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Case report

Translocation Associated Renal Cell Carcinoma in Pediatric Age Group: Review of Two Cases

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Summary

Renal Cell Carcinoma (RCC) are rare in children, constituting less than 0.3% of all tumors and 1.8 – 6.3% of renal neoplasms in children and adolescents younger than 15 years. Xp11.2 RCC is estimated to represent one-third of pediatric RCC. RCC associated with Xp11.2 translocation has recently been discovered and integrated into the World Health Organization (WHO) classification of renal tumors in 2004. We report 2 young children who presented with gross hematuria, and had RCC. Radical nephrectomy was done. Histopathology revealed Xp11.2 variant of RCC. No adjuvant chemotherapy or radiotherapy was given and patient is doing well with no recurrence or residual at 2 years follow up.

Abstract

Renal Cell Carcinoma (RCC) is a rare pediatric renal neoplasm. Of these, Xp11.2 RCC is commonest, representing one-third of pediatric RCC. It is characterized by various translocations, all involving gene fusion with the transcription factor E3 (TFE3) gene at chromosome Xp11.2. It is usually diagnosed in an advanced stage and has poor prognosis. Surgical resection is the choice of treatment. Adjuvant therapy is not effective. We report 2 young children who presented with gross hematuria, and had RCC. Radical nephrectomy was done. Histopathology revealed Xp11.2 variant of RCC.

Key words: Pediatric; Renal Tumor; RCC; Translocation; Xp11.2

Introduction

The incidence of RCC in childhood is estimated to be from 1.8% to 6.3% of all malignant renal tumors. Its incidence increases with age. According to the survey of Japanese Society of Paediatric Surgeons, RCC accounted for 1.4% of all renal tumors in patients younger than 4 years, 15.2% in patients aged 5 to 9 years, and 52.6% in patients aged 10 to 15 years [1]. Even on detailed review of literature recent statistics of incidence of RCC in children in India, could not be documented. Xp11.2 RCC is estimated to represent one-third of pediatric RCC [2]. RCC associated with Xp11.2 translocation has recently been discovered and integrated into the World Health Organization (WHO) classification of renal tumors in 2004 [3]. Prior history of cytotoxic chemotherapy for malignancy is the only known risk factor for Xp11 translocation RCC and is associated with up to 15% of cases [4].

Case Report

Case 1

A 10 year old female child presented with history of gross hematuria 20 days back which subsided spontaneously. There was no history of pain, fever, vomiting, abdominal lump or distension of abdomen. Abdominal examination was normal. Abdominal ultrasonography (USG) showed a 2.7cm X 2.1cm X 2.3cm hyperechoic mass at lower & mid-pole of left kidney with mild vascularity most likely to be angiomyolipoma. Contrast enhanced CT scan of abdomen revealed a 2.7cm X 2.3cm, enhancing mass lesion in lower and mid-pole of left kidney invading the pelvicalyceal system suggestive of left renal neoplasm (Figure 1). Magnetic Resonance Imaging revealed a benign neoplasm with hemorrhage, possibly angiomyolipoma. An USG- guided biopsy of the mass was done which was suggestive of RCC. The patient underwent left radical nephroureterectomy. Intraoperatively, external surface of kidney was unremarkable.

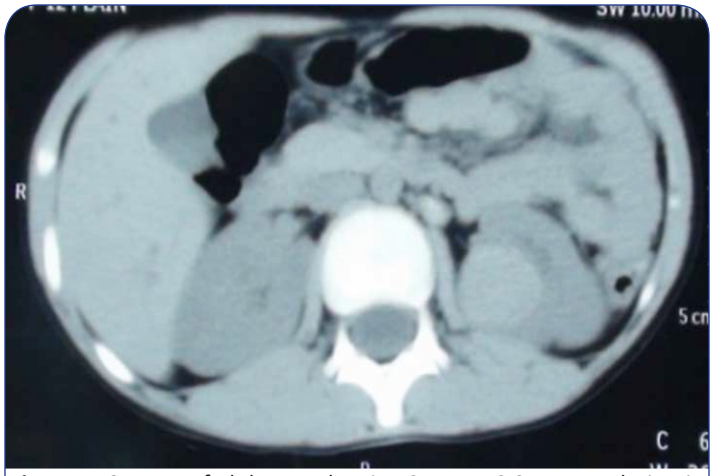

Figure 1: CT scan of abdomen showing 2.7cm X 2.3cm mass lesion in lower and mid-pole of left kidney with invasion of pelvicalyceal system.

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There were no enlarged lymph nodes. On cut section, a 3cm x 3cm x 3 cm oval mass was found in the lower pole of kidney which was hemorrhagic, friable and necrotic and abutting the pelvicalyceal system. (Figure 2) Microscopy was suggestive of a poorly circumscribed tumor composed of cells arranged in branching papillary architecture with few cells arranged in nests. Individual cells were round to polygonal in shape with clear to pale eosinophilic cytoplasm and hyperchromatic pleomorphic nuclei. There were many foci of multilayering, psammomatous calcification, necrosis and hemorrhage with few multinucleate giant cells; suggestive of Xp 11.2 translocation RCC (Figure 3). Ureteric cut margin and vascular pedicles were free of tumor. Immunohistochemistry was positive for LD 10 and negative for EMA HMB 45 & Melan A; likely to be translocation associated RCC. TFE3 was not available. No adjuvant chemotherapy or radiotherapy was given and patient is doing well at 1 year follow up.

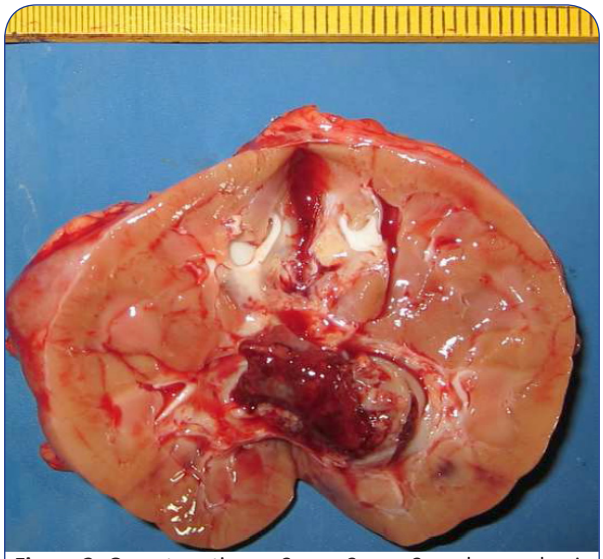

Figure 2: On cut section, a 3cm x 3cm x 3 cm hemorrhagic, friable and necrotic mass, abutting pelvicalyceal system.

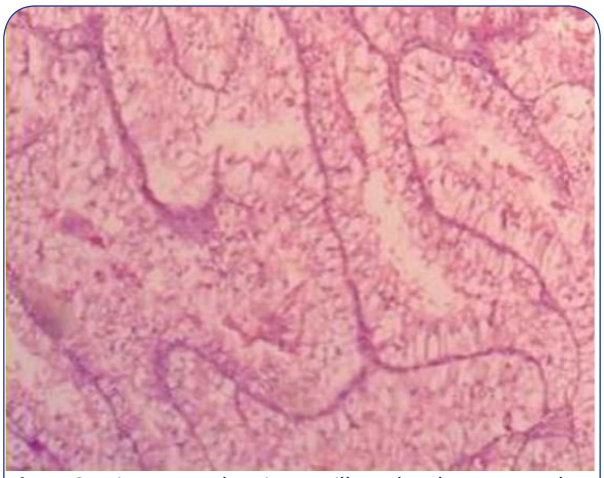

Figure 3: Microscopy showing papillary alveolar pattern, clear to eosinophilic cytoplasm with prominent psammomatous calcification.

Case 2

A 5 year old boy presented to us with gross hematuria. Abdominal examination was normal. USG showed a 2.1cm X 1.6 cm hypoechoic mass at upper pole of right kidney most likely to be angiomyolipoma. Contrast enhanced CT scan of abdomen showed a 2.1cmX 1.6cm enhancing mass lesion in upper pole of left kidney suggestive of left renal neoplasm (Figure 4). The patient underwent an extraperitoneal left radical nephroureterectomy. There was a single lymph node at hilum 0.5 cm x 0.5 cm. On cut section, there was a 1.5cm x1.5 cm unencapsulated, hemorrhagic, friable mass lesion arising from upper pole of right kidney with intact capsule (Figure 5). Microscopy was suggestive of renal tumor having papillary alveolar pattern. Tumor cells had voluminous clear to eosinophilic

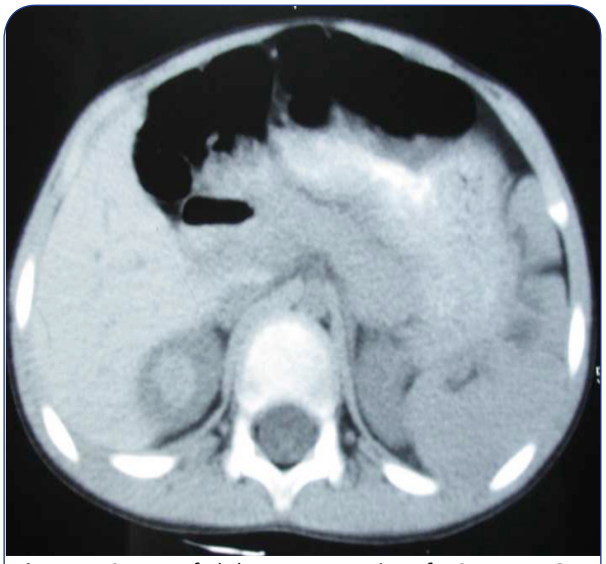

Figure 4: CTscan of abdomen suggestive of a 2.1cmX 1.6cm enhancing mass lesion in upper pole of left kidney

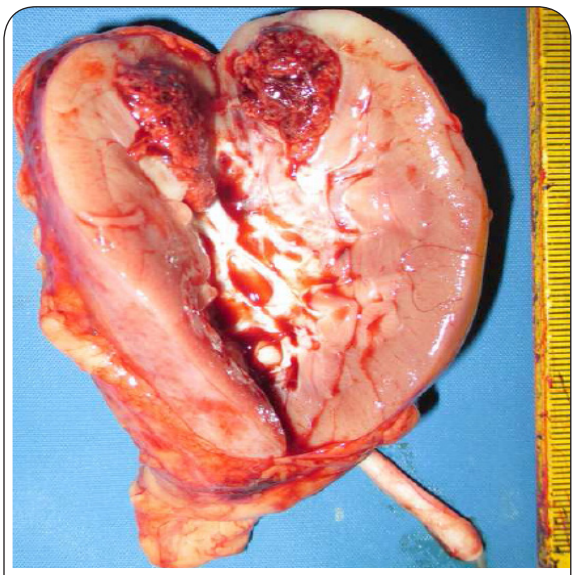

Figure 5: On cut section 1.5cm x1.5 cm unencapsulated , hemorrhagic, friable mass lesion arising from upper pole of right kidney.

cytoplasm with prominent psammomatous calcification suggestive of translocation associated RCC. Ureteric cut margin and vascular pedicles were free of tumor. Immunohistochemistry was weakly positive for CK and EMA, HMB 45 was negative likely to be translocation associated RCC. TFE3 immunohistochemical analysis showed that tumor cells expressed strong nuclear staining (Figure 6). Postoperative course was uneventful. No adjuvant chemotherapy or radiotherapy was required and patient is doing well at 6 months follow up.

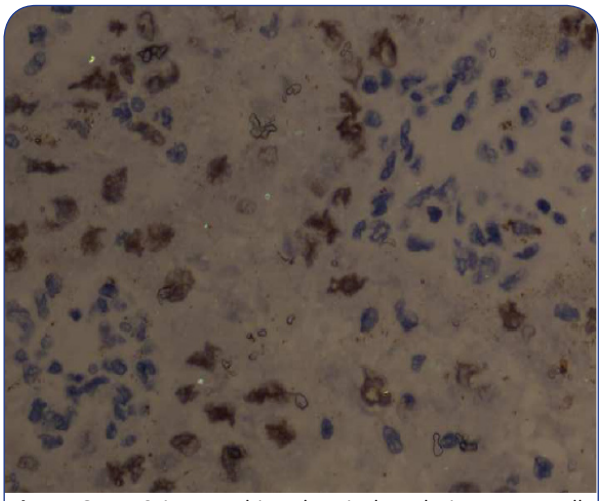

Figure 6: TFE3 immunohistochemical analysis- tumor cells expressing prominent nuclear staining.

Discussion

RCC is a malignancy arising from renal tubular epithelial cells. This rare childhood tumor constitutes less than 0.3% of all tumors and 1.8–6.3 % of renal neoplasms in children and adolescents younger than 15 years [1]. Xp11.2 RCC is the commonest pediatric subtype of RCC; almost one-third is translocation associated [3].

RCC associated with Xp11.2 translocations and TFE3 fusions (Xp 11.2 RCC) was first reported by de Jong et al in 1986 in a 2 year old child (5) and later by Tomlinson et al in 1991 in 17 month old child [6]. However it was only recognized as a distinct entity in 2004 WHO classification of kidney tumors [4]. Xp 11.2 RCC has been reported in all ages, ranging from 17 months to 78 years.

The pathological features of pediatric RCC are different from those seen in adolescents and young adults [7]. In children, most cases consist of papillary features, whereas the clear cell subtype predominates in adults [8]. Pediatric and young adult patients are usually symptomatic at presentation and only a few cases are incidentally discovered during abdominal imaging. The most common symptom is hematuria, followed by abdominal mass, pain and weight loss. Rare atypical presentations in adult patients include a heavily calcified renal mass, outflow obstruction with persistent pyelonephritis, renal cyst or nephrolithiasis [4, 9].

The radiological findings of Xp11.2 RCC are similar to any RCC [10].

Argani P et al (2006) recently identified an association of previous chemotherapy with the development of translocation RCC. In his study, out of 39 genetically confirmed translocation associated RCCs, 6 (15%) have arisen in patients who had received cytotoxic chemotherapy in the past [4]. Hence they believe that translocation associated RCCs should be added to the list of chemotherapy-associated secondary neoplasms in children along with acute leukemias, soft tissue sarcomas, and malignant gliomas. A similar study by Ramphal et al showed 1 patient in the series who received chemotherapy for ganglioneuroblastoma, years before developing genetically confirmed ASPLTFE3 RCC [11].

XP11.2 RCCs are characterized by various translocations, all involving a gene fusion with the transcription factor E3 (TFE3) gene at chromosome Xp11.2 [12, 13]. Five patterns of fusion with the TFE3 gene, with APSL (alveolar soft part sarcoma locus), PRCC (papillary renal cell carcinoma), PSF (polypyrimidine tract-binding proteinassociated splicing factor), NonO (non-POU domain-containing octamer-binding) and CLTC (clathrin heavy-chain genes), have been found. Since the translocations lead to overexpression of the TFE3 protein, immunohistochemical staining for TFE3 is widely used as a surrogate marker for the Xp11.2 translocation [14]. Strong nuclear TFE3 expression is associated with metastatic spread and a poor prognosis. There is little data concerning the mechanism and factors associated with this tumor yet [15, 16].

The histological features that are useful in differentiating RCC associated with Xp11.2 translocations from the other types of RCC include the combinations of nested and papillary architecture, clear cytoplasm and extensive psammomatous calcifications. Immunochemical staining of TFE3 protein is the distinct feature of Xp11.2 translocation RCCs for histologic diagnosis; RT-PCR and DNA sequencing is required for the final genetic diagnosis. In our patients, microscopy was suggestive of cells arranged in branching papillary architecture and few in nests, with clear to pale eosinophilic cytoplasm, psammomatous calcification, necrosis, hemorrhage and few multinucleate giant cells which were suggestive of XP 11.2 translocation RCC. We performed immunohistochemistry in both patients and TFE 3 Immunostaining in one patient.

On routine hematoxylin and eosin staining, these neoplasms may be misdiagnosed as conventional clear cell or papillary renal cell carcinoma in adult cases. In such a case, the diagnosis of Xp11.2 translocation carcinoma can be confirmed by immunohistochemistry using antibodies against TFE3. The nuclear reactivity for TFE3 at low-power magnification under a microscope is specific to Xp11.2 translocation carcinomas. In addition, molecular and cytogenetic methods such as reverse-transcriptase polymerase chain reaction (RT-PCR), karyotype analysis and fluorescence in situ hybridization (FISH) can further provide a reliable histological diagnosis although not absolutely necessary once positive diagnosis is obtained on immunohistochemistry [17].

Reports regarding the prognosis of Xp11. 2 RCC in children and young adults are controversial. Initially, it was believed that the biological behavior of Xp11.2 RCC is indolent. Recently, both

prospective and retrospective studies have shown that Xp11. 2 RCC is associated with significantly decreased overall survival [11, 18]. They show poor prognosis, because apart from surgery there is no other effective treatment. Moreover, many patients already have local invasion and/or metastasis at the time of diagnosis [19]. In adults, Xp11.2 RCC has a more aggressive clinical course with advanced stage at diagnosis, development of hematogenous metastases and rapid relapse [20, 21, 22, 23, 24]. There are increasing recent reports of Xp11.2 translocation RCC with aggressive clinical course in patients aged 16 or older [14, 19, 23, 25-35].

The poor clinical outcome associated with Xp11.2 RCC warrants early detection, accurate diagnosis and close follow-up. The current management of Xp11.2 RCC is similar to conventional RCC. For localized Xp11.2 RCC including patients with positive regional lymph nodes, surgery is the treatment of choice [5, 36].

Immunotherapy plays a significant role in the management of renal cell carcinoma (RCC) patients with metastatic disease because RCC is highly resistant to both chemotherapy and radiation therapy. Because of the complexity of the immune responses involved, it is difficult to evaluate the efficacy of immunotherapy compared with other treatments. However, as it is clear that the immune system plays a significant role in the control of these tumors, continued analysis of the mechanisms involved in tumor immunity and the development of new immunotherapies are vital [37].

Amongst these most commonly used and also maximum data available is of IL-2. It was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma. Several different routes of administration may be used: IV bolus, subcutaneous (SC), and continuous IV infusion (CIV). These are further classified as high-dose (IV bolus) or low-dose (SC and CIV). Recent statistics on long-term survival in patients treated with high-dose IL-2 continue to demonstrate that this therapy is effective for selected patients with metastatic renal cell carcinoma who can tolerate these large doses. These results confirm the premise that immunotherapy has curative potential in metastatic renal cell carcinoma. In some cases, IL-2 therapy produces what are known as "durable complete responses" (results lasting greater than 10 years) in a small percentage of treated patients and represented a significant milestone in the treatment of kidney cancer [38].

However significant toxicities are associated with usage of IL-2. Hence other options available and being used are like Immunotherapy Using Inactivated Tumor Cells and Gene Modified Tumor Vaccines (GMTV), Peptide-Based Immunotherapy, DC-Based Immunotherapy, Nonmyeloablative Stem Cell Transplantation (NST) [37, 38].

The optimal treatment approach for Xp11.2 RCC remains to be determined.

Conclusion

RCCs are rare in pediatric age group. Diagnosis using the immunohistochemistry of TFE3 is important to predict the prognosis of such patients and new strategies are needed to treat patients with these tumors.

References

1. Aissa Abdellah, Kadri Selma, Marnouche Elamin, Touil asmae, Rouas Lamia, et al. (2015) Renal cell carcinoma in children: case report and literature review. Pan Afr Med J 20: 84.
2. Bernstein L, Linet M, Smith MA, Ries LAG, Smith MA, et al. (1999) Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995, SEER Program. Bethesde MD National Cancer Institute 79–90.
3. Argani P, Ladanyi M (2005) Translocation carcinomas of the kidney. Clin Lab Med 25: 363-378.
4. Argani P, Landanyi M, Eble JN, Sauter G, Epstein J, et al. (2004) Renal carcinomas associated with Xp11.2 translocations/TFE3 gene fusions. In Pathology and Genetics of Tumors of the Urinary System & Male Genital Organs. France IARC Press 37–38.
5. Argani P, Lae M, Ballard ET (2006) Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 24: 1529-1534.
6. de Jong B, Molenaar IM, Leeuw JA, Idenberg VJ, Oosterhuis JW, et al. (1986) Cytogenetics of a renal adenocarcinoma in a 2-year-old child. Cancer Genet Cytogenet 21: 165-169.
7. Tomlinson GE, Nisen PD, Timmons CF, Schneider NR (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: 11-7.
8. Indolfi P, Terenziani M, Casale F (2003) Renal cell carcinoma in children: a clinicopathological study. J Clin Oncol 21: 530-535.
9. Renshaw AA, Granter SR, Fletcher JA (1999) Renal cell carcinoma in children and young adults: increased incidence of papillary architecture and unique subtypes. Am J Surg Pathol 23: 795-802.
10. Argani P, Ladanyi M (2003) Distinctive neoplasms characterised by specific chromosomal translocations comprise a significant proportion of paediatric renal cell carcinomas. Pathology 35: 492-498.
11. Prasad SR, Humphrey PA, Catena JR (2006) Common and uncommon histologic subtypes of renal cell carcinoma: imaging spectrum with pathologic correlation. Radiographics 26: 1795-1806.
12. Rao Q, Chen JY, Wang JD (2011) Renal cell carcinoma in children and young adults: clinicopathological, immunohistochemical, and VHL gene analysis of 46 cases with follow-up. Int J Surg Pathol 19: 170-179.
13. Ramphal R, Pappo A, Zielenska M (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. Hemesath TJ, Steingrimsson E, McGill G (1994) Microphthalmia, a critical factor in melanocyte development, defines a discrete transcription factor family. Genes Dev 8: 2770-2780.
15. Beckmann H, Su LK, Kadesch T (1990) TFE3: a helix-loop-helix protein that activates transcription through the immunoglobulin enhancer muE3 motif. Genes Dev 4: 167- 179.
16. Komai Y, Fujiwara M, Fujii Y (2009) Adult Xp11 translocation renal cell carcinoma diagnosed by cytogenetics and immunohistochemistry. Clin Cancer Res 15: 1170-1176.
17. Argani P, Antonescu CR, Illei PB, Lui MY, Timmons CF, 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.

18. Argani P, Lui MY, Couturier J, Bouvier R, Fournet JC, et al. (2003) A novel CLTC-TFE3 gene fusion in pediatric renal adenocarcinoma with t(X;17)(p11.2;q23). Oncogene 22: 5374-5378.

19. Megumi Hirobe, Naoya masumori, Toshiaki Tanaka, Hiroshi Kitamura, Taiji Tsukamoto, et al. (2013) Establishment of an ASPL-TFE3 renal cell carcinoma cell line (S-TFE). Cancer Biol Ther Jun 1 14(6): 502–510.

20. Rao Q, Guan B, Zhou X (2010) Xp11.2 Translocation Renal Cell Carcinomas Have a Poorer Prognosis Than Non-Xp11.2 Translocation Carcinomas in Children and Young Adults: A Meta-analysis. Int J Surg Pathol: 458-464.

21. Rais-Bahrami S, Drabick JJ, De Marzo AM (2007) Xp11 translocation renal cell carcinoma: delayed but massive and lethal metastases of a chemotherapy-associated secondary malignancy. Urology 70: 1783-1786.

22. Jing H, Tai Y, Xu D, Yang F, Geng M (2010) Renal cell carcinoma associated with Xp11.2 translocations, report of a case. Urology 76: 156–158.

23. Argani P, Olgac S, Tickoo SK (2007) Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol 31: 1149-60.

24. Hung CC, Pan CC, Lin CC, Lin AT, Chen KK, et al. (2011) XP11.2 Translocation renal cell carcinoma: Clinical experience of Taipei Veterans General Hospital. J Chin Med Assoc 74: 500-504.

25. Meyer PN, Clark JI, Flanigan RC, Picken MM, et al. (2007) Xp11.2 translocation renal cell carcinoma with very aggressive course in five adults. Am J Clin Pathol 128: 70-79.

26. Mir MC, Trilla E, de Torres IM (2011) Altered transcription factor E3 expression in unclassified adult renal cell carcinoma indicates adverse pathological features and poor outcome. BJU Int 108(2 Pt 2): E71-6.

27. Wu A, Kunju LP, Cheng L, Shah RB (2008) Renal cell carcinoma in children and young adults: analysis of clinicopathological, immunohistochemical and molecular characteristics with an emphasis on the spectrum of Xp11.2 translocation-associated and unusual clear cell subtypes. Histopathology 53: 533-544.

28. Dal CP, Stas M, Sciot R, De WI, Van DB, et al. (1998) Translocation (X;1) reveals metastasis 31 years after renal cell carcinoma. Cancer Genet Cytogenet 101: 58-61.

29. Salles PG, Soto M Jr (2005) Kidney carcinoma associated with Xp11.2 translocation/TFE3 (ASPL-TFE3) gene fusion. Int Braz J Urol 31: 251-254.

30. Mansouri D, Dimet S, Couanet D, Terrier-Lacombe MJ, Vasiliu V, (2006) et al. Renal cell carcinoma with an Xp11.2 translocation in a 16-year-old girl: a case report with cytological features. Diagn Cytopathol 34: 757-760.

31. Schinstine M, Filie AC, Torres-Cabala C, Abati A, Linehan WM, et al. (2006) Fineneedle aspiration of a Xp11.2 translocation/ TFE3 fusion renal cell carcinoma metastatic to the lung: report of a case and review of the literature. Diagn Cytopathol 34: 751- 756.

32. Suzigan S, Drut R, Faria P, Argani P, De Marzo AM, et al. (2007) Xp11 translocation carcinoma of the kidney presenting with multilocular cystic renal cell carcinoma-like features. Int J Surg Pathol 15: 199-203.

33. Armah HB, Parwani AV (2008) Renal cell carcinoma in a 33-year-old male with an unusual morphology and an aggressive clinical course: possible Xp11.2 translocation. Pathology 40: 306-308.

34. Camparo P, Vasiliu V, Molinie V, Couturier J, Dykema KJ, 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.

35. Geller JI, Argani P, Adeniran A, Hampton E, De Marzo A, Hicks J, et al. (2008) Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer 112: 1607-1616.

36. Hintzy MC, Camparo P, Vasiliu V, Peyromaure M, Vieillefond A, et al. (2008) Renal carcinoma associated with MiTF/TFE translocation: report of six cases in young adults. Prog Urol 18: 275-280.

37. Bovio IM, Allan R, Oliai B, Hampton T, Rush D, et al. (2011) Xp11.2 Translocation Renal Carcinoma With Placental Metastasis: A Case Report. Int J Surg Pathol 19: 80-83.

38. Koie T, Yoneyama T, Hashimoto Y, Kamimura N, Kusumi T, et al. (2009) An aggressive course of Xp11 translocation renal cell carcinoma in a 28-year-old man. Int J Urol 16: 333-335.

39. Aoyagi T, Shinohara N, Kubota-Chikai K, Kuroda N, Nonomura K, et al. (2011) Long-term survival in a patient with node-positive adult-onset Xp11.2 translocation renal cell carcinoma. Urol Int 86: 487-490.

40. Momoe Itsumi, Katsunori Tatsugami (2010) Immunotherapy for Renal Cell Carcinoma. Japan Clinical and Developmental Immunology.

41. B. Escudier (2012) Department of Medical Oncology, Institut Gustave-Roussy, Villejuif/Paris-Sud, France Emerging immunotherapies for renal cell carcinoma.