Hypertension Research (2020) 43:473–475
https://doi.org/10.1038/s41440-020-0400-x

CORRESPONDENCE

A case of adrenaline-predominant paraganglioma diagnosed with a state of shock after glucagon injection

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Received: 23 October 2019 / Revised: 3 December 2019 / Accepted: 5 December 2019 / Published online: 22 January 2020

Pheochromocytoma-paraganglioma (PPGL), a catecholamine-secreting tumor, is a rare and curable cause of hypertension, with frequent complications of headache, sweating, palpitation, and hyperhidrosis. PPGL may precipitate hypertensive crisis with several agents, such as contrast medium, glucagon, and metoclopramide. We report a case of a recurrent right retroperitoneal paraganglioma that was diagnosed by hypertensive crisis with glucagon administration for pretreatment for endoscopic examination 17 years after surgery on a right adrenal pheochromocytoma.

A 75-year-old woman who had headache, paroxysmal hypertension, and hyperhidrosis for 3 years was diagnosed with a pheochromocytoma from an endocrine profile and computed tomography (CT) scan, which showed a right adrenal tumor in 1999.

Approximately 10 years after the surgery, she had paroxysmal hypertension again. In 2016, she was scheduled for gastroscopy. Immediately before the gastroscopy, 1 mg of glucagon was administered to inhibit gastrointestinal motility. Within minutes, she went into shock. The gastroscopy was canceled, and she was transferred to the emergency department of our hospital. On initial examination, imaging at the time of admission included an abdominal CT scan. The enhanced CT scan revealed a defined mass of 62 × 50 mm in size at the hilum of the right kidney (Fig. 1). She received a multidisciplinary treatment because of significant hypertension and tachycardia. The blood pressure and the pulse were gradually controlled after intravenous administration of an α-adrenergic blocker, phentolamine. No patient with pheochromocytoma, paraganglioma, or related genetic disease (such as von Hippel-Lindau (*VHL*) disease) was found in her family history. Considering that right total adrenalectomy had been previously performed, these physiological findings were assumed to be the result of catecholamine crisis derived from an extra-adrenal paraganglioma. Adrenal magnetic resonance imaging (MRI) in T2WI images showed a markedly high intensity and heterogeneous mass of 50 × 56 × 79 mm in size at the hilum of the right kidney. The data for urine catecholamine before the right adrenalectomy are listed in Table 1. The hypersecretion of adrenaline as well as noradrenaline, but not dopamine, was confirmed by a 24-h urine test. Impaired glucose tolerance was also observed. The patient underwent ^{123}I-meta-iodobenzylguandine (^{123}I-MIBG)

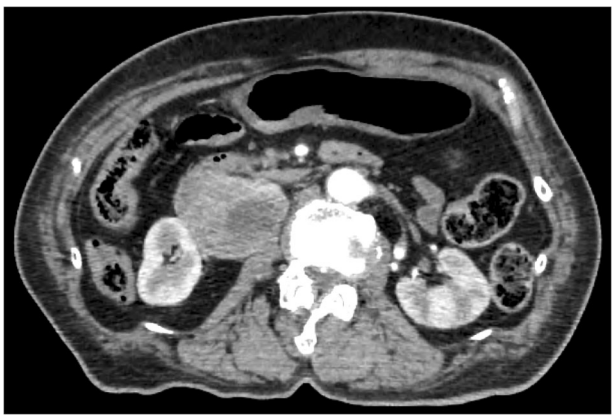

Fig. 1 CT scan showing a defined mass (62 × 50 mm) at the hilum of the right kidney. At the emergency department, as diagnosis of PPGL was not suspected, CT scan was done with contrast enhancement

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Table 1 Perioperative alterations in catecholamine productions

	Preoperative examinations	Postoperative examinations[a]	Reference
Metanephrine (mg/day)	14.0	0.11	(0.05–0.2)
Normetanephrine (mg/day)	1.9	0.28	(0.1–0.28)
Vanillyl mandelic acid (mg/day)	13.5	4.3	(1.4–4.9)
Adrenaline (μg/day)	815.1	9.0	(3.0–41.0)
Noradrenaline (μg/day)	490.0	119.0	(31.0–160.0)
Dopamine (μg/day)	355.5	631.0	(280–1100)
HbA1c (%)	6.5	5.6	(<6.2)

[a]Postoperative examinations (except HbA1c) are from spot urine, corrected with creatinine

scintigraphy, which showed an area of increased uptake above the right kidney, compatible with the result observed in MRI. Based on these findings, the final diagnosis was a right retroperitoneal paraganglioma. An α-blocker, doxazosin, was administered for crisis prevention, and the patient's blood pressure decreased to approximately normal levels before operation. Tumor resection was performed as the primary focus. Pathological findings showed that tumors arranged in cell nests were surrounded by vascular stroma, compatible with paraganglioma. The MIB-1 index was <1%.

After surgery, the endocrine tests, including glucose metabolism results, normalized (Table 1). Genetic testing for mutations related to paraganglioma was performed after obtaining ethics committee approval and the patient's informed consent because mutations in genes encoding subunits of mitochondrial succinate dehydrogenase (*SDH*), rearranged during transfection (*RET*), neurofibromatosis type 1 (*NF-1*), *VHL*, transmembrane protein 127 (*TMEM127*), and myc-associated factor X (*MAX*) are associated with a high rate of malignancy. Germline mutations of the *SDHD* gene (exon 3, c.270G > A), which encodes one of the SDH subunits, the *RET* gene (exon 13, c.2307G > T), and the *TMEM127* gene (exon 4, c.621G > A) were found in this patient, although amino acid substitutions were not observed.

Paragangliomas are rare neuroendocrine tumors arising from the extra-adrenal autonomic paraganglia. They are similar to pheochromocytomas, which are catecholamine-producing tumors derived from chromaffin cells of adrenal medulla [1]. Biochemical tests measuring the levels of catecholamines and their metabolites in plasma or urine as well as imaging techniques, including CT, MRI, and ^{123}I-MIBG scintigraphy, are required to make the diagnosis [2]. Historically, the glucagon-stimulation test was used to confirm the diagnosis of PPGL in patients with mildly elevated plasma or urinary catecholamine, but it is no longer recommended because of its low sensitivity and potential risk of precipitating hypertensive crisis [3, 4]. However, glucagon is used for preparation for upper gastroendoscopy to inhibit gastrointestinal motility as well as for insulin stimulation tests to investigate endogenous insulin secretory capacity in clinical practice [5]. In the patient we describe, glucagon administration caused the tumor to produce excessive amounts of catecholamines, leading to fatal hypertensive crisis and multiorgan dysfunction.

The diagnosis of PPGL relies on biochemical evidence of excess catecholamine production. Catecholamine synthesis depends on three specific enzymes: tyrosine hydroxylase, dopamine-β-hydroxylase, and phenylethanolamine-N-methyltransferase (PNMT). Normetanephrine and vanillyl mandelic acid levels are also assessed. The PNMT gene promoter contains glucocorticoid-responsive elements, and PNMT transcription is increased by cortisol secreted from the adrenal cortex [6]. It is generally believed that paraganglioma produces mainly noradrenaline but not adrenaline because PNMT is absent in paraganglioma. However, some studies showed positive immunohistochemical PNMT staining in these tumors, as PNMT gene transcription is also regulated by transcription factors other than glucocorticoid receptor, compatible with our finding of the elevation of adrenaline despite the diagnosis of an extra-adrenal paraganglioma [7].

One-third of PPGL patients carry a constitutional mutation in a predisposing gene, such as *SDHA*, *SDHAF2, SDHB*, *SDHC*, or *SDHD*, each of which belongs to the *SDH* gene family, or in *RET*, *NF-1*, *VHL*, *TMEM127*, or *MAX* [8, 9]. Three germline mutations (exon 3, c.270G > A; exon 13, c.2307G > T; exon 4, c.621G > A) identified in this patient are known nonfunctional polymorphisms according to websites such as NCBI (http://www.ncbi.nlm.nih.gov/) and Mutation Taster (http://mutationtaster.org/), suggesting that these mutations are not associated with the development of paraganglioma.

In summary, we illustrate this case report for three reasons. First, this was an unexpected case of recurrent PPGL with a state of shock after glucagon administration for preparation for upper gastroendoscopy. Second, the PPGL presented an untypically adrenaline-predominant secretion phenotype. Lastly, although the incidence of PPGL in the general population is quite low, the outcome of inadvertent crises resulting from the use of glucagon in patients with occult paraganglioma may be catastrophic. Therefore, health care professionals who use glucagon, particularly in the presence of a past medical history of PPGL, must consider this unusual and potentially life-threatening complication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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