Syndrome of Inappropriate Secretion of Antidiuretic Hormone Caused by Pituitary Macroadenoma with Hemangiomatous Stroma

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A 55-year-old Japanese man was referred to our hospital because of disturbance of consciousness and hyponatremia. He had been aware of general fatigue, nausea, and headache for two weeks. Tests revealed hyponatremia, plasma hypoosmolarity with urine hyperosmolarity, an elevated level of urine sodium excretion, and normal functions of the kidney, adrenal gland, and thyroid. These findings were compatible with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Head magnetic resonance imaging (MRI) demonstrated a pituitary tumor measuring 20 x 22 x 21 mm that pushed the pituitary stalk upward. Endocrinological evaluations suggested that the pituitary adenoma was non-functional. The pituitary adenoma was surgically removed, and histological examination revealed a biphasic appearance characterized by endocrine cells and a hemangiomatous stroma. After surgery, the patient developed pituitary hypothyroidism, pituitary adrenal insufficiency, and pituitary gonadal failure. Therefore, levothyroxine sodium, 50 μg per day, and hydrocortisone, 10 mg per day, were administered orally. Androgen depot, 250 mg every two months, was also injected intramuscularly. The hyponatremia did not recur, and the patient has done well for the last five years. The pituitary adenoma in this case showed two features: one was the cause of SIADH, and the other was a biphasic histological picture of endocrine cells with a hemangiomatous stroma.

Key words: Pituitary adenoma, SIADH, Biphasic histological features

INTRODUCTION

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs when the plasma level of arginine vasopression (AVP) is elevated when its physiological secretion would normally be suppressed. The criteria for diagnosis include hyponatremia, hypoosmolarity, and hypertonic urine with neither dehydration nor edema, with no dysfunction of the kidney or adrenal gland [1, 2]. There are two sources of AVP in SIADH: either increased central secretion of AVP from the posterior pituitary gland, or ectopic production of AVP. Many disorders, including those of the central nervous system (CNS) or pulmonary system, administration of drugs, infection, and collagen diseases such as adult Still's disease are able to cause SIADH [1–4].

Pituitary macroadenoma, exceeding 10 mm in diameter, can be accompanied by hyponatremia. In most clinical settings, hyponatremia is closely related to secondary hypopituitarism, particularly dysfunction of the pituitary-adrenal axis [5, 6]. Such hyponatremia is a disorder distinct from SIADH. However, a few case reports have described hyponatremia in patients with pituitary macroadenoma whose pituitary function was normal, suggesting that the increased secretion of AVP could have been due to local mechanical stress, thus producing SIADH [7–9].

Here we describe a patient with SIADH caused by pituitary macroadenoma. We evaluated the possible mechanisms of non-suppressive release of AVP in this patient. In addition, the pituitary macroadenoma showed biphasic histological features involving endocrine cells and a prominent hemangiomatous stroma.

CASE REPORT

A 55-year-old Japanese man was referred to our hospital because of disturbance of consciousness with hyponatremia. He had been aware of general fatigue, nausea, and headache for two weeks. He had been admitted to another hospital, but as disturbance of consciousness had appeared and become aggravated, he was then transferred to our hospital. The patient had no medical history including head injury. His height was 180 cm and body weight 55 kg. His blood pressure was 120/64 mmHg and heart rate 66 beats/min and regular. Body temperature was 36.4°C. His consciousness level was Japan Coma Scale (JCS) I-2. He had neither dry mucous membrane nor edema. Auscultation of the chest revealed normal heart and breathing sounds.

The clinical laboratory findings are summarized in Tables 1 and 2. The patient had hyponatremia, plasma hypoosmolarity relative to urine hyperosmolarity, an elevated level of urine sodium excretion (more than 20 mEq/l), and normal functions of the kidney, adrenal gland, and thyroid. These findings were compatible with SIADH.

Chest X-ray and computed tomography (CT) showed

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Table 1 Clinical laboratory findings

	Initial values	Five years later	Normal ranges
WBC (/μl)	5200	6500	4000 – 8000
RBC (x 10^4/μl)	492	458	410 – 530
Hemoglobin (g/dl)	15.1	13.9	13.5 – 17.5
Hematocrit (%)	46.2	42.5	40.0 – 48.0
MCV (fl)	93.9	92.8	84.0 – 99.0
MCH (pg)	30.7	30.3	27.0 – 32.0
MCHC (%)	32.7	32.7	32.0 – 36.0
Platelets (x 10^4/μl)	20.6	21.3	14.0 – 40.0
Total protein (g/dl)	7.0	7.5	6.5 – 8.0
Albumin (g/dl)	4.0	4.4	3.9 – 4.8
AST (IU/l)	23	27	< 30
ALT (IU/l)	16	34	< 35
Creatinine (mg/dl)	0.4	0.6	0.5 – 0.8
Urea nitrogen (mg/dl)	9	8	8 – 20
Plasma glucose (mg/dl)	87	96	70 – 109
Total cholesterol (mg/dl)	224	167	140 – 220
Triglyceride (mg/dl)	57	72	50 – 150
Serum Na (mEq/l)	115	142	136 – 145
Serum K (mEq/l)	4.3	4.3	3.5 – 4.8
Serum Cl (mEq/l)	86	104	98 – 108
Plasma osmolarity (mmol/kg)	243	–	278 – 305
Urine osmolarity (mmol/kg)	536	–	50 – 1300
Urine Na excretion (mEq/l)	225	–	None

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration, AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2 Endocrinological Findings

	Values	Normal range
ACTH (pg/ml)	19.5	7.4 – 55.7
Cortisol (μg/dl)	5.9	4.0 – 18.3
TSH (μU/ml)	3.77	0.3 – 4.0
Free T4 (ng/dl)	1.27	0.75 – 1.75
PRA (ng/ml/h)	0.3	0.3 – 2.9
Aldosterone (pg/ml)	44.5	30 – 159
ADH (pg/ml)	1.3	0.3 – 3.5
Anti-pituitary antibody	–	–

ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; T4, thyroxine; PRA, plasma renin activity; ADH, antidiuretic hormone.

no abnormalities. Head magnetic resonance imaging (MRI) showed a pituitary adenoma measuring 20 x 22 x 21 mm, which compressed the pituitary stalk (Fig. 1A and 1B).

As the serum Na level was 115 mEq/l and the consciousness level was JCS I-2, 3% NaCl solution was initially infused. Then the hyponatremia was controlled by restriction of water intake (15 ml/kg weight per day) and administration of furosemide 20 mg per day [10]. The serum Na level increased to 136 mEq/l after 22 days, and the patient's consciousness level and general fatigue ameliorated. Anterior pituitary function was assessed using a stimulation test described previously [11]. Corticotropin-releasing hormone (CRH) (human corticorelin 100 μg), thyrotropin-releasing hormone (TRH) (protirelin 500 μg), GRH (somatorelin acetate 100 μg), and luteinizing hormone-releasing hormone (LH-RH) (gonadorelin acetate 100 μg) were administered intravenously. The results of the stimulation test are summarized in Table 3. Normal basal levels and responses of adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), prolactin (PRL), growth hormone (GH), follicular stimulating hormone (FSH), and luteinizing hormone (LH) were observed. The patient was discharged after 24 days.

He was later re-admitted, and the pituitary adenoma was removed by transsphenoidal adenomectomy. After the operation, the patient developed pituitary hypothyroidism, pituitary adrenal insufficiency, and pituitary gonadal failure. Therefore, levothyroxine sodium, 50 μg per day, and hydrocortisone, 10 mg per day, were administered orally. Androgen depot, 250 mg every two months, was also injected intramuscularly.

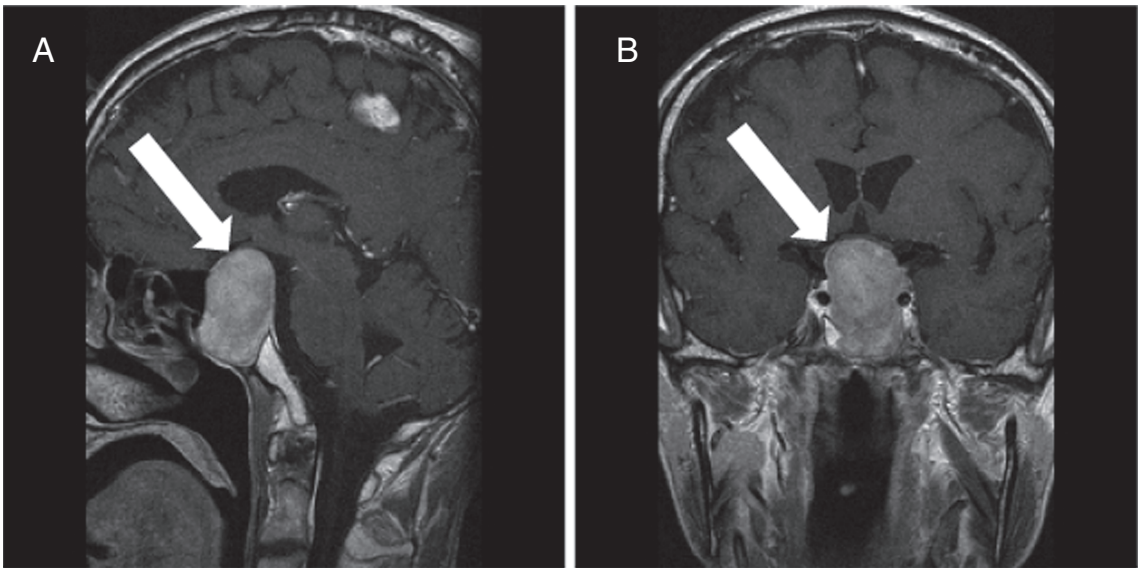

Fig. 1 T1-weighted and gadolinium-enhanced MRI of the head. Sagittal projection (A), and coronal projection (B). White arrows indicate a pituitary adenoma measuring 20 x 22 x 21 mm.

Table 3 Responses of anterior pituitary hormone to stimulation tests (CRH, LH-RH, TRH, and GRH)

	Basal	30 min	60 min	120 min
ACTH (pg/ml)	19.4	58.8	83.4	102
Cortisol (μg/dl)	5.2	12.0	14.2	19.7
LH (m U/ml)	0.0	3.8	5.8	5.5
FSH (m U/ml)	3.8	5.6	7.2	8.0
TSH (μ U/ml)	3.77	22.49	29.31	28.63
Prolactin (ng/dl)	19.4	58.8	44.6	33.1
GH (ng/ml)	0.13	2.09	4.41	1.31

min, minutes; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicular stimulating hormone; TSH, thyroid stimulating hormone; GH, growth hormone.

The patient has been doing well for the last five years, and the hyponatremia has not recurred (Table 1).

PATHOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS

The surgical specimen was fixed in 10% buffered formalin, processed in paraffin and cut into serial sections 4 μm thick. Hematoxylin and eosin (HE) and elastica van Gieson (EVG) stainings were performed.

Microscopical examination of HE-stained sections showed basophilic and epithelial-like cuboidal cells (Fig. 2A and 2B) and a hemangiomatous stroma (Fig. 2A and 2C), presenting a characteristic biphasic appearance.

Immunohistochemical stainings were performed with the antigen retrieval method as described previously [12, 13]. We examined the expression of AE1/AE3 cytokeratin, chromogranin A (CgA), CD56, α-subunit (α-SU), ACTH, TSH, PRL, GH, FSH, LH, vimentin, CD46, smooth muscle antigen (SMA), and desmin.

The endocrine cells were positive for α-subunit, AE1/AE3 cytokeratin, CgA, and CD56 (Fig. 3A, 3B, 3C, and 3D), but negative for ACTH, TSH, LH, FSH, GH, and PRL (data not shown). This suggested that the endocrine cells were non-functional. These immunohistochemical features of the endocrine cells were compatible with the results of endocrine examinations. The stroma was stained with EVG (Fig. 4A), but showed no immunoreactivity for SMA or desmin (data not shown); the endothelial cells were positive for vimentin and CD46 (Fig. 4B and 4C). These findings suggested that the stroma was composed of collagen fibers and endothelial cells.

DISCUSSION

The pituitary adenoma in the present patient had two features: it was a cause of SIADH, and also showed a biphasic histological nature, comprising pituitary endocrine cells admixed with a hemangiomatous stroma.

A large number of different CNS disorders are known to be related to SIADH. However, the mechanism by which inappropriate AVP secretion from the posterior pituitary causes disorders of the CNS remains unclear. With regard to the pathogenesis of increased AVP secretion in the present patient, it was important to evaluate the anatomical interaction between the pituitary adenoma and the hypothalamo-neurohypophyseal system. As shown in Fig. 1, the pituitary adenoma occupied the sella turcica and compressed the pituitary stalk and the hypothalamus. After removal of the

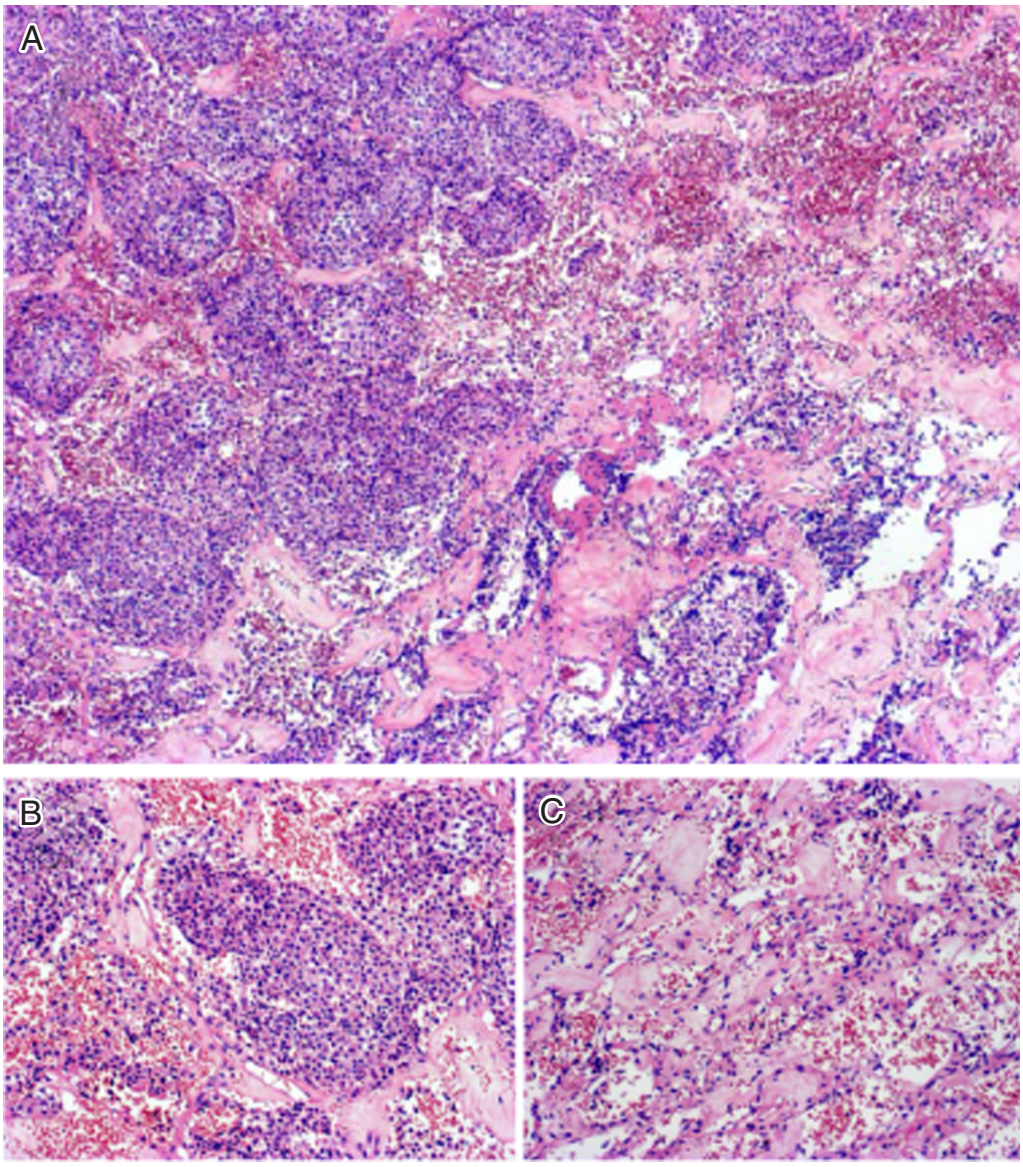

Fig. 2 Microscopical findings, demonstrating a moderately biphasic nature (A). The tumor was characterized by basophilic cuboidal cells showing the morphological features of endocrine cells of the pituitary (B) and a hemangiomatous stroma (C). Original magnification x40.

pituitary adenoma, the compression was relieved and SIADH did not recur. These findings suggested that mechanical compression by the pituitary adenoma had induced hypersecretion of AVP, as previously described [7–9].

The majority of pituitary adenomas are composed of monomorphic proliferations of cells with uniform round nuclei, delicate stippled chromatin, inconspicuous nucleoi, and moderate quantities of cytoplasm [14]. In the present specimen, histological examination showed a biphasic nature with endocrine cells and a hemangiomatous stroma. To our knowledge, there was no previous report of the pituitary adenoma with the biphasic nature.

Pituitary apoplexy is usually secondary to hemorrhage in the pituitary adenoma [15]. It was suggested that the risk for pituitary apoplexy was significantly dependent on properties of the pituitary adenoma itself (macroadenoma, non-functioning adenoma, and male patient) [16]. Our patient was compatible with the risk for pituitary apoplexy. The specimen of pituitary apoplexy showed hemorrhage and necrotic tumor [15]. Cavernous hemangioma in the sella turcica can occur, but the lesion is extremely rare [17–20]. It was reported that the histological findings of a large hemangioma in the sella turcica associated with neurofibromatosis had many cavernous vessels and a compressed component of endocrine cells [20]. Histological features of pituitary apoplexy and intrasellar hemangioma differed from our histological features with a biphasic appearance. Thus, the cause of the hemangiomatous stroma in our patient was unclear.

The descriptive diagnostic term “leiomyomatoid angiomatous neuroendocrine tumor” (LANT) has been proposed to address both the conspicuous stroma and the secretory element of the tumor [21]. It has been reported that most stromal cells in LANT are positive for SMA and vimentin. In the present case,

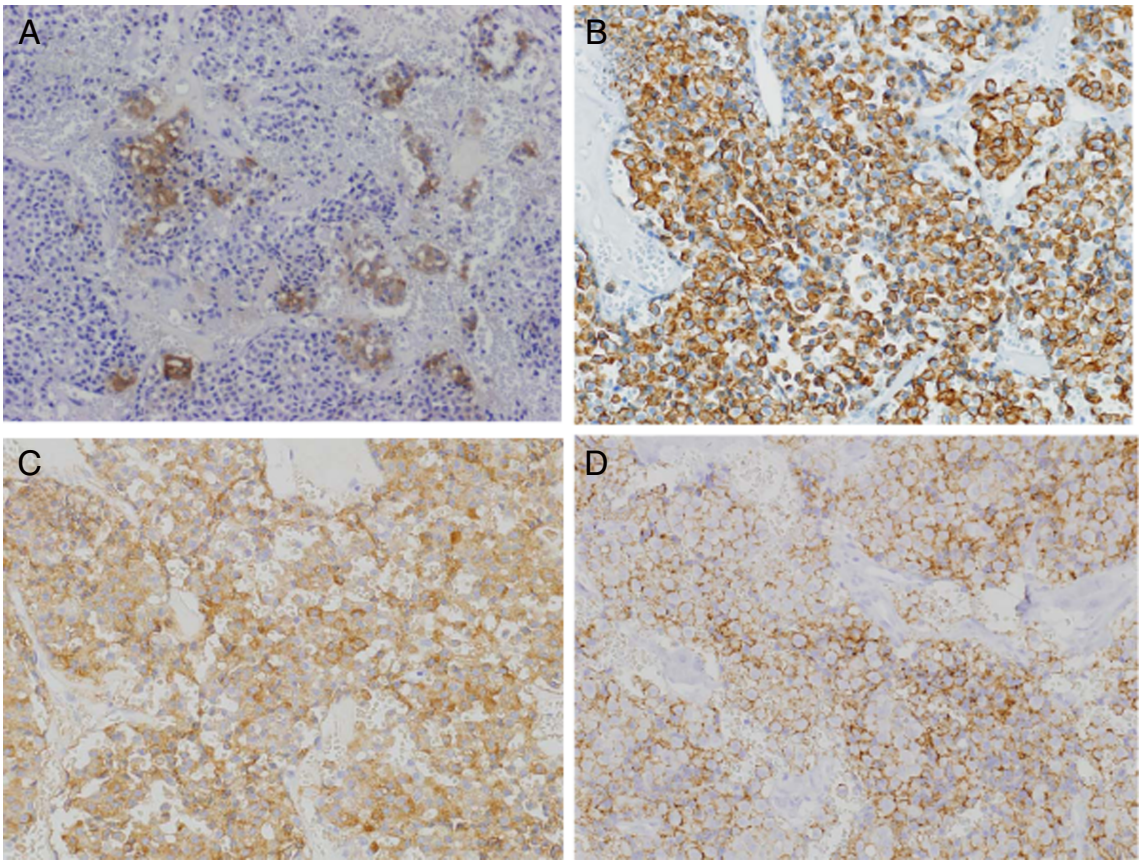

Fig. 3 The endocrine cells showed expression of α-subunit (A), AE1/AE3 cytokeratin (B), chromogranin A (C), and CD56 (D). Original magnification x100.

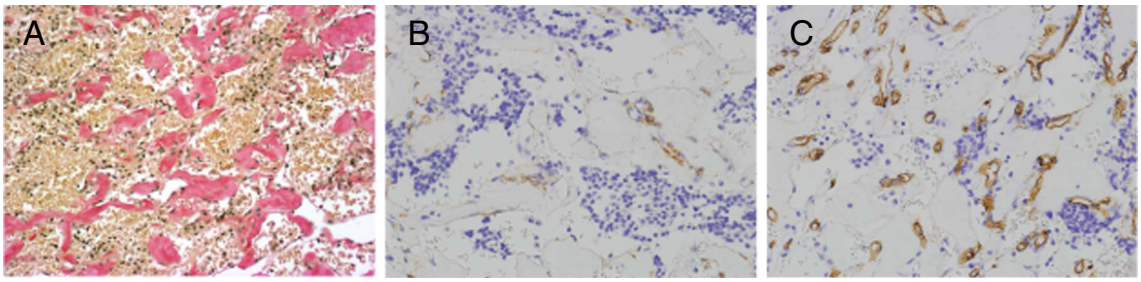

Fig. 4 The stroma was stained with EVG (A), and the endothelial cells were positive for vimentin (B) and CD46 (C). Original magnification x40. EVG: elastica van Gieson stain.

the endothelial cells were positive for vimetin, but most of the stroma cells were negative for SMA. These findings were not compatible with LANT, and indicated that this was another type of pituitary adenoma with biphasic features.

In conclusion, we have described a case of pituitary macroadenoma causing SIADH and showing a biphasic nature, suggesting that it differed from LANT of the pituitary.

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