Frequency of Abnormalities of Cortisol Secretion and Water Metabolism in Patients With Small Cell Carcinoma of the Lung and Other Malignancies*

Donald L. Trump, M.D.; Martin D. Abeloff, M.D.; and Tah Hsiung Hsu, M.D.

Previous studies have suggested that ectopic production of adrenocorticotropic hormone (ACTH) or antidiuretic hormone (ADH) may occur commonly in patients with small cell carcinoma of the lung (SCCL) and that evidence of such production may be elicited only by provocative tests of water excretion and adrenal function. We studied 28 patients with SCCL and 29 patients with other cancers. Adrenal function, assessed by measuring the 8 AM plasma cortisol, the 8 AM to 4 PM diurnal variation in plasma cortisol, and the suppressibility of the 8 AM plasma cortisol following administration of 1 mg of dexamethasone, was found to be abnormal in 28.5, 71, and 25 percent, respectively, of the patients with SCCL, compared with 18, 65, and 29.5 percent in patients with other types of cancer (P > 0.3). The possibility of ectopic ADH secretion was assessed by a standard water loading test, which showed excretion impairment in 60 percent of patients with SCCL and 68 percent of patients with other cancers (P > 0.9). Neither the stage of neoplastic disease, sites of metastatic deposits, nor performance status of the patients correlated with abnormalities of water and cortisol metabolism, indicating that such abnormalities are common in patients with all types of cancer. These data do not suggest that subclinical disturbances of adrenal function or water excretion are characteristic of any histologic type of cancer. The precise mechanism(s) underlying these abnormalities are unknown.

Clinically evident hypercortisolism and water intoxication are seen more often in patients with small cell carcinoma of the lung (SCCL) than in patients with other types of cancers.\(^1\) In patients with SCCL these abnormalities are generally thought to be caused by the ectopic production of adrenocorticotropic hormone (ACTH) or antidiuretic hormone (ADH) by tumor tissue.\(^2\) Clinically inapparent abnormalities of cortisol secretion and water metabolism have also been documented in patients with SCCL. Previous studies have suggested that in some patients these subclinical abnormalities result from ectopic secretion of small quantities of ACTH and ADH, and that such findings may be characteristic of SCCL.\(^3\) The precise mechanisms leading to both clinical and subclinical disturbances in water and cortisol metabolism in patients with SCCL, however, have not been defined. Two recent reports indicate that the disturbances in water metabolism in patients with lung cancer have a complex etiology, beyond ectopic ADH production.\(^4,5\)

Since clinically evident disturbances in water and cortisol metabolism are relatively uncommon in patients other than those with SCCL, one might expect a similar low incidence of subclinical defects. However, few data are available regarding water and cortisol metabolism in patients with cancers other than SCCL.

The present study was undertaken to determine the frequency of disturbances in water metabolism and adrenal function in patients with SCCL and other types of malignancies. We sought to determine whether subclinical impairment in the ability to excrete free water and subclinical evidence of adrenal hyperfunction were more common in SCCL and whether such abnormalities were of prognostic value in either group of patients.
Table 1—Histologic Diagnoses in Patients Evaluated

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma of the lung</td>
<td>28</td>
</tr>
<tr>
<td>Other malignancies</td>
<td></td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>13</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>1</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

Study Parameters

Twenty-eight patients with biopsy-proved SCCL were studied prior to administering any antineoplastic therapy. Twenty-four patients had extensive disease, defined as disease beyond the lung and hilum on the side of the primary tumor. Four patients had disease limited to ipsilateral lung and hilar nodes. Median age for SCCL patients was 58.5 years (range, 32 to 74 years). All patients were subsequently given cyclophosphamide, VP-16-213, and doxorubicin according to our previously described protocols.10,11

Twenty-eight cases of other types of malignancies were evaluated (Table 1). All of those patients had evidence of active disseminated neoplasms and had been admitted to The Johns Hopkins Oncology Center for management of their cancers or of complications resulting from therapy. Median age of these patients was 54.5 years (range, 24 to 81 years).

Patients with clinical problems known to influence cortisol and water metabolism were excluded from this study: no patient had fever or clinical signs of infection; no patient had clinical evidence of cortisol deficiency or excess; in all patients the serum creatinine level was ≤1.5 mg/dl and the serum bilirubin level was ≤1.5 mg/dl; all patients undergoing evaluation of water metabolism had a serum sodium concentration of greater than 135 mEq/dl on an unrestricted water intake; in no patient was evidence of salt depletion or fluid retention present; patients with SCCL had received no prior antineoplastic therapy, and patients with other tumors had received no antineoplastic therapy for seven days prior to evaluation. Patients with clinical or radiologic evidence of CNS metastases were excluded. No patient was receiving drugs known to interfere with free water excretion or cortisol metabolism. No patient had received corticosteroids within the preceding 30 days. Patients were generally studied within seven to ten days of admission to the hospital.

Testing Procedures

Water metabolism was evaluated by a standard water loading test. Tobacco, coffee, tea, and other caffeine-containing beverages were withheld for 12 hours prior to testing, and on the morning of evaluation serum and urine samples were obtained for osmolality determination. The bladder was emptied and the patient drank 20 ml/kg of water. Over the next five hours urine output was measured, and aliquots of urine were obtained hourly for osmolality determination. A normal response to water loading was defined as the excretion of a volume of urine over the five-hour period of 80 percent or more of the volume of water administered and dilution of the urine to <100 mOsm/kg during the monitoring period. Adrenal function was evaluated by measuring morning plasma cortisol, assessing the diurnal variation in cortisol secretion by measuring morning and afternoon plasma cortisol, and investigating the suppressibility of cortisol secretion with the 1-mg dexamethasone suppression test. Plasma cortisol was measured in blood samples obtained at 8 AM and 4 PM; 1 mg of dexamethasone was administered at 12 midnight, and plasma samples for cortisol determination obtained at 8 AM the next morning. Cortisol was measured by a competitive protein-binding method. Normal values in our laboratory are: 8 AM cortisol, 7 to 21 μg/dl; 4 PM cortisol, <50 percent of prior 8 AM cortisol; 8 AM cortisol following 1 mg of dexamethasone, <5 μg/dl. Adrenal function was not evaluated on a day during which the water loading test was administered.

Comparisons of frequencies of abnormal tests between groups were made using 2 × 2 contingency tables and the x² statistic. Survival curves were compared utilizing the log rank test.

RESULTS

Adrenal Function

Small cell lung cancer. An increased 8 AM plasma cortisol concentration was found in eight of 28 (28.5 percent) patients with SCCL (Table 2). The 4 PM plasma value cortisol fell to the normally expected value of one half of the 8 AM value in only eight patients (29 percent); that is, 20 of 28 patients (71 percent) had lost the normal diurnal pattern of cortisol secretion. Twenty patients underwent the 1-mg dexamethasone suppression test; in 15 (75 percent), cortisol concentrations were suppressed normally. No further evaluation of those patients without suppression of the 8 AM cortisol was carried out.

No survival differences were seen either between groups who had lost or maintained a normal diurnal variation of plasma cortisol. However, survival was shorter in patients whose 8 AM cortisol was not suppressed by 1 mg of dexamethasone compared with patients in whom cortisol was normally suppressed (P < 0.05; Fig 1). Age, sites of disease,
stage of disease, length of hospitalization prior to testing, and performance status did not correlate with the abnormalities of cortisol metabolism observed.

Other malignancies. Of 22 patients with other cancers, the 8 AM plasma concentration of cortisol was increased in four (18 percent). In 13 of 20 patients (65 percent) the diurnal variation of plasma cortisol was abnormal. In 12 of 18 patients (70.5 percent) the 8 AM plasma cortisol was normally suppressed by 1 mg of dexamethasone. The frequencies of increased 8 AM plasma cortisol, loss of diurnal variation of plasma cortisol, and loss of 8 AM plasma cortisol suppressibility were not statistically different between the groups of patients with SCCL and those with other cancers (P > 0.3, P > 0.4, and P > 0.8, respectively).

In patients with tumors other than SCCL, survival differences were evident in each of the subgroups of cortisol evaluation: patients with a normal 8 AM plasma cortisol survived longer than those whose cortisol was elevated (0.05 < P < 0.075); patients with an intact diurnal variation survived longer than those who had lost the normal diurnal change (P < 0.001), and patients who retained sensitivity to low-dose dexamethasone suppression survived longer than patients with non-suppressible 8 AM cortisol (P < 0.025; Fig 2 and 3). There were no differences between those patients with normal cortisol values and those with abnormal values with respect to extent of disease, sites of metastases, duration of hospitalization prior to testing, age, performance status, or type of cancer.

One patient with SCCL had documented hypercortisolism four months after initial adrenal function testing. At the time of initial evaluation 8 AM cortisol determination, diurnal variation and cortisol suppressibility were all normal.

Water Metabolism

Small cell lung cancer. Twelve of 20 (60 percent) patients with small cell lung cancer could not ex-
crete an exogenous water load in a normal fashion. Extent of disease, sites of involvement, age, length of hospitalization, and performance status were similar in groups with normal and abnormal responses to water loading. There was no statistically significant difference in survival between patients with normal and abnormal responses to water loading (0.075 < P < 0.1).

Other malignancies. Fifteen of 22 (68 percent) patients with other tumors responded in an abnormal manner to the water loading test. Extent of disease, type of neoplasm, sites of involvement, age, duration of hospitalization, and performance status and survival were similar in the groups with normal and abnormal responses to water loading. There was no statistically significant difference in the frequency of an abnormal response to the water loading test between patients with small cell lung cancer and patients with other cancers (P > 0.9). Overall survival from the date of water and cortisol evaluation was similar in the group of patients with small cell cancer and the group of patients with tumors other than small cell cancer (P > 0.8).

Discussion

Small cell carcinoma of the lung is clearly the tumor most frequently associated with the paraneoplastic syndromes of water intoxication and hypercortisolism. This observation, together with data indicating that tumor tissue and plasma from patients with a variety of lung tumors frequently contain increased concentrations of ACTH, has led other workers to investigate the incidence of subclinical evidence of autonomous cortisol secretion in patients with SCCL.5-7 These workers have noted that abnormalities such as loss of diurnal variation and lack of suppressibility of plasma cortisol, which are suggestive of autonomous and perhaps ectopic secretion of ACTH, occur in at least 10 percent and perhaps as many as 50 percent of patients with SCCL. Our data confirm that abnormalities in cortisol secretion and suppressibility are common in SCCL but also suggest that these abnormalities are equally common in other advanced neoplasms. Our data do not suggest that ectopic production of small amounts of biologically active ACTH is common. In addition, the frequency of disturbances in cortisol secretion in our studies is similar to those reported in other studies of cancer patients, as well as in studies of hospitalized noncancer patients.12,15 These data suggest that such disturbances in cortisol secretion are not unique to any histologic type of cancer, and, in fact, may occur frequently in any group of hospitalized patients.

Our studies do not define the mechanisms by which disturbances in cortisol secretion occur. Odell and Wolfson16 have recently reviewed data indicating that most kinds of cancer produce small quantities of polypeptide hormones. This observation suggests that ectopic secretion of physiologically active ACTH may be evident in both of our subgroups of cancer patients. However, as those authors pointed out, the dominant immunoreactive species of ACTH in the tumor tissue of most patients studied is a biologically inactive form (proACTH or "big ACTH"). Plasma of patients with tumors that contain increased quantities of proACTH contain normal concentrations of biologically active ACTH.17,18 Further evidence against the universality of subclinical ectopic secretion of biologically active ACTH is the observation of similar rates of disturbances in cortisol secretion in hospitalized cancer and noncancer patients.

Previous workers have noted a correlation between elevated cortisol secretion, advanced disease, and shortened survival in lung cancer.19,20 Although the number of patients studied was relatively small, our data also indicate that patients in whom cortisol secretion is disturbed have a shorter survival than patients with normal adrenal function. In the absence of detailed data regarding the mechanisms
of these abnormalities, this observation is consistent with the hypothesis that these parameters of adrenal function are nonspecific measures of "stress." In our studies these parameters appear to be separate from the clinical data used to describe tumor stage and estimate a patient's prognosis. Although the mechanisms for the occurrence of adrenal function abnormalities are unclear, analysis of these parameters may offer complementary prognostic information in patients with small cell lung cancer and other types of tumors.

Comis and co-workers\(^6\) have recently reported data similar to ours which indicate that the ability to excrete an exogenous water load is impaired commonly in patients with SCCL. These workers were also unable to demonstrate a clear-cut relationship between survival or stage and response to a water load. As in the case of cortisol metabolism, our data indicate that subclinical disturbances in water metabolism are common in a wide range of different types of cancer and suggest that these disturbances may not be due simply to "ectopic" production of small quantities of ADH. Even in patients with water intoxication and lung cancer, two groups have noted complex and multifactorial etiologies for this abnormality.\(^7,8\) Evidence supporting ectopic ADH production by the lung tumor, persistent secretion of ADH by the pituitary gland despite water intoxication, and water intoxication by mechanisms independent of ADH have all been demonstrated.\(^8\) The mechanisms underlying the subclinical disturbances in water metabolism are probably equally complex.

Further studies to determine the mechanisms of the observed abnormalities in cortisol and water metabolism may delineate multiple etiologies for these abnormalities. Such studies will need to include careful evaluation of plasma ACTH and ADH concentrations. At the present time, although clinically evident hypercortisolism and water intoxication are uncommon in tumors other than SCCL, subclinical disturbances in cortisol and water metabolism seem to be equally common in patients with a variety of different types of cancer. These subclinical disturbances may represent "reactive" or "stress" phenomena rather than being direct products of tumor growth.

**REFERENCES**