CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 14 (2015) 85–88

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Pheochromocytoma as a rare cause of arterial hypertension in a patient with autosomal dominant polycystic kidney disease: A diagnostic and therapeutic dilemma

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ARTICLE INFO

Article history:
Received 9 June 2015
Accepted 18 July 2015
Available online 28 July 2015

Keywords:
Adrenalectomy
Hypertension
Polycystic kidney
Polycystic liver
Pheochromocytoma
Retroperitoneoscopy

ABSTRACT

INTRODUCTION: Individuals with autosomal dominant polycystic kidney disease (ADPKD) frequently suffer arterial hypertension even prior to significant loss of renal function, a clinical situation that obscures detection of modifiable secondary causes of hypertension.
PRESENTATION OF CASE: A 50-year-old man with ADPKD and polycystic liver and resistant hypertension is diagnosed with a 4-cm right adrenal mass. Cross-sectional MRI is indicative of pheochromocytoma versus adrenocortical carcinoma or metastasis, though there are no typical PCC symptoms and plasma and urine metanephrines are within normal ranges. Since malignancy cannot be excluded, right adrenalectomy is performed. Considering that the enlarged liver poses an obstacle for transperitoneal open and laparoscopic approaches, a retroperitoneoscopic approach is used. Surgical pathology reveals a 4.5-cm pheochromocytoma; the patient no longer requires antihypertensive therapy.
DISCUSSION & CONCLUSION: Pheochromocytoma is a rare but treatable cause of hypertension in ADPKD; given the anatomical complexities these patients present, careful preoperative planning and surgical technique are essential to a favorable outcome.

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal cystic disease, occurring in 1 of every 400–1000 live births. Arterial hypertension is present in 50–75% of patients even before there is significant loss of renal function. The typical pathogenesis of hypertension in ADPKD involves cystic compression of renal microvasculature, resulting in ischemia and activation of the renin-angiotensin-aldosterone system [1,2]. It is important to recognize that some patients may have modifiable secondary causes of hypertension, as well, given that cardiovascular disease is the main cause of death in this population, and early detection and treatment of hypertension significantly decrease the risk for proteinuria, hematuria, decline in renal function, and morbidity and mortality from valvular heart disease and aneurysms [3–5].

2. Presentation of case

The patient is a 50-year-old man with ADPKD with preserved renal function, polycystic liver, and hypertension treated with four agents, with blood pressure on presentation of 140/70 mmHg. He has a family history of ADPKD (affected father); there is no family history of neoplastic disease.

On routine imaging performed to monitor the progression of his ADPKD, a right adrenal mass measuring 40 × 27 mm is detected. Based on MRI characteristics (intense and heterogeneous contrast uptake and increased T2 signal intensity), the lesion is suggestive of pheochromocytoma (PCC) versus adrenocortical carcinoma or metastatic lesion of unknown primary (Fig. 1). The patient denies any previous hypertensive crises, episodic headache, diaphoresis, tachycardia, and/or palpitations, and metanephrines in plasma and urine are within the reference ranges (Table 1). Given the size of the lesion and the inability to exclude malignancy, the decision is made to perform right adrenalectomy. A retroperitoneoscopic approach is chosen in consideration of the size of the patient's liver (tip extending well below the umbilicus).

The patient is admitted preoperatively for blood pressure control and intravenous fluid and salt loading. In the operating room, after induction of general anesthesia and orotracheal intubation, the patient is placed in prone position. A 1.5-cm incision is made

Abbreviations: ACTH, adrenocorticotropic hormone; ADPKD, autosomal dominant polycystic kidney disease; PCC, pheochromocytoma; VHL, von Hippel Lindau.

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http://dx.doi.org/10.1016/j.ijscr.2015.07.015

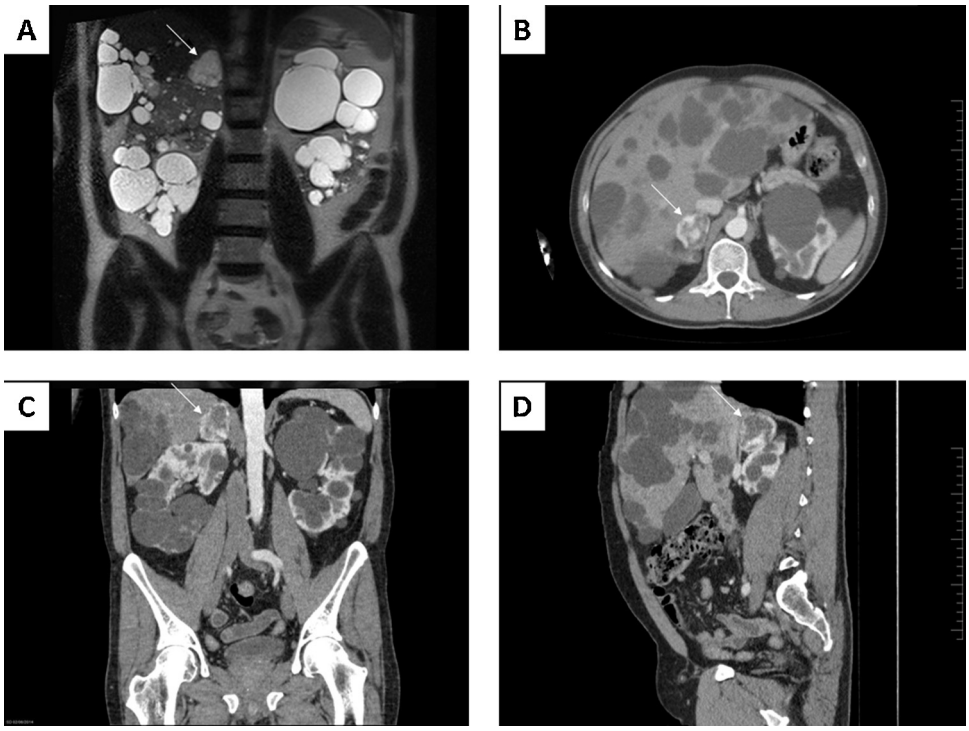

Fig. 1. Contrast-enhanced cross-sectional imaging of the patient's abdomen demonstrates a 40 × 27 mm lesion in the right adrenal gland (white arrows). The lesion has heterogeneous contrast uptake and increased signal intensity on T2-weighted MRI (A) and is suggestive of pheochromocytoma versus adrenocortical carcinoma or metastatic lesion of unknown primary. The lesion is situated posterior to the enlarged polycystic liver and inferior vena cava (B) and anterior and superior to the superior pole of the polycystic right kidney (C, D).

Table 1
Laboratory values.

	Value	Reference range
Blood		
Serum creatinine (mg/dL)	1.12	0.30–1.30
Serum sodium (mEq/dL)	142	135–145
Serum potassium (mEq/dL)	4.9	3.5–5.5
Serum cortisol (μg/dL)	14.9	10–25
Serum ACTH (pg/mL)	41	10–60
Plasma aldosterone (ng/dL)	5.5	<30
Plasma renin activity (ng/mL*h)	0.88	0.5–2.3
Plasma free metanephrine (pg/mL)	18	<90
Plasma free normetanephrine (pg/mL)	118	<200
Urine		
Fractionated epinephrine (mcg/24 h)	6.6	0.5–20
Fractionated norepinephrine (mcg/24 h)	50.6	15–80
Fractionated dopamine (mcg/24 h)	149	60–400
Fractionated metanephrine (mcg/24 h)	32	24–96
Normetanephrine (mcg/24 h)	184	75–375

Preoperative laboratory values. Plasma free metanephrines and urine fractionated catecholamines and metanephrines are all within the reference ranges.

immediately caudal and parallel to the right twelfth rib, and blunt dissection is used to enter the retroperitoneal space. The dissection is carried out laterally in order that a 5-mm trocar may be placed several centimeters to the right of the initial incision. A 12-mm Blunt Tip Trocar with an inflatable balloon (OMST12BT, Covidien, Dublin, Ireland) is placed in the initial incision, the balloon is inflated, and pneumoretroperitoneum is created, with a maximum pressure of 25 mmHg.

Retroperitoneoscopy is performed using a 30° 10-mm endoscope. Further blunt dissection is performed medially in order to place a third 10-mm trocar under direct visual control. The superior pole of the right kidney, which is enlarged and presents multiple cysts, is visualized and mobilized caudally. The right adrenal gland with the lesion is visualized superiorly and adjacent to the inferior vena cava. The gland is dissected circumferentially using bipolar diathermy (LigaSure™, Covidien), placed inside a laparoscopic specimen pouch (Endo Catch™, Covidien), and extracted.

Intraoperatively, the patient presents a sudden decrease in blood pressure when the right adrenal vein is ligated; in addition to intravenous fluids, low-dose norepinephrine is required to maintain mean arterial pressure >60 mmHg for the first several post-operative hours. The patient is discharged from the intensive care unit on the first post-operative day. He no longer requires any antihypertensive therapy.

Pathological examination of the surgical specimen reveals PCC measuring 4.5 cm in its largest dimension.

3. Discussion

Pheochromocytoma is an uncommon tumor of neural crest origin arising from adrenomedullary paraganglial tissue. The incidence of PCC is between 2 and 8 cases per million persons per year and peaks between the third and fifth decades of life. It is the cause of arterial hypertension in 0.1–0.4% of cases, and approximately 5% of patients with incidental adrenal masses have PCC. Among patients with ADPKD, PCC is exceptionally rare: only two other cases have been reported in the medical literature [6,7], though neither had concomitant polycystic liver.

Clinical signs and symptoms of PCC are the result of excess catecholamine production. Between 90 and 100% of patients experience arterial hypertension, which is episodic in half and continuous in the remainder. Other symptoms include headache (70–90%), diaphoresis (60–70%), and palpitations (50–70%). Clinical suspicion for PCC may be raised in patients with typical symptoms, resistant hypertension, a family history of PCC or a familial genetic syndrome that predisposes to PCC, or an incidentally discovered adrenal mass. Given the present patient's history of resistant hypertension, sus-

picion might have been raised for PCC; the clinical scenario was obscured, however, by his underlying diagnosis.

Up to one quarter of all PCC are hereditary and associated with one of six pheochromocytoma syndromes: multiple endocrine neoplasia type 2; neurofibromatosis type 1; von Hippel-Lindau (VHL); and paraganglioma syndromes types 1, 3, and 4 [8,9]. In the present patient with renal cystic disease and PCC, it is important to rule out VHL. Von Hippel-Lindau disease occurs as the result of a mutation in the VHL gene located on chromosome 3p25-26, which encodes pVHL, a protein located in the cytoplasm and endoplasmic reticulum and required for ciliogenesis. Apart from renal cysts, manifestations of VHL include central nervous system hemangioblastoma, renal cell carcinoma, pancreatic cysts and islet cell tumors, endolymphatic sac cysts and tumors, and cystadenomas of the epididymis and broad ligament. Pheochromocytoma develops in 15–20% of cases, with an average age at diagnosis of 16 years [10]. Considering the present patient's age, his family history of ADPKD, and the absence of additional typical neoplastic lesions in both himself and his family, a diagnosis of VHL can effectively be ruled out.

The diagnosis of PCC is based on biochemical tests followed by radiological imaging for tumor localization. Traditionally, biochemical tests were performed to detect elevated levels of catecholamines themselves; however, advances in the ability to detect low levels of catecholamine metabolites together with a better understanding of catecholamine metabolism have led to a shift toward metabolite-based tests [11]. In adrenal medullary chromaffin cells, norepinephrine and epinephrine leak from storage vesicles into the cytoplasm, where immediate monoamine degradation by membrane-bound catechol-O-methyltransferase leads to the formation of normetanephrine and metanephrine, respectively. This process of catecholamine metabolism functions continuously and independently from catecholamine release from the cell, making tests to detect metanephrines particularly advantageous in tumors that release catecholamines in low levels or in a discontinuous fashion [12].

Currently, the most reliable test for the diagnosis of PCC is the measurement of plasma free metanephrines; urine fractionated metanephrines may also be used, though somewhat less reliably [13]. False positive results occur in the context of stress and certain drugs, while false negative results occur in relation to small tumor size and intermittent catecholamine secretion, necessitating serial measurements to detect elevated values. In the present patient with false negative tests, additional measurements would have most certainly come back as elevated; they were not performed, however, as the decision was made to resect his tumor regardless.

Treatment of PCC is surgical and involves tumor removal after alpha blockade. Surgical resection of PCC is a high-risk procedure that should only be performed by experienced surgeons and anesthesiologists. Intraoperative tumor manipulation may result in hypertensive crisis, which is managed with sodium nitroprusside, phentolamine, or urapidil. Once tumor venous outflow has been ligated, hypotension may occur, which is best treated with intravenous fluids, though a limited period of vasoactive therapy may be required.

Adrenalectomy is performed for sporadic PCC, while adrenal-sparing surgery is considered in hereditary cases. Minimally invasive surgery (laparoscopy, retroperitoneoscopy) is the preferred approach. While laparoscopy may be considered in patients with polycystic kidneys only [14], achieving safe and adequate access to the adrenal gland – the right gland, in particular – is very difficult when the liver is enlarged.

This is only the second case reported in the medical literature of adrenalectomy performed in a patient with polycystic kidneys and liver; one other group describes bilateral retroperitoneoscopic adrenalectomy after ineffective transsphenoidal microadenomectomy in a patient with an ACTH-secreting pituitary adenoma [15]. Given that PCC resection is a delicate operation and tumor manipulation must be kept to a minimum, retroperitoneoscopy may be considered the approach of choice in a patient with polycystic kidneys and liver. The enlarged liver is anterior to the surgical field and does not pose an impediment to the operator, while the polycystic kidney may be retracted inferiorly or, alternatively, large cysts may be unroofed and drained.

4. Conclusions

Pheochromocytoma is an exceptionally rare but treatable cause of hypertension among ADPKD patients. Clinical suspicion for PCC may be raised in the presence of typical symptoms or refractory hypertension. Considering that PCC is much more commonly associated with another renal cystic disease, VHL, this alternate diagnosis must be ruled out. Treatment of PCC is surgical and should only be undertaken by endocrine surgeons experienced in minimally invasive surgery. When there is cystic affectation of the liver in addition to the kidneys, a retroperitoneoscopic approach is the approach of choice.

Conflict of interest

None.

Funding

None.

Ethical Approval

This is a case report, not a research study.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Author contribution

AJH – data collection, analysis, and interpretation; writing of the paper.

OV – data collection, analysis, and interpretation; critical review of the manuscript.

MV – data collection, analysis, and interpretation.

JCGV – critical review of the manuscript.

Guarantor

Amelia J. Hessheimer & Oscar Vidal.

Acknowledgments

None.

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