Original paper

The incidence of renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusion in Saudi adult patients with renal cancer: a retrospective tissue microarray analysis

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Renal cell carcinoma (RCC) is the most common renal tumour. RCC with Xp11.2 translocation/TFE3 (transcription factor E3) gene fusions (Xp11.2 RCC) is positive for immunostain labelling by TFE3 antibody. This tumour is rarely described in adults. This study aims to evaluate the frequency of RCC with Xp11.2 in a subset of Saudi adult patients with RCC.

112 RCCs diagnosed in 1995–2016 were retrieved from the Department of Pathology at King Abdulaziz University and King and Faisal Specialist Hospital and Research Centre, Saudi Arabia. Tissue microarrays were constructed and TFE3 immunostaining was performed. TFE3 immunostaining was considered positive when diffuse strong nuclear immunostaining was detected. TFE3 immunostaining-positive tumours were confirmed by fluorescence *in situ* hybridisation.

4.5% of RCCs were shown to be Xp11.2 RCC by TFE3 immunostaining. TFE3-positive tumours have a papillary configuration, nested pattern, or both. Positive tumours show male predominance, more occurrences in middle age, high grade, and large-sized tumours with necrosis. Two tumours were FISH-positive.

Xp11.2 RCC is rare in Saudi adult patients. Xp11.2 RCCs tend to be large sized and higher grade. TFE3 immunostaining should be considered in RCC that are histologically suggestive to confirm the diagnosis of Xp11.2.

Key words: renal cell carcinoma, translocation, Xp11.2, TFE3, immunohistochemistry.

Introduction

Renal cell carcinoma (RCC) is the most common malignant neoplasm of the kidney. It constitutes about 2-3% of all cancers worldwide. In 30% of tumours, patients present with metastasis. The prognosis of patients with RCC varies according to the stage and histological grade [1]. In Saudi Arabia, renal tumours constitute 3.6% of all tumours in males and 2.2% in females. RCC is the most common renal tumour both in males and females [2]. RCC associated with Xp11.2 translocation/TFE3 (transcription factor E3) gene fusions (Xp11.2 RCC) was first reported by de Jong *et al*. [3]. It is uncommon and characterised by several different translocations involving the TFE3 gene. This tumour may have been previously diagnosed as other types of renal tumours. However, in the 2004 WHO classification of kidney

tumours, it was recognised as a distinct entity [4, 5]. In 2016, a World Health Organisation classification of tumours of the kidney was issued. A new entity was introduced named microphthalmia-associated transcription factor family (MiT) RCC. This group has two varieties: RCCs associated with Xp1 1 translocations with gene fusions involving TF3; and RCCs with t(6;11) translocation with a MALA T1-TFEB gene fusion [6]. Xp11.2 RCC is thought to be more common in children and less frequent in adults [7, 8]. However, Xp11.2 RCC is increasingly reported in adults, and these patients have a clinicopathologically poor prognosis [9, 10, 11].

The overexpressed TFE3 protein is now detectable using a sensitive and specific polyclonal immunohistochemical marker, which reflects nuclear overexpression of the TFE3 protein [7, 8]. The detection of TFE3 protein overexpression by immunohistochemistry is commonly used in diagnostic practice. Nuclear immunohistochemical labelling for TFE3 is used as a marker of Xp11.2 RCC. Strong nuclear TFE3 immunostaining represents its overexpression as a fusion of proteins relative to native TFE3 [7]. TFE3 immuno-labelling is absent in conventional clear-cell and papillary RCC [12].

The scientific value of the available evidence for using TFE3 immunohistochemical expression in screening for Xp11.2 RCC needs to be evaluated. The aim of this retrospective study is to determine the prevalence of nuclear immunoreactivity for TFE3 in a subset of Saudi adult patients diagnosed with RCC. Additionally, we aimed to evaluate the usefulness of TFE3 immunostain screening for Xp11.2 RCC.

Material and methods

Patients

The study was retrospective and included paraffin wax blocks of tumours from 112 adult patients with RCC from 1995 to 2016. Blocks were retrieved from the archives of the Department of Pathology at King Abdulaziz University, Jeddah, Saudi Arabia and King Faisal Specialist Hospital and Research Centre. Clinical and pathological data were collected from patients' record. Data are presented in Table I. Pathological staging of tumours was performed according to the seventh edition of the American Joint Committee on Cancer [13]. The study was approved by the Research Committee of the Biomedical Ethics Unit, Faculty of Medicine, King Abdulaziz University.

Tissue microarray construction

Tissue microarrays were constructed from formalin-fixed and paraffin-embedded blocks, as previously described [14]. New sections were prepared from the donor blocks and stained with haematoxylin-eosin (HE). These slides were used to guide the sampling from morphologically representative regions. A tissue array instrument (TMA Master 3D Histech, EU Ltd., Budapest, Hungary) was used to make holes in the recipient paraffin block and to retrieve 1.5-mm tumour tissue cores from the donor paraffin block. After construction of the array blocks, 4-μm thick sections were cut.

Immunohistochemistry

TMA paraffin blocks were cut at 4 μm and mounted on positively charged slides (Leica Microsystems plus slides, Menzel, Braunschweig, Germany). Immunostaining was performed in an automated immunostainer (BenchMark XT, Ventana® Medical Systems Inc., Tucson, AZ, USA). Sections were deparaffinised in xylene and rehydrated. Pre-treatment was done using a prediluted cell conditioning solution (CC1) for 60 min. TFE3-MRQ-37 (Cell Marque, Sierra College Blvd, Rocklin, CA 95677, USA) primary antibody was incubated at 37°C for 16 minutes with TMA sections. The Ventana® I-view DAB detection kit was used according to the manufacturer's instructions. Subsequently, slides were washed, counterstained with Mayer's haematoxylin, and mounted. Negative control tissue (by substitution of primary antibody with Tris-buffered saline) and positive control tissue were included.

Scoring of immunohistochemistry

The interpretation of immunoreactivity for TFE3 was evaluated as previously described using the intensity of nuclear immunostaining. Tumours were scored as negative (0), weak positive (1+), moderate positive (2+), and strongly positive (3+) [8, 15, 16]. A tumour was considered positive for TFE3 when diffuse strong TFE3 immunopositivity was reported.

Fluorescent *in situ* hybridisation

A dual-colour, break-apart fluorescent *in situ* hybridisation (FISH) assay was performed to detect rearrangement of the TFE3 locus with probes for the 5' and 3' regions of the TFE3 gene at Xp11.2. DXZ1 used as a probe. FISH was performed at the Mayo Clinic Cytogenetics Laboratory.

Statistical analysis

Descriptive statistics of patients and the frequency of TFE3 immunostaining in RCC were performed. To test the difference between two variables, the Wilcoxon signed-rank test was used. A two-sided p-value of ≤ 0.05 was used to determine the statistical significance. SPSS® Version 16.0 (SPSS, Chicago, Ill) was used.

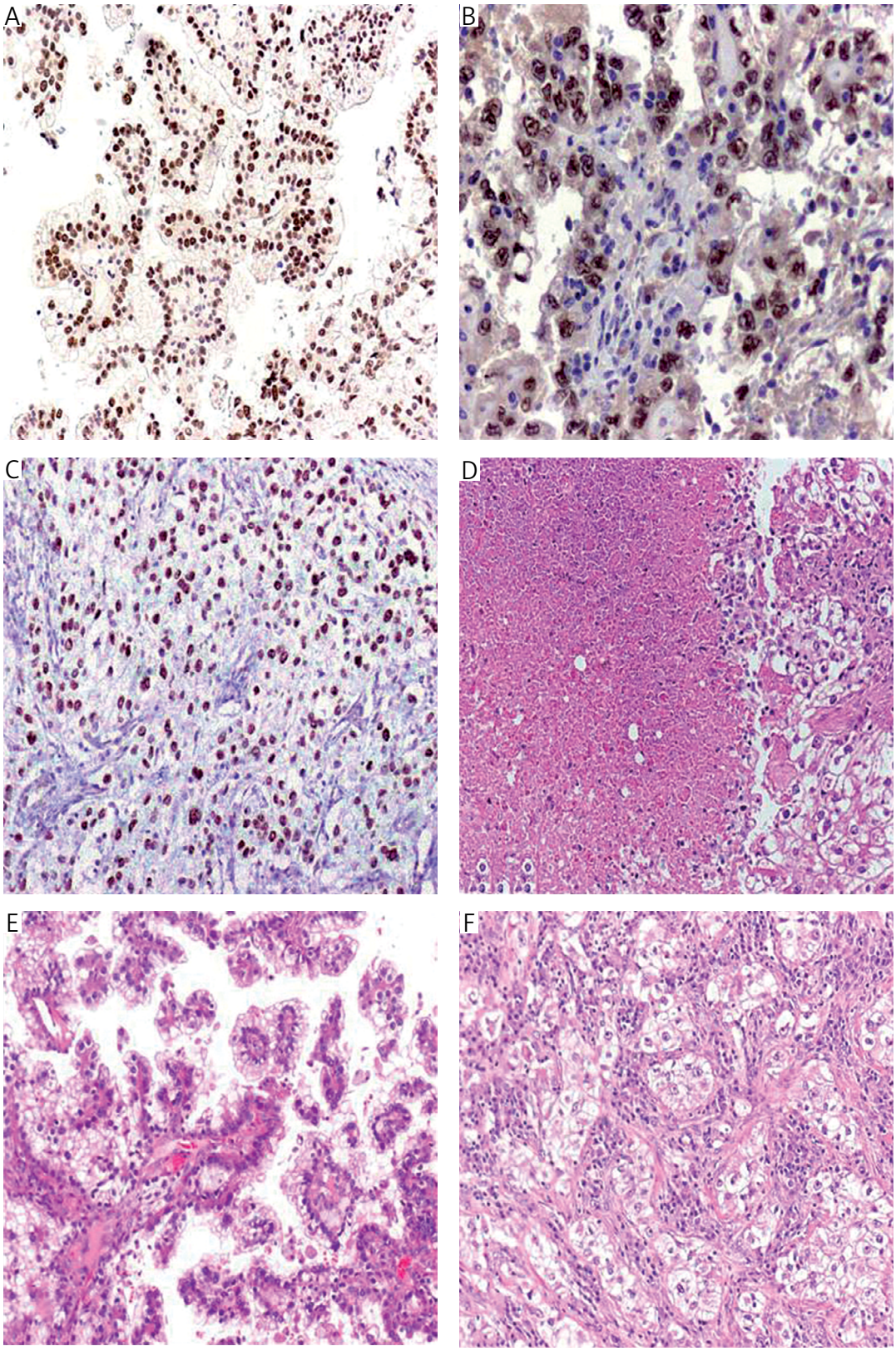

Fig. 1A-F. Representative images of TFE3 immunostaining and corresponding histopathological appearance. TFE3 nuclear immunoreactivity in RCC is noted as a strong diffuse nuclear immunoreactivity of tumour cells (3+) with papillary and nested patterns (A, B, and C). TFE3 immunostaining was performed using immunohistochemical labelling with anti-TFE3, with diaminobenzidine used as the chromogen. Haematoxylin was used as a counterstain. The microscopic appearance of representative tumours is shown in D, E, and F (haematoxylin and eosin stain). Characteristic necrosis with clear and eosinophilic cytoplasm of tumour cells (D). The papillary pattern (E) and the nested pattern (F) show voluminous, clear, and eosinophilic cells. The original magnification is 200×

Table I. Clinicopathological parameters of tumours (n = 112)

Clinicopathological Parameter	n (%)
Sex	
Male	81 (72.3%)
Female	31 (27.3%)
Age	
< 60 years	76 (67.9%)
≥ 60 years	36 (32.1%)
Tumour location	
Right kidney	58 (51.8%)
Left kidney	54 (48.2%)
Tumour focality	
Unifocal	111 (99.1%)
Multifocal	1 (0.9%)
Tumour size	
< 4 cm	18 (16.1%)
4-7 cm	42 (37.5%)
> 7 cm	52 (46.4%)
Histological subtype	
Clear cell	83 (74.1%)
Papillary	17 (15.2%)
Chromophobe	11 (9.8%)
Multilocular cystic	1 (0.9%)
Fuhrman nuclear grade	
1	18 (16.1%)
2	46 (40.1%)
3	17 (15.2%)
4	31 (27.6%)
Nodal metastasis	
Cannot be assessed	82 (73.2%)
Negative	26 (23.2%)
Positive	4 (3.6%)
Perinephric fat invasion	
Negative	94 (83.9%)
Positive	18 (16.1%)
Lymphovascular invasion	
Negative	98 (87.5%)
Positive	14 (12.5%)
Renal vein involvement	
Free	97 (86.6%)
Involved	15 (13.4%)
Inferior vena cava involvement	
Free	110 (98.2%)
Involved	2 (1.8%)

Results

Immunostaining of TFE3

We determined the incidence of Xp11.2 RCC by immunostaining for TFE3. Among all tumours (112), five showed diffuse strong-positive TFE3 immunostaining (Xp11.2 RCC; 4.5%). Figure 1 shows tumours that demonstrate diffuse and strong nuclear immunoreactivity for TFE3. Weak immunostaining was reported in eight tumours (7.1%). The clinical and pathological TFE3-positive characteristics are shown in Table II. There was significantly more positivity in males ($p = 0.046$), middle-aged population ($p = 0.025$), and in higher tumour grades ($p = 0.035$). Positivity was exclusively associated with all large sized-tumours ($p = 0.025$) and tumours with the presence of necrosis ($p = 0.025$). Most positive tumours show a clear and papillary morphology.

Histopathological features

The HE slide whole tissue sections of TFE3-positive tumours were retrieved to re-examine the histological pattern. Tumours showed a heterogeneous morphology including a papillary configuration, a nested pattern, and/or a mixed pattern. The mixed pattern is a clear-cell or papillary RCC papillary structures lined by clear-to-eosinophilic cells. The cells show voluminous cytoplasm that is clear-to-eosinophilic. Nuclear features were also variable, ranging from small, uniform nuclei to larger nuclei with prominent nucleoli (Fig. 1).

Fluorescence *in situ* hybridisation

FISH analysis was positive for TFE3 gene rearrangements in only two tumours (two out of five TFE3 immunopositive tumours = 40%), while 60% were negative. According to FISH positivity, 1.7% of the overall tumour population are positive. Results are shown in Table III.

Discussion

Before the current study, we thought that some tumours that were diagnosed as RCC (clear-cell, papillary, or chromophobe) were originally Xp11.2 RCC. Thus, we re-evaluated a subset of renal tumours that were diagnosed as other RCC types by immunostaining for TFE3. To the best of our knowledge, this is the first report to evaluate the incidence Xp11.2 RCC in Saudi adult patients with RCC.

Xp11.2 RCC is a rare subtype of RCC [16]. The results from our study show that 4.5% of our subset was positive for TFE3 immunostaining in tumours that were previously diagnosed as other types of RCC. Two were confirmed by FISH (1.7% of the tumour

Table II. Distribution of strong-positive TFE3 immunostaining (n = 5) related to clinicopathological parameters

Clinicopathological Parameters	n (%)	p value*
Sex		
Male	4 (80%)	0.046
Female	1 (20%)	
Age		
< 60 years	5 (100%)	0.025
Tumour size		
> 7 cm	5 (100%)	0.025
Tumour necrosis		
Present	5 (100%)	0.025
Histological patterns (heterogeneous)		
Clear cell areas	5 (100%)	0.025
Papillary areas	5 (100%)	0.025
Fuhrman nuclear grade		
Low grade	1 (20%)	0.035
High grade	4 (80%)	
Stage		
2	2 (40%)	0.083
3	3 (60%)	
Nodal metastasis		
Cannot be assessed	2 (40%)	0.983
Negative	2 (40%)	
Positive	1(20%)	
Perinephric fat invasion		
Negative	4 (80%)	0.046
Positive	1(20%)	
Lymphovascular invasion		
Negative	4 (80%)	0.046
Positive	1(20%)	
Renal vein		
Negative	5 (100%)	0.025
Positive	0 (0%)	

**Wilcoxon signed-rank test.*

Table III. Distribution of strong-positive TFE3 immunostaining related to FISH results

	TEF3 Immunostaining	FISH (positive)
Negative	99 (88.4%)	Not done
Weak	8 (7.1%)	Not done
Strong	5 (4.5%)	2 (1.7%)

population). This finding is comparable to previous studies [17, 18]. The age incidence of this tumour was originally thought to be specific to paediatric and adolescent age groups [19]. However, Xp11.2 RCC is increasingly reported in middle-aged people [11, 17, 20]. The age incidence in our study was 24-81 years, which is similar to previous reports [21, 22]. Pathologists should take into account the possibility that Xp11.2 RCC may occur in adults. Xp11.2 RCC should be suspected in any RCC with an unusual histology, regardless of the patient's age. Many studies revealed a female predominance of Xp11.2 RCC [1, 18, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30]. However, in the present study most patients were males, as reported in previous studies [21, 31, 32, 33]. A difference in the incidence of Xp11.2 RCC related to gender remains controversial [1]. We reported a small percentage of Xp11.2 RCC with nodal metastasis. Positive nodal metastasis was associated with Xp11.2 RCC in many studies [1, 15, 25, 26]. However, there was no difference in incidence of tumour stages [1, 15, 25, 26]. Some case reports showed low stage I incidence [34, 35], while in another report it was associated tumour stage III [36].

Microscopically, the most characteristic histological feature of Xp11.2 RCC is a mixture of papillary and nested/alveolar architecture with extensive psammoma bodies. Cytological features include clear and/or eosinophilic, voluminous, granular cytoplasm; discrete cell borders; vesicular chromatin; and prominent nucleoli. However, the Xp11.2 RCC is morphologically heterogeneous [9, 12, 21, 28, 37]. Whenever this tumour as well as RCC with t(6;11)(p21;q12) are grossly suspected, extensive sections should be taken [38]. In the current study, tumours shown to be positive for TFE3 immunostaining showed similar histological features without reporting psammoma bodies. A histological clue for this type of RCC should be suspected during microscopic examination. The presence of the above-mentioned histological features should guarantee the use of TFE3 immunostaining to diagnose Xp11.2 RCC.

Translocation of Xp11.2 RCC is accompanied by TFE3 protein overexpression. Thus, immunostaining for TFE3 is a commonly used diagnostic technique in diagnostic practice [8, 12, 16, 25, 39, 40, 41]. We used a score of 3+ in staining intensity as the cut-off point for TFE3 positivity, which is similar to previous reports [21, 42]. Other studies used a staining intensity of 2+ or 3+ to represent a positive result [8, 19]. In the present study, five tumours showed the criteria for positive TFE3 immunostaining (strong diffuse nuclear immunostaining). For these tumours, a TFE3 break-apart FISH assay was performed to confirm the diagnosis of Xp11.2 RCC. FISH was confirmatory in only 40% of the tumours. The results of our study are comparable with previous reports [31]. There was an increase in reporting of TFE3 immunostaining false-positive results [12,

23, 31, 41, 43, 44]. This may be because break-apart FISH probes cannot detect each translocation partner, which leaves significant room for FISH-negative cases to still be harbouring a particular gene translocation [45]. Although there are false-positive results, nuclear TFE3 immunostaining in Xp11.2 RCC is a useful tool to screen for this type of tumour. However, FISH is a helpful tool and should be used alongside immunostaining to diagnose patients with Xp11.2 RCC [25, 31, 40, 41, 46].

Another issue in TFE3 immunostaining is false-negative results. False-negative TFE3 immunostaining results were previously reported [12, 21, 31, 44]. False-negative and -positive immunostaining can be explained by technical problems, including tissue fixation issues, antigen retrieval, scoring method, and the anti-TFE3 antibody [12, 23, 31, 41, 43]. Anti-TFE3 antibody binds to the C-terminus, which is retained in TFE3 fusion proteins. Xp11.2/TFE3 gene fusion consistently leads to TFE3 over-immunostaining [8]. The sensitivity and specificity in TFE3 immunostaining differs between overnight manual incubation and automated incubation (30 minutes). TFE3 immunostaining using overnight manual incubation may provide more accurate results than the short automated incubation. The shorter incubation time and enhanced automated detection system creates a more sensitive but less specific method to detect the TFE3 protein [47]. However, in daily diagnostic practice, it is impractical to use manual immunostaining only for TFE3. TFE3 automated immunostaining showed false-positive staining without any false-negative tumours. TFE3 automated immunostaining is considered to be a sensitive method to diagnose Xp11.2 translocation RCC, but it is less specific [31]. In our study, we used the automated immunostaining method and applied a strict cut-off for positive results, which are diffuse and strong immunoreactivity. Limitations of the current study include the small number of tumours diagnosed as Xp11.2 RCC. This may be attributable to the rare incidence of this RCC subtype.

Conclusions

In summary, we reported the incidence of Xp11.2 RCC in a subset of adult Saudi patients diagnosed with RCC. Clinicians and pathologists should be aware of this tumour entity, not only in children but also among the adult population. These tumours classically have papillary pattern. Distinguishing Xp11.2 RCC from papillary RCC subtype is important because they tend to have worse prognosis. Immunostaining for TFE3 can be used as a screening method, and TFE3 break-apart FISH might be used as a confirmatory method for specific translocation. The results from our study and other reports suggest that we cannot determine whether the gold standard for detection of the Xp11.2 RCC is immunostaining or FISH. The issue remains controversial, and a combination of morphological, TFE3 immunostaining, and FISH should be applied for tumours that are expected to be Xp11.2 RCC based on the morphological features. The molecular pathogenesis of Xp11.2 RCC remains unclear, and thus, further larger cohort studies are required to validate the gold standard for pathological diagnosis.

List of abbreviations

FISH, fluorescence *in situ* hybridisation; RCC, renal cell carcinoma; TFE3, transcription factor E3; Xp11.2 RCC, RCC with Xp11.2 translocation

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The authors declare no conflict of interest.

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