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【 CASE REPORT 】

Successful Management of Subacute Thyroiditis Following SARS-CoV-2 Infection

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Abstract:
Subacute thyroiditis (SAT) is a disorder of the thyroid gland and difficult to diagnose. It is probably triggered by a viral infection. Recently, several articles have reported SAT after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, reports describing SAT after SARS-CoV-2 in Japan are lacking. We herein report the first case of SAT after SARS-CoV-2 infection in Japan. After SARS-CoV-2 infection, some patients can develop not only pneumonia but also SAT. Thus, a careful follow-up is recommended for patients after SARS-CoV-2 infection. Furthermore, the effect of SARS-CoV-2 infection on thyroid dysfunction should not be ignored.

Key words: subacute thyroiditis, SARS-CoV-2, thyroid dysfunction

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since December 2019. Its common symptoms are a fever and cough, similar to those of common viral infections (1). Subacute thyroiditis (SAT) is a self-limited inflammatory disorder of the thyroid gland that tends to be triggered by viral infections, such as coxsackievirus, Epstein-Barr virus, adenoviruses, influenza viruses, mumps, measles, and primary human immunodeficiency virus infection (2). Since May 2020, several reports have shown that SAT has occurred during or after SARS-CoV-2 infection (3).

We herein report the first patient who was diagnosed with SAT after SARS-CoV-2 infection in Japan. The symptoms were managed, and the patient recovered.

Case Report

A 31-year-old woman with a low-grade fever and a painful sore throat for 3 days was admitted to the hospital. She did not have any remarkable medical history or family history of thyroid disease.

Her oropharyngeal swab for SARS-CoV-2 RNA was positive and consequently, a diagnosis of COVID-19 was established. Her partner, who was living with her, was also diagnosed with COVID-19. She recuperated at home and was managed with no specific treatment, including steroid therapy.

Two weeks later, the low-grade fever persisted, rising to above 37°C and up to 38°C. She developed symptoms of anterior neck pain that did not improve. After another two weeks, she revisited the hospital. On an examination, her body temperature was 37.8°C, heart rate was 88 beats/min, blood pressure was 111/61 mmHg, respiratory rate was 16/min, and oxygen saturation was 99% on room air. A physical examination revealed that the left side of the thyroid gland was painful, hard, and slightly enlarged. The pain had spread to the right lobe. Her neck pain had radiated to the jaw. Of note, she was referred to our hospital for malaise and not any upper respiratory symptoms.

Laboratory test results showed undetectable serum thyrotropin (TSH) levels (0.0 μIU/mL; normal ranges, 0.4-4.0); free thyroxine (FT4) levels of 3.2 ng/dL (normal ranges, 0.8-1.9); and free triiodothyronine (FT3) levels of 7.3 pg/mL (normal ranges, 2.2-4.1). Her white blood cell count, eryth-

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Table. Clinical Laboratory Results.

Variable	Normal range	Patient's value	Variable	Normal range	Patient's value	Variable	Normal range	Patient's value
CPK, IU/L	41-153	65	Glu, mg/dL	73-109	93	TSH, μIU/mL	0.4-4.0	0.0
AST, IU/L	13-30	19	PCT, ng/dL	0-0.05	0.04	FT3, pg/mL	2.2-4.1	7.3
ALT, IU/L	7-23	20	CRP, mg/dL	0.00-0.14	3.6	FT4, ng/dL	0.8-1.9	3.2
LDH, IU/L	122-228	170	WBC, $\times 10^2/\mu L$	33-86	100	ESR(1h), mm	1-15	93
BUN, mg/dL	8.0-20.0	9.4	RBC, $\times 10^4/\mu L$	386-492	430	TPOAb, U/mL	0-15.9	<9.0
Cre, mg/dL	0.5-0.8	0.8	Hb, g/dL	11.6-14.8	12.7	TRAb, %	-10-10	<0.1
Na, mmol/L	138-145	135	Ht, %	35.1-44.4	36.5	TgAb, IU/mL	0-28	51.4
K, mmol/L	3.6-4.8	3.9	Plt, $\times 10^4/\mu L$	15.8-34.8	37	PT, %		70.3
Cl, mmol/dL	101-108	99	Neutrophil, %	36.6-79.9	73.5	APTT, s		30.5
Ca, mg/dL	8.8-10.1	9.9	Lymphocyte, %	17.1-55.5	19.2			
IP, mg/dL	2.7-4.6	3.8	Monocyte, %	3.5-9.7	6.9			
TP, g/dL	6.6-8.1	7.8	Basophil, %	0.0-1.2	0.1			
Alb, g/dL	4.1-5.1	3.3	Eosinophil, %	0.4-6.0	0.3			

CPK: creatine phosphokinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, IP: inorganic phosphorus, TP: total protein, Alb: albumin, PCT: procalcitonin, CRP: C-reactive protein, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, FT3: free triiodothyronine, FT4: free thyroxine, Glu: glucose, PT: Prothrombin time, APTT: Activated partial thromboplastin time, ESR: erythrocyte sedimentation rate, TPOAb: thyroperoxidase antibodies, TRAb: TSH receptor antibodies, TgAb: thyroglobulin antibody

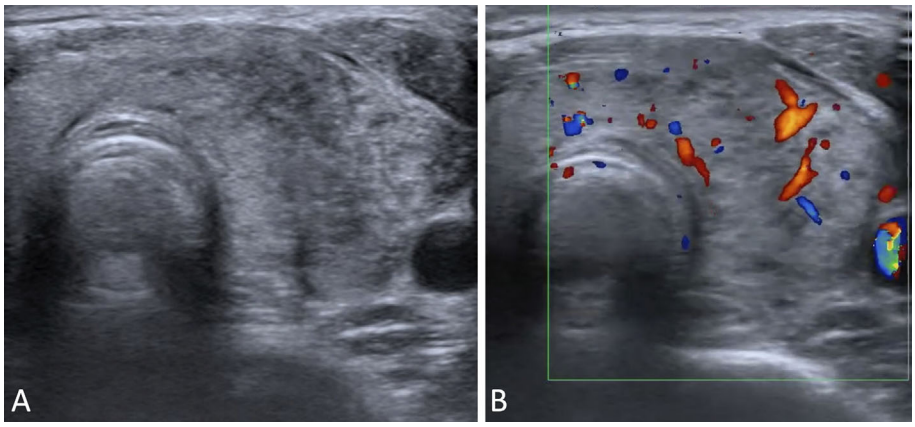

Figure 1. (A) Transverse view of thyroid ultrasound with B-mode showed that the left lobe was enlarged with a hypoechoic area. (B) Transverse view of left thyroid lobe with Doppler image revealed the absence of vascularization.

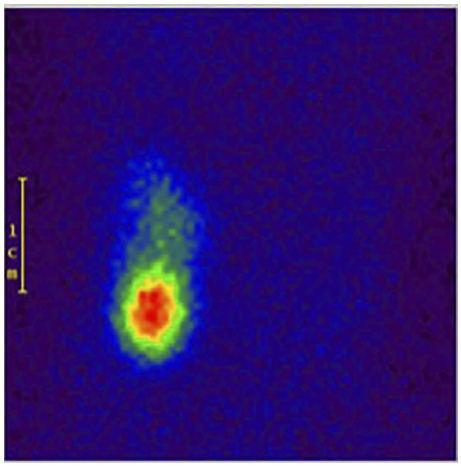

Figure 2. No technetium-99m uptake in the left side of the thyroid gland. Technetium-99m uptake: right thyroid uptake: 0.5%, left thyroid uptake: 0.1%; normal ranges 0.4-3.0.

rocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were high (Table). Thyroperoxidase antibodies and TSH receptor antibodies were negative. The patient tested positive for the thyroglobulin antibody.

Her chest radiograph findings were normal. Thyroid ultrasound showed diffuse hypoechoic areas consistent with the pain (Fig. 1). Thyroid scintigraphy showed no remarkable uptake of technetium-99m within the left lobe of the thyroid gland (Fig. 2). She was fully vaccinated against mumps, measles, and rubella. She was found to have an IgM index value of 1.98 (normal range, <1.0) and IgG index value of 8.29 (normal range, <1.4) for antibodies to SARS-CoV-2. Thus, she was diagnosed with SAT and started nonsteroidal anti-inflammatory drugs (NSAIDs) for three days.

However, this treatment was not effective. Therefore, we switched from NSAIDs to oral prednisolone (PSL) (15 mg/day as the initial dose). The neck pain and fever disappeared

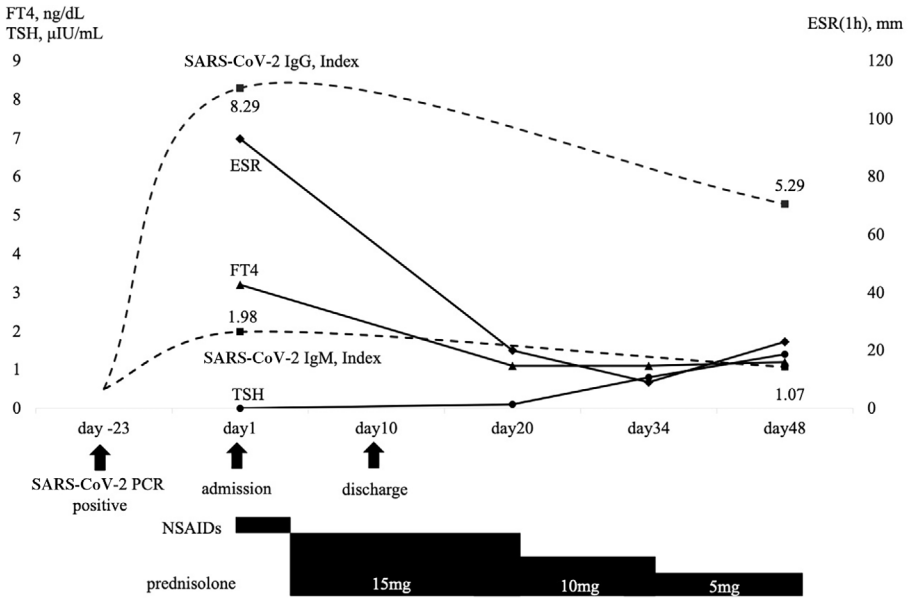

Figure 3. Transition of thyroid dysfunction, inflammatory markers, and anti-SARS-CoV-2 IgG/IgM antibodies. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, FT4: free thyroxine

within the next day, and other symptoms improved within a week. We tapered the dose of PSL by 5 mg for two weeks. Thereafter, we reduced the dose to 3 mg for two weeks, and then further reduced the dose to 2 mg for another two weeks. Seven weeks after the diagnosis of SAT, PSL was discontinued, and inflammatory markers and thyroid function test findings had also returned to normal (Fig. 3).

Discussion

SAT, also called de Quervain's thyroiditis, is a self-limited inflammatory thyroid disease (2). It is often diagnosed based on clinical symptoms. Its characteristic symptoms include a low-grade fever, fatigue, myalgia, anorexia, neck pain, and pharyngitis. This neck pain can occasionally radiate to the upper neck, jaw, or ear. Several case reports worldwide have reported cases SAT after SARS-CoV-2 infection (4-17). These reports indicated that, in most cases, the symptoms of COVID-19 were not serious, with only a mild fever and upper respiratory signs noted. Typical clinical SAT-related features related to SARS-CoV-2 infection were neck pain, tenderness, and tachycardia (18).

Some laboratory and imaging tests can confirm this diagnosis. The inflammatory markers ESR and CRP were also elevated in the acute phase, and ultrasound imaging identified hypoechoic areas and low-to-absent vascularization in the thyroid gland (19). On TSH suppression, the thyroid uptake of technetium-99m is typically diffusely cold (20). Our patient had a mild fever and neck pain but not tachycardia. Thyroid scintigraphy showed no remarkable uptake of technetium-99m within the left side of the thyroid gland. It was estimated that the patient was already in the subacute stage of SARS-CoV-2 infection at the time of the diagnosis of SAT.

The clinical course of SAT can be divided into three phases: thyrotoxicosis, hypothyroidism, and euthyroidism. During the first phase, thyrotoxicosis, TSH is suppressed, and thyroid hormone is released. Thereafter, TSH and T4 levels become low in the hypothyroidism phase. However, the TSH and T4 levels gradually increase after that. Recovering from SAT often takes three to six months, and the thyroid function eventually normalizes (21). Thyrotoxicosis is associated with hypercalcemia following increased bone resorption (22). Conversely, patients with COVID-19 infections present with hypocalcemia due to vitamin D deficiency (23). In the present case, the serum corrected Ca levels were high at admission, but the serum corrected Ca level was normal by one month after the start of the treatment. This is probably due to dehydration, as the blood urea nitrogen/creatinine ratio was widened in the laboratory test due to the appearance of low-grade fever. Also, 3 weeks have passed since the diagnosis of COVID-19.

The etiology of SAT is unclear. However, viral infection has been suggested to stimulate SAT and cause damage to the thyroid gland. In the present case, we examined anti-SARS-CoV-2 IgG and IgM antibodies; both were positive, indicating that she had recently been infected with SARS-CoV-2, which might have caused thyroiditis. Indeed, Fig. 3 shows that when she was admitted to our hospital at the thyrotoxicosis phase, both anti-SARS-CoV-2 IgG and IgM antibodies were positive. On day 48 after admission, although the anti-SARS-CoV-2 IgM antibody levels had declined, they remained positive. According to the previous reports, the longest time interval from the diagnosis of COVID-19 to the onset of SAT symptoms was 49 days (14). The time interval between the diagnosis of SAT and the thyroid function recovery was 4-10 weeks (4-17). In our case, these time intervals were 23 days and 34 days, respectively, indicating

that our case's clinical course was similar to those of previous cases. Furthermore, the course of SAT caused by SARS-CoV-2 was similar to that of SAT caused by other viruses according to previous reports.

The first-line treatment of thyroid pain in SAT is NSAIDs, but pain resolution is faster with glucocorticoids than with NSAIDs. Typical PSL dosages are 30-40 mg/day for 1-4 weeks, followed by tapering of the doses (2). The administration of PSL during the acute phase results in a faster resolution of symptoms and a lower risk of recurrence (24). The lower dose of PSL (15 mg/day) as the initial dose for the treatment of SAT was shown to be particularly effective and safe in Japanese patients (25). In the present case, we initially prescribed NSAIDs. However, the patient's symptoms did not improve. We then administered PSL at 15 mg, with tapering every 2 weeks, and she achieved a full recovery.

Although the number of reported cases of SAT related to SARS-CoV-2 infection is increasing, there are few reports of it despite the extremely large number of COVID-19 patients. With SARS-CoV-2 infection, the risk of infection may delay the diagnosis of SAT due to insufficient testing. SARS-CoV-2 infection leads to thyroid dysfunction, SAT, and nonthyroidal illness syndrome (26). Steroid therapy for COVID-19 may sometimes mask the symptoms of SAT. As a result, the diagnosis of SAT was therefore sometimes be underestimated. Among Asian countries, SAT following SARS-CoV-2 infection has been reported only in the Philippines, Singapore, India, and Iran (8, 12, 13, 15, 17), so awareness may be low, or SAT secondary to COVID-19 may be underreported. We need to follow the monitor and thyroid function in patients after SARS-CoV-2 infection.

In conclusion, we described the first case of SAT related to SARS-CoV-2 in Japan. We should carefully follow patients after SARS-CoV-2 infection, and the effect of SARS-CoV-2 infection on thyroid dysfunction should not be ignored.

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

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