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Abstract

Hyponatremia is a common clinical problem and results from various causes. Hypothyroidism is known to be one of the causes of this disorder. We report here a case having metastatic thyroid cancer presenting severe hyponatremia in association with hypothyroidism induced by pretreatment of I^{131} therapy, such as a low-iodine diet and withdrawal of thyroid hormone. Serum arginine vasopressin (AVP) was elevated and urine osmolality was higher than serum one. Saline infusion and thyroid hormone replacement normalized serum sodium and AVP. Inappropriate secretion of AVP in hypothyroid state was thought to be one of the causes of this hyponatremia.

Key words: hypothyroidism, hyponatremia, thyroid cancer, I^{131} therapy, arginine vasopressin

Introduction

Patients with differentiated thyroid carcinoma, especially those belonging to high-risk groups, are often treated with radioactive iodine (I^{131}) approximately 6 weeks after thyroidectomy (1). In order to increase the ability to get I^{131} into the residual thyroid tissue for successful ablation, a low-iodine diet and withdrawal of thyroid hormone are required for at least the last 2 weeks before I^{131} therapy (1,2). Hyponatremia, which is a common disorder, results from various causes, and sometimes induces fatal complications (3). It is well known that hypothyroidism is one of the causes, and recently hyponatremia in association with hypothyroidism induced by pretreatment of I^{131} therapy or testing occurred in patients with thyroid cancer was reported (4,5). Although this complication seems rare, but there is a possibility that symptomatic hyponatremia may occur in any patients undergoing this therapy or testing. Therefore, physicians should recognize it well, and manage their patients adequately.

In this report, we described a patient with metastatic papillary thyroid cancer who developed severe hyponatremia after I^{131} therapy. The mechanisms of this electrolyte imbalance were also discussed.

Case Report

The case presented in this paper was 77-year-old woman. She had a history of transient cerebral ischemia attack and underwent left carotid endarterectomy in 2004. In June, 2005, she developed papillary cancer of thyroid and left lobe thyroidectomy was performed. In July, 2009, metastasis of left cervical lymph node was detected. Since she had already undergone operation in the neck, cervical lymph node dissection was supposed to be difficult because of technical reasons. Moreover, increase of the risk of

arterial thrombus in association with antiplatelet drug withdrawal was anticipated, radioactive iodine therapy was employed. She underwent right lobe thyroidectomy in August, 2009, followed by I^{131} therapy in March, 2010. The first radioactive iodine therapy was performed without any complications, but metastatic lymph node had been gradually enlarged after the therapy. The clinical course thereafter was summarized in Figure 1. The second I^{131} therapy was performed at the department of radiology, Asahikawa Medical University Hospital in November 16, 2010, with 2 weeks' pretreatment such as discontinuation of thyroid hormone replacement and a low-iodine diet, which was the same protocol as the first therapy. In November 18, thyroid hormone replacement was restarted and she was discharged in November 22. In the following day, she developed poor appetite and general fatigue, and these symptoms had been gradually deteriorated. Then she visited to our department and was admitted in November 29, 2010. At that time, her symptoms were drowsiness, lethargy, nausea and vomiting. Physical examination revealed a heart rate of 70/min, blood pressure 116/76 mmHg. She had no edema and no evidence of hyperhydration or dehydration in spite of having had poor appetite and vomiting before visiting. Magnetic resonance imaging and computed tomography of the brain were normal. Chest radiograph showed normal cardiothoracic ratio (CTR). Laboratory values were summarized in Table 1. She had severe hyponatremia which was thought to be cause of impaired consciousness, together with other electrolyte abnormalities such as hypokalemia, hypocalcemia and hypophosphatemia. Urine osmolality was higher than serum one, and arginine vasopressin (AVP) was elevated. Hypothyroid state was also indicated. The function of adrenal gland, intact parathyroid hormone (PTH) and 1,25-$(OH)_2$ vitamin D were all normal. However, plasma renin activity (PRA) and N-terminal pro brain natriuretic

peptide (NT-proBNP) were elevated. Blood gas analysis demonstrated metabolic alkalosis. Fractional excretion (FE) of sodium, potassium and calcium were all reduced, but phosphorus excretion was not suppressed despite reduced serum level. She was treated with intravenous infusion of normal saline with potassium and calcium replacement. Moreover, dose of levothyroxine was increased and administration of liothyronine was also added in order to achieve euthyroid smoothly. On the day following admission, her all symptoms were improved, and 3 days after, she began to take food. All electrolyte abnormalities were gradually normalized until December 8, and at that time, euthyroid was achieved, and serum AVP returned to normal. She was discharged at December 15 with full recovery.

Discussion

Hyponatremia, which is a common clinical problem, frequently develops in elderly and/or hospitalized patients (6). Although morbidity varies widely in severity, serious complications such as brain edema and demyelination can arise from the disorder itself as well as from errors in management (3). Present case with metastatic thyroid cancer, developed severe symptomatic hyponatremia in association with I^{131} therapy. Laboratory data demonstrated she did not have adrenal insufficiency, and antihypertensive drugs including diuretics were not administered. No dietary sodium restriction was performed. Although N-terminal proBNP level was high, she did not develop edema and CTR was not increased, indicating there was no significant congestive heart failure inducing dilutional hyponatremia. In this context, hypothyroidism resulting from the preparation of this therapy was thought to be the main cause of hyponatremia in our case.

There have been 2 papers from the States reporting the cases with symptomatic hyponatremia occurred in the patients with thyroid cancer, associated with the preparation-induced hypothyroidism (4,5), and these 6 cases together with present case were summarized in Table 2. Most of the cases were elderly female having a metastasis to lung and/or brain. The histological types were papillary and follicular, i.e., differentiated thyroid cancer. These tumors with a metastasis are indication for I^{131} therapy, and frequently occur in female. These lines of evidence may explain the fact of female predominance of concerned cases. Hyponatremia occurred after the withdrawal of thyroid hormone (mean 4.2 weeks) together with a low-iodine diet (mean 2.3 weeks) in the previous reported cases. The sodium concentration at the time of symptoms occurring, such as lethargy, nausea and general fatigue was between 110 – 121 mEq/L. The treatment was made by fluid restriction and/or normal saline infusion, and thyroid hormone replacement was performed in all cases, which achieved full recovery. Most of the cases developed hyponatremia during the preparation period, before the therapy. On the other hand, our case developed it with relatively short duration of the preparation (2 weeks), and severe hyponatremia (98 mEq/L) occurred 12 days after restarting thyroid hormone replacement and cessation of diet restriction, suggesting that it may occur not only in the preparation period but also later after the therapy.

The mechanisms of hyponatremia under hypothyroidism have been explored. Patients and experimental animals with hypothyroidism demonstrated impaired water excretion, failure to achieve maximal urinary dilution, and exaggerated natriuresis in response to volume alterations caused by water loading leading to hyponatremia (7-11). Previous study demonstrated that hypothyroid rats showed less water excretion, higher urinary osmolality, decreased serum osmolality, and elevated plasma AVP concentration

after water load (9). Hypothyroidism may be associated with a decrease in blood pressure secondary to diminished myocardial contractility and heart rate, which would be expected to activate baroreceptor-mediated, non-osmotic AVP release leading to dilutional hyponatremia, which is thought to be one of the mechanisms of hypothyroidism-induced hyponatremia (12). Shakir et al. demonstrated that inappropriate high level of AVP (7.80 ± 2.33 pg/mL) was observed in the 5 cases with hyponatremia occurred in the patients with thyroid cancer, associated with the preparation of I^{131} therapy (4). Moreover, despite hyponatremia, urine osmolality was not reduced (165 ± 31.9 mOsm/kg), and thyroid hormone replacement with water restriction and/or administration of saline normalized serum sodium and AVP level (1.90 ± 0.55 pg/mL). Although it was unknown that blood pressure was decreased enough to stimulate AVP release in the present case, because it was not recorded before the therapy, these above laboratory findings were completely compatible with those in our case. Since one of the criteria required to make a diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) includes exclusion of hypothyroidism, the concerned cases were not regarded as SIADH. However, inappropriate secretion of AVP may play an important role in this disorder under hypothyroidism. In our case, in addition to these above results, urine output was not reduced, even though she had complained of poor appetite for several days before admission, which may further support the hypothesis. The high level of NT-proBNP may be also explained by this reason.

Meanwhile, marked sodium loss was observed in hypothyroidism, and the rats receiving antithyroid drugs together with a sodium-deficiency diet were rapidly dying from negative sodium balance (13). The observed sodium loss was attributed to a

diminished reabsorptive ability of the renal tubule (14,15). Shmitt et al. showed that the expression of two major sodium transporters of the proximal tubule, type 3 Na/H exchanger and type 2 Na-phosphate cotransporter was reduced in hypothyroid rats kidney (16), and these sodium transporters were directly stimulated by triiodo-L-thyronine (17,18). These lines of evidence suggest that hypothyroidism reduces these transporters in the proximal tubule leading diminished sodium reabsorption, resulting in hyponatremia, which is thought to be another mechanism other than AVP related one.

Other mechanisms in relation to the preparation were also suggested in the previous papers (4,5). The authors suggested reduced sodium intake during this preparation period might contribute. In the States, table and cooking salt are iodized, and the patients are counseled to avoid taking the salt and products during this period. Even though iodine-free salt is recommended during the period of dietary restriction, patients may severely restrict sodium intake (4). A low-salt diet may also occur in the patients living in the country in which salt is not iodized because of poor appetite induced by thyroid hormone withdrawal and a low-iodine diet (4), which may be one of the factors inducing hyponatremia in our case.

It has been demonstrated that mineralcorticoid-responsive hyponatremia of the elderly (MRHE) is an important and frequent cause of hyponatremia occurred in elderly (19). Since MRHE resembles SIADH in laboratory findings (20), discrimination of these disorders are frequently difficult. MRHE is thought to be caused by degradation of the response to the renin-aldosterone in addition to increasing weakness of the renal capacity for sodium retention due to aging (21), leading to slightly decrease the circulatory blood volume and be dehydrated, which is different from SIADH. Although

physical finding of slight dehydration in the elderly is not always easy, our case did not demonstrate any signs of dehydration, and inadequate high urinary output was observed after admission, suggesting she may be rather hyperhydrated. Her hyponatremia was ameliorated without administration of mineralcorticoid, and serum sodium was normal before I^{131} therapy and after discharge. These results suggest that MRHE may less contribute to the hyponatremia in our case.

Present case showed severe hyponatremia together with other electrolyte abnormalities such as hypokalemia, hypocalcemia and hypophosphatemia. It was shown that additional electrolyte disturbances are frequently observed in patients with hyponatremia of any origin (22). Since the patient developed poor appetite and vomiting before admission, both reduced intake of potassium and extrarenal potassium loss were thought to be the cause. The level of 1,25-dihydroxy vitamin D was within normal limit but intact-PTH level was not elevated. Definite mechanisms were not determined but transient hypoparathyroidism after I^{131} therapy may be the reason of hypocalcemia observed in the present case (23). It was shown that hypophosphatemia was the most frequent electrolyte disorder especially in the patients with hyponatremia due to SIADH (22). It can be attributed to volume expansion, since experimental studies clearly showed that volume expansion evoked an inhibition of phosphate uptake by the renal proximal tubules (24). As inappropriate secretion of AVP is thought to contribute to the hyponatremia in our case, this mechanism may also apply. In fact, inappropriate phosphaturia ($FEPO_4^{3-}$ 22.6%) was observed.

The management of this hyponatremia with evidence has not been determined. Since AVP is thought to contribute to this condition, water restriction may be the most effective treatment. The present case was not subjected to restrict water, because she

had a history of transient cerebral ischemia attack, indicating high risk of cerebral infarction. Fluid restriction to correct hyponatremia due to SIADH was reported to be potentially dangerous in the patients with risk of cerebral ischemia (25).

The present case underwent I^{131} therapy for 2 times before admission. The pretreatment was the same in both therapy, but this episode only occurred in the second one. The reason was not known. However, this suggests that symptomatic hyponatremia may occur in the patients undergoing this therapy without any specific triggers.

In conclusion, the patients with metastatic thyroid cancer may develop symptomatic hyponatremia in association with the pretreatment of I^{131} therapy. Hypothyroidism and possible low-sodium intake during the preparation period are thought to be the cause of this electrolyte disorder, but our case demonstrated that hyponatremia may occur in several days after restarting thyroid hormone replacement. Physicians should recognize this disorder well, and careful monitoring of serum sodium is needed.

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Figure legends

Figure 1

Clinical course. Hyponatremia together with other electrolyte abnormalities occurred after I^{131} therapy. Notice that urine osmolality was not reduced despite hyponatremia, and serum AVP level was inappropriately elevated. Saline infusion with potassium and calcium replacement, and normalization of thyroid function resulted in full recovery. At this time, AVP level returned to normal. Serum calcium level was corrected by the serum albumin value.

Table 1. Laboratory Findings on Admission

WBC 8650 /μL
RBC 376×10^4 /μL
Hb 12.2 g/dL
Ht 31.1%
Plt 18.4×10^4 /μL

Urinalysis
Urine specific gravity 1.020
pH 6.0
Protein 2+
Sugar 3+
Occult blood 2+
Ketone 1+

Urine osmolarity 228 mOsm/Kg·H_2O

Serum osmolarity 199 mOsm/Kg·H_2O

Urine Na 24.4 mEq/gCre
Urine K 34.1 mEq/gCre
Urine Ca 195 mg/gCre
Urine P 683 mg/gCre

$FENa^+$ 0.13 %
FEK^+ 6.96 %
$FECa^{2+}$ 1.34 %
$FEPO_4^{3-}$ 22.6 %

TP 6.3 g/dL
Alb 4.1 g/dL
AST 42 IU/L
ALT 45 IU/L
LDH 604 IU/L
ALP 217 IU/L
γ-GTP 33 IU/L
LAP 50 IU/L
CPK 952 IU/L
T.Chol. 214 mg/dL
Na 98 mEq/L
K 2.5 mEq/L
Cl 58 mEq/L
Ca 8.0 mg/dL
P 1.7 mg/dL
Mg 1.7 mg/dL
UA 1.6 mg/dL
BUN 9 mg/dL
Cre 0.57 mg/dL
CRP 6.03 mg/dL
Glucose 172 mg/dL
HbA1c 6.0 %

TSH 25.1 μU/mL
Free-T3 < 0.260 pg/mL
Free-T4 0.32 ng/dL
AVP 7.8 pg/mL
LH 2.21 mIU/mL
FSH 52.75 mIU/mL
PRL 87.57 ng/mL
Cortisol 33.13 μg/dL
ACTH 18.27 pg/mL
PRA 15.0 ng/mL/h
Aldosterone 116.0 pg/mL
DHEA-S 16 μg/dL
NT-proBNP 973.9 pg/mL
intact PTH 35 pg/mL
1,25-OH_2 vitamine D 104 pg/mL

Blood gas analysis
pH 7.597
PCO_2 31.8 mmHg
PO_2 64.6 mmHg
HCO_3^- 31.2 mEq/L

FE; fractional excretion, TSH; thyroid stimulating hormone, AVP; arginine vasopressin, LH; luteinizing hormone, FSH; follicle-stimulating hormone, PRL; prolactin, ACTH;

adrenocorticotropin, PRA; plasma renin activity, DHEA-S; dehydroepiandrosterone sulfate, PTH; parathyroid hormone, NT-proBNP; N-terminal pro brain natriuretic peptide

Table 2. Hyponatremia occurred in the patients with thyroid cancer, associated with the preparation of I^{131} therapy or treatment

Age	Sex	Thyroid hormone withdrawal	Low-iodine diet	Sodium concentration	Treatment	Types of thyroid cancer	Metastasis	References
87	F	4 w	10 d	118	FR	Follicular	Lung	Shakir et al.(4)
66	F	6 w	6 w	114	FR	Papillary	Brain, Lung	Shakir et al.(4)
72	F	5 w	1 w	121	FR	Papillary	Lung	Shakir et al.(4)
68	M	4 w	10 d	115	FR + INF	Papillary	Lung	Shakir et al.(4)
71	F	2 w	2 w	110	FR + INF	Follicular	(Vascular invasion)	Shakir et al.(4)
70	M	?	2 w	115	INF	Papillary	None	Krishnamurthy et al.(5)
77	F	2 w	2 w	98	INF	Papillary	Cervical L/N	Present case

F; female, M; male, w; weeks, d; days, FR; fluid restriction, INF; saline infusion, L/N; lymph node.