CASE REPORT

Unusual case of pheochromocytoma presenting with diabetic ketoacidosis

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SUMMARY

Pheochromocytoma is a rare catecholamine-secreting tumour that arises from chromaffin cells in the adrenal medulla or extra-adrenal sympathetic ganglia. It classically presents with paroxysmal headaches, hypertension, palpitations and sweating related to catecholamine excess. Diabetes is reported to be present in approximately one-third of patients with pheochromocytoma; however, diabetic ketoacidosis is an extremely rare complication. We present a case of an African-American male aged 30 years who initially presented with diabetic ketoacidosis and hypertensive urgency whose blood pressure and glycaemic control improved remarkably following tumour excision. We will discuss this unusual presentation of pheochromocytoma along with a management approach for such adrenal incidentalomas.

CASE PRESENTATION

A previously healthy African-American male aged 30 years presented to the emergency room with sudden onset of nausea and vomiting associated with palpitations, dyspnoea and chest pain with radiation to the back. He further revealed experiencing the symptoms of paroxysmal episodes of palpitation, dyspnoea and anxiety for the past 1 year, but was unable to seek medical attention due to financial constraints. He denied any family history of diabetes, hypertension, heart disease, cancer or premature death and denied illicit drug use. At presentation, his heart rate was regular at a rate of 109 bpm, blood pressure was 222/132 mm Hg, temperature 99.9°F and was saturating 97% on room air. General examination revealed diaphoresis with dry mucous membranes in the absence of papilloedema. He was overweight and body mass index measured 28 kg/m². Neurological examination was non-focal and examination of other systems, including cardiovascular and respiratory, was otherwise unremarkable.

INVESTIGATIONS

Laboratory evaluation showed white cell count of 8000/ μ L, cardiac enzymes were negative and serum creatinine was 1.1 mg/dL. Plasma sodium was 138 meq/dL; potassium was 3.6 meq/dL; anion gap was 27 and serum bicarbonate was 15 mmol/dL. Blood glucose measured 536 mg/dL, glycosylated haemoglobin (HbA1C) 7.4%, pH 7.19, serum β -hydroxybutyric acid level was 3.3 mmol/dL (normal 0–0.3 mmol/dL), urine analysis was positive for ketones and serum lactate was 1.1 mmol/dL. C peptide level was 2.1 ng/mL (normal range

0.8–3.1 ng/mL). The metabolic derangement on presentation was consistent with diabetic ketoacidosis.

Given his initial presentation with palpitations, chest pain radiating to the back, dyspnoea and hypertensive urgency, computed tomographic angiography (CTA) of the chest was performed to rule out an aortic dissection. CTA of the chest was negative for aortic dissection and pulmonary embolism; however, it revealed a 43×56 mm right suprarenal mass with 52 Hounsfield units enhancement. MRI of the abdomen with and without contrast showed the same mass with homogeneous T1 hypointensity with slight T2 hyperintensity in the centre of the lesion (figure 1).

Diabetic ketoacidosis (DKA) and hypertensive crisis resolved with medical management, and we approached our patient as an adrenal incidentaloma presenting with hypertensive crisis. Antibody to glutamic acid decarboxylase (anti-GAD) was negative. Morning serum cortisol after 1 mg overnight dexamethasone was 3 μ g/dL. Plasma aldosterone concentration was 8 ng/dL (normal 2–9 ng/dL), and plasma aldosterone concentration to plasma renin activity ratio was 12. On further biochemical testing, 24 hour free urinary metanephrines and normetanephrine levels were 1300 μ g (normal 140–785 μ g/24 hours) and 750 μ g (normal 75–375 μ g/24 hours), respectively.

DIFFERENTIAL DIAGNOSIS

The adrenal mass detected through CT imaging in our patient raised two differentials: an incidentaloma versus an adrenal-dependent syndrome. An adrenal incidentaloma is described as a mass lesion

Figure 1 T2-weighted MRI of the abdomen showing right suprarenal mass with areas of cystic changes marked by red circle.

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measuring >1 cm unexpectedly detected on radiological examination.^{1–3} Given the widespread use of abdominal imaging, adrenal incidentalomas are more commonly found, and one study reports incidentalomas to be present in 4.4% of all abdominal CTs.⁴

Discovering an adrenal mass in our patient raised two questions: (1) is it functional? (2) Is it malignant?

Thus, following recovery from diabetic ketoacidosis and with the resolution of hypertensive urgency, we did a thorough endocrine evaluation. Our patient did not have obvious stigmata of Cushing's syndrome; nevertheless, he had newly detected diabetes in the absence of risk factors and family history. Our initial differential included subclinical Cushing's syndrome—a syndrome with autologous cortisol secretion independent of hypothalamic–pituitary control in patients without obvious clinical features of hypercortisolism. An article summarising 13 studies reported that autologous cortisol secretion was detected in 5.3% of patients with adrenal incidentalomas.⁵ Such patients are at increased risk of diabetes, hypertension and osteoporosis due to the increased endogenous cortisol secretion.⁶ We evaluated our patient with an overnight dexamethasone (1 mg) suppression test, which revealed a morning serum cortisol level of 3 µg/dL. A value >5 µg/dL is regarded as a cut-off for adrenocorticotrophic hormone (ACTH)-independent cortisol production; therefore, the possibility of clinical and subclinical hypercortisolism was ruled out.

Plasma aldosterone concentration was 8 ng/dL, and plasma aldosterone concentration to plasma renin activity ratio was 12. He was not on any interfering medications, such as spironolactone and amiloride, when hormonal assays were performed. Plasma aldosterone concentration ≥15 ng/dL and plasma aldosterone concentration to plasma renin activity ratio ≥20 would have suggested primary aldosteronism; therefore, this too was ruled out in our patient.

Given the paroxysmal nature of presenting symptoms, pheochromocytoma was on top of our differential list. We diagnosed pheochromocytoma based on 24 hour urinary metanephrines >400 µg and normetanephrine >900 µg. It has a reported sensitivity and specificity of 91% and 98%, respectively.⁷ The use of

24 hour urinary fractionated metanephrines and plasma metanephrines to diagnose pheochromocytoma is recommended by the 2014 Endocrine Society Clinical Practice Guideline,⁸ and the use of plasma metanephrines is avoided given the high false-positive rates. After diagnosing pheochromocytoma biochemically, we obtained plasma intact parathyroid hormone level and serum calcitonin level as part of the evaluation for multiple endocrine neoplasia syndrome type 2. Both assays were normal, intact parathyroid hormone level was 44 pg/mL (normal 10–60 pg/mL) and serum calcitonin level was 4.8 pg/mL (normal <8.8 pg/mL).

TREATMENT

We treated our patient initially with volume resuscitation and protocol-driven insulin infusion. Additionally, given our already high suspicion for pheochromocytoma, the elevated blood pressure was controlled with intravenous nicardipine drip, while β blockers were not used for the first 48 hours to avoid the unopposed α-adrenergic effect. He had an uneventful recovery from diabetic ketoacidosis and hypertensive urgency, and was discharged on a basal bolus regime with insulin glargine and insulin lispro. Oral prazosin and labetalol were chosen as bridge therapy for blood pressure control until surgery due to its combined α and β blockade. He was referred to a tertiary care centre where right-sided adrenalectomy was performed laparoscopically. On pathological examination of the resected specimen, the tumour was necrotic on gross and microscopic specimens. The residual gland was positive on chromogranin immunohistochemical staining, suggesting neuroendocrine origin of the tumour (figure 2).

OUTCOME AND FOLLOW-UP

Our patient was followed up 2 years after right adrenalectomy and he reported to be symptom-free. His blood pressure and blood glucose control notably improved postoperatively. Subcutaneous insulin was stopped after 1 month postoperatively, and metformin was continued for 8 months. Repeat glycosylated haemoglobin (HBA1C) at 8 and 14 months postsurgery was 6.4 and 5.1, respectively. Currently, he is not on any antihypertensive, insulin or oral hypoglycaemic agent.

Figure 2 Histological sections of resected right suprarenal mass. (A) Extensive area of infarct, with a residual adrenal gland visible in the top left corner; the outlined region corresponds to the higher magnifications pictured in (B–D); H&E stain, ×40 magnification. (B) Histological features are consistent with residual adrenal medulla; H&E stain, ×200 magnification. (C) The residual gland is positive for chromogranin, highlighting its neuroendocrine origin; chromogranin immunohistochemical stain, ×200 magnification. (D) The proliferative index is low (<2%), which is not suggestive of a tumour; Ki67 immunohistochemical stain, ×200 magnification.

DISCUSSION

Pheochromocytoma and paraganglionomas (PPGLs) commonly present with the classic triad of symptoms, which include episodic headaches, sweating and tachycardia, and 50% of patients may have paroxysmal hypertension.⁸ Symptoms appear as paroxysmal spells, which are related to the release of one or more catecholamines.

Pheochromocytoma is diagnosed with biochemical testing for urine and plasma fractionated metanephrines and catecholamines. The 2014 endocrine society guidelines⁸ for PPGLs recommend initial testing with 24 hour urinary fractionated metanephrines and catecholamines or plasma fractionated metanephrine drawn by an indwelling catheter (following 30 min of supine rest). Results may be false positive with the use of α -methyldopa, labetalol or sotalol, and false negatives may result with the use of radiological contrast agents. All positive results require follow-up imaging, for which CT is the initial imaging study of choice. MRI may also be useful in detecting possible metastatic disease or when radiation exposure is a concern, while ¹²³I-metaiodobenzylguanidine scintigraphy is a useful imaging modality for metastatic PPGLs. Given that pheochromocytoma was discovered incidentally on imaging in outpatient, biochemical testing was performed following mass detection.

All patients with functional PPGLs should undergo tumour excision and require extensive preoperative preparation. Preoperative preparation includes α blockade to prevent perioperative hypertension and arrhythmia. Phenoxybenzamine, an irreversible, long-acting, non-specific α -adrenergic blocking agent, is commonly used as the α blockade agent. After achieving adequate α blockade for 2–3 days, β -adrenergic blockade should be performed. β Blockade should not be performed prior to α blockade as the resultant loss of the vasodilatory property of the β -adrenoceptors, and the unopposed α -adrenergic effect may produce a hypertensive crisis. Preoperative preparation also includes high sodium diet and fluid intake to prevent postoperative hypotension.⁸ Minimally invasive adrenalectomy is recommended for most pheochromocytomas.⁸ Open adrenalectomy is reserved for tumour size >6 cm, invasive pheochromocytoma and paraganglionomas.⁸ Partial adrenalectomy may be performed for patients with hereditary pheochromocytoma, with small tumours who have already undergone contralateral complete adrenalectomy to prevent permanent hypocortisolism.⁸ All patients operated for PPGLs should be followed up postoperatively, for at least 10 years, to monitor for possible local or metastatic recurrences and new tumours.⁹ High-risk patients (young patients, patients with a genetic disease, large tumour or a paraganglionoma) should be offered an annual lifetime follow-up.⁹ The current European guideline recommends annual plasma or urine metanephrine or 3-methoxytyramine to screen for local or metastatic recurrence or new tumours.⁹

Diabetes mellitus is one of the metabolic complications of pheochromocytoma. A retrospective study of 191 patients with pheochromocytoma found diabetes to be present in one-third of the patients;¹ however, developing diabetic ketoacidosis is extremely rare. The mechanisms underlying catecholamine-induced impaired carbohydrate metabolism in pheochromocytoma have not been fully investigated.

Catecholamines are stress hormones that mobilise fuel from their storage site to meet the energy requirements, thus playing an important role in carbohydrate metabolism through various mechanisms. One mechanism includes the inhibition of pancreatic insulin release via α -2 receptor effect and stimulation of

liver β -adrenoceptors, resulting in a transient increase of hepatic glucose output via increased gluconeogenesis and glycogenolysis.^{10–11} Another major mechanism involving catecholamines is the inhibition of skeletal muscle glucose uptake.^{12–13}

In a small study (n=5) by Diamanti-Kandarakis *et al*,¹⁴ a slight but statistically significant improvement in glucose homeostasis was seen with the use of adrenergic receptor-blocking agents, and glucose tolerance significantly improved after surgical resection of the tumour. This may be due to the effect of tumour-secreted peptides other than catecholamines.¹⁵ The adrenal medulla secretes an array of hormonal peptides, including vasoactive intestinal peptide (VIP), parathyroid hormone (PTH)-related peptide, enkephalins, endorphins, substance P, interleukin-6, insulin-like growth factor 2, chromogranin A, calcitonin, corticotropin-releasing hormone, atrial natriuretic peptide, neuropeptide Y and catecholamines. Some of these peptides, apart from catecholamines, alter glucose homeostasis as seen with VIP, which is molecularly homologous to glucagon and stimulates lipolysis and glycogenolysis.¹⁴

Along with the mechanisms outlined here, other unidentified mechanisms driven by tumour-producing hormones, impairing carbohydrate metabolism, may exist. Studies have shown improvement in insulin resistance following adrenalectomy in pheochromocytoma.^{10–14} Diabetic ketoacidosis is an extremely rare presentation of pheochromocytoma, and the literature is merely reported to few anecdotal case reports.^{15–19}

Given that our patient had an elevated HbA1c on admission, this suggests that he had elevated blood glucose at least 8–12 weeks prior to presentation. He had normal C peptide level, suggesting normal endogenous insulin secretion. He did not have any other identifiable contributor for diabetes, except chronic catecholamine excess and overweight. Significant improvement in glucose homeostasis after adrenalectomy in our patient suggested that diabetes was probably related to excessive production of catecholamines and other hormonal substances released by the tumour. This is further justified by the fact that our patient did not have any significant weight loss or increase in physical activity in the follow-up period that would contribute to his glycaemic control. We were unable to identify any trigger mechanisms, such as stress, dehydration or infection, which would have led to ketoacidosis. We suspect that DKA resulted from suppressed insulin secretion and reduced peripheral glucose uptake secondary to sustained catecholamine excess. Chronic elevation of catecholamines may have resulted in increased metabolic demand, leading to increased fatty acid metabolism and ketosis.

Learning points

- ▶ Pheochromocytoma produces a significant influence on carbohydrate metabolism.
- ▶ Diabetes mellitus is a metabolic complication, though diabetic ketoacidosis is rare in pheochromocytoma. Further studies are required to understand the mechanisms underlying ketosis.
- ▶ Besides the metabolic complications discussed in this case report, pheochromocytoma is well known to result in potentially lethal cardiovascular complications. The diagnosis of pheochromocytoma may be elusive, but early diagnosis is important, following which all patients should undergo surgical resection of the tumour.⁹

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Contributors YRS conceived the concept, performed the literature review and wrote the entire manuscript. KR contributed in writing the manuscript and carried out proofreading of the manuscript. DP contributed to the literature review. JAL is a preceptor of authors and helped the authors by supervision and guidance.

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