

NOTE

A case of postpartum thyroiditis following SARS-CoV-2 infection

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Abstract. Postpartum thyroiditis (PPT) is characterized by mild thyrotoxicosis occurring within one year of parturition commonly followed by transient hypothyroidism. Having genetic background of autoimmune thyroid disorders is a risk factor for it because the immune reactivation during postpartum period is a trigger for PPT. Pandemic of COVID-19: caused by SARS-CoV-2 infection is a global health problem, and occurrence of Graves' disease and Hashimoto's thyroiditis after the viral infection have been reported but occurrence of PPT with COVID-19 has never been reported. A 29-year-old woman developed general fatigue four and a half months after parturition, and was diagnosed as having PPT: one month before, she had COVID-19. Hereafter, we define the date of delivery as *Day 0* to make timeline clear. SARS-CoV-2 infection was diagnosed by PCR on *Day 103*, its disappearance from the upper airway confirmed on *Day 124*, and the thyroiditis diagnosed on *Day 136*. She had been euthyroid on *Day 0* and *95*, but thyrotoxic on *Day 136*. Serum thyroglobulin (Tg) concentration was normal in the presence of anti-Tg antibody, other thyroid-related autoantibodies were negative, and by ultrasonography, the thyroid gland was normal in size and no evidence of increased vascularity. Thyroid function returned to normal by *Day 172* without any specific drug therapy. In conclusion, although a clear causal relationship could not be found, we documented the world's first case of PPT developed following COVID-19.

Key words: COVID-19, SARS-CoV-2, Postpartum thyroiditis, Thyrotoxicosis, Hashimoto's thyroiditis

CORONAVIRUS DISEASE 2019 (COVID-19): caused by SARS-CoV-2 infection, which results in serious respiratory and other systemic complications, has spread worldwide since December 2019 [1]. In the patients with the infection, many organ systems can be damaged, including respiratory, cardiovascular and coagulation systems, with potentially fatal results, for which robust, disorganized systematic immune activation is responsible [2]. Thyroidal complication, meanwhile, has been reported only scarcely [3-6]. To our knowledge, there

have been no single case report of postpartum thyroiditis (PPT) occurred after COVID-19.

Case Presentation

A 29-year-old woman presented with general fatigue four and a half months after giving birth: this was just nine days after discharge from a hospital where she had been admitted for 4 weeks for the treatment of COVID-19. She had painless thyroiditis (PT) under the background of Hashimoto's thyroiditis (HT) five years ago: anti-thyroglobulin autoantibody (TgAb) was 167.4 IU/mL (reference range was <28.0 in the assay) at that time. For the sake of clarity, Table 1 was created in which the day of the current delivery was designated as *Day 0* (Table 1).

On *Day 0* and *95*, *i.e.*, before the SARS-CoV-2 infection, the patient had been euthyroid. Before and during the pregnancy, the white blood cell (WBC) count and its fraction were normal. After close contact with an individual infected with SARS-CoV-2, she was confirmed to

Submitted Aug. 28, 2020; Accepted Oct. 22, 2020 as EJ20-0553
Released online in J-STAGE as advance publication Nov. 12, 2020
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Abbreviations: PTT, postpartum thyroiditis; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory coronavirus 2; RT-PCR, real-time polymerase chain reaction; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine

Table 1 Key events and laboratory data along the timeline

Measurement	Day										Ref. Range
	0	95	103	104	124	126	127	136	172	205	
WBC/ μ L	N.D.	N.D.	N.D.	6,100	N.D.	N.D.	N.D.	4,800	4,140	5,300	4,000–9,500
Neu (%)	N.D.	N.D.	N.D.	82.5	N.D.	N.D.	N.D.	51.1	55.6	50.8	35–75
Lym (%)	N.D.	N.D.	N.D.	10.0	N.D.	N.D.	N.D.	35.6	35.5	39.2	25–50
Lymphocytes (μ L)	N.D.	N.D.	N.D.	610	N.D.	N.D.	N.D.	1,708	1,469	2,077	1,000–3,000
FT4, ng/dL	0.91	1.09	N.D.	N.D.	N.D.	N.D.	N.D.	2.00	1.23	0.88	0.9–1.7
FT3, pg/mL	N.D.	3.04	N.D.	N.D.	N.D.	N.D.	N.D.	5.44	3.61	2.76	2.3–4.0
TSH, μ IU/mL	0.818	1.37	N.D.	N.D.	N.D.	N.D.	N.D.	0.020	0.043	2.01	0.5–5.0
Tg, ng/mL	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	5.26	5.20	1.23	<33.7
TgAb, IU/mL	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	12.24	N.D.	35.1	<5
TPOAb, IU/mL	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	<3	<3	<3	<3
TRAb, IU/mL	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	<0.9	<0.9	<0.9	<2.0
SARS-CoV-2 PCR	N.D.	N.D.	(+)	N.D.	(–)	(–)	N.D.	N.D.	N.D.	N.D.	N.A.

Events				
\uparrow Delivery	Admission High fever (39.0°C)	Hospital Discharge	Onset of PPT	Recovery from PPT

Footnotes: WBC, white blood cell; Neu, proportion of neutrophils; Lym, proportion of lymphocytes. The day of delivery was defined as Day 0 in this communication, so that the clinical onset of postpartum thyroiditis (PPT) is Day 136. Tg, thyroglobulin; TgAb, Anti-Tg autoantibody; TPOAb, anti-thyroperoxidase autoantibody; TRAb, anti-TSH receptor autoantibody (3rd generation assay); N.D., not determined; N.A., not applicable.

be positive for SARS-CoV-2 in the samples of nasopharyngeal and oropharyngeal swabs by real-time polymerase chain reaction test on Day 103.

Her total WBC count, 6,100/ μ L, was normal but the number of lymphocyte was reduced down to 610/ μ L (10%, references range 25–50%); the entire picture of the fraction of the white cells was, 10% lymphocyte (reference range, 25–50%), 82.5% neutrophils, 0.7% eosinophils, 0.2% basophils, and 6.6% monocytes (Table 1). The serum CRP level, 0.03 mg/dL (<0.3) was normal. She was admitted to a hospital on Day 104, her body temperature was increased to 39.0°C and she developed a sore throat. She was observed without specific treatment, and fever and sore throat had subsided by Day 107. Swabs for SARS-CoV-2 taken on Day 124 and 126, longer than 24 hours apart, were both negative. She was discharged on Day 127.

On Day 136, at a follow-up visit for COVID-19, she had general fatigue. There was no goiter, and no tenderness was elicited by palpation of the neck. TSH level was suppressed and fT3 and fT4 levels were elevated (Table 1). Her total WBC count, 4,800/ μ L, was normal and lymphocyte fraction, 35.6%, lymphocytes (1,708/ μ L) was normal, as well (Table 1). Serum thyroglobulin (Tg) level was not elevated in the presence of TgAb.

Other thyroidal autoantibodies including anti-TSH receptor autoantibodies were all negative (Table 1). The thyroid gland was normal in size (the right lobe: 14.2 mm, 12.8 mm, and 46.2 mm in width, depth, and height, respectively; the left lobe: 14.5 mm, 12.5 mm, and 48.3 mm in width, depth, and height, respectively) with coarse echotexture. No focal hypoechoic areas suggesting inflammation were observed. The ultrasonographic findings were similar to those when she developed PT 5 years before. No increase of the blood flow was observed. Thyroid scintigram was avoided because she was breastfeeding. Under the most possible diagnosis of PPT, she was observed without specific treatment. Her symptoms disappeared, and she regained euthyroidism by Day 172. The titer of TgAb increased on Day 205 (Table 1). HLA-typing test revealed that she had HLA-A*24:02, B*51:01/52:01, C*12:02/14:02, DRB1*12:01/15:02, DRB3*01:01:02, DRB5*01:02, DQA1*01:03/05:08, DQB1*03:01/06:01, DPA1*02:02, and DPB1*03:01/05:01.

Discussion

PPT is painless thyroiditis seen in the postpartum period [7]. It typically develops within six months of

parturition with the prevalence ranges being 3% to 8% of all pregnancies [8]. PPT is characterized by the initial thyrotoxicosis followed by hypothyroidism, and then recovery. It may occur in patients with positive thyroid autoantibodies. Diagnosis is based on clinical manifestations, thyroid function tests, and thyroid scintigrams. Most women with PPT have only mild symptoms during the thyrotoxic phase, and the disease usually requires no treatment. The etiology of PPT is not completely understood, but it occurs on background of autoimmune thyroid disorders and is histologically characterized by focal or diffuse chronic thyroiditis [9]. An immune rebound is a proposed mechanism for its development. COVID-19, in its severe form, is associated with hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure, in which interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, interferon-gamma inducible protein 10, monocyte chemoattractant protein-1, and tumor necrosis factor- α in the serum are elevated [2]. Elevation of those cytokines, such as IL-2, can possibly be related to the development of HT [10]. Various forms of thyroid dysfunction, such as central hypothyroidism, primary hypothyroidism, and thyrotoxicosis were clinically recognized. Additionally, damage of the thyrocytes was demonstrated in autopsy material of patients with SARS-CoV during the 2002 outbreak [11]. Considering that cytokine storm is also a shared feature for SARS-CoV, absence of SARS-CoV *per se* in the damaged thyrocytes was strongly indicative of autoimmune reactivation rather than direct viral infection being causal for the thyroidal diseases during human coronavirus infections at large [12]. It is reasonable to assume the activation of thyroid autoimmunity in our patient who had TgAb. She possessed HLA-B51 and HLA-DP5 which are the alleles with increased susceptibility to HT and Graves' disease (GD) in Japanese, respectively [13, 14]. Accordingly, we hypothesize that infection of SARS-CoV-2 might reactivate thyroid autoimmunity in the postpartum period through cytokine overproduction. In comparison to the regular patients with PPT who does not have SARS-CoV-2 infection, the degree of thyroidal immune reactivation may have been relatively strong in those having passed the viral infection like ours. Elefsiniotis *et al.* reported that 4 of 16 chronic hepatitis C virus (HCV)-infected women developed PPT, proposing "viral-triggered PPT" as a subtype of the thyroiditis [15]. The two patients exhibited thyrotoxicosis on third and sixth months after delivery, respectively. The other two women developed hypothyroidism. Remarkably, none of 64 chronic hepatitis B virus (HBV)-infected women developed PPT. Considering that SARS-CoV-2 and HCV are RNA virus, and HBV is a DNA virus, a clear-cut

difference in the incidence of PPT after the HBV infection. Differently from the general viral infection, lymphopenia has been observed in 85% patients with severe COVID-19 [1], which was also the case in the current patient. Occurrence of PPT kept pace with the increment of lymphocytes in the circulation, suggesting link between the infection with SARS-CoV-2, the increase of lymphocytes and the development of PPT.

Two cases of Graves' disease [3], and a case of HT [4] after COVID-19 were reported. In those patients with the background of autoimmune thyroid disorders like ours, upon the viral infection, the thyroid gland may have been affected by the activated thyroid autoimmunity. It has been reported that the prevalence of PPT is increased in those who have HLA-A1, HLA-B8, HLA-DR3 or 'HLA-B8 and HLA-DR3' in combination in the case of Caucasians [16]. Whereas PPT-susceptible HLA alleles or haplotypes if any has not been established in Japanese subjects. It has been reported that both intrathyroidal helper-T-cell numbers and HLA-DR antigen expression in the thyroid follicular cells had increased in PPT than those in HT [8]. Therefore, the molecular mimicry of the viral and thyroid epitope relating to the presentation on HLA molecule might be a possible mechanism for post COVID-19-PPT in our patient.

Recently, 4 case of subacute thyroiditis (SAT) developed after COVID-19 infection was reported [5]. Muller, *et al.* also reported cases of atypical SAT after infection with SARS-CoV-2 [6]. Considering that SAT [5, 6] and PPT (current case) both belong to self-limiting inflammatory disorder, inflammatory and/or autoimmune thyroid disorders related to SARS-CoV-2 infection may be not so uncommon but often overlooked. In cases of SAT, the angiotensin-converting enzyme 2 (ACE2) has been thought to be a receptor of SARS-CoV2 and direct cell damage in the thyroid gland may occur [6]. Typically, absence of pre-existed thyroid autoimmunity, serum elevated levels of CRP, neck pain, and focal hypoechoic areas in thyroid glands have been considered as characteristics of SAT [5]. Neck pain is often not recognized in cases of atypical SAT [6]. In PPT like our patient, neither elevation of serum CRP level nor focal hypoechoic areas in the thyroid is found. Prednisone is used for treatment of SAT, but PPT can be observed. Recently, Lania, *et al.* reported that 20.2% of patients with COVID-19 infection developed thyrotoxicosis possibly based on systemic immune activation induced by the SARS-CoV-2 infection [17].

Further investigations including thyroid cytology in a large number of patients is apparently needed to better understand thyroid illnesses including PPT after SARS-CoV-2 infection.

There are limitations in our study. Above all, histological

evidence of thyroiditis was not obtained, so that a direct evidence for causality of the viral infection for the thyroiditis was not provided. Also, serological evidence for immune activation was lacking in this patient, leaving the possibility that the viral infection was an innocent by-stander.

In conclusion, to our knowledge, this is the world's first case of PPT occurred shortly after SARS-CoV-2 infection. The close chronological association let us hypothesize that SARS-CoV-2 infection may have been causally related to occurrence of painless thyroiditis. At least we believe there exists a theoretical background for the link between the viral infection and PPT. Clinicians should not overlook possible SARS-CoV-2 infection-activated thyroid abnormalities.

Acknowledgements

The authors would like to thank the Wakayama City

Health Center and Wakayama City Institute of Public Health for SARS-CoV-2 PCR tests. We acknowledge editing and proofreading by Dr. Toru Aizawa at Aizawa Hospital, and Benjamin Phillis from the Clinical Study Support Center at Wakayama Medical University. We thank Dr. Hidetoshi Inoko (Tokai University) and Yuko Okudaira (GenoDive Pharma Inc.) for technical advice.

Authorship

All authors designed the study, and participated in treatment of the patient, collected data, interpreted the data, and wrote the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Statement

The authors have no conflict of interests to disclose.

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