Syndrome of inappropriate secretion of thyrotropin associated with thymoma-related peripheral nerve hyperexcitability

Kenji Ohba1), Kentaro Shirakawa2), Yuta Okawa1), Hiroyuki Iwaki1), Hideyuki Matsunaga1), Shingo Suzuki1), Akio Matsushita1), Hiroshi Morita1), Shigekazu Sasaki1), Yutaka Oki1) and Hirotoshi Nakamura1)

1)Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan
2)First Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan

Abstract. Syndrome of inappropriate secretion of thyrotropin (SITSH) is a clinical state of inappropriately elevated secretion of thyrotropin (TSH) in the presence of elevated free thyroid hormones. Peripheral nerve hyperexcitability (PNH) is a rare disorder characterized by muscle twitching at rest. No relation between them is known. A 49-year-old man was referred to our hospital because of elevated serum free thyroxine (2.6 ng/dL; normal range, 0.9–1.7) and normal TSH (2.7 mIU/L; normal range, 0.5–5.0). Genetic analysis revealed no mutations of the thyroid hormone receptor β gene. Magnetic resonance imaging visualized no pituitary adenoma. He complained of appetite loss, weight loss, myokymia, paraesthesia, hyperhydrosis and insomnia. Chest X ray and computed tomography (CT) scan showed a mediastinal tumor diagnosed as a thymoma by CT-guided biopsy. Electromyography disclosed fasciculations and myokymic discharges. Nerve conduction studies showed prolonged after-discharges following evoked compound muscle action potential. The patient was diagnosed with thymoma-associated PNH based on neurological manifestations and neurophysiological findings, and was treated with pulse therapy with methylprednisolone after thymectomy. Interestingly, the SITSH state became less prominent as his neurological manifestations improved. This is the first case of SITSH possibly caused by thymoma-associated PNH.

Key words: Syndrome of inappropriate secretion of thyrotropin, Peripheral nerve hyperexcitability, Syndrome of inappropriate antidiuretic hormone secretion, Voltage-gated potassium channel, Thymoma

SYNDROME of inappropriate secretion of thyrotropin (SITSH) is a clinical state defined as inappropriately non-suppressed serum thyrotropin (TSH) in the presence of elevated free thyroid hormones [1]. TSH-secreting pituitary adenoma (TSH-oma) and syndrome of resistance to thyroid hormone (RTH) are the two main etiologies of SITSH. Although other causes such as hypersecretion of TSH-releasing hormone (TRH) are suspected [2], no clearly supporting case report has been demonstrated.

Peripheral nerve hyperexcitability (PNH) is a rare disorder characterized by generalized hyperexcitability of the motor nerves resulting in continuous and spontaneous muscle fiber activity (e.g., fasciculations or myokymia). Many patients present with paraesthesia, implying sensory nerve involvement, and hyperhydrosis, which might indicate autonomic dysfunction [3]. No diagnostic criteria have been published and the diagnosis depends on clinical and electromyographic features. We report here a very interesting patient with thymoma-associated PNH probably causing SITSH.

Case Report

A 49-year-old man was referred to our hospital because of suspected SITSH. At his first visit, he complained of gradually developing appetite loss, weight loss of 20 kg in a year, myokymia in the lower extremities, paraesthesia in the distal extremities, hyperhydrosis, insomnia and seemed distressed. His past medical history was unremarkable. Neither his parents nor other relatives had thyroid disease. He was 171 cm tall and weighed 61 kg. His pulse rate was 83 beats/min and regular. Blood pressure was 122/88 mmHg and
positive at 30 nmol/L (normal range, <0.2, AChRAb cosmic II; Cosmic Corporation, Tokyo, Japan), but no clinical signs of myasthenia Graves’ were observed and repetitive nerve stimulation showed no significant decrement. Electromyography (EMG) revealed continuous activities of myokymic discharges and fasciculation potentials at rest (Fig. 2A). Nerve conduction studies (NCS) showed prolonged after-discharges following evoked compound muscle action potential without evidence of axonal or demyelinating neuropathy (Fig. 2B). The diagnosis of thymoma-associated peripheral nerve hyperexcitability was made based on the clinical manifestations and supported by EMG and NCS findings, which are different from those in patients with hyperthyroidism; however, the antibody against voltage-gated potassium channel (VGKC), measured by an immunoprecipitation method with 125I-α-dendrotoxin-labeled extracts of human frontal cortex [4], was not detected.

In the evaluation of SITSH, we first measured serum thyroid hormones after precipitation by polyethylene glycol [5] to eliminate the presence of anti-thyroid hormone antibodies. The results showed no significant reduction in free thyroxine (FT4) and free triiodothyronine (FT3). Both urinary deoxypyridinoline and serum sex hormone-binding protein, peripheral markers of thyroid hormone action, were in hyperthyroid state (20.1 nmol/mmolCr; normal range, 2.1–5.4, and 86.3 mmol/L; normal range, 10–60, respectively).

Chest X-ray film showed a mediastinal tumor and he was admitted to our hospital. Chest-computed tomography (CT) scan and CT-guided biopsy revealed a mediastinal thymoma of 9.9 cm in maximum diameter (Fig. 1). Serum acetylcholine receptor antibody was positive at 30 nmol/L (normal range, <0.2, AChRAb cosmic II; Cosmic Corporation, Tokyo, Japan), but no clinical signs of myasthenia Graves’ were observed and repetitive nerve stimulation showed no significant decrement. Electromyography (EMG) revealed continuous activities of myokymic discharges and fasciculation potentials at rest (Fig. 2A). Nerve conduction studies (NCS) showed prolonged after-discharges following evoked compound muscle action potential without evidence of axonal or demyelinating neuropathy (Fig. 2B). The diagnosis of thymoma-associated peripheral nerve hyperexcitability was made based on the clinical manifestations and supported by EMG and NCS findings, which are different from those in patients with hyperthyroidism; however, the antibody against voltage-gated potassium channel (VGKC), measured by an immunoprecipitation method with 125I-α-dendrotoxin-labeled extracts of human frontal cortex [4], was not detected.

In the evaluation of SITSH, we first measured serum thyroid hormones after precipitation by polyethylene glycol [5] to eliminate the presence of anti-thyroid hormone antibodies. The results showed no significant reduction in free thyroxine (FT4) and free triiodothyronine (FT3). Both urinary deoxypyridinoline and serum sex hormone-binding protein, peripheral markers of thyroid hormone action, were in hyperthyroid state (20.1 nmol/mmolCr; normal range, 2.1–5.4, and 86.3 mmol/L; normal range, 10–60, respectively).

Chest X-ray film showed a mediastinal tumor and he was admitted to our hospital. Chest-computed tomography (CT) scan and CT-guided biopsy revealed a mediastinal thymoma of 9.9 cm in maximum diameter (Fig. 1). Serum acetylcholine receptor antibody was

---

**Table 1** Basal hormone levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal range</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>0.5–5.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Free thyroxine (ng/dL)</td>
<td>0.9–1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Free triiodothyronine (pg/mL)</td>
<td>2.3–4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Thyroxine binding globulin (µg/mL)</td>
<td>15.9–35.6</td>
<td>19.0</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>3.6–12.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Adrenocorticotrophin (pg/mL)</td>
<td>7.2–63.3</td>
<td>27.7</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>5.3–11.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/mL)</td>
<td>0.8–5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (mIU/mL)</td>
<td>2.0–8.3</td>
<td>14.6</td>
</tr>
</tbody>
</table>

---

Fig. 1 (A) Contrast-enhanced transaxial computed tomography revealing a soft tissue density mass with a maximum diameter of 9.9 cm in the anterior mediastinum (arrowhead). (B) Histological section of the mediastinal tumor showing neoplastic epithelial cells surrounded by lymphocytes. These findings confirmed the diagnosis of type B1 thymoma (WHO classification).
excluded possible interference by endogenous anti-T3 and anti-T4 antibodies and other antibodies. Genetic analysis of the thyroid hormone receptor β (TRβ) gene was performed after providing genetic counseling and obtaining written informed consent, as described previously [6]. TRβ gene analysis revealed no mutation. Magnetic resonance imaging disclosed no pituitary adenoma. Regarding anterior pituitary hormones, the basal serum prolactin (PRL) level was high as 25.0 pmol/L (normal range, 3.6–12.8) (Table 1). A TRH stimulation test showed delayed TSH, exaggerated PRL and normal T3 responses (Fig. 4). A corticotropin-releasing hormone (CRH) administration test revealed increased adrenocorticotropic (ACTH) secretion.

The patient underwent total thymectomy and was treated with pulse therapy with methylprednisolone (1,000 mg intravenously for 3 days) just after surgery. The surgically resected specimen exhibited negative immunostaining for TSH. His neurological manifestations gradually improved, except for paraesthesia, but he complained of severe intercostal neuralgia of chronic post-thoracotomy pain syndrome. After thymectomy, his serum sodium concentration decreased to 129 mEq/L (Fig. 5). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was diagnosed on the basis of elevated ADH (4.1 pg/mL; normal range, 0.3–3.5) in spite of decreased serum osmolality (264 mOsm/kg; normal range, 276–292) and normal urine osmolality (347 mOsm/kg). Treatment with furosemide and water restriction increased the serum sodium concentration to normal. Thyroid function tests still demonstrated SITSH with elevated FT4 (2.3 ng/dL) and normal TSH (1.5 mIU/L) at the time of hospital dis-
charge. He returned to his hometown and four months later revisited our hospital. The patient exhibited only paraesthesia as a neurological manifestation but complained of severe intercostal neuralgia. Interestingly, his serum TSH was 2.9 mIU/L and FT4 had fallen to 1.8 ng/dL (Fig. 5). Additional pulse methylprednisolone was applied twice to relieve the symptoms, getting no improvement. To avoid the possible effect of glucocorticoid on TSH secretion, a TRH stimulation test was performed one month after the last pulse therapy, which showed a normal TSH response. CRH-stimulated ACTH secretion was also normal (Fig. 4). One year later, we were informed by his local primary doctor about the persistent very mild SITSH and mod-

Fig. 4 Endocrine stimulation tests with TSH-releasing hormone (TRH) or corticotropin-releasing hormone (CRH) before (●–●) and after (○–○) treatment. Blood samples were obtained before and 15, 30, 60, 90 and 120 min after injecting 500 µg TRH or 100 µg human CRH (Mitsubishi Tanabe Pharma, Osaka, Japan). TSH, thyrotropin; PRL, prolactin; T3, triiodothyronine; ACTH, adrenocorticotrophin.

Fig. 5 Clinical course of the present patient. Solid and open arrowheads indicate total thymectomy and pulse methylprednisolone (1,000 mg intravenously for 1–3 days), respectively. FT4, free thyroxine; TSH, thyrotropin; ADH, antidiuretic hormone. *appetite loss, myokymia, hyperhydrosis, and insomnia.
erate PNH conditions of the patient.

**Discussion**

The present patient referred to us because of SITSH was revealed to have thymoma-associated PNH. His SITSH became less obvious as his neurological manifestations improved after thymectomy and steroid pulse treatment. Since patients with thymoma are prone to produce endogenous antibodies, we first considered the possibility that elevated FT4 could have been due to antibody-mediated interference. The results of a polyethylene glycol precipitation test and HPLC gel filtration excluded possible interference by anti-T4 and anti-T3 antibodies and nonspecific binding with endogenous antibodies in the patient serum. Peripheral indices (i.e., urinary deoxypyridinoline and serum sex hormone binding protein) of the patient, which were in the hyperthyroid range, were consistent with functionally elevated FT4.

PNH is classified as autoimmune-mediated (e.g. thymoma, myasthenia gravis or rheumatoid arthritis) and non-immune-associated type (e.g. toxic exposure or genetic disorder) [7]. Recent evidence indicates that nerve hyperexcitability in most patients with the former type is associated with the antibody against VGKC [8]. Arimura reported that sera from patients cause suppressed potassium currents measured in a neuroblastoma cell line [9]. Shillito and his colleagues found that injection of purified IgG, obtained from sera of patients with PNH, into mice produced potassium channel inhibition and induced nerve hyperexcitability [4]. Although VGKC antibody was not detected in our patient, this was due to the relatively low sensitivity of the immunoprecipitation assay. In fact, Hart et al. [8] compared an immunoprecipitation assay with a molecular-immunohistochemical assay that detects serum binding to frozen sections of Xenopus oocytes injected previously with cRNA for an individual VGKC α subunit. The immunoprecipitation assay detected a VGKC antibody in only 35% of patients with PNH, while the molecular-immunohistochemical assay could detect it in almost all patients.

A VGKC antibody affects neuronal excitability in both peripheral and central nervous systems (CNS). Hart et al. reported that about 25% of patients with PNH had CNS symptoms, such as mood changes or sleep disorders [8]. Tan et al. reported that the incidence of hyponatremia was 32.5% in their study of 80 patients with VGKC antibodies [10]. Vincent et al. found SIADH in at least 3 of 10 patients with VGKC antibody-associated encephalopathy [11]. Our patient also exhibited hyponatremia after admission and was diagnosed with SIADH. The reason why SIADH did not appear initially was due to his severe appetite loss, resulting in reduced water intake. Although the precise mechanism of SIADH in PNH is not clear, Vincent et al. proposed that the effects of VGKC antibody on the hypothalamus were considerable [11]. Yang et al. demonstrated extensive immunoreactivity of VGKCs in the paraventricular hypothalamic nucleus (PVN) [12], where ADH is secreted. Since a decrease in voltage-gated potassium currents increases the frequency, duration and amplitude of action potentials in endocrine cells, contributing to hormone secretion [13, 14], it is likely that the inhibition of potassium currents by VGKC antibody caused excessive ADH secretion from PVN.

To our knowledge, no reports are available showing the relationship between PNH and thyroid functions. Although no direct evidence is present, we hypothesize that a similar mechanism could account for SITSH in the present patient. Firstly, the parvocellular region of the PVN is the source of TRH. If VGKC antibody causes excessive secretion of TRH from PVN, similarly to ADH, TSH is elevated, resulting in SITSH. Secondly, our patient exhibited a delayed TSH response to exogenous TRH before treatment (Fig. 4). This may support our hypothesis, since Sheppard et al. reported that prolonged exposure of a rat anterior pituitary gland to TRH impaired the ability of the thyrotrophs to secrete TSH in response to a subsequent pulse of TRH [15]. Thirdly, our patient showed increased ACTH response to CRH. This may be in part explained by excessive secretion of CRH from PVN, similarly to ADH or TRH, while it can be considered that elevated endogenous ADH or psychological stress of PNH caused ACTH hypersecretion. Hashimoto et al. proposed that VGKC antibody on the hypothalamus could have been responsible for elevated ACTH in their case of subclinical Cushing syndrome associated with VGKC antibody-related limbic encephalitis [16]. Finally, the SITSH state of the patient became nearly normal as his PNH condition ameliorated. The TRH and CRH test after readmission showed normal TSH and ACTH responses. Consequently, it is tempting to speculate that VGKC antibodies induced SITSH via TRH excessive secretion from PVN. The further exaggerated PRL secretion at the second TRH stimu-
lation test was apparently due to severe post-thoracotomy pain syndrome after surgery, which had not been observed at the first TRH test, as various chest diseases cause hyperprolactinemia [17].

This is the first case report of SITSH associated with PNH. Our patient raises the possibility that careful examination may reveal altered thyroid functions in patients with autoimmune-mediated PNH.

Acknowledgements

We are grateful to Dr. Masakatsu Motomura (First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University) for examining antibodies against VGKC. We also thank Drs. Toru Itaya and Kazuya Suzuki (First Department of Surgery, Hamamatsu University School of Medicine) for performing the thymectomy, and Tomoaki Satoh (Roche Diagnostics K.K.) for examining the gel filtration chromatography. This work was supported, in part, by a Health Sciences Research Grant to H. Nakamura and a Grant-in-Aid for Scientific Research to H. Nakamura from the Ministry of Education, Culture, Sports, Science and Technology in Japan.

Conflict of Interest

The authors have nothing to declare.

References