

[CASE REPORT]

Systemic Sarcoidosis with Thyroid Involvement

Hideyuki Okuma^{1,2}, Koshi Hashimoto^{2,3}, Xin Wang¹, Noriaki Ohkiba¹, Nozomi Murooka¹,
Norikazu Akizuki⁴, Takeshi Inazawa¹ and Yoshihiro Ogawa²

Abstract:

A 66-year-old woman, who was diagnosed with iritis, visited our hospital due to general malaise. A blood analysis revealed hypercalcemia. Computed tomography revealed mediastinal and hilar lymph node hyperplasia. Moreover, ⁶⁷Gallium scintigraphy demonstrated strong accumulation in the lesions, suggesting sarcoidosis. A core needle biopsy (CNB) of the hypoechoic areas of the thyroid was performed because the patient refused to undergo a bronchoscopic examination. The scattering of slightly acidophilic epithelioid cell granulomas was observed in the pathological examination of the biopsy specimen. Based on this finding, the patient was diagnosed with sarcoidosis. Although sarcoidosis rarely involves the thyroid gland, in the present case, thyroid CNB was an alternative diagnostic method that allowed a pathological diagnosis to be obtained.

Key words: thyroid sarcoidosis, thyroid needle biopsy

(Intern Med 56: 2181-2186, 2017)

(DOI: 10.2169/internalmedicine.8324-16)

Introduction

Sarcoidosis is a systemic disorder that is pathologically characterized by the formation of non-caseating epithelioid cell granulomas. It is also known that sarcoidosis widely expands to various organs throughout the body including the lungs, eyes and skin (1). However, thyroid infiltration is extremely rare and only a limited number of case reports of systemic sarcoidosis have been diagnosed by thyroid core needle biopsy (CNB). We herein report a case of systemic sarcoidosis that was diagnosed by thyroid CNB. We also review the clinical characteristics of similar cases in the literature.

Case Report

A 66-year-old woman visited a local ophthalmic clinic with a main complaint of blurred vision, and she was diagnosed with iritis for both eyes and posterior synechia for left eye. The symptoms were improved with the administration of ophthalmic steroids. The following month, she visited the department of neurology in our hospital complaining

general malaise. A blood analysis revealed hypercalcemia with an extremely high serum calcium (Ca) concentration [measured Ca, 11.9 mg/dL; corrected Ca (measured Ca + 4.0- serum albumin concentration), 12.2 mg/dL]. She was therefore immediately hospitalized to undergo further examination for hypercalcemia and referred to our department.

A physical examination on admission revealed the following findings: body height, 144.7 cm; weight, 41.8 kg; body temperature, 36.8°C; blood pressure, 96/56 mmHg; and pulse rate, 89 beats/min. No anemia, jaundice, edema or cyanosis was found. No enlarged lymph nodes were palpable. Her thyroid was not swollen and oppressive thyroid pain was not found. A physical examination of the chest, abdomen, skin and extremities were unremarkable. No neurological abnormalities were found.

The complete blood cell count showed mild anemia (Hb 11.1 g/dL). A biochemical analysis revealed elevated serum levels of corrected Ca and phosphate (P) (12.2 mg/dL and 5.4 mg/dL, respectively). Her FT3 and FT4 levels were within the normal ranges while her serum thyroid stimulating hormone (TSH) level was low (0.01 µU/mL), and her thyroglobulin (Tg) concentration was elevated (368.9 ng/mL). The patient was negative for thyroid autoantibodies.

¹Department of Endocrinology and Metabolism, Kashiwa City Kashiwa Hospital, Japan, ²Department of Molecular Endocrinology and Metabolism, Tokyo Medical and Dental University, Japan, ³Department of Preemptive Medicine and Metabolism, Tokyo Medical and Dental University, Japan and ⁴Department of Respiratory Medicine, Kashiwa City Kashiwa Hospital, Japan

Received: September 26, 2016; Accepted: January 20, 2017; Advance Publication by J-STAGE: August 1, 2017

Correspondence to Dr. Koshi Hashimoto, khashimoto.mem@tmd.ac.jp

Table 1. Laboratory Data on Admission.

[Urine]		Na	141 mEq/L	[Endocrine]	
protein	(-)	K	4.1 mEq/L	1,25(OH) ₂ VitD ₃	121 pg/mL
blood	(-)	Cl	101 mEq/L	PTH-intact	3 pg/mL
[Hematology]		Ca	11.9 mg/dL	PTHrp	negative
WBC	5,580 /μL	iP	5.4 mg/dL		
Neutro	62.8 %	T-Bil	0.6 mg/dL	[Thyroid function]	
Eosino	7 %	AST	20 IU/L	Free T3	3.05 pg/mL
Bas	0.5 %	ALT	18 IU/L	Free T4	1.17 ng/dL
Lym	21.5 %	LDH	255 IU/L	TSH	0.01 μU/mL
Mon	8.2 %	ALP	204 IU/L	Tg	368.9 ng/mL
RBC	378×10 ⁴ /μL	γGTP	15 IU/L	Tg-Ab	11.6 U/mL
Hb	11.1 g/dL	CK	112 IU/L	TPO-Ab	<5.0 U/mL
Ht	33.7 %			TRAb	<1.0 IU/L
Plt	38.6×10 ⁴ /μL	[Immunology]			
[Biochemistry]		CRP	1.46 mg/dL	[Pulmonary function test]	
TP	6.6 g/dL	ACE	38.3 IU/L	VC	2.23 L
Alb	3.7 g/dL	sIL-2R	5,560 IU/mL	%VC	102 %
BUN	22.1 mg/dL			FEV1.0	1.9 L
Cr	0.81 mg/dL			FEV1.0%	85.6 %
UA	6.7 mg/dL				

WBC: white blood cell, Neutro: neutrophil, Eosino: eosinophil, Bas: basophil, Lym: lymphocyte, Mon: monocyte, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, UA: urea, Ca: calcium, P: phosphate, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, CRP: C-reactive protein, ACE: angiotensin converting enzyme, sIL-2R: soluble interleukin-2 receptor, 1,25(OH)₂Vit.D₃: 1,25-dihydroxyvitaminD₃, PTH-intact: intact parathyroid hormone, PTHrp: parathyroid hormone related protein, Tg: thyroglobulin, Tg-Ab: anti-thyroglobulin antibody, TPO-Ab: anti-thyroid gland peroxisome antibody, TRAb: thyrotropin receptor antibody, VC: vital capacity, FEV1.0: forced expiratory volume 1.0 (sec)

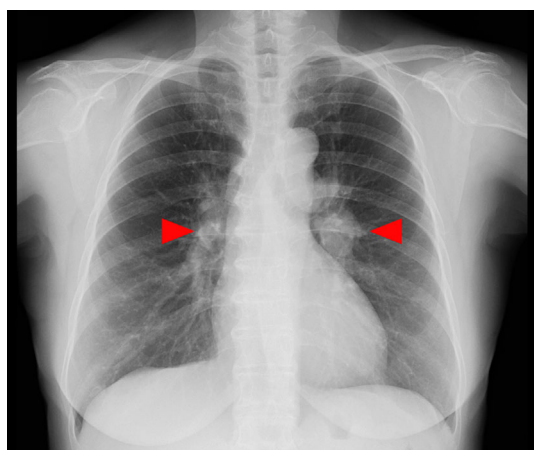


Figure 1. A chest X-ray film on admission. Arrowheads indicate hilar lymphadenopathy.

Elevated levels of 1,25-dihydroxyvitamin D₃ (1,25 (OH)₂Vit.D₃) (121 pg/mL), and angiotensin converting enzyme (ACE) (38.3 U/L) were noted. A urine examination and a respiratory function test revealed no remarkable findings (Table 1). Electrocardiography revealed normal findings. A tuberculin skin test was negative. A chest X-ray revealed mild enlargement in the bilateral hilar region (Fig. 1). The patient's respiratory function was normal. Contrast-enhanced computed tomography (CT) revealed a well-defined low ab-

sorption mass of approximately 8 mm in diameter in the right thyroid lobe, in which a poor contrast effect was found. Several enlarged hilar lymph nodes were found in the chest region (Fig. 2).

The patient's serum corrected Ca levels were lowered to 9.5-10.0 mg/dL by the intravenous administration of saline on the second week of the hospitalization, then malaise was disappeared (Fig. 3). Based on hypercalcemia, a high level of 1,25 (OH)₂Vit.D₃ and the CT findings, malignant lymphoma and sarcoidosis were included in the differential diagnoses. ⁶⁷Gallium (Ga) scintigraphy showed enlargement and accumulation in the bilateral hilar regions, the mediastinal lymph nodes, the bilateral parotid gland, the submandibular gland and the lachrymal gland, which reflected the characteristic distribution of sarcoidosis (Fig. 4). However, no accumulation was detected in the thyroid gland. She refused to undergo a bronchoscopic examination, which would have been used to determine the pathological diagnosis. Her clinical manifestations disappeared and she was discharged from our department at two weeks after admission.

We recognized the scattering of hypoechoic areas (average diameter: 10.0 mm) and a rough internal echo pattern by thyroid ultrasonography (Fig. 5A). At six weeks after admission, percutaneous thyroid CNB was conducted in our outpatient clinic. A Bard[®] Monopty[®] Disposable Core Biopsy Instrument (Bard Biopsy Systems, Tempe, USA) (nee-

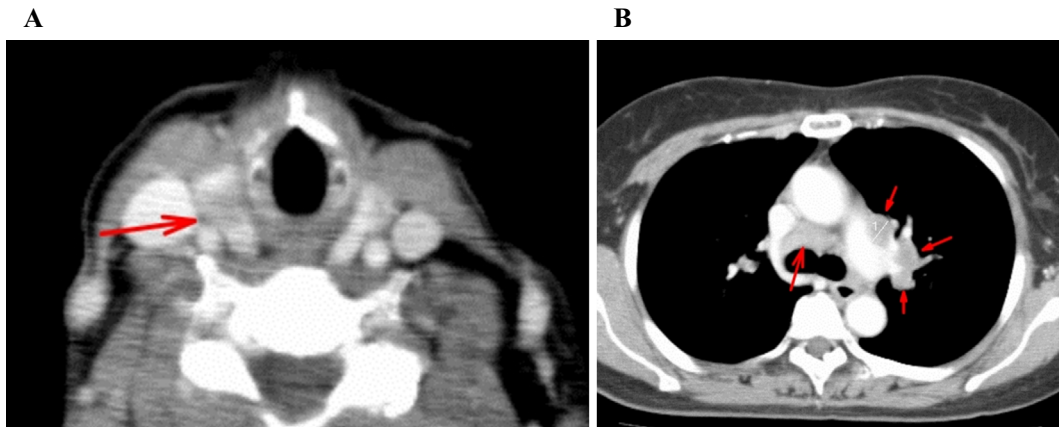


Figure 2. Contrast-enhanced CT on admission A: The arrow indicates the low absorption area in the right thyroid lobe. B: Arrows indicate the enlarged hilar lymph nodes.

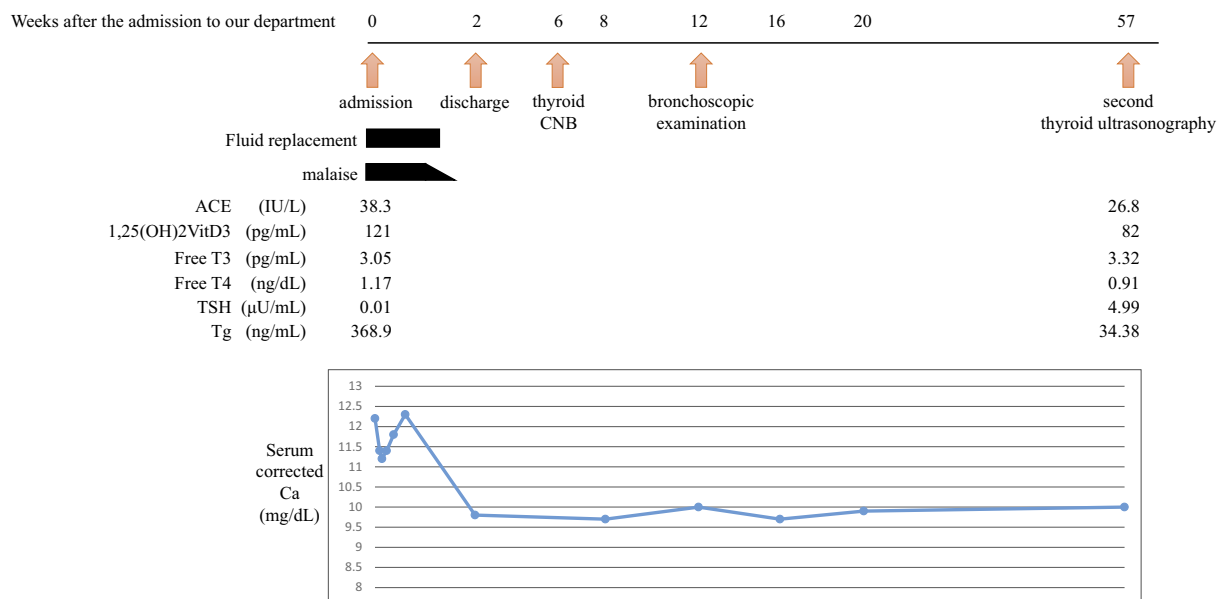


Figure 3. The clinical course until 57 weeks after admission to our department. The serum calcium concentration (Ca) was corrected for the serum albumin concentration with the following equation when the serum albumin concentration was <4.0 g/dL: serum Ca (mg/dL) = measured calcium concentration (mg/dL) + 4 - serum albumin concentration (g/dL).

dle outer diameter: 16 gauge, needle length: 90 mm, penetration depth: 11 mm, specimen notch width: 7 mm) was used to perform the tissue biopsy. Briefly, we reconfirmed a hypoechoic region in the right lobe (Fig. 5A) by thyroid ultrasonography prior to the puncture, and then made a 5-mm skin incision with a surgical knife under local anesthesia. Echo-guided biopsy was then conducted in the region. A pathological examination revealed a scattering of slightly acidophilic non-caseating epithelioid cell granulomas and lymphocytic infiltration; these findings were compatible with the final diagnosis of sarcoidosis (Fig. 6). Later, in December 2015 (at 12 weeks after admission), after the patient agreed to undergo a bronchoscopic examination, we performed bronchoalveolar lavage (BAL) and found an increase in the CD4/CD8 ratio of the patient's BAL fluid (data not

shown), which reinforced the diagnosis. The serum corrected Ca concentration remained in the normal range from the second week of admission and the ophthalmic lesion resolved following local steroid treatment. No recurrence was observed. At 57 weeks after admission, the patient's serum ACE, 1,25 (OH)₂Vit.D₃, and Tg levels were decreased in comparison to the levels that were recorded on admission (Fig. 3) and the hypoechoic areas that were observed on thyroid ultrasonography were found to have decreased in size (Fig. 5B). Even though no systemic medical treatment was administered to treat the patient's sarcoidosis, none of the patient's symptoms has been exacerbated since her discharge.

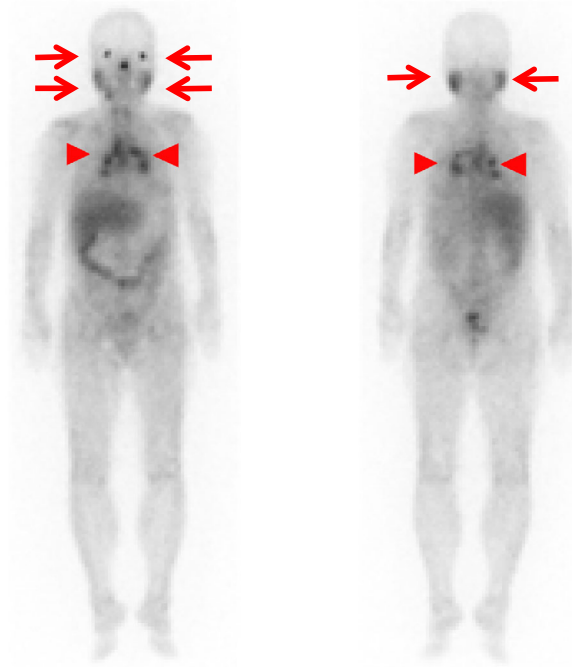


Figure 4. ^{67}Ga scintigraphy on admission (whole body image). Arrowheads indicate the accumulation in each bilateral hilar region and the mediastinal lymph nodes. Arrows indicate the accumulation in the bilateral parotid gland, submandibular gland and lachrymal gland.

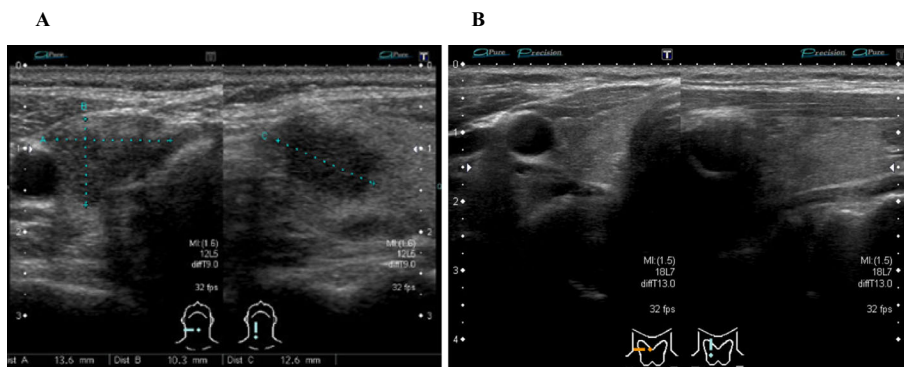


Figure 5. Thyroid ultrasonography on admission (A), and 57 weeks after the admission (B). The largest low-echoic area (ϕ 13.6×10.3×12.6 mm), in which CNB was performed (A).

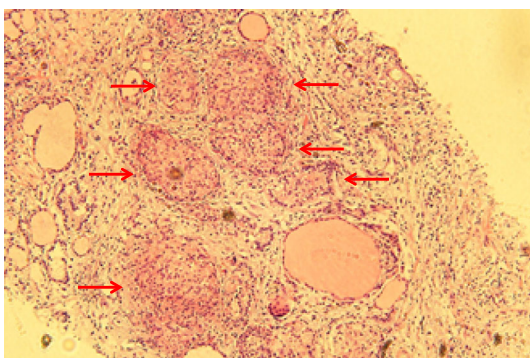


Figure 6. Histopathological examinations of the thyroid (Hematoxylin and Eosin (H&E) staining 40×). Arrows indicate non-caseating granulomas surrounded by lymphocyte infiltration.

Discussion

Sarcoidosis is usually found in the lungs (95%), skin (15.9%), lymph nodes (15.2%) and eye 11.8% (1). In 1938, Spencer et al. reported the first case of sarcoidosis in the thyroid-which was referred to as thyroid sarcoidosis-in a 51-year-old male patient with granuloma formation. The case was identified during an autopsy for hyperthyroidism (2). Sarcoidal granuloma of the thyroid has only been found in 4.5% outside of Japan (3) and 4% (4) of the autopsy cases inside Japan. Thyroid sarcoidosis is rarely diagnosed in living patients in any country. To date, only 65 cases of systemic sarcoidosis with thyroid gland involvement have been reported in the literature. Thyroid sarcoidosis can be ob-

Table 2. Cases of Thyroid Sarcoidosis in Japan.

Age	Sex	Main complaint	Thyroid function	Thyroid autoantibody	Thyroid Ultrasonography	Diagnostic procedure of thyroid sarcoidosis	Treatment	[Ref.]
49	F	weight loss malaise	aggravated	negative	N/A	postoperative pathology	PTU, MMI→ subtotal excision	[6]
50	F	finger tremor	aggravated	TPO-Ab positive	N/A	postoperative pathology	subtotal excision	[7]
27	F	weight loss goiter	aggravated	negative	N/A	postoperative pathology	PTU→ subtotal excision	[8]
27	F	diffuse goiter	aggravated	TPO-Ab positive	N/A	postoperative pathology	MMI→ subtotal excision	[8]
74	F	cough breathlessness	lowered	TPO-Ab positive	N/A	open biopsy	no medication	[9]
51	F	pharyngeal oppression	normal	TPO-Ab positive	scattering of nodular shadows(1-3cm)	open biopsy	no medication	[10]
55	F	pharyngeal uncomfort	normal	N/A	N/A	postoperative pathology	subtotal excision→ steroid	[11]
60	F	pharyngeal oppression	normal	N/A	iso-echoic nodular appearance	postoperative pathology	subtotal excision	[12]
54	F	chest abnormal shadow	lowered	negative	hypoechoic confluent nodular appearance	open biopsy	no medication	[13]
66	F	malaise blurred vision	aggravated	negative	hypoechoic confluent nodular appearance	Thyroid CNB	no medication	current case

F: female, N/A: not applicable, Ref: reference, yr: year, TPO-Ab: anti-thyroid gland peroxisome antibody, CNB: core needle biopsy, PTU: propylthiouracil, MMI: mercaptomethylimidazole

served in <10% of all sarcoidosis patients, and less than 1% of patients with cold thyroid nodules have non-caseating granulomas (5).

We reviewed the case reports of thyroid sarcoidosis in Japan, including our own case (6-13) (Table 2). To date, only female patients have been reported (average age 51.3 years). The main complaints at the first visit included oppressive thyroid pain (n=4) as well as typical symptoms of thyrotoxicosis, such as palpitation and weight loss (n=3). In the cases of thyroid sarcoidosis, both hypothyroidism and thyrotoxicosis were reported (14). Hypothyroidism due to extensive infiltration by epithelioid granulomas has been reported (15). Thyroid autoantibody positivity is reported in 20-30% of patients with systemic sarcoidosis (16), while the incidence of Hashimoto's thyroiditis is high (17).

Although some cases of thyroid sarcoidosis are complicated by Graves' disease, there is no evidence to suggest that thyroid sarcoidosis predisposes an individual to thyrotoxicosis (18).

In the current case, the patient demonstrated subclinical hyperthyroid status with elevated serum Tg levels on admission, which suggests the destruction of the thyroid. Given that the pathological examination of the area that was hypoechoic on thyroid ultrasonography revealed lymphocytic infiltration and the fact that the patient's serum TSH levels were elevated thereafter-even though she was negative for thyroid autoantibodies-we assumed that the patient was seronegative for Hashimoto's thyroiditis.

Scattered nodular shadows (1-3 cm) and irregular hypoechoic areas-which reflect granuloma formation-are reported to be the representative ultrasonographic findings of thyroid sarcoidosis (10). These findings are similar to typical

ultrasonographic images in thyroid malignant lymphoma, which should be differentially diagnosed from thyroid sarcoidosis (19).

⁶⁷Ga scintigraphy did not detect a sarcoidosis mass in the thyroid gland-presumably due to the relatively mild inflammation of the mass. The sensitivity of ⁶⁷Ga scintigraphy in detecting pulmonary and extrapulmonary sarcoidosis is reported to be 81% and 48%, respectively. On the other hand, ¹⁸F-fluorodeoxy glucose-positron emission tomography (FDG-PET) detects 100% and 90% of clinically observed pulmonary and extrapulmonary sarcoidosis, respectively (20). Thus, we hypothesize that ¹⁸F-FDG-PET would have detected thyroid sarcoidosis in the current case.

The pathological examination of a tissue biopsy specimen-the findings of which are characterized by the non-caseating epithelioid granuloma-is required for a final diagnosis of sarcoidosis (21). According to a statement from the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), transbronchial lung biopsy (TBLB) should first be considered for the final diagnosis (22). In the current case, since the patient refused to undergo a bronchoscopic examination, we conducted percutaneous CNB of the hypoechoic area, which was observed on thyroid ultrasonography, and performed a pathological examination, which revealed a scattering of slightly acidophilic epithelioid cell granulomas. The indications for CNB have been limited in comparison to fine needle aspiration cytology (FNAC), which is less invasive. However, in a previous report, FNAC failed to detect thyroid sarcoidosis and open biopsy was necessary to make the final diagnosis (13). We therefore decided to conduct CNB,

which is more diagnostic than FNAC and much less invasive than open biopsy. In light of the diagnostic accuracy, CNB should be employed to make a histological diagnosis in cases that involve features such as the rapid development of undifferentiated cancer, malignant lymphoma, and metastatic tumors in the thyroid. To the best of the authors' knowledge, the number of case reports in which systemic sarcoidosis was diagnosed by thyroid CNB (including our case) is limited.

The ATS guidelines recommend that systemic steroid therapy be administered to treat patients with systemic sarcoidosis who have organ disorders (22). The administration of glucocorticoid can also be indicated when patients with sarcoidosis present hypercalcemia, since it suppresses the secretion of $1.25(\text{OH})_2\text{Vit.D}_3$. The administration of steroids is reported to be effective for reducing the size of sarcoidosis masses in the thyroid (11). In our case, we did not administer steroids because the patient's serum Ca levels were immediately improved by the administration of saline and because the hypoechoic areas that were detected by thyroid ultrasonography were found to spontaneously decrease in size. Based on the subsequent clinical course, we hypothesize that in the current case, the patient's systemic sarcoidosis went into spontaneous remission without the administration of steroids. The serum ACE and $1.25(\text{OH})_2\text{Vit.D}_3$ levels are surrogate markers that reflect the disease activity of systemic sarcoidosis. In the current case, both levels were found to be clearly decreased—indicating disease remission—at 57 weeks after admission to our department (Fig. 3). The patient's serum Tg levels, which were suspected to have been associated with the thyroid ultrasonography findings (which demonstrated the shrinkage of the thyroid mass)—also decreased.

We reported a rare case of systemic sarcoidosis that was diagnosed by thyroid CNB. Sarcoidosis can involve the thyroid and thyroid CNB is an alternative method for obtaining a pathological diagnosis, especially in cases in which areas of the thyroid appear hypoechoic.

The authors state that they have no Conflict of Interest (COI).

References

- Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* **164**: 1885-1889, 2001.
- Spencer J, Warren S. Boeck's sarcoid: report of a case with clinical diagnosis confirmed at autopsy. *Arch Intern Med* **62**: 285-288, 1938.
- Harach HR, Williams ED. The pathology of granulomatous diseases of the thyroid gland. *Sarcoidosis* **7**: 19-27, 1990.
- Iwai K, Takemura T, Kitaichi M, Kawabata Y, Matsui Y. Pathological studies on sarcoidosis autopsy. II. Early change, mode of progression and death pattern. *Acta Pathol Jpn* **43**: 377-385, 1993.
- Ozkan Z, Oncel M, Kurt N, et al. Sarcoidosis presenting as cold thyroid nodules: report of two cases. *Surg Today* **35**: 770-773, 2005.
- Kubo T, Nakase S, Taniuchi S, et al. Sarcoidosis of the thyroid and hyperthyroidism - report of a case. *Naika (Internal Medicine)* **32**: 361-365, 1973 (in Japanese, Abstract in English).
- Yoshida H, Tomichi N, Suzuki S, et al. A case of Basedow's disease with histologically sarcoidosis involving the thyroid and the parathyroid gland. *Nihon Geka Gakkai Zasshi (Journal of Japan Surgical Society)* **83**: 702-706, 1982 (in Japanese).
- Katayama S, Matsuzuka F, Matsubayashi S, Kobayashi A, Kuma K. Sarcoid reaction in the Grave's disease. *Naibunpitsu Geka (Official Journal of the Japan Association of Endocrine Surgeons)* **1**: 253-256, 1984 (in Japanese, Abstract in English).
- Hirayama M, Uetake T, Kudoh S, Kimura H, Hongo O, Fukayama M. A case of sarcoidosis involving the thyroid gland. *Naika (Internal Medicine)* **57**: 191-195, 1986 (in Japanese, Abstract in English).
- Sasaki H, Harada T, Eimoto T, Matsuoka Y, Okumura M. Concomitant association of thyroid sarcoidosis and Hashimoto's thyroiditis. *Am J Med Sci* **294**: 441-443, 1987.
- Date T, Kinoshita T, Ishiki M, et al. A case of thyroid sarcoidosis. *Nihon Naika Gakkai Zasshi (Journal of Japanese Society of Internal Medicine)* **84**: 1742-1743, 1995 (in Japanese).
- Ogata M, Araki K, Hamada S, Kobayashi M, Matsuura K, Ogata T. A case of adenomatous goiter with sarcoidosis of the thyroid gland. *Rinsho Geka (Journal of Clinical Surgery)* **51**: 369-372, 1996 (in Japanese, Abstract in English).
- Uto T, Inui N, Miyazaki H, et al. A case of thyroid sarcoidosis. *Nihon Kokyuuiki Gakkai Zasshi (The Journal of the Japanese Respiratory Society)* **46**: 667-672, 2008 (in Japanese, Abstract in English).
- Winnacker JL, Becker KL, Katz S. Endocrine aspects of sarcoidosis. *N Engl J Med* **278**: 483-492, 1968.
- Brun J, Mouriquand C, Combey P, Vauzelle JL. Sclerous thyroiditis of sarcoidotic origin with myxedema and diffuse pulmonary fibrosis. *Lyon Med* **91**: 179-188, 1959.
- Nakamura H, Genma R, Mikami T, et al. High incidence of positive autoantibodies against thyroid peroxidase and thyroglobulin in patients with sarcoidosis. *Clin Endocrinol (Oxf)* **46**: 467-472, 1997.
- Papadopoulos KI, Hörnblad Y, Liljebadh H, Hallengren B. High frequency of endocrine autoimmunity in patients with sarcoidosis. *Eur J Endocrinol* **134**: 331-336, 1996.
- Porter N, Beynon HL, Randeva HS. Endocrine and reproductive manifestations of sarcoidosis. *QJM* **96**: 553-561, 2003.
- Parulekar SG, Katzman RA. Primary malignant lymphoma of the thyroid: sonographic appearance. *J Clin Ultrasound* **14**: 60-62, 1986.
- Nishiyama Y, Yamamoto Y, Fukunaga K, et al. Comparative evaluation of ^{18}F -FDG PET and ^{67}Ga scintigraphy in patients with sarcoidosis. *J Nucl Med* **47**: 1571-1576, 2006.
- Diagnosis criteria and guidance for sarcoidosis *Nihon Sarukoidosisu/Nikugeshuseisikkan Gakkai (Japan Society of Sarcoidosis and Other Granulomatous Disorders)*, 2015 (in Japanese).
- Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* **16**: 149-173, 1999.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).