Two different adrenal adenomas causing Cushing's syndrome

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Although nonsecreting suprarenal embryonic remnants are frequently found in the urogenital tract, tumors originating from ectopic adrenal tissue are very rare, as is secretion of aldosterone, cortisol, or androgens from such tissue, and adenomatous transformation resulting in glucocorticoid excess is an extremely rare phenomenon.[1] We present an interesting case of a tumor arising in presumed ectopic adrenal tissue causing Cushing's syndrome in a 52-year-old woman who already had an adrenal tumor, and both were managed by retrolaparoscopy. We observed this dynamic case for over 10 months after operation. In this light, we review the etiology, location, and possible pathophysiology of ectopic or aberrant adrenocortical tumor and search for effective and minimally invasive treatment to help future work.

A 52-year-old woman developed moderate hypertension without any symptoms 10 years ago. She began to markedly gain weight of a central character, and a dorsal-cervical fat pad appeared, followed by muscle weakness and fatigue, easy bruisability, and bluish stretch marks on the abdomen. The medical history was otherwise relevant for osteoporosis and hemiparesis by earlier encephalorrhagia. Physical examination on admission revealed a yellow middle-aged woman with a moon face and marked central obesity. The blood pressure was 177/115 mm Hg. Facial plethora was present, and the abdomen was obese, exhibiting bluish striae. There were scattered ecchymoses and a dorsal-cervical fat pad. The muscle strength of her right side was rather weak. The 8:00AM, 4:00PM, and 12:00PM plasma cortisol levels tested 3 times in one day were higher than the normal and the diurnal variation of cortisol lost. The 24 hour urinary free cortisol was 268.7 ug (normal, 20.26-127.55). An overnight 1-mg dexamethasone suppression test revealed a plasma cortisol level of 603.60 nmol/L, and 24 hour urinary free cortisol was 252.67 ug. After the administration of 2 mg dexamethasone per day for 2 days, the plasma cortisol was 638.40 nmol/L, and the 24 hour urinary free cortisol was 243.55 ug. After the administration of 8 mg dexamethasone for 2 days, plasma cortisol was 684.20 nmol/L, and 24 hour urinary free cortisol was 259.21 ug. Blood chemistries, complete blood count, urinalysis, and the other related hormones including renin, angiotensin, aldosterone, epinephrine, norepinephrine, and total testosterone were within normal range. The abdominal CT scan revealed a 1.5×1.1×1.0 cm mass located near the left adrenal gland and there was no other mass. A repeated abdominal CT scan after 7 months, revealed a 1.5×1.2×1.0 cm mass in the same position and a 3.0×1.5×1.0 cm newly found pararenal lesion adjacent to the hilum almost riding on the renal artery with clear edge. No enlarged lymph node, vascular or organic invasion was obvious (**Figure 1**). In light of the information above, the diagnosis of corticotropin-independent Cushing's syndrome caused by a primary adrenocortical adenoma combined with an ectopic adrenocortical adenoma was highly suspected. Because of the poor condition including high blood pressure, osteoporosis, hemiparesis, and possible infection, she was planned for laparoscopic exploration and removal of the masses for minimally invasive purpose. Complete resection of both the tumors was successfully performed by retroperitoneal-laparoscopy. Both the resection specimens were oval masses with the entire capsule surrounded by a rim of fat. The pathological results demonstrated a 1.5×1.0×1.0 cm round shaped primary adrenocortical adenoma weighing 3.0 g combined with a 3.0×2.0×2.0 cm regular shaped ectopic adrenocortical adenoma weighing 7.0 g. The pathological report was "adrenal cortical adenomas surrounded by adrenal tissue and fat without capsular or vascular invasion. The one adjacent to the left renal hilum is apt to arise from the remnant of the adrenal gland and the fat containing adrenal gland." Further immunohistochemistry (**Table 1**) demonstrated the benign results of both tumors and eliminated the possibility of malignance or metastasis. The postoperative course was uneventful. No complications were observed either intraoperatively or postoperatively. She was discharged home on glucocorticoids 7 days after the operation. Close follow-up persisted after her discharge from hospital. She did well on reducing dosages of glucocorticoids regularly,

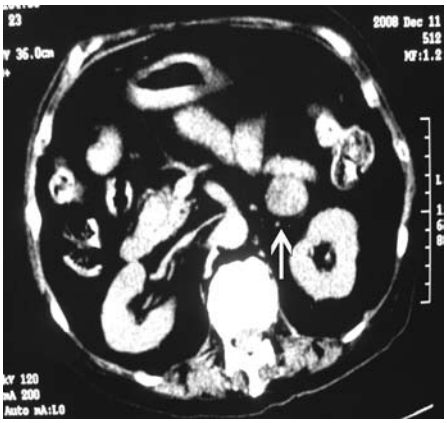

Figure 1 - A CT showing a 3.0×1.5×1.0 cm newly found pararenal tumor adjacent to the hilum with clear edge. No enlarged lymph node, vascular, or organic invasion was obvious.

Table 1 - Immunohistochemistry results.

Variable	Primary adrenocortical adenoma	Ectopic adrenocortical adenoma
Cytokeratin	(-)	(-)
Vimentin	(+)	(+)
Soluble protein-100	(-)	(-)
Synaptophysin	(+)	(+)
Chromogranin A	(-)	(-)
Proliferating cell nuclear antigen	(-)	(-)
p53 protein	(-)	(-)
Epithelial membrane antigen	(-)	(-)
Neuron specific enolase	(-)	(-)

(-) - negative, (+) - positive

and her symptoms gradually improved. The hirsutism, facial plethora, and centripetal obesity resolved, and her blood pressure is almost normal without any drugs. The serum adrenocorticotropic hormone levels remained suppressed (<1.00 ng/L) 6 months after the surgery. A repeated CT scan of the abdomen did not reveal any recurrence, and the right adrenal gland was normal in size. The persistently low early morning cortisol levels requiring 5 mg cortisone supplementation and a 24 hour urinary free cortisol level of 32.2ug/day documented complete cure.

Aberrant or ectopic adrenocortical tissue is more frequently found in children, but is less common in adults.[1] Accessory and heterotopic adrenal tissue can be found along the embryological migration path of the adrenal glands, mainly in the area of the celiac axis. Several authors[1-3] summarized that accessory and heterotopic adrenal tissue was most commonly found in the area of the celiac axis (32%), followed by the broad ligament (23%), adnexa of testes (7.5%), and spermatic cord (3.8-9.3%). Most cases reported in the literature[1-3] were characterized by nonsecreting ectopic adrenal accessory tissues, which meant hormonally inactive. Ectopic tissue may become hormonally functional and/or undergo tumorous transformation. Under rare circumstances, corticosteroid-secreting heterotrophic adrenal tissue may cause Cushing's syndrome. Tumorous transformation of ectopic embryonic rests resulting in adrenal carcinomas or adenomas is an exceedingly uncommon phenomenon. The pathophysiology of adrenocortical tumorigenesis is poorly understood. Some authors[1-3] documented that cytokines (interleukin-5 and 6) and growth factors under normal conditions might play a role in physiological paracrine regulation of the adrenal cortex, which had been implicated in this process. Thus, it is assumed that under the stimulation of corticotropin, ectopic or accessory adrenal cortical tissue can reach the point of producing Cushing's syndrome. When an adrenocortical adenoma is obvious and the diagnosis of Cushing's syndrome is reached, it is also advisable to search for other possible reasons for Cushing's syndrome, even during surgical exploration. Ectopic adrenocortical adenoma cannot be neglected, as it is of vital importance for the curative effect of Cushing's syndrome. Special attention is indispensable when we encounter some new and unexpected situations. For instance, after bilateral adrenalectomy, corticosteroid-secreting heterotrophic adrenal tissue may cause Cushing's syndrome presumably under corticotropin stimulation. It is also highly suspicious when there is recurring Cushing's syndrome after adrenalectomy, without any evidence of local recurrence. Thus, complete evaluation of Cushing's syndrome before operation is necessary. There are cases reporting bilateral adrenal tumors causing Cushing's syndrome, even, one side leading to Cushing's syndrome and the other causing primary aldosteronism,[2] or any other disease.

In our case, by comparing the 2 abdominal sequential CT scans over 6 months before the operation, we obtained meaningful and dynamic information. The later CT showed a new mass near the left renal hilum that rapidly had grown to 3.0×1.5×1.0 cm in 6 months, and was larger than the primary one, and the possibility of malignance was suspected. However, the existing symptoms and signs of Cushing's syndrome combined with the distinct images on the CT disproved the malignant possibility. Consequently, the pathology and immunohistochemistry demonstrated benign results. Surgical excision of the masses is the treatment of choice, and glucocorticoid supplements are also required. The 2 tumors were resected laparoscopically, without any damage to the surrounding structures or rupture of the tumors. During exploration, no tissues, organs, or vessels were involved. Retro laparoscopy surgery enabled a fast recovery in our patient. Additionally, close follow-up should be carried out every 3 months after discharge. Although complete resolution of the symptoms was observed in our case, we believe that periodic biochemical screening for Cushing's syndrome, as well as repeated imaging studies on a yearly basis would represent a prudent approach.[3]

In summary, we described a patient with Cushing's syndrome due to a primary adrenocortical adenoma combined with a rapid growing ectopic adrenocortical adenoma cured by retro laparoscopic surgical excision of the 2 masses. The case represents the unusual circumstance in which the sequential development and adenomatous transformation of ectopic adrenal tissue was documented with serial imaging studies.

It is important to consider ectopic corticosteroid-secreting tumors in the context of corticotropin-independent Cushing's syndrome. Complete resolution of endogenous glucocorticoid excess with minimal invasiveness and best curative effect, as observed here, is seldom achieved. Our case confirms the feasibility of complete retro laparoscopic resection of ectopic adrenal tumor, even if deeply located and with vital vessels referred.[4] Retro laparoscopic excision[5] of ectopic adrenal tumor provides the patient with all the benefits of a minimally invasive surgical procedure.

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References

1. Savaş C, Candir O, Bezir M, Cakmak M. Ectopic adrenocortical nodules along the spermatic cord of children. ***Int Urol Nephrol*** 2001; 32: 681-685.
2. Onoda N, Ishikawa T, Nishio K, Tahara H, Inaba M, Wakasa K, et al. Cushing's syndrome by left adrenocortical adenoma synchronously associated with primary aldosteronism by right adrenocortical adenoma: report of a case. ***Endocr J*** 2009; 56: 495-502.
3. Bi YF, Ye L, Chen YH, Ning G, Sun SY, Jiang L, et al. Characteristics of ectopic adrenocorticotropic hormone syndrome due to thymic carcinoid and analysis of the molecular mechanism. ***Chin Med J*** 2008; 121: 667-670.
4. Vecchio R, Bakhtri M, Shebani A, Minona E, Gelardi V, Barbaros U. Incidental paracaval retroduodenal hemangiolymphangioma in adult patient: report of case removed laparoscopically. ***Surg Laparosc Endosc Percutan Tech*** 2009; 19: e8-e10.
5. Zhang X, Lang B, Ouyang JZ, Fu B, Zhang J, Xu K, et al. Retroperitoneoscopic adrenalectomy without previous control of adrenal vein is feasible and safe for pheochromocytoma. ***Urology*** 2007; 69: 849-853.

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Dutta P, Bhansali A, Bhat MH, Sinha SK. Cytomegalovirus infection in a patient with endogenous Cushing's syndrome. ***Saudi Med J*** 2005; 26: 1137-1138.

Alzahrani AS, Al-Hajjaj A, Al-Watban J, Kanaan I. Severe hypertension secondary to renal artery stenosis and Cushing's syndrome. ***Saudi Med J*** 2005; 26: 668-673.

Al-Mansari AA, Najjar MW, Lingawi SS. Cushing's syndrome. Case illustration and guidelines in management. ***Saudi Med J*** 2004; 25: 1274-1276.