Relapsing, remitting hypercortisolism in Cushing's disease due to intratumoral hemorrhages in pituitary microadenoma

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ABSTRACT

We report two patients with Cushing's disease (CD) from adrenocorticotropic hormone-secreting microadenomas in whom intralesional hemorrhage caused an episodic, remitting and relapsing pattern of hypercortisolism. To our knowledge this is the first report of patients in whom hemorrhage within a microadenoma caused cyclic CD. Both patients were treated successfully with transsphenoidal surgery.

1. Introduction

Cyclic, episodic, or variable secretion of excess cortisol has been recognized in Cushing's syndrome (CS) for half a century.[1,2] A summary of 65 cases of cyclic CS (CCS) conducted by Meinardi et al.[3] suggested that the disorder was uncommon; however, Alexandraki et al. have reported more recently that up to 15% of patients with CS exhibit *bona fide* variability or cyclic periodicity in either clinical or biochemical features of the disease.[4] Most cases of episodic CS have been identified in patients with Cushing's disease (CD).[1–6]

Although the incidence of CCS may be more common than previously considered, symptomatic hemorrhage or apoplexy in pituitary microadenomas is rarely reported. To our knowledge, only four patients have been described in the English literature; of these, two had prolactin-secreting tumors while two tumors were non-functional.[7,8] No patient exhibited other pituitary hormone abnormalities. Only one patient was treated with surgery.[7,8]

We describe two patients with CD identified from a prospectively maintained pituitary database who exhibited relapsing, remitting hypercortisolism following intra-tumoral hemorrhage. Both patients presented with episodic CS and were treated successfully with transsphenoidal surgery (TSS).

2. Methods and patients

2.1. Methods

The patients described in this report were identified from a prospectively maintained pituitary database approved by the Cleveland Clinic Institutional Review Board (IRB). This study was approved by the same IRB. Biochemical evaluation of CS primarily consisted of 24-hour urinary free cortisol (UFC), late night salivary cortisol (LSC) and 2-day low dose dexamethasone suppression test (DST; Quest Diagnostics; San Juan Capistrano, CA, USA).[9–12] All UFC collections had appropriate urine creatinine levels suggestive of adequate collection. With respect to peri-operative testing, the patients were followed closely after surgery (while off steroid replacement), with serum cortisol levels obtained at 6-hourly intervals until the morning of the postoperative day 3. Hydrocortisone replacement was started on the third day after surgery after additional testing in which we used a modification of the protocol by Chen et al. We administered 1 mg of dexamethasone orally between 22:00 and 23:00 on the night of post-operative day 2, and the 07:00 serum cortisol level was measured on the morning of post-operative day 3.[13] The patients were discharged later that morning on 30 mg to 40 mg hydrocortisone per day, which was gradually tapered based on the periodic evaluation of the hypothalamic–pituitary–adrenal (HPA) axis.[10,14] If the patient developed signs and symptoms of hypocortisolism prior to this, cortisol concentrations were tested at random and patients were started on glucocorticoid replacement.

2.2. Illustrative patients

2.2.1. Patient 1

A 27-year-old woman presented with a 1-year history of hirsuitism, weight gain of 20 kg, fatigue, decreased libido, secondary amenorrhea, easy bruising, weakness, alopecia, and worsening of pre-existing gastroesophageal reflux. Medical history was otherwise insignificant. Physical examination revealed an obese woman (body mass index 35.0) with abdominal striae, a moon face, acne, hirsuitism, muscle atrophy, and supraclavicular fat pads. A UFC of 871 μg/day (normal <50 μg/day) and plasma adrenocorticotropic hormone (ACTH) of 90 pg/mL (normal 8–42 pg/mL) were obtained at a local hospital. Morning serum cortisol concentrations, before and after administration of 8 mg dexamethasone, were 36.5 μg/dL and 22.1 μg/dL. The patient demonstrated a >100% increase in cortisol and ACTH levels after a corticotropin-releasing hormone (CRH) stimulation test. MRI showed a microadenoma measuring 5 mm × 5 mm × 7 mm (Fig. 1). Two months later, the patient was referred to our center for further evaluation.

At the time of our initial evaluation, the UFC was normal (μg/day), as were two consecutive salivary cortisol concentration tests (22 ng/dL and 36 ng/dL), which suggested cyclic CS.[3,4,6] The UFC remained in the low-to-normal range at further interval follow-up at 1 month (4.1 μg/day) and 3 months (13.9 μg/day) later. In addition,

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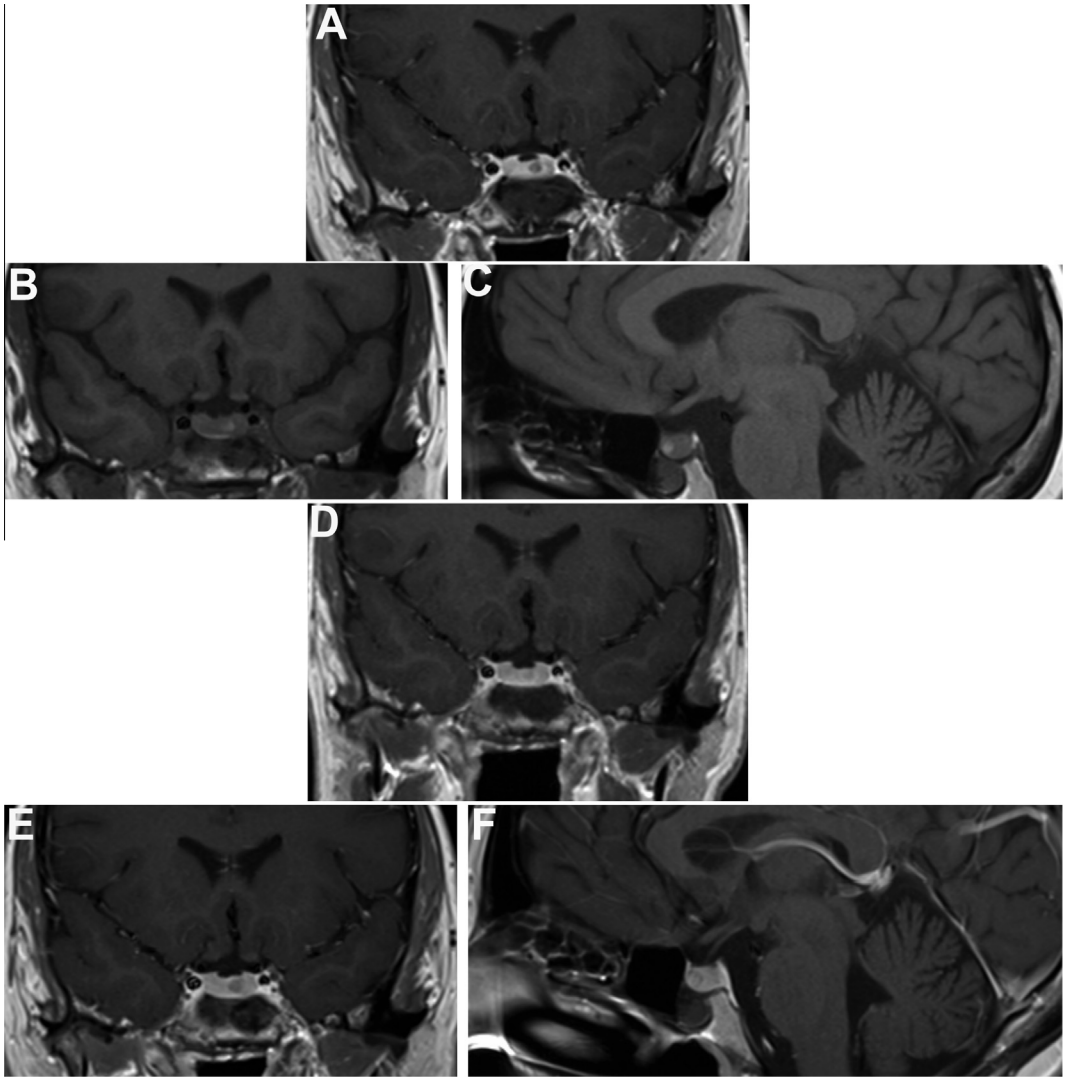

Fig. 1. Patient 1. (A) Coronal, T1-weighted, contrast-enhanced MRI at presentation showing the pituitary adenoma. (B) Coronal and (C) sagittal T1-weighted, non-enhanced MRI during the relapse of symptoms, roughly 1 year after the first scan, showing hyperintensity within the previous adenoma, consistent with hemorrhage. (D) Coronal, T1-weighted, contrast-enhanced MRI about 1 year after (B) and (C), after the delivery of her child, while the patient had a normal urinary-free cortisol (29.4 μg/days), showing a less-dense and smaller microadenoma. (E) Coronal and (F) sagittal T1-weighted, contrast-enhanced MRI immediately before surgery showing tumor growth.

the patient spontaneously began to lose weight with exercise, and her early fatigue, easy bruising, weakness, abdominal striae, and hirsuitism receded. The patient resumed normal menses. With resolution of her symptoms and normal biochemistry, the patient elected management consisting of observation and close follow-up only. One year later, while in clinical remission, MRI revealed hemorrhage within the adenoma (Fig. 1). At 18 months, a repeat UFC was normal (15 μg/day). The patient subsequently became pregnant and delivered a healthy, full-term boy. The patient returned to her pre-pregnancy weight within approximately 3 months of delivery.

For the next 12 months, the patient continued with normal menses and produced breast milk without difficulty. A UFC at the end of this 12-month period was 29.4 μg/day. MRI showed a decrease in the size of the pituitary microadenoma (Fig. 1). Six months later, approximately 3 years after her initial presentation, the patient again noted the insidious development of fatigue, hirsuitism, acne, headaches, worsening gastro-esophageal reflux, alopecia, depressed libido, dysmenorrhea, weight gain, and an increase in abdominal girth despite continued exercise. Repeat biochemical testing suggested recurrent hypercortisolism: Salivary cortisol levels were elevated (115 and 227 ng/dL), and UFC was 116 μg/day. Morning cortisol and ACTH levels following a 2-day, low dose DST were 23.6 μg/dL and 94 pg/mL, respectively. The patient declined inferior petrosal sinus sampling. MRI at surgery (see below) showed a recurrent tumor (Fig. 1).

A TSS with sellar exploration and selective adenomectomy was performed. A pseudoencapsulated, 6 mm × 5 mm, ACTH-staining adenoma, paramedian to the left of midline, was removed. Post-operative hypocortisolemia was induced by surgical resection of the adenoma, with a post-operative day 2 serum cortisol concentration at 23:00 of 1.0 μg/dL, and an ACTH of 7 pg/dL. Eight hours after administration of dexamethasone, the post-operative day 3, cortisol level at 07:00 was undetectable, and the ACTH was 6 pg/dL. Physiologic hydrocortisone replacement was initiated, following the protocol described above. The patient remained in remission 25 months after surgery, with a cumulative 25 kg weight loss, reduction or elimination of the stigmata of CD, and resumption of normal menses. Hydrocortisone replacement therapy was discontinued at approximately 9 months post-operatively.