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Case Report

Case Report

Case of Cyclic Cushing's Disease with Improvement of Psoriatic Skin Lesions During a Period of Hypercortisolemia

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Abstract

Cushing's syndrome (CS) is known to involve periodic cortisol secretion in some patients. It has also been demonstrated that resolution of cortisol hypersecretion in CS may cause autoimmune-related disease to become apparent. At least 3 cases of psoriasis that became apparent after resolution of hypercortisolism in CS have been reported. We describe a 45-year-old man with cyclic Cushing's disease in whom psoriasis vulgaris, an autoimmune-related disease, was ameliorated during a period of hypercortisolemia. He had complained of intermittent sensations of "whole-body swelling" and improvement of his psoriatic skin lesions, which lasted 2 to 3 weeks at 2- to 3-month intervals over several years. During a 2-week hospitalization for endocrine investigations, an episode of hypercortisolemia appeared unexpectedly. During this time period, the peak serum cortisol level reached 75.7 μg/mL (adrenocorticotropic hormone level, 585 pg/mL) and 24-hour urinary free cortisol reached 10 500 μg/day. A diagnosis of Cushing's disease was made based on a markedly elevated urinary free cortisol level, an adequate increase in adrenocorticotropic hormone level in response to corticotropin-releasing hormone stimulation, and the presence of a giant pituitary tumor with a maximum diameter of approximately 4 cm. Interestingly, during this time period, there was a marked improvement in the psoriatic skin lesions and whole-body swelling sensations.

Key Words: cyclic Cushing's disease, psoriasis vulgaris, autoimmune disease

Some patients with Cushing's syndrome (CS) exhibit cyclic hypersecretion of cortisol with intermittent periods of normal secretion [1]. The episodes of hypercortisolism can occur in intercyclic phases ranging from days to months [2]. It has also been demonstrated that some patients with CS develop an autoimmune

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disease, such as autoimmune thyroid disease, rheumatic disease, and psoriasis, after resolution of the hypercortisolism [3]. At least 3 cases of psoriasis that became apparent after resolution of hypercortisolism in CS have been reported [3–5].

Here, we describe for the first time a dramatic improvement in psoriasis vulgaris, an autoimmune-related condition, during a short period of hypercortisolemia in a patient with cyclic pituitary CS.

Case Presentation

A 45-year-old man presented to a local neurology clinic with positional vertigo and nausea. A computed tomography (CT) scan of the head incidentally showed a large pituitary tumor. Neurological examination revealed right-sided temporal hemianopsia, and magnetic resonance imaging showed a large pituitary tumor that extended superiorly in the suprasellar cistern and elevated the optic chiasm (Fig. 1). He did not report any headache. Almost all of the mass showed contrast enhancement with a partial low-intensity area after injection of gadolinium on T1-weighted images (Fig. 1). The tumor diameter was 24 × 20 × 39 mm. At that time, a random serum cortisol level and a plasma adrenocorticotropic hormone (ACTH) level obtained at 3:00 PM were 29.4 μg/dL and 154 pg/mL, respectively. Although the laboratory tests might have been performed under stressful conditions from the patient's point of view, the results indicated an ACTH-producing/secreting pituitary tumor.

The patient was subsequently referred to us for further endocrine evaluation 6 weeks after the previous doctor's visit. According to his medical history, he was visiting a local dermatologist who had prescribed topical glucocorticoids and methotrexate for psoriasis vulgaris and psoriatic arthritis. He had attended annual medical check-ups and there was no other significant medical history such as diabetes mellitus or hypertension. Interestingly, he reported intermittent sensations of "whole-body swelling" that had lasted for 2 to 3 weeks at 2- to 3-month intervals over several years. His story seemed to be reliable, and he also mentioned that his psoriatic skin lesions and arthralgia showed transient but dramatic improvement during the periods of the whole-body swelling sensation even when the medications prescribed by the dermatologist were discontinued.

In addition to the already known psoriatic skin lesions and arthritis, physical examination revealed central obesity with supraclavicular and dorsocervical fat pads and a round face without red cheeks. There was no skin thinning, red-purple striae on the abdomen, or ecchymoses. There was no proximal muscle weakness.

Several endocrine investigations were performed during the patient's hospital stay. On the 1st day of admission, the serum cortisol level measured at 11:00 PM was 5.4 μg/dL. At 8:00 AM on day 2 after admission, the serum cortisol

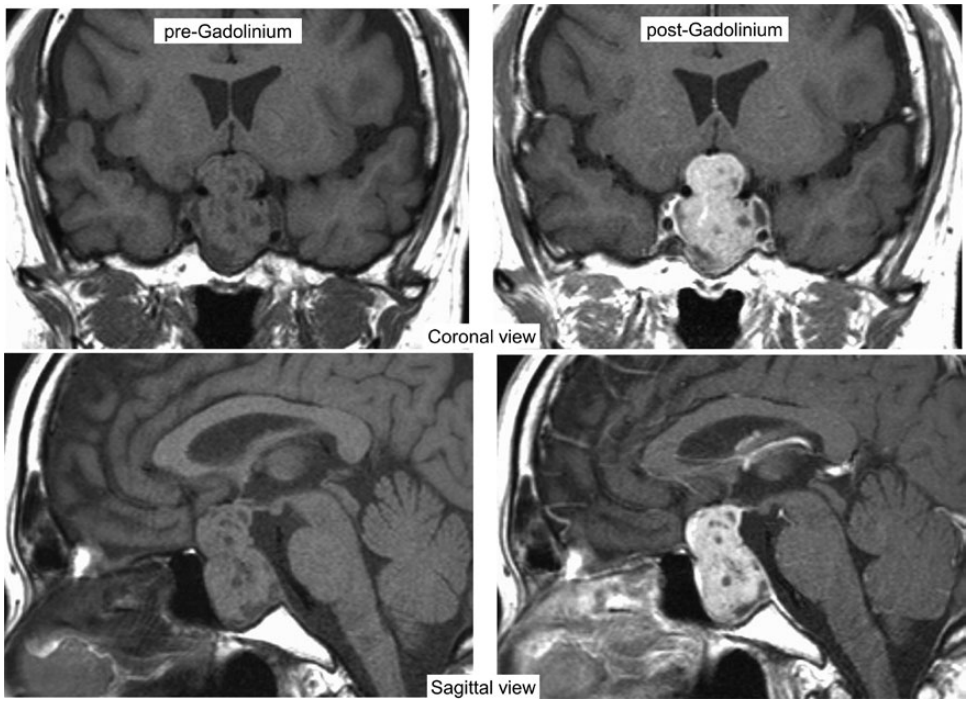
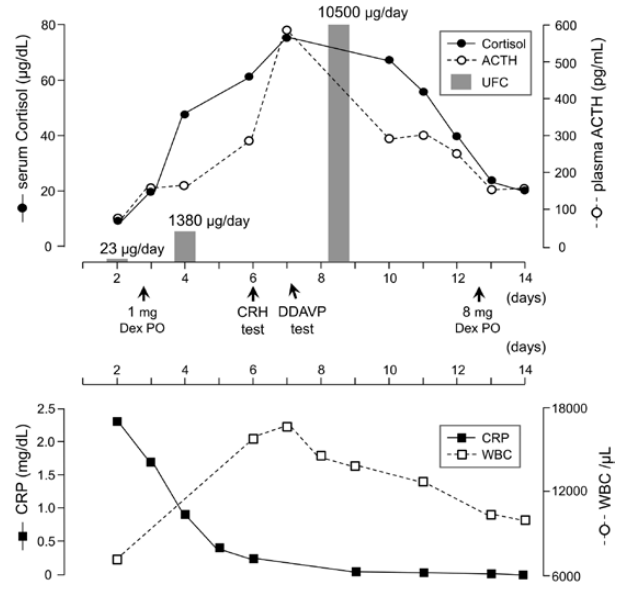


Figure 1. Pre- and post-Gadolinium-enhancedT1-weighted magnetic resonance imaging showing a large pituitary tumor measuring 24 × 20 × 39 mm that extended superiorly in the suprasellar cistern to elevate the optic chiasm. The mass showed contrast enhancement with partially hypointense areas.

level was 9.3 µg/dL and the 24-hour urinary free cortisol value was 23.0 µg/day (reference range [RR]: 11.2–80.3), indicating normal cortisol secretion. On day 3, after a low-dose (1 mg) overnight dexamethasone suppression test, the serum cortisol level at 8:00 AM was 19.6 µg/dL (normal, <1.8 µg/dL), suggesting hypercortisolemia. During his 14-day hospital stay, cortisol secretion gradually increased and then decreased in an inverted U-shaped manner (Fig. 2). The peak serum cortisol level was 75.7 µg/mL (ACTH 585 pg/mL) and the 24-hour urinary free cortisol value was 10 500 µg/day (Fig. 2). The serum cortisol level eventually decreased to 20.5 µg/mL on the day of discharge (day 14). Consistent with transient hypercortisolism, there was leukocytosis, a decrease in C-reactive protein suggesting anti-inflammatory activity, and hypokalemia (Fig. 2). Furthermore, the patient had low urinary sodium excretion (urine sodium undetectable), indicating sodium retention due to glucocorticoid excess (Fig. 2). Even more surprisingly, the rise in cortisol levels coincided with amelioration of his red psoriatic plaques during the hospital stay (Fig. 3). These clinical findings were consistent with his reports of



S-K (mEq/L)	4.6	3.9	3.0	3.0
U-K (mEq/L)		22.7	29.9	21
U-Na (mEq/L)		6	< 5	84

Figure 2. Timeline of ACTH and cortisol levels (upper graph) and indicators of the inflammatory response (lower graph).The table at the bottom shows the changes in serum potassium and urine potassium and sodium. Serum cortisol (µg/dL) and plasma ACTH (pg/mL) were collected under fasting conditions in the early morning each day. Dex 1 mg PO, oral administration of dexamethasone 1 mg at 11:00 PM; Dex 8 mg PO, oral administration of dexamethasone 8 mg at 11:00 PM. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; DDAVP, desmopressin; S-K, serum potassium concentration; UFC, 24-hour urinary free cortisol; U-K, urine potassium concentration; U-Na, urine sodium concentration; WBC, white blood cells.

periodic whole-body swelling sensations and transient improvement in his skin lesions.

A corticotropin-releasing hormone (CRH) stimulation test showed a more than 2-fold increase in plasma ACTH from 285 pg/mL to 595 pg/mL after injection of 100 µg of CRH (RR > 50% increase in plasma ACTH), consistent with Cushing's disease due to an ACTH-producing pituitary tumor (Fig. 4). There was no increase in the ACTH level after administration of desmopressin 10 µg (Fig. 4). A high-dose (8 mg) overnight dexamethasone suppression test resulted in a nearly 40% reduction in the morning serum cortisol level at 8:00 AM from 39.7 µg/mL to 23.6 µg/mL (RR > 50% reduction in serum cortisol), indicating inadequate suppression.

Unexpectedly, a thin-slice CT scan of the abdomen did not show bilateral adrenal enlargement due to chronic ACTH stimulation (image not shown). In addition, the large size of the pituitary tumor raised concerns for a malignant primary or metastatic pituitary tumor. A subsequent whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT scan showed only the known pituitary tumor, which had a maximum standardized uptake value of 6.4 to 7.7 (image not shown).

The other pituitary function tests were as follows: thyroid-stimulating hormone (TSH) 3.43 µIU/mL (RR 0.5–5), free T4 0.56 ng/dL (RR 1.0–1.8), growth hormone (GH) 0.03 ng/mL (RR 0–2.47), insulin-like growth factor-1 39 ng/mL (RR 91–253), luteinizing hormone (LH) 0.16 mIU/mL (RR 0.79–5.72), follicle-stimulating hormone (FSH) 0.78 mIU/mL (RR 2.0–8.3), total testosterone < 0.03 ng/mL (RR 1.31–8.71), and prolactin (PRL) 23.0 ng/mL (RR 4.3–13.7). Thyrotropin-releasing hormone (protirelin; Nipro Corporation, Osaka, Japan), GH-releasing peptide-2, and LH releasing-hormone stimulation tests indicated hyposecretion of thyroid, growth, and gonadal hormones due to compression of the normal pituitary tissue by the large pituitary mass (data not shown). The patient had normal serum sodium levels and urine osmolality without polydipsia and polyuria suggestive of diabetes insipidus.

The patient eventually underwent transsphenoidal surgery for his large pituitary tumor. The pathologic findings were consistent with an ACTH-producing pituitary tumor. There was no necrosis in the specimen. Immunohistopathology confirmed pituitary adenoma positive for ACTH and negative for GH, PRL, TSH, FSH, and LH. Only a few cells showed Crooke's degeneration, which was confirmed by low molecular weight keratin (CAM 5.2) staining and a Ki-67/MIB-1 labeling index of less than 1%. The patient's transient whole-body swelling sensations and visual field defect resolved completely after surgery, but he developed postoperative diabetes insipidus. The patient

received hydrocortisone, levothyroxine, and desmopressin replacement therapy.

Discussion

It is generally accepted that a minority of patients with CS demonstrate cyclic hypersecretion of cortisol [6]. Although approximately half of cases of cyclic CS are attributable to an ACTH-producing pituitary adenoma (Cushing's disease), other pathologic causes, including ectopic ACTH syndrome and adrenal CS (adenoma or primary pigmented nodular adrenocortical disease), have been recognized [2, 7, 8].

In this case, the CRH stimulation test indicated a meaningful rise in ACTH secretion (Fig. 4). Moreover, an FDG-PET/CT scan revealed no evidence of lesions other than the known pituitary tumor. Therefore, hypersecretion of ACTH was thought to be caused by a pituitary tumor (Cushing's disease) rather than ectopic ACTH syndrome.

Although no endocrine investigations had been performed previously, this patient is likely to have had periodic secretion of ACTH and cortisol for several years, given his report of transient sensations of whole-body swelling and improvement of the skin lesions. Indeed, he experienced sensations of whole-body swelling and a concomitant marked decrease in urinary sodium excretion and progressive hypokalemia when there was a rise in his cortisol secretion during the hospital stay (Fig. 2), indicating water retention as a result of the mineralocorticoid effect of a marked increase in serum cortisol. This observation lent credibility to his unusual story.

Although Cushing's disease is usually associated with pituitary microadenoma, our case presented as pituitary macroadenoma. However, there are no reports suggesting a difference in the frequency of cyclic Cushing's disease between macroadenoma and microadenoma [6].

Our patient is currently being treated with topical glucocorticoids, namely, dexamethasone (class 2, potent) or clobetasol (class 1, superpotent) for psoriasis vulgaris that first developed 20 years ago. Although a paradoxical increase in urinary free cortisol in response to a

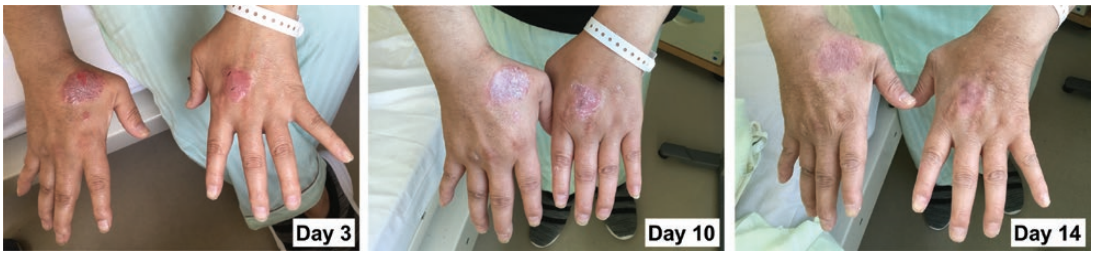


Figure 3. Chronological changes in psoriatic skin lesions. Improvement in red psoriatic plaques coincided with the increase in serum cortisol levels.

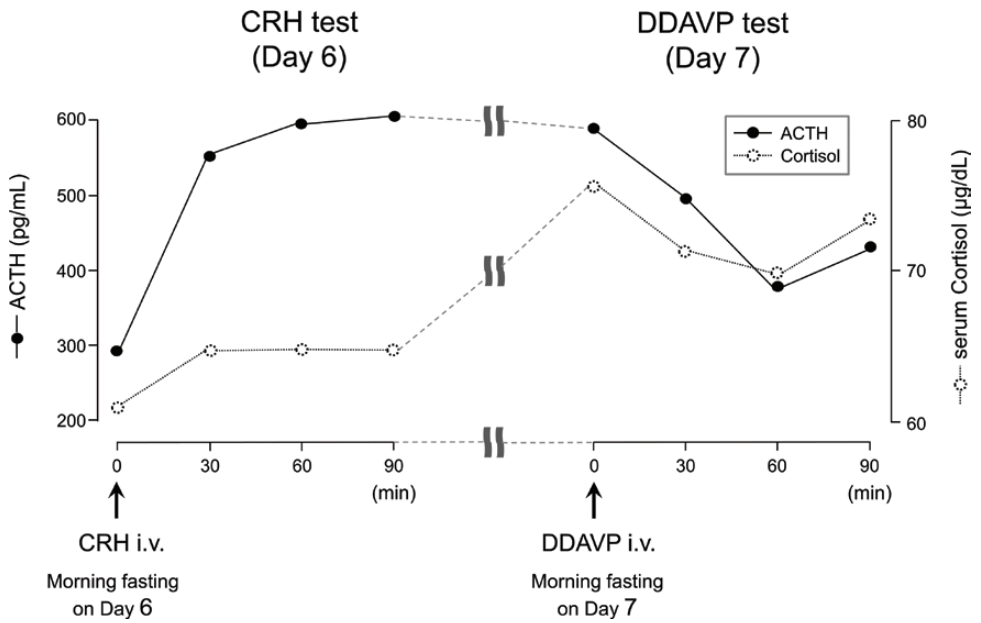


Figure 4. Results of CRH and DDAVP stimulation tests performed on hospital days 6 and 7, respectively. The CRH test revealed a significant increase in the plasma ACTH level, whereas the DDAVP test found a decrease rather than an increase in ACTH. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DDAVP, desmopressin.

dexamethasone suppression test has been reported in patients with primary pigmented nodular adrenal disease [9], a paradoxical increase in ACTH and cortisol levels may also occur after administration of dexamethasone in cyclic Cushing's disease [10]. However, in our case, it was unclear how the topical glucocorticoids were previously involved in cyclic secretion of ACTH. The topical glucocorticoid was discontinued after admission to avoid an effect on the hypothalamic-pituitary-adrenal axis. On hospital days 1 and 2, the cortisol levels were almost normal (Fig. 2). The morning serum cortisol level was high (19.6 μg/dL) on day 3 after oral administration of dexamethasone 1 mg at 11:00 PM on day 2. This finding raised the possibility that the paradoxical response was caused by dexamethasone. Nevertheless, a higher (8 mg) dose of dexamethasone was administered at 11:00 PM on day 12, and the serum cortisol levels continued to decline thereafter. Therefore, transient ACTH and cortisol hypersecretion may have occurred regardless of administration of dexamethasone.

Several mechanisms have been put forward to explain the cyclicity of Cushing's disease, including episodic hemorrhage or fluctuations in the hypothalamic-pituitary-adrenal axis feedback; however, the pathophysiology remains to be elucidated [6]. Although the postoperative pathology specimen showed no necrosis in this case, there were small patchy hypointense areas suggestive of tumor necrosis in the pituitary magnetic resonance imaging. Therefore, we believe that spontaneous episodic hemorrhage might cause cyclicity of ACTH secretion.

Psoriasis is an immune-mediated inflammatory disease that is treated by immunosuppressive or immunomodulatory agents [11]. It is also known that autoimmune-related diseases, such as Graves' disease, rheumatoid arthritis, and psoriasis, may occur after resolution of hypercortisolemia due to CS [3–5]. However, to the best of our knowledge, there have been no reports of improvement in an autoimmune-related disease during a period of cortisol hypersecretion in cyclic CS.

We have encountered a very rare case of cyclic pituitary CS in which we observed dramatic improvement of psoriasis vulgaris due to transient hypersecretion of cortisol during a short hospital stay.

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Additional Information

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Disclosures: The authors have nothing to disclose.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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