LATE RECURRENCE OF OPERATED ADRENOCORTICAL CARCINOMA: ATRIAL NATRIURETIC FACTOR BEFORE AND AFTER TREATMENT WITH MITOTANE

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Reprinted from
SURGERY
St. Louis

Vol. 105, No. 5, PP. 690-692, May, 1989

Late recurrence of operated adrenocortical carcinoma: Atrial natriuretic factor before and after treatment with mitotane

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A 62-year-old man arrived at our hospital with recurrence of Cushing's syndrome 14 years after successful surgery for adrenocortical carcinoma. Investigations demonstrated recurrence of a large tumor above the right adrenal area; it was found to be inoperable. The patient was treated initially with a new glucocorticoid antagonist, RU 486, and later with the adrenolytic agent mitotane (o,p'DDD). The latter achieved hypoadrenocorticism and a substantial reduction of tumor size. During the initial period, worsening hyperadrenocorticism resulted in a rise of atrial natriuretic factor and an inhibition of renin activity, consistent with an increase of cortisol and plasma volume. Changes in opposite direction were observed after treatment with mitotane. (SURGERY 1989;105:690-2.)

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HYPERADRENOCORTICISM IS A condition associated with salt and fluid retention. Hypervolemia is known to stimulate the release of the atrial natriuretic factor (ANF).[1] Indeed, plasma ANF concentrations have been reported to increase in syndromes characterized by fluid overload, such as primary hyperaldosteronism,[2] or inappropriate secretion of antidiuretic hormone[3] Because ANF has never been studied in Cushing's syndrome, we measured its plasma levels in a patient with recurrent adrenocortical carcinoma before and after chemotherapy with mitotane (o,p'DDD).

CASE REPORT

A 62-year-old man was admitted to our hospital in April 1986 for treatment of diabetes. He had a past history of Cushing's syndrome due to an adrenal carcinoma that was removed successfully in 1971. The tumor entirely removed weighed 420 gm and histologically was considered malignant. In 1983 the patient had mild diabetes and hypertension. Two years later he noticed recurrence of a moon face. Clinically, he looked cushingoid, with truncal obesity and wasting of leg muscles. His pulse rate was 60 beats/min and blood presure, 165/95 mm Hg. A diagnostic assessment showed a high urine free cortisol value of 1435 nmol/24 hours (normal, less than 247 nmol/24 hours). Plasma cortisol levels at 8 AM and 8 PM were, respectively, 593 nmol/L (normal, 221 to 607 nmol/L) and 740 nmol/L (normal, 83 to 248 nmol/L), with no suppression with dexamethasone 2 and 8 mg/day. Cortisol levels remained unchanged during the adrenocorticotropic hormone (250 μg tetracosactrin) and corticotropin releasing factor (0.1 mg ovin corticotropin releasing factor) stimulation tests. A computed tomographic scan of the abdomen showed a large tumor above the right renal area, probably developed from a lymph node. A venocavogram showed compression and thrombosis of the inferior vena cava, which made impossible further surgical treatment. Chest x-ray film showed scars over the left apex. Electrocardiogram was normal. The patient was then treated with insulin and RU 486 (400 mg/day), a new glucocorticoid antagonist (Roussel, UCLAF, Paris, France) that has been reported effective in the control of Cushing's syndrome.[4] This drug was given from June 1986 to March 1987. At that stage, and during the following months, ANF, renin and cortisol levels, and plasma volumes were measured.

Plasma volumes were determined with use of iodine-125 labeled albumin. Plasma ANF concentrations were measured after plasma extraction (Sep-pak C18 cartridges, Waters Associates, Milford, Mass.), by radioimmunoassay with antibodies from Peninsula Laboratories (Belmont, Calif.). As shown in Fig. 1, from July 1986 to March 1987, cortisol levels rose,

Accepted for publication Sept. 13, 1988.

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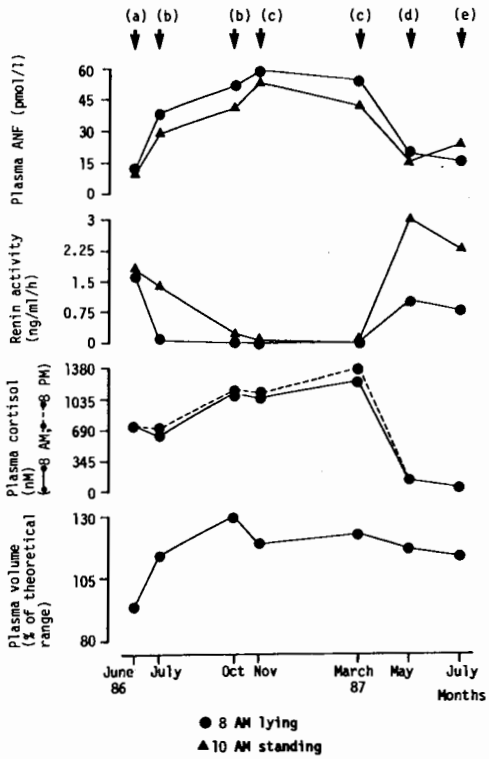

Fig. 1. Plasma ANF concentrations, renin activity, plasma cortisol, and plasma volumes measured before treatment *(a)*, with RU 486 *(b)*, after 10 days' withdrawal of RU 486 *(c)*, with mitotane, *(d)* and with mitotane combined with steroid replacement therapy *(e)*.

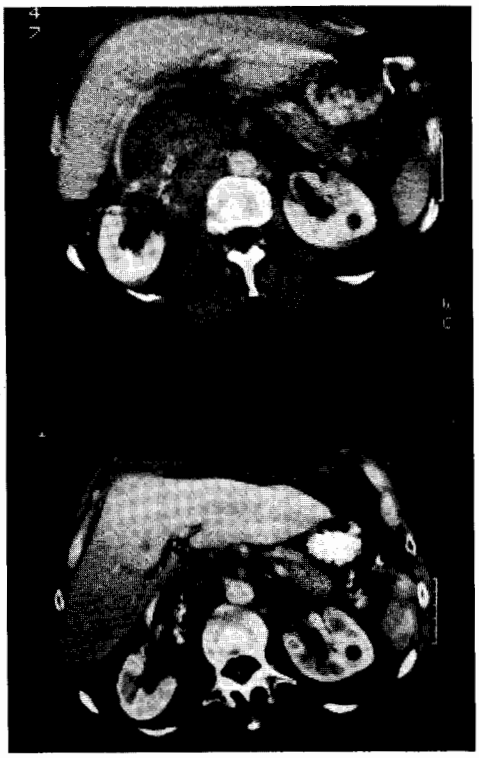

Fig. 2. Computed tomographic scan of the right adrenal tumor before **(top)**, and 5 months after **(bottom)**, chemotherapy with mitotane.

concomitantly with a fivefold increase of plasma ANF concentrations, a drop of renin activity, and an increase of plasma volume. During this period, beneficial effects of RU 486 were observed on hypokalemic alkalosis and diabetes.

In March 1987 effects of cortisol overproduction, resulting from tumor growth, worsened. RU 486 therapy was discontinued. A new treatment was commenced with mitotane at 2 gm/day and increased to 8 gm/day,[5] which 1 month later led to hypoadrenocorticism, necessitating steroid replacement therapy. Meanwhile, insulin and potassium supplements were discontinued. Before replacement therapy, ANF concentrations decreased and renin activity increased substantially. Two months after replacement therapy, these measurements had nearly returned to initial values.

Five months after starting mitotane, the tumor size, measured by CT scan, was reduced by more than 50% (Fig. 2). The only side effect encountered with the drug was dizziness.

DISCUSSION

This case report illustrates the great tendency for adrenocortical carcinoma producing Cushing's syndrome to recur, even late after successful surgery. As previously suggested, it also shows that mitotane remains an alternative and effective treatment when adrenal carcinoma is inoperable.[5]

The hormonal assessment showed that progressive hyperadrenocorticism resulted in a rise of plasma volumes and ANF concentrations and an inhibition of renin activity. Both ANF and renin normalized after mitotane-induced hypoadrenocorticism, whereas plasma volumes decreased less markedly. Changes of ANF and renin in opposite direction are consistent with changes of volume states,[1] but this might also partly result from the ANF-suppressive effect on renin activity.[6] Besides hypervolemia, it is possible that steroids may directly stimulate ANF release[7,8] and could thus account for the parallel changes of cortisol and ANF. Recently this has been demonstrated with steroid therapy,[8] but it has never before been shown in Cushing's syndrome.

In conclusion, in this report we have shown increasing ANF levels associated with Cushing's syndrome and their decrease after treatment with mitotane. After hyperadrenocorticism worsened and overrode RU 486

antagonism, good evidence was provided of the effectiveness of mitotane to induce a regression both in cortisol secretion and in measurable size of the tumor.

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