Concomitant Cushing's Syndrome Due to Adrenal Adenoma in a Patient with Systemic Lupus Erythematosus

Masatoshi SHIMIZU, Masahito KAWATA, Toshio OKADA*, Housai YUU*, Toshifumi KURAHASHI**, Kunito YAMANAKA** and Keiichi UMEZU**

Abstract

A 51-year-old woman had been administered 5 mg/day of prednisolone due to systemic lupus erythematosus (SLE). She developed hypertension, hypokalemia and a pathologic pubic fracture during two years before admission. Although iatrogenic Cushing's syndrome was initially suspected, we diagnosed her as concomitant Cushing's syndrome due to a left adrenal tumor. The elevated endogeneous glucocorticoids were evaluated from urinary excretions of 17-hydroxycorticosteroids, which was 2-fold higher than normal and equivalent to 10 mg of prednisolone. After laparoscopic left adrenalectomy, SLE was favorably controlled with 15 mg of prednisolone, the dosage of which was equivalent to the estimated amount of preoperative glucocorticoids. (Internal Medicine 41: 1044–1046, 2002)

Key words: prednisolone, autoimmune disease, hypokalemic hypertension, glucocorticoid, corticosterone

Introduction

Endogenous glucocorticoid excess could be obscured and erroneously interpreted as iatrogenic, if a patient is receiving steroids for a preceding autoimmune disease. Cushing's syndrome may be found unexpectedly during examinations for intractable hypertension (1). Following treatment of Cushing's syndrome, abrupt reduction of the endogenous glucocorticoids may induce a rebound in abnormal autoimmune activities (1–4). We present here a case of systemic lupus erythematosus (SLE) complicated by Cushing's syndrome. After the removal of an adrenal adenoma, SLE was favorably controlled with postoperative prednisolone equivalent to the estimated amount of preoperative glucocorticoids.

Case Report

A 51-year-old woman was referred to our division because of hypertension and fatigability in February 2000. She had been administered prednisolone for seven years due to SLE. At the age of 43, she experienced dryness of the mouth and eyes. In the following year, she presented with malar rash, photosensitivity, arthritis and positive test for anti-DNA antibody. She was diagnosed as SLE and Sjögren's syndrome by a local physician, and steroid therapy was started. At the age of 49, she became hypokalemic and hypertensive with a blood pressure of 156/92 mmHg. She was treated with a calcium antagonist. However, her blood pressure was gradually aggravated. In January 2000, she was admitted to our hospital because of a pathologic pubic fracture, which was managed conservatively for a month. She had been almost relieved from SLE with 5 mg/day of prednisolone as a maintenance dose, but her blood pressure was poorly controlled despite treatment with nicardipine hydrochloride, alacepril and doxazosin mesilate.

On admission, the blood pressure was 198/106 mmHg without difference between the two arms. Height was 159 cm, and body weight was 37.2 kg. The body mass index was 14.7 kg/m², which remained unchanged throughout the clinical course. She lacked signs of Cushing's syndrome such as central obesity, buffalo hump or moon-face appearance. Complete blood cell count showed the following: erythrocyte 416×10⁴/mm³, hemoglobin 12.2 g/dl, white cell count 10,400/mm³ with 8,450/mm³ of neutrophils, and platelet count 27.0×10⁴/mm³. Evaluation of serum chemistry revealed lactate dehydrogenase 674 IU/l, alkaline phosphatase 879 IU/l, potassium 2.1 mEq/l, C3 60 mg/dl. C-reactive protein was negative and erythrocyte sedimentation rate was 12 mm/h. Anti-nuclear, anti-SS-A and anti-SS-B antibodies were ×320 (speckled type), 437.6 U/ml and 75.8 U/ml, respectively. Assays for anti-DNA, anti-RNP, anti-Sm, anti-Scl-70 and anti-Jo-1 antibodies were all negative. Abdominal ultrasonography revealed a low echogenic mass in the left adrenal gland 30 mm in diameter (Fig. 1A). Abdominal computed tomography (Fig. 1B) and magnetic resonance im-

From the Division of Cardiology, *the Department of Internal Medicine and **the Department of Urology, Kobe National Hospital, Kobe

Received for publication April 30, 2002; Accepted for publication July 4, 2002

Reprint requests should be addressed to Dr. Masatoshi Shimizu, the Division of Cardiology, Kobe National Hospital, 3-1-1 Nishi-cho, Suma-ku, Kobe 654-0155

Figure 1. Abdominal ultrasonography (A) revealed a low echogenic mass in the left adrenal gland 30 mm in diameter (arrow). Abdominal computed tomography (B) also suggested a left adrenal tumor (arrow).

Table 1. Hormonal Evaluations

Serum cortisol (μg/dl)		(5.0–17.9)
8:00 AM	29.2	
3:00 PM	30.6	
9:00 PM	29.0	
+ dexamethasone 1 mg	20.6	
8 mg	24.2	
24h urinary 17-OHCS (mg/day)	15.7	(2.3–7.8)
Serum corticosterone (ng/ml)	17.3	(0.21–8.48)
Plasma ACTH (pg/ml)	<4.0	(4.4–48.0)
DHEA-S (ng/ml)	90	(60–1,230)
24h urinary 17-KS (mg/day)	6.80	(2.4–11.3)
Plasma renin activity (ng/ml/h)	0.12	(0.2–2.7)
Serum aldosterone (pg/ml)	26.0	(56.9–150.3)

17-OHCS: 17-hydroxycorticosteroids, 17-KS: 17-ketosteroid, ACTH: adrenocorticotropin, DHEA-S: dehydroepiandrosterone sulfate.

aging also suggested a left adrenal tumor. We initially considered that her hypertension and hypokalemia could be due to long-term prednisolone therapy, but these findings prompted us to undertake further hormonal evaluations (Table 1). We obtained the following measurements after cessation of oral prednisolone for two days. Serum concentrations of cortisol determined at 8:00 AM, 3:00 PM, and 9:00 PM were 29.2, 30.6, and 29.0 μg/dl (normal; 2.7–15.5) respectively, which were constantly high without circadian changes. Twenty-four hour urinary excretion level of 17-hydroxycorticosteroids (17-OHCS) was elevated to 15.7 mg/day (normal; 2.3–7.8). Serum

corticosterone level was also elevated to 17.3 ng/ml (normal; 0.21–8.48). Plasma adrenocorticotropin (ACTH) was undetectable. Plasma renin activity was 0.12 ng/ml/h (normal; 0.2–2.7), and serum aldosterone concentration was 26.0 pg/ml (normal; 56.9–150.3). Both of which were below the lower limit. Serum cortisol and urinary 17-OHCS excretion were not suppressed either by low dose (1 mg for 2 days) or high dose (8 mg for 2 days) of dexamethasone administration. Levels of other hormones were within normal range, including plasma dehydroepiandrosterone sulfate and urinary 17-ketosteroid. An adrenal scintigram showed exaggerated uptake of adosterol-I¹³¹ at the left adrenal gland. Based on these findings, we diagnosed her as concomitant Cushing's syndrome due to a left adrenal tumor.

The patient underwent laparoscopic left adrenalectomy in May 2000. A round adenoma 30×25 mm in diameter was found at the left adrenal cortex. Microscopic examination revealed that the tumor consisted mainly of large clear cells. After surgery, she was administered 15 mg/day of prednisolone as a replacement therapy for two months. She did not experience an exacerbation of SLE. Serum potassium level was elevated to 3.8 mEq/l, and her blood pressure declined to 138/88 mmHg with doxazosin mesilate alone. Prednisolone was successfully tapered to 10 mg/day. Two years after surgery, she remained well with relief of symptoms.

Discussion

Autoimmune disease is rarely complicated by Cushing's syndrome. There have been only five case reports in the literature including the present case (1–4). Notably, four of these five patients were Japanese females. The preceding autoimmune disease was SLE in two cases (1), and rheumatoid arthri-

tis in the other three cases (2–4). The causes of subsequently developed Cushing's syndrome were due to adrenal adenoma in four and pituitary adenoma in one. When Cushing's syndrome was finally diagnosed, all of the patients were in a remissive state of their autoimmune disease. Two patients were under prednisolone treatment, one patient had been discontinued steroid therapy for eight years, and the remaining two patients had never received steroids. The symptoms related to concomitant Cushing's syndrome were hypertension, hypokalemia, pathologic fractures, and specific features such as central obesity and moon face. These conditions have played a clue to endogenous glucocorticoid excess in patients without steroid therapy. Iatrogenic Cushing's syndrome, however, was initially suspected in the three patients who had received steroid treatment for the preceding autoimmune disease. In the latter patients, adrenal tumors were unexpectedly found during examinations for intractable hypertension, or after an attempt to discontinue steroid therapy. In the present patient, hypokalemic hypertension and pathologic fractures were initially considered as iatrogenic, because she had been receiving long-term prednisolone treatment and lacked specific signs observed in Cushing's syndrome. Cushing's syndrome was diagnosed after we suspected hypokalemic hypertension of mineralocorticoid excess, and evaluated adrenal glands. We could not determine precisely when the present patient developed Cushing's syndrome, but we consider that the onset was two years before admission when she became hypertensive and hypokalemic.

The present case is the first report that the preceding autoimmune disease was favorably controlled after the treatment of concomitant Cushing's syndrome. In all four previous cases, a marked exacerbation of the preceding autoimmune disease was observed after removal of adrenal tumors or metyrapone treatment. These exacerbations occurred even when physiological dosage of hydrocortisone was administered subsequently. One patient with RA died of complicated pneumonia (2). Intensive prednisolone therapy was required in one patient with SLE (1), and the remaining two patients with RA needed methotrexate therapy (3, 4). Endogenous glucocorticoids have some anti-inflammatory effects. It is speculated that endogenous excess of glucocorticoids could have suppressed autoimmune activities. A rebound in abnormal autoimmune activities may be induced by abrupt reduction of the endogenous glucocorticoids following treatment of Cushing's syndrome. Physiological replacement with hydrocortisone may not be adequate to control disease activities. Therefore, it is reasonable to assess the elevated endogenous glucocorticoids and replace them with a sufficient dosage of prednisolone. We estimated endogenous

glucocorticoids from the 24 hour urinary excretion level of 17-OHCS, which was 2-fold higher than normal and equivalent to 10 mg/day of prednisolone (1). Adding the preoperative 5 mg/day of prednisolone, we started 15 mg/day of oral prednisolone postoperatively in the present patient. Because the relative anti-inflammatory effect of prednisolone is 4-fold stronger than cortisol, we considered that the dosage was sufficient to inhibit rebound exacerbation of SLE.

Another unique characteristic of the present case is an elevated serum corticosterone level (5) with low plasma renin activity and low serum aldosterone concentration. Corticosterone, a precursor of aldosterone, is a weak mineralocorticoid, but is capable of causing hypokalemic hypertension. Corticosterone excess may explain low plasma renin activity and low serum aldosterone concentration in the present patient (6). Cushing's syndrome exceptionally demonstrates concurrent hypercortisolism and hypermineralocorticoidism (7, 8). We did not measure other mineralocorticoids such as deoxycorticosterone. Therefore, a possibility can not be thoroughly precluded that other undetermined mineralocorticoids had caused hypokalemic hypertension in the present patient. Although prednisolone dosage was adjusted to be equivalent to preoperative glucocorticoids, hypokalemic hypertension subsided after the removal of an adrenal adenoma.

References

- 1) Arima K, Higuchi M, Yoshizawa S, et al. Improvement of systemic lupus erythematosus activity by the association of delayed onset Cushing's syndrome. *J Rheumatol* **25**: 2456–2458, 1998.
- 2) Nakamoto Y, Tabuchi Y, Saeki S, Mikami H, Ogihara T. Cushing's syndrome found during long-term glucocorticoid treatment for rheumatoid arthritis in an elderly woman. *Jpn J Geriatr* **29**: 54–58, 1992 (in Japanese, Abstract in English).
- 3) Senécal JL, Uthman I, Beauregard H. Cushing's disease-induced remission of severe rheumatoid arthritis. *Arthritis Rheum* **37**: 1826, 1994.
- 4) Yakushiji F, Kita M, Hiroi N, Ueshiba H, Monma I, Miyachi Y. Exacerbation of rheumatoid arthritis after removal of adrenal adenoma in Cushing's syndrome. *Endocr J* **42**: 219–223, 1995.
- 5) Edwards OM, Galley JM, Tait AD, Mills IH. Steroid production rates in two patients with corticosterone producing adenomata. *J Endocrinol* **65**: 52–53, 1975.
- 6) Yasuda G, Shionoiri H, Hayashi S, Umemura S, Ikeda Y, Ishii M. Cushing's disease: evaluation of mineralocorticoid —induced hypertension. *Intern Med* **32**: 784–788, 1993.
- 7) Hogan MJ, Schambelan M, Biglieri EG. Concurrent hypercortisolism and hypermineralocorticoidism. *Am J Med* **62**: 777–782, 1977.
- 8) Hobma S, Hermus A, Pieters G, Smals A, Kloppenborg P. Concurrent hypercortisolism and hyperaldosteronism due to an adrenal adenoma. *Klin Wochenschr* **68**: 981–983, 1990.