

Ectopic Cushing's syndrome due to retroperitoneal ACTH-producing paragangliomas

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Abstract

Extra-adrenal pheochromocytomas, or paragangliomas, are rare tumours that derive from extra-adrenal chromaffin cells. Cushing's syndrome (CS) caused by paragangliomas is extremely rare. We report a 53-year-old man with hypertension, diabetes, and symptoms of hypokalemia. Computer tomography (CT) revealed two retroperitoneal masses and bilateral adrenal hyperplasia. Together with the laboratory examinations, ectopic CS caused by multiple paragangliomas was highly suspected. The patient underwent resections of retroperitoneal tumours, left kidney, and left adrenal; post-operative histopathology confirmed two paragangliomas that were both positively stained for adrenocorticotropic hormone (ACTH). He got clinical and biochemical recoveries without any recurrent evidence at the nine-month followup.

Introduction

Cushing's syndrome (CS) is a very rare disease with an incidence of around five per million. CS can be divided into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent disease.¹ Of the ACTH-dependent cases, 80–90 % of cases are due to Cushing's disease, a pituitary adenoma; the others are the ectopic ACTH syndrome (EAS).² Paraganglioma is a kind of tumour that arises from extra-adrenal paraganglia and consists of specialized neural crest-derived cells.³ EAS caused by paraganglioma is extremely uncommon, especially those caused by abdominal paraganglioma. Here, we present a case of multiple retroperitoneal ACTH-secreting paragangliomas — the first one to be reported.

Case report

A 53-year-old man was admitted to the hospital due to a two-month history of polyphagia, polyuria, and polydipsia, and a 10-day history of severe limb numbness, fatigue, generalized weakness, dizziness, and bilateral blurry vision. He suffered from diabetes mellitus and hypertension (180/116 mmHg) for nine months and experienced a 10 kg weight loss. He denied being prescribed any drugs recently, including steroids. During his hospitalization, mental disorders, such as dysphoria, mental excitement, and hallucination occurred several times.

Physical examination manifested typical CS features, including buffalo hump, moon face, and violaceous striae in his abdomen and thighs. Mild edema could be found in his lower extremities and red patches were scattered on his whole body, especially the chest.

No apparent abnormality was found on pituitary contrast-enhanced computed tomography (CT) scan. A severe pulmonary infection of *Streptococcus pneumoniae* was identified by CT and sputum culture. Abdominal contrast-enhanced CT scan revealed a left retroperitoneal mass measuring about 4.8 cm in diameter; extra-adrenal paraganglioma was highly suspected, with a minor lymph node-like mass adjacent to it and bilateral adrenal hyperplasia (Fig. 1). The patient's serum potassium was low (2.0 mmol/L) and routine blood test suggested ongoing infection. He also had hyperglycemia (11.5 mmol/L). Furthermore, the multiple determinations of blood cortisol and ACTH showed they were in high levels and lost their intrinsic diurnal variations. Cortisol failed to be suppressed by large-dose dexamethasone. However, 24-hour urinary catecholamine and blood catecholamine were within normal range. Based upon these findings, the diagnosis of EAS caused by ACTH-producing retroperitoneal

paragangliomas was suspected.

The patient was given phenoxybenzamine hydrochloride for two weeks before surgery to control his high, erratic blood pressure. Then, he underwent resections of retroperitoneal tumours, left kidney, and left adrenal, for which it was difficult to separate the tumours from the left kidney and adrenal gland safely. Postoperative pathological examination was compatible with extra-adrenal paragangliomas, which were both immunostained with ACTH, chromogranin A, Syn, and S100 positively (Fig. 2). The histopathology of the removed adrenal gland showed a normal gland tissue.

After the surgery, the patient's blood pressure, serum glucose, and potassium normalized gradually, with no symptomatic medication. Postoperative levels of plasma ACTH and cortisol switched back to normal in three days. At the nine-month followup, the patient showed complete clinical recovery without any evidence of recurrence.

Discussion

Paragangliomas are rare neuroendocrine tumours that arise from extra-adrenal paraganglia and consist of specialized catecholamine-secreting chromaffin cells. Hormonal and immunohistological studies suggested that our patient suffered from functional paragangliomas with ACTH secretion. EAS cases due to paraganglioma have been reported in only 10 patients (Table 1).⁴⁻¹³ The tumour was located in the mediastinum in four of them, in paranasal sinus in three, and in the retroperitoneum in three patients. Only one patient had malignant tumours located throughout the thorax and abdomen. Our patient is the only one reported to have multifocal ACTH-producing paragangliomas that were benign. The ages of all the patients ranged from 12–70 years and eight of them were female. Ten patients had hypertension

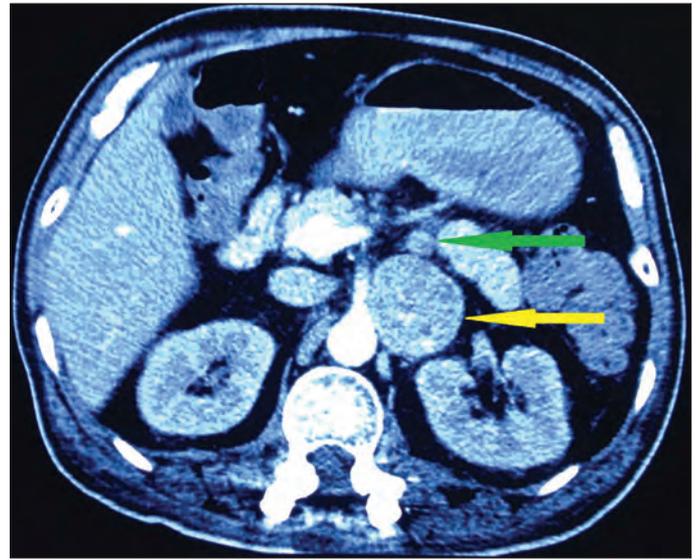


Fig. 1. Contrast-enhanced computed tomography of abdomen showed a larger retroperitoneal mass (yellow arrow), measuring about 4.8cm in diameter, a minor retroperitoneal mass (green arrow) and bilateral adrenal hyperplasia.

and nine presented hyperglycemia. Hypokalemia was seen in seven patients. Excess excretion of catecholamine was reported in only three patients, conforming to the previous study that about 20% of the paragangliomas had been documented with catecholamine hypersecretion.¹⁴

Ectopic ACTH-producing tumours produce ACTH, but they usually can not reduce the secretion of ACTH via classic negative feedback loops successfully. Consequently, the glucocorticoid excess in EAS cases is often more severe than Cushing's disease.⁹ The excessive cortisol secretions may lead to hypertension, hypokalemia, hyperglycemia, and suppression of the immune system. Infections are more apt to occur and difficult to control before the tumour resection.

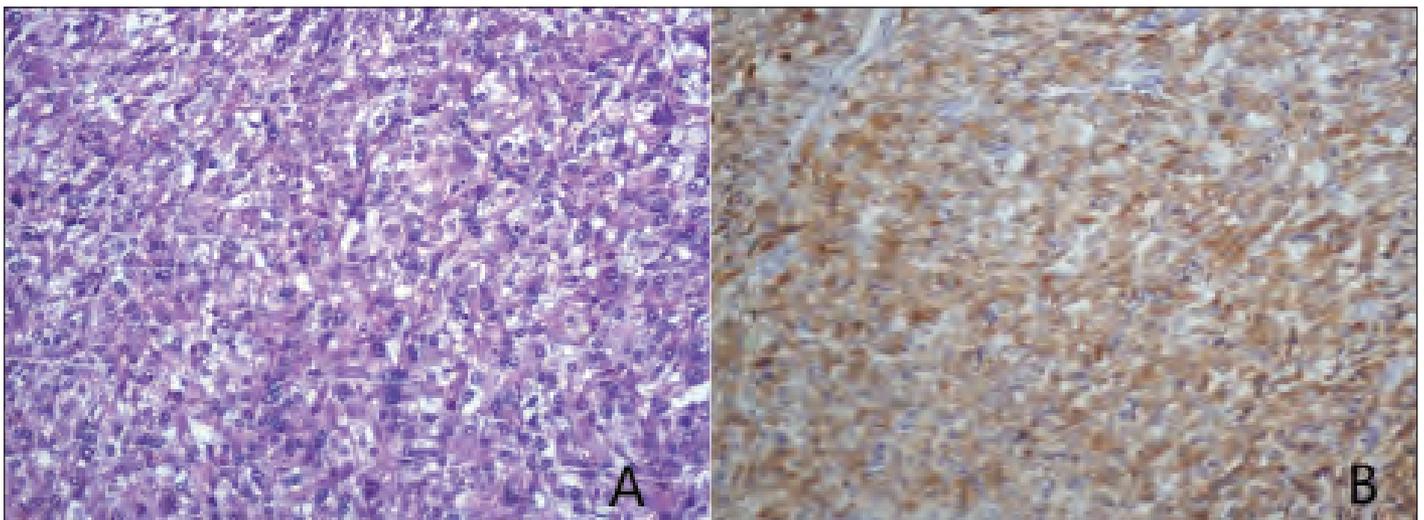


Fig. 2. Pathologic finding of the resected larger mass. **(A)** Hematoxylin-eosin staining; **(B)** Positively staining for adrenocorticotropin (ACTH).

Table 1. Clinical characteristics of patients with ACTH-producing paraganglioma published in the literature

Authors	Age/ gender	Cortisol (ug/dl)	Hypertension	Hyperglycemia	Potassium (mmol/L)	ACTH (pg/ml)	Catecholamine excess	Location	Outcome
Kitahara et al, 1993 ⁴	12/F	107.1	+	+	4.2	13.6	+	Lung; retroperitoneum	Died; malignant paraganglioma Died of mediastinitis with combined pneumonia 22 days after operation
Park et al, 2000 ⁵	51/F	59	+	+	2.5	278	-	Anterior mediastinum	Recovery
Lieberum et al, 2003 ⁶	64/M	High	+	+	Low, ND	95.6	-	Paranasal sinus	Recovery
Dahir et al, 2004 ⁷	39/F	30.6	+	ND	ND	73.0	-	Mediastinum	Recovery
Otsuka et al, 2005 ⁸	55/F	76.5	+	+	1.3	318.4	+	Retroperitoneum	Recovery
Willenberg et al, 2006 ⁹	61/F	176.0	+	+	3.1	1078	+	Retroperitoneum	Died of pulmonary bleeding 6 months after operation
Palau et al, 2006 ¹⁰	55/M	High, ND	ND	ND	ND	High, ND	ND	Mediastinum	Recovery
Fohr et al, 2011 ¹¹	23/M	38	+	+	ND	287	ND	Anterior mediastinum	Recovery
Thomas et al, 2013 ¹²	70/F	74.4	+	+	1.7	273.0	-	Left paranasal sinus	Recovery
Serra et al, 2013 ¹³	68/F	98.7	+	+	1.9	317.0	ND	right nasal sinuses	Recovery
Present case	53/F	89.6	+	+	2.63	432.4	-	Retroperitoneum	Recovery

All are paraganglioma proved by immunohistochemistry. ACTH: adrenocorticotropin; F: female; M: male; ND: not documented.

In the literature, five of 11 patients had infections and one patient died of mediastinitis and pneumonia 22 days after the surgery. In our case, the patient had refractory pneumonia, which led to respiratory failure. His pulmonary infection didn't get better until the resection operation.

CS can show metabolic syndrome manifestations, such as obesity, facial plethora, decreased libido, thin skin, menstrual irregularity, hirsutism, and hypertension. Biochemical diagnostic examinations — including 24-hour urinary free cortisol, low-dose dexamethasone suppression test, and assessment of midnight plasma cortisol or late-night salivary cortisol — should be done when there is clinical suspicion. Once a diagnosis of CS is established, the first step is to measure the concentration of ACTH in plasma, which is almost greater than 3.3pmol/L in ACTH-dependent diseases. The high-dose dexamethasone suppression test and bilateral inferior petrosal sinus sampling can also help the etiologic diagnosis.²

Seeking the source of ACTH in CS can prove extremely challenging. Axial thin-section multislice CT of thorax and abdomen, MRI, or a combination of both procedures has the highest detection rate for EAS.² Positron emission tomography (PET) CT using somatostatin analogue, ⁶⁸Ga-DOTA-

TOC, is also effective in identifying neuroendocrine tumours.¹⁵ If traditional images make it difficult to detect catecholamine-secreting tumours, scintigraphic localization with ¹²³I-metaiodobenzylguanidine is indicated.¹⁶

Surgical resection is the preferred and definitive treatment for ACTH-producing paragangliomas. Nine of the 11 patients recovered after tumour resection. To minimize the surgical complications and prevent intraoperative hypertensive crises, controls of hypercortisolemia and combination use of α - and β -adrenergic blockades are always required preoperatively.^{16,17}

Conclusion

Ectopic ACTH syndrome caused by paraganglioma is remarkably uncommon. Here, we present a case that illustrates that diagnosis, localization, and treatment are indeed a huge challenge.

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This paper has been peer-reviewed.

References

1. Plotz CM, Knowlton AJ, Ragan C. The natural history of Cushing's syndrome. *Am J Med* 1952;13:597-614. [http://dx.doi.org/10.1016/0002-9343\(52\)90027-2](http://dx.doi.org/10.1016/0002-9343(52)90027-2)
2. Newell-Price J, Bertagna X, Grossman AB, et al. Cushing's syndrome. *Lancet* 2006;367:1605-17. [http://dx.doi.org/10.1016/S0140-6736\(06\)68699-6](http://dx.doi.org/10.1016/S0140-6736(06)68699-6)
3. DeLellis RA. *Pathology and Genetics of Tumours of Endocrine Organs, World Health Organization Classification of Tumours*. Lyon: IARC Press, 2004:320.
4. Kitahara M, Mori T, Seki H, et al. Malignant paraganglioma presenting as Cushing syndrome with virilism in childhood. Production of cortisol, androgens, and adrenocorticotrophic hormone by the tumour. *Cancer* 1993;72:3340-5. [http://dx.doi.org/10.1002/1097-0142\(19931201\)72:11<3340::AID-CNCR2820721133>3.0.CO;2-Z](http://dx.doi.org/10.1002/1097-0142(19931201)72:11<3340::AID-CNCR2820721133>3.0.CO;2-Z)
5. Park HK, Park CM, Ko KH, et al. A case of Cushing's syndrome in ACTH-secreting mediastinal paraganglioma. *Korean J Intern Med* 2000;15:142-6. <http://dx.doi.org/10.3904/kjim.2000.15.2.142>
6. Lieberum B, Jaspers C, Munzenmaier R. ACTH-producing paraganglioma of the paranasal sinuses. *HNO* 2003;51:328-31. <http://dx.doi.org/10.1007/s00106-002-0695-8>
7. Dahir KM, Gonzalez A, Revelo MP, et al. Ectopic adrenocorticotrophic hormone hypersecretion due to a primary pulmonary paraganglioma. *Endocr Pract* 2004;10:424-8. <http://dx.doi.org/10.4158/EP.10.5.424>
8. Otsuka F, Miyoshi T, Murakami K, et al. An extra-adrenal abdominal pheochromocytoma causing ectopic ACTH syndrome. *Am J Hypertens* 2005;18:1364-8. <http://dx.doi.org/10.1016/j.amjhyper.2005.01.019>
9. Willenberg HS, Feldkamp J, Lehmann R, et al. A case of catecholamine and glucocorticoid excess syndrome due to a corticotropin-secreting paraganglioma. *Ann N Y Acad Sci* 2006;1073:52-8. <http://dx.doi.org/10.1196/annals.1353.006>
10. Palau MA, Merino MJ, Quezado M. Corticotropin-producing pulmonary gangliocytic paraganglioma associated with Cushing's syndrome. *Hum Pathol* 2006;37:623-6. <http://dx.doi.org/10.1016/j.humpath.2005.12.006>
11. Flohr F, Geddert H. Images in clinical medicine. Ectopic Cushing's syndrome. *N Engl J Med* 2011;365:e46. <http://dx.doi.org/10.1056/NEJMim1010540>
12. Thomas T, Zender S, Terkamp C, et al. Hypercortisolemia due to ectopic adrenocorticotrophic hormone secretion by a nasal paraganglioma: A case report and review of the literature. *BMC Res Notes* 2013;6:331. <http://dx.doi.org/10.1186/1756-0500-6-331>
13. Serra F, Duarte S, Abreu S, et al. Cushing's syndrome due to ectopic ACTH production by a nasal paraganglioma. *Endocrinol Diabetes Metab Case Rep* 2013:130038. <http://dx.doi.org/10.1530/edm-13-0038>
14. Erickson D, Kudva YC, Ebersold M J, et al. Benign paragangliomas: Clinical presentation and treatment outcomes in 236 patients. *J Clin Endocrinol Metab* 2001;86:5210-6. <http://dx.doi.org/10.1210/jcem.86.11.8034>
15. Venkitaraman B, Karunanithi S, Kumar A, et al. 68Ga-Dotatoc PET-Ct in the localization of source of ectopic ACTH in patients with ectopic ACTH-dependent Cushing's syndrome. *Clin Imaging* 2014;38:208-11. <http://dx.doi.org/10.1016/j.clinimag.2013.10.007>
16. Young WF Jr. Paragangliomas: Clinical overview. *Ann N Y Acad Sci* 2006;1073:21-9. <http://dx.doi.org/10.1196/annals.1353.002>
17. Isidori AM, Kaltsas GA, Pozza C, et al. The ectopic adrenocorticotropin syndrome: Clinical features, diagnosis, management, and long-term followup. *J Clin Endocrinol Metab* 2006;91:371-7. <http://dx.doi.org/10.1210/jc.2005-1542>

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