Unusual sequel of successful laparoscopic unilateral adrenalectomy in a hypertensive adolescent

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An 18-year-old male presented with episodic headache and excessive sweating for two months; and diminished vision in left eye for 15 days. During these episodes, highest blood pressure (BP) recorded was 290/90 mmHg. He didn’t have urinary complaints, nor history of weight gain or muscle weakness. There was no contributory family history, nor significant past history. This average-built boy had BP recordings of 120 to 220 mmHg-systolic and 90 to 120 mmHg-diastolic. Cardiovascular examination was suggestive of LVH; no murmurs were heard. Peripheral vascular examination was normal and there were no abdominal bruit. He didn’t have any stigmata of multiple endocrine neoplasias (MEN) syndrome Type-2 (marfanoid habitus, mucosal fibromata, thyroid nodules). Hypertensive retinopathy was evident on fundus examination.

What is the differential diagnosis?
The presence of the classical triad of episodic hypertension, headache and diaphoresis make hypercatecholaminism or pheochromocytoma (PCC) as the first differential diagnosis. PCC can have extremely varied presentations, to the extent of being called “the great mimic”[1], yet, the classical triad, when present is highly specific for hypercatecholaminism. Some of these clinical features can overlap with other conditions. In patients with essential hypertension and “hyperadrenergic” features such as tachycardia, sweating and high cardiac output and in patients with anxiety attacks associated with blood pressure elevations, urinary or plasma catecholamines estimation is usually helpful in excluding the diagnosis of PCC. Intracranial tumors and subarachnoid hemorrhage can cause headaches, hypertension and hypercatecholaminism, but are accompanied by other neurological manifestations as well which were absent in our patient. Diencephalic seizures rarely cause paroxysmal hypertension with symptoms of excessive catecholamine secretion that are often preceded by an aura. Cocaine abuse can cause a marked increase in blood pressure, hyperadrenergic symptoms and myocardial damage. Factitious crises may be produced by self-administration of sympathomimetic amines.

Other causes of secondary hypertension—renovascular hypertension, renal arterial stenosis, hyperthyroidism, hypercortisolism, hyperaldosteronism and cardiac/vascular anomalies like aortic co-artcation need to be ruled out. Renovascular hypertension is usually associated with history of renal disease, deranged renal functions and urinary symptoms, renal failure and features of fluid overload and uremia. Hyperthyroidism may be associated with a hyperkinetic, hyperadrenergic state, but these manifestations are typically persistent, not paroxysmal, as was the case in presented patient. Hypercortisolism (Cushing’s syndrome) is associated with fluid retention, obesity and muscle weakness. Classical features of Hyperaldosteronism are hypokalemia and periodic paralysis. None of these features were present in our patient.

How to establish the diagnosis?
The diagnosis of hypercatecholaminism is established biochemically.[2] Patient’s 24th urinary total-metanephrines (dual-column resin-exchange assay, Bio-rad, Hercules, USA) were elevated (12.5 mg/24h, normal<0.9), confirming hypercatecholaminism. The 24th urinary metanephrines or fractionated catecholamines and plasma-free catecholamines and metanephrines are commonly employed diagnostic tests with comparably high accuracy.[1] Urinary VMA estimation is not as sensitive and specific in diagnosing PCC and should be avoided. Recent literature supports plasma-free catecholamines as the most sensitive and highly specific test.[2]

With the diagnosis of PCC established, imaging for PCC localization was done. Abdominal ultrasonography revealed a 4.5 x 3.3 cm right adrenal mass and normal right kidney with no evidence of renal arterial stenosis. However, left kidney was not visualized. Contrast-enhanced CT of abdomen confirmed a well-circumscribed right adrenal mass suggestive of PCC [Figures 1 and 2] and absent left kidney and adrenal gland. 131-meta-iodo-benzyl-guanidine scintigraphy revealed a solitary focus of radio-tracer concentration in right supralateral area, consistent with PCC. Patient was thus diagnosed as right adrenal PCC, with left renal and adrenal agenesis.

What associated syndromes are known with PCC?
PCC are uncommon tumors of adrenal-medulla and sympathetic...
ganglia and account for <1% of all hypertensives. Conventionally, these have been known as the “10% tumors”. It has been believed, with little evidence, that 10% of PCC are extra-adrenal, bilateral, malignant, familial, multicentric, normotensive and occur in childhood. In recent years, this arbitrary 10% rule has been challenged by robust data. In our experience of 102 PCC patients managed over 15 years at SGPGIMS, Lucknow, only bilateral and normotensive disease occurred in about 10% cases. Yet, the majority of the PCC are benign, sporadic and unilateral and are cured by unilateral adrenalectomy. Fifteen to twenty per cent of all PCC patients have a familial form of this disease, the majority occurring in settings of MEN-II a and b due to RET-proto-oncogene mutations. About 18% PCCs are currently discovered by screening families with MEN-II or neuro-cutaneous syndromes, especially vonHippel-Lindau’s disease (VHL) and Neurofibromatosis Type-1. Gastric leiomyoma, pulmonary chordoma and neuro-cutaneous syndromes (tuberous-sclerosis, Sturge-Weber) are known to coexist with extra-adrenal PCC. Succinate dehydrogenase-B and D mutations are associated with aggressive, malignant PCC. The best way of investigating these syndromes is by genetic testing, which is currently unavailable for routine use at our hospital or other Indian centers and could not be carried out in the presented patient and family, MEN-II and other syndromes were excluded in the patient and family members. None of them had typical phenotype of MEN-II-b. Medullary thyroid carcinoma was ruled out by normal serum-calcitonin and thyroid ultrasonography. Normal serum calcium and PTH levels excluded primary-hyperparathyroidism. Though designated as sporadic PCC, in the absence of genetic information, the possibility of our patient being the index case of MEN-II cannot entirely be ruled out.

How to manage adrenal PCC and what implications would contralateral adrenal agenesis have in this patient?

Adrenal PCC are managed surgically, after adequate alpha and if needed beta adrenoceptors blockade. As preoperative preparation, the patient was treated with alpha-adrenoceptor blocker Prazosin, starting with 6mg/day, gradually increasing to maximum 18 mg/day when adequate BP control (<130/90 mmHg) and features of alpha blockade (orthostatic hypotension >10 mmHg, nasal stuffiness, weight gain, falling hematocrit) were achieved. Appropriate fluids, salt replacement and plasma infusion were administered. Anticipating postadrenalectomy hypocortisolism in view of a nonvisualized left adrenal gland, Hydrocortisone infusion was started the morning of the operation. Lateral transperitoneal laparoscopic-assisted right adrenalectomy was performed. Per-operative BP fluctuations were controlled with sodium-nitroprusside. He didn’t require peri-operative blood transfusions. Post-PCC excision hypotension, an anticipated sequel, was successfully managed with colloids and vasopressors.

The 5 cm circumscribed right adrenal tumor removed was reported as benign PCC on histopathology, in view of absence of metastases, local invasion and histological features of malignancy. Following an uneventful postoperative recovery, the patient was discharged on postoperative day 4 on corticosteroid supplements (prednisolone 15 mg/day). He was normotensive, off anti-hypertensives, had normal kidney functions and free of any complications.

In follow-up at one, three, six and 12 months, the patient has remained asymptomatic, normotensive without any anti-hypertensive medications and had normal 24h urinary total-metanephrines. Serum-cortisol and short-ACTH stimulation tests performed have been suggestive of continued hypocortisolism, confirming the contralateral adrenal agenesis.

When is postadrenalectomy corticosteroid replacement/ supplementation required?

Peri-operative corticosteroid replacement or supplementation is required in patients who have or are expected to develop hypocortisolism postoperatively. This usually occurs following bilateral adrenalectomy or unilateral adrenalectomy for cortisol-producing adenomas which cause suppression of the contralateral adrenal. In the present case, unilateral laparoscopic adrenalectomy for adrenal PCC resulted in long-term hypocortisolism because the contralateral adrenal was congenitally absent. He has remained dependent on glucocorticoids and mineralo-corticoids supplements for over one year of follow-up.

How do patients undergoing unilateral adrenalectomy for PCC fare?

With appropriate peri-operative management, operative mortality in PCC patients in most endocrine centers is <3%. In our operative experience in 91 PCC patients operated over...
15 years at SGPGIMS, Lucknow, there has been no perioperative mortality. Following a successful PCC removal, rapid restoration of hemodynamic and cardiac indices permits accurate judgment regarding completeness of tumor resection. Up to a fifth of the patients may remain hypertensive, mostly due to essential hypertension.[12]

Unilateral adrenalectomy results in no functional derangements and adrenal insufficiency. Corticosteroid and mineralo-corticoids from the contralateral adrenal are sufficient to provide for physiological and stress needs. An exception to this rule is Cushing’s adenoma, where the contralateral adrenal is suppressed and patients require temporary corticosteroids supplementation for a few months. Reports of adrenal insufficiency after Conn’s adenoma removal are exceptional.[1]

What is the appropriate surgical approach to adrenal pheochromocytoma?
For most benign adrenal pathologies, laparoscopic adrenalectomy is currently favored for its superiority over conventional-open adrenalectomy with regard to lesser postoperative pain and shorter convalescence, while being equally effective.[1] Laparoscopic adrenalectomy, specially for PCC is technically demanding and currently offered in India by only a few surgeons at centers of excellence.

Can adreno-cortical function be preserved following bilateral adrenalectomy?
Adrenal-Cortex-preserving adrenalectomy or adrenal-sparing adenomectomy has been proposed for small adrenal adenomas or PCCs in recent years,[1,6-8] which can be performed laparoscopically also.[7] These procedures are of unproven efficacy for PCC and have invited widespread criticism owing to high recurrence rates,[1] especially as most recurrences of benign-curable pathologies (at first instance) surface as unresectable- incurable disease.[8] Moreover, not all patients undergoing the cortex-preserving adrenalectomy derive the benefits of avoidance of corticosteroid replacement.[8] Because of these concerns, the authors do not practice this for PCC, reserving this option for small Conn’s adenomas alone. In the presented patient with large PCC and no discernable cortical tissue, cortex-preserving option was not entertained. Another option with doubtful efficacy is orthotopic autotransplantation of adrenocortical tissue.[1]

Are PCC and URA known to coexist commonly?
URA is a common congenital abnormality, reported in 1:1000 autopsies.[9,10] Ipsilateral adrenal agenesis is more rarely encountered, seen in ~10% of URA subjects at autopsy[10] and in 17% on CT scan.[12] URA may occur in isolation or may be associated with other congenital syndromes.[11] Coexistence of URA and PCC is not a known association and in the absence of a common embryological basis for the two conditions, such an association in our patient seems merely a chance coexistence. To the best of the authors’ information, there are no reports of coexistent URA and adrenal tumors in the scientific literature. The known associated renal affections in PCC patients are renal cell carcinoma and cysts seen in VHL patients. Two VHL patients rendered anephric after bilateral nephrectomy for multiple renal cell carcinomas have been reported to have laparoscopic removal of PCC.[13] Renal arterial stenosis may be associated with PCC, more commonly in childhood, with about 100 reported cases.[14]

References

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