid RCCs that harbor t(6:11)(p11.2;q12), which fuses the Alpha gene and TFEB transcription factor gene, has been described [8]. A novel translocation of t(X,3)(p11;q23) has recently been reported in a 32-year-old female patient [9]. As TFEB and TFE3 are closely-related members of the microphthamia transcription factor (MiTF) family (a subfamily of basic helix-loop-helix leucine zipper transcription factors), it has been proposed that these tumors are classified as "MiTF/TFE translocation carcinomas" [2].

In the English literature, most case reports and series studies originate from Western countries [3, 6, 9–14], and case reports and series studies of pediatric RCCs in Asia are rare [15, 16]. Recently, Chen et al described a molecularly-documented Xp11.2 translocated RCC in a 6-year-old Taiwanese boy [17]. Herein, we report a case of an Xp11.2 translocated RCC in a 5-year-old Taiwanese boy. The diagnosis was established based on the histopathologic features, nuclear expression of TFE3 protein, and the presence of the type 1 TFE3-ASPL fusion gene as detected by reverse transcriptase-polymerase chain reaction. A literature review of translocation RCCs is also included.

Clinical History

A 5-year-old boy was referred to Changhua Christian Hospital due to recurrent gross hematuria for about one month; no associated symptoms such as fever, chills or flank pain were present. Renal echography revealed a right renal tumor, and non-enhanced computed tomography (CT) showed a well-defined, homogeneous mass measuring 4.8 × 4.7 cm, over the middle pole of right kidney (Fig. 1a). Neither lymph node enlargement nor distant metastasis was present. This tumor was classified as stage I (pT1N0M0) according to the criteria of American Joint Committee in

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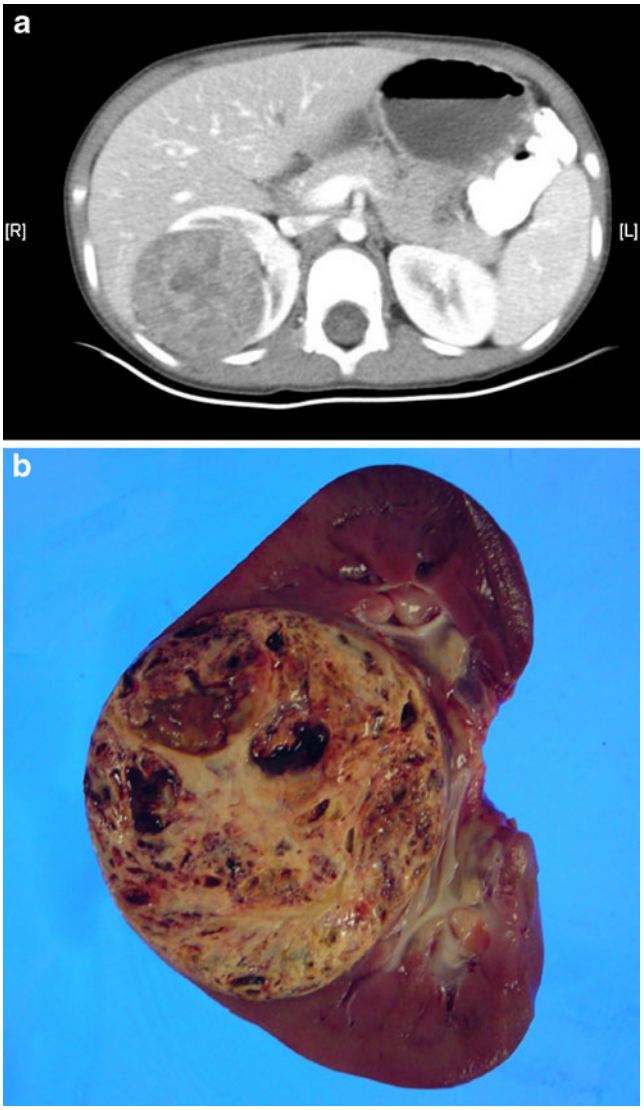

Fig. 1 **a** Computed tomography (CT) scan showed a 5.5×5.0×5.0 cm tumor in the middle pole of the right kidney. **b** Macroscopically, the tumor was well-circumscribed and was composed of yellowish to tan sectioned surfaces exhibiting necrosis, hemorrhage and cystic degeneration

2002, the patient underwent right total nephrectomy under the impression of Wilms' tumor. The operation was performed smoothly without any complications. No adjuvant therapy was given, and the patient has been alive without manifestations of disease or any other signs or symptoms for two years.

Material and Methods

Immunohistochemistry

The specimen was fixed in 10% neutral-buffered formalin and paraffin-embedded, following which sections were stained with hematoxylin and eosin for histological evaluation. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using a panel of antibodies including CD10 (clone 56C6, 1:60 dilution; Thermo Scientific, Fremont, CA , USA), renal cell carcinoma marker (clone 66.4C2, 1:50 dilution; Novocastra, Newcastle upon Tyne, UK), pan-cytokeratin (clone AE1/AE3, 1:200 dilution; Dako, Carpinteria, CA, USA), vimentin (clone V9, 1:200 dilution; Dako), cytokeratin 7 (clone OV-TL 12/30, 1:100 dilution; Dako), α-methylacyl-coenzyme A racemase (p504s) (clone 13H4, 1:80; Zeta, Sierra Madre, CA, USA), and HMB45 (clone HMB45, 1:60 dilution; Dako). A BenchMark XT IHC/ISH autostaining system (Ventana Medical System, Tucson, AZ, USA) was used, and TFE3 immunostaining (clone P-16, 1:300 dilution; Santa Cruz Biotechnology, Santa Cruz, CA, USA) was performed as previously described [17].

Molecular Analysis

RNA extraction from paraffin sections was performed as previously described [17]. 1 μg of total RNA was subject to cDNA synthesis using an Omniscript RT kit (Qiagen GmbH, Hilden, Germany), following which detection of ASPL-TFE3 by PCR was performed as described by Argani et al [6, 17]. To evaluate the adequacy of the RNA used for analysis, RT-PCR was performed using primers spanning an intron of the ubiquitously-expressed 18S ribosomal RNA, resulting in amplification of a 315-bp fragment. Adjacent normal kidney tissue was used as the negative control. The amplified fragments were identified by electrophoresis, and the identity of all positive results was further confirmed by sequencing using a fluorescent DNA sequencer (Applied Biosystems Inc, Foster City, CA, USA). DNA sequence analysis was performed by BLAST sequence similarity searches using the National Center for Biotechnology Information database.

Results

Histopathologic Findings

The right kidney measured 8.0×5.5×5.0 cm and weighed 115.0 g. A well-defined and unencapsulated tumor measuring 5.5×5.0×5.0 cm was located at the cortex of the middle pole, which was soft and yellow to tan in color, with foci of hemorrhage, necrosis and cystic degeneration (Fig. 1b). There was no gross invasion to the capsule, renal pelvis, hilar vessels, or ureter.

Microscopically, the tumor showed nested and papillary growth patterns surrounded by delicate vascular networks. Tumor cells displayed centrally located, vesicular nuclei with

mild atypia, indistinct nucleoli and abundant clear to eosinophilic cytoplasm (Fig. 2a). Occasional psammomatous-like calcification was observed. Immunohistochemically, the tumor cells revealed diffuse nuclear TFE3 staining (Fig. 2b); they were also positive for CD10 and RCC marker antigen but negative for pan-cytokeratin, vimentin, CK7 and HMB45.

Molecular Study

The efficacy of the RT-PCR analyses was excellent, as shown by the amplification of 18S ribosomal RNA. Detection of fusion gene transcripts revealed an approximate 200-bp band in type 1 TFE3–ASPL (Fig. 3). Sequencing of this PCR product confirmed a 218-bp transcript encoding type 1 TFE3–ASPL rearrangement with an in-frame fusion of TFE3 exon 3 to ASPL. No transcript was detected in ASPL–TFE3 and type 2 TFE3–ASPL. None of the negative controls showed any amplification products.

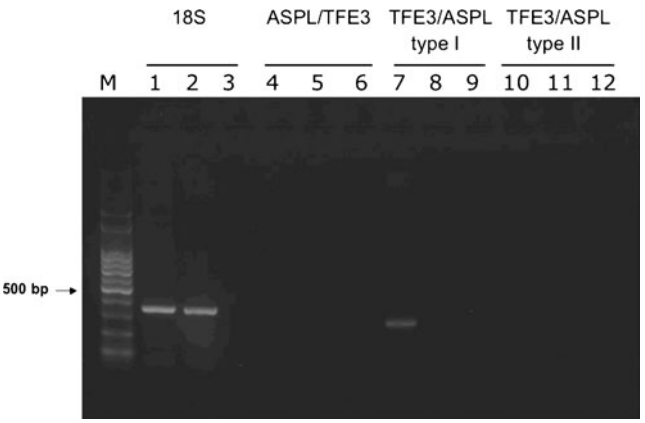

Fig. 3 Analyses of TFE3-ASPL and ASPL-TFE3 fusion transcripts by RT-PCR. RT-PCR was performed as described in the text with the primer combinations indicated. The tumor showed type 1 TFE3-ASPL fusion transcript (218-bp product) (lane 7), whereas the adjacent normal kidney tissue showed amplification of 18S ribosomal RNA (lane 2) and an absence of fusion transcripts (lanes 5, 8 and 11). The PCR controls were negative (lanes 3, 6, 9 and 12). M indicates the marker lane (100-bp marker)

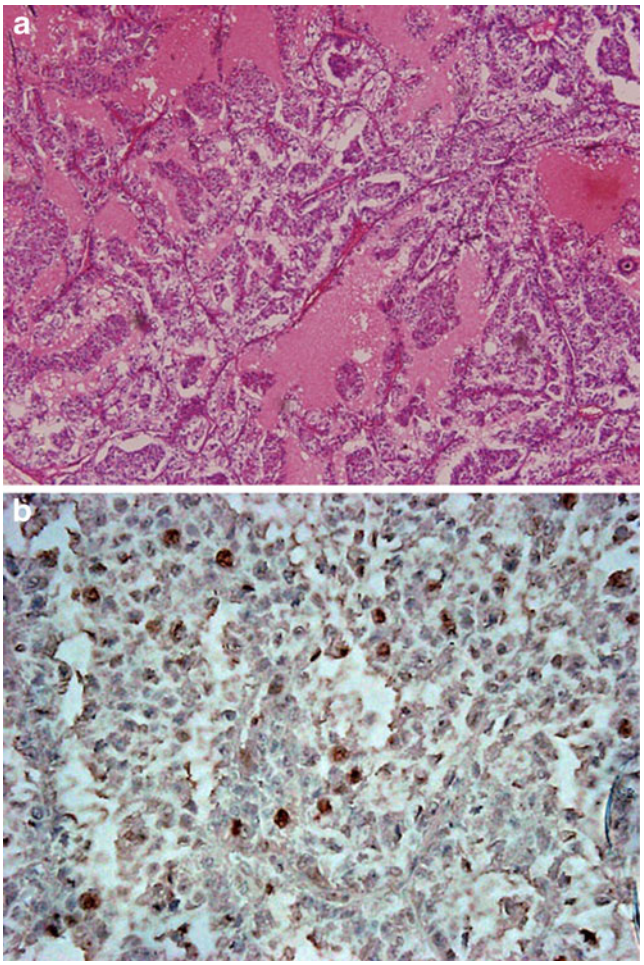

Fig. 2 **a** Microscopically, the tumor revealed marked papillary structures lined by voluminous clear to acidophilic cytoplasm cells (H&E stain, original magnification 200×). **b** Most tumor cells showed positive nuclear staining for TFE3 (original magnification, 400×)

Discussion

Historical Background

Recognition of translocation carcinoma in children and adolescents with unique genetic features took years of research. After Tomlinson et al first described Xp11.2 translocation in a 17-month-old child in 1991 [18], other groups subsequently published similar findings [19, 20]. The genes involved in translocations were not known at the time. In 1996, two independent research groups reported that the TFE3 transcription factor gene was fused to a novel PRCC gene in t(X;1)(p11.2;q21)-positive papillary RCCs [4, 21]. Subsequent studies have shown that there are at least 5 other genetic variants, including t(X;1)(p11.2;p34) translocation with PSF-TFE3 fusion [5], inv(X)(p11;q12) translocation with *NonO* ($p54^{nrb}$)-TFE3 fusion [5], t(X;17)(p11.2;q25) translocation with ASPL-TFE3 fusion [6], t(X;17)(p11.2;q23) with CLTC-TFE3 fusion [7], and the recently-described t(6:11)(p11.2;q12) with Alpha-TFEB fusion [8]. A novel translocation of t(X,3)(p11;q23) has also been recently reported in a 32-year-old female patient [9]. Xp11.2 translocation carcinomas are now recognized as a distinct entity in the 2004 World Health Organization's renal tumor classification guidelines [1].

Clinical Features

Pediatric RCC is rare, with a cumulative incidence of 2.2 per million, accounting for only 1.9–6% of pediatric malignant renal tumors [12]. Based on histopathological and immunohistochemical analyses of TFE3 protein expression, the frequency of TFE+ RCCs in institution-based studies varies from 20–83.3% [2, 11]. However, one German population-based study reported a translocation RCC rate of 22.4% [12]. Nevertheless, existing data indicate that the percentage of TFE+ tumors in pediatric RCCs is close to 70% [14].

Female predominance has been noted several large series studies [3]. The most common clinical presentations include hematuria, abdominal pain and an abdominal mass; however, only a small proportion of patients show the classical triad. Other symptoms include fever, anorexia, fatigue and body weight loss [3, 6, 9–14]. In some rare cases, polycythemia, rheumatoid arthritis, tuberous sclerosis or abdominal non-Hodgkin lymphoma was noted at the time of diagnosis [22], and in some instances the tumor developed following treatment for ganglioneuroblastoma [13]. Most notably, approximately 10–15% of translocation RCCs have been associated with previous exposure to cytotoxic chemotherapy in some studies [13, 22, 23]. It is therefore suggested that translocation RCCs should be added to the list of chemotherapy-associated secondary neoplasms in children [24].

Pathologic Findings

Histopathology

The gross appearance of Xp11.2 translocation RCCs is very similar to that of conventional (clear cell) renal carcinomas; they usually are tan–yellow and are often necrotic and hemorrhagic [1]. A calcified fibrous pseudocapsule, which may be grossly apparent, is usually seen in PRCC-TFE3 tumors [1]. The approximate mean tumor size of TFE3+ tumors is reported to be in the range of 6.1–6.86 cm in series studies and in the overall literature [6, 9, 25, 26]. Microscopically, the most distinctive histopathologic feature is that of a carcinoma with a papillary architecture composed of clear cells [1, 2]; however, a nested architecture is frequently observed and the tumors often contain cells with granular eosinophilic cytoplasm. However, microscopic features can vary among different translocation variants [1, 2]. ASPL-TFE3 RCCs are characterized by cells with voluminous, clear to eosinophilic cytoplasm, discrete cell borders, vesicular nuclear chromatin, and prominent nucleoli [1, 2, 6]. Tumor cells often are loosely adhesive and form an alveolar and pseudopapillary architecture. Psammoma bodies are almost universal and sometimes extensive, and usually form upon characteristic hyaline nodules [1, 2, 6]. In contrast, PRCC-TFE3 RCCs typically have less abundant cytoplasm, fewer psammoma bodies, fewer hyaline nodules, and a more nested, compact architecture [2, 25]. Alpha-TFEB RCCs frequently have a nested architecture and are composed of a biphasic population of large and small epithelioid cells [2, 26]. Smaller epithelioid cells are typically clustered around hyaline basement membrane material. Nevertheless, some cases may be morphologically indistinguishable from Xp11.2 translocation carcinomas. The morphologic characteristics of other Xp11.2 translocation carcinomas (PSF-TFE3, NonO-TFE3, CLTC-TFE3) have not been defined clearly owing to the scarcity of cases.

Immunoprofile

Immunophenotypes of renal Xp11.2-associated translocation carcinomas are different from those of conventional RCCs. They typically underexpress epithelial markers such as cytokeratin and epithelial membrane antigen [1, 2]. Only approximately one half of cases are focally positive, whereas approximately 85% of conventional RCCs are positive for cytokeratin [2]. The same applies for vimentin immunostaining [1, 2]. PSF-TFE3, CLTC-TFE3 and *Alpha*-TFEB carcinomas are usually positive for melanocytic markers such as HMB45 and Melan A [7], but negative for S-100 protein and desmin are consistently negative [2]. The Xp11.2-associated translocation renal carcinomas consistently express RCC marker antigen and CD10, similar to conventional (clear cell) and papillary renal carcinomas [16, 25]. Expression of α-methylacyl-coenzyme A racemase (p504s) is present in both TFE3 and TFEB RCCs [3]. p504s is also strongly expressed in prostate cancer and mucinous tubular and spindle carcinoma of the kidney [27, 28]. It has also been shown that Xp11 translocation RCCs and alveolar soft part sarcoma both express high levels of MET tyrosine kinase protein, as detected both by immunohistochemistry and Western blotting [29]. Expression of MET tyrosine kinase protein has rarely been examined in other studies.

Nuclear expression of TFE3 or TFEB protein is the most distinctive immunophenotype [1–3]. This is because both chromosome translocations effectively result in promoter substitution, such that the fusion gene protein is overexpressed and hence can be detected in archival material by immunohistochemistry [2]. Additionally, Ramphal et al reported that 5 of the 13 cases in their study showed focal, weak MiTF immunostaining, suggesting that the MiTF gene may be involved in some cases [13]. Interestingly, one tumor was TFE3+ and MiTF+ and another was TFE3− and MiTF+. The significance of this finding warrants further investigation. However, liposarcomas have been reported to

be MiTF+ by immunohistochemistry [30]; therefore, the specificity of MiTF immunostaining requires additional stringent analyses.

Ultrastructure

Ultrastructurally, despite the unusual immunophenotype, these neoplasms show predominantly epithelial features similar to these of conventional renal carcinomas, while a few may have membrane-bound rhomboidal crystals as seen in soft-tissue ASPS [6]. Some PRCC-TFE3 renal carcinomas have distinctive intracisternal microtubules similar to those noted in malignant melanoma and extra-skeletal myxoid chondrosarcoma [25].

Pathogenesis

Genetic Alterations

TFE3 transcription factor gene is the major gene involved in pediatric translocation RCCs [1, 2]. TFE3 is 1 of 4 closely-related members of the MiTF/TFE transcription factor family of basic helix-loop-helixleucine zipper transcription factors [31]. The other members are MiTF, TFEB, and TFEC. These MiTF members share virtually perfect homology in their DNA binding domains and bind a common DNA motif [32]. TFEB is involved in chromosomal translocation in a subset of epithelioid RCCs harboring t(6:11)(p11.2;q12) [8]. To date, 30 PRCC-TFE3, 23 ASPL-TFE3, 8 PSF-TFE3, and 1 NonO-TFE3 cytogenetically confirmed cases have been reported [3]. So far, there are reports of translocation involving the MiTF or TFEC genes. Detection of ASPL-TFE3 and PRCC-TFE3 fusion genes can be achieved readily by reverse transcription-polymerase chain reaction using specific primer sets [6, 25]. There are two types of ASPL-TFE3 fusion transcripts, in which the ASPL gene is fused to TFE exon 4 (type 1) or exon 3 (type 2) [6]. Four types of PRCC-TFE3 fusion transcripts have been described [25]. Significant differences in the clinicopathologic features between cases with different fusion types remain to be established. In contrast, detection of *Alpha*-TFEB gene fusion by RT-PCR is more difficult due to its larger size (>1.5 kb) [26]. Because RNA isolated from clinical samples is usually partially degraded, detection of *Alpha*-TFEB fusion by long-range DNA PCR can be considered as a useful alternative for molecular diagnosis [2].

Besides recurring translocation, translocation RCCs also display other complex cytogenetic abnormalities [2, 13, 25]. The roles of specific oncogenes and tumor suppressor genes have rarely been investigated. By microarray profiling, the gene expression file of Xp11 translocation RCC was found to be closer to that of alveolar soft part sarcoma than to that of adult-type RCC [33]. Camparo et al employed whole genome microarray expression profiling analyses and identified TRIM 63 glutathione S-transferase A1 and alanyl aminopeptidase as the main differentially expressed genes [3].

Prognosis and Treatment

Accumulated evidence shows that the clinical behavior of pediatric translocation RCCs is actually quite heterogeneous and they behave in a clinically distinct fashion, in contrast to their adult counterparts [11]. Translocation RCCs tend to present strong extrarenal extension with nodal involvement at the time of diagnosis [14]. The largest hospital-based retrospective study included 41 pediatric RCC patients from Italian pediatric oncology centers, 46% of whom had localized RCCs with an 88.9% 20-year overall survival rate (OS) and 46% had RCCs with regional lymph node or distant metastases and a 22.6% OS [10]. Geller and Dome analyzed 230 pediatric RCC cases in the literature and 13 patients from their institution [11], and found that local lymph node involvement is not an adverse prognostic factor in pediatric RCCs. Ramphal et al reported one patient with a genetically confirmed ASPL-TFE3 RCC who had hematogenous metastases at the time of diagnosis and died of cancer within 1 year [13]. Among 8 patients with ASPL-TFE3 RCC reported by Argani et al, one 17-year-old female patient died of progressive bony and lymph node metastasis 2 years after surgery and another 17-year-old female developed lung metastasis after 15 months. The remaining 6 patients showed no evidence of disease after an average of 4.2 years of follow-up (range, 2 months to 10 years) [6]. At present, the prognostic influence of different biological features in pediatric RCCs is not well-defined. Because of the rarity of pediatric RCCs, a collaborative international study is required to enable delineation of their clinical behavior.

The optimal treatment for translocation RCCs remains to be determined. For localized tumors, surgery without adjuvant therapy is adequate. Partial instead of simple or radical nephrectomy for stage I RCCs may be adequate if both macroscopic and microscopic margins are free of malignancy [13, 34]. Surgical resection of tumor and metastases appears to be the crucial mainstay of successful treatment of advanced pediatric RCCs [12]. The value of adjuvant radiation therapy, chemotherapy or immunotherapy is uncertain. Selle et al analyzed the correlation between treatment and outcome in 84 pediatric metastatic RCC patients and found no consistent advantage for radiotherapy or chemotherapy [12]. Immunotherapy seemed to have little survival benefit for a small subgroup. An international clinical trial is required to establish the appropriate therapy for advanced pediatric RCC.

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Conflict of interest statement The authors declare that they have no conflict of interest.

References

1. Eble JN, Sauter G, Epstein J et al (2004) WHO Classification of Tumours. Pathology and genetics of tumours of the urinary system and male genital organs. IARC Press, Lyon, pp 37–38
2. Argani P, Ladanyi M (2005) Translocation carcinomas of the kidney. Clin Lab Med 25:363–378
3. Camparo P, Vasiliu V, Molinie V et al (2008) Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. Am J Surg Pathol 32:656–670
4. Weterman MA, Wilbrink M, Geurts van Kessel A (1996) Fusion of the transcription factor TFE3 gene to a novel gene, PRCC, in t (X;1)(p11;q21)-positive papillary renal cell carcinomas. Proc Natl Acad Sci USA 93:15294–15298
5. Clark J, Lu YJ, Sidhar SK et al (2007) Fusion of splicing factor genes PSF and NonO (p54nrb) to the TFE3 gene in papillary renal cell carcinoma. Oncogene 15:2233–2239
6. Argani P, Antonescu A, Illei PB, Lui MY et al (2001) Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol 159:179–192
7. Argani P, Lui MY, Couturier J et al (2003) A novel CLTC-TFE3 gene fusion in pediatric renal adenocarcinoma with t(X;17)(p11.2; q23). Oncogene 22:5374–5378
8. Davis IJ, Hsi BL, Arroyo JD et al (2003) Cloning of an Alpha-TFEB fusion in renal tumors harboring the t(6;11)(p21;q13) chromosome translocation. Proc Natl Acad Sci USA 100:6051–6056
9. Argani P, Olgac S, Tickoo SK et al (2007) Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol 31:1149–1160
10. Indolfi P, Terenziani M, Casale F et al (2003) Renal cell carcinoma in children: a clinicopathologic study. J Clin Oncol 21:530–535
11. Geller JI, Dome JS (2004) Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer 101:1575–1183
12. Selle B, Furtwangler R, Graf N et al (2006) Population-based study of renal cell carcinoma in children in Germany, 1980–2005: more frequently localized tumors and underlying disorders compared with adult counterparts. Cancer 107:2906–2914
13. Ramphal R, Pappo A, Zielenska M et al (2006) Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the mit transcription factor family. Am J Clin Pathol 126:349–364
14. Geller JI, Argani P, Adeniran A et al (2008) Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 112:1607–1616
15. Goto S, Ikeda K, Nakagawara A et al (1986) Renal cell carcinoma in Japanese children. J Urol 136:1261–1263
16. Tsai HL, Chin TW, Chang JW et al (2006) Renal cell carcinoma in children and young adults. J Chin Med Assoc 69:240–244
17. Chen CK, Hsueh C, Lai JY et al (2007) Renal cell carcinoma with t(X;17)(p11.2;q25) in a 6-year-old Taiwanese boy. Virchows Arch 450:215–219
18. Tomlinson GE, Nisen PD, Timmons CF et al (1991) Cytogenetics of a renal cell carcinoma in a 17-month-old child. Evidence for Xp11.2 as a recurring breakpoint. Cancer Genet Cytogenet 57:11–17
19. Hernandez-Marti MJ, Orellana-Alonso C, Badia-Garrabou L et al (1995) Renal adenocarcinoma in an 8-year-old child, with a t (X;17)(p11.2;q25). Cancer Genet Cytogenet 83:82–83
20. Dijkhuizen T, van den Berg E, Wilbrink M et al (1995) Distinct Xp11.2 breakpoints in two renal cell carcinomas exhibiting X; autosome translocations. Genes Chromosom Cancer 14:43–50
21. Sidhar SK, Clark J, Gill S et al (1996) The t(X;1)(p11.2;q21.2) translocation in papillary renal cell carcinoma fuses a novel gene PRCC to the TFE3 transcription factor gene. Hum Mol Genet 5:1333–1338
22. Bruder E, Passera O, Harms D et al (2004) Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol 28:1117–1132
23. Argani P, Lae M, Ballard ET et al (2006) Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 24:1529–1534
24. Argani P (2006) The evolving story of renal translocation carcinomas. Am J Clin Pathol 126:332–334
25. Argani P, Antonescu CR, Couturier J et al (2002) PRCC-TFE3 renal carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t (X;1)(p11.2;q21). Am J Surg Pathol 26:1553–1566
26. Argani P, Lae M, Hutchinson B et al (2005) Renal carcinomas with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 29:230–240
27. Jiang Z, Woda BA, Rock KL et al (2001) P504S: a new molecular marker for the detection of prostate carcinoma. Am J Surg Pathol 25:1397–1404
28. Paner GP, Srigley JR, Radhakrishnan A et al (2006) Immunohistochemical analysis of mucinous tubular and spindle cell carcinoma and papillary renal cell carcinoma of the kidney: significant immunophenotypic overlap warrants diagnostic caution. Am J Surg Pathol 30:13–19
29. Tsuda M, Davis IJ, Argani P et al (2007) TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 67:919–929
30. Chang KL, Folpe AL (2001) Diagnostic utility of microphthalmia transcription factor in malignant melanoma and other tumors. Adv Anat Pathol 8:273–275
31. Hemesath TJ, Steingrimsson E, McGill G et al (1994) Microphthalmia, a critical factor in melanocyte development, defines a discrete transcription factor family. Genes Dev 8:2770–2780
32. Mansky KC, Sulzbacher S, Purdom G et al (2002) The microphthalmia transcription factor and the related helix-loop-helix zipper factors TFE-3 and TFE-C collaborate to activate the tartrate-resistant acid phosphatase promoter. J Leukoc Biol 71:304–310
33. Lae M, Argani P, Olshen AB et al (2004) Global gene expression profiles of renal carcinomas with Xp11 translocations (TFE3 gene fusions) suggest a closer relationship to alveolar soft sarcoma than to adult renal cell carcinoma. Mod Pathol 17(S1):163A
34. Lam JS, Shvarts O, Pantuck AJ (2004) Changing concepts in the surgical management of renal cell carcinoma. Eur Urol 45:692–705