Diagnosis of Xp11.2 Translocation Renal Cell Carcinomas in the Thai Patients

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Background: *Xp11.2 translocation renal cell carcinomas (TRCCs) are rare tumors recently accepted as a separated tumor type in 2004 WHO classification. To diagnose these tumors, histological recognition and confirmation of translocation are necessary. While the incidence of overall renal cell carcinomas (RCCs) is increased after the age of 40, Xp11.2 TRCCs are predominantly reported in young patients. The incidence of these tumors in Thailand has not been evaluated.*
Objective: *To identify the frequency of Xp11.2 TRCCs, clinical presentation and follow-up information in 40 year-old or younger patients by using TFE3 immunostaining to confirm the translocation.*
Material and Method: *All cases of 0- to 40-years-old patients diagnosed as RCCs from nephrectomy specimens between 2001 and 2011 at Siriraj Hospital were reviewed by one pathology resident and two pathologists. Immunohistochemical staining for TFE3 was performed on cases morphologically suspected for TRCC or showing unusual histology.*
Results: *Four cases consistent with Xp11.2 TRCC were identified by TFE3 immunostaining from all 31 cases (12.9%). Three cases were females and one was male. Two cases were at stage 4 and passed away several months after the operation. The other two patients were at stage 2. One patient is alive without recurrence for at least 36 months after surgery alone. The other died from underlying SLE.*
Conclusion: *TFE3 immunostaining is a useful and practical tool for screening and diagnosis of Xp11.2 TRCCs, but staining results can be difficult to interpret. Thus, genetic analysis is still necessary especially when immunostaining shows problematic result. Fresh tumor tissue sampling in all young patients is recommended in case of further genetic studies needed.*

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 (TRCCs) are rare tumors that were accepted as a separated tumor type in 2004 WHO classification[1]. While renal cell carcinomas (RCCs), in general, are recognized as tumor of adults, which increased in their incidence after the age of 40[1], Xp11.2 TRCCs are predominantly reported in children and young adults[2-6]. Their incidence ranges from 20 to 54% of all rare pediatric RCCs[2-4]. These tumors also affect adults and more likely to be misdiagnosed[4,5,7,8] due to overlapping histology with other well-known subtypes of RCCs and lacking of awareness[4,5,7]. The incidence in adults is very low, ranging from 0.9 to 5% in large series[9-12]. To diagnose these rare tumors, histological recognition, and confirmation of translocation are necessary. To the best of our knowledge, the incidence of Xp11.2 TRCCs in Thailand has not yet been studied. Thus, the authors designed to start searching in Siriraj Hospital from the most possible age groups (≤40 years old) by using TFE3 immunostaining to confirm the translocation.

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Material and Method

All cases of 0- to 40-years-old patients diagnosed as RCCs from nephrectomy specimens between February 1, 2001 and March 31, 2011 were retrieved from the computer filing system of the Department of pathology, Faculty of Medicine Siriraj Hospital, Mahidol University. Slides of all cases were reviewed and re-classified according to 2004 WHO classification of kidney tumors. Roche's rabbit monoclonal TFE3 (MRQ-37) antibody was used to identify Xp11.2 translocation. Immunohistochemical staining would be performed by autostainer (Ventana Benchmark XT) on cases morphologically suspected for Xp11.2 TRCCs or showing unusual histology. Alveolar soft part sarcomas which also have ASPL-TFE3 gene fusion were used as positive control and normal kidney tissue was a negative control. Obvious nuclear staining at low power magnification would be

interpreted as positive while weak and focal nuclear staining and cytoplasmic staining would be considered as negative.

Results

Thirty-two cases were retrieved from the computer filing system. One case was excluded due to absence of paraffin block. Thus, 31 cases remained in the present study. Fifteen cases were males and 16 cases were females. Mean age of males was 33 years (range 13-40 years) and females was 32 years (range 14-40 years).

Slides of all 31 cases were reviewed and re-classified according to 2004 WHO classification. Four of 31 cases showing morphologically suspected for Xp11.2 TRCCs (case 3, 5, 27, and 31), and other five cases showing unusual histologic pattern for "classic" RCCs were chosen for further immunohistochemical staining. Four cases with histologically suspected of

Table 1.

Case	Sex	Age	Symptom	Site	Specimen	Size	Stage	Tumor type
1	F	39	Asymptomatic renal mass	L	RN	4.5	T1bN0M0	CRCC
2	M	40	Flank pain	R	RN	10.8	T2N0M1	CRCC
3	F	31	Asymptomatic renal mass	R	RN	6.0	T3NxM1	TRCC
4	M	36	Asymptomatic renal mass	L	RN	13.0	T2NxMx	CRCC
5	M	13	Hematuria	L	RN	15.0	T3N1M1	TRCC
6	F	39	Abdominal pain	L	PN	6.0	T1NxM0	CRCC
7	M	35	Hematuria	R	RN	6.0	T1NxMx	CRCC
8	F	38	Asymptomatic renal mass	R	PN	2.3	T1NxM0	CRCC
9	M	40	Hematuria	L	RN	4.0	T1N0M0	CRCC
10	M	31	Flank pain	R	N	3.0	T1NxM0	TCRCC
11	F	37	Hematuria	R	RN	12.5	T3N1M1	CRCC
12	M	37	Asymptomatic renal mass	L	RN	4.7	T1N0M0	CRCC
13	M	36	Hematuria	R	RN	6.0	T1N0M0	CRCC
14	F	14	Asymptomatic renal mass	L	RN	10.5	T2NxM0	ChRCC
15	F	25	Asymptomatic renal mass	R	RN	6.0	T1NxM0	CRCC
16	M	40	Hematuria	R	N	8.0	T2NxM0	CRCC
17	M	20	Hematuria	L	RN	21.0	T3N1M1	PRCC
18	F	40	Asymptomatic renal mass	L	N	2.3	T3N0M1	CRCC
19	M	35	Asymptomatic renal mass	R	RN	9.0	T3NxM1	CRCC
20	M	33	Abdominal pain	L	RN	3.3	T1N0M0	CRCC
21	F	35	Asymptomatic renal mass	R	RN	3.7	T1N0M0	ChRCC
22	F	38	Hematuria	L	N	4.5	T1N0M0	ChRCC
23	M	39	Hematuria	R	RN	5.0	T1NxM0	CRCC
24	F	39	Asymptomatic renal mass	R	PN	1.8	T1N0M0	CRCC
25	F	37	Asymptomatic renal mass	R	RN	7.8	T2N0M0	PRCC
26	M	23	Asymptomatic renal mass	R	PN	2.6	T1NxM0	CRCC
27	F	13	Asymptomatic renal mass	R	RN	9.6	T2N0M0	TRCC
28	F	37	Asymptomatic renal mass	R	RN	2.7	T1N0M0	CRCC
29	M	30	Hematuria	L	RN	8.0	T2N0M0	TCRCC
30	F	19	Abdominal pain	R	RN	8.3	T2N0M0	PRCC
31	F	18	Asymptomatic renal mass	R	RN	7.3	T2N0M0	TRCC

F = female; M = male; R = right; L = left; N = nephhrectomy; RN = radical nephrectomy; PN = partial nephrectomy; ChRCC = chromophobe renal cell carcinoma; CRCC = clear cell renal cell carcinoma; PRCC = papillary renal cell carcinoma; TCRCC = tubulocystic renal cell carcinoma; TRCC = Xp11.2 translocation renal cell carcinoma

Xp11.2 TRCCs (case 3, 5, 27, and 31) were positive for TFE3 while the remaining six "non-classic" cases showed negative result. It should be noted that case 15 showed focal nuclear staining for TFE3 at the edge of the tissue that was interpreted as negative.

The tumor type that showed the highest incidence was clear cell RCCs (61.3%) followed by Xp11.2 TRCCs (12.9%), chromophobe RCCs (9.68%), papillary RCCs (9.68%), and tubulocystic RCCs (6.45%) (Table 1). Interestingly, the incidence of Xp11.2 TRCCs increased to 50% if calculated in not more than 20 years old age group. All four Xp11.2 TRCC cases showed typical histological and immunohistochemical profiles of Xp11.2 TRCCs. Three cases were females and one was male. Three of them were teenagers. The male case is the only one that presented with gross hematuria while other three females presented with asymptomatic right renal mass detected by the patients themselves and during ultrasonographic workup in case 31 who had underlying lupus nephritis class IV and was treated with cytotoxic drug (cyclophosphamide). All cases were treated by radical nephrectomy. Case 3 and 5 were at stage 4. Case 3 had bone metastasis and passed away 5 months after surgery. Case 5 had local recurrence at surgical wound with lung metastasis and passed away 3 months after surgery. Case 27 and 31 were at stage 2 (T2N0M0) and were treated by surgery alone. Case 27 is healthy without evidence of recurrence for at least 36 months, while case 31 died from her underlying systemic lupus erythematosus (SLE) on the 19th month after surgery. Microscopically, the tumors of all four cases show nested or alveolar arrangement of tumor cells with abundant clear to eosinophilic cytoplasm. Papillary architecture was also observed in three cases. Psammoma bodies, which are frequently detected in Xp11.2 TRCCs, were found in two cases (Fig. 1, Table 2).

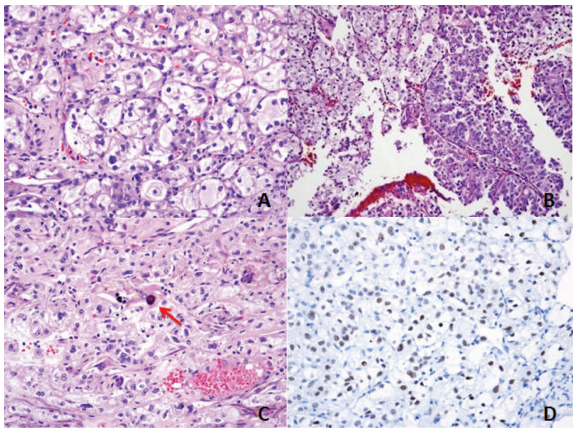

Fig. 1 Morphology of Xp11.2 translocation renal cell carcinomas. A, B) tumor cells showing voluminous clear to eosinophilic cytoplasm in mixed nested and papillary architecture. C) Sheet and nests of the tumor cells with a psammoma body (arrow). D) The tumor cells showing positive nuclear staining for TFE3.

Discussion

Xp11.2 TRCCs are rare tumor that associated with Xp11.2 translocations and TFE3 gene fusions. Many translocations and gene fusions have been detected, and the 2 most common forms are TFE3 gene with ASPL gene on chromosome 17q25 or t(X;17)(p11.2;q25) and TFE3 gene with PRCC gene on chromosome 1q211 or t(X;1)(p11.2;q21)[2,3,7]. Association with prior chemotherapy or DNA damaging drugs exposure is observed[5,13]. The case 31 also had history of cytotoxic drug (cyclophosphamide) administration for her lupus nephritis. The clinical presentations as well as macroscopic findings are indistinguishable from other renal tumors[4,5,12].

Recognition of their histologic findings is an important part for diagnosis. Their common microscopic appearance is as mixed papillary, nested or alveolar

Table 2.

Case	2	3	5	10	15	17	27	29	31
Architecture									
Nest/alveolar	x	x	x	x	x	x	x	x	x
Papillary		x	x	x	x	x		x	x
Psammoma body							x		x
TFE3	0	1+	1+	0	0	0	2+	0	2+
Diagnosis	CRCC	TRCC	TRCC	TCRCC	CRCC	PRCC	TRCC	TCRCC	TRCC

IHC = immunohistochemistry; CRCC = clear cell renal cell carcinoma; PRCC = papillary renal cell carcinoma; TCRCC = Tubulocystic renal cell carcinoma; TRCC = Xp11.2 translocation renal carcinoma
x = present; 0 = no staining; 1+ = <10%; 2+ = 10-50%; 3+ = >50%

arrangement of tumor cells with abundant clear to pale granular eosinophilic cytoplasm; psammomatous calcifications are frequently detected[2-4,6,9,11,12,14]. Radiologically, numerous psammomatous calcifications, if present, can give a clue for diagnosis[4,8,15]. The microscopic appearance can be overlap with other RCCs, especially clear cell RCCs, papillary RCCs, and RCCs with clear cell and papillary feature. Thus, confirmation of translocation is necessary for definite diagnosis.

Translocation can be detected by genetic analysis such as conventional karyotyping that need fresh tissue or fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR) that can be used in paraffin-embedded tissue and/or immunohistochemical staining for TFE3. This immunohistochemical staining is an antibody against C-terminal part of TFE3 protein[16]. Initially, many studies claimed that this antibody was reliable with high sensitivity and specificity[2-4,9,16,17], but over time, its reliability was questioned by several studies and some individual experience.

Despite an ideal that immunoreactivity for TFE3 should be diffuse and strong in Xp11.2 TRCCs, Mosquera et al[7] shared their experience using polyclonal TFE3 antibody that the staining results can be difficult to interpret such as weak, scattered, and patchy staining pattern. We also observed nuclear staining at the edge of the tissue in one case (case 15) that was the same problem described as "edge artifact" in their study[7]. TFE3 immunoreactivity was also reported in perivascular epithelioid cell neoplasms (PEComas) even though no Xp11.2 translocation is detected by genetic analysis[18,19]. Thus, interpretation of TFE3 immunohistochemical staining result should be made carefully and genetic analysis should be applied especially when the result is equivocal, difficult to interpret or negative in highly suspicious cases[4,7,15,20].

Despite of small number of cases and limited follow-up periods Xp11.2 TRCCs in pediatric patients are believed to be indolent and have a favorable prognosis[3,5,21] while seem to be aggressive in adults[5,8,11,17]. According to Sukov et al's series, Xp11.2 TRCCs showed worsen cancer survival than papillary RCCs but no significant difference to clear cell RCCs[11]. Xp11.2 TRCCs appear to resist to traditional chemotherapy used for other RCCs[5,8,22]. Optimal treatment and follow-up protocol have not been fully established; surgery with close follow-up still seems to be the most effective management for patients[5,22,23].

Three forth of Xp11.2 TRCCs cases in the present study were teenagers. The incidence in children and young adults is not much difference to other previous studies[2-4]. There is a high tendency to have more cases in more than 40-years-old group because although the incidence of Xp11.2 TRCCs in adults is lower than children and young adults but the population of RCCs is much higher[8].

Conclusion

Incidence of Xp11.2 TRCCs in 0- to 40-years-old patients is 12.9%. The incidence is much higher (50%) in 20 years old and under. Histological recognition and confirmation of translocation are necessary for diagnosis of Xp11.2 TRCCs. TFE3 immunostaining is a useful and practical tool for screening and diagnosis of Xp11.2 TRCCs although recently, its reliability was questioned. Thus, genetic analysis is still needed especially when immunohistochemical staining is equivocal, difficult to interpret or negative in highly suspicious cases. Fresh tissue sampling for further studies should be considered in all renal tumors especially in young patients.

What is already known on this topic?

Xp11.2 TRCCs are rare tumors that need both histological recognition and confirmation of translocation for the diagnosis.

These tumors still have not been recognized by most physicians and pathologists in Thailand. Their incidence in Thailand has not been evaluated.

The causes of the under recognition are not only lacking of the experience due to their rarity but also lacking of tools to confirm the translocation.

What this study adds?

The incidence of Xp11.2 TRCCs in Thailand is undeniably high in a certain age groups.

TFE3 immunostaining is a useful and practical tool for screening and diagnosis of Xp11.2 TRCC but sometimes difficult to interpret.

Changing in method of specimen handling to keep fresh tissue available for further studies if necessary would be benefit for the diagnosis.

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Potential conflicts of interest

None.

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การวินิจฉัยมะเร็งไตชนิด Xp11.2 translocation renal cell carcinomas ในผู้ป่วยไทย

บุญฑริกา จุนถาวร, คณาพร ปราชญ์นิวัฒน์, สุชานัน หาญอมรรุ่งเรือง

ภูมิหลัง: *Xp11.2 translocation renal cell carcinomas (TRCCs) เป็นมะเร็งไตชนิดที่พบได้น้อย ซึ่งเพิ่งได้รับการบรรจุใน WHO classification ปี ค.ศ. 2004 การวินิจฉัยอาศัยลักษณะทางจุลพยาธิวิทยาและการยืนยันการเกิด translocation มะเร็งชนิดนี้มีรายงานบ่อยในผู้ป่วยอายุน้อยซึ่งต่างจากมะเร็งไตทั่วไปซึ่งมีอุบัติการณ์เพิ่มขึ้นหลังอายุ 40 ปี ความชุกของมะเร็งชนิดนี้ในประเทศไทยยังไม่ได้มีการทำการศึกษา*

วัตถุประสงค์: *เพื่อหาความชุกของ Xp11.2 TRCCs ในกลุ่มผู้ป่วยอายุไม่เกิน 40 ปี โดยใช้ลักษณะทางจุลพยาธิวิทยาและการย้อมพิเศษทางอิมมูโน TFE3 เป็นตัวการยืนยันการเกิด translocation ตลอดจนหาลักษณะอาการแสดงและการดำเนินโรคของมะเร็งชนิดนี้*

วัสดุและวิธีการ: *ชิ้นเนื้อมะเร็งไตของผู้ป่วยอายุไม่เกิน 40 ปี จากการผ่าตัดตัดไต (nephrectomy) ใน พ.ศ. 2544 ถึง พ.ศ. 2554 จะถูกนำมาพิจารณาลักษณะทางจุลพยาธิวิทยาใหม่โดยแพทย์ประจำบ้านพยาธิวิทยา 1 คน และพยาธิแพทย์ 2 คน ในรายที่มีลักษณะเข้ากับ Xp11.2 TRCCs หรือ ไม่เข้ากันกับมะเร็งไตชนิดใดชนิดหนึ่งตาม WHO classification ปี ค.ศ. 2004 อย่างเด่นชัด จะถูกนำมายืนยันการเกิด translocationโดยย้อมด้วย TFE 3 แอนติบอดี*

ผลการศึกษา: *พบผู้ป่วย 4 ราย ที่มีลักษณะทางพยาธิวิทยาและผลย้อมพิเศษทางอิมมูโน (TFE3) เข้าได้กับ Xp11.2 TRCCs จากจำนวนทั้งหมด 31 ราย (12.9%) ประกอบด้วยผู้ป่วยชาย 1 ราย หญิง 3 ราย ผู้ป่วย 2 ราย เป็นผู้ป่วยระยะที่ 4 ซึ่งถูกส่งตัวกลับภูมิลำเนาเนื่องจากรักษาไม่ได้และเสียชีวิตในเวลาต่อมา ผู้ป่วยอีก 2 ราย อยู่ในระยะที่ 2 ซึ่งหนึ่งในนั้นเสียชีวิตจากโรค SLE ส่วนอีกรายยังไม่พบการกลับมาของโรคเป็นเวลาอย่างน้อย 36 เดือน หลังการรักษาโดยการผ่าตัดอย่างเดียว*

สรุป: *แม้การย้อมพิเศษทางอิมมูโนหา TFE3 เพื่อยืนยัน translocation นั้นจะทำได้สะดวก และสามารถนำมาใช้คัดกรองและวินิจฉัยได้ แต่ในทางปฏิบัติพบว่าการย้อมและการแปลผลทำได้ยากในหลายกรณี จึงเป็นเหตุให้การตรวจทางพันธุกรรมยังมีความจำเป็นโดยเพาะเมื่อผลการย้อม TFE3 มีปัญหา ดังนั้นจึงควรมีการเก็บชิ้นเนื้อสดในมะเร็งไต โดยเฉพาะในผู้ป่วยอายุน้อย เพื่อใช้ในกรณีมีความจำเป็นต้องตรวจทางพันธุกรรม*
