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CASE REPORT

Greg Kraushaar · Sheldon Wiebe

Renal cell carcinoma as a second malignant neoplasm in a patient with non-syndromic hemihypertrophy and previous Wilms tumor

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Abstract Survivors of childhood Wilms tumors are at an increased risk of second malignant neoplasms. Recently, it has been postulated that renal cell carcinoma is among the malignancies for which this population is at risk. We present the unique case of an adult Wilms tumor survivor with non-syndromic hemihypertrophy (NSHH) who developed renal cell carcinoma. This case highlights the need for close follow-up in two populations: adults who have survived Wilms tumor and those with NSHH.

Keywords Hemihypertrophy · Renal cell carcinoma · Second malignant neoplasm · Wilms tumor

Introduction

The National Wilms Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP) have provided long-term follow-up to Wilms tumor survivors for more than 30 years. The close follow-up has revealed these patients to be at increased risk for the development of second malignant neoplasms (SMN) [1, 2]. These two groups found no cases of renal cell carcinoma (RCC) as an SMN. In 2001, Cherullo et al. [3] reported three cases of RCC in adults who were childhood survivors of Wilms tumors.

Non-syndromic hemihypertrophy (NSHH) is an uncommon growth discrepancy associated with an increased risk of childhood abdominal neoplasms including Wilms tumor, hepatoblastoma and adrenal carcinoma [4]. There are a few case reports describing malignancies in adults with NSHH. We report a case that highlights the potential need for close follow-up in these two populations: adults who have survived Wilms tumors and those with NSHH.

G. Kraushaar (✉) · S. Wiebe
Department of Medical Imaging, Royal University Hospital,
103 Hospital Drive, Saskatoon, SK, S7N0W8, Canada
E-mail: krotchee@gmail.com
Tel.: +1-306-6552402
Fax: +1-306-6552370

Case report

A 31-year-old woman with NSHH of the left abdomen presented to our institution for evaluation of recurrent right lower quadrant abdominal pain associated with nausea and vomiting. An abdominal CT examination was done to evaluate for bowel pathology. This revealed a well-defined 3.6 cm by 3.2 cm solid enhancing mass in the upper pole of the left kidney with no extension into the collecting system, renal vein or through the renal capsule (Fig. 1). The left kidney itself was markedly enlarged (15×9×8 cm), likely a result of nephromegaly associated with the hemihypertrophy as well as compensatory hypertrophy secondary to previous right nephrectomy.

The patient's medical history revealed that at 29 months she was diagnosed with stage IV Wilms tumor involving the right kidney, right adrenal gland and right lobe of the liver. It was treated surgically via right nephrectomy, adrenalectomy and right hepatectomy. Postoperatively, a 3-week course of whole abdominal radiation was employed in addition to chemotherapy with vincristine and actinomycin D.

Eleven months after the initial diagnosis, a solitary Wilms tumor metastasis to the upper lobe of the left lung was found on chest radiograph. Surgically, this was treated with left segmental lobectomy. Additional therapy consisted of a 3-week course of radiation therapy to the mid- and upper-lung fields as well as combination chemotherapy with vincristine, actinomycin D and Adriamycin, which was continued for 18 months after the second operation.

CT-guided biopsy of the left renal lesion revealed a low-grade (Fuhrman's grade 1/4) clear-cell renal carcinoma (Fig. 2). The mass was removed surgically with a left partial nephrectomy and the patient was discharged home in good condition.

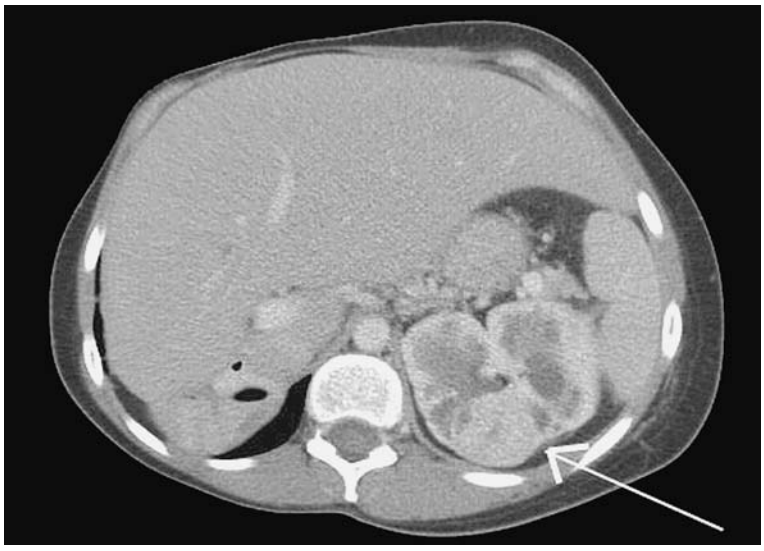

Fig. 1 Contrast-enhanced axial CT scan displays a 3-cm enhancing mass (*arrow*) in the upper pole of the left kidney

Discussion

There is an increased risk of SMN in adult survivors of Wilms tumors [1, 2]. The majority of these SMN are blood dyscrasias, CNS neoplasms or osteogenic malignancies. The major risk factors postulated to account for such a propensity to tumor growth are radiation therapy and chemotherapy with doxorubicin, which is noted to potentiate the effects of radiation therapy [1]. Recently, RCC were added to the list of SMN in Wilms tumor survivors. Cherullo et al. [3] presented three cases of adults (aged 40, 42 and 57 years) who developed RCC in the remaining kidney. Our case is unique in that at age 31 years the patient presented 28 years after treatment for Wilms tumor. This is a shorter latency period than in the previous three reported cases. This young age of development of RCC in these patients suggests a predisposition to malignancy, but it is unclear whether there is evidence to suggest that the incidence of RCC is increased in these patients.

This case brings the total number of pathologically confirmed cases of RCC in Wilms tumor survivors to four. The reported cases are all from the United States and Canada and occurred at an average age of 43 years. The latency period from the original diagnosis of Wilms tumor to the subsequent discovery of RCC has been from 28 to 47 years. Thus, if we were to consider all North American Wilms tumor patients from 1950 until 1975, a span encompassing the known cases of RCC as SMNs, and follow them to the present day we could figure out an incidence of RCC for the cohort. The reported number of cases in the United States in the 1970s was 400 per year [5]. Assuming a similar incidence in

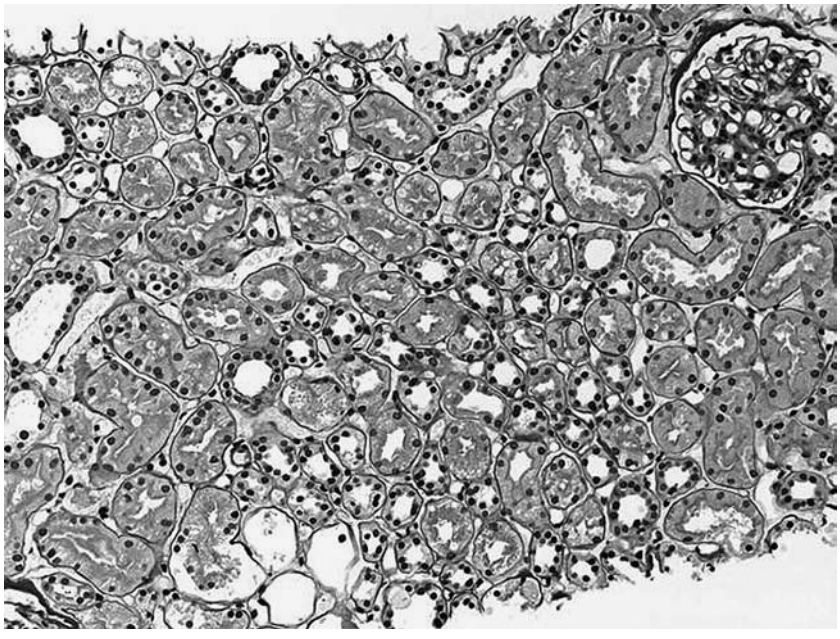

Fig. 2 High-power magnification of biopsy specimen from enhancing region in Fig. 1 depicts low-grade clear-cell renal carcinoma

Canada would add 10% to that total to account for Canadian Wilms tumor survivors. If we multiply 440 people by 25 years (to cover all Wilms tumor patients from 1950 to 1975) and multiply that by 43 (the length of time from the mid-point of the cohort, 1962, until the present) the total is 473,000 person years. By dividing this number by four we get an incidence of 0.85 cases per 100,000 person years in this cohort.

In the United States fewer than 10% of all RCC occur before the age of 45 years; the incidence at this time is 0.63 cases per 100,000 person years [6, 7]. The relative risk in the Wilms tumor cohort is 1.35. This number is not staggering, but it is possible that cases of RCC in Wilms tumor survivors have gone unreported in the literature. Although this is an interesting case, the evidence is currently not definitive to say that Wilms tumor patients are at an increased risk of developing RCC. But if Wilms tumor patients are at even a slightly increased risk of developing RCC, then strategies to maximize nephron mass would be imperative. This would include close follow-up of Wilms tumor survivors to detect RCC at an early stage so that partial nephrectomy could be employed. Additionally, the value of partial nephrectomy in the treatment of childhood Wilms tumors should be reexamined [3].

This patient presents another interesting dilemma given the presence of her left segmental hemihypertrophy. Hemihypertrophy has been described as the asymmetry between two sides of the body to a degree greater than could be attributed to normal variation [8]. This condition can be complete, one entire side of the body, or segmental. Hemihypertrophy is associated with multiple syndromes such as Beckwith-Wiedemann (BWS), Proteus, neurofibromatosis type-1 and Klippel-Trénaunay-Weber. In addition, it can occur as NSHH, as in our patient.

Of particular interest in this case was to separate hemihypertrophy from atrophy secondary to childhood radiation therapy. Firstly, the left abdomen was proportionately larger than not just the right hemiabdomen but the remainder of the left side of the body as well. In addition, the patient received radiation to the entire abdomen. Furthermore, the pattern of skeletal asymmetry is inconsistent with that seen purely in radiation atrophy. Specifically, the vertebral growth plate is thought to be most sensitive to the effects of radiotherapy. As such, the most constant changes seen in radiation atrophy are height loss of the vertebral bodies on the affected side and a resulting scoliosis [9]. In this patient, neither of those findings was present. The degree of asymmetry was best appreciated in the soft tissue and muscles on the patient's left side (Fig. 3). A three-dimensional reconstruction of the skeletal elements revealed maintenance of the height of the vertebral bodies, an absence of scoliosis and hypertrophied ribs and transverse processes of the lumbar vertebra on the left side (Fig. 4).

NSHH occurs with a birth incidence of 1:86,000 [10]. The true incidence is difficult to define, as many patients with NSHH, such as in the case described here, do not present until later childhood. The major risk of this disorder is a propensity for tumor formation. Hoyme et al. [4] demonstrated a 5.9% (10/168) incidence of neoplasia in a prospective multicenter study. The majority of these tumors were Wilms tumors, with adrenal carcinoma the next most common. These results might have been anticipated given that the presence of hemihypertrophy in BWS markedly increases the likelihood of developing a malignancy. Those with BWS in the absence of hemihypertrophy demonstrate a 5–9% incidence of tumor development, but BWS patients with hemihypertrophy have an incidence of malignancy of 24–27% [11, 12]. In response to these findings, it has been advised that routine abdominal US examinations be undertaken in all patients with BWS [11, 13] and also in those with NSHH [4].

An unanswered question regarding NSHH is whether the increased incidence of malignancy continues into adult life. A case of adrenal carcinoma diagnosed in a young woman with NSHH has been recorded [14]. Also of note, Parker et al. [15] reported the case of a 50-year-old man with right segmental hemihypertrophy and an

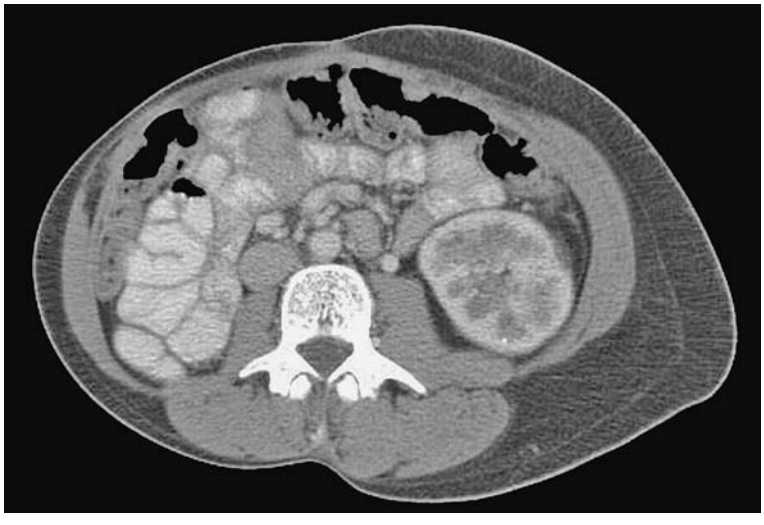

Fig. 3 Contrast-enhanced axial CT scan displays hemihypertrophy of the left abdomen, which includes subcutaneous fat and abdominal, paraspinal and psoas muscles

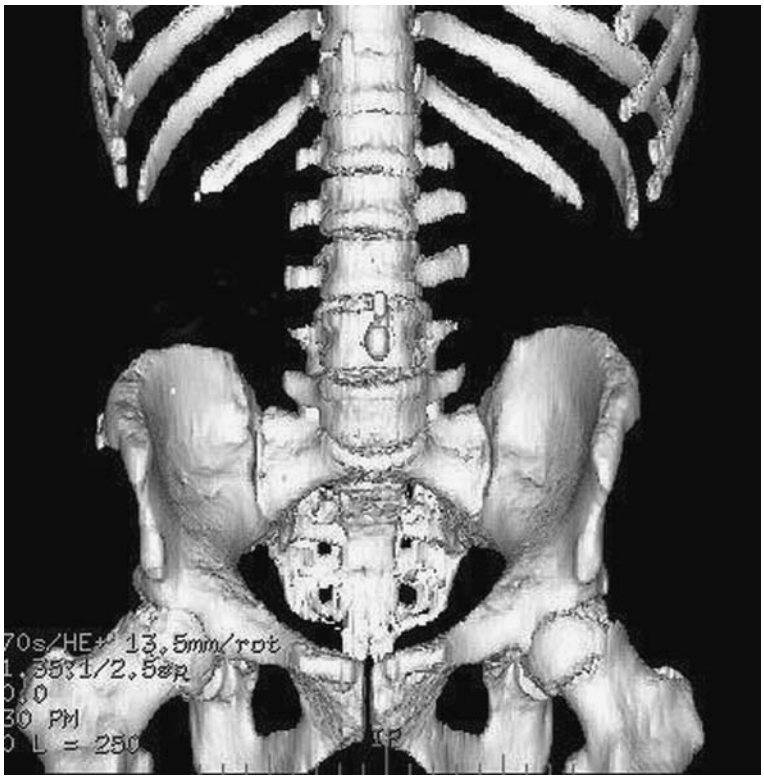

Fig. 4 Three-dimensional reconstruction of the skeletal elements depicts asymmetry of ribs and transverse processes. There is maintenance of vertebral body height and no scoliosis

ipsilateral RCC. To our knowledge this is the only other reported case of such a combination.

Whether there is a true increased risk of RCC in Wilms tumor survivors will be elucidated in the coming years. As the NWTSG and SIOP follow patients into their fifth and sixth decades, it will become apparent whether there is a true association. For now, the fourth documented case of RCC in a Wilms tumor survivor heightens suspicion of such an association and stresses the role of close follow-up.

To our knowledge, there are no prospective studies examining the incidence of malignancy in adults with NSHH. A small but growing body of evidence suggests that this question should be considered. In the reported cases of pediatric and adult malignancies in this population, most have been intraabdominal [4, 16]. Thus, if this population is at increased risk for neoplasia, there might be a role for routine abdominal US. At the very least, this case highlights that close observation of both adult survivors of Wilms tumors and adults with NSHH seems prudent.

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