Pediatric renal cell carcinoma as second malignancy: reports of two cases and a review of the literature

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Pediatric renal cell carcinoma (RCC) is relatively rare and appears to comprise a group of tumors distinct from RCCs typically seen in adults. Recently described tumors show an association with neuroblastoma or specific chromosomal translocations. Only rarely have other childhood cancers been associated with pediatric RCC. We present two cases of pediatric RCC following treatment of other childhood malignancies not previously described, supratentorial primitive neuroectodermal tumor and acute lymphoblastic leukemia, and review the literature on pediatric RCC. As the RCCs were discovered as incidental radiologic findings, we emphasize the importance of close follow-up (including imaging) at routine intervals in survivors of childhood malignancies, not only to monitor for recurrence or metastasis, but also for development of a second malignancy.

Key Words: renal cell carcinoma, children, second primary neoplasms

Introduction

As treatments for pediatric malignancies become more successful, a greater proportion of children survive cancer. However, therapy may be a double-edged sword. The development of a second malignancy following the apparent initial success of therapy is well-documented.[1] In addition to therapy, second malignancies may result from the "effect of shared etiologic factors, environmental exposures, host characteristics, and combinations of influences, including gene-environment and gene-gene interactions."[2]

Pediatric renal cell carcinoma (RCC), is relatively rare, representing only 1% of all cases of RCC[3] and approximately thirty times less common than Wilms' tumor.[4] Its description in children as young as 3 months

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old and lack of association with the risk factors for RCC in adults (tobacco, obesity, occupational exposure to hydrocarbons, thiazide diuretics and urinary tract infection)[5] suggest that childhood RCC is fundamentally different from RCC in adults.[6] Moreover, many of the more recently described RCCs occur mainly in children and young adults, including those seen in association with neuroblastoma[7-18] and translocations involving the *TFE3*[3,19,20] and *TFEB*[20,21] genes.

Pediatric RCC is otherwise not very well-understood, although a handful of cases have occurred following treatment of another childhood cancer. Recent evidence shows that at least a small proportion of genetically confirmed translocation RCCs have arisen in patients who received cytotoxic chemotherapy during childhood.[22] We report here two cases of pediatric RCC developing after treatment for previously unassociated malignancies, supratentorial primitive neuroectodermal tumor in case one and acute lymphoblastic leukemia in case two, and review the literature.

Case one

The patient was a male born at 36-weeks' gestation, who at the age of 2 months was transferred to our hospital from an outside institution where he was being evaluated for failure to thrive. During the work-up, he had become apneic and developed generalized tonic-clonic seizures. Brain imaging showed a right temporal mass. Due to his age and weight, aggressive nutritional therapy was instituted prior to surgery to decrease his anesthesia risk. The following month, he underwent craniotomy with resection of the mass.

Operative material consisted of multiple small fragments of hemorrhagic and tan-pink soft tissue. Histologic examination revealed markedly atrophic and gliotic cerebral cortex with underlying hemorrhage and cavitation, intermixed with foci of tumor. The tumor cells were small and round, with deeply basophilic nuclei and aggregated in small clusters and focally in large rosettes with fine fibrillary cores, Figure 1a. In one area, a wave-like or glomeruloid pattern was observed. The cores of the large rosettes as well as the stroma of smaller tumor clusters were immunoreactive for synaptophysin and, to a lesser extent, neurofilaments. Immunohistochemistry for glial fibrillary acidic protein decorated cell processes in these same areas. A diagnosis of supratentorial primitive neuroectodermal tumor, or cerebral medulloblastoma, was rendered.

Postoperatively, he was started on the Pediatric Oncology Group 9233 chemotherapeutic protocol ('Baby POG #2') in an effort to avoid radiation to his neuraxis. He received a total of 73 weeks of chemotherapy with cyclophosphamide, vincristine, cisplatin and etoposide which he tolerated fairly well, despite frequent transfusions and hospitalizations for neutropenia and fever. Serial imaging of the brain and spine had shown stable postoperative changes in the tumor bed, but around the time of his fourth birthday a lesion was incidentally discovered in the left kidney. He underwent nephrectomy.

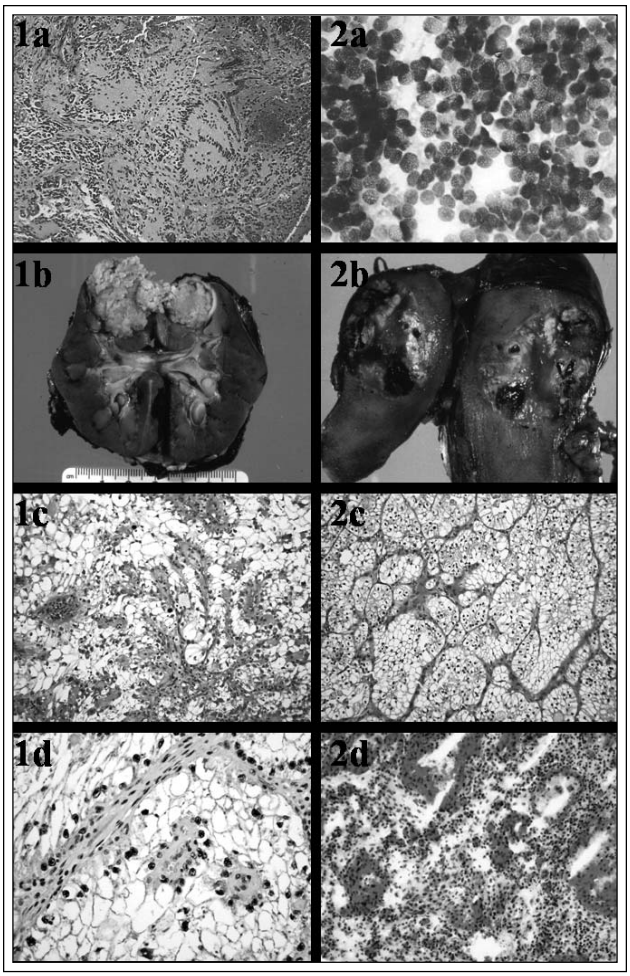
The kidney contained a 2.4 cm tan friable mass at the upper pole which was surrounded by a pseudocapsule and had a somewhat gritty cut surface, Figure 1b. Small satellite tumor nodules were seen beyond the fibrous pseudocapsule, but none extended to the renal capsule proper. Microscopically, the tumor displayed predominantly papillary architecture, and tumor cells had voluminous clear cytoplasm, discrete cell borders, and visible to prominent nucleoli. Psammomatous calcifications were present throughout the lesion, Figure 1c. The tumor cells were negative for Cam 5.2, epithelial membrane antigen and vimentin, and showed nuclear staining for TFE3 protein by immunohistochemistry, Figure 1d, confirming the diagnosis of renal carcinoma associated with an Xp11.2 translocation/*TFE3* gene fusion.

Case two

The patient was a white male who, at the age of 15 months presented with lymphadenopathy, hepatosplenomegaly and leukocytosis (150000 white blood cells/μL), and was diagnosed with acute lymphoblastic leukemia. Cytogenetic analysis showed t(4;11); this finding is associated with a poor prognosis.[23] Chemotherapy was initiated under protocol CCG-106 (New York regimen) and included vincristine, methotrexate, prednisone, ara-C, daunomycin, 6-TG, adriamycin and cyclophosphamide and lasted for approximately 38 months. Preventive cranial radiation therapy was given during the second month of chemotherapy to a total dose of 1800 cGy.

Nine months after chemotherapy was discontinued, the patient developed bone marrow and testicular relapse, Figure 2a. He was treated with 300 mg/m^2 of anthracycline under protocol BFM-87 and 2 months later underwent conditioning with fractionated total body irradiation (1320 cGy and an additional 1000 cGy to the testes) and two doses of cyclophosphamide (60 mg/kg each) and received an allogeneic related bone marrow progenitor cell transplant from his mother.

He had since been lost to follow-up while living with his mother in another state but was involved in a motor vehicle accident 2 months before his eighteenth birthday. Computed tomography was performed to evaluate for



Figures 1a-d (case one) and Figures 2a-d (case two). 1a: Supratentorial primitive neuroectodermal tumor. Note large rosettes of tumor cells and adjacent hemorrhage. 1b: Gross photograph of bivalved kidney with friable papillary mass at upper pole. 1c: RCC with papillary architecture, clear cells with voluminous cytoplasm and psammomatous calcifications. 1d: Immunoperoxidase stain for TFE3 protein showing strong nuclear reaction. 2a: Touch imprint from testicular biopsy showing leukemic infiltrate: a monomorphous population of cells with scant light blue cytoplasm, vacuolated dispersed nuclear chromatin and indistinct nucleoli. 2b: Gross photograph of cortically based golden yellow, hemorrhagic tumor. 2c: Clear cell RCC with alveolar arrangement of tumor cells and delicate vascular framework. Nuclei are generally small and hyperchromatic with little chromatin detail and no visible nucleoli. 2d: Oil red O stain performed on cryosection of tumor shows rich lipid content of cells. This accounts for the typical golden yellow gross appearance of clear cell RCCs.

trauma and multiple bilateral renal masses were incidentally discovered, with the largest lesion seen in the left kidney. The following month, repeat computed tomography of the chest and abdomen showed an interval increase in size of the left-sided kidney mass.

Needle biopsies of the mass showed RCC with variably sized nests of clear cells with small, monomorphic nuclei and inconspicuous nuclei, separated by fine vascular septa. Areas of myxoid degeneration and fibrosis/hyalinization were present.

The patient underwent left nephrectomy the following week. The kidney contained a 3.7 cm x 2.5 cm x 2.3 cm cortically based yellow-orange lesion with focal hemorrhage and necrosis, surrounded by a pseudocapsule, Figure 2b. Additionally, there were three cortical cysts ranging from 0.3 cm-0.8 cm and areas of subcapsular hemorrhage at the upper and lower poles. The contralateral kidney was examined intraoperatively and it was felt that the lesions seen on imaging represented benign cysts.

Microscopic examination revealed a tumor consisting entirely of nests and glandular structures lined by large epithelioid cells with abundant clear cytoplasm and central oval nuclei, Figures 2c and 2d. The tumor focally extended through the renal capsule and lymphatic invasion was noted although no hilar lymph nodes were identified. The neoplastic cells were positive for Cam 5.2, epithelial membrane antigen and vimentin, and negative for HMB45 and TFE3 protein. PAS and trichrome stains highlighted focal segmental mesangial expansion in glomeruli of the uninvolved parenchyma, along with glomerular cyst formation. Based on the findings, the tumor was classified as a clear cell RCC, and although there were no extrarenal lesions radiologically, given the patient's age, it was recommended to exclude von Hippel-Lindau disease.

Discussion

We add to a growing body of literature, two cases of pediatric RCC occurring after chemotherapy and radiation for a supratentorial primitive neuroectodermal tumor (case one) and acute lymphoblastic leukemia (case two). RCC has been described as a second malignancy following treatment of advanced stage neuroblastoma (21 cases, including 16 children)[3,7-18] and in a child treated for acute promyelocytic leukemia (one case).[24] Argani et al recently reported six cases of translocation RCC arising after childhood chemotherapy.[22] In addition, renal cell carcinoma has been described in three adult patients after treatment for childhood Wilms'

tumor.[25,26] This begs the question of whether therapy is responsible for the subsequent development of a second cancer (i.e., RCC), whether there is an underlying genetic association or susceptibility, if an immunosuppressed state (by virtue of treatment or the primary cancer itself) is permissive, or if these cases merely represent unfortunate coincidence.

Alkylating agents and topoisomerase II inhibitors have been implicated in therapy-related hematologic malignancies,[27] and it is well-known that solid tumors can develop following irradiation.[1,28] This puts survivors of childhood cancer at particularly high risk for developing a second malignancy because, although the elevated risk of a second cancer appears relatively constant over time, the absolute risk increases with length of follow-up.[28] Cumulative incidence of second cancers may be up to 12% at 20 years.[28] In their cohort of 4400 patients treated for a cancer in childhood, de Vathaire and colleagues found that the excess absolute risk of solid second malignant neoplasms increased for at least 30 years after diagnosis of the first cancer.[29] They also showed that adding chemotherapy to radiation increases the risk of a solid second cancer.[29] Green et al, using Cox proportional hazards modeling, found that prior therapy with BCNU and doxorubicin were the only factors significantly associated with developing a second malignant tumor in their cohort of 1406 previously untreated patients less than 20 years old at diagnosis of their first cancer.[30]

As radiation is commonly employed in the treatment of neuroblastoma, some have speculated that it caused the associated cases of RCC. RCC associated with neuroblastoma is currently recognized as a distinct neoplasm according to the World Health Organization histological classification of tumors of the kidney.[31] These tumors are morphologically heterogeneous, with some showing cells with abundant eosinophilic (oncocytoid) cytoplasm growing in solid sheets and papillae, and others comprising clear cells. While a causal association with therapy remains possible, this is not the favored explanation for later developing RCC, because one patient with stage IV-S neuroblastoma had spontaneous resolution without treatment of that tumor (the RCC developed 7 years later),[16] and another was diagnosed simultaneously with both tumors.[17] At least two additional patients received chemotherapy without radiation.[32] It is perhaps more likely that these patients have a genetic susceptibility for developing cancer.[31] However, RCC only appears to develop in a minority of patients with a history of neuroblastoma.

The World Health Organization has also recently recognized the category of renal carcinomas associated with Xp11.2 translocations/*TFE3* gene fusions.[19] RCCs in children have traditionally been described as having either papillary or non-papillary architecture, and either clear or eosinophilic cells or a mixture of the two. While some cases may in fact represent papillary RCC as seen in adults (with identical morphologic and genetic features), an increasing number of cases are being re-evaluated and assigned to this new category of translocation RCCs, primarily seen in children and young adults.[3] As illustrated in our first case, these tumors characteristically show papillary projections of tumor cells surrounding a fibrovascular core, and the tumor cells have voluminous clear cytoplasm. Psammomatous calcifications are commonly seen. Less frequently, the tumor cells have eosinophilic cytoplasm or are arranged in nests. Immunostaining for the TFE3 protein appears highly sensitive and specific regardless of the exact translocation;[33] four translocations have been described but all involve the *TFE3* gene which encodes a basic helix-loop-helix transcription factor that regulates genes whose promoters contain E-boxes, such as the immunoglobulin heavy chain enhancer[34] and genes involved in glucose and lipid metabolism.[35]

Another recently identified translocation RCC, associated with t(6;11)(p21;q12), appears to constitute a distinct subset of renal tumors of children and young adults. These tumors are less commonly recognized but show many similarities to the Xp11 translocation RCCs. The t(6;11) results in fusion of a gene called *Alpha*, mapped to chromosome 11q12, with *TFEB*, which encodes a transcription factor in the same family as *TFE3*. Histologically, these tumors resemble the standard RCC save for a second population of smaller cells that usually cluster around hyaline nodules.[20,21]

At least a small proportion of genetically confirmed translocation RCCs have arise post-cytotoxic chemotherapy; Argani reported that six of the 39 cases of either *TFE3* or *TFEB*-associated RCCs they have seen were in patients who received chemotherapy as a child.[22]

Pediatric RCC can be associated with inherited cancer syndromes such as von Hippel-Lindau disease[36,37] and tuberous sclerosis[38]. Von Hippel-Lindau disease shows an autosomal dominant pattern of inheritance for germline mutations in the *VHL* tumor suppressor gene located on chromosome 3p25-26. Clinical features include retinal and central nervous system hemangioblastomas, in combination with one of the typical extraneural tumors (pheochromocytoma, pancreatic cysts or neuroendocrine tumors, inner ear endolymphatic sac tumors, cystadenomas of the epididymis or broad ligament, and in the kidney, multiple bilateral clear cell carcinomas or renal cysts) or a suggestive family history. The renal tumors are clear

cell carcinomas exclusively (the presence of other histologic types excludes this syndrome) and can number in the hundreds on microscopic examination. They manifest at a mean age of 37 versus 61 years for sporadic clear cell RCC, and although somewhat exceptional in the pediatric age group, have been described in patients as young as 16 years old.[36,37] In contrast, angiomyolipoma,[39] particularly the epithelioid type,[40] is more commonly a feature of the multisystem neurocutaneous disorder, tuberous sclerosis, though RCC has been described in affected adults as well as children.[38]

RCC has also been reported in children transplanted with adult kidneys.[41-43] One such case was that of an 8-year-old girl who underwent cadaveric renal transplant from a 25-year-old male donor for chronic renal failure secondary to renal dysplasia and branchio-oto-renal syndrome. At age 12, she developed severe chronic rejection and because of persistent gross hematuria, a transplant nephrectomy was performed 3 years later that showed a 1.5 cm RCC.[41] Another case involved a 17-year-old boy who received an adult cadaveric donor kidney 2 years prior, for chronic renal failure related to obstructive uropathy. Work-up for painless macroscopic hematuria revealed RCC with multiple pulmonary metastases. Restriction fragment length polymorphism analysis showed the tumor to be of donor origin, and the metastases completely regressed after transplant nephrectomy and cessation of immunosuppression.[42] More recently, Greco and colleagues reported chromophobe RCC in a 13-year-old boy with fever and inguinal lymphadenopathy, 5 years after receiving a living-related kidney transplant.[43]

Our study supports the notion established in prior studies that pediatric RCC, although an heterogenous group including newly described entities, is different from its adult counterpart in genetic background, pathogenesis, morphology and biological behavior. The contribution of therapy to genetic alterations is unclear and should be addressed in further studies. Advances in our understanding of the molecular genetics of these tumors may ultimately reveal heretofore undiscovered relationships between primary and second malignancies in survivors of childhood cancer, which we cannot clearly attribute to therapy. We would like to emphasize that the two cases of pediatric RCC we described in this paper were discovered at early stage as incidental radiologic findings. This underscores the importance of close follow-up (including imaging) at routine intervals in survivors of childhood malignancies, not only to monitor for recurrence or metastasis, but also for development of a second malignancy. □

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