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# RENAL NEOPLASMS IN ADULT SURVIVORS OF CHILDHOOD WILMS TUMOR

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## ABSTRACT

Purpose: Survivors of childhood Wilms tumor have been followed by large collaborative studies for approximately 31 years. In this time a number of second malignant neoplasms have been documented in these Wilms tumor survivors and they are at higher risk for such development compared with the general population. To our knowledge no renal neoplasms have been previously reported in patients successfully treated for Wilms tumor in childhood.

Materials and Methods: We reviewed the cases of 4 adults in whom Wilms tumor was treated in childhood by radical nephrectomy and adjuvant therapy and who presented to our institution with complex cystic or solid renal masses in the contralateral kidney. Parameters, including patient age at Wilms tumor diagnosis, Wilms tumor treatment modalities, age at second malignant neoplasm presentation and resected renal lesion pathology were outlined. A thorough literature review was performed to identify the development of renal malignancies as second malignant neoplasms in survivors of Wilms tumor in childhood.

Results: The International Society of Pediatric Oncology and National Wilms Tumor Study have followed patients treated for Wilms tumor for no greater than 31 years. Renal neoplasms, including 2 renal cell carcinomas, 1 oncocytoma and 1 atypical cyst, in the solitary remaining kidney of relatively young adults 34 to 50 years old who were treated for Wilms tumor greater than 31 years ago were successfully treated with partial nephrectomy at our institution. Neither the International Society of Pediatric Oncology nor National Wilms Tumor Study has identified renal cell carcinoma as a second malignant neoplasm in patients successfully treated for Wilms tumor.

Conclusions: Our experience suggests that relatively young adults with a history of childhood treatment for Wilms tumor may be at increased risk for renal neoplasms at ages not yet achieved by those enrolled in large multicenter trials. This possibility should be considered when planning the long-term followup of these patients. The potential to develop this type of second malignant neoplasm again raises the clinical issue of performing a primary nephron sparing procedure in children presenting with Wilms tumor.

KEY WORDS: nephroblastoma; kidney; carcinoma, renal cell; neoplasms, second primary

The International Society of Pediatric Oncology (SIOP) and National Wilms Tumor Study (NWTS) have followed patients treated for Wilms tumor since 1971 and 1969, respectively. The thorough nature with which these patients and their therapeutic regimens have been followed has directly impacted their survival and quality of life. Overall survival of the patients in these 2 large study groups has increased from approximately 64% in 1970 to almost 90% today.[1] This increase is directly attributable to the standardization of surgical techniques, and the refinement of adjuvant chemotherapeutic and radiation protocols.[2]

With improved patient survival and surveillance these successfully treated patients have been identified as at risk for second malignant neoplasms later in life, predominantly lymphoma, leukemia and neoplasms of the skeletal system. NWTS and SIOP have identified a marked increase in the incidence of second malignant neoplasms over that predicted by the Surveillance, Epidemiology, and End Result program of the National Cancer Institutes in the general population.[3, 4] It has been postulated that these tumors develop with increased frequency secondary to adjunctive radiotherapy or chemotherapy given in conjunction with radical nephrectomy as treatment for Wilms tumor or to an underlying genetic predisposition to tumor formation.[5, 6] To our knowledge no previous reports of second malignant neoplasms manifesting as renal tumors exist in the literature in this group of patients. We report on 4 adults with a renal mass presenting in the contralateral kidney who were treated in childhood for Wilms tumor.

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## METHODS

We reviewed the cases of four patients treated for Wilms tumor in childhood by radical nephrectomy with or without adjuvant therapy and who presented to our institution with contralateral renal lesions. Age at Wilms tumor diagnosis, treatment modalities, age at second malignant neoplasm presentation, the specific second malignant neoplasm and resected renal lesion pathology are outlined. A thorough literature review was performed to identify the occurrence and types of second malignant neoplasms in survivors of childhood Wilms tumor. Table 1 lists patient age at Wilms tumor presentation, Wilms tumor treatment, the interval until presentation of the second malignant neoplasm, treatment of the second malignant neoplasm and renal lesion pathology.

## CASE HISTORIES

*Case 1.* D. C., a 42-year-old woman, presented to our institution for evaluation of a left renal mass discovered during

TABLE 1. *Demographic data on 4 patients treated for Wilms tumor in childhood who presented with renal neoplasia*

| Pt.—Age—Sex | Wilms Tumor | | | Second Renal Malignancy Presentation | Contralat. Renal Lesion Treatment | Pathological Condition |
|---|---|---|---|---|---|---|
| | Age at Diagnosis | Yrs. Since Treatment | Treatment* | | | |
| DC—42 —F | 3 | 39 | Rt. radical nephrectomy, adjuvant radiation | Painless gross hematuria | Lt. lower pole heminephrectomy | Renal cell Ca, clear cell type, stage T1N0M0 grade II/IV |
| KN—34 —F | 4 | 31 | Rt. radical nephrectomy | Microhematuria | L. partial nephrectomy | Oncocytoma |
| PF—40 —M | 3 | 37 | Rt. radical nephrectomy, adjuvant radiation, chemotherapy | Lt. flank pain | Lt. partial nephrectomy | Renal cell Ca, clear cell type, stage T1N0M0 grade III/IV |
| LS—50 —M | 3 | 47 | Neoadjuvant radiotherapy, rt. partial nephrectomy, simple nephrectomy at age 18 yrs. for local discomfort | Incidental finding | Lt. partial nephrectomy | Atypical hemorrhagic cyst suspicious for malignancy |

* Adjuvant therapy based on patient report.

assessment of a recent episode of painless gross hematuria. Medical history was significant for right radical nephrectomy performed at age 3 years for Wilms tumor. The patient underwent adjuvant radiotherapy to the right nephrectomy bed. Pathological stage and grade of this tumor were not available and the amount of total adjuvant radiation and specific anatomical field treated were unverifiable. Three-dimensional computerized tomography (CT) at our institution revealed a 6.5 cm. enhancing solid left lower pole renal lesion. The patient underwent successful partial nephrectomy. Preoperatively serum creatinine was 1 mg./dl. and it stabilized at 1.5 mg./dl. postoperatively. Pathological examination of the mass revealed stage pT1N0M0 Fuhrman grade II/IV clear cell renal cell carcinoma.

*Case 2.* K. N., a 34-year-old woman, presented to her primary physician with left back pain and microhematuria 30 years after right radical nephrectomy and adjuvant radiotherapy were performed for Wilms tumor at age 4 years. Grade and stage of the lesion were unavailable and the radiation dose and field were unverifiable. Three-dimensional CT done after referral to our institution showed an enhancing 4.2 cm. central left solid renal lesion. The patient underwent successful partial nephrectomy. Preoperatively serum creatinine was 0.9 mg./dl. and it remained 0.9 mg./dl. postoperatively. Pathological examination of the lesion demonstrated oncocytoma.

*Case 3.* P. F., a 40-year-old man, was referred for a 4 cm. enhancing left renal mass discovered by CT during the evaluation of vague left flank pain. Medical history was significant for right radical nephrectomy with adjunctive chemotherapy and radiotherapy performed for Wilms tumor at age 3 years. Tumor grade and stage as well as the specific chemotherapeutic and radiotherapy protocols were unavailable. The patient underwent successful left partial nephrectomy. Preoperatively serum creatinine was 1 mg./dl. and it remained stable postoperatively at 1.3 mg./dl. Pathological examination revealed stage pT1N0M0 Fuhrman grade III/IV clear cell renal cell carcinoma.

*Case 4.* L. S., a 50-year-old man, was diagnosed with a right renal mass at age 3 years. He received neoadjuvant radiotherapy to this lesion, followed by right partial nephrectomy. Pathological examination of the lesion confirmed the diagnosis of Wilms tumor. Tumor grade and stage were unavailable. The patient had worsening right flank discomfort and ultimately underwent right simple nephrectomy at age 18 years. Specific pathological information on the specimen was unavailable. He was referred for the evaluation of an incidentally discovered, complex left renal cyst. Three-dimensional CT at our institution showed a 2.3 × 2.0 cm. exophytic complex left superior pole renal lesion. Rim enhancement and modest central attenuation were consistent with a Bosniak III cyst. In addition, 2 other equivocal renal lesions were identified that were 1.3 and 2.5 cm., respectively, in axial diameter. A complete metastatic survey was negative. Subsequently the patient underwent successful left partial nephrectomy. Preoperatively serum creatinine was 0.9 mg./dl. and it was stable at 1 mg./dl. at hospital discharge. Pathological examination revealed a hemorrhagic cyst with atypical epithelial lining, prominent nucleoli and irregular nuclear borders. While no definite clear cell epithelium was identified, multiple deposits of hemosiderin and hemosiderin laden macrophages were noted within the cyst wall, suggestive of a neoplastic process. The other 2 lesions were classified as benign epithelial lined cysts.

## DISCUSSION

A number of second malignant neoplasms have been identified by NWTS and SIOP in patients successfully treated for Wilms tumor in childhood. These neoplasms are predominantly lymphoma, leukemia and skeletal system malignancies. However, neoplasms of many organ systems have been reported. Table 2 lists all 51 second malignant neoplasms recorded by SIOP and NWTS according to major organ system.[3,4] No primary renal second malignant neoplasms have been identified to date in these 2 large multicenter studies of patients in whom Wilms tumor was successfully treated in childhood.

The major risk factors for a second malignant neoplasm in this population are a genetic susceptibility to tumor formation, and the chemotherapy and radiotherapy used to treat the primary Wilms tumor. To our knowledge the genetics of Wilms tumor development have not been completely elucidated. The 2 alleles WT1 and WT2 have been identified on the short arm of chromosome 11 (11p13 and 11p15).[7,8] These genes seem to code for transcription factors that regulate the activation of other genetic signals. Because no abnormality at allele WT1 or WT2 has been demonstrated in familial WT, it is likely that at least 1 additional locus may be implicated. Abnormalities at these Wilms tumor loci have been demonstrated in the Denys-Drash, WAGR and Beckwith-Wiedemann syndromes.

A genetic predisposition to tumor formation may manifest as precursor lesions in the affected tissue. The histological association of Wilms tumor cells with the foci of abnormally persistent embryonal renal cells (nephrogenic rests) is well established. Strong circumstantial evidence implies that Wilms tumor arises from abnormally persistent nephrogenic rests that do not undergo spontaneous regression or involution.[9] Beckwith proposed a nomenclature system for identi-