Case Report

A 13-Year-Old Female with Xp11.2 Translocation Renal Cell Carcinoma; The First Case Diagnosed at Siriraj Hospital

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Xp11.2 translocation renal cell carcinomas are rare tumors characterized by translocations involving chromosome Xp11.2. These tumors are predominantly reported in pediatric patients.

The authors report Xp11.2 translocation renal cell carcinoma in a 13-year-old girl who presented with asymptomatic palpable right renal mass. Right radical nephrectomy was performed and revealed a well-defined solid mass at the lower pole of the kidney. Microscopically, the tumor was composed of sheets and nests of clear to pale eosinophilic cells with some alveolar growth pattern. Psammoma bodies were detected. Immunohistochemically, the tumor cells marked with TFE3, focally marked with smooth muscle actin, HMB-45, CD68, progesterone receptor (PR) and CD10 but did not mark with epithelial markers (AE1/AE3, EMA and CAM5.2), vimentin, S-100 and p53.

The presence of psammoma bodies is an important diagnostic clue for these tumors. Cytogenetic study and/or immunohistochemistry for TFE3 protein are needed for confirming the diagnosis. Currently, surgery seems to be the most effective therapy. Pediatric patients with these tumors are believed to have a favorable prognosis.

Keywords: *Translocation renal cell carcinoma, Renal cell carcinoma, Pediatric renal carcinoma, Xp11.2 translocation, TFE3*

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Xp11.2 translocation renal cell carcinomas are rare tumors that were recently accepted as one separated type of tumor from 2004 WHO classification of kidney tumors. This type of tumor is characterized by numbers of translocations involving chromosome Xp11.2, which bears transcription factor E3 (TFE3) gene[1-12]. Thus, cytogenetic study and/or immunohistochemistry for TFE3 protein are necessary for definite diagnosis of these tumors[1-10,12]. The tumors are predominantly reported in children and adolescents[1-4,7-10,12]. Here, the authors report the case of translocation renal carcinoma in a 13-year-old girl, which is the first case diagnosed at Siriraj Hospital and to the best of our knowledge, the first reported case in Thailand.

Case Report

A 13-year-old healthy female, who first complained about asymptomatic palpable abdominal mass for 6 months, came to Siriraj Hospital for evaluation. The patient was normotensive. Physical examination revealed a large firm mass at right upper abdomen. No sign of tuberous sclerosis was detected. Urinalysis showed no hematuria. Other laboratory investigation was unremarkable. Computed tomography (CT) of the abdomen revealed a large hypervascular right renal mass measuring 8.6 x 9.4 cm. CT chest and bone scan were performed and showed no evidence of distant metastasis. Radiologically, renal cell carcinoma was suspected. Radical nephrectomy was performed. The surgical specimen submitted in formalin (including right kidney, segment of right ureter, right adrenal gland, mesenteric and paraaortic lymph nodes) was sent to the department of pathology for pathological examination.

The kidney measured 12.5 x 8.5 x 8 cm, and weighed 570 gm. The renal capsule was smooth and glistening. Cut surfaces of the kidney showed a well-defined, solid, round, friable, non-homogeneous dark brown and yellow mass measuring 9.6 x 9 x 8.2 cm at the lower pole of the kidney. Large areas of hemorrhage and necrosis were noted (Fig. 1). The pelvocalyceal system and the attaching ureter were moderately

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dilated. The perinephric fat, renal vessels and adrenal gland were uninvolved. The mesenteric and paraaortic lymph nodes were grossly unremarkable.

Microscopically, the tumor was composed of sheets and nests of clear to pale eosinophilic predominantly epithelioid cells with some alveolar growth pattern. Their nuclei were low-grade and relatively uniform. Areas of hemorrhage and necrosis were noted, corresponding to the findings in gross examination. Psammoma bodies were found (Fig. 2). The maximal mitotic rate was 1 per 50 high power fields. The tumor was confined within the renal capsule. Neither lymphovascular invasion nor perineural invasion was seen. Right adrenal gland, right ureter, mesenteric and paraaortic lymph nodes were also unremarkable.

Intracytoplasmic glycogen was detected by Periodic Acid-Schiff (PAS) stain with diastase. Immunohistochemically, the tumor cells focally marked with smooth muscle actin (SMA), HMB-45, CD68, progesterone receptor (PR) and CD10 but did not mark with cytokeratins AE1/AE3, cytokeratin CAM 5.2, epithelial membrane antigen (EMA), vimentin, S-100 and p53. Proliferation index measured by an antibody against the Ki-67 antigen was less than 1%. According to the histology and the immunohistochemical findings initially performed in Siriraj Hospital, differential diagnoses included translocation renal carcinoma and epithelioid angiomyolipoma (EAML). Since the diagnosis of Xp11.2 translocation renal carcinoma should be based on detection of TFE3 overexpression, a representative paraffin-embedded tissue block of the tumor was sent to the Department of Pediatric Laboratory Medicine, The Hospital for Sick Children in Toronto, Ontario, Canada for TFE3 immunostaining. The diagnosis of Xp11.2 translocation renal carcinoma was confirmed by positive result of TFE3 immunostaining.

After surgery, the patient was doing well without immediate postoperative complication. CT scan of chest and bone scan were performed and showed no evidence of distant metastasis. She currently remains free of disease one year after the surgery. The authors plan to perform a CT scan of chest and abdomen every three months and bone scan every six months to detect recurrence and distant metastasis.

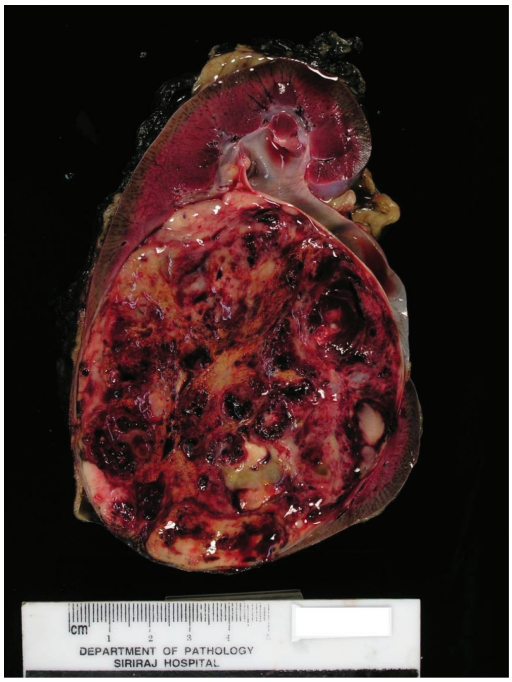

Fig. 1 Gross photograph of right kidney shows well-defined solid mass with hemorrhage and necrosis

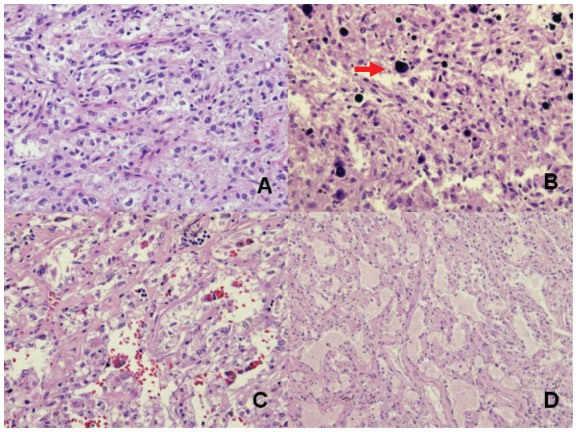

Fig. 2 (A and B) Microscopic photograph of tumor shows sheet of clear to pale eosinophilic epithelioid cells with some psammoma bodies (arrow). (C and D) The tumor cells show alveolar growth pattern.

Discussion

Renal cell carcinomas (RCCs) in pediatric populations are rare (approximately 2 to 6% of all pediatric renal neoplasms)[5,7,12] and approximately one third of pediatric renal cell carcinomas are Xp11.2 translocation renal cell carcinomas[1-3,8,9]. Although translocation renal cell carcinomas are usually recognized as pediatric tumors, adult cases also have been reported but the overall frequency remains unknown[1,9]. Males and females are equally affected[1,3,12] or female predominance in some series[5,9]. No definite

risk factor of these tumors has been identified but some studies found an association with prior history of chemotherapy exposure[1,2,4,5]. Mostly, clinical presentation is asymptomatic renal mass[2,7] like the presented case. Other presenting symptoms such as hematuria, abdominal pain, flank pain, dysuria, fever, and weight loss also have been reported[3,4,6,7,9].

Xp11.2 translocation renal cell carcinomas are associated with Xp11.2 translocations and TFE3 gene fusions. TFE3 gene on chromosome Xp11.2 belongs to microphthalmia-associated transcription factor family[1-11]. Various translocations and gene fusions have been identified in recent years but the 2 most common forms are TFE3 gene with ASPL gene on chromosome 17q25 and TFE3 gene with PRCC gene on chromosome1q21[5,6,12]. Other previously reported gene partners were PSF gene on chromosome 1p34, NONO gene on chromosome Xq12, CLTC gene on chromosome 17q23, unknown gene on chromosome 3q23[2,6,8-10] and recently, Armah et al reported translocation involving gene on chromosome 19q13.1[8].

Apart from detection of the associated translocations by cytogenetics or molecular genetic technique, TFE3 immunostaining, which is an antibody against C-terminal part of TFE3 protein, can be used for confirming the diagnosis of Xp11.2 translocation renal cell carcinomas[1-9]. This reliable immunostaining has high sensitivity and specificity (97.5% and 99.6%, respectively)[1,5,8].

Grossly, Xp11.2 translocation renal cell carcinomas are usually well defined tan-yellow to grey solid mass[2,4,7]. Mixed solid cystic and cystic appearances also have been described[4,8]. It is almost impossible to distinguish these tumors from other renal tumors especially conventional (clear cell) renal cell carcinomas by gross appearances[2,4,8].

Microscopically, Xp11.2 translocation renal cell carcinomas show mixed papillary, nested, or alveolar arrangement of tumor cells with well-defined cell borders, abundant clear to pale granular eosinophilic cytoplasm, vesicular nuclear chromatin, and prominent nucleoli. Psammoma bodies are detected in the majority of the cases[1-12]. By microscopic appearance, these tumors must be differentiated from clear cell renal cell carcinomas, papillary renal cell carcinomas[1-4,8-10] and EAML, rare potentially malignant tumors that are frequently associated with tuberous sclerosis[10,13,14]. The presence of psammoma bodies seems to be an important diagnostic clue for Xp11.2 translocation renal cell carcinomas[1,7-10].

Immunohistochemically, tumor cells are negative or rare and weak for epithelial markers (AE1/AE3, CK7, CAM5.2 and EMA) and melanocytic markers (HMB-45 and Melan-A). Tumor cells are positive for CD10, E-cadherin and RCC antigen. Expression for vimentin is variable[1,2,5,7-11]. In contrast to Xp11.2 translocation renal cell carcinomas, clear cell and papillary renal cell carcinomas show positive for epithelial markers and vimentin. Thus, these immunostainings are useful to distinguish Xp11.2 translocation renal cell carcinomas, clear cell and papillary renal cell carcinomas. In cases which EAML enter the list of differential diagnosis, as in this case, the mentioned immunophenotype might not be helpful since both EAML and Xp11.2 translocation renal cell carcinomas can express melanocytic markers and being negative for epithelial markers[10,13,14]. Immunohistochemistry for TFE3 and/or detection of Xp11.2 translocation using cytogenetics or molecular genetic study technique are useful to diagnose such cases.

Prognosis of these tumors and their optimal therapy has not been fully establishe[d(1-3,5,9,10)] due to the small number of cases and limited follow-up periods. The tumors are believed to have a favorable prognosis in pediatric groups[2,4,7-9]. Nowadays, surgery seems to be the most effective therapy for these tumors while radiation, chemotherapy, and immunotherapy are still questioned about their benefit[6,7]. Geller, et al also reported pediatric patients with translocation carcinoma having a favorable short-term prognosis after surgery alone even though there is presence of local lymph node involvement[12].

Conclusion

Xp11.2 translocation renal cell carcinomas are rare tumors that are predominantly reported in pediatric patients. Gross and microscopic appearances of the tumors can be confused with other renal cell carcinomas or epithelioid AML. The presence of psammoma bodies is an important diagnostic clue. Cytogenetic study and/or immunohistochemistry for TFE3 are necessary for the diagnosis.

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Potential conflicts of interest

None.

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รายงานการพบ Xp11.2 translocation renal cell carcinoma เนื้องอกไตที่พบได้ยากซึ่งได้รับการวินิจฉัยในเด็กหญิงอายุ 13 ปี

สุชานัน หาญอมรรุ่งเรือง, จิตสุภา ตรีทิพย์สถิตย์, บุญชู พงศ์ธนากุล, ณปกรณ์ แสงฉาย

คณะผู้นิพนธ์ได้รายงาน Xp11.2 translocation renal carcinoma ในเด็กหญิงอายุ 13 ปีที่มาพบแพทย์เนื่องจากคลำก้อนได้ที่ไตขวาโดยไม่มีอาการผิดปกติอื่น การตรวจทางพยาธิวิทยาของชิ้นเนื้อจากการผ่าตัด right radical nephrectomy พบก้อนเนื้อขอบเขตชัดเจนที่บริเวณด้านล่างของไตขวา ลักษณะทางจุลพยาธิวิทยาพบเซลล์เนื้องอกมี cytoplasm ค่อนข้างมากและมีลักษณะใสหรือมีสี eosinophilic การจัดเรียงตัวของเซลล์เนื้องอก ส่วนใหญ่เป็น sheetsและ nests บางส่วนพบการเรียงตัวแบบ alveolar growth pattern นอกจากนี้ในก้อนเนื้องอกยังพบมี psammoma bodiesอยู่ด้วย การย้อมพิเศษทาง immuno-histochemistry พบว่าเซลล์เนื้องอกย้อมติด TFE3 บางส่วนย้อมติด smooth muscle actin, HMB-45, CD68, progesterone receptor (PR) และ CD10 แต่ย้อมไม่ติด epithelial markers (AE1/AE3, EMA และ CAM5.2), vimentin, S-100 และ p53

การพบ psammoma bodies นับเป็นตัวบอกใบ้ที่สำคัญในเนื้องอกชนิดนี้ อย่างไรก็ดีการตรวจทาง cytogenetic หรือการย้อม TFE3 protein นั้นก็จำเป็นสำหรับการวินิจฉัย ในปัจจุบันการผ่าตัดเอาไตข้างที่มีเนื้องอกออกนับเป็นการรักษาที่มีประสิทธิภาพที่สุด เชื่อกันว่าเนื้องอกชนิดนี้มีการพยากรณ์ที่ดีในผู้ป่วยเด็ก