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

Fan Chen, MD;1,2* Xiangyu Wang, MD;3* Yang Wang, MD;4* Hui Meng, MD;1 Xinguo Hou, MD;5 Yaofeng Zhu, MD;1 Wei Gao, MD;6,7 Xuewen Jiang, MD;1 Shouzhen Chen, MD;1 Zhaocun Zhang, MD;1 Zhichuan Zou, MD;1 Tianyi He, MD;6 Yue Yang, MD;1 Kejia Zhu, MD;1 Yong Wang, MD;1 Yaxiao Liu, MD;1 Jianfeng Cui, MD;1 Benkang Shi, MD;1 Gang Yin, MD1

1Department of Urology, Qilu Hospital, Shandong University, Jinan, Shandong, China; 2College of Medicine, University of Kentucky, Lexington, KY, United States; 3Department of Urology, The People’s Hospital of LiaoCheng, LiaoCheng, Shandong, China; 4Department of Urology, Affiliated Hospital of Chengdu University, Chengdu, Sichuan, China; 5Department of Endocrinology, Qilu Hospital, Shandong University, Jinan, Shandong, China; 6Department of Pathology, Qilu Hospital, Shandong University, Jinan, Shandong, China; 7Department of Pathology, Jinan Central Hospital, Shandong University, Jinan, Shandong, China

*Equal contributors

Published online September 13, 2016

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 adrenocorticotropin 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 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.
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 3.3 pmol/L in ACTH-dependent diseases. The high-dose dexamethasone suppression test and bilateral inferior petrosal sinus sampling can also help the etiologic diagnosis.

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. Positron emission tomography (PET) CT using somatostatin analogue, 68Ga-DOTA-TOC, is also effective in identifying neuroendocrine tumours. If traditional images make it difficult to detect catecholamine-secreting tumours, scintigraphic localization with 123I-metaiodobenzylguanidine is indicated.

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.

**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.

**Competing interests:** The authors report no competing personal or financial interests.
References


Correspondence: Dr. Gang Yin, Department of Urology, Qilu Hospital, Shandong University, Jinan, Shandong, China; drgang_yin@126.com