

FAMILIAL RENAL ONCOCYTOMA

CLINICOPATHOLOGICAL STUDY OF 5 FAMILIES

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Abstract

Purpose: We analyzed familial renal oncocytoma to provide a foundation for studies aimed at defining genes involved in the pathogenesis of renal oncocytoma.

Materials and Methods: We describe 5 families with multiple members affected with renal oncocytoma. Tumors were analyzed pathologically, and affected and nonaffected members were screened clinically and genetically.

Results: We identified 12 affected male and 3 affected female (ratio 4:1) individuals in the 5 families. In affected family members renal oncocytomas were often multiple and bilateral. No metastatic disease was observed. Most renal oncocytomas were detected incidentally in asymptomatic individuals or during screening of asymptomatic members of renal oncocytoma families. One identical twin pair was affected with bilateral multiple renal oncocytomas.

Conclusions: Renal oncocytoma may be inherited in some families.

Key Words: kidney neoplasms, hereditary diseases

There are 3 well-defined types of inherited renal neoplasms. [1] In von Hippel-Lindau disease individuals with germline mutations of the tumor suppressor gene (3p25-26) have a predisposition to clear cell renal cell carcinomas along with tumors in the brain, spine, eye, pancreas, epididymis and adrenal gland. A second mode of inheritance of renal neoplasms occurs in individuals with a balanced translocation between the short arm of chromosome 3 and chromosome 6 or 8 who have a predisposition to clear cell renal cell carcinomas without other tumors. A third type of hereditary renal cancer is hereditary papillary (chromophilic) renal cell carcinoma, and these tumors caused by

mutations in the MET proto-oncogene (7q31-34) have been described in large and small kindred.

Renal oncocytoma accounts for 3 to 5% of renal neoplasms, [2,3] and is thought to originate from intercalated cells in the collecting duct. [4] Histologically, the tumors are comprised of cells with eosinophilic cytoplasm caused by an abundance of mitochondria. [5] The tumor cells react with antibodies to cytokeratins but not vimentin. [6] Cytogenetic changes in sporadic renal oncocytomas include loss of chromosome 1p, 14q, loss of the Y chromosome in male patients or translocation between chromosome 11q13 and other chromosomes (Table 1). [7-20] Renal oncocytomas are usually asymptomatic and detected incidentally during examination for other health problems. Sporadic renal oncocytomas usually are not symptomatically detected until the seventh decade and there is a 2:1 male predominance. Usually renal oncocytomas are single but they may be multifocal and bilateral. [2,3] The differential diagnosis of renal tumors with eosinophilic cytoplasm may be difficult. Renal oncocytoma must be distinguished from the eosinophilic variants of chromophobe and clear cell renal cell carcinomas. [21]

Table 1. Review of cytogenetic alterations of renal oncocytoma

Genetic tests to help distinguish renal oncocytoma from malignant renal epithelial tumors would be useful. A necessary first step is to identify families with a hereditary predisposition to renal oncocytoma. We describe 5 families with multiple members affected with renal oncocytoma. The results suggest that predisposition to renal oncocytoma may be inherited, which may define another type of inherited kidney neoplasm. These families provide a foundation for studies aimed at defining genes involved in the pathogenesis of renal oncocytoma.

MATERIAL AND METHODS

Patients.

Families with a history of renal neoplasms were referred for evaluation to the Urologic Oncology Branch, National Cancer Institute. A total of 30 members of families 166, 167, 168 and 169 were examined at the clinical center of the National Institutes of Health (NIH) after informed consent was obtained. This project was approved by the Clinical Research Subpanel of the National Cancer Institute. At the NIH the evaluation consisted of a family and personal medical history, physical examination, dermatological examination, and computerized tomography (CT) of the abdomen with and without contrast media followed by ultrasound of the kidneys. In patients with elevated creatinine magnetic resonance imaging of the abdomen with gadolinium was substituted. Urinalysis, measurement of serum creatinine, blood urea nitrogen, electrolytes, chemistry studies and complete blood count were done in all subjects. Creatinine clearance was measured in select patients. An individual with a renal tumor was considered affected if he or she had single or multiple renal oncocytomas and a first or second-degree relative with renal oncocytoma. The diagnosis of renal neoplasms of deceased family members was determined from death certificates, medical records, and pathology and autopsy reports. Histological slides on renal tumors were reviewed by 5 authors (G. W., M. M., I. L., S. S. and M. A.).

Laboratory tests.

Blood samples were obtained from each family member. Lymphoblastoid cell lines were established from isolated blood leukocytes to provide a source of additional deoxyribonucleic acid (DNA). DNA was extracted from peripheral blood leukocytes, lymphoblastoid cell lines and renal tumors by the phenol chloroform method. Blood leukocytes from 1 or more affected individuals from all except family 170 were examined for chromosomal rearrangements, including the constitutional rearrangement observed in a single patient with renal oncocyoma. [20] Blood samples from select affected individuals were tested for mutations in the von Hippel-Lindau tumor suppressor gene and the MET proto-oncogene. To detect von Hippel-Lindau mutations DNA was tested for deletions by Southern blotting and DNA sequencing. To detect mutations in the MET proto-oncogene exons 16-19 of the MET gene were scanned by conformation sensitive gel electrophoresis. Samples that showed an abnormal migrating band were sequenced.

Pathology.

A renal tumor with nested or organoid architecture and compact areas surrounded by a delicate connective tissue framework or tubulocystic growth was classified as a renal oncocyoma. Cytoplasmic characteristics included eosinophilia of the majority of tumor cells, and clearing of the cytoplasm was considered acceptable if focally present. Nuclear features included regular nuclear contours, inconspicuous nucleoli, absence of mitotic activity and focal nuclear pleomorphism. [2,22]

RESULTS

In 5 families we identified 11 patients affected with renal oncocyoma, 3 with renal tumors on CT or ultrasound and 1 with a history of surgical removal of a renal oncocyoma. Renal oncocyoma/renal neoplasms were identified in members of 3 generations of family 169, in members of 2 generations of families 166, 167 and 168, and in 1 generation of family 170. The number of affected individuals within a family ranged from 2 (family 170) to 4 (family 169). All families were white, and there were 12 affected male and 3 affected female subjects for a male-to-female ratio of 4:1. Two brothers in family 170 had renal oncocytomas and no renal tumors were detected throughout hospitalization for other illnesses in their parents. Median age at diagnosis was 55.8 years. Renal oncocytomas were detected incidentally in 13 individuals during ultrasound or screening by CT of the abdomen and ultrasound of the retroperitoneum of asymptomatic family members. In 1 subject (I-4 family 168), renal oncocytomas were first detected at autopsy. The number of renal tumors in affected individuals ranged from 1 (subjects II-3 and III-3 family 169) to multiple throughout both kidneys (subject II-2 family 169). No subject had evidence of metastatic disease and no deaths were caused by renal oncocyoma. Family pedigrees are given in [Figure 1](#).



Figure 1. Pedigrees of 5 families with renal oncocyoma. Solid symbols represent subjects affected with renal oncocyoma or tumors of kidney. Renal tumors of 4 subjects were not examined histologically (subject II-1 family 166, subject II-2, family 167 and subjects I-2 and III-3 family 169). Symbols with central black dot represent subjects examined by CT and ultrasound of abdomen and no tumors were found. Open symbols represent subjects with no history of renal tumors.

Description of families. Family 166: Subjects III-2 and III-3, identical twin 38-year-old brothers, were affected with bilateral, multiple renal oncocytomas. Renal oncocytomas were detected in subject III-3 as an incidental finding during ultrasound of the gallbladder and liver. Subject III-2 was examined because of the findings in subject III-3. Screening of the father (subject II-1) revealed a 3 cm. solid tumor in the left kidney and a 2 cm. solid tumor in the right kidney (Figure 2). Basilar lung cysts were incidentally seen on abdominal CT of the twins, neither of whom smokes.



Figure 2. CT of subject II-1 in family 166 shows protruding solid hypodense and well circumscribed homogeneous mass of left kidney dorsomedially. This patient had another solid mass in upper pole of right kidney.

Family 167: Subject II-2, an 80-year-old man, had undergone nephrectomy for a renal tumor at age 65 years that was diagnosed as renal oncocytoma on pathological examination. The sons of subject II-2 (subjects III-1 and subject III-2) were affected with bilateral renal oncocytomas. Subject III-1 underwent bilateral partial nephrectomy for multiple renal oncocytomas at age 45 years (Figure 3B). This patient also had a history of episodic spontaneous pneumothorax, multiple bullae or lung cysts on chest CT and no alpha-1-antitrypsin deficiency. Subject III-2 underwent total right nephrectomy at age 31 years and left partial nephrectomy at age 48 for renal oncocytomas. This patient reported a single episode of spontaneous pneumothorax, chest CT revealed bullae or cysts in both lungs and alpha-1-antitrypsin was normal. Neither son smoked.



Figure 3. Histopathological features of oncocytomas. A, subject III-2 family 166. Tumor is arranged in nests surrounded by loose connective tissue (organoid pattern). Tumor cells are mostly eosinophilic and intermingled with lower number of cells with cytoplasmic clearing. B, subject III-1 family 167. Solid growth pattern. Tumor cells are arranged in nests surrounded by delicate connective tissue. Tumor cells are eosinophilic with central uniform nuclei. C, subject III-2 family 166. Solid growth pattern. Many tumor cells exhibit clearing of cytoplasm, and there is no difference in size between clear and eosinophilic tumor cells. H & E, reduced from X200.

Family 168: This family has 3 individuals affected with renal oncocytomas. Subject I-4 died at age 60 years with coronary arteriosclerotic heart disease. Autopsy revealed "multiple gray-yellow nodules ranging in size from 2-27 mm. in the right kidney." In the left kidney "a soft bulging yellowish 25 mm. nodule" was identified. Pathological examination at the NIH indicated that these tumors were renal oncocytomas. Subject II-2, the son of subject I-4, underwent enucleation of 2 renal oncocytomas from the right kidney at age 47 years, left nephrectomy for multiple renal oncocytomas at age 50 and complete resection of the remaining right kidney for multiple renal oncocytomas at age 57, following which he began hemodialysis 3 times a week. Subject II-5, a sister of subject II-2, had a 5 mm. solid lesion on the left kidney that grew to 1.2 cm. in diameter in 6 years. The tumor was a renal oncocytoma. Subject III-9, the daughter of member II-5, had no renal tumor but had documented pneumothorax at age 19 years, basal pulmonary cysts on CT and normal alpha-1-

antitrypsin.

Family 169: This family consists of 4 subjects affected with renal oncocytoma or renal tumor. Subject I-2 died at age 92 years. At age 83 ultrasound revealed a 6.2 cm. complex mass in the left upper pole and a 5.3 cm. mass with a central cystic component in lower pole of the kidney. The lesions were thought to be renal neoplasms. Two children were affected with renal oncocytomas, and both had a record of sudden onset of hypertension less than a year before the detection of renal oncocytoma. Subject II-2 had sudden onset of arterial hypertension at age 62 years and underwent a screening abdominal ultrasound. Solid tumors were detected in both kidneys, and serum creatinine and blood urea nitrogen were elevated. He underwent enucleation of 2 oncocytomas from the left kidney and right nephrectomy for multiple renal oncocytomas. Subject II-3 had a greater than 3-year history of arterial hypertension with chronic renal failure and nephrosclerosis. She had a left renal oncocytoma removed by partial nephrectomy at age 70 years. In subject III-3, the 49-year-old grandson of subject I-2, a 1 cm. solid renal tumor was detected on CT.

Family 170: Two brothers of 8 siblings had renal oncocytomas. Both subjects had a record of arterial hypertension for more than 20 years before the detection of renal oncocytoma. In subject II-3 bilateral renal oncocytomas were initially detected as renal neoplasms on ultrasound and CT at age 63 years. Subject II-5 underwent right nephrectomy at age 55 for a renal oncocytoma. Both have nephrosclerosis.

Laboratory tests.

Tests for mutations in the von Hippel-Lindau tumor suppressor gene and the MET proto-oncogene were performed in 1 or more affected members of families 166, 167, 168 and 169, and no germline mutations were detected. Cytogenetic studies were performed on the peripheral blood of 1 or more affected members of families 166, 167, 168 and 169, and no complete constitutional chromosomal alterations were detected.

Pathology.

Most tumors showed classical histological features of renal oncocytoma (Figure 3, A and B, and Table 2). However, some tumors had characteristics that were atypical for renal oncocytoma, including tumor cells with cytoplasmic clearing (Figure 3, A and C, and Table 2) and hemorrhage within the tumor (subject II-2 family 169). Hale's colloidal iron histochemical stain was negative on eosinophilic cells and showed a fine reticular staining pattern in cells with cytoplasmic clearing. Electron microscopy studies were performed on subject II-5 in family 168 and subject II-3 in family 169. Electron microscopic photographs showed abundant round to oval mitochondria in both cases, and round membrane bound vacuoles in 1 (subject II-5 family 168). HMB-45 stain, a stain that reacts with renal angiomyolipomas from tuberous sclerosis, did not react with renal oncocytomas in our study.

Table 2. Clinicopathological data from affected members of renal oncocytoma families 166 to 170

DISCUSSION

We identified 15 patients affected with renal oncocytoma or renal tumors in 5 families. Kidney tumors were detectable by CT of the abdomen with contrast medium, followed by ultrasound of the retroperitoneum. Magnetic resonance imaging was substituted when creatinine was elevated. The identification of multiple family members affected with this rare neoplasm, presence of the neoplasm in 3 generations and bilateral, multiple tumors support the concept that some renal oncocytomas may be inherited. Additional support for this concept comes from the identification of identical twins, both of whom had bilateral multifocal renal oncocytomas detected at a young age (38 years). Their father was found to have bilateral solid renal tumors on screening.

Although the data suggest that there may be an inherited predisposition to renal oncocytomas, there are several cautionary notes. All pedigrees were small nuclear families. It remains possible that the renal oncocytomas detected in multiple family members may be a consequence of an environmental factor. Resolving this question will require long-term followup of families 166 to 170 and the identification of additional families with this disorder.

Because renal oncocytomas were in most cases asymptomatic, occurred at a late age and required imaging studies for detection, it was difficult to discern the hereditary pattern of this disorder. Families 167 and 169 illustrate the effect of age at onset on recognizing the inherited pattern of renal oncocytoma. In these 2 families 20 to 30 years lapsed between the detection of renal oncocytoma in 1 generation and the next. The time required to detect transmission of a predisposition to renal oncocytoma from 1 generation to the next would have been even greater than 20 to 30 years if family members had not been under strict surveillance. The difficulty of detecting a hereditary pattern was compounded by the fact that obligate carriers (for example family 168 subject I-4) did not always have renal tumors detected within their lifetime.

The results raise the possibility that there is a specific gene(s) that predisposes to the development of renal oncocytomas. Clues to the location of this gene may come from cytogenetic studies of sporadic renal oncocytomas ([Table 1](#)). The most consistent finding in sporadic renal oncocytomas is a loss of chromosome 1 or 1p deletion and loss of chromosome Y in male patients. van den Berg et al recently identified another subset of renal oncocytomas based on cytogenetics of which 1 group exhibited a translocation t(9;11)(p23;q12) and the other t(5;11)(q35;q13). [\[19\]](#) Schwerdtle et al recently described sporadic renal oncocytoma with a loss of chromosome 14q (149) as a unique finding. [\[23\]](#) Teh et al described a single patient with bilateral multiple renal oncocytomas and a constitutional balanced reciprocal translocation between chromosomes 8q and 9q. [\[20\]](#) The cytogenetic data suggest that chromosomes 1, 8, 9, 11 and 14 may harbor the renal oncocytoma gene(s). We found no consistent complete germline cytogenetic abnormality in members of our families 166 to 169. The results of mutation analysis suggest that neither the von Hippel-Lindau tumor suppressor gene nor the MET proto-oncogene is involved in the pathogenesis of renal oncocytoma.

Our data suggest that mutations in a different gene, 1 predisposing to renal oncocytoma, lead to the development of renal oncocytoma. The next step will be to identify the chromosomal location of the renal oncocytoma gene. The families described in this report contain 26 meioses, which may be sufficient to map a putative renal oncocytoma gene.

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University assisted with electron micrographs, Cia Manolatos patient management, Jami Lipan sectioning of blocks, Dr. Laura Schmidt, Laura Geil and Tracy Kinjersky B cell preparation and DNA extraction, Dr. Elizabeth Henske, Fox Chase Cancer Center, Department of Medical Oncology, Philadelphia, HMB-45 immunostain of select tumors.

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