Ectopic ACTH-secreting neuroendocrine tumor: a rare etiology of a pediatric solid renal mass

Neil J. Kocher, MD,[1] Justin Loloi, BS,[2] Joshua Warrick, MD,[3] Amy S. Burns, MD,[1] Ross M. Decter, MD[1]

[1]Department of Surgery, Division of Urology, The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania, USA
[2]The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania, USA
[3]Department of Pathology, The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania, USA

KOCHER NJ, LOLOI J, WARRICK J, BURNS AS, DECTER RM. Ectopic ACTH-secreting neuroendocrine tumor: a rare etiology of a pediatric solid renal mass. *Can J Urol* 2019;26(5):9956-9959.

Neuroendocrine tumors (NETs) are rare tumors with varying clinical presentations. We describe the case of an 11-year-old female presenting with Cushingoid features in the setting of a left-sided flank mass. Her presentation and evaluation suggested a paraneoplastic ectopic ACTH syndrome. She underwent open left radical nephrectomy and final pathology confirming a high-grade NET with nodal metastasis. Although exceedingly rare, ACTH-secreting tumors of the kidney can cause significant morbidity and mortality and so we recommend it be included in the differential diagnosis of pediatric renal masses.

Key Words: pediatric, neuroendocrine, ACTH, tumor; ectopic

Introduction

Neuroendocrine tumors (NETs) are rare malignancies that develop from the diffuse neuroendocrine system, which can arise from a variety of tissues including the lungs, pancreas, kidney, rectum, and small bowel.[1] The annual age-adjusted incidence is approximately 7 per 100,000 patients, and NETs are more likely to occur in young adults (ages 20-29 years old) compared to the pediatric population.[1,2] The clinical presentation is highly variable and dependent on whether functional endocrine pathology is present. Renal NET is an exceedingly rare malignancy with approximately 80 cases in the literature.[3] Herein, we discuss the case of an 11-year-old female who initially presented acutely with left abdominal pain, Cushingoid features, and a large left renal mass with spontaneous hemorrhage, noted to have renal NET following extirpative therapy. This study was approved by our Institutional Review Board and consent was obtained by the patient.

Accepted for publication July 2019

Address correspondence to Dr. Ross M. Decter, The Pennsylvania State University College of Medicine, Department of Surgery, Division of Urology, 500 University Drive, Hershey, PA 17033 USA

Case report

An 11-year-old Caucasian female presented to the emergency room for evaluation of left upper quadrant abdominal/flank pain. Her pain, which progressively worsened since its onset 3 days prior to arrival, was initially attributed to constipation. She developed increased abdominal distension despite regular bowel movements. Additional symptoms include worsening fatigue, nausea, and diminished appetite. Review of systems was positive for a 30 pound weight gain over the past 3 months, with rapid development of acne and facial hair.

Her past medical history is significant for bladder-bowel dysfunction. No prior surgery. She was full term and has no allergies or home medications. She lives with her mother and father in separate homes without known pesticide exposure. Her paternal grandmother was diagnosed with melanoma, otherwise family history was noncontributory.

Initial ED triage vital signs included a temperature of 37.2°C, HR 160 BPM, RR 20 br/min, BP 134/77 mmHg, and 99% O_2 saturation on RA. Focused physical exam revealed an obese, pale child in no distress. She demonstrated stigmata of Cushing syndrome with round facies, acne, thin facial hair, and a markedly distended abdomen with prominent striae. She had a tender, palpable left-sided mass and Tanner stage 2 pubic hair.

Outside records identified severe acute blood loss anemia (Hgb/Hct 6.4/20.2), leukocytosis without bandemia (21.7), acute kidney injury (Cr 1.19), elevated CRP (42), and lactic acidosis (1.8). Prior abdominopelvic CT scan with IV contrast revealed a 13.6 cm x 11.8 cm x 10.9 cm mixed solid/cystic septated left renal mass and extensive perinephric hematoma without active extravasation, Figure 1. The right kidney and bilateral adrenal glands appeared grossly normal.

She received 1 L crystalloid and 2 units pRBC with an appropriate physiologic response. She was admitted for further resuscitation and work up of a left renal mass. A 24-hour urine collection study performed 1 week prior identified a markedly elevated free cortisol level of 2782 mcg/24 hr. Pediatric Endocrinology, Nephrology, and Oncology services were consulted for management of her steroid levels, AKI, and disease staging, respectively. Inpatient hormone studies were significant for an elevated ACTH level (290 pg/mL), serum cortisol (49.9 ug/dL), and low DHEA-S (630 ng/mL).

An open left radical nephrectomy with left renal hilar and para-aortic lymphadenectomy was performed. Grossly, within the inferior aspect of the kidney was a 13.8 cm x 13.2 cm x 8.7 cm tan-white, well-defined, centrally necrotic mass with petechial hemorrhage replacing approximately 80% of the kidney parenchyma and extending through the pelvis, Figure 2. Final pathology confirmed stage III, malignant, high-grade neuroendocrine tumor with

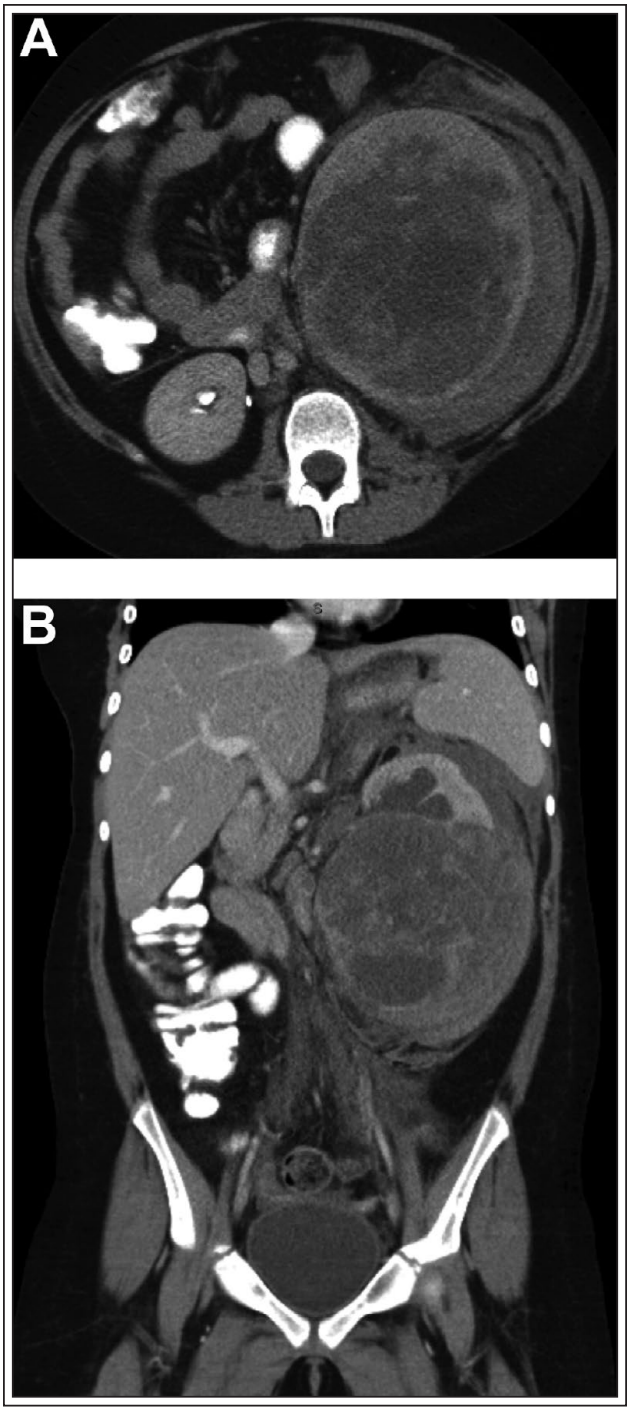

Figure 1. Axial **(A)** and sagittal **(B)** CT urogram showing a mixed solid and cystic left-sided renal mass.

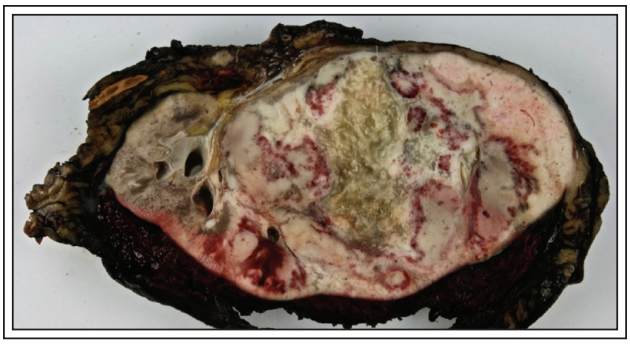

Figure 2. Gross photograph of left kidney revealing a tan-white, well-defined, centrally necrotic mass replacing a majority of the native renal tissue.

atypical mitotic activity and 13/13 positive lymph nodes, Figure 3. Preoperative CXR was unremarkable.

Postoperative PET-CT imaging revealed multiple enhancing calvarial lesions and hypermetabolic lymphadenopathy along the left retroperitoneal surgical bed. She underwent two cycles of adjuvant cisplatin-etoposide chemotherapy with worsening retroperitoneal lymphadenopathy. Salvage therapy with sunitinib was initiated. She subsequently developed pulmonary metastases and atezolizumab with whole brain radiation therapy was administered for leptomeningeal enhancement. She presented 8 months postoperatively with acute respiratory failure secondary to fungal pneumonia and increased metastatic burden. She was placed on comfort care and passed peacefully during admission.

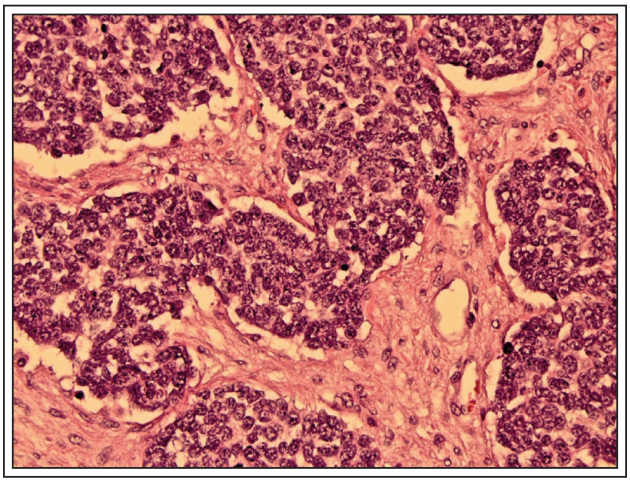

Figure 3. High-power photomicrograph demonstrating a malignant, high-grade neuroendocrine tumor of the left kidney (hematoxylin-eosin stain).

Discussion

We present the case of an 11-year-old Caucasian female who presented with a large renal mass after spontaneous hemorrhage with clinical signs and lab work concerning for a paraneoplastic ectopic ACTH syndrome. Paraneoplastic syndromes are most common in lung and pancreatic cancers but can occur in solid renal masses and have the potential to be highly aggressive malignancies. Paraneoplastic syndromes resulting in Cushing's Syndrome have been reported in the setting of renal cell carcinoma[4] and have rarely occurred in Wilm's Tumor.[5] The differential diagnosis in our patient included nephroblastoma, adrenocortical carcinoma, Ewing sarcoma/primitive neuroectodermal tumor, and renal neuroendocrine tumor.

The exceptionally rare ectopic ACTH-secreting tumors of the kidney are generally characterized by hypercortisolism leading to Cushing's Syndrome. As seen in our patient, patients with an ectopic-ACTH secreting renal tumor may present with symptoms suggestive of a hypercortisol-state, including weight gain, hirsutism, acne, abdominal striae, and moon-like facies.[6]

Primary renal NETs are generally classified as renal carcinoid or neuroendocrine cancer of the kidneys.[4] Renal NETs are a rare entity, in part due to the scarcity of neuroendocrine cells within the renal parenchyma, although there is evidence for their existence within the renal pelvis.[7] To our knowledge, a primary renal NET causing a Cushing's Syndrome has been reported only once in the literature, that being an oncocytic carcinoid of the kidney associated with periodic Cushing's Syndrome.[8] In that case, over the span of 3.5 years, the patient experienced three severe episodes of Cushing syndrome symptoms, which included muscle weakness, lethargy, and physical findings of Cushingoid facies, striae, and virilization. After a lengthy work up, the renal mass was excised and the patient remained normal at follow up 2.5 years later.[8] A more recent report described an 18 month male presenting with Cushing's Syndrome with markedly elevated ACTH in the setting of a retroperitoneal mass.[9] Imaging revealed a large heterogeneous retroperitoneal mass with significant extension into local structures, including the right kidney. The mass was excised and confirmed histologically to be an ACTH-secreting NET. Following surgical resection, the patient's symptoms completely resolved.

Given the paucity of cases, the management of ectopic-ACTH secreting tumors of the kidney is not well described. The first-line pharmacological options for paraneoplastic Cushing's syndrome, such as

Ketoconazole, Metyrapone, and Mitotane, are directed towards inhibition of steroid production. However, these treatments do not address the underlying tumor and so, surgical intervention is usually warranted, as demonstrated in the cases described above. Prognosis is dependent on underlying pathology. Prognostic factors in patients with renal carcinoids associated with a worse prognosis include age above 40 years, tumors measuring greater than 4 cm or extending outside the renal parenchyma, and purely solid tumors with a mitotic rate higher than 1/10 HPF.[10]

While exceedingly rare, ectopic ACTH-secreting tumors of the kidney can cause significant morbidity and mortality and should be included in the differential of renal masses. □

References

1. Navalkele P, O'Dorisio MS, O'Dorisio TM, Zamba GK, Lynch CF. Incidence, survival, and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975-2006. *Pediatr Blood Cancer* 2011;56(1):50-57.
2. Dasari A, Shen C, Halperin D et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017;3(10):1335-1342.
3. Lane BR, Jour G, Zhou M. Renal neuroendocrine tumors. *Indian J Urol* 2009;25(2):155-160.
4. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. *Rev Urol* 2002;4(4):163-170.
5. Coppes MJ. Serum biological markers and paraneoplastic syndromes in Wilms tumor. *Med Pediatr Oncol* 1993;21(3):213-221.
6. Tutal E, Yilmazer D, Demirci T et al. A rare case of ectopic ACTH syndrome originating from malignant renal paraganglioma. *Arch Endocrinol Metab* 2017;61(3):291-295.
7. Lane BR, Chery F, Jour G et al. Renal neuroendocrine tumours: a clinicopathological study. *BJU Int* 2007;100(5):1030-1035.
8. Hannah J, Lippe B, Lai-Goldman M, Bhuta S. Oncocytic carcinoid of the kidney associated with periodic Cushing's syndrome. *Cancer* 1988;61(10):2136-2140.
9. Rahbar M, Rahbar M. Peripheral primitive neuroectodermal tumor associated with paraneoplastic Cushing's Syndrome: The rare case. *Ann Med Surg* 2019:37:21-24
10. Romero FR, Rais-Bahrami S, Permpongkosol S, Fine SW, Kohanim S, Jarrett TW. Primary carcinoid tumors of the kidney. *J Urol* 2006;176(6 Pt 1):2359-2366.