An Adolescent with Tuberous Sclerosis and Hypocalcemia and a Renal Mass

Dear Editor,

A 13-year-old girl, a known case of tuberous sclerosis, presented with complaints of paresthesias for the last one year and documented severe hypocalcemia (serum calcium 5.5 mg/dl). She had a history of multiple episodes of myoclonic seizures since the last 10 years, which was being managed with multiple anti-epileptic drugs, namely, valproic acid, lamotrigine, and lacosamide. Her surgical history revealed a left frontal craniotomy with near-total excision of subependymal giant cell astrocytoma (2016; at age seven). Her laboratory parameters are listed in Table 1, and MRI scans are shown in Figure 1a. Contrast-enhanced MRI axial imaging of kidneys showed a T1 hypointense and T2 hyperintense exophytic heterogeneously enhancing mass arising from medial cortex of the lower pole of the right kidney. Cystic lesions were seen as hypointense lesions in the remaining visualized parenchyma. Axial short tau inversion recovery (STIR) image showed a heterogeneous mass with multiple internal hyperintense areas that were suggestive of necrosis.

The child received intravenous calcium gluconate and oral 1,25-vitamin D supplements to rapidly raise serum calcium. The child also received weekly 25-hydroxyvitamin D supplementation. The valproate dose was reduced based on the serum levels (126 mcg/ml; normal range 50–100 mcg/ml). The mass lesion revealed papillary renal cell carcinoma [Figure 1b]. Right open partial nephrectomy was performed. The child's serum calcium and the need for oral calcium and active vitamin D supplement reduced over the next two weeks. Currently, at a follow-up of six months, the child is doing well, having a normal serum creatinine of 0.6 mg/dl, and is on RDA supplement of oral calcium.

Tuberous sclerosis (TSC) is caused by germline loss-of-function mutations of either the *TSC1* or *TSC2* gene. Approximately 60% of germline TSC gene mutations are *de novo* and 40% are inherited. TSC is a multisystemic neurocutaneous disorder affecting the brain (subependymal giant cell astrocytomas, cerebral cortical tubers), heart (rhabdomyomas), kidney (angiomyolipomas, cysts, renal cell carcinomas), lung (lymphangioleiomyomatosis [LAM]), and skin (angiofibromas). TSC patients can also develop seizures, autism, and cognitive disability.[1]

Hypocalcemia is a serious medical condition in patients with TSC who develop seizures and are on anti-epileptic drugs, namely, valproic acid, which increases degradation of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D3 by upregulation of 24-hydroxylase CYP24A causing inhibitory effects on calcium absorption and end-organ resistance and inhibition of calcitonin secretion.[2]

The renal manifestations of TSC include angiomyolipomas, epithelial cysts which can resemble polycystic kidney disease, and renal cell carcinoma (RCC). Angiomyolipomas are the most frequent lesion (75%) followed by simple renal cysts (17%).[1,2] Around 4% of patients develop RCC.[2–5] Careful morphological studies of such RCC have permitted their subdivision into groups: clear cell (most common); others being papillary, chromophobe and unclassified RCC, and benign renal cell oncocytoma.[3,4] Tumors in TSC, including angiomyolipomas and RCCs, develop after somatic "second hit" inactivation of the remaining wild-type allele of *TSC1* or *TSC2*.[5]

RCC, though rare, should be kept in mind as a differential diagnosis when encountering a TSC patient with renal mass, even in children. Regular radiological surveillance

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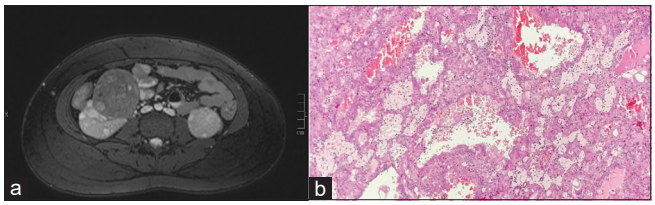

Figure 1: (a) Contrast-enhanced MRI axial image of kidneys. There is a T1 hypointense and T2 hyperintense exophytic heterogeneously enhancing mass arising from the medial cortex of the lower pole of the right kidney. Cystic lesions are seen as hypointense lesions in the remaining visualized parenchyma. Axial short tau inversion recovery image shows a heterogeneous mass with multiple internal hyperintense areas suggestive of necrosis. (b) Papillary pattern composed of cells with abundant eosinophilic cytoplasm and hyperchromatic irregular nuclei with punctate nucleoli. Hob-nailing of cells is also seen focally.

Table 1: Laboratory parameters at admission

Blood	Values at presentation	Reference range
Serum calcium	5.5 mg/dl	8.4–10.2 mg/dl
Serum parathyroid hormone	906.3 pg/ml	15.0–68.3 pg/ml
25-hydroxyvitamin D	16.6 ng/ml	20–40 ng/ml
Serum phosphorus	6.8 mg/dl	2.5–4.5 mg/dl
Blood urea	24 mg/dl	15–36 mg/dl
Serum creatinine	0.50 mg/dl	0.7–1.2 mg/dl
Serum uric acid	3.9 mg/dl	2.5–6.2 mg/dl
Serum sodium	141 mmol/L	137–145 mmol/L
Serum potassium	3.5 mmol/L	3.5–5.1 mmol/L
Hemoglobin	11.5 g/dl	12–15 g/dl
Serum albumin	2.6 g/dl	3.5–5 g/dl

may help in early detection and timely intervention to decrease renal morbidity and mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflicts of interest

There are no conflicts of interest.

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