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FROM THE DEPARTMENT OF ONCOLOGY ONB, FINSEN INSTITUTE, THE MEDICAL DEPARTMENT C, BISPEBJERG HOSPITAL, AND THE MEDICAL DEPARTMENT P (NEPHROLOGY), RIGSHOSPITALET, COPENHAGEN, DENMARK.

HYPOURICEMIA AND URATE EXCRETION IN SMALL CELL LUNG CARCINOMA PATIENTS WITH SYNDROME OF INAPPROPRIATE ANTIDIURESIS

J. B. SØRENSEN, K. ØSTERLIND, P. E. G. KRISTJANSEN, M. HAMMER and M. HANSEN

Abstract

Urate concentrations in serum and renal urate clearance were prospectively evaluated in patients with small cell lung cancer (SCLC). Serum urate and renal urate clearance were measured before and during cytostatic treatment until disease progression (PD) in 12 patients with the syndrome of inappropriate antidiuresis (SIAD) and in 8 patients without. Hypouricemia occurred in 4 SIAD patients before treatment and also when tumor regression was obtained. Two normouricemic SIAD patients developed hypouricemia when PD occurred. No patient without SIAD experienced hypouricemia. Serum urate in patients with SIAD was lower than in those without SIAD before cytostatic treatment but not 3 months after the treatment. Hypouricemic patients had higher urate clearance than normouricemic and it remained higher even after tumor regression. Serum urate was invalid as marker of tumor regression or relapse. SIAD patients have higher glomerular filtration rates than patients without SIAD, which may influence the renal excretion of cytostatic drugs.

Key words: Small cell lung cancer; hypouricemia, syndrome of inappropriate antidiuresis, chemotherapy.

Hypouricemia is frequently found in patients with hyponatremia due to the syndrome of inappropriate antidiuresis (SIAD), and it has been suggested that hypouricemia may be diagnostic for the occurrence of SIAD in patients with hyponatremia (2). Passamonte (11) reported a retrospective study in patients with small cell lung carcinoma (SCLC) where 6 out of 8 patients with SIAD had hypouricemia and the coexistence of hypouricemia and hyponatremia predicted SIAD reliably (6/6 patients). However, the concentration of serum urate alone was found in a prospective study to have rather low sensitivity and specificity for the diagnosis of SIAD, though SIAD patients as a group had significantly lower serum urate concentrations than other SCLC patients (9). It was proposed that measurements of serum urate during antineoplastic therapy in SCLC patients with SIAD might add to the clinical and radiological evaluation of tumor regression and relapse (9).

The purpose of the present study was to investigate prospectively whether serum concentrations of urate or the renal urate clearance could be a marker of tumor regression or relapse in SCLC patients with SIAD. Concomitantly, the mechanism of the low serum urate concentration in SIAD patients could be elucidated in a clinical setting together with the alterations in renal function and body fluid compartments during cytostatic treatment of the malignant disease.

Material and Methods

Patients. Patients with newly diagnosed and untreated SCLC, admitted to the Finsen Institute or Bispebjerg Hospital for cytostatic treatment, were eligible for the study. Histologic classification was performed according to the WHO classification (14) by pathologists at the respective hospitals. Patients receiving drugs influencing the salt-water balance and patients with neurological disorders were not included.

Further criteria for inclusion were normal liver, cardiac and renal functions, as evidenced by plasma concentrations of liver enzymes, electrocardiography and serum

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Table 1

Median values of serum urate, renal urate clearance and 24-h urate excretion before cytostatic treatment, at remission and, for serum urate, at progression of the malignant disease

Patient group	Pretreatment				At remission				At disease progression	
	p-sodium (mmol/l)	s-urate (mmol)	Urate-clearance (mmol)	24-h urate excretion (mmol)	p-sodium (mmol)	s-urate (mmol/l)	Urate-clearance (ml/min)	24-h urate excretion (mmol)	p-sodium (mmol/l)	s-urate (mmol/l)
Hypouricemic SIAD (n=4)	119	0.13	21.2	3.6	127	0.15	13.1	2.8	126	0.19
Normouricemic SIAD (n=8)	130	0.21	8.8 *	2.7	133	0.26	9.3	3.0	125	0.19
Patients without SIAD (n=8)	142	0.28**	8.2	2.9	142	0.26	6.9	2.5	140	0.22

* $p<0.05$; **<0.02.

creatinine, and a urine free of protein and glucose. The 24-h urine cortisol excretion should be normal. Informed consent was obtained from all patients.

For inclusion of patients both with and without a possible SIAD, SCLC patients with plasma sodium below 136 mmol/l and a group of SCLC patients with plasma sodium above 140 mmol/l were examined.

Treatment. Chemotherapy was given according to one of three regimens in a controlled trial, consisting of either a 6-drug alternating combination, a continuous 6-drug combination or an alternating 9-drug chemotherapy as described elsewhere (10). All 3 regimens included lomustine, cyclophosphamide, methotrexate, vincristine, etoposide and doxorubicin while vindesine, cisplatin and hexamethylmelamine were added in the 9-drug regimen.

Response assessment was performed every 4 weeks according to the WHO criteria (13) and, in case of treatment cessation, the patients were followed until death. The effect of treatment was defined as complete and partial responses. Complete response (CR) is disappearance of all known disease, while partial response (PR) is a decrease in total tumor size of 50% or more without appearance of new lesions or progression of any lesion.

Examination program. All patients were examined before initiation of cytostatic treatment and, if remission occurred, they were reexamined after 3 months with the initial program.

SIAD was defined by the presence of hypoosmolality of plasma (less than 280 mosm/kg), hyponatremia (less than 136 mmol/l) and inappropriately concentrated urine, i.e. urine osmolality exceeding that of plasma. Patients without SIAD all had normal plasma osmolality, normal plasma sodium concentration, and a urine osmolality below that of plasma.

Plasma and urine osmolalities were measured by freezing point depression. Glomerular filtration rate (GFR) was evaluated by inulin-clearance (reference limits: 57–162 ml/min in males and 58–146 ml/min in females).

The plasma volume was recorded as ^{125}I-albumin space and the extracellular volume (ECV) as inulin space.

The urate concentration in a 24-h urine sample and morning urate concentration in serum were measured in order to calculate the renal urate clearance and the 24-h urate excretion (reference limits were for serum urate 0.20–0.45 mmol/l in males and 0.15–0.35 mmol/l in females; plasma sodium 136–146 mmol/l).

Serum urate and plasma sodium were recorded every 4 weeks in all patients until tumor progression.

Statistical analyses were made using Wilcoxon's rank sum test for paired data and Mann-Whitney's rank sum test for unpaired data (1). The correlation between concomitant observations were analyzed by Spearman's nonparametric correlation coefficient (3).

Results

Patient characteristics. Twelve patients with SIAD and 8 patients without the syndrome were included in the study. There were 14 males and 6 females. Six patients had extensive disease (spread beyond one hemithorax and supraclavicular lymph nodes), 3 had a performance status of 0, 14 of 1 and 3 a performance status of 2 (Zubrod scale, 15)

The median survival was 369 days (range 212–1 006) for patients without SIAD and 351 days (210–870) for SIAD patients.

Remission of the malignant disease occurred within 3 months in 10 SIAD patients (5 PR, 5 CR) and in 4 patients without SIAD (2 PR, 2 CR). One additional partial response occurred after 3 months among the SIAD patients

Table 2

Extracellular volume (ECV) and plasma volume (PV) before cytostatic treatment (Pretreatment) and after tumor remission (At remission)

Patient group	ECV (% of body weight) median (range)		PV (% of body weight) median (range)	
	Pretreatment	At remission	Pretreatment	At remission
Hypouricemic SIAD	21.9 (18.2–27.6) n=4	19.4 (16.1–25.5) n=4	5.3 (4.7–5.5) n=4	4.8 (4.4–5.0) n=4
Normouricemic SIAD	20.6 (16.9–28.2) n=8	20.3 (15.8–27.0) n=6	4.9 (4.1–7.0) n=8	5.2 (4.8–6.3) n=6
Without SIAD	20.1 (13.0–28.5) n=8	21.8 (19.6–23.4) n=4	5.0 (4.0–6.1) n=8	5.6 (5.0–6.4) n=4

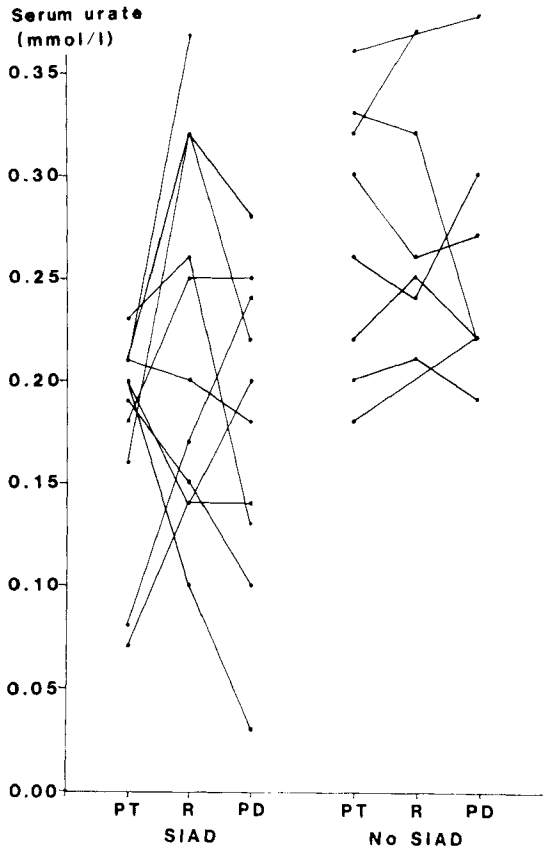

Figure. Serum urate concentration in 19 patients with small cell cancer, 11 patients with and 8 without the syndrome of inappropriate antidiuresis (SIAD). Pretreatment (PT), time of tumor remission (R), time of tumor progression (PD).

and 2 additional partial responses among the patients without SIAD.

Serum urate. Results of serum urate concentrations before treatment, at remission and relapse, are shown in Table 1. Before treatment, hypouricemia was observed in 4 of the 12 SIAD patients, but was not found in the patients without SIAD. At this initial examination serum urate concentrations were lower in SIAD patients than in patients without SIAD ($p<0.02$).

At the time of remission, hypouricemia was observed in 5 out of 11 responding patients with SIAD (1 CR, 4 PR) and in none of 6 responding patients without the syndrome. No statistically significant difference in serum urate concentration could be detected between the 2 groups of responding patients. One of the initially hypouricemic SIAD patients had normal serum urate at the time of remission. Two initially normouricemic SIAD patients developed hypouricemica at the time of remission (1 CR, 1 PR), and 2 additional patients had hypouricemia at the time of disease progression.

All patients in the control group remained normouricemic during treatment and at disease progression. The serum urate values for patients with and without SIAD before treatment and at the time of tumor remission and progression are shown in the Figure.

24-h urate excretion. Differences in serum urate concentrations at the initial examination were not related to the 24-h urate excretion. The excretions were similar for hypouricemic SIAD patients, normouricemic SIAD patients and patients without SIAD (Table 1).

Urate clearance. Urate clearance was higher in hypouricemic patients than in patients with serum urate concentrations within reference limits at the initial examination ($p<0.05$). In spite of tumor remission (1 CR, 3 PR) the urate clearance remained higher than in ($p<0.01$) compared to normouricemic patients at reexamination though not significantly (Table 1). There was a significant inverse correlation between the values of serum urate and the concomitant values of renal urate clearance (Spearman's correlation coefficient $R=-0.6739$; $p<0.001$).

Plasma- and extracellular volume. No significant changes occurred in extracellular volume after tumor regression in either of the patient groups. Similarly, the plasma volumes remained constant (Table 2). Neither extracellular volume nor plasma volume of hypouricemic

SIAD patients were significantly different from normouricemic patients with or without SIAD (Table 2).

Glomerular filtration rate. Two out of 4 SIAD patients with hypouricemica and one out of 8 SIAD patients with normal serum urate had GFR above normal limits. The median inulin clearance was for all SIAD patients 137 ml/min (range 74–177) and for patients without SIAD 99 ml/min (70–122) ($p<0.05$) at the initial examination. Inulin clearance was within normal limits in all patients at reexamination with a median of 130 ml/min (87–148) and 90 ml/min (86–123) in SIAD patients and in patients without SIAD respectively.

Discussion

It has been reported that symptoms of inappropriate antidiuresis normalize when objective tumor response is achieved (4), but the presence of SIAD does not appear to be valid as a marker of tumor response or relapse (5). It is not known whether an associated hypouricemia might be useful as tumor marker. Østerlind et al. (9) proposed that measurements of serum urate in patients with SCLC and SIAD might be more sensitive than clinical and radiological evaluation during antineoplastic therapy. The present study shows that measurements of serum urate concentrations are not useful as tumor marker in patients with SCLC due to lack of sensitivity and specificity. As a marker it is definitely inferior to the conventional clinical and radiological evaluation of tumor response. Serum urate measurements were of only limited value in the detection of PD, since only 2 out of 12 pretreatment normouricemic patients developed decreased concentrations when PD occurred.

SIAD in patients with concomitant hypouricemia was described in 1971 by Mees et al. (7). In subsequent studies, SIAD was found to be common among patients with SCLC (6), and Passamonte (11) reported that the coexistence of hypouricemia and hyponatremia predicted SIAD reliably (6/6 patients). This is supported by the present prospective study as hypouricemia occurred in 4 patients with hyponatremia and SIAD while no patient with hypouricemia was observed in the normonatremic patient group. It was, however, not the purpose of the study to evaluate this matter, and no hyponatremic patients without SIAD were included.

The present study confirms the finding of other authors (6, 9) that SIAD patients in general have significantly lower serum urate concentrations than SCLC patients without the syndrome. However, the frequency of hypouricemia among SIAD patients (33%) was lower than the 75% reported from a retrospective study by Passamonte (11).

Hypouricemia in patients with SIAD may be caused by decreased urate production, dilution due to water retention or enhanced renal clearance. Beck (2) did not find low daily urate production in 3 hypouricemic (and hyponatremic) patients. In the present study, the 24-h urate excretion was found to be similar in hypouricemic and normouricemic patients. According to the present data the hypouricemia seems to result from an elevated urate clearance, as also demonstrated by Mees (7) in experimentally induced water retention.

Hypouricemia is not due to simple dilution of body fluid compartments, but expansion of the extracellular fluid compartment has been proven to reduce the tubular reabsorption of urate (6, 8). In the present study a significantly higher renal urate clearance was found in hypouricemic patients. The extracellular volume and plasma volume were both initially higher in hypouricemic patients than in normouricemic ones.

In conclusion, it is apparent that the serum urate concentration is invalid as a marker of tumor response or relapse in patients with SCLC. The study corroborates that hypouricemia in SIAD is caused by an increased renal clearance, while the production seems to be unaffected. The patients with SCLC and SIAD have higher glomerular filtration rates as a group than SCLC patients without the syndrome, which may influence the renal excretion of drugs, e.g. methotrexate.

Request for reprints: Dr Jens Benn Sørensen, Dept. of Oncology ONB, Finsen Institute, 49 Strandboulevarden, DK-2100 Copenhagen, Denmark.

REFERENCES

1. ARMITAGE P.: Statistical methods in medical research. Blackwell, New York 1971.
2. BECK L. H.: Hypouricemia in the secretion of inappropriate secretion of antidiuretic hormone. N. Engl. J. Med. 301 (1979), 528.
3. FIENBERG S. E.: The analyses of cross-classified categorial data. MIT Press, Cambridge, Mass. 1978.
4. HAINSWORTH J. D., WORKMAN R. and GRECO A.: Management of the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer. Cancer 51 (1983), 161.
5. HANSEN M., HAMMER M. and HUMMER L.: ACTH, ADH and calcitonin as markers of response and relapse in small cell carcinoma of the lung. Cancer 46 (1980), 2062.
6. — — — Diagnostic and therapeutic implications of ectopic hormone production in small cell carcinoma of the lung. Thorax 35 (1980), 101.
7. MEES E. J. D., VAN ASSENDELFT P. B. and NIEUWENHUIS M. G.: Elevation of uric acid clearance caused by inappropriate antidiuretic hormone secretion. Acta Med. Scand. 189 (1971), 69.
8. MEISEL A. and DIAMOND H.: Effect of vasopressin on uric acid excretion. Evidence for distal nephron reabsorption of urate in man. Clin. Sci. Mol. Med. 51 (1976), 33.
9. ØSTERLIND K., HANSEN M. and DOMBERNOWSKY P.: Hypouricemia and inappropriate secretion of antidiuretic hormone in small cell bronchogenic carcinoma. Acta Med. Scand. 209 (1981), 289.
10. — PEDERSEN A. G., VINDELØV L. et al.: Alternating or continuous chemotherapy of extensive stage small cell lung cancer (SCC). Lung Cancer 2 (1986), 127.
11. PASSAMONTE P. M.: Hypouricemia, inappropriate secretion of antidiuretic hormone, and small cell carcinoma of the lung. Arch. Intern Med. 144 (1984), 1569.

12. STEELE T. H.: Evidence for altered renal urate reabsorption during changes in volume of the extracellular fluid. J. Lab. Clin. Med. 74 (1969), 288.
13. WORLD HEALTH ORGANIZATION: WHO handbook for reporting results of cancer treatment. Publication No 48. World Health Organization, Geneva 1979.
14. — The World Health Organization histologic typing of lung tumors, second edition. Am. J. Clin. Pathol. 77 (1982), 123.
15. ZUBROD C. G., SCHNEIDERMAN M., FREI III E. et al.: Appraisal of methods for the study of chemotherapy of cancer in man. Comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. J. Chron. Dis. 11 (1960), 7.