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RENAL ONCOCYTIMA WITH t(5;12;11), DER(1)t(1;8) AND ADD(19): “TRUE” ONCOCYTIMA OR CHROMOPHOBIC ADENOMA?

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Renal oncocytomas reveal a considerable (cyto)genetic heterogeneity. At least 2 genetic subsets are currently recognized. Characterized by (1) translocations involving breakpoints 11q13 and (2) the combined loss of chromosomes 1 and X/Y. We present a case of oncocytoma revealing a 3-way translocation involving breakpoint 11q13, a der(1)t(1;8) and an add(19). The der(1) resulted in loss of chromosome 1 sequences. Using fluorescence in situ hybridization, the 11q13 breakpoint of the present case proved to be slightly different from the one observed previously in 3 cases of renal oncocytoma. Whether the 11q13 breakpoint observed in our case resides in or near another gene remains to be elucidated. Int. J. Cancer: 73:521-524, 1997. © 1997 Wiley-Liss, Inc.

Renal oncocytoma is a distinct subtype of renal cell cancer (RCC) comprising approximately 4% of cases, in which the male to female ratio is 2.5:1. It is an essentially benign neoplasm; clinically, most of these tumours are discovered incidentally (Weiss et al., 1995). However, malignant renal oncocytomas have been described, indicating that at least some of these neoplasms may have malignant potential (Jockie et al., 1987; Psiriramis et al., 1988; Weiss et al., 1995). Histologically, renal oncocytomas consist of enlarged cells with small, centrally located nuclei. A prominent feature of renal oncocytic cells is the accumulation of enlarged mitochondria in the cytoplasm. Specific changes in the mitochondrial DNA of renal oncocytoma have been observed (Welter et al., 1989; Kovacs, 1993). The frequent finding of telomeric associations, reflecting a specific type of chromosome instability, is another characteristic property (Holzmann et al., 1993).

Cytogenetic analysis of renal oncocytomas has revealed a variety of chromosomal patterns, suggesting the existence of distinct subsets (Psiriramis et al., 1988; Crotty et al., 1992; Dobin et al., 1992; Meloni et al., 1992; Kovacs, 1993; van den Berg et al., 1995; Dal Cin et al., 1996). At least 2 genetically defined subsets appear to emerge, characterized by (1) the combined loss of chromosomes 1 and X/Y and (2) translocations involving chromosome 11 with breakpoint 11q13. Sinke et al. (1997) mapped this oncocytoma-specific 11q13 breakpoint in 2 (5;11)-positive renal oncocytomas between D11S443/D11S146 and the BCL1 locus. The 11q13 breakpoint of a third case revealing a t(9;11)(p23;q13) has been found to be located within the same region (data not shown), suggesting that in the t(5;11)- and the t(9;11)-positive renal oncocytomas, the same gene at chromosome 11 may be involved in the development of these neoplasms. The remaining cases of oncocytoma display mixed populations of cells with normal and abnormal karyotypes, which fail to show any cytogenetic similarity (Kovacs, 1993).

Because little is known about the genetic changes responsible for the development of renal oncocytomas, additional studies concerning the genetic constitution of these neoplasms are mandatory. Furthermore, the cases of renal oncocytoma with malignant potential might reveal genetic changes distinct from those showing benign behavior. In these cases, the genetic constitution may prove to be a valuable diagnostic and prognostic tool. Hence, we analyzed a case of renal oncocytoma using cytogenetic techniques and fluorescence in situ hybridization (FISH) and compared the observed findings with data published by others. In addition, we aimed to find a relation between the biologic behavior of renal oncocytomas and their genetic profile. In this light, we comment on a possible, genetically defined distinction among renal oncocytomas, chromophobe adenomas and chromophobe carcinomas.

CASE HISTORY

A 63-year-old man presented with a solid renal mass. Tumor nephrectomy revealed a sharply demarcated tumor nodule measuring 5 X 5 X 4.5 cm with extension into the hilar fatty tissue. On cut surface the tumor was light brown. Microscopic examination of 9 slides showed large, eosinophilic, granular tumor cells with increase of double nuclei and focal, extremely pleomorphic nuclei arranged in a mostly solid acinar and partially tubulocystic architecture. Hale's staining was performed and revealed neither a typical oncotypic nor chromophobic staining pattern; only a few slightly positive signals were seen in a few cells. No ultrastructural studies were performed. No peri-tumoral fibrous pseudocapsule was observed, and no lymphocytic infiltration was seen. The tumor was diagnosed as a renal oncocytoma (Fig. 1).

MATERIALS AND METHODS

Fresh representative samples of the tumor and adjacent non-tumor renal tissue were submitted for cytogenetic investigation. Cultures were maintained for 13 days in RPMI 1640 supplemented with FCS (16%), glutamine and antibiotics. The cultures were harvested and chromosome preparations were made according to standard cytogenetic techniques. The chromosomes were G-banded using pancreatin, and karyotypes were described according to the ISCN (1995) guidelines for cancer cytogenetics.

For FISH studies, specific libraries for chromosomes 5, 11 and 12 (Oncor, Malvern, PA) were used. To identify chromosome 5, a hybridization with CEPH YAC 933A7 was performed. Identification of chromosome 12 was done using probe pXH8. For labeling of the YAC and pX12H8, the Bio-Nick Labeling System (GIBCO BRL, Gaithersburg, MD) was used. In situ hybridization was carried out essentially according to the manufacturer's protocol (Fig. 3). Cosmids CcII-44 (D11S443), Bc1-c19 and CcII-59 (D11S146) were used to further define the breakpoint at 11q13. These experiments were performed as described previously (Sinke et al., 1997). Cosmid cCLGW454 (D11S688) located at 11q15 served to identify chromosome 11.

RESULTS

Cytogenetic and FISH analyses of the present case resulted in a 46,XY,der(1)t(1;8)(q43;q31.1),t(5;11;12)(q22;p12;q13q24),ISH(wcp5+;933A7+;wcp12+;wcp11+;D11S688+;D11S443+;D11S146+;Bc1-c19+;wcp5+;wcp12+;pXH8+).

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add(19)(p13)[cp10] chromosomal pattern. A karyotype of one of the metaphases is given in Figure 2. FISH results defining the 3-way translocation are shown in Figure 3. Cytogenetic analysis of 10 cells of the non-tumor kidney tissue revealed clonal loss of the Y chromosome.

**DISCUSSION**

Translocations involving chromosome 11 at 11q13 are a recurrent finding in a subset of renal oncocytomas [see for review Neuhaus et al., 1997]. In these tumors, chromosome 11 is specifically translocated to either chromosome 5 or 9. The genes involved in the oncocytoma-specific 11q13 translocations are not known, but the 11q13 breakpoint has been mapped between D11S443/D11S146 and the BCL1 locus (Sinke et al., 1997).

Cytogenetic analysis and FISH of the present case revealed an apparently balanced translocation between chromosomes 5, 11 and 12 in all cells examined. The breakpoint at chromosome 5 clearly differed from that observed in the t(5;11)-positive oncocytomas published thus far. Surprisingly, the breakpoint at chromosome 11q13, which appeared to be similar at a cytogenetic level, proved to be (slightly) different using FISH. Cosmid BCL1-c19, found to be located distal to the 11q13 breakpoint in the t(5;11)- and t(9;11)-positive oncocytomas, was located proximal to the 11q13 breakpoint of the present case. Whether the latter breakpoint resides in or near another gene remains to be elucidated.

Both the der(1)t(1;8)(q43;q11.1) and the add(19)(q13) were present in 4 of 10 cells analyzed. The der(1) resulted in a loss of a small segment of chromosome 1 and a gain of almost the whole 8q arm. Loss of chromosome 1 sequences has been described in renal oncocytomas (Psihramis et al., 1988; Crotty et al., 1992; Meloni et al., 1992; Brown et al., 1996; Thrash-Bingham et al., 1996). Usually, the whole chromosome 1 is missing in these cases, but loss of 1p appears particularly important (Thrash-Bingham et al., 1996). In most cases, loss of chromosome 1 sequences occurs concurrently with loss of the X or Y chromosome. In the present case, retention of the Y chromosome was observed and loss of chromosome 1 sequences involved the region 1q43-qter, not 1p. Gain of chromosome 8 has not been associated with renal oncocytomas thus far. An add(19)(q13) has been described in one of the cases of oncocytoma published by van den berg et al. (1995). In this case, loss of chromosomes 1 and Y and a t(9;?11) was also observed, but

**Figure 1** - Histology of the present oncocytoma (H&E).

**Figure 2** - A representative karyotype of the present case. Karyotype description is given in the text.
Figure 3 - FISH on metaphase spreads of the present case using (a) a paint for chromosome 11 (arrows) in conjunction with YAC 933A7 (arrowheads), (b) a paint for chromosome 12 (arrows) in conjunction with YAC 933A7 (arrowheads) and (c) a paint for chromosome 5 (arrows) in conjunction with p12H8 (arrowheads) defining the 3-way translocation among chromosomes 5, 11 and 12.

the latter showed breakpoints different from the t(9;11) reported in other renal oncocytomas.

Although malignant oncocytomas can in principle not exist (Eble, 1997) if the diagnosis is made properly, some cases have been described in the past (Jockle et al., 1987; Pishrmis et al., 1988; Weiss et al., 1995). When comparing renal oncocytomas with other malignant RCC subtypes, morphological and immunohistochemical data point to a close relationship between renal oncocytoma and chromophobe renal cell carcinomas (Störl et al., 1988, 1989; Noguchi et al., 1995; Renshaw et al., 1996). Both tumor types find their origin in the intercalated cells of the collecting tubules and express carbonic anhydrase C. The findings of telomere shortening, telomeric associations and mitochondrial DNA changes are other common features (Welter et al., 1989; Kovacs et al., 1992; Holzmann et al., 1993; Kovacs, 1993). Comparison of the genetic profile of both RCC subtypes reveals that a subset of oncocytoma and chromophobe renal cell carcinomas consistently show loss of chromosomes 1 and X/Y (Kovacs and Kovacs, 1992; Schwerdtle et al., 1996; Shuin et al., 1996). In addition, chromophobe carcinomas reveal loss of chromosomes 2, 6, 10, 13, 17 and 21. These findings present the possibility of a genetic model for an adenoma/carcinoma sequence for chromophobe tumors postulating that a subgroup of oncocytomas characterized by -1,-Y in a strict sense should be called chromophobic adenomas. Subsequent loss of chromosomes 2, 6, 10, 13, 17 and 21 might result in progression toward a carcinoma stage, explaining the malignant potential occasionally observed in renal oncocytoma. Evidence substantiating such a proposed oncogenetic pathway includes the following: 1) the finding of an oncocytoma containing chromophobe cell nests (Noguchi et al., 1995), pointing to a possible transition between the two tumor types, 2) cytogenetic analysis of a case of oncocytoma revealing multiple chromosome losses among chromosomes 1, 2, 6, 17, 21 and Y (Gregori-Romero et al., 1997) and 3) loss of heterozygosity studies showing loss of chromosome regions 1p, 2pq, 13q, 17pq and Xpq in one case of oncocytoma and loss of 1pq, 14q and 21q in another (Thrash-Bingham et al., 1996). Clinical follow-up is mandatory to draw conclusions concerning the above proposed oncogenetic pathway but has been seldom published in combination with cytogenetic results. The only case of malignant oncocytoma for which cytogenetic data have been provided revealed a 44,X,-Y,-1 chromosomal pattern (Pishrmis et al., 1988), which is in agreement with the proposed malignant potential of tumors exhibiting loss of chromosomes 1 and X/Y. Clinical follow-up has not been provided for the cases with 11q13 translocations published thus far, but the 2 patients with t(5;11)-positive oncocytomas published by van den Berg et al. (1995) are currently alive without evidence of disease after 46 and 96 months, respectively. In addition, to our knowledge, no (5;11) or (9;11) translocations have been described in chromophobe carcinomas or in other RCC subtypes.

Therefore, oncocytomas showing translocations involving 11q13, may be “true” oncocytomas, behaving invariably benign. Whether our case belongs to the group of “true” oncocytomas must await the identification of the gene(s) responsible for the development of these neoplasms.

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