Translocation (X;1) in Papillary Renal Cell Carcinoma
A New Cytogenetic Subtype

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ABSTRACT: We report a consistent t(X;1)(p11.2;q21) that was observed in four cases of papillary renal tumors. In one of the cases, two cells showed the cytogenetic abnormality as the only change, whereas the other cases showed additional chromosomal anomalies particularly involving chromosomes 7 and 17. One identical t(X;1) has been reported previously in a papillary renal cell carcinoma. To date, all of the patients carrying this translocation been males.

INTRODUCTION

Papillary renal cell carcinomas (PRCCs) have histologic and pathologic characteristics that distinguish them from non-papillary renal carcinomas [1, 2]. Cytogenetically, the distinction is more evident because PRCCs fail to show involvement of 3p14-p23 often seen in non-papillary tumors [3-6], but do have numerical abnormalities, particularly of chromosomes 7, 16, and 17 [5-8].

We report the cytogenetic findings in four PRCCs which showed the following common characteristics: 1) The presence of an identical t(X;1) and 2) the fact that the patients were all males.

A similar case was previously described by de Jong et al. in a 2-year-old boy [9], in which the tumor was defined as a trabecular papillary renal cell carcinoma.

We think that the cytogenetic and pathologic findings presented here, together with the case from the literature, are sufficient to consider the cases with t(X;1) as a separate new entity among renal neoplasms. We discuss the findings in relation to other tumors which show X chromosome involvement, with particular emphasis on those in which Xp11.2 is involved [8-14], and also discuss the possible molecular implications of a putative tumor suppressor gene which could be located at Xp11.2.

CASE REPORTS

Case 1
A 68-year-old male was diagnosed in June, 1989 as having a granular papillary renal cell carcinoma, grade 4, affecting the right kidney. The final pathologic diagnosis revealed that the neoplasm extensively invaded perinephric adipose tissue in the area of the renal sinus and close to the margin of excision. The carcinoma invaded the renal vein at the margin of resection. The ureteral margin of resection was free of neoplasm, nor did the carcinoma invade the pelvocalyceal system.

Case 2
In September, 1989, a 55-year-old male was diagnosed as having a papillary renal cell carcinoma, grade 3, affecting the right kidney. Extensive invasion of the renal vein was present, though no evidence of neoplasm could be seen at the venous line of resection.

Case 3
No information was available for this patient besides the fact that he is an adult male diagnosed with a papillary renal cell carcinoma, grade 3.

Case 4
A 24-year-old male was diagnosed in August, 1991 as having a moderately differentiated papillary renal cell carcinoma affecting the left kidney [Fig. 1]. The surgically removed tissue revealed nodules of tumors invading the renal capsule and extending into the perirenal fat, forming a tumor mass up to 2.9 cm in diameter, which extended within 3.0 cm of the perinephric fat surface. No tumor was present in the ureter and renal veins and arteries. No evidence of metastatic disease was found.

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MATERIALS AND METHODS

In all four cases the tumor was collected under sterile conditions and shipped to our laboratory for chromosome analysis.

The samples were processed according to previously described methods [15]. Each tissue was disaggregated in collagenase (200 U/ml overnight). The following day the suspensions were seeded (in flasks and coverslips) with RPMI medium supplemented with 17% bovine serum, 1% glutamine (2 mM) and penicillin; streptomycin (5000 U/ml; 5000 μg/ml) and placed in a humid environment with 5% CO₂ for a period of 2–6 days.

Harvest was performed by overnight Colcemid exposure, hypotonic shock, and fixation with methanol:acetic acid (3:1). Air-dried chromosome preparation were G-banded using trypsin and the karyotypes were expressed according to the ISCN (1991) [16].

RESULTS

Case 1
The tumor cells grow very poorly in culture and after 5 days a total of only 8 cells could be analyzed. One cell showed a normal male chromosome complement whereas the other 7 showed the following karyotype: 49,XY,t(X;1)(p11.2;q21),+7,+15,+17 (Fig. 2).

Case 2
A total of 19 metaphase cells were analyzed after 2–4 days of culture. The results of the cytogenetic analysis were the following: 41,XY,t(X;1)(p11.2;q21),i(1q),der(3)t(3;13)(p12;q12),-4,-5,inv(7)(q11.1p22),-9,-10,-11,-13,der(16)t(16;?),+17,-18,+20 (Fig. 3) [8]/40,idem,-Y [6]/46,XY [5].

Case 3
The tumor was harvested after 2 days of culture. All 25 metaphases analyzed showed the same karyotype: 45,XY,t(X;1)(p11.2;q21),-22 (Fig. 4). Peripheral blood cells were also processed and the metaphases analyzed had a normal 46,XY complement.

Case 4
A total of 15 metaphases was obtained after 6 days in culture. Two clones were seen: 46,XY,t(X;1)(p11.2;q21.1) [2]/46, idem,inv(13)(q12q22) (Fig. 5). No normal cells were observed in the tumor tissue. A peripheral blood study yielded only normal 46,XY metaphases.

DISCUSSION

In 1965 de Jong et al. [9] reported a case of trabecular papillary renal adenocarcinoma in a 2-year-old boy. The tumor cells were characterized by a unique cytogenetic abnormal-
Figure 2  G-banded karyotype of Patient 1. Other changes were present in addition to t(X;1). See Results for detailed karyotype description.

Figure 3  G-banded karyotype of Patient 2. The karyotype was complex and showed other chromosome abnormalities in addition to t(X;1). See Results for detailed karyotype description.
itiy involving chromosomes X and 1. Because this was the first case described with such a translocation, it was viewed as a report of a papillary tumor with an unusual translocation. The possibility that t(X;1)(p11.2;q21) may characterize a subtype of renal tumor with papillary features arose from the observation of additional cases with the same translocation. This cytogenetic abnormality has not been described in tumors other than renal tumors with papillary characteristics. When the chromosomal change involves two chromosomes, as in the t(X;1), the question arises as to which chromosome is more important in the development of the tumor.

Chromosome 1 abnormalities involving different breakpoints along the whole chromosome have been previously reported in numerous other neoplastic disorders [5, 6], and in general the presence of extranumerary 1q portions is considered to be crucial for tumor progression.

On the other hand, X chromosome involvement is less frequent, but generally the breakpoints most involved are p22→p11.2 in the short arm, and q13 in the long arm [17-19]. The breakpoint Xp11.2 has been reported in synovial sarcomas, involved in the t(X;18) [10, 11], in some cases of leiomyoma (a benign tumor of the uterus) [13, 14] and recently, in one case of renal cell carcinoma, clear cell, with a t(X;17) [12].

Apparent, the breakpoint on the Xp11.2 is involved in a number of tumors. Recently, a member of the helix-loop-helix family of transcription factors, TFE3, has been localized to Xp11.2 [20, 21]. The human TFE3 is a ubiquitous DNA binding protein that binds to the μE3 motif within the immunoglobulin chain enhancer. To date, the physiologic function of TFE3 is not known. Based on the findings of Henthorn et al. on TFE3 [20], defects of this transcription factor, even if it is ubiquitously expressed, could cause diseases limited to specific tissues. This may be an explanation of why the same breakpoint is involved in synovial sarcomas, leiomyomas, and renal tumors.

Of importance is the fact that all of the five patients, including the case from the literature [9], were male. A speculative assumption could be that males are at greater risk than females, because they are hemizygous for all the X-linked genes. This assumption was first proposed by Tomlinson et al. in a report of a renal cell carcinoma in a 17-month-old child characterized by a t(X;17)(p11.2;q21.2) [12].

It has been reported recently that the inactivated X in females is not completely silent; thus, there are four regions on the short arm and two on the long arm that escape this inactivation [22]. Potentially, then, a tumor suppressor gene located in any of these regions could protect females against a defective or deleted tumor suppressor gene; such protection is not present in males.

Figure 4 G-banded karyotype of Patient 3: 45,Y,t(X;1)(p11.2;q21), -22. Loss of chromosome 19 was random.
Figure 5  G-banded karyotype of Patient 4 showing the main line, consisting of t(X;1)(p11.2;q21) and the sideline (inset) characterized by the presence of an inv(13)(q12q22) as additional change.

These findings require more investigation from a molecular point in order to elucidate the role of the X chromosome in tumor development and from a cytogenetic point in order to describe more of such cases, which could lead to more understanding of the biology and behavior of this type of renal papillary carcinomas.

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