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Case Report

Metachronous bilateral adrenocortical functional adenomas causing adrenocorticotropic hormone-independent Cushing's syndrome

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Abstract: Metachronous bilateral adrenocortical adenomas causing adrenocorticotropic hormone-independent Cushing's syndrome is a surgical case that scarcely occurs. A 38-year-old woman diagnosed with bilateral adrenocortical adenomas one by one in 2006 and 2013. Both of the two adenomas were functional and caused typical Cushingoid symptoms. The patient underwent a laparoscopic adrenolectomy in 2006 and a laparoscopic adrenocortical adenoma resection in 2013. After surgery, the symptoms of Cushing's syndrome withdrew and the woman started steroid replacement therapy as a following treatment.

Keywords: Adrenal, adenomas, ACTH-independent, bilateral, Cushing's syndrome

Introduction

Cushing's syndrome is very rare if we don't count exogenous steroids-induced Cushing's syndrome. An analysis from a national register in Denmark reported an annual incidence of two cases per million people [1]. Those patients were initially suspected Cushing's syndrome for having the symptoms of depression, buffalo hump, amenorrhoea, loss of libido, plethora, hirsutism, muscle weakness, edema, purple striae, hypertension, diabetes, and osteoporosis [2]. Most Cushing's syndrome is caused by pituitary ACTH hypersecretion. Only 10%~20% Cushing's syndrome is related to adrenocortical adenoma which is ACTH-independent [3]. Bilateral adrenocortical adenomas are extremely rare especially when they develop successively. A female patient who developed a right adrenocortical adenoma 7 years after resection of a left adrenocortical adenoma causing Cushing's syndrome is presented as follows.

Case presentation

A 38-year-old woman was referred to the endocrinology department due to the symptoms of edema, a weight gain of 2.5 kg, moon face, increased urine output and muscle weakness in May 2013. Physical examination and laboratory analysis showed that the blood pressure and blood glucose level were within the normal range. No apparent abnormalities were observed in the thyroid hormones, sexual hormones and the electrolytes except that serum potassium stayed in a mild low level (3.32 mmol/L). Indicators of hepatic and renal function were also at normal level. Laboratory studies demonstrated an elevated serum cortisol and declined ACTH levels (**Table 1**). Bone mineral density measurement implied osteopenia. Abdominal CT scan and enhancement detected a 2.84 cm * 1.89 cm nodular lesion in the right adrenal gland (**Figure 1**). The pituitary MR scan and enhancement showed aberrant signals in the right wing of pituitary gland, which indicated the possibility of pituitary micro-adenoma. In view of the above information, the endocrinologists gave a diagnosis of the ACTH-independent Cushing's syndrome with a right adrenal adenoma. The patient was transferred to urology department and performed a laparoscopic adrenal adenoma resection which went smoothly and uneventful. A week later the patient was discharged and began steroids replacement therapy.

Table 1. Serum, urine chemicals and DXM suppression tests' results for 2006 and 2013

Test	2006	2013	nomal
Serum cortisol 8 am	28.9	17.04	6.7-22.6 μg/dl
Serum cortisol 4 pm	27.0	15.33	6.7-22.6 μg/dl
Serum cortisol 12 pm	24.1	14.18	6.7-22.6 μg/dl
24-hours urine 11st	682.3	370.44	21-111 μg/dl
24-hours urine 11st	477.7	300.00	21-111 μg/dl
ACTH 1st	9.10	10.20	12.00-78.00 pg/ml
ACTH 2st	14.20	10.59	12.00-78.00 pg/ml
K	3.11	3.32	3.5-5.1 mmol/L
NMN (HPLC measurement)	99.1		19.0-121.0 pg/ml
MN (HPLC measurement)	45.6		14.0-90.0 pg/ml
2 mg DXM suppression test	negative	negative	
8 mg DXM suppression test	negative	negative	

Negative: indicated not being suppressed.

When asking about the medical history, the endocrinologist surprisingly learned that Cushingoid features had occurred to her since her pregnancy in September 2003. The patient had the symptoms of her face becoming rounder, a weight gain for two years and waist pain for one year in February 2006. Compared to her symptoms in 2013, she got acne on her face and back, hirsutism, easy bruising and irregular menstruation in 2006. The sexual hormones and thyroid hormones were both within the normal range. The serum cortisol was extremely high and the exact figures along with some other tests' results are presented in **Table 1**. The result of abdominal CT scan clearly demonstrated that there is a 2.7 cm * 2.6 cm * 3.2 cm low density mass in the left adrenal gland (**Figure 1**). The pituitary CT scan and enhancement detected nothing abnormal. Thusly, the patient was diagnosed as having left adrenal space-occupying lesion. As a result the patient underwent a left adrenalectomy. The surgery went smoothly and uneventful. Based on the result of the next three months' follow- up, the patient's cushingoid syndrome had retreated and the patient gradually stopped using anti-corticosteroid drugs since then.

Both of the two postoperative gross specimens were golden. Based on the microscopic histological findings in 2006 and 2013, the successively occurred adenomas were composed of lipid-containing large vacuolar clear cells with good differentiation, without any evidence of PPNAD or AIMAH (**Figure 2**). The normal adrenocortical tissues adjacent to adenomas were markedly atrophic.

Discussion

Bilateral adrenocortical adenomas causing Cushing's syndrome is a condition that arises very infrequently. To the best of our knowledge, only one case described a similar condition as this one, which was 24 years ago [5]. That is to say this case is the only second report of bilateral adrenocortical adenomas occurred successively causing Cushing's syndrome. In the present case, given to the fact that the patient had only one adenoma each time she suffered from Cushing's syndrome, the two adenomas must be both functional. However for majority of bilateral adrenocortical adenomas there is only one adenoma in action with the other one non-functional. Under this circumstance, to discriminate the functional adenoma, an AVS might be helpful.

When the cortisol ratio of adrenal vein to peripheral vein from the AVS was ≥6.5, it was defined as a cortisol-secreting adenoma. If the ratio was ≤3.3, it was considered a nonfunctional adenoma [7].

When one of the two adrenal glands is excised, basically majority of its function can be compensated by the other one. However, if both of the adrenal glands are excised totally without any usage of exogenous steroid hormone subsequently, the patient will die soon. The 38-year-old woman experienced a laparoscopic left adrenalectomy in 2006 and a laparoscopic right adrenal adenoma resection in 2013. Most of her glands' tissue was removed and the patient had to depend on the steroids replacement therapy. Since completely physiological replacement therapy is not available at present, long period steroids replacement therapy would cause all kinds of complications. Some recent reports demonstrated the use of bilateral partial adrenalectomy instead of bilateral total adrenalectomy [4, 6]. By sparing part of normal adrenal gland, some patients achieved normalized adrenal function without corticosteroid replacement therapy. Promising as it may

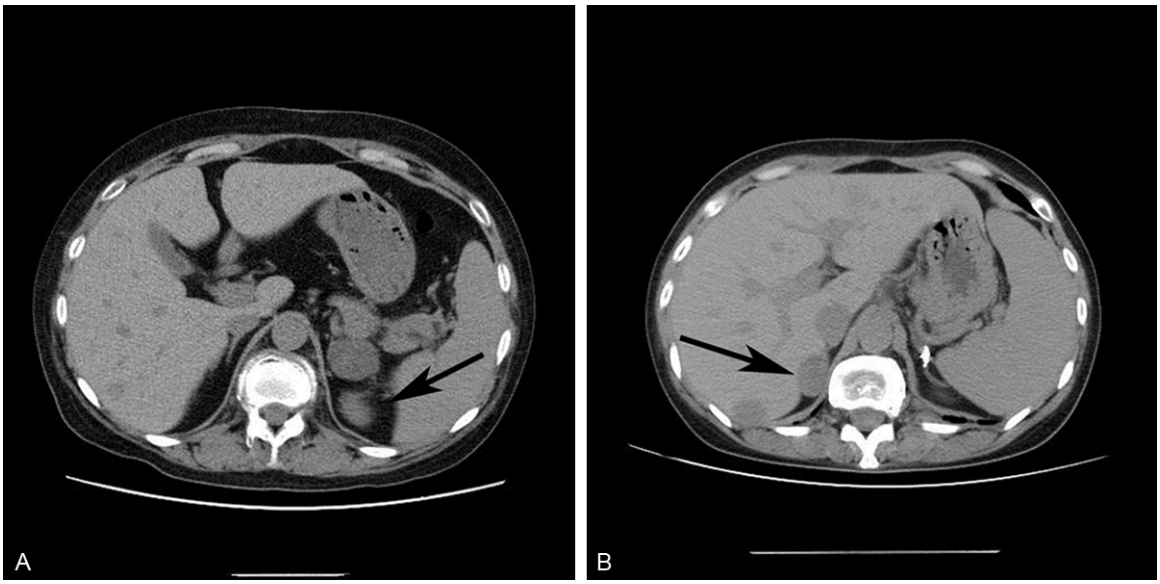

Figure 1. Abdominal CT showing a left adrenal adenoma in 2006 (A) and a right adrenal adenoma in 2013 (B) which are pointed out by black arrows.

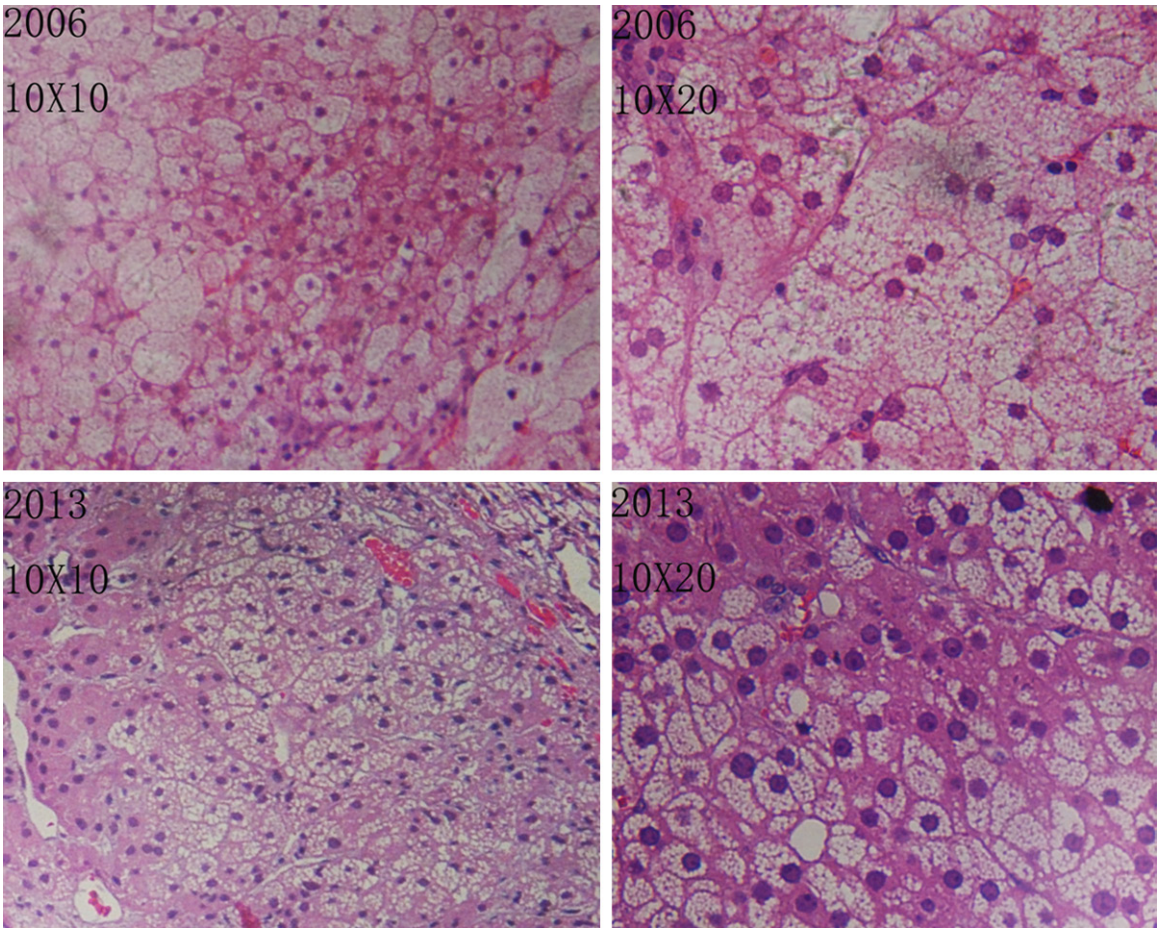

Figure 2. HE-stained histological characteristics of the two adenomas.

be, data demonstrating the superiority of this operational manner is still lacking.

The result of this patient's MR scan and enhancement in 2013 demonstrated a great chance of pituitary micro-adenoma. Because of the low blood serum ACTH level and the condition that the pituitary micro-adenoma appeared secondary to the first adrenalectomy, it's not difficult to conclude that the pituitary micro-adenoma has nothing to do with the generation of adrenocorticoid adenoma. Recent studies have shown that ACTH itself can be locally synthesized and secreted by adrenochromaffin cells and these intraadrenal-produced ACTH can stimulate the cortisol's overproduction and hyperplasia of cortex [8]. Based on this, we made the hypothesis that the present patient's intraadrenal-produced ACTH was overproduced or the patient's adrenal cortex was extremely sensitive to ACTH. Long period of ACTH stimulation to adrenal cortex ultimately caused the generation of the adrenal adenomas. The left and right adrenal cortex might have different intraadrenal-produced ACTH levels and sensitivity to ACTH, which determined the priority of the two adenomas' appearance.

In summary the present report is the second to demonstrate bilateral adrenocortical adenomas that developed in different time. And the two adenomas exerted a great many similarities in functionality, gross appearances and histological characteristics, which suggesting a possible new subtype of cortisol-producing adenoma.

Disclosure of conflict of interest

None.

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