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Case Report

A case of pulmonary hyalinizing granuloma characterized by pseudohyponatremia due to hyperproteinemia

Mariko Yamauchi^a, Sahoko Kamejima^{a,*}, Izumi Yamamoto^a, Ichiro Ohkido^a, Jun Araya^b, Takashi Yokoo^a^a Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan^b Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

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ABSTRACT

A 57-year-old man presented with multiple pulmonary nodules. Thoracoscopic lung biopsy led to a pathological diagnosis of pulmonary hyalinizing granuloma (PHG) at the age of 39 years. The disease was progressive, refractory to therapy, and necessitated home oxygen therapy 10 years after the diagnosis. Hyponatremia progressed gradually along with lung disease. His serum sodium level was 129 mEq/L but serum osmolality was normal (287 mOsm/kg). Concomitant hyperproteinemia (12.1 g/dL) was attributable to hyperglobulinemia. Direct ion-selective electrode measurement revealed a normal sodium level (137 mmol/L). We herein report a case of PHG characterized by pseudohyponatremia due to hyperproteinemia, an uncommon finding in this rare entity. A left lung transplant was successfully performed, and no pseudohyponatremia was observed. Pseudohyponatremia should be suspected and diagnosed to prevent a misdiagnosis that could lead to complications from inappropriate treatment with sodium supplementation or restriction of drinking water. The direct ion-selective electrode measurement was useful for diagnosing pseudohyponatremia.

1. Introduction

Pulmonary hyalinizing granuloma (PHG) was first reported by Benfield in 1962 [1] and further described by Engleman in 1976 [2]. PHG is a rare disease characterized by one or multiple pulmonary masses of unknown etiology and homogeneous hyaline lamellae, usually surrounded by infiltrates of plasma cells, lymphocytes, and histiocytes with a perivascular distribution. The largest review of 135 cases reported to date showed that about half of all cases are associated with primary mediastinal or retroperitoneal fibrosis, autoimmune disease, neoplastic disease, infectious disease, or thromboembolism, with a variety of clinical courses. About 40% of patients are asymptomatic, while the disease develops slowly and may include respiratory failure in others [3]. Notably, about half of all patients with PHG have concomitant hyperglobulinemia. However, cases of severe hyperglobulinemia, such as the present case, are rare, and this is the first report of a PHG patient with pseudohyponatremia. The findings in this case report provide a better understanding of the course of PHG after transplantation.

* Corresponding author. Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo, Japan.

E-mail address: ms03kamejima@jikei.ac.jp (S. Kamejima).

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2. Case report

Multiple pulmonary nodules were detected incidentally in a 57-year-old Japanese man during a routine physical examination at the age of 39 years. He had smoked five cigarettes/day for 2 years when he was 30 years old. He had no history of dust exposure and no history of respiratory infection. He was referred to our hospital for a thorough examination. A chest X-ray revealed pulmonary nodules and diffuse interstitial shadows, and a computed tomography (CT) scan of his lungs indicated multiple nodular lesions surrounded by ground-glass opacities (Fig. 1A). Thoracoscopic lung biopsy led to a pathological diagnosis of PHG (Fig. 2). Immunologi-

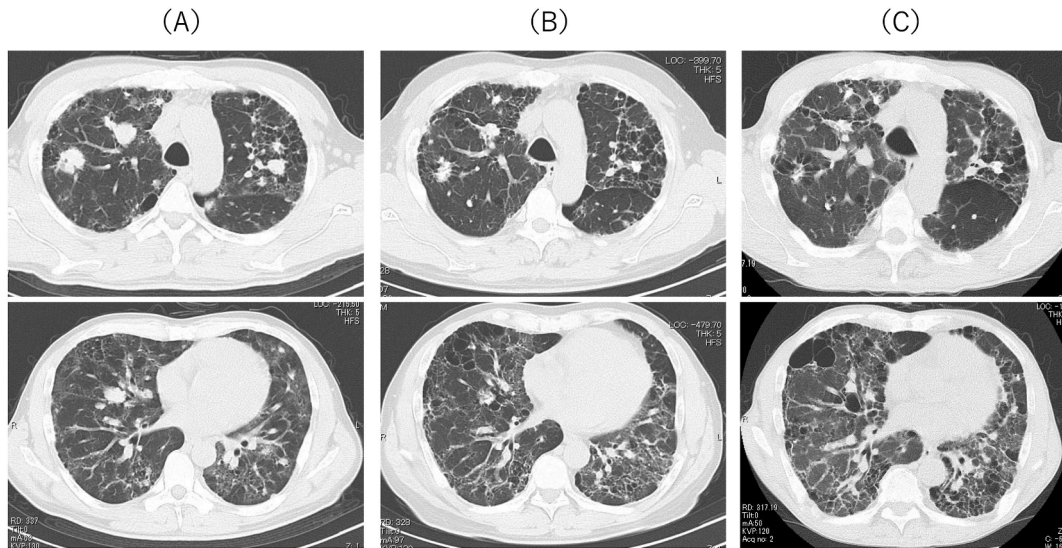


Fig. 1. Chest CT (A) Images at diagnosis Chest CT showing bilateral multiple nodular lesions surrounded by ground-glass opacities and fibrotic changes are evident. (B) Images 7 years after the diagnosis The nodules decreased slightly and calcification appeared compared to the diagnostic images. The fibrotic changes have progressed, suggesting chronic inflammation. (C) Images 18 years after the diagnosis The emphysematous changes progressed.

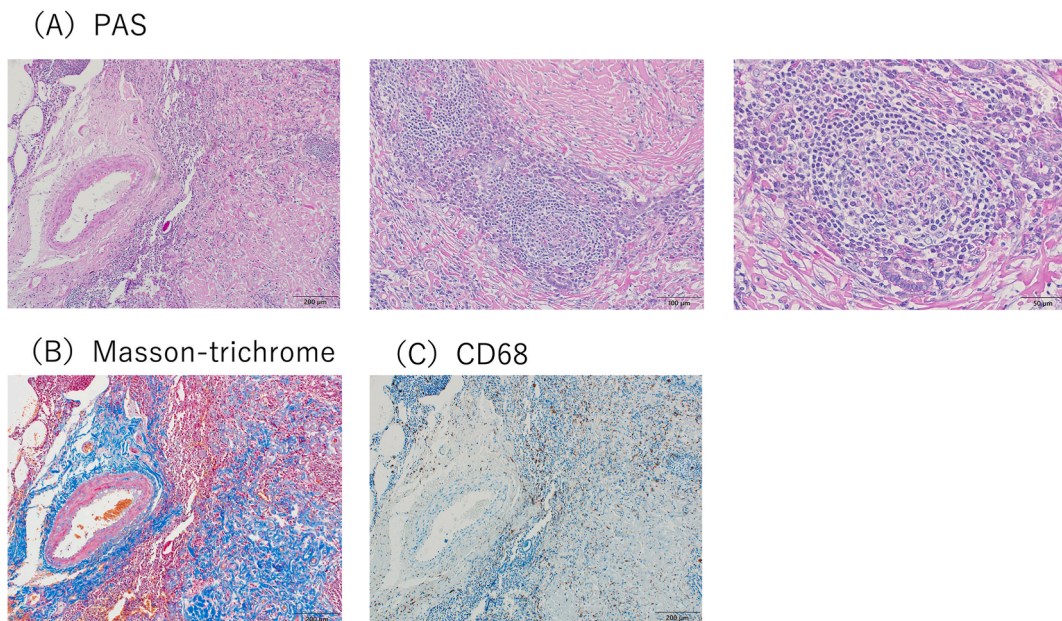


Fig. 2. Pathological features of the lung tissue obtained from the patient. (A) Periodic acid-Schiff staining: Hyalinized lamellar collagen bundles were found centrally, surrounded by lymphocytic and plasma cell infiltrates in a perivascular distribution (left panel $\times 10$; scale bar, 200 μm), Images of organizing granulomatous nodules of the lung with a high degree of chronic inflammation, and a mixture of lymphocytes and plasma cells at the margins (middle panel $\times 20$; scale bar, 100 μm , right panel $\times 40$; scale bar, 50 μm). (B) Masson's trichrome staining: Inflammatory cells, including lymphocytes and occasional plasma cells and macrophages were seen between the collagen bundles ($\times 10$; scale bar, 200 μm). (C) Immunohistochemical staining for CD68 revealed macrophages ($\times 10$; scale bar, 200 μm).

cal abnormalities were also identified, including hyperglobulinemia and positivity for proteinase-3 anti-neutrophil cytoplasmic antibody (PR3-ANCA:13–20 U/mL) and antinuclear antibodies. A renal biopsy was performed because of microscopic hematuria and mild urinary protein (0.28 g/day), but no findings of vasculitis suggested Wegener's granuloma. The patient had no subjective symptoms and was therefore placed under outpatient observation. Respiratory function tests at diagnosis were forced vital capacity (FVC): 3.03 L, %VC: 80, forced expiratory volume (FEV) 1: 2.55 L, diffusion capacity of the lungs for carbon monoxide (DLCO): 11.01 ml/min/mmHg. His serum KL-6 level remained at 1500–2000 U/mL while lung capacity decreased by 100 mL per year. He developed dyspnea during physical activity 7 years after the diagnosis, with X-rays showing exacerbation of the pulmonary nodules, diffuse ground-glass opacities, and reticular shadows (Fig. 3A). A CT scan revealed extensive ground-glass opacities (Fig. 1B). Respiratory function tests at this time were FVC: 2.58 L, %VC: 71.5, FEV1: 2.06 L. He was started on 30 mg prednisolone (PSL), which relieved his symptoms, but the dyspnea returned during PSL tapering, and cyclosporine was added to the treatment regimen. His arterial oxygen saturation had decreased to 87% during a 6 min walk 10 years after the diagnosis, and home oxygen therapy was initiated. The KL-6 level remained at about 2000 U/mL and dyspnea during physical activity increased. He was treated with cyclosporine (200 mg) and PSL (12.5 mg). Hyponatremia (serum sodium: 127–131 mEq/L) developed 18 years after the disease onset, and he was referred to a nephrologist from the respiratory medicine department at our hospital. The chest imaging findings at this time were more aggravated than before (Figs. 1C and 3B). His serum sodium level was 129 mEq/L (Table 1) and a physical examination indicated no signs of dehydration. Despite the hyponatremia, his plasma osmolality was normal (287 mOsm/kg). Psychogenic polydipsia was excluded, as urine osmolality was maintained at 120 mOsm/kg and his drinking rate was 1–2 L/day. Fasting blood glucose and triglyceride levels were within normal limits, but the blood protein level was high (12.1 g/dL). An examination revealed serum IgG, IgA, IgM, and IgE levels of 7125, 637, 350, and 843 mg/dL, respectively, suggesting pseudohyponatremia associated with hyperglobulinemia. Urinalysis and serum immunoelectrophoresis did not indicate monoclonality. Direct ion-selective electrode measurement indicated a serum sodium level of 137 mmol/L, which was within the normal range. This value was 8 mmol/L higher than that measured by indirect ion-selective electrode measurements. Therefore, he was diagnosed with pseudohyponatremia. The patient has since been followed up in the outpatient clinic, where his serum sodium level determined by direct ion-selective electrode measurement was determined. The appropriate diagnosis prevented a recommendation of fluid restriction and/or hypertonic saline, both of which would have had dangerous consequences. A left lung transplant was successfully performed at the age of 58 years. Dyspnea on effort improved after the transplantation, and home oxygen therapy was no longer required. Serum levels of immunoglobulin decreased (IgG, IgA, and IgM levels were 3,691, 286, and 188 mg/dL, respectively) and the total protein level in serum improved to 7.8 mg/d after oral administration of 1.6 mg tacrolimus, 5 mg prednisolone, and 250 mg mycophenolate mofetil BID. Serum levels of sodium were 134 and 135 mmol/L according to indirect and direct ion-selective electrode measurements, respectively. Thus, there was little difference between the two and no pseudohyponatremia.

3. Discussion

PHG is a rare benign condition characterized by single or multiple pulmonary masses of unknown etiology [1,2]. It mostly occurs in middle-aged patients, who present with nonspecific respiratory or general symptoms, such as cough, chest pain, dyspnea, hemoptysis, malaise, or fatigue. Hyalinized lamellar collagen bundles are found in the central lung, surrounded by lymphocytic and plasma cell infiltrates. Confirmation of the diagnosis typically requires CT-guided percutaneous biopsy or surgical resection. Although the nodules tend to grow slowly, spontaneous regression and maintenance of disease status have also been described [3,4]. Lung lesions are thought to arise from an underlying autoimmune process, and our patient was positive for antinuclear antibodies and PR3-ANCA. A high immunoglobulin level, particularly IgG, is a common finding in PHG [3]. Our patient had high polyclonal immunoglobulin levels in the IgG, IgM, IgA, and IgE fractions, resulting in severe hyperproteinemia.

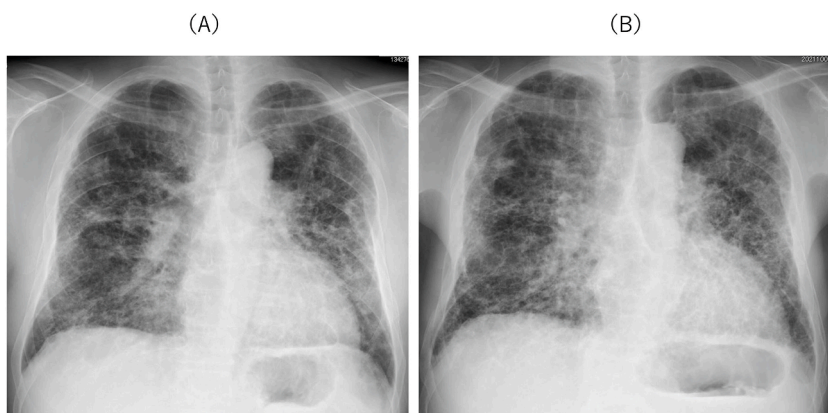


Fig. 3. Chest X-ray (A) Image 7 years after the diagnosis Chest X-ray shows pulmonary nodules, diffuse ground-glass opacities, and reticular shadows. (B) Image 18 years after the diagnosis The diffuse ground-glass opacities and reticular shadows progressed.

Table 1
Biochemical data.

Parameter	Measured value	Reference range
Complete blood cell count		
White blood cell count (/mm ³)	11,400	3300–8600
Hemoglobin (g/dL)	9.2	13.7–16.8
Serum chemistry		
TP (g/dL)	12.1	6.6–8.1
Albumin (g/dL)	1.9	4.1–5.1
Cr (mg/dL)	1.13	0.65–1.07
Urea (mg/dL)	27	8.0–20.0
Sodium (mEq/L)	129	138–145
Chloride (mEq/L)	99	101–108
Fasting blood glucose (mg/dL)	84	73–199
HbA _{1c} (%)	5.7	4.9–6.0
TG (mg/dL)	38	40–149
HDL-C (mg/dL)	41	40–90
LDL-C (mg/dL)	42	65–139
IgG (mg/dL)	7125	861–1747
IgA (mg/dL)	637	93–393
IgM (mg/dL)	350	33–183
IgE (mg/dL)	843	0–250
KL-6 (U/mL)	865	<500
Osmolality		
Plasma osmolality (mOsm/kg)	287	
Urine osmolality (mOsm/kg)	120	
Hormone related to Na regulation		
ACTH (pg/mL)	1.5	7.2–63.3
ADH (pg/mL)	2.2	
Cortisol (μg/dL)	1.64	3.8–18.4
PRA (ng/mL/hr)	1.6	
Aldosterone (pg/mL)	189.5	
TSH (ng/mL)	4.54	
FT3 (pg/mL)	2.71	
FT4 (ng/dL)	1.48	
Peripheral venous blood gas		
pH	7.377	7.35–7.45
Na ⁺ (mEq/L)	137	
PCO ₂ (mmHg)	44.3	35–45
Bicarbonate (mEq/L)	25.4	
Urinalysis		
Urinary protein/Urinary Cr (g/gCr)	0.75	
Urinary sodium/Urinary Cr (mEq/gCr)	209	
Urinary potassium/Urinary Cr (mEq/gCr)	51.5	
Urinary chloride/Urinary Cr (mEq/gCr)	149.3	

TP: total protein, TSH: thyroid-stimulating hormone, PRA: plasma renin activity, ADH: antidiuretic hormone, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, Cr: Creatinine.

The prognosis of PHG is generally favorable. A single nodule can be cured by surgical resection, whereas multiple nodules cannot [4]. Several reports have recommended glucocorticoid therapy for PHG, with immunosuppressive drugs added in refractory cases, such as recurrence after surgery, or for patients with multiple nodules [3,5]. PHG was refractory in our patient and consisted of multiple pulmonary nodules. His clinical presentation was slowly progressive even after PSL and cyclosporine therapy, finally resulting in left lung transplantation. In severe cases, such as the case presented here, a therapeutic intervention consisting of aggressive treatment with isotonic or hypertonic saline due to a misdiagnosis of hyponatremia may worsen the patient's condition and can cause death [6–8].

Hyponatremia is a common problem in hospitalized patients with respiratory disease, with a prevalence rate of 12% [9]. Serum osmolality, urine osmolality, and urine sodium should be measured to correctly diagnose hyponatremia. However, pseudohyponatremia should also be considered before this workup. Pseudohyponatremia is an uncommonly encountered laboratory abnormality defined as a serum sodium concentration <135 mEq/L in the setting of normal serum osmolality (280–300 mOsm/kg). It is an artifact that results from the processing of blood samples for serum sodium measurements [10]. Our patient's serum osmolality was 287 mOsm/kg, despite a low serum sodium concentration (129 mEq/L), suggesting pseudohyponatremia. As blood glucose and serum urea levels were normal (84 and 27 mg/dL, respectively), hyperglobulinemia and hypertriglyceridemia were considered. Subsequent tests demonstrated that the patient's triglyceride level was normal (38 mg/dL) but that his total protein level was extremely high (12.1 g/dL), such that polyclonal hyperglobulinemia was diagnosed and pseudohyponatremia due to hyperglobulinemia was consid-

ered. He had hypoalbuminemia due to wasting and low food intake (weight loss of about 5 kg) without complications of nephrotic syndrome.

Direct ion-selective electrode measurement is extremely useful for diagnosing pseudohyponatremia. Although a large number of direct-potentiometry instruments have been used to analyze blood gases, routine sodium measurements are largely indirect and mostly rely on potentiometry. In direct potentiometry, undiluted serum samples are used to measure the transmembrane potential resulting from electrolyte gradients; therefore, the measurement is independent of the water content of the sample. As the water fraction accounts for 93% and the nonaqueous fraction accounts for 7% of normal serum, the serum values obtained using an indirect method are lower due to the influence of lipids and proteins in the serum. If the patient is hyperproteinemic, as in our patient, the measured value will be even lower [11]. The serum levels of sodium in our patient were 129 and 137 mmol/L according to indirect and direct ion-selective electrode measurements, respectively. If the measured value in a hyperlipidemic or hyperproteinemic sample is misleading, it can be corrected by estimating the water fraction of serum. Hyperlipidemia and hyperproteinemia cause predictable decreases in the amount of water per unit volume of plasma (Wp), which is estimated using Waugh's empirical equation: $(Wp \text{ (g/dL)}) = 99.1 - 0.73 \times Ps \text{ (g/dL)} - 1.03 \times Ls \text{ (g/dL)}$ Wp: the amount of water per unit volume of plasma, Ps: protein concentrations, Ls: serum triglyceride concentration [11,12]. One study reported that 70% of samples with total protein concentrations above the reference interval have much lower sodium concentrations compared to results obtained with the direct ion-selective electrode method [13]. Depending on the baseline sodium value, hyperproteinemia can lead to pseudohyponatremia. As hyponatremia complicated by pulmonary disease is often associated with syndrome of inappropriate secretion of antidiuretic hormone, it is important to use direct ion-selective electrode monitoring to accurately diagnose pseudohyponatremia, as in the present case. Although pseudohyponatremia is rare, it should be suspected in patients with hyperproteinemia to prevent a misdiagnosis that could lead to complications from aggressive treatment with isotonic or hypertonic saline [6,14]. Particular attention should be paid to patients in whom serum proteins, which increase the nonaqueous phase of plasma and decrease the plasma water volume, are high. Although well-known cases of pseudohyponatremia have been reported in patients administered intravenous immunoglobulins [15] and in those with multiple myeloma [16], this is the first report of pseudohyponatremia in a patient with PHG. This is a valuable report showing the course of PHG after transplantation.

4. Conclusion

We herein report a case of PHG characterized by pseudohyponatremia due to hyperproteinemia, an uncommon finding in this rare entity. Lung transplantation was beneficial in this case of PHG. Hyponatremia is one of the most common electrolyte abnormalities in daily practice, including in the area of respiratory disease, and should be diagnosed appropriately. Evaluating pseudohyponatremia by direct ion-selective electrode monitoring is important to avoid dangerous errors in patient management.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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None.

Declaration of competing interest

No authors have any conflicts of interest to declare.

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