

ADRENOCORTICAL FUNCTION COMPARED WITH  
COMPUTED TOMOGRAPHY OF THE ADRENALS IN SMALL  
CELL CARCINOMA OF THE LUNG

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Patients with pulmonary small cell carcinoma frequently have metastases in the adrenal glands at autopsy (HANSEN 1974). At the time of the clinical diagnosis of the pulmonary lesion it is uncertain to what extent the adrenals are metastatically involved. Diagnostic methods for examining the adrenal glands for primary or secondary tumors such as adrenal phlebography and  $^{131}\text{I}$  cholesterol scanning are cumbersome and not easily accessible. With the advent of CT means of a non-invasive method demonstrating the adrenal glands has emerged. HARPER et coll. (1979) observed that 7 of 50 patients with small cell carcinoma had enlarged adrenal glands as evidenced by CT at the time of diagnosis of the pulmonary lesion. As this tumor is known to secrete ectopic ACTH (HANSEN et coll. 1980a) metastatic involvement as well as ectopic ACTH secretion might be the cause of enlarged adrenal glands.

A comparison was made between the morphologic appearance (bilateral or unilateral enlargement of the adrenal glands) as evidenced by CT, and the adrenocortical function evaluated by means of the 30 min ACTH stimulation test, free urinary cortisol excretion and an overnight dexamethasone suppression test.

**Material and Methods**

In 25 unselected patients with pulmonary small cell carcinoma referred to this Department of Chemotherapy body CT was performed for comparison

with pretherapeutic routine staging methods (HANSEN et coll. 1980b). Adrenal functional tests were performed in 15 of these patients.

CT was done within 2 days before the functional tests, employing an EMI 5005 scanner with a nominal section thickness of 13 mm. Scans of 18 s were obtained at one cm intervals in the suprarenal region. Iodinated oral contrast medium (Gastrografin 4 ml/500 ml water) was given the evening before and again one hour before the examination. The images were displayed and analysed at a variety of window settings.

The 3 adrenal function tests were carried out as follows:

(1) ACTH stimulation test: 250  $\mu\text{g}$  of alpha-ACTH (tetracosactrin, Synacthen) was injected intravenously at 9 a.m. in the fasting patient on day 1. Blood samples for plasmacorticosteroid determinations were drawn immediately before and 30 min after the injection. A normal ACTH stimulation test was defined as a plasma cortisol concentration of more than 540 nmol/l 30 min after ACTH injection (KEHLET et coll. 1976, LINDHOLM et coll. 1978, HASSELBALCK et coll. 1980).

(2) Dexamethasone suppression test: Between 10 and 12 p.m. on day 1 8 mg dexamethasone (Decadron) was given by mouth. The next morning blood

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Table

*Relationship between CT scanning of the adrenal glands and adrenal functional tests in patients with pulmonary small cell carcinoma of the lung*

CT scan of the adrenal glands	ACTH stimulation test		Free urine cortisol		Dexamethasone suppression	
	Normal	Low	Normal	Increased	Normal	Negative
Bilateral enlargement	4	0	1	3	1	3
Unilateral enlargement	3	0	2	1	3	0
Normal	8	0	7	1	6	2

samples were drawn at 7 a.m. for plasma corticosteroid determination. A normal dexamethasone suppression test was defined as a plasmacorticosteroid concentration of less than 195 nmol/l on the morning following dexamethasone.

(3) Twenty-four hour urinary excretion of cortisol was measured on a separate day (EDDY et coll. 1973). Normal values of free urinary cortisol excretion are with the present method of analysis between 30 and 160 nmol/24 h.

All blood samples were immediately centrifuged at 4°C and the plasma was kept below -20°C until analysis. The plasmacorticosteroids were determined fluorimetrically as 11-hydroxycorticosteroids (NIELSEN & ASFELDT 1967). Free urinary cortisol was measured by a competitive binding assay after thinlayer-chromatographic extraction.

### Results

The relationship between the CT findings and the results of the functional tests appears in the Table.

None of the 15 patients showed functional insufficiency despite the morphologic suggestion of metastases in 7 cases. In 4 patients with bilateral adrenal enlargement, only one had completely normal functional tests, while in 3 remaining patients an increased level of 24 h free cortisol in urine and a lack of suppression after dexamethasone was found, implying that in these patients ectopic ACTH production existed.

Among the 3 patients with unilaterally enlarged adrenal glands one had an increased 24 h excretion of cortisol. All other tests were normal in these 3 patients. Among the 8 patients with normal CT findings one had elevated 24 h excretion of cortisol

while 2 others had non-suppressive plasmacorticosteroid level.

The number of patients is too small to allow an evaluation of a statistically significant difference in the distribution of the test results between the groups in the table (Fisher's exact test,  $p > 0.05$ ).

In 6 of the 15 patients autopsy was performed between 4 and 16 months after the initial staging procedure. Three had bilateral adrenal metastases. The long interval and the limited number of patients prevent any conclusion to be drawn.

### Discussion

With the advent of CT scanning a convenient procedure for staging patients with various malignant diseases was anticipated by many. Before accepting any new diagnostic procedure it is necessary carefully to evaluate the specificity and sensitivity of such a procedure.

In a review of the literature including 593 patients with pulmonary small cell carcinoma, HANSEN found the frequency of adrenal metastases demonstrated at autopsy to be 39 per cent. In a retrospectively analysed autopsy series, including 19 patients dying within one month of supposedly curative surgery for pulmonary small cell carcinoma, MATTHEWS et coll. (1973) found 13 patients with persistent disease and 4 (21%) with metastases in the adrenal glands.

The clinical significance of possible hypofunction of the adrenal glands at the time of diagnosis of the pulmonary tumor has never been thoroughly elucidated.

On the other hand, it is well known that adrenal hyperfunction is frequent in these patients. Thus, HANSEN et coll. (1980a) in 75 unselected patients

with small cell carcinoma found one patient with clinical indication of ectopic ACTH production, while 5 patients had hypokalaemic alkalosis, and 22 elevated plasma ACTH; 50 per cent had increased urinary excretion of free cortisol including 18 of 47 patients (38%) with normal plasma ACTH, and 15 of 19 (78%) with elevated plasma ACTH. All the patients in the present series had a normal response to the 30 min ACTH stimulation test implying that no hypofunction due to metastases was present. However, adrenal metastases might be present without detectable decrease in the function of the adrenal glands. Using CT in search of such metastases, the finding of enlarged glands is of particular interest. In the present small series, 7 of 15 patients had enlarged adrenal glands, thereby suggesting metastatic involvement. According to the results of free cortisol in a 24 h urine and the suppression test, the enlargement appeared related to increased function in at least 4 patients. On the other hand, increased function was also found in patients with normal CT findings. Thus, the morphologic appearances do not necessarily correspond to the biochemical functional tests, and CT appears to be invalid in defining metastatic spread to the adrenal glands in patients with pulmonary small cell carcinoma.

In these patients enlargement and hyperfunction of the adrenal glands may be explained by stimulation of the adrenals by ectopically produced ACTH. However, adrenal hyperfunction is a common finding not only in small cell carcinoma but also in patients with pulmonary carcinoma of other types (WERK et coll. 1963). Furthermore, enlarged adrenal glands without metastases may frequently be found at autopsy (WERK & SHOLITON 1960). Accordingly the evaluation of enlarged adrenal glands in malignant diseases appears to be rather difficult and do not necessarily imply the presence of metastases.

At present it is reasonable to conclude that no feasible non-invasive method exists for diagnosing metastatic spread to the adrenal glands in patients with pulmonary small cell carcinoma.

### SUMMARY

Autopsy in patients with pulmonary small cell carcinoma frequently reveals metastases to the adrenal glands. In order to test the hypothesis that CT scanning might demonstrate such metastases at the time of clinical diagnosis of the pulmonary disease, the results of adrenal CT in 15 patients were correlated to adrenocortical function tests.

No statistically significant relationship was found. It is concluded that no reliable non-invasive method exists to diagnose adrenal metastases in patients with pulmonary small cell carcinoma.

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