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Clinical and Morphological Heterogeneity of the Xp11.2 Translocation Renal Cell Carcinoma

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Abstract

Xp11.2 translocation cell carcinoma represents a particular neoplasia with advanced stage at diagnosis, complex morphology and unpredictable progression. We describe five different scenarios involving patients with ages ranging from 7 to 79 years old, different tumor morphology and therapy management, focusing on prevalent features of this cancer. Diagnosis was assessed using the validated methods: Immunohistochemistry for TFE3 and break-apart FISH assay. Four out of five cases were T3 stage at presentation, with high grade nuclei on microscopy. All tumors displayed a papillary, nested and solid mixed architecture, while 3/5 associated psammoma bodies and hyaline nodules. One case showed rhabdoid differentiation. Prognosis was independent of tumor size or nuclear grade. Three patients are currently free of disease from their last periodical examination. The younger patient had an adrenal recurrence two years following the diagnosis. Unfortunately, one patient succumbed to cancer within 14 months. Adjuvant treatment didn't prove significant efficacy.

Keywords: Kidney; Xp11.2 translocation carcinoma; FISH assay; TFE3 marker

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Introduction

Since the Xp11.2 translocation renal cell carcinoma has been delineated as a distinct subtype of renal carcinoma in 2004, many articles regarding this malignancy have been published. It was described as a new entity due to its morphological features and specific genetic mutations. The translocation concerns the Xp11 breakpoint, resulting in gene fusions involving the TFE3 gene [1]. Due to genetic similarities, the t(6;11) translocation has been added in 2013 as a distinct subtype, forming together the MiT translocation family renal cell carcinoma [2]. Both transcription factors act on the same targets and induce over expression of the TFE3 or TFEB proteins. This type of cancer was firstly described in the pediatric population and young adults, but nowadays it is known to affect the elderly as well.

Materials and Methods

We explain the heterogeneity of the Xp11.2 translocation RCC using as examples five cases in which the tissue was fixed in 10% buffered formalin, routinely processed and embedded in paraffin wax. Section that was 3 μm thick was stained with hematoxylin and eosin. Immunohistochemical staining was performed using a standardized procedure. We used TFE3 antibody, clone MRQ-37 monoclonal rabbit, Cell Marque. Work has been done on the ventana machine bench mark ultra following steps: Dewaxing at 72 degrees Celsius, ultra pretreatment CC1 (pH 6) for 36 minutes; adding the antibody TFE3 - for 16 min; hematoxylin - 4 min; Bluing-reagent for 2 min; cleaning and blade assembly. Intensive nuclear expression TFE3 was interpreted as a positive reaction, being, according to latest data available in the literature, highly sensitive and specific for translocation Xp11 RCC. Other markers were processed in the same systematized manner. We performed also:-

Case 1 confirmed in 2016, was a 32 year old lady who was admitted to the "Prof. Dr. Th.

Table 1: Clinicopathological characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	F	F	M	F	F
Age (years)	32	39	79	7	35
Symptoms	Lumbar pain	Dysuria	Urinary obstruction syndrome	Recurrent urinary tract infections	Lumbar pain Dysuria Hematuria
Tumor dimension (cm)	9.5/8/7	10/9/8.5	7.5/6.5/6	15.5/15/11.7	4.3/3/3
TNM stage (WHO 2016)	T3aN1M0	T3aNxM0	T3aN1M0	T3aN1M0	T1bN1M0
Tumor morphology					
Architecture	nested, papillary, tubular, alveolar	nested, papillary, tubular, alveolar	papillary, solid	papillary, solid, alveolar, acinar, cystic	papillary, solid, alveolar, acinar
ISUP/WHO grade	4	4	3	3	3
Case particularities	psammoma bodies and hyaline nodules	psammoma bodies and hyaline nodules	scattered multinucleated giant cell	dystrophic calcification and psammoma bodies	scattered giant cells with two or more highly pleomorphic nuclei, rhabdoid differentiation

Burghele" Clinical Hospital for lumbar pain. Ultrasound and CT imaging revealed a poorly circumscribed renal tumor and para-aortic lymphadenopathy. The patient underwent surgery for both lesions.

Case 2 was a 39 year old woman who presented at the Urology Department for dysuria. Further investigations detected mild anemia and proteinuria. An abdominal ultrasound performed subsequently revealed a tumor mass affecting the kidney with echogenicity suggestive for a benign tumor. Owing to the tumor dimensions and impaired renal function, a decision of nephrectomy was made.

Case 3 involved an elderly man (79 year old) admitted for urinary obstruction symptoms. Clinical examination and abdominal ultrasound revealed a kidney enlargement due to a tumor mass. A radical nephrectomy was performed.

Case 4 was diagnosed in a 7 year old girl with recurrent urinary tract infections. The MRI examination detected a right kidney mass with renal vein invasion and enlarged lymph nodes in the pericaval region. The tumor biopsy was interpreted as nephroblastoma for which she received neoadjuvant chemotherapy (3 sessions according to the SIOP scheme). The tumor was unresponsive and kept growing, reaching 20/16/12 cm in less than a month. A right nephroureterectomy with extended lymphadenectomy was intended as a curative surgical resection.

Case 5 was recently documented in a 35 year old woman who was admitted with hematuria, dysuria and lumbar pain beginning in the last 24 h. The imaging tests identified a left kidney tumor and regional lymphadenopathies. Radical nephrectomy was further performed as the curative treatment.

Results

Clinicopathological characteristics are shown in Table 1.

Case 1

Histopathologically, the tumor was composed of polyhedral cells with voluminous, pale to eosinophilic cytoplasm, large nuclei with conspicuous nucleoli and frequent mitoses. The para-aortic lymph node was metastatic. Given the patient age and the tumor morphology we requested ancillary tests for an Xp11.2 translocation RCC suspicion. The diagnosis was confirmed using immunohistochemistry and break-apart FISH assay.

Case 2

Microscopically, the malignant cells are of intermediate size, with a clear and eosinophilic cytoplasm (more often with a clear cell appearance). The final diagnosis was established based on the strong positive for cathepsin K break-apart FISH test for TFE3 rearrangement (Figure 1). The genomic alteration suspected in this case involves a t(X; 1) (p11.2; q21) translocation, which characteristically results in a PRCC-TFE3 gene fusion 1. The patient didn't receive any adjuvant therapy and is currently free of disease recurrence, with a 22 months follow-up.

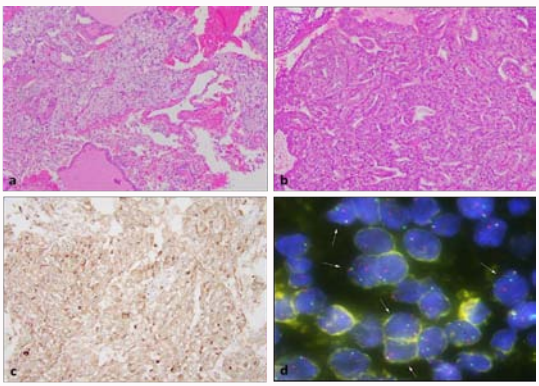

Figure 1: Case 2: a) Pseudopapillary areas with clear cells, HE, 5x; b) trabecular areas with eosinophilic cytoplasm, HE, 20x; c) Positive IHC reaction for Cathepsin K, 40x; d) Break apart-FISH essay showing nuclei with TFE3 rearrangement (Courtesy of prof. Argani, Johns Hopkins Hospital, USA).

Case 3

On microscopy, cells were medium-sized, with clear to pale eosinophilic cytoplasm and large pleomorphic nuclei. Notwithstanding the patient age, the tumor morphology suggested an Xp11.2 translocation RCC. TFE3 over expression was confirmed by immunohistochemistry due to a strong and diffuse positive nuclear reaction (+++) (Figure 2). The patient didn't opt for any additional treatment and is free of disease according to the 3 months post-operative examination.

Case 4

The surgical specimen revealed a medium-large cell proliferation, with clear or eosinophilic cytoplasm and G3 nuclei (ISUP 2016). An Xp11.2 translocation RCC was suspected, but remained to be confirmed due to TFE3 staining being unavailable at that time. Two years later, a PET CT scan detected a 3.6/2.1 cm tumor abutting the

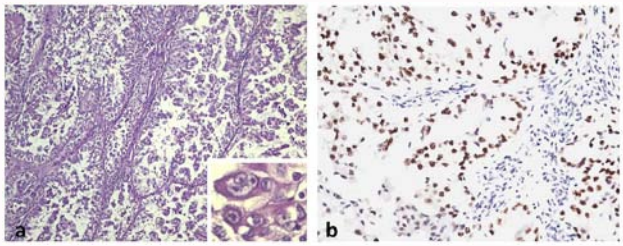

Figure 2: a) Papillary architecture with highly pleomorphic cells (detail), HE, 10x; b) Strong and diffuse positive nuclear reaction (+++) for TFE3, IHC, 20x.

right adrenal gland and a few regional enlarged lymph nodes. A second tumor resection surgery was performed and the microscopic examination confirmed a renal cell carcinoma resembling the primary tumor. In addition to usual markers for renal cell carcinoma (CD10+, PAX8+, CK7-), the tumor cells displayed an intense and diffuse positive reaction for TFE3, which confirmed the Xp11.2 translocation RCC.

Case 5

The tumor morphology depicted a peculiar morphology with classic clear cells with G3 nuclei and almost 35% of the tumor showing rhabdoid differentiation. An IHC test for TFE3 was requested, which showed intense and diffuse positivity. Eventually, An Xp11.2 translocation RCC diagnosis was straightforward.

Discussions

Regarding the clinical presentation of our cases, the symptoms weren't specific for a renal tumor, but have guided the patient to seek medical attention. Careful examination and basic imaging techniques (ultrasound, CT scans) are mandatory, even without any signs of malignant pathology. Besides classical cases confirmed among children and young women, there are Xp11.2 translocation RCC documented in older individuals, including men, as is our case [3]. All tumors were detected at an advanced development stage, having large dimensions and invading at least the renal hilum. We encountered psammoma bodies and hyaline nodules in every specimen, features that are described to be very frequent in this type of renal cell carcinoma [4]. All patients underwent open radical nephrectomy as the main treatment. In our first case, para-aortic lymphadenectomy was performed because of tumor metastasis suspicion, which was histologically confirmed. By reason of such an advanced stage, these patient received 10 fractions of radiotherapy and then a chemotherapy regimen with Sunitinib in a 2/2 scheme (2 weeks treatment/2 weeks pause). Her para-aortic lymphadenopathies didn't respond to treatment. The patient succumbed to cancer 14 months following surgery, during her adjuvant treatment, as a consequence of systemic complications. In our fourth case, the external radiation dose (19.8 Gy), prescribed for retroperitoneal lymphadenopathies, proved to be effective and the patient is currently free of disease, five months later from the last intervention.

The pathologist should consider this entity whenever he encounters a renal cancer with nested and papillary architecture, composed of cells with clear or pale eosinophilic cytoplasm, regardless of the patient age. It frequently associates psammoma bodies or occasionally depicts melanotic features. The main differentials are the clear cell RCCs with predominant papillary features and the papillary RCC with clear features [5]. Diagnosis of the Xp11.2 translocation renal cell carcinoma is now easier to confirm using immunohistochemistry for TFE3 and break-apart fluorescence in situ hybridization on paraffin-embedded tissue [6]. Useful additional markers are cathepsin K, PAX8, CD10, HMB455. Argani et al. [7] stated in 2016 that the immunohistochemistry profile can vary in this group according to the gene fusion partner. The PRCC-TFE3 translocation subtype harbors consistently a positive reaction for cathepsin K whereas the SFPQ-TFE3, NONO-TFE3, DVL2-TFE3, and ASPL-TFE3 gene fusions cancers are almost always negative for this marker [8]. A cytogenetic technique is mandatory to establish the final diagnosis of the Xp11.2 translocation provided that over expression of TFE3 has been reported other genomic alterations (ALK-TMP3 fusion) [9].

Conclusion

Recent scientific reports conclude that the number of Xp11.2 translocation RCC is increasing among adults [10]. This could be attributable to its distinct morphology which conducts the experienced pathologist to require ancillary tests for this diagnosis. A strong positive reaction for TFE3 is highly diagnostic for this renal cancer subtype. Break-apart FISH assay is a rapid test useful to confirm TFE3 gene translocation in paraffin embedded tissues [11]. One should include the Xp11.2 translocation RCC in the differential diagnosis for a renal cancer that shows a mixed clear and papillary architecture, associated with hyaline nodules and psammoma bodies, regardless of the patient sex or age [12]. The only validated treatment at the moment is open surgery for partial or radical nephrectomy, depending on tumor dimensions. Nephron-sparing surgery is safe and feasible for tumors sized 4 cm to 7 cm and located in one pole [13]. There has been no established effective adjuvant therapy to date, although some recent case reports demonstrated an equivocal response to VEGF-targeted, mTOR inhibitor treatment and the tyrosinekinase inhibitor receptor (Sunitinib or Sorafenib) [10,14].

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