Addison's Disease and Pituitary Enlargement

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Abstract: A 60-year-old man with Addison's disease, primary hypothyroidism and type 2 diabetes mellitus who was treated with stable doses of hydrocortisone and fludrocortisone developed increasing skin pigmentation and a bitemporal hemianopia. The plasma ACTH level was 14,464 pg/mL, and an invasive pituitary macroadenoma with suprasellar extension was found on magnetic resonance imaging leading to transnasal-transsphenoidal adenomectomy. The tumor demonstrated features of an eosinophilic adenoma and stained uniformly for ACTH. Residual tumor was treated with stereotactic radiotherapy. This case and the 13 cases published previously indicate that primary adrenal failure may predispose to corticotroph hyperplasia, and in some patients to the development of an invasive corticotroph adenoma. The ACTH level should be measured, and a pituitary magnetic resonance imaging is indicated when skin pigmentation increases in a patient with primary adrenal failure who is receiving customary treatment with glucocorticoids and mineralocorticoids.

Key Indexing Terms: Corticotroph; Addison's disease; ACTH; Pituitary tumor. **[Am J Med Sci 2015;349(6):526–529.]**

Long-standing deficiency of thyroxine in either children or adults can result in enlargement of the pituitary that is most often due to thyrotroph hyperplasia because it regresses with thyroxin replacement.[1,2] Although hyperplasia of anterior pituitary cells also follows gonadectomy or adrenalectomy in experimental animals[3] and has been reported in patients with long-standing untreated primary hypogonadism[4] or adrenal failure,[5] clinically evident pituitary enlargement in patients with gonadal[6] or adrenal failure is thought to occur rarely. Accordingly, we report the occurrence of a corticotroph macroadenoma in a man with Addison's disease who developed progressive hyperpigmentation while receiving conventional glucocorticoid and mineralocorticoid treatment, and review several similar cases that have been published previously.

CASE REPORT

A 60-year-old man was found to have a pituitary tumor. At age 29, he lost 50 pounds in weight over several months and developed fatigue, vomiting and shortness of breath. He was hospitalized and diagnosed with Addison's disease and

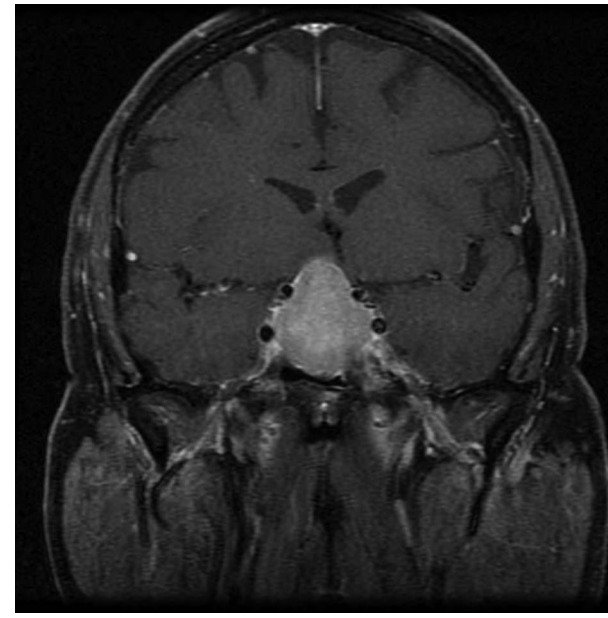

FIGURE 1. Postenhanced coronal MRI image of a large sellar/suprasellar homogenously enhancing mass. The mass extends superiorly and is severely compressing the optic chiasm and also extends bilaterally into the cavernous sinuses.

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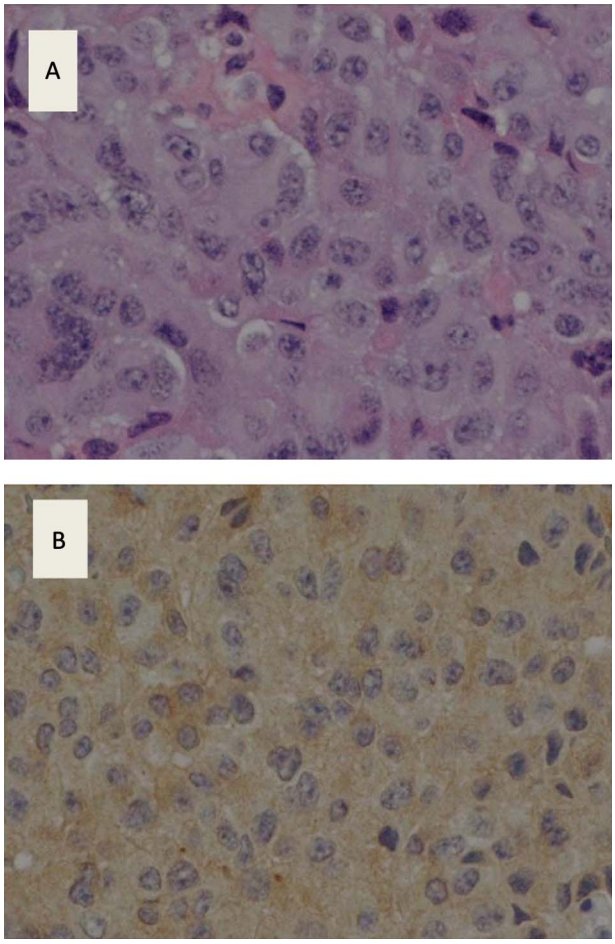

FIGURE 2. (A) H&E stain of the pituitary adenoma (400×) showing a monomorphic population of slightly eosinophilic tumor cells with fine cytoplasmic granularity. (B) Immunohistochemical staining for ACTH showing diffuse cytoplasmic positive staining (400×).

was treated with hydrocortisone 20 mg in the morning and 10 mg in the evening together with 0.1 mg of fludrocortisone daily. At age 48, he developed primary hypothyroidism and was treated with 0.1 mg of thyroxin, and at age 55, he was found to have type 2 diabetes, which was initially treated with oral hypoglycemic drugs but then with a combination of insulin glargine at bedtime and insulin aspart before meals, and dyslipidemia. Soon thereafter, he noticed increasing skin pigmentation, and ultimately his skin became entirely dark brown. He developed cataracts, and blurry vision may have been partly responsible for a motor vehicle accident after which a bitemporal hemianopia was discovered. Magnetic resonance imaging (MRI) (Figure 1) revealed a large sellar mass (3.0 × 2.6 × 3.7 cm) with suprasellar extension and compression of the optic chiasm. The plasma adrenocorticotropic hormone (ACTH) level was 14,464 pg/mL (normal, 7–50), PRL was 36.2 ng/mL (normal, < 17.9) and insulin-like growth factor 1 was 119 ng/mL (normal, 87–225). He underwent transnasal-transsphenoidal adenomectomy. Histological evaluation revealed an eosinophilic adenoma (Figure 2A) that stained positively for ACTH (Figure 2B). Some staining for PRL and growth hormone was also seen (not shown) suggesting a plurihormonal pituitary tumor, and immunostaining for Ki-67 to assess proliferative potential revealed <3% positive cells. Postoperatively, the ACTH level declined, but remained elevated at a level of 885 pg/mL, and residual tumor was seen on an MRI. The patient was treated by stereotactic radiotherapy with 4,000 cGy in 10 fractions. The skin pigmentation began to fade and the ACTH level declined to 245 pg/mL 12 months later.

DISCUSSION

Enlargement of the pituitary, together with increasing skin pigmentation and a progressive rise in the level of ACTH in plasma has historically occurred in 8% to 43% of adults and 25% to 66% of children after bilateral adrenalectomy as treatment for Cushing's disease.[7] This constellation of symptoms and signs, known as Nelson's syndrome,[8] has become uncommon because bilateral adrenalectomy is usually reserved for patients with Cushing's disease who are not cured by pituitary surgery, or whose disease recurs and whose clinical condition mandates rapid and effective reduction in hypercortisolemia.[9]

Our patient and 13 others reported previously (Table 1) reveal that similar symptoms and signs may develop in patients with primary adrenal failure. Adrenal insufficiency in these 14 patients has had various etiologies, including tuberculosis, autoimmune adrenalitis and familial glucocorticoid deficiency. Most patients have been middle-aged adults and were female. Some patients were inadequately treated for adrenal failure by current standards or were noncompliant with their medications. In those patients, the level of ACTH declined and hyperpigmentation improved with increased glucocorticoid and mineralocorticoid replacement suggesting corticotroph hyperplasia.

Over the course of several years, our patient's level of ACTH rose to 14,464 pg/mL, a value that was more than 200-fold above the upper limit of the reference range. In 1 study[10] of 13 patients with Addison's disease who were treated with 25 mg cortisone acetate orally at 7 AM and 12.5 mg at 4 PM, ACTH levels were highest before the morning dose and ranged from 45 to 2,249 pg/mL whereas nadir levels occurred in the early evening (median, 19 pg/mL; range, 2–434 pg/mL). Thus, although increased ACTH secretion is a characteristic of primary adrenal failure, but with substantial between-individual variation despite similar treatment, the ACTH level in our patient far exceeded the values seen in treated patients with Addison's disease. Moreover, the hyperpigmentation of untreated Addison's disease usually fades after weeks-months of adequate therapy as ACTH levels decline.

Many of the case reports that are listed in Table 1 were published before the era of computed tomography and MRI scans, and therefore, little is known about their detailed radiographic findings. However, tumors seemed to range from microadenomas to invasive macroadenomas. Pituitary tumors have been removed surgically in 4 cases[11,12] including ours. Three patients had visual field defects, and 1 patient had surgery because of increasing ACTH levels and pigmentation. Tumors were of the chromophobe or eosinophilic type and were immunoreactive for ACTH. Pituitary enlargement with Addison's disease may also represent pituitary hyperplasia[13] as occurs in patients with severe untreated primary hypothyroidism[2] or during normal pregnancy.[14] A pathological study of the pituitary in 18 patients who died of untreated Addison's disease revealed diffuse and nodular hyperplasia of corticotroph cells.[5] In 1 clinical case,[15] a pituitary microadenoma in a woman with hypothyroidism due to Hashimoto's thyroiditis and mild adrenal failure disappeared after treatment with thyroxin and hydrocortisone.