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CLINICAL CASE SEMINAR

Corticotropin-Independent Cushing's Syndrome Caused by an Ectopic Adrenal Adenoma

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ABSTRACT

Although nonsecreting suprarenal embryonic remnants are frequently found in the urogenital tract, adenomatous transformation resulting in glucocorticoid excess is a rare phenomenon. We report a case of a 63-yr-old woman that presented with new-onset hirsutism, facial plethora, hypertension, centripetal obesity, and a proximal myopathy. The 24-h urinary free cortisol excretion rate was elevated, and the serum ACTH level was suppressed. The patient failed an overnight and low dose dexamethasone suppression test and did not respond to CRH stimulation. In light of the undetectable baseline morning ACTH levels and the blunt response to CRH, the diagnosis of corticotropin-independent Cushing's syndrome was made. Imaging studies revealed normal adrenal glands and enlargement of a left pararenal nodule incidentally observed 4 yr before the onset of symptoms. Dramatic resolution of symptoms was observed after surgical removal of the 3.5-cm mass. Pathological exam confirmed adrenocortical adenoma in ectopic adrenal tissue. The case reported here represents the unusual circumstance in which the development of adenomatous transformation of ectopic adrenal tissue has been prospectively observed with imaging studies. It illustrates the importance of considering ectopic corticosteroid-secreting tumors in the context of corticotropin-independent Cushing's syndrome. (*J Clin Endocrinol Metab* **85:** 2903–2906, 2000)

HETEROTOPIC adrenal tissue can be found along the embryological migration path of the adrenal glands, mainly in the area of the celiac axis. The vast majority of the cases reported in the literature are represented by nonsecreting (hormonally inactive) ectopic adrenal accessory tissues. Under rare circumstances, after bilateral adrenalectomy (presumably under corticotropin stimulation), corticosteroid-secreting heterotrophic adrenal tissue may cause Cushing's syndrome. We report the case of a woman with intact adrenal glands who presented with spontaneous corticotropin-independent Cushing's syndrome caused by an ectopic adrenal adenoma. In doing so, we review the pertinent literature and emphasize the importance of considering this rare entity in the differential diagnosis of the glucocorticoid excess syndrome.

Case Report

A 63-yr-old woman developed hirsutism and moderate hypertension 1 yr before presentation. She had gained 9 kg and complained of easy bruisability associated with fatigue and generalized weakness, predominantly involving the proximal musculature of the extremities. She denied headaches or vision loss. Physical examination revealed facial plethora, centripetal obesity, and the presence of darkened terminal hair on the superior lip, side burns, abdomen, and forearms. She had required treatment with short courses of oral corticosteroids for chronic bronchitis, which were discontinued 2 yr before presentation. The past medical history was otherwise relevant for osteopenia and a pelvic fracture resulting from minor trauma. She had a history of spastic colon. A computed tomography (CT) scan of the abdomen obtained 4 yr before the onset of the above symptoms revealed a small nodular structure of undetermined significance in the left renal hilum (Fig. 1). She had hypercholesterolemia, Hashimoto's thyroiditis, and hypothyroidism, which was adequately treated with levothyroxine. Screening tests for Cushing's syndrome included a morning cortisol level of 690 nmol/L (normal, <138) obtained after a 1-mg overnight dexamethasone suppression test. The 24-h urinary free cortisol (determined by high performance liquid chromatography) was 358.8 nmol/day (normal, <138 nmol/day) after a 2-day low dose (2 mg/day) dexamethasone suppression test. An ovine CRH stimulation test (1 mg/kg) revealed an early morning baseline ACTH level of less than 0.22 pmol/L (normal, 1.98–11.44) with a peak ACTH level of 0.484 pmol/L at 90 min. Further laboratory evaluation revealed a serum total testosterone level of 6.90 nmol/L (normal, 0.17–1.74) and a dehydroepiandrosterone level of 0.81 μmol/L (normal, 0.8–7.04). The routine serum biochemical profile was otherwise unremarkable, including liver and kidney function tests. In light of the undetectable baseline morning ACTH levels and the blunt response to CRH, the diag-

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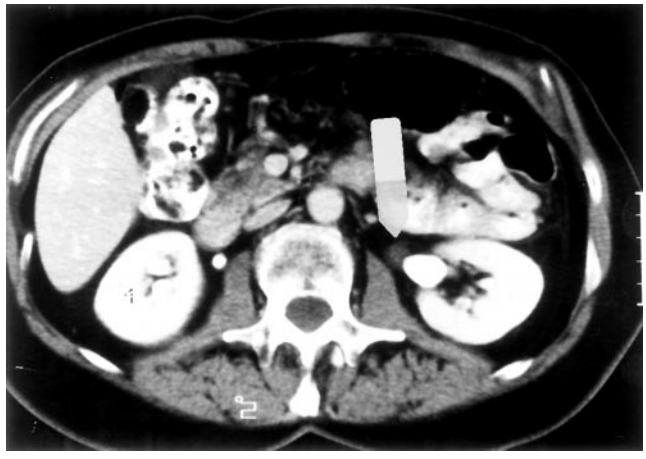

FIG. 1. CT scan of the abdomen performed 4 yr before the onset of symptoms, showing a small nodular lesion near the left renal hilum (*arrow*).

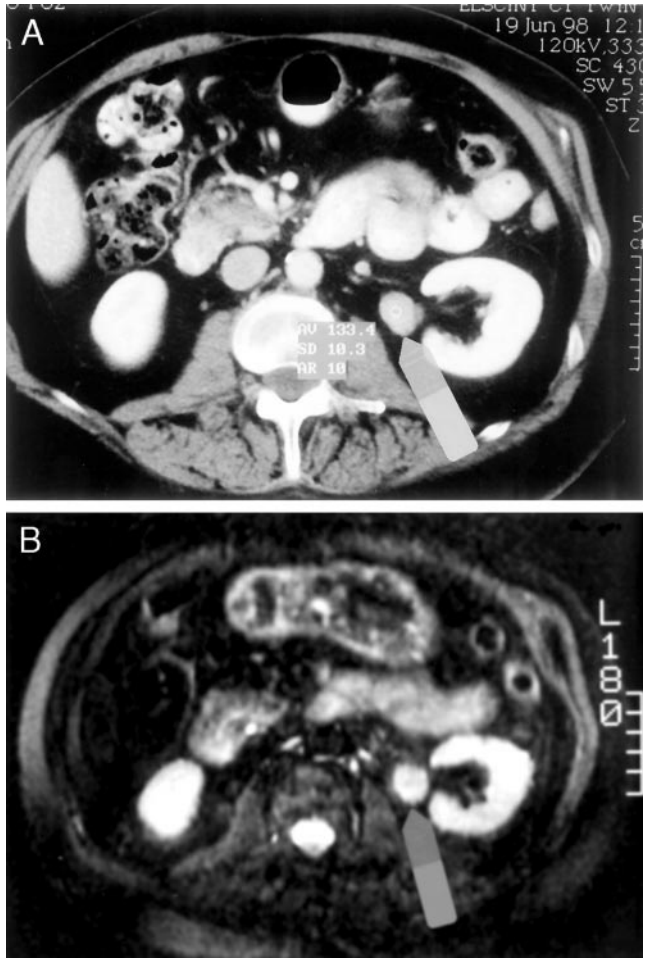

FIG. 2. Recent CT (A) and MRI (B) of the abdomen showing growth in the lesion seen in Fig. 1 (*arrow*). The nodule was approximately 3.5 cm in diameter.

nosis of corticotropin-independent Cushing's syndrome was made. The differential diagnosis included primary micronodular adrenal hyperplasia, corticosteroid abuse, and an ectopic glucocorticoid-secreting adrenal tumor. Both a contrast CT scan and magnetic resonance imaging of the abdomen revealed significant enlargement of the previously noted left pararenal lesion interpreted as an ureteral tumor adjacent to the hilum and measuring approximately 3.5 cm (Fig. 2, A and B). There was no evidence of ureteral obstruction. Both adrenal glands were normal in size. An iodocholestrol scan was negative. Incidentally, a 2-cm speculated left lower lobe lung nodule was observed. Because the patient had been a heavy smoker, a wedge resection of the pulmonary nodule was performed. Histopathology revealed a hypocellular area with dense fibrosis and scarring suggestive of a remote infection or infarct without evidence of malignancy. The possibility of an ectopic pulmonary cortisol- and testosterone-secreting tumor was therefore excluded after surgical removal of the lung nodule. The patient was examined, and the left kidney was mobilized. The mass was intimately associated with the left renal vein, but was easily excised without evidence of invasion or ureteral involvement. A complete resection of the left pararenal mass was performed. The postoperative course was uncomplicated. She was discharged home on glucocorticoids.

The resection specimen consisted of an oval nodule surrounded by a rim of fat. The nodule weighed 7 g and measured 3.5 cm. On cut section, the nodule was unencapsulated but sharply circumscribed, without infiltration of the surrounding fat. The cut surface was solid, homogenous, and dark brown (Fig. 3). By light microscopy, the tumor was composed of broad fields of pink cells arranged in nests and interconnecting trabeculae (Fig. 4, A and B). The cells had uniform round nuclei with prominent nucleoli. Their cytoplasm was abundantly pink and granular and contained pigmented granular material representing lipofuscin. Mitotic activity was very low, and there was no evidence of necrosis or invasive tumor growth. Nonneoplastic adrenal tissue was not apparent. Ultrastructurally, the cells were remarkable for abundant smooth endoplasmic reticulum, large stacks of rough endoplasmic reticulum, and mitochon-

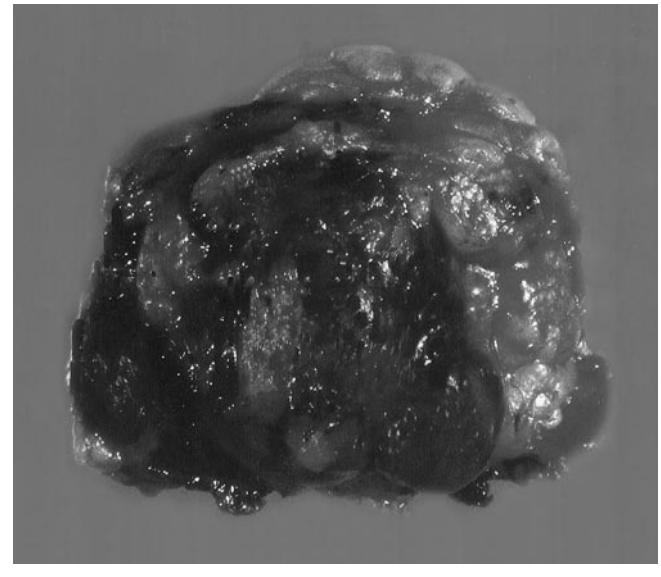

FIG. 3. Gross appearance of ectopic adrenocortical adenoma. Typical of black adenoma associated with Cushing's syndrome, the cut surface is darkly pigmented.

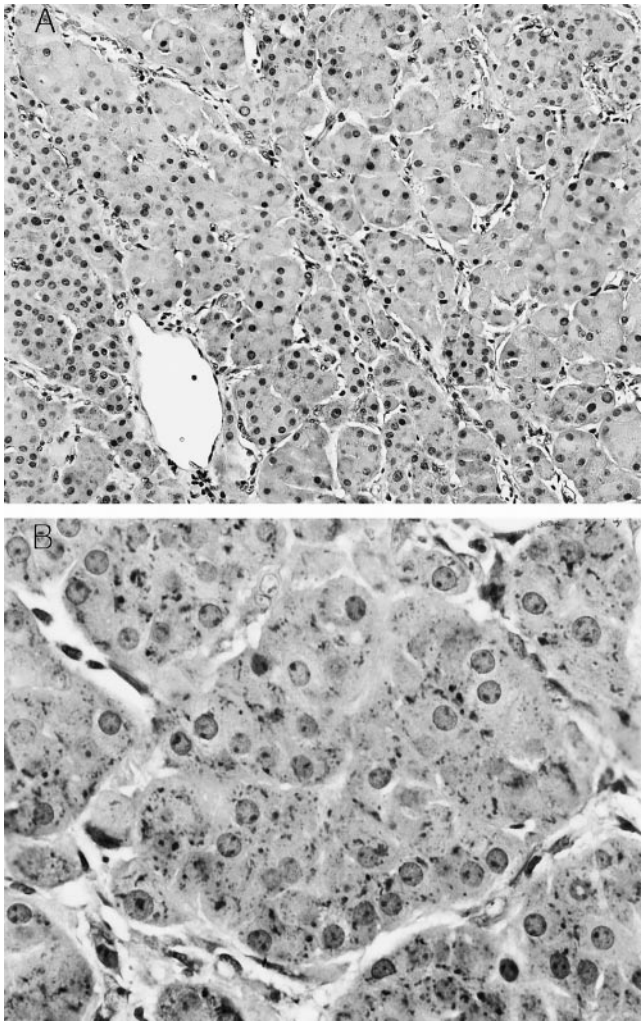

FIG. 4. Histological features of ectopic adrenocortical adenoma. A, The tumor cells are arranged in nests and trabeculae (hematoxylin and eosin stain; magnification, ×160). B, The black coloration seen grossly is due to the presence of abundant intracytoplasmic lipofuscin (Kinyoun's stain; magnification, ×630).

dria containing tubulovesicular cristae. These pathological features are very characteristic of an adrenal cortical adenoma associated with Cushing's syndrome. Due to the intracellular accumulation of lipofuscin, tumors associated with Cushing's syndrome are often darkly pigmented. When this pigmentation is diffuse, as in our case, they are sometimes referred to as "black adenomas" of Cushing's syndrome.

Nine months after surgery, the serum ACTH levels remained suppressed (<0.22 pmol/L). A repeat CT scan of the abdomen failed to reveal recurrence of the tumor. The adrenal glands were normal in size. Complete cure was documented by persistently low early morning cortisol levels requiring hydrocortisone supplementation and by a 24-h urinary free cortisol level of 63.4 nmol/day. The hirsutism, facial plethora, and centripetal obesity have resolved. The total serum testosterone level fell to 0.69 nmol/L. Mild hypertension persists.

Discussion

Aberrant or ectopic adrenocortical tissue is frequently found in children, but is less common in adults (1). The majority of the cases reported in the literature are represented by nonsecreting remnants found along the path of embryonic migration within the urogenital tract (2). Adrenal cortical rests have been found in the testis, spermatic cord (3), broad ligament, kidney, retrocaval space (4), and celiac region. Less frequently, they can be found in the lungs, (5) central nervous system (6), and gastrointestinal tract (colon, pancreas, and gallbladder). A comprehensive review of the literature revealed that accessory and heterotopic adrenal tissue was most commonly found in the area of the celiac axis (32%) followed by the broad ligament (23%), adenexa of testes (7.5%), and spermatic cord (3.8–9.3%). Accessory adrenal tissue was found in the kidney in only 0.1–6% of the cases reviewed, predominantly located in the subcapsular area of the upper pole (7).

Tumoral transformation of ectopic embryonic rests resulting in adrenal carcinomas (8) or adenomas is an exceedingly uncommon phenomenon. Moreover, the pathophysiology of adrenocortical tumorigenesis is poorly understood. Cytokines (interleukin-5 and -6) and growth factors that under normal conditions play a role in physiological paracrine regulation of the adrenal cortex have been implicated in this process. Some tumors may express aberrant or ectopic receptors as well as activating mutations of G protein-coupled receptors resulting in cortisol, aldosterone, and gonadal steroid hypersecretion. (9)

There are few cases in the literature of ectopic adrenocortical neoplasms causing Cushing's syndrome. Ney *et al.* (10) reported the case of a man who continued to have Cushing's syndrome after bilateral adrenalectomy. During surgical exploration, a cortisol-secreting tumor was found in the retrohepatic space. Leibowitz *et al.* (11) recently reported recurrence of Cushing's syndrome in a 33-yr-old-woman with an ectopic adrenocortical adenoma. The patient had undergone a total left adrenalectomy for a left adrenal gland adenoma 4 yr before recurrence.

In this case, we report the development of glucocorticoid excess 4 yr after radiographic documentation of a left pararenal tumor, strongly suggesting that the tumor arose from displaced cortical adrenal tissue. The embryological relationship between the adrenal cortex and the urogenital ridge explains the location of the tumor. Given the paucity of reports describing similar cases, the rate of neoplastic transformation of adrenocortical embryonic remnants is probably very low. In any extent, ectopic adrenal adenomas should be considered in the context of corticotropin-independent Cushing's syndrome when the adrenal glands appear normal or when symptoms recur after adrenalectomy (12, 13). Although complete resolution of the symptoms was observed in our case, we believe that periodic biochemical screening for Cushing's syndrome as well as repeat imaging studies on a yearly basis would represent a prudent approach.

In summary, cortisol-secreting adrenal adenomas arising from ectopic adrenocortical embryonic remnants are rare, and early detection is only possible when a high index of suspicion is present. Furthermore, early detection is partially responsible for the increase in survival rates observed in patients with sustained endogenous hypercortisolism (14).

The case we report represents the unusual circumstance in which the sequential development and adenomatous transformation of ectopic adrenal tissue have been documented with serial imaging studies. Complete resolution of endogenous glucocorticoid excess with minimal therapeutic morbidity, as observed in this case, is seldom achieved. It is therefore important to consider ectopic corticosteroid-secreting tumors in the context of corticotropin-independent Cushing's syndrome.

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