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Successful Long-Term Treatment of Refractory Cushing's Disease with High-Dose Mifepristone (RU 486)

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An extremely ill patient, with Cushing's syndrome caused by an ACTH-secreting pituitary macroadenoma, experienced complications of end-stage cardiomyopathy, profound psychosis, and multiple metabolic disturbances. Initially treated unsuccessfully by a combination of conventional surgical, medical, and radiotherapeutic approaches, he responded dramatically to high-dose long-term mifepristone therapy (up to 25 mg/kg·d). Treatment efficacy was confirmed by the normalization of all biochemical glucocorticoid-sensitive measurements, as well as by the significant reversal of the patient's heart failure, the resolution of his psychotic depression, and the eventual unusual return of his adrenal axis to normal. His 18-month-long mifepristone treatment course was notable for development of severe hypokalemia that was attributed to excessive cortisol activation of the mineralocorticoid receptor, which responded to spironolactone administration. This case illustrates the efficacy of high-dose long-term treatment with mifepristone in refractory Cushing's syndrome. The case also demonstrates the potential need for concomitant mineralocorticoid receptor blockade in mifepristone-treated Cushing's disease, because cortisol levels may rise markedly, reflecting corticotroph disinhibition, to cause manifestations of mineralocorticoid excess. (*J Clin Endocrinol Metab* 86: 3568–3573, 2001)

CHRONIC EXPOSURE TO excessive corticosteroids in Cushing's syndrome (CS) leads to the development of multiple metabolic abnormalities, including glucose intolerance, dyslipidemia, hypertension, osteoporosis, and weight gain (1). Cushing's disease (CD) accounts for approximately 70% of cases of endogenous CS. The standard initial treatment of CD is transsphenoidal adenomectomy, which achieves cure rates of 70–80% (1). Pituitary macroadenomas (size $>$ 1 cm) are more difficult to cure than microadenomas (size $<$ 1 cm). Patients suffering residual or recurrent disease undergo repeat transsphenoidal hypophysectomy, external beam pituitary irradiation, medical adrenolytic therapy, or surgical adrenalectomy to control the hyperadrenocorticism (1, 2). However, no particular therapy is completely satisfactory. Repeat transsphenoidal surgery results in high relapse rates, therapeutic effects from pituitary radiotherapy are delayed, the steroidogenic enzyme inhibitors for chemical adrenalectomy (metyrapone, mitotane, aminoglutethimide, ketoconazole) are often limited by severe toxicity and inadequate cortisol suppression, and surgical approaches to accomplish total adrenalectomy may not fully extirpate adrenocortical tissue (1, 2). Adrenalectomy also carries the risk of rapid residual pituitary corticotroph growth, *i.e.* Nelson's syndrome.

We describe a patient with refractory CD and multiple medical comorbidities who exhausted conventional therapies but was successfully treated with high-dose mifepristone (RU 486), a glucocorticoid receptor (GR) antagonist (3), as a bridge until the therapeutic effects of delayed radiation therapy became manifest. Not only did the patient's hypothalamic-pituitary-adrenal axis return to normal, but his multiple medical problems all dramatically reversed. During mifepristone therapy, the patient, in addition, required spironolactone, a mineralocorticoid receptor (MR) antagonist, to ameliorate cortisol-induced MR activation, a result of elevated serum cortisol produced by mifepristone-induced corticotroph disinhibition.

Abbreviations: 11βHSD, 11β-hydroxysteroid dehydrogenase; BPRS, brief psychiatric rating scale; CD, Cushing's disease; CS, Cushing's syndrome; GR, glucocorticoid receptor; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MR, mineralocorticoid receptor; MRI, magnetic resonance imaging.

Case Report

The patient was a 51-yr-old African-American retired mechanic who was diagnosed with diabetes mellitus type 2 and hypertension, 6 yr before his evaluation at our institution. One year before admission, he developed recurrent syncope. Transthoracic echocardiography showed severe left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) of 20%. Coronary angiography revealed an isolated 60% occlusion of the left anterior descending artery that underwent percutaneous transluminal angioplasty and stenting. In the 6 months before admission, the patient was treated, at three other hospitals, for recurrent upper and lower extremity abscesses. Several incision and drainage procedures did not yield any microbial etiology. An increased frequency of syncopal episodes, concomitantly with New York Heart Association functional class IV symptoms, led to the patient's referral for evaluation of cardiac transplantation at our facility.

At the time of arrival at our institution, the patient's medications included digoxin, captopril, carvedilol, hydralazine, isosorbide, and insulin. Physical examination showed a wheelchair-bound man, with rounded facies, appearing chronically ill and acutely in distress. His blood pressure was

130/82, pulse was 92 and regular, height was 1.78 m, and weight was 80 kg. The patient was somnolent and unable to provide any medical history. He was extremely weak and had striking muscular atrophy of the extremities. There were no abdominal striae, but there was palpable hepatomegaly and prominent pedal edema. He had fluctuant, warm, red, tender lesions involving the right upper and left lower extremities. When the patient tried to stand, he developed syncope.

During the subsequent hospitalization, chest radiography showed diffuse cardiomegaly, an electrocardiogram revealed LVH with secondary repolarization abnormality, and a repeat echocardiogram demonstrated LVEF of 22%, concentric LVH, and left ventricular enlargement. The patient's cardiomyopathy was deemed out of proportion to the isolated coronary atherosclerosis. *Cryptococcus neoformans* was cultured from the extremity abscesses, serum *Cryptococcus* antigen titers were positive (1:512), urine and sputum cultures revealed *Candida albicans*, and a left toe skin culture grew *Trichophytum rubrum*. The patient was started on flucytosine and fluconazole to treat the cryptococcosis. His glycemic control was poor, despite using more than 100 U insulin per day. Retinal examination showed diabetic retinopathy, and urine studies revealed proteinuria.

To screen for possible CS, a low-dose (1 mg) dexamethasone overnight suppression test was performed, demonstrating a nonsuppressed serum cortisol (1493 nM). ACTH-dependent CS was diagnosed by finding concomitant elevated ACTH (81 pM) and serum cortisol levels (>828 nM). High-dose (8 mg) dexamethasone did not suppress the cortisol (1294 nM). CRF levels were undetectable. Magnetic resonance imaging (MRI) revealed a cystic 2 × 1-cm pituitary mass (Fig. 1). Formal visual field testing was negative. Computed tomography of the adrenal glands showed bilateral hyperplasia. Despite failure of the high-dose dexamethasone suppression (including a repeat test using 32 mg dexamethasone), the patient was diagnosed with CD (4) but was deemed too ill to undergo confirmatory inferior petrosal sinus sampling. The patient's antifungal regimen was changed to include ketoconazole, because this imidazole derivative can inhibit steroidogenesis (5). However, ketoconazole was incompletely effective, and metyrapone was started, but the latter was abruptly discontinued after coincident development of atrial arrhythmias, requiring cardioversion.

During the patient's transsphenoidal adenomectomy, all visible traces of a soft cystic tumor were removed, but invasion of adjacent structures precluded complete surgical extirpation. A postoperative MRI scan confirmed residual tissue in the sella turcica. Histopathological analysis revealed a necrotic adenoma. A predominant pituitary cell type was unidentifiable by immunohistochemistry, because all immunostaining was inadequate because of the necrotic state of the specimen. Postoperatively, ACTH and cortisol levels declined but remained abnormally elevated (Fig. 2). Ketoconazole was reinstituted at 1200 mg/d to inhibit steroidogenesis. One month later, the patient underwent 3-dimensional conformal external beam radiotherapy, receiving 5040 cGy to the pituitary bed in 28 fractions over 6 wk. On ketoconazole, the patient developed extreme nausea and elevated transaminases (ALT 228 IU/L), necessitating a change to mitotane therapy (2 g/d) for 2 months. His ACTH remained more than 18 pM; and serum cortisol, more than 773 nM. His gonadal axis declined: total testosterone, 1.9 nM (normal, 12.1–24.9); free testosterone, 0.01 nM (normal, 0.04–0.11); and FSH, less than 1 IU/L (normal, 1.55–9.74). He was started on im testosterone therapy.

On psychiatric evaluation, the patient was severely depressed, with a 21-item Hamilton depression rating scale score of 27 (normal, <5). Although he denied symptoms of overt psychosis, his brief psychiatric rating scale (BPRS) was 38 (normal, <18). He showed significant cognitive impairment, as indicated by grossly diminished scores on multiple aspects of the paragraph recall test and the Stroop color-word test.

Materials and Methods

Serum cortisol was measured using the IMMULITE competitive immunoassay (Diagnostic Products Corp., Los Angeles, CA), whereas ACTH was determined by ARUP Laboratories (Salt Lake City, UT) using a chemiluminescent immunoassay. Other measurements were per-

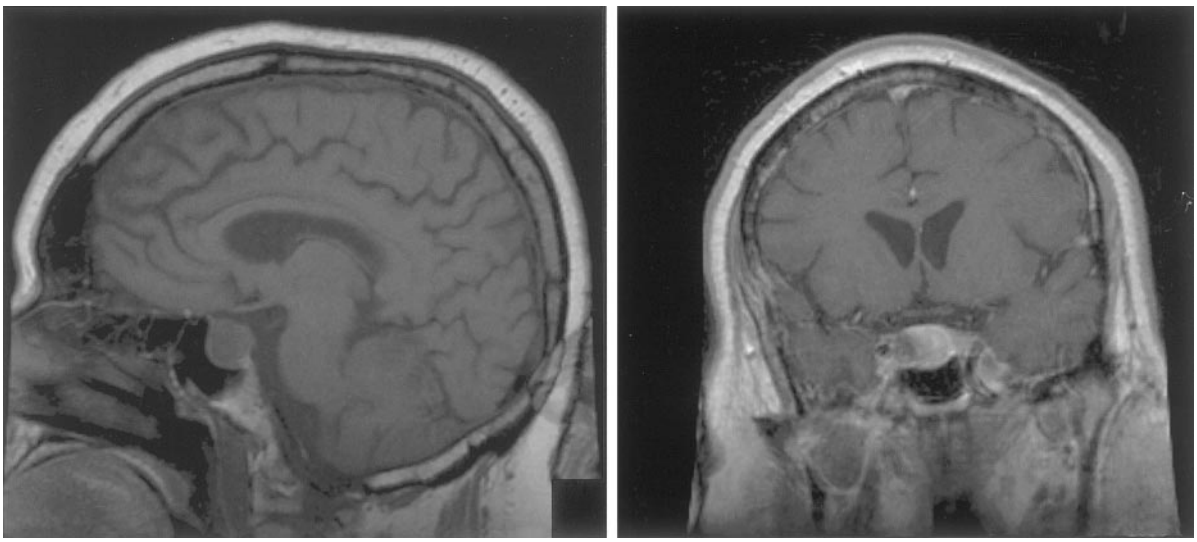

FIG. 1. Brain MRI images of a 51-yr-old man with CD. Sagittal T1-weighted (*left panel*) and coronal T1-weighted postgadolinium (*right panel*) MRIs of the brain demonstrate a cystic pituitary mass measuring approximately 2 × 1 cm.

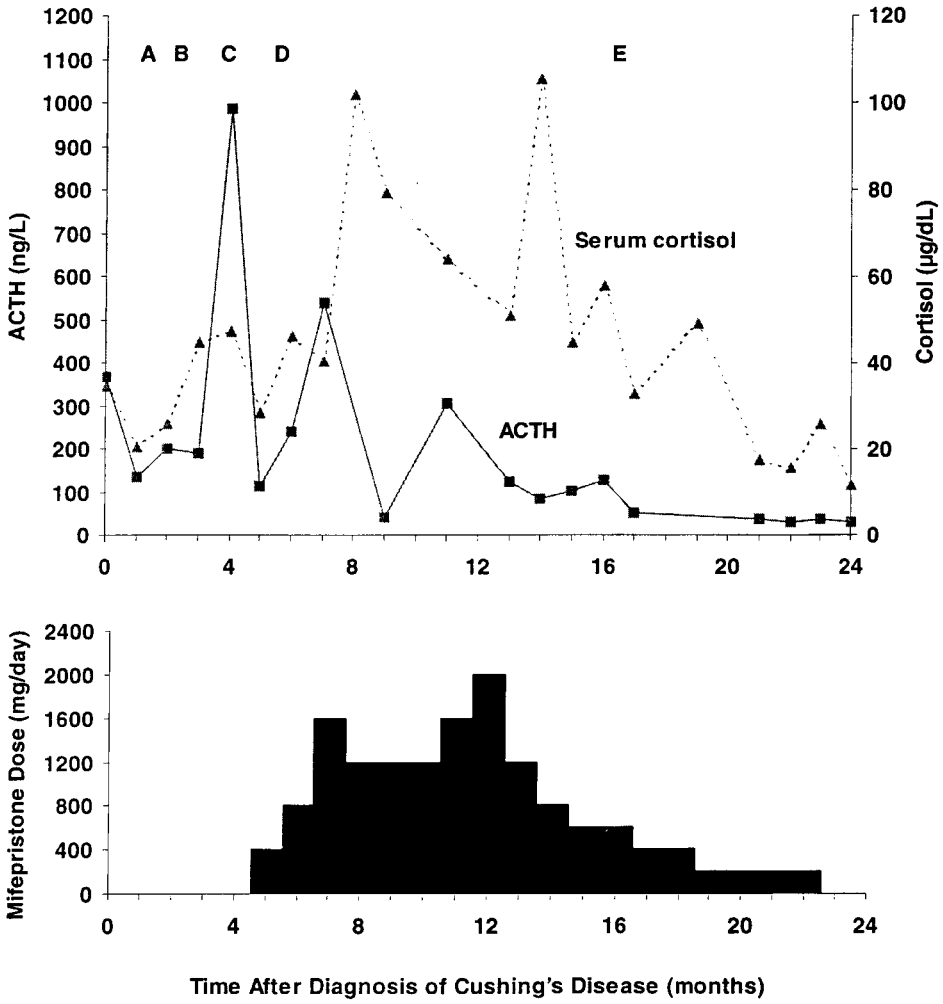

FIG. 2. Adrenal axis function in a man with CD treated with mifepristone. Note that measurements of serum cortisol are expressed in μg/dl (1 μg/dl = 27.59 nM), and those of ACTH are expressed in ng/L (1 ng/liter = 0.22 pM). A, Transsphenoidal resection of pituitary adenoma; B, start of external beam radiotherapy; C, end of external beam radiotherapy; D, medical adrenolytic therapy; E, acute adrenocortical insufficiency.

formed in the Stanford Clinical Laboratory using standard procedures. Bone mineral densitometry was assessed by dual-x-ray absorptiometry employing a Hologic, Inc. (Bedford, MA) QDR 4500 apparatus. Neuropsychiatric testing used the Hamilton depression rating Scale (HAMD-21), brief psychiatric rating scale, Stroop color-word test, and paragraph recall test, as reported previously (6).

Results

The patient remained extremely ill, and it was anticipated that the radiotherapy would not show benefit for at least 1 yr. Chemical adrenalectomy had been unsuccessful, and the patient's cardiac status was considered too tenuous to undergo adrenalectomy, even via a laparoscopic approach. Given the lack of feasible effective therapies, the patient was initiated on mifepristone at 400 mg/d (~6 mg/kg·d). This was done with his informed consent, permission from the human subjects committee, and an Investigational New Drug approval from the Food and Drug Administration. It was hoped that mifepristone, begun 5 months after diagnosis of CD, would control the hypercortisolism until the radiotherapy took effect.

During the initial 8 months of mifepristone treatment, the dose was gradually increased to a maximum of 2000 mg/d (~25 mg/kg·d) in response to continued signs of hypercortisolism (Fig. 2). It was recognized that the fluctuating, but persistently elevated, serum ACTH and cortisol could not accurately reflect therapeutic efficacy, because mifepristone antagonizes the hypercortisolemic effects at the receptor level, not by altering corticosteroid production (7). Severe hypokalemia (potassium < 3 mM) developed, requiring high-dose potassium replacement and initiation of spironolactone therapy. However, clinical findings attributable to CS slowly improved, and the mifepristone dosage was titrated downwards over the following 10 months. The accompanying fall in ACTH and cortisol concentrations likely represented delayed effects of radiotherapy, although spontaneous improvement could not be ruled out (8). In month 10 of mifepristone therapy, at 800 mg/d (~10 mg/kg·d), the patient experienced an episode of suspected adrenocortical insufficiency, manifested by weakness, orthostatic hypotension, and hypoglycemia (serum glucose ~1.1 mM, not on antidiabetic drugs), which necessitated dexamethasone bolus therapy and mifepristone dose reduction, to which he responded.

By month 18 of mifepristone therapy, the patient's overall appearance was markedly improved, and he now walked unassisted. The ACTH had fallen (<8.8 pM), and the serum cortisol was not only suppressible, by low-dose dexamethasone to 30 nM, but was also normally responsive to exog-

enous corticotropin (from 433 to 1112 nM). Presuming an intact hypothalamic-pituitary-adrenal axis, the mifepristone dose was tapered and discontinued.

Of the severe metabolic, cardiovascular, and neuropsychiatric dysfunction (Table 1) associated with CD, the most remarkable improvement in this patient was his transformation from a wheelchair-bound heart-transplant candidate to an active individual walking 1–2 miles a day. The echocardiographic finding of a marked increase in LVEF, to 35–40%, corroborated this observation. The multiple fungal infections did not recur after cessation of antifungal agents. The severe insulin resistance abated, and glycemic control remained in a desirable range without the use of antidiabetic medications. The marked hypertriglyceridemia regressed without therapy. Markers of bone turnover and bone mineral density improved. The hypokalemia resolved, and the blood pressure has been well controlled, with the remaining antihypertensives consisting of carvedilol and furosemide to treat the congestive heart failure. Other medications included levothyroxine [to treat mild hypothyroidism; FT_4, 10.2 pM (normal, 9.0–25.7); TSH, 7.22 U/L (normal, 0.4–4.0)], im testosterone, and digoxin.

The patient's neuropsychiatric status improved dramatically. His elevated BPRS score, indicating psychosis, entirely resolved; and his mood normalized. His cognition improved substantially, with dramatic correction in all aspects of the Stroop color-word and paragraph recall tests. After recovery, the patient revealed that he had been far more psychotic than he had admitted at the onset of mifepristone treatment, describing previous visual hallucinations and feelings of being observed by unseen people. He had not initially acknowledged these symptoms because he thought that he would "sound crazy" (which indicates preserved insight).

Discussion

17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one, also known as RU 38486, RU 486, or mifepristone is a potent antagonist of both glucocorticoid and progestin receptors (3). Its clinical properties yield an effective contraceptive, as well as abortifacient; and it may have potential benefit in treating CS, unresectable meningioma and leiomyoma, refractory endometriosis, metastatic breast cancer, and even psychotic depression (6, 9). We describe a patient with a pituitary macroadenoma, causing refractory CD, associated with multiple severe physiologic derangements that regressed after amelioration of hypercortisolism. Mifepristone was used successfully to antagonize the effects of hypercortisolism while awaiting the delayed remission induced by pituitary irradiation. Our report, describing the highest dose of mifepristone achieved for the longest duration reported in a patient with CS, coincides with the recent approval of mifepristone for usage in the United States, and it supports the utility of this therapy in managing hypercortisolism.

Previous reports have described clinically therapeutic mifepristone usage in more than 14 patients with CS (10, 11). A potential adverse effect experienced by these and other patients treated with high-dose mifepristone for long periods involves episodes of possible adrenal insufficiency that cannot be confirmed biochemically but that resolve after exogenous glucocorticoid administration and mifepristone

TABLE 1. Hormonal, metabolic, cardiovascular, and neuropsychiatric indices at diagnosis of Cushing's disease and before, during, and after mifepristone therapy

Index	At initial diagnosis	At start of mifepristone therapy	During mifepristone therapy	After mifepristone therapy	Normal values
Hormonal					
ACTH (pM)	81	20	28	6	2.9–11.4
Serum cortisol (nM)					
Fasting	949	1076	1402	320	166–580
After dexamethasone, 1 mg	1493	—	—	30	<138
Exogenous insulin use (U/d)	115	70	40	0	0
Metabolic					
Serum osteocalcin (nM)	—	0.80	6.43	7.66	0.99–2.39
Bone mineral density (g/cm^2)					
Left total hip	—	—	0.795	0.822	age-dependent
Lumbar spine (1–4)	—	—	0.977	0.989	age-dependent
Hemoglobin A1c (%)	11.5	10.4	7.7	6.9	4–6%
Serum cholesterol (mM)					
Total	—	8.11	7.17	5.28	<5.18
HDL	—	0.91	0.54	0.85	>0.91
LDL	—	—	—	3.52	<3.37
Fasting triglycerides (mg/dl)	—	4.83	5.48	2.00	<2.26
Potassium (mM)	4.0	4.2	3.0	4.4	3.5–5.0
Cardiovascular function					
New York Heart Association functional class	IV	IV	II–III	I	0
Estimated left ventricular ejection fraction	19%	—	30%	35–40%	>50%
Neuropsychiatric function					
21-Item Hamilton-D score	—	27	18	8	<5
BPRS score	—	38	20	18	18

HDL, High-density lipoprotein; LDL, low-density lipoprotein; —, not available.

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