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ORIGINAL

An autopsy case of macroglobulinemia complicated with syndrome of inappropriate secretion of ADH (SIADH) like hyponatremia, hypopituitarism and AL amyloidosis

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Abstract. An 88-year-old male patient with macroglobulinemia was admitted to our hospital because of severe hyponatremia and unconsciousness. Laboratory findings showed decreased inhibition of antidiuretic hormone (ADH) and he was diagnosed with syndrome of inappropriate secretion of ADH (SIADH). Hyponatremia improved with only limitation of water intake and the patient was followed up on a continuing outpatient basis. However, soon after discharge from hospital, his legs started swelling with edema and hyponatremia worsened. He was re-admitted due to a fall at home. Hyponatremia was observed at re-admission. A CRH challenge test showed partial dysfunction of ACTH secretion. Corticosteroid therapy was performed, but the patient subsequently died from pneumonia. Pathological findings at autopsy revealed invasion of plasma cells and amyloid depositions in multiple organs, including the pituitary, adrenal cortex, heart, liver, kidney, lymph nodes and bone marrow. Consistent with these results, fibrosis was observed in the anterior lobe of the pituitary, suggesting that the autopsy findings were related to the clinical observations and diagnosis. This is the first reported case of macroglobulinemia complicated with multiple hormone dysfunction.

Key words: Macroglobulinemia, SIADH, Hypopituitarism, AL amyloidosis

MACROGULOBULINEMIA is caused by neoplastic proliferation of B cells, which produce IgM in organs such as lymph nodes and bone marrow. This causes symptoms such as lymph node swelling, hepatomegaly, splenomegaly, anemia and hyperviscosity syndrome. Macrogulobulinemia is a rare disease, with a rate of only 10% that of myeloma, and is sometimes accompanied by AL amyloidosis [1-2]. Occurrence with hormone dysfunction is rare and there have been no reports of macroglobulinemia and multiple endocrine disorders. Herein, we describe a case of macroglobulinemia with pituitary hormonal deficiency and syndrome of inappropriate secretion of antidiuretic hormone (SIADH), in which we discuss the detailed clinical characteristics and histological findings.

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Case Report

An 88-year-old male with macroglobulinemia was admitted to our hospital because of unconsciousness in September 2011. Laboratory findings at admission indicated hyponatremia (Na 101 mEq/L) with a plasma osmotic pressure of 207 mOsm/kg, AVP 21.9 pg/mL, urinary osmotic pressure 511 mOsm/kg, and urinary sodium 150 mEq/L (Table 1). SIADH was diagnosed because basal ACTH and cortisol concentrations were normal. Hyponatremia improved (Na 131 mEq/L) with diuresis and limited water intake and the patient was discharged. However, after two months his legs started swelling with edema and hyponatremia had worsened to Na 117 mEq/L. He fell at home just before a visit

Table 1 Clinical laboratory test data on the first admission

Biochemistry				Hormonal examination	
TP	6.2 g/dL	IgM	1865 mg/dL	TSH	11.806 μIU/mL
ALB	3.0 g/dL	CEA	3.8 ng/mL	fT3	1.61 pg/mL
AST	42 IU/L	CA19-9	18 U/mL	fT4	0.93 ng/dL
ALT	25 IU/L	HS-PSA	<0.01 ng/mL	Thyroglobulin Ab	<0.3 U/mL
LDH	155 IU/L			TPO Ab	<0.3 U/mL
ALP	419 IU/L			AVP	21.9 pg/mL
G-GTP	14 IU/L	Hematology		Serum Osm	207 mOsm/kg
		WBC	6.36 $\times 10^3$/μL	ACTH	20.8 pg/mL
T-BIL	1.2 mg/dL	RBC	2.38 $\times 10^6$/μL	Cortisol	17.9 mg/dL
CK	98 IU/L	HGB	8.2 g/dL	PRA	0.5 ng/mL
BUN	12.7 mg/dL	HCT	21.6 %	aldosteron	83 mIU/mL
CRE	0.45 mg/dL	MCV	90.8 fL		
Na	101 mEq/L	MCH	34.5 pg		
K	4.8 mEq/L	MCHC	38.0 d/dL	Urinary Osm	511 mOsm/kg
Cl	73 mEq/L	PLT	10.0 $\times 10^4$/μL		
CRP	4.92 mg/dL				
PG	167 mg/dL				

Table 2 Clinical laboratory test data on the second admission

Biochemistry				Hormonal examination	
TP	5.2 g/dL	IgM	1550 mg/dL	TSH	18.06 μIU/mL
ALB	2.7 g/dL	CEA	6.8 ng/mL	fT3	0.74 pg/mL
AST	34 IU/L	CA19-9	20 U/mL	fT4	0.73 ng/dL
ALT	14 IU/L	HS-PSA	<0.01 ng/mL	Thyroglobulin Ab	<0.3 U/mL
LDH	216 IU/L	s-IL2R	8130 U/mL	TPO Ab	<0.3 U/mL
ALP	392 IU/L			AVP	7.38 pg/mL
G-GTP	141 IU/L	Hematology		Serum Osm	244 mOsm/kg
Ch-E	359 mg/dL	WBC	6.22 $\times 10^3$/μL	ACTH	20.6 pg/mL
T-BIL	1.2 mg/dL	RBC	2.55 $\times 10^6$/μL	Cortisol	16.8 mg/dL
CK	224 IU/L	HGB	8.6 g/dL	GH	0.977 pg/mL
BUN	5.9 mg/dL	HCT	24.5 %	LH	<0.2 mIU/mL
CRE	0.29 mg/dL	MCV	96.1 fL	FSH	<0.1 mIU/mL
Na	107 mEq/L	MCH	33.7 pg	PRL	14.29 ng/mL
K	4.7 mEq/L	MCHC	35.1 d/dL	Urinary Osm	280 mOsm/kg
Cl	78 mEq/L	PLT	11.3 $\times 10^4$/μL		
CRP	0.23 mg/dL				
BNP	228.9 pg/mL				
PG	74 mg/dL				

s-IL2R, soluble Interleukin 2 receptor; HS-PSA, high sensitive prostate-specific antigen, TPO Ab, thyroid peroxidate antibody, AVP, arginine vasopressin

to hospital for a detailed examination of hyponatremia, and thus he was re-admitted to hospital.

At re-admission, the patient was 157 cm tall and weighed 45 kg. His blood pressure was 110/50 mmHg and his pulse rate was 100 beats per minute. He had significant pitting edema on both legs from the femur to cruris, but did not have engorgement of the cervical veins or a swollen thyroid gland. Laboratory data on re-admission are shown in Table 2. A blood cell count revealed normocytic anemia due to macroglobulinemia. Endocrine data indicated hypothyroidism because of elevation of TSH and negative findings for thyroglobulin antibody and anti-thyroperoxidase (TPO) antibody. LH and FSH were undetectable. A chest X-ray showed the presence of pleural fluid (Fig. 1A) and cardiac ultrasonography showed normal left ventricular function. The brain natriuretic peptide (BNP) level was increased, but there were no symp-

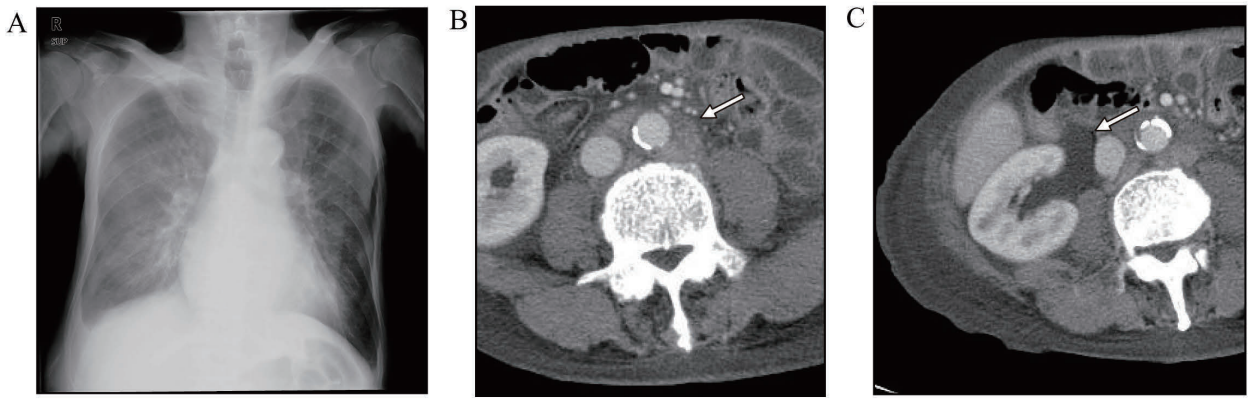

Fig. 1 (A) Chest X-ray on admission. (B) Abdominal computed tomography with contrast media showed swelling of the abdominal paraaortic nodes. (C) A mass due to swelling of the external iliac lymph nodes and hydronephrosis derived from compression of both urinary tracts.

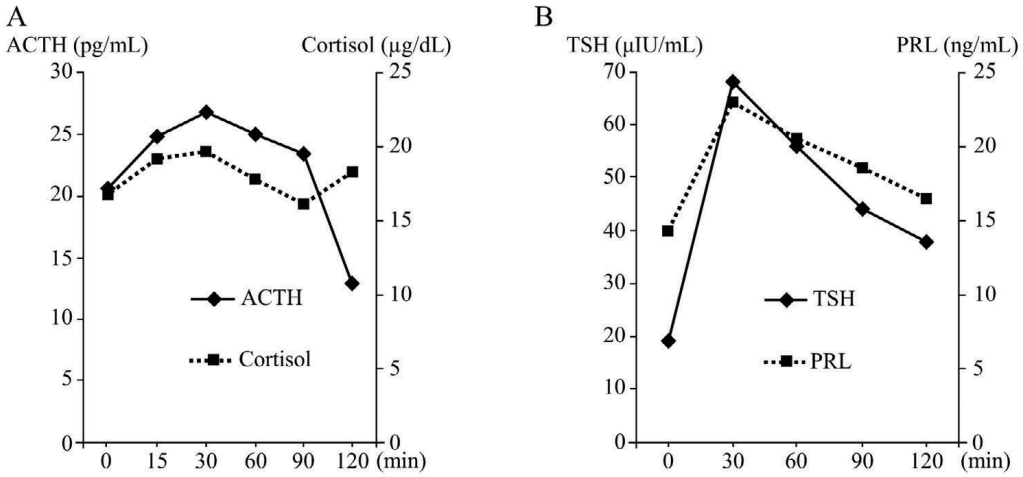

Fig. 2 (A) A CRF challenge test showed partial impairment of secretion of ACTH and cortisol, consistent with the presence of hyponatremia. (B) A TRH challenge test showed that TSH and PRL secretion were within the normal range in response to TRH.

toms of cardiac failure such as engorgement of the cervical veins, pulmonary congestion and hypoxia. Abdominal computed tomography with contrast media showed swelling of the abdominal paraaortic lymph nodes, a mass due to swelling of the external iliac lymph nodes, and hydronephrosis that seemed to be derived from compression of both urinary tracts (Fig. 1B, C: arrow).

Challenge tests on the pituitary gland and adrenal cortex were performed. Partially impaired secretion of ACTH and cortisol under the condition of hyponatremia was evident in a corticotrophin releasing factor (CRF) load test (Fig. 2A). The levels of LH and FSH did not respond before and after loading with LHRH (Fig. 3B). In a rapid ACTH test, the basal cortisol concentration was increased (16 μg/dL) and reached a peak of 20 μg/dL at 30 min, indicating that the secretion response was somewhat decreased due to hyponatremia (data not shown).

After the hormonal tests, furosemide 10 mg/day and hydrocortisone 100 mg/day were started for treatment and the patient was followed for a few days [3-7]. His consciousness became clear in parallel with improvement of hyponatremia. His clinical condition improved greatly and he could eat breakfast by himself. However, unfortunately he developed hypoxia and had a high grade fever at night. Arterial blood gas data showed severe acidemia and hypoxia (pH 7.172,

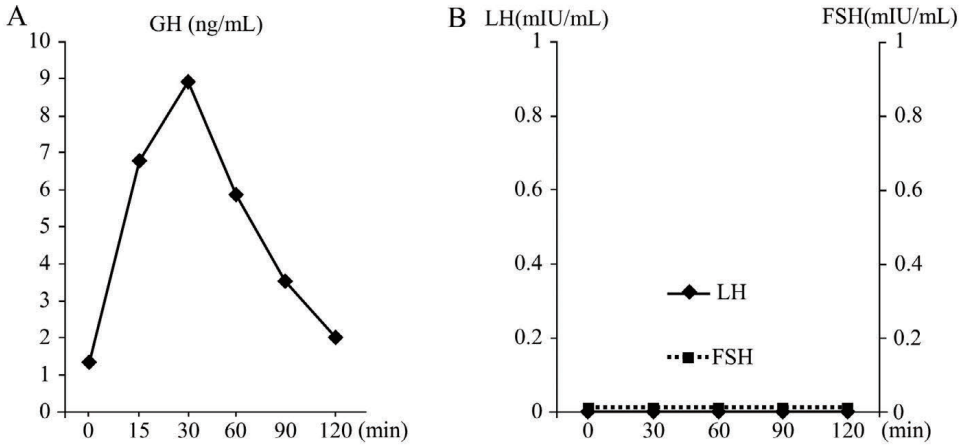

Fig. 3 (A) A GRF challenge test showed a normal GH secretion response. (B) The levels of LH and FSH were undetectable before and after the load. There was no response in a LHRH load test.

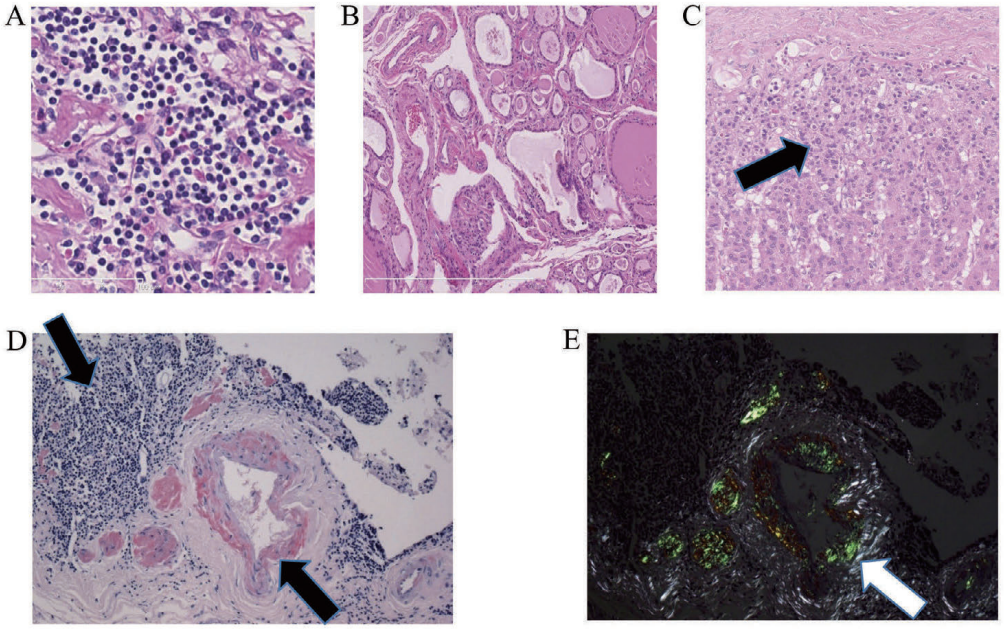

Fig. 4 Plasmacyte infiltration in the portal vein area in (A) paraaortic lymph nodes (×200), (B) thyroid gland (×40), and (C) adrenal gland (×80). (D) Many plasma cells due to macroglobulinemia had invaded around the capsula and in the parenchyma of the pituitary gland (left arrow) (objective lens (OB)×10). In the thyroid gland, the colloid was slightly atrophic and slight plasma cell infiltration was observed. Congo-red staining showed an amyloid deposit in a vascular lesion (right arrow). (E) The amyloid deposits showed apple-green birefringence in polarization microscopy (arrow) (OB×10).

pO_2 60.3mmHg, pCO_2 70.4 mmHg). An X-ray on the same day showed pneumonia in the upper right lung, which was not observed on the day of re-admission. The patient subsequently died from pneumonia combined with difficulty of retraction of sputum.

The mechanisms underlying hyponatremia and multiple hormonal disorders and the association of macroglobulinemia with pathogenic factors were examined at autopsy. Plasma cell invasion was observed in several organs, including the paraaortic lymph nodes (Fig. 4A), thyroid gland (Fig. 4B), and adrenal gland (Fig. 4C). Many plasma cells due to macroglobulinemia were found around the capsula and in the parenchyma of the pituitary gland and amyloid deposits in vascular lesions (Fig. 4D). However, there was no defluxion of parenchymal cells or amyloid deposits in the

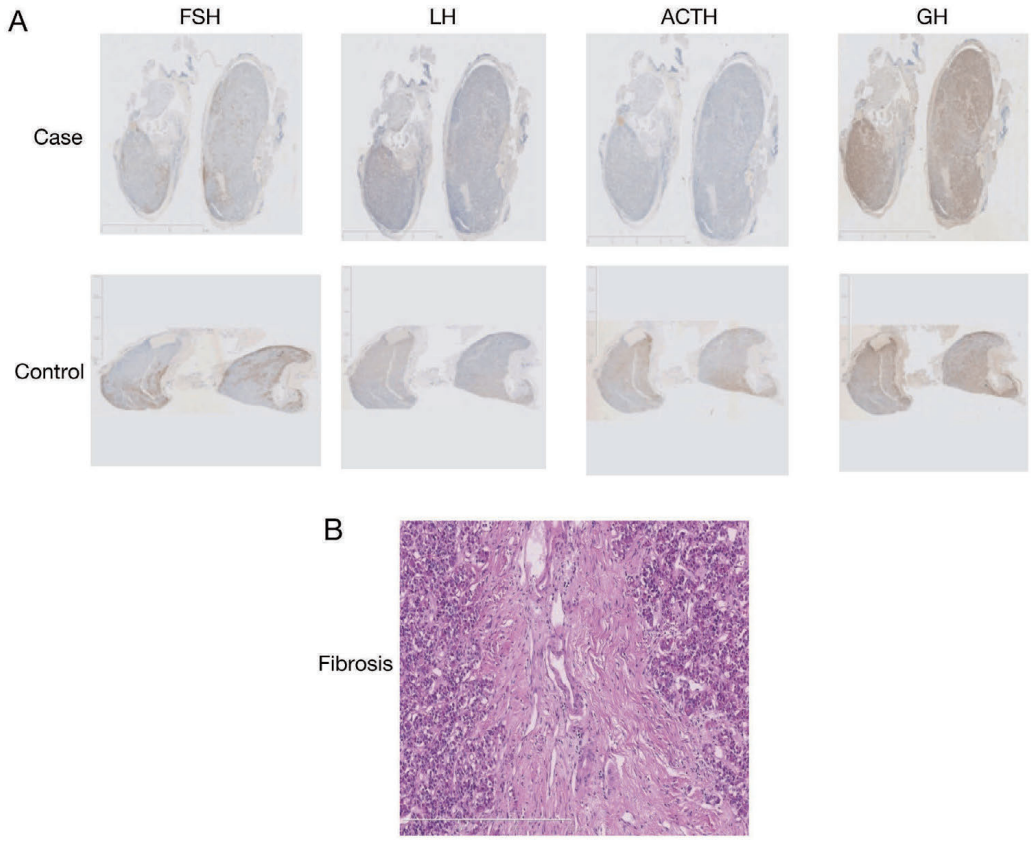

Fig. 5 (A) Immunostaining of the pituitary gland using anti-FSH, LH, ACTH, and GH antibodies in tissue from the patient and from a normal control. (B) Area of fibrosis in the pituitary gland (×60).

parenchyma. Amyloid deposits showed apple-green birefringence in polarization microscopy (Fig. 4E). Staining of the pituitary gland was negative for LH and FSH, and ACTH staining in the middle of the pituitary gland was weak compared with a control (Fig. 5A). These findings were consistent with the results of the hormone tests. In addition to the invasion of plasma cells and amyloid deposits in the parenchyma in the pituitary gland, segmental fibrosis was observed in the anterior lobe of the hypophysis (Fig. 5B).

The abdominal paraaortic lymph nodes were negative for permanganic acid staining, ruling out AA amyloidosis (data not shown). There were small amyloid deposits in the pituitary gland, heart, liver, kidney, and bone marrow; and medium or large amyloid deposits in lymph nodes. Senile amyloidosis commonly has deeper deposits, especially in the heart, in contrast to the findings in this case. Therefore, these findings suggested the presence of AL amyloidosis [8, 9].

Discussion

The patient in this case had macroglobulinemia, SIADH and pituitary hormonal deficiency. At the initial admission, we diagnosed SIADH because the basal ACTH and cortisol concentrations, rennin activity, and serum aldosterone concentration were within the normal ranges; there was no sign of congestive heart failure; and there was an absence of inhibition of ADH by decreased serum osmotic pressure. At the second admission, the serum BNP level was high, but there was no hypoxia or jugular venous dilatation, and chest X-ray did not show pulmonary congestion. An ultrasound cardiogram showed normal contraction of the heart, which suggested that heart failure was not the cause of edema. The ultrasound cardiogram suggested diastolic failure that might have been due to aging and we suspected that this accounted for the increased serum BNP concentration. Therefore, we suggest that hyponatremia was not mainly caused by cardiac failure

or SIADH, but by adrenal insufficiency.

A diagnosis of ACTH deficiency after treatment for an initial diagnosis of SIADH has been reported in several cases, suggesting that evaluation of ACTH or cortisol secretion is difficult in a patient with hyponatremia [6, 7]. Elderly people with symptoms of hyponatremia have been found to have a good response to a low dose of steroids, and this has diagnostic and therapeutic importance [3]. In our case, the patient had normal levels of ACTH and cortisol when diagnosed with SIADH, but later his legs started to swell with edema and hyponatremia worsened, with a decrease in the levels of ACTH and cortisol. Thus, the symptoms gradually became clearer over the time course.

In the clinical course in this case, hyponatremia may have been caused by aggravation of SIADH, hypoadrenocorticism due to hypopituitarism, and hypothyroidism. However, at the first and second admission the thyroid hormonal concentration was only slightly decreased, cardiac function was normal, and cardiac effusion was not observed. These findings suggest that hypothyroidism was not the main cause of hyponatremia. It is difficult to identify the cause of SIADH, but in macroglobulinemia complicated with hyponatremia the influence of dedifferentiation of malignant cells can cause secretion of vasotocin or another antidiuretic hormone that differs from ADH. However, in our case, the serum ADH concentration was not decreased, and thus plasma cells that produce macroglobulin might also secrete ADH [10-12]. At the first admission, we did not perform a CRF load test or an insulin tolerance test, and thus we cannot comment on a possible defect of ACTH or cortisol secretion. Diagnosis of adrenal insufficiency under a hyponatremic condition requires caution because several reports have described diagnosis of adrenal insufficiency after treatment for hyponatremia as SIADH.

Regarding the mechanism of pituitary hormonal deficiency and hypopituitarism, we speculate that systemic macroglobulinemia had strong effects on hormonal function. A histological examination of endocrine organs showed plasma cell infiltration with AL amyloid deposition in the pituitary gland, adrenal gland, and thyroid gland. This systemic plasma cell infiltration may have induced local hypercytokinemia, with cytokines such as interleukins and TNF-alpha produced by malignant macroglobulinemia cells, given that these cells were found in many organs, including in the endocrine system in the thyroid gland and adrenal cortex.

Another possibility is that amyloid deposition and fibrosis might have affected secretion in multiple endocrine organs. Several case reports have described endocrine abnormalities with systemic amyloidosis and amyloid deposition in these organs. One case described amyloid goiter with endocrine dysfunction and another showed functional impairment of the thyroid and testes [13]. Our case also had cell invasion or amyloid deposits in the pituitary gland and adrenal cortex, which may lead to endocrine impairment. The patient had no family history and had not received dialysis, thus making familial amyloidosis or dialysis amyloidosis unlikely. This suggests the presence of immunocytochemical AL amyloidosis due to basal macroglobulinemia or senile amyloidosis due to old age [14].

Pathological histological changes have been described in the pituitary gland of elderly patients with malnutrition [15]. Seventy autopsy cases were divided into two groups on the basis of a boat-shaped or normally shaped pituitary gland, and these groups were found to have differences in the gland weight and extent of fibrosis. The boat-shaped group was more likely to have a lighter gland and wide-ranging fibrosis. In addition, the frequency increased with age and was more than 17% above 65 years old [15]. In our case, we did not have an exact weight of the gland, but the width of 8-9 mm was thinner than normal. There was an area of segmental fibrosis in the parenchyma that could not be explained based only on aging, but no invasion of plasma cells in the fibrosis. Thus, it was unclear if the fibrosis resulted from invasion of plasma cells or from obstruction of the circulation accompanied with invasion of cells. Cases of hypopituitarism due to inflammatory myofibroblastic tumor around the sella turnica have been described, suggesting that plasma cell infiltration may lead to pituitary hormonal disorder through fibrosis and inflammation [5, 16].

In conclusion, we have reported a case of severe hyponatremia induced by SIADH and adrenal insufficiency, with a description of histological data obtained at autopsy. This is the first reported case of macroglobulinemia complicated with multiple endocrine failure.

Disclosure

None of the authors have any potential conflicts of interest associated with this report

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