CASE REPORT

Hyponatremic-Hypertensive Syndrome in Ovarian Paraganglioma

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Background: Hyponatremic-hypertensive syndrome (HHS) is characterized by combination of polyuria, polydipsia, hypertension, hyponatremia and hypokalemia in association with unilateral renal artery stenosis. **Case characteristics:** A 10-year- old girl presented with polyuria, polydipsia, hypertension, hyponatremia, hypokalemia and proteinuria. Ultrasonography with doppler study revealed bilateral normal renal arteries. Completed tomography of abdomen detected a left adnexal mass, which was later confirmed as ovarian paraganglioma on histopathology. **Outcome:** After tumor excision, polyuria subsided and blood pressure normalized. **Message**: Hyponatremic-Hypertensive Syndrome does not always result from unilateral renal artery stenosis. High index of clinical suspicion with appropriate imaging technique may clinch rare endocrine causes of hypertension, like paraganglioma.

Keywords: *Hypertension, Nocturnal enuresis, Paraneoplastic syndrome, Polyuria*.

Severe hypertension in children usually results from secondary causes, with renovascular diseases constituting 5-10% of all pediatric cases of hypertension [1]. Hyponatremic-Hypertensive syndrome (HHS) is characterized by hyponatremia, severe hypertension, polyuria and polydipsia in association with unilateral renal artery stenosis [2-4]. Pheochromocytoma and paraganglioma constitute 0.5-2% of all cases of childhood hypertension [5]. We report a girl presenting with features of HHS and later diagnosed to have an ovarian paraganglioma.

CASE REPORT

A 10-year-old girl presented with complaints of bed-wetting at night, increased daytime uninary frequency and increased thirst for last six months. On examination, her weight was 27.5 kg (25th centile), height was 129 cm (10 th centile), and blood pressure (BP) varied from 180/140 to 124/100 mmHg. BP was elevated in all four limbs (right upper 160/110, left upper 156/112, right lower 170/116 and left lower 176/120), and did not show any significant postural variation. All the peripheral pulses were well palpable and there was no radio-radial or radio-femoral delay. Fundus examination revealed bilateral grade IV hypertensive retinopathy. Electrocardiogram (ECG) showed evidence of left ventricular hypertrophy. A 24-hour urine output was documented as 8 mL/kg/hour, confirming polyuria.

Laboratory investigations showed a hemoglobin of 12.4 g/dL, serum sodium (Na) ranging from 118-126 meq/L, serum potassium (K) ranging from 2.5-3.2 meq/L, urea 24 mg/dL, creatinine 0.8 mg/dL, serum albumin 4.2 g/dL and random blood sugar 67mg/dL. Urinalysis revealed urine protein of 3+ (300mg/dL) and no RBCs or pus cells. Spot urine protein to creatinine ratio (Up/Uc) was 6.4 mg/mg. Venous blood gas analysis showed mild metabolic alkalosis (PH 7.47, HCO3 28.3). Thyroid function test and serum parathormone (PTH) report was normal. A possibility of HHS due to renal artery stenosis was kept in view of polyuria, polydipsia, hypertension, hyponatremia and hypokalemia.

Abdominal ultrasound and renal doppler showed bilateral normal kidneys and renal arteries. Plasma renin activity was raised (19 ng/mL/h; normal 0.5-6 ng/mL/h). Computed tomography (CT) abdomen with CT angiography revealed normal bilateral kidneys and renal arteries, but incidentally detected a well circumscribed lobulated soft tissue mass (4.1 × 3.4 cm) in left adnexa showing heterogeneous poor contrast enhancement **(*Fig.* 1)**. A 24-hour urinary catecholamines report was normal; vanillylmandelic acid 3.85 µcg (normal 0-15), adrenaline 3.5 µcg (normal 0-20) and nor-adrenaline 26.25 µcg (normal 0-90). Serum catecholamine measurement showed elevated nor-adrenaline (916.66 pg/mL; normal 0-600 pg/mL) and normal adrenaline (58.3 pg/mL; (normal 0-100 pg/mL). Based on CT finding and serum catecholamine report, diagnosis of left ovarian paraganglioma was made. ^{123}Metaiodobenzyl-guanidine scan did not show any increased tracer uptake.

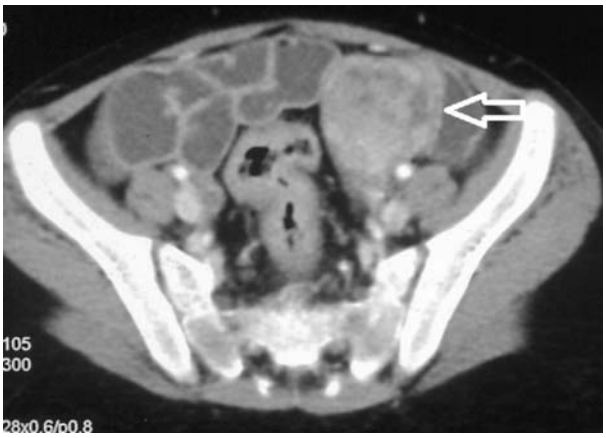

FIG. 1 *CECT abdomen showing a well circumscribed 4.1 × 3.4 cm lobulated soft tissue mass in left adnexa (arrow) showing heterogeneous poor contrast enhancement.*

As the child presented with hypertensive emergency, injection labetalol was administered, which was later substituted with oral formulation. Subsequently, other antihypertensives were added in combination (Amlodipine, Clonidine and Enalapril). Despite using multiple antihypertensives, BP remained elevated above 95th centile. Prazosin was added in the pre-operative period, which resulted in near normalization of BP.

The child underwent open laparotomy and left salpingo-oophorectomy was performed. An ovarian mass measuring 5x4x3.5 cubic centimeter with an external pearly white capsule was removed. Microscopic examination revealed a monomorphic population of round cells with abundant granular cytoplasm arranged in the classical zellballen pattern. On immunohisto-chemistry, tumor cells expressed synpatophysin and cytokeratin (***Web Fig***. **1**). A final diagnosis of ovarian paraganglioma was made based on histopathology report. Two weeks after surgery, her BP was normal (112/66 mm Hg), polyuria subsided and biochemical parameters (serum Na and K) normalized. Antihypertensives were gradually tapered and omitted over next 6 weeks. At last follow-up (2 years after surgery), she was normotensive, off medication and had not shown any sign of tumor recurrence.

DISCUSSION

Paragangliomas are rare extra-adrenal catecholamine-secreting tumors located in paravertebral axis and sympathetic nerve branches in pelvic organs, and secrete nor-epinephrine. Parasympathetic variety is located in head and neck, and are generally non-secretory [5]. Paragangliomas have been rarely reported in ovary, uterus and vagina, constituting only 2% of all gynecological tract tumors [6-8]. Clinical features are often nonspecific and tumor detection may be incidental. Polyuria and polydipsia as presenting complaints have been reported earlier in a 9-year-old boy with pheochromocytoma [9].

The child in our report presented with polyuria, polydipsia, hypertension and hyponatremia – similar to clinical and biochemical features of HHS. Release of natriuretic peptides (BNP and ANP) with rapid elevation of BP might have resulted in polyuria and hyponatremia by pressure natriuresis. Natriuretic peptides suppress sodium reabsorption at thiazide-sensitive distal convoluted tubules and thereby increase its delivery to the downstream collecting ducts, where aldosterone stimulates secretion of potassium resulting in hypokalemia [10]. Unlike renovascular hypertension, where renal ischemia is central to activation of renin-angiotensin system (RAS) and subsequent HHS, in our case, hypovolemia secondary to polyuria might have resulted in activation of RAS. We postulate that intense thirst and release of anti-diuretic hormone due to hypovolemia resulting from polyuria could have also contributed to the development of hyponatremia in our case. Proteinuria could have resulted from glomerular hyperfilteration secondary to hypertension; resolution of proteinuria with BP control after surgery validates the same.

Paragangliomas can occur sporadically or in association with familial syndromes like multiple endocrine neoplasia (MEN) type 2, Von Hippel-Lindau disease, and neurofibromatosis type 1. Our case did not have any features suggestive of familial syndromes. However, genetic testing, urinary/plasma metanephrines, plasma aldosterone and FDG PET could not be performed because of financial constraints.

Treatment of paragangliomas is chiefly surgical. Adequate preoperative BP control is mandatory to avoid intra operative rise in BP due to excessive release of catecholamines. Use of selective alpha-1 adrenergic receptor blocker in preoperative period is more rationale and effective way to control BP in children with pheochromocytoma/paraganglioma. Beta blockade is instituted following alpha blockade to offset reflex tachycardia and should never be started before adequate alpha blockade to prevent risk of severe hypertensive crisis from unopposed alpha-1 receptor stimulation [5].

To conclude, HHS may be a manifestation of paraneoplastic syndrome. A high index of clinical suspicion, CT or MRI of abdomen, and estimation of urinary and serum catecholamines may help to clinch these rare causes.

Contributors: MK,AD,KM: initial work-up and case management; VM: performed the surgery; NM: made the histopathological diagnosis; AD: prepared the initial draft; MK,NM,KM: revised the draft. All the authors approved the final version of the manuscript.

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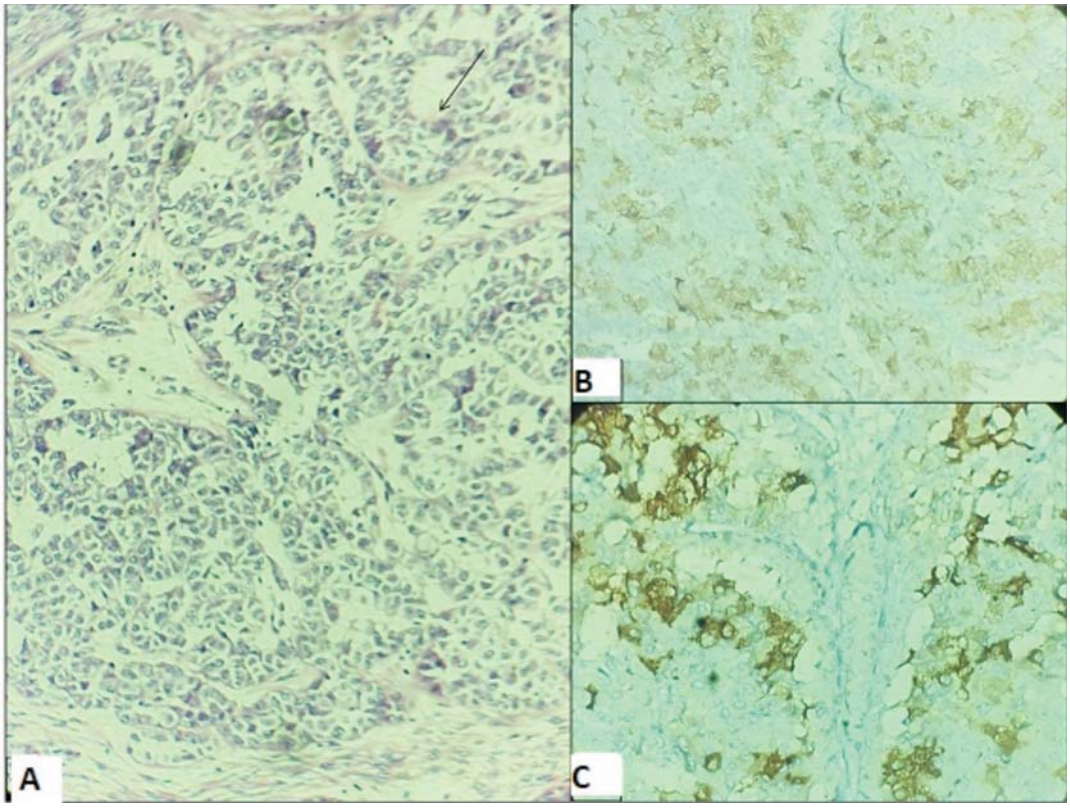

WEB FIG. 1. *(a) Photomicrograph showing prominent 'zellballen' pattern (arrow) of the tumor. The tumor cells have abundant granular cytoplasm with minimal nuclear pleomorphism. Hematoxylin & Eosin, 200 X; (b) Tumor cells express Synpatophysin on immunohistochemistry, DAB chromogen, 200 X; (c) Tumor cells show focal positivity for Cytokeratin. DAB chromogen 200X.*