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Diagnostic and therapeutic implications of ectopic hormone production in small cell carcinoma of the lung

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ABSTRACT In 75 unselected and untreated patients with small cell carcinoma of the lung, plasma ACTH, serum calcitonin, and antidiuretic hormone (ADH) in plasma and urine were related to corresponding clinical symptoms and biochemical findings at the time of diagnosis. The significance of elevated concentrations of these substances in relation to treatment was also investigated. Plasma ACTH concentrations were increased in 22 patients (29%), and 25 patients (33%) were considered to have inappropriate ADH secretion. Only one patient had definite hypokalaemic alkalosis, and one patient pronounced hyponatraemia, with associated clinical syndromes of ectopic ACTH and ADH secretion. Serum calcitonin concentrations were increased in 48 patients (65%). No related clinical symptoms were disclosed, and all these patients had normal serum calcium concentrations. Thirty-three of 66 patients (50%) had raised levels of free cortisol in a 24-hour urine and these levels were significantly related to plasma ACTH concentrations. The median survival was slightly shorter in patients with increased values of the three substances, but this was not related to increased plasma ACTH concentrations and was not statistically significant. Survival rates and results of treatment were independent of the pretreatment levels of the three substances.

Ectopic production of ACTH and ADH in malignant tumours is well documented, and usually occurs in relation to small cell carcinoma of the lung (scc).[1-3] Recently the production of calcitonin in scc has also been documented.[4-6] While no clinical signs related to hypercalcitonaemia have been observed, clinical syndromes have been related to the ectopic production of ACTH and ADH.[2 7 8]

In a review of 138 cases with scc Kato *et al*[9] found Cushing's syndrome in 2·8% of the patients. Investigating 41 treated and untreated patients with scc Gilby *et al*[10] found increased concentrations of plasma cortisol before and after dexamethasone suppression in half of the patients, but only three were considered to have the ACTH syndrome. The inappropriate ADH syndrome (SIADH) is claimed to occur in up to 20% of patients with scc,[11] and Gilby *et al*,[10] using water loading, found an overall prevalence in about 40% of their sample. Both ACTH[12-14] and ADH[15] appear to be produced in almost all cases of scc.

We have studied ectopic ACTH, ADH, and calcitonin production at the time of diagnosis in 75 unselected patients with scc. The relationships between these three substances, their clinical features, and the implications for response to treatment and survival have been investigated.

Methods

The study included 75 unselected patients with scc[16] referred to Medical Department C, Bispebjerg Hospital, between May 1975 and March 1976 (46 patients), and to the Finsen Institute between May 1976 and February 1977 (29 patients). Fifty-three patients (71%) were men and 22 (29%) were women with a median age of 64 years (range 38–75 years). Sixty-two patients

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below the age of 70 years were treated in randomised trials.[17 18]

Before starting chemotherapy or radiotherapy or both two 24-hour urine samples were collected, the second being acidified with 10 ml 0·1 HCl. Between these two collections a fasting blood sample was collected. Blood was taken on ice and centrifuged at 4°C immediately, and plasma and serum were kept below −20°C until analysis.

Plasma ACTH[19] and serum calcitonin[20] were measured by radioimmunoassay techniques. Two samples for analysis of plasma ACTH were obtained with a 10-minute interval, and the lower value was used (in healthy control subjects 76 ng/l=mean+2 SD).

Arginine-vasopressin (ADH) was measured by radioimmunoassay in acidified urine[21] and in plasma.[22] Analyses on urine were attempted in the first 46 patients, but a sample was not obtained in five patients. If frozen plasma was available, analysis were performed in patients with raised urine ADH or decreased plasma osmolality or both, thereby including 31 patients, 15 of whom had also urine ADH measured.

In the first 24-hour urine sample free cortisol,[23] ketogenic steroids (KGS),[24] creatinine, and osmolality were measured. Routine plasma analyses were performed for osmolality, sodium, chloride, potassium, standard bicarbonate, calcium, and phosphorus.

Results

ACTH

None of the patients had the physical signs of Cushing's syndrome and only one was clinically suspected of ectopic ACTH production because of oedema, polyuria, and thirst. This patient also had hypokalaemic alkalosis (K : 2·2 mmol/l, HCO_3^- : 34·2 mmol/l) and a plasma ACTH of 199 ng/l. Five other patients had hypokalaemia, the lowest value being 2·8 mmol/l. Serum bicarbonate in these five patients ranged from 24·4 to 29·5 mmol/l. Plasma ACTH concentrations were above 76 ng/l in 22 patients (29%–95% confidence limits: 19–41%). The highest value, 199 ng/l, was obtained in the above-mentioned patient, while the remaining results had values below 157 ng/l. The median value of ACTH in all patients was 64 ng/l, twice the median value in healthy control subjects.[19] Thirty-three of 66 patients (50%) had increased urinary excretion of free cortisol, including 18 of 47 patients (36%) with plasma ACTH below 76 ng/l, and 15 of 19 patients (79%) with plasma ACTH above 76 ng/l. The median value of urinary cortisol was 726 nmol/24 hours (range: 468–13 500) in the 18 patients with plasma ACTH below 76 ng/l, and 750 nmol/l (range: 455–10 020) in the 15 patients with plasma ACTH above 76 ng/l. Only nine patients (14%) had significantly increased ketogenic steroids, and eight of these also had increased free cortisol. The patient with increased ketogenic steroids and normal free cortisol had an increased plasma ACTH, while eight patients with raised plasma ACTH and free cortisol had normal ketogenic steroid levels.

ANTIDIURETIC HORMONE

Only one patient was clinically suspected of SIADH because of lethargy, weakness, and oliguria. This patient had hyponatraemia (Na^+ : 123 mmol/l), hypotonic plasma with higher urine osmolality (plasma: 244 and urine 345 mosmol/kg H_2O), and inappropriately increased concentrations of urine ADH (34 mU/l) and plasma ADH (3·1 pg/ml). Eleven more patients had plasma sodium between 132 and 135 mmol/l. Altogether, 32 patients (43%) had hypotonic plasma (osmolality below 280 mosmol/kg H_2O). In only two of these patients was the osmolality of urine below that of plasma. Urine ADH was measured in 15

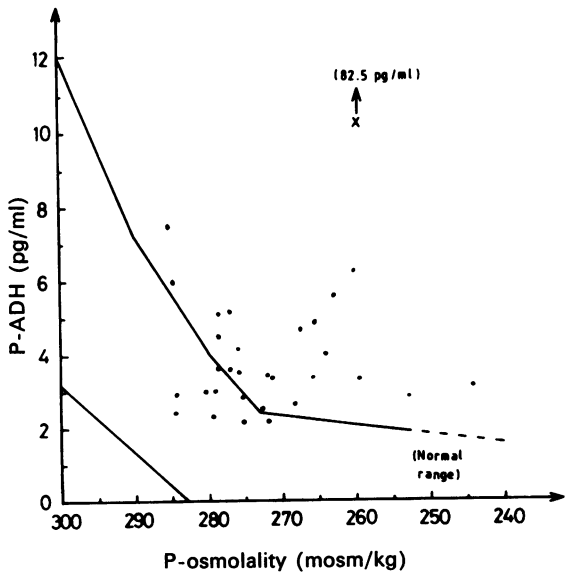

Figure *Corresponding values of plasma ADH and plasma osmolality in 31 patients with small cell carcinoma of the lung. The range of similar values in healthy control subjects falls between the two solid lines.*

of these patients and was increased in 13, from 6 to 6250 mU/l.

The relation between plasma ADH and plasma osmolality in 31 patients is shown in the figure. Twenty-two of 31 patients (71%) had inappropriately increased ADH concentrations, including two with normal plasma osmolality. Taking both ADH and osmolality in plasma and urine into account, 25 patients (33%–95% confidence limits: 23–45%) had inappropriate ADH secretion.

CALCITONIN

Serum calcitonin concentrations were measured in 74 patients and were increased in 48 (65%–95% confidence limits: 53–76%), while serum calcium concentrations were normal in all patients. These data have been presented in detail elsewhere.[25]

RELATIONSHIPS

The relationships between increased plasma ACTH and serum calcitonin and inappropriate ADH secretion are seen in table 1. The estimated frequency calculated from the occurrence of elevations of the individual substance is also shown in table 1. It appears that the frequency of concomitant elevations found was the same as the estimated one. Altogether, 63 patients (84%) had either increased plasma ACTH or serum calcitonin concentrations or inappropriately increased ADH values.

Table 1 *Relationship between increased plasma ACTH, serum calcitonin (CT) and inappropriate ADH secretion (ADH)*

Increased substance	*Frequency*	
	*Estimated**	*Found (95% confidence limits)*
ACTH+ADH	0·10	0·08 (0·03–0·17)
ACTH+CT	0·18	0·20 (0·12–0·31)
ADH+CT	0·21	0·21 (0·13–0·32)
ACTH+ADH+CT	0·06	0·07 (0·02–0·15)

*Calculated from the frequency of individual increases: ACTH 0·29; ADH 0·33; calcitonin (CT) 0·65.

Table 2 *Response to treatment in 61 patients with small cell carcinoma of the lung in relation to levels of plasma ACTH, serum calcitonin (CT), and inappropriate ADH secretion (SIADH)*

	Number responding/ total number	*Ratio*	*p**
ACTH ⩽76 ng/l	30/43	0·70	
>76–			>0·20
	12/18	0·67	
	12/20	0·60	
CT ⩽1·0 ng/ml			>0·20
>1·0	30/41	0·73	
	30/41	0·73	
SIADH –			>0·20
+	12/20	0·60	
All three normal	6/10	0·60	
			>0·20
Two or three raised	16/23	0·73	

*χ^2 test.

RESPONSE TO TREATMENT

Sixty-one patients with measurable or evaluable disease were treated. Forty-two patients (69%) responded with a decrease by more than 50% of the product of the longest perpendicular diameters of measurable lesions or by more than 75% of evaluable lesions. Minor or no changes or progressive disease were found in 19 patients (non-responding). The relation of responding and non-responding patients to the levels of plasma ACTH and serum calcitonin and the occurrence of inappropriate ADH secretion is given in table 2. No statistically significant differences were found for the response rate in patients with one of the substances raised and in patients with normal levels. Nor was any statistically significant difference observed between patients with normal levels of all three substances and patients with two or three concomitantly increased substances.

SURVIVAL

Sixty-two patients were treated in prospective clinical trials.[17 18] Survival data for these patients with regard to the level of the three substances are given in table 3. The median survival was somewhat longer for patients with normal levels of each of the three hormones and for patients with no increased levels, compared to patients with increases of the respective substance and patients with two or three increased substances, but none of these differences was statistically significant. Considering the long-term results, the proportions of patients surviving more than one year, and the number of patients still alive without treatment and free of disease are almost identical (table 3). There is a slight increase in long-term survival in patients without inappropriate ADH secretion as well as for patients with none of the three substances raised, but these differences are not statistically significant.

Discussion

The finding of Cushing's syndrome in a middle-aged man might very well be the result of small cell carcinoma, thereby indicating a diagnostic value,[3 26] though the present results show that the

Table 3 *Survival results for 62 patients with small cell carcinoma treated in randomised trials in relation to levels of plasma ACTH, serum calcitonin (CT), and inappropriate ADH secretion (SIADH)*

		Median survival (days)	*Range (days)*	*p**	*Number alive >365 days*	*Number alive and free of disease§*	*Ratio (%)*
ACTH	≤76 ng/l	325	1–1210+	>0·05	17/44 (39%)	3	7
	>76 ng/l	298	5–1057+		8/18 (44%)	2	11
CT	≤1·0 ng/ml	357	8–1187+	>0·05	9/21 (43%)	2	10
	>1·0 ng/ml	262	1–1210+		15/40 (38%)	3	8
SIADH	–	360	5–1210+	>0·05	18/41 (44%)†	4	10
	+	260	1–874+		6/21 (29%)†	1	5
All three normal		363	161–1187+	>0·05	6/11 (55%)‡	1	9
Two or three raised		262	1–1057+		9/24 (38%)‡	2	8

*Mann-Whitney's test
† $p>0·20$ ($\chi^2=1·37$)
‡ $p>0·20$ (Fisher's exact test)
§ without treatment, which was discontinued 18 months after diagnosis

clinical syndrome is uncommon in such patients. Clinical symptoms and hypokalaemic alkalosis were extremely rare, and moderately increased values of urinary cortisol and plasma ACTH are not specific for patients admitted with scc. Increased levels of plasma and urinary corticoid levels have been demonstrated previously in patients with lung cancer.[10 27 28] Lichter and Sirett[28] found that the increased levels occurred particularly in patients within six months of death. These results are not in disagreement with the demonstration of ACTH in tumour tissue, as the secretion of ACTH from tumour suppresses pituitary production of ACTH.[8 29 30] To cause increased plasma ACTH concentrations the secretion from a tumour must, therefore, exceed the normal pituitary secretion. In this regard it should be noted that the median value of plasma ACTH in our patients is twice the median value in healthy control subjects, thus suggesting subclinical ectopic production of ACTH. This may also explain some of the increased urinary cortisol values in patients with plasma ACTH concentrations below 76 ng/ml. It is also noteworthy that increased plasma ACTH concentrations are within the usual range for the pituitary Cushing syndrome,[2] which may account for the rare occurrence of hypokalaemic alkalosis in the present patients. Although Bagshawe[31] and Ross[26] suggested that hypokalaemic alkalosis was particularly related to the ectopic ACTH syndrome, Prunty *et al*[32] found that potassium depletion was related to the degree of adrenal hyperfunction independently of the source of ACTH.

The inappropriate ADH syndrome was also extremely rare. In only one patient was plasma sodium decreased to a degree that caused clinical symptoms. When ADH was related to plasma osmolality, inappropriate ADH secretion was, however, found in one-third of the patients. Inappropriately increased plasma ADH concentrations in asymptomatic patients were also found by Padfield *et al*.[33]

In this investigation ACTH, ADH, and calcitonin levels were increased in a significant number of patients with untreated and newly diagnosed scc. According to the estimated and actual frequencies of concomitant increases, each of the three hormonal polypeptides appeared to be raised independently of the others. This suggests that the property of ectopic hormone production is not confined to a particular group of scc. However, preliminary results produced by Coombes *et al*[34] indicate that tumour content of ACTH and calcitonin may be related. The mechanisms that cause ectopic production as well as secretion of the products are not known. The present results indicate that production and secretion occur concomitantly in one tumour in more than half the cases. The concept of multiple production is further supported by the findings of multiple peptide and amine products in plasma and tumour from some patients with the ectopic ACTH syndrome.[4 13 35 36] Investigations on the occurrence of these three polypeptides in the same tumours related to the histological subtypes and electronmicroscopical studies would be of interest.

Median and long-term survival was almost the

same for patients with and without increased plasma ACTH concentrations. Similarly, Yalow *et al*[87] did not observe any relation between median survival and the pre-treatment plasma level of immunoreactive "big" ACTH in patients with metastatic disease. Median survival was shorter and long-term results appeared to be inferior for patients with inappropriate ADH secretion compared to patients without. Although no statistical significance was obtained for the ADH related data, these results are contrary to previous general statements claiming that the ectopic ACTH syndrome shortened life, while the SIADH had no influence.[2 3 29] Possibly, the ectopic ACTH syndrome may complicate the condition in untreated patients, while all clinical symptoms, hyperglycaemia, and electrolyte disturbances disappear in patients responding to chemotherapy (Hansen, unpublished observations). Accordingly, if tumour response is obtained by the treatment, survival might be suggested to be independent of the initial ectopic hormonal levels. This suggestion is supported by the response rates and long-term results in this investigation.

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References

1 Amatruda TT, Mulrow PJ, Callagher JC, Sawyer WH. Carcinoma of the lung with inappropriate antidiuresis. Demonstration of antidiuretic-hormone-like activity in tumor extract. *N Engl J Med* 1963; **269**:544–9.

2 Rees LH, Ratcliffe JG. Ectopic hormone production by non-endocrine tumours. *Clin Endocrinol* 1974; **3**:263–99.

3 Said SI. Endocrine role of the lung in disease. *Am J Med* 1974; **57**:453–65.

4 Abe K, Adachi I, Miyakawa S *et al.* Production of calcitonin, adrenocorticotropic hormone, and β-melanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. *Cancer Res* 1977; **37**:4190–4.

5 Baylin SB, Weisburger WR, Eggleston JC *et al.* Variable content of histaminase, L-dopa decarboxylase and calcitonin in small-cell carcinoma of the lung. *N Engl J Med* 1978; **299**:105–10.

6 Silva OL, Becker KL, Primack A, Doppman J, Snider RH. Ectopic secretion of calcitonin by oat-cell carcinoma. *N Engl J Med* 1974; **290**: 1122–4.

7 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; **42**: 790–806.

8 Meador CF, Liddle GW, Island DP *et al.* Cause of Cushing's syndrome in patients with tumors arising from "non-endocrine" tissue. *J Clin Endocrinol Metab* 1962; **22**:693–703.

9 Kato Y, Ferguson TB, Bennett DE, Burford TH. Oat cell carcinoma of the lung. A review of 138 cases. *Cancer* 1969; **23**:517–24.

10 Gilby ED, Rees LH, Bondy PK. Ectopic hormones as markers of response to therapy in cancer. *Amsterdam: Excerpta Medica*, 1975.

11 Vorherr H. Para-endocrine tumor activity with emphasis on ectopic ADH secretion. *Oncology* 1974; **29**:382–416.

12 Bloomfield GA, Holdaway JM, Corrin B *et al.* Lung tumours and ACTH production. *Clin Endocrinol* 1977; **6**:95–104.

13 Horai T, Nishihara H, Tateishi R, Matsuda M, Hattori S. Oat-cell carcinoma of the lung simultaneously producing ACTH and serotonin. *J Clin Endocrinol Metab* 1973; **37**:212–9.

14 O'Neal LW, Kipnis, DM, Luse SA, Lacy PE, Jarett L. Secretion of various endocrine substances by ACTH-secreting tumours—gastrin, melanotropin, norepinephrine, serotonin, parathormone, vasopressin, glucagon. *Cancer* 1968; **21**:1219–32.

15 Morton JJ, Kelly P, Padfield PL. Antidiuretic hormone in bronchogenic carcinoma. *Clin Endocrinol* 1978; **9**:357–70.

16 Kreyberg L. *Histological typing of lung tumours.* Geneva: World Health Organisation, 1967.

17 Hansen HH, Dombernowsky P, Hansen M, Hirsch F. Chemotherapy of advanced small-cell anaplastic carcinoma. *Ann Intern Med* 1978; **89**:177–81.

18 Hansen M, Hansen HH, Dombernowsky P. Restaging of long-term survivors with small cell anaplastic carcinoma of the lung. *Proc Am Soc Clin Oncol* 1979; **20**:511.

19 Hummer L. A radioimmunoassay of plasma corticotropin. In: *Radioimmunoassay and related procedures in medicine 1977, vol 2.* Vienna: *International Atomic Energy Agency*, 1978:391–403.

20 Almqvist S, Telenius-Berg M, Wästhed B. Serum calcitonin in medullary thyroid carcinoma. Radioimmunoassay technique and diagnostic value. *Acta Med Scand* 1974; **196**:177–80.

21 Christensen JD, Jensen SE. A comparative study on bioassay and radioimmunoassay of vasopressin in human urine. *Acta Endocrinol* 1978; **87**:283–91.

22 Hammer M. Radioimmunoassay of 8-arginine-vasopressin (antidiuretic hormone) in human plasma. *Scand J Clin Lab Invest* 1978; **38**:707–16.

23 Kehlet H, Binder C, Nielsen MD. Urinary free corticosteroids determined by competitive protein-binding technique in Cushing's syndrome. *Ugeskr Laeger* 1972; **134**:2438–41.

24 Wilson H, Lipsett MB. Use of periodase oxidation in the clinical analysis of urine corticoids. *Anal Biochem* 1963; **5**:217–25.
25 Hansen M, Rehfeld JF, Stadil F. Small cell carcinoma of the lung: relation of calcitonin to bone marrow metastases, parathormone and gastrin. *Acta Med Scand* 1979; **206**:215–8.
26 Ross EJ. Endocrine and metabolic manifestations of cancer. *Br Med J* 1972; **1**:735–8.
27 Hatch HB, Segaloff A, Ochsner A. Adrenocortical function in bronchogenic carcinoma: study of 100 patients. *Ann Surg* 1965; **161**:645–8.
28 Lichter I, Sirett NE. Serial measurement of plasma cortisol in lung cancer. *Thorax* 1975; **30**: 91–4.
29 Bower BF, Gordan GS. Hormonal effects of non-endocrine tumors. *Ann Rev Med* 1965; **16**: 83–118.
30 Liddle GW, Island DP, Ney RL, Nicholson WE, Shimizu N. Nonpituitary neoplasms and Cushing's syndrome. *Arch Intern Med* 1963; **111**: 471–5.
31 Bagshawe KD. Hypokalaemia, carcinoma and Cushing's syndrome. *Lancet* 1960; **2**:284–7.
32 Prunty FTG, Brooks RV, Dupré J *et al.* Adrenocortical hyperfunction and potassium metabolism in patients with "non-endocrine" tumors and Cushing's syndrome. *J Clin Endocrinol Metab* 1963; **23**:737–46.
33 Padfield PL, Morton JJ, Brown *et al.* Plasma arginine vasopressin in the syndrome of antidiuretic hormone excess associated with bronchogenic carcinoma. *Am J Med* 1976; **61**:825–31.
34 Coombes RC, Ellison ML, Neville AM. Biochemical markers in bronchogenic carcinoma. *Br J Dis Chest* 1978; **72**:263–87.
35 Liddle GC, Givens JR, Nicholson WE, Island DP. The ectopic ACTH syndrome. *Cancer Res* 1965; **25**:1057–61.
36 Rees LH, Bloomfield GA, Rees GM, Corrin B, Franks LM, Ratcliffe JG. Multiple hormones in a bronchial tumor. *J Clin Endocrinol Metab* 1974; **38**:1090–7.
37 Yalow RS, Wolf J, Lee LE. Ectopic ACTH in bronchogenic carcinoma. *Proc Am Soc Clin Oncol* 1977; **18**:277.