A 10-Year Old Girl with Resistant Hypertension without Significant Indication of an Underlying Renal Cell Carcinoma, Misdiagnosed as Malaria

Patient:
Female, 10

Final Diagnosis:
Arterial hypertension secondary to renal cell carcinoma

Symptoms:
Recurrent headaches • excessive sweating • anorexia • weight loss • easy fatigability

Medication:
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Clinical Procedure:
Nephrectomy

Specialty:
Pediatrics and Neonatology

Objective:
Rare disease

Background:
Blood pressure (BP) is not routinely screened in children in clinical practice. Renal cell carcinoma (RCC) is a rare cause of renal hypertension and accounts for less than 0.3% of all childhood tumors. The clinical manifestation of hypertension in children requires a high index of suspicion, as does RCC, which can have many different manifestations.

Case Report:
We report the case of a 10-year-old girl with 1-year history of persistent symptoms of recurrent episodes of headache and excessive sweating and a 6-months history of weight loss and loss of appetite. She was repeatedly managed as having malaria in the center where she was referred, without recovery. Persistent high BP was discovered in our center, which ranged between 180/120 and 200/120 mmHg. This was not controlled by 3 different classes of drugs. Abdominal ultrasonography showed a right kidney with a well circumscribed lower pole mass with internal echoes, compressing the pelvicicalyceal system. Abdominal computed tomography revealed a huge, circumscribed, expansile, isodense mass arising from the renal cortex in the lower pole of the right kidney. Intraoperative findings included a mass seen at the lower pole of the right kidney with histology diagnosis of RCC. Other laboratory tests were normal. To date, the patient remains normotensive and symptom-free after nephrectomy.

Conclusions:
The nonspecific clinical manifestation found in this case show the need for hypertension screening in children. The resolution of symptoms after nephrectomy confirms RCC as the underlying cause of symptoms, making this case a unique presentation.

MeSH Keywords:
Blood Pressure • Carcinoma, Renal Cell • Hypertension • Pediatrics

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Background

Blood pressure (BP) is not routinely screened for in children in clinical practice. Renal cell carcinoma (RCC) is a rare cause of secondary hypertension in children. RCC has a 0.3% age-adjusted incident rate in children ages 0–14 years of all races and both sexes, and accounts for 3.8% of all renal tumors [1]. It is the most common renal tumor in adolescents [1,2] and the average age at presentation is approximately 10–11 years [3,4].

The clinical manifestations of RCC are protean in nature and have been referred to as a “tumor of internal medicine” because there are a constellation of signs, symptoms, and laboratory data abnormalities not related to tumor local effect or its metastases.

The potential mechanisms of hypertension (HTN) in patients with RCC include increased renin secretion, parenchymal or ureteral compression, polycythemia, venous fistula, ischemia, and tumor from juxtaglomerular apparatus (JGA) [5–8].

The rarity of this condition in children and the mode of presentation prompted us to report this case of a girl with resistant hypertension without significant indication of an underlying RCC, misdiagnosed as malaria.

Case Report

A 10-year-old African girl with no significant past medical history was referred from her primary health care center with a 1-year history of recurrent episodes of headache and excessive sweating and a 6-month history of weight loss and loss of appetite. Despite treatment, these symptoms failed to resolve, leading to referral to our hospital.

On further evaluation, the headache was found to be severe, throbbing in nature, and worse at the right temporal area, but without vomiting. Symptoms associated with the headaches included excessive sweating and palpitations. Sweating was present throughout the day irrespective of whether the patient was active or inactive, and it was worse in the evening, starting insidiously and progressively worsening. There was no associated fever or chills.

The palpitations were described as fast, regular, usually of insidious onset, but progressively increasing in intensity until reaching a crescendo, then gradually decreasing and usually resolving spontaneously. There was also a 6-month history of weight loss, anorexia, and easy fatigability.

There were no features suggestive of hyperthyroidism, Cushing’s syndrome, MEN’s syndrome, Carney’s triad, Von Hippel-Lindau syndrome, or skin lesions indicating neurofibromatosis or tuberous sclerosis.

Physical examination revealed a lean body habitus. Her weight was 23 kg (71% of expected) and height was 134 cm (23rd percentile, normal stature). The body mass index (BMI) was 12.8, placing her BMI-for-age at less than the first percentile (underweight).

The pulse rate was 100 bpm, normal volume, regular, symmetrical, and other peripheral pulses were normal. Blood pressure (BP) ranged between 180/120 and 200/120 mmHg, with no significant difference when measured on the opposite arm. Cardiac apex beat was located at the 5th left intercostal space mid-clavicular line, and cardiovascular system and other body systems were otherwise unremarkable.

The BP control was not achieved by 3 different classes of antihypertensive drugs: labetalol, captopril, and hydrochlorothiazide. On invitation by the cardiology team, BP control was achieved within 5 days at 92/68 mmHg with hydrochlorothiazide, carvedilol, and Valsartan, and a single dose of intravenous labetalol.

Laboratory investigations showed normal full blood count, blood electrolytes, urea, and creatinine levels. Urinalysis was also normal. The chest x-ray (PA) revealed a prominent aortic knuckle, but was otherwise normal.

Abdominal ultrasonography (US) showed a right kidney with a well circumscribed lower pole mass with internal echoes, compressing the pelviccalyceal system, measuring 3.6×3.5 cm. Other abdominal structures were normal.

Abdominal computed tomography (CT) revealed a huge, circumscribed, expansile, isodense mass (HU=37) arising from the renal cortex involving the middle third and lower pole of the right kidney (Figure 1A, 1B), measuring 4.4×3.7×4.5 cm, with an estimated volume of 38.1 cc (Figure 1A).

There was heterogeneous enhancement after contrast administration, with prominent vessels seen coursing through the mass (Figure 2). No fat density was seen. There was an associated mass effect evidenced by compression of the middle pole of the right kidney.

The image shown in Figure 3 suggests a filling defect within the proximal portion of the right renal artery (extension into the renal vein). The inferior vena cava was within normal limits.

Maximum intensity projection images (Figure 4A–4C) revealed compression of the right renal artery by the aforementioned mass. The left kidney showed prompt and satisfactory excretion.
of the intravenously administered contrast medium. Contrast was not seen in the right ureter, but there was excretion into the upper pole calyces.

Intraoperative findings included a mass seen at the lower pole of the right kidney, infiltrating into the renal parenchyma and extending into the renal vein, compressing on the ureter and right renal artery, but no extension to the inferior vena cava. All examined lymph nodes were essentially normal. The left kidney was grossly normal.

The anti-hypertensive drugs were discontinued 2 h postoperatively due to BP falling to 60/40 mmHg. Postoperatively, the patient’s BP became normal without anti-hypertensive drugs, all symptoms resolved, and she was subsequently discharged with a BP of 102/60 mmHg after 5 days.

The histology report diagnosed renal cell carcinoma (chromophobe type) as shown in Figure 5. The normal renal tissue in same right kidney is shown in Figure 6.

She is being followed-up in the clinic and remains well to date.
Figure 4. Delayed series, axial (A, C) and coronal reformatted images (B) of the same patient revealed normal contrast excretion on the left, with contrast excretion only in the upper calyces on the right.

Figure 5. The right kidney showing solid sheets of tumor cells with round to polygonal shape and abundant granular cytoplasm; the tumor has delicate branching vasculature. The cells have mildly pleomorphic and hyperchromatic vesicular nuclei with a prominent chromatin pattern. There is infrequent abnormal mitosis. Hematoxylin and eosin staining; magnification ×40.

Figure 6. Normal renal tissue of the right kidney (hematoxylin and eosin staining; magnification, ×40).
Discussion

Hypertension in the pediatric population is now commonly observed [9]. It is known to be a major cause of morbidity and mortality in many countries. The long- and short-term health risks to children may be substantial.

The true incidence of hypertension in children is not known. This vagueness partly stems from the arbitrary definition of hypertension and is in part related to incomplete BP screening during routine pediatric clinical visits. These reasons were partly why the girl’s BP was not checked at the referral center.

According to the fourth report of the Task Force on BP Control in Children, commissioned by the National Heart, Lung, and Blood Institute (NIH), BP is considered normal when the systolic and diastolic values are less than the 90th percentile for the child’s age, sex, and height [10].

Our patient presented with BP ranging between 180/120 mmHg and 200/120 mmHg instead of ≤118/76 mmHg recommended for girls by age and height percentile [10]. Accordingly, our patient had severe HTN.

In general, the younger the child and the higher the BP, the greater the likelihood that HTN is secondary to an identifiable cause. A secondary cause of HTN is most likely to be found before puberty; after puberty, the cause of HTN is increasing likely to be essential [11]. The most common cause of secondary HTN in young patients is renal parenchymal abnormality [11]. Therefore, the profile of presentation in our patient suggested renal causes of hypertension.

The most common forms of presentation of RCC in children are macroscopic hematuria and abdominal or flank pain [5,8], but our patient had none of these manifestations. RCC presentation as an incidental finding in children is less common than in adults.

The history of our patient could have been missed if not well evaluated, because the weight loss reported could easily be explained by anorexia. The presence of easy fatigability in addition to these symptoms could easily be linked to possible hypertensive heart failure.

Generally, there is no sex predominance for RCC in children, unlike in adults, in whom the tumor predominates in males [5]. The incidence of RCC increase with age; RCC in children presents at between 9 and 15 years of age, as in our patient [8,12]. In children, only 2% to 3% of malignant renal tumors are proved to be RCC [5,6].

According to a survey by the Japanese Society of Pediatric Surgeons, RCC accounted for 1.4% of all renal tumors in patients aged 5 to 9 years and 52.6% in patients aged 10 to 15 years [7].

The incidence of HTN among age-matched controls is close to 20%, and almost 40% of those with RCC experience HTN [13]. Evaluation of our patient via abdominal US revealed a right kidney with a well circumscribed lower pole mass with internal echoes compressing the pelvicalyceal system. Similarly, the abdominal CT showed a huge mass with associated mass effect evidenced by compression of the middle pole of the right kidney. This mass effect was confirmed intraoperatively.

In fact, RCC is a unique and challenging tumor because of the frequent occurrence of paraneoplastic syndromes, including hypertension, among others. Therefore, the mechanism of hypertension in our patient may be multiple, one of which may be a consequence of impeding blood flow to the right kidney or to the intrarenal segments [14–16].

Another mechanism may be the local renal parenchymal compression from the large tumor. This may lead to intrarenal ischemia and further increase in renin secretion by the JGA [17]. Ureteral obstruction can cause renin secretion by a similar mechanism [18].

Neoplastic proximal tubular cells themselves may secrete renin, as evidenced by immunohistochemical studies on RCC tissues [18]. An immunohistochemistry study was not done in this study to identify the specific renal tissue involved due to lack of capacity in our center, and this is a limitation of our study. About 70% of RCC tumors are radiographically hypervascular; HTN in these cases may be due to increased cardiac output.

In certain cases, as seen in our patient, 85% of those with HTN secondary to RCC are normotensive following tumor resection [13,19].

Our findings in this report further confirm the validity of previous recommendations on BP screening in children [10]. These recommendations state that children over the age of 3 years who are seen in medical care settings should have their BP measured at least once during every health care visit. Children under age 3 years should have their BP measured in special circumstances.

Conclusions

The nonspecific clinical manifestation found in this case show the need for hypertension screening in children. The causes of HTN are complex, which explains the difficulties often
encountered in identifying the mechanism underlying HTN in a particular patient. These difficulties are the main reason why treatment is often designed to affect regulatory factors rather than the cause of the disease. The resolution of symptoms after nephrectomy confirms RCC as the underlying cause of symptoms, making this case a unique presentation.

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Conflicts of interest

None.