

Three Cases of Subacute Thyroiditis Following SARS-CoV-2 Vaccine: Post-vaccination ASIA Syndrome

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Abstract

Context: Autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) can be seen as a post-vaccination phenomenon that occurs after exposure to adjuvants in vaccines that increase the immune responses. There is very limited data regarding ASIA syndrome following SARS-CoV-2 vaccines.

Objectives: This work aims to report cases of subacute thyroiditis related to the SARS-CoV-2 vaccine.

Methods: We describe the clinical, laboratory, and imaging features of three cases of subacute thyroiditis after inactivated SARS-CoV-2 vaccine (CoronaVac®). Three female healthcare workers have applied to our clinic with anterior neck pain and fatigue four to seven days after SARS-CoV-2 vaccination. Two of them were in the breastfeeding period. They were negative for thyroid antibodies, and there was no previous history of thyroid disease or upper respiratory tract infection, or COVID-19. Laboratory test results and imaging findings were consistent with subacute thyroiditis.

Results: SARS-CoV-2 vaccination can lead to subacute thyroiditis as a phenomenon of ASIA syndrome. Subacute thyroiditis may develop within a few days after the SARS-CoV-2 vaccination. Being in the postpartum period may be a facilitating factor for the development of ASIA syndrome after the SARS-CoV-2 vaccination.

Conclusions: This is the first report of subacute thyroiditis as a phenomenon of ASIA syndrome after inactivated COVID-19 vaccination. Clinicians should be aware that subacute thyroiditis may develop as a manifestation of ASIA syndrome after the inactive SARS-CoV-2 vaccine.

Keywords: Subacute thyroiditis, SARS-CoV-2, COVID-19, Vaccine, ASIA Syndrome, Breastfeeding, Case report

Introduction

The new coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV) 2 resulted in the pandemic, affecting more than 140 million people by April 2021. SARS-CoV-2 tends to multi-organ involvement due to the widespread expression of angiotensin-converting enzyme-2 receptors, the virus entry point (1). Therefore, COVID-19 causes various clinical scenarios ranging from a flu-like syndrome to more severe conditions such as acute respiratory distress syndrome and death. COVID-19 may also affect the endocrine system (1,2), and thyroid dysfunction appears to be a common problem during and after the infection (3-5). Subacute thyroiditis has been associated with many viruses and often presents a history of preceding respiratory tract infections (6). In addition, subacute thyroiditis has been reported after SARS-CoV-2 infection (5).

Under the catastrophic COVID-19 pandemic, vaccines have been developed rapidly, and more than 1 billion people have been currently vaccinated for SARS-COV-2 with various vaccines, and mass vaccination continues. Initial reviews of vaccination campaigns document a satisfactorily high profile of protection and safety against the disease (7); however, side effects of vaccines should be monitored and reported similarly to newly administered drugs (8,9). Adjuvants found in vaccines are mainly used to increase the response to vaccination. In genetically susceptible individuals, the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) may develop by disrupting the immunological balance of the host, by molecular mimicry, triggering polyclonal activation of B lymphocytes or other similar etiopathogenetic mechanisms (9). Several autoimmune and subacute thyroiditis cases have been reported after exposure to vaccines, reflecting the clinic of ASIA syndrome (9-15). However, there is very limited data regarding ASIA syndrome following SARS-CoV-2 vaccination (16).

To our knowledge, no cases of subacute thyroiditis have been reported after the SARS-CoV-2 vaccination to date. Here, we present three cases diagnosed with subacute thyroiditis as a clinical phenomenon of ASIA syndrome after the SARS-CoV-2 vaccine (CoronaVac[®], Sinovac Life Sciences, Beijing) administration.

Material and Methods

Case presentation

Case 1

A thirty-five-year-old female nurse was admitted to our outpatient clinic with severe anterior neck pain and palpitation. Her medical history did not indicate any thyroid disease or preceding upper respiratory system infection or COVID-19. She had been breastfeeding for 15 months. She did not have any family history of autoimmune diseases. She received her first CoronaVac[®] dose on January 18, 2021, and her second dose on February 15, 2021. Four days after the second dose of the vaccine, she felt left-side anterior neck pain, fever, fatigue, and palpitations. She took 500 mg of paracetamol twice a day for four days. The anterior neck pain has progressed to the right side just before admission to the hospital.

Case 2

A thirty-four-year-old female medical doctor presented to our outpatient endocrinology clinic with complaints of anterior neck pain, fatigue, and weight loss. In her past medical history, she had a mild COVID-19 infection in August 2020 and did not report any past medical history for thyroid disease or preceding upper respiratory system infection. She did not have any family history of autoimmune disease. She received her first dose of CoronaVac[®] on January 15, 2021. Four days after the vaccination, she felt anterior neck pain, fever, fatigue, and palpitations.

Case 3

A thirty-seven-year-old female medical doctor presented with mild anterior neck pain seven days after the second dose of CoronaVac® on February 12, 2021. She did not report any past medical history of thyroid disease or preceding upper respiratory system infection or COVID-19. She had been breastfeeding for five months. She did not have any family history of autoimmune disease.

Results

Case 1: On her physical examination, her heart rate was 88/min, body temperature was 37.7°C. On palpation, the thyroid gland was quite sensitive and painful and enlarged. The nasopharyngeal swab PCR test for SARS-CoV-2 was negative. At laboratory investigations, her thyroid functions were within normal range. Anti-thyroglobulin (anti-Tg), anti-thyroid peroxidase (anti-TPO), and antibodies to TSH receptor (TRAB) were negative, and levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were high. Laboratory findings are summarized in Table 1. Thyroid ultrasonography (USG) showed bilateral focal hypoechoic areas with decreased blood flow on Doppler USG (Figure 1A). Thus, the diagnosis of subacute thyroiditis was made, and methylprednisolone 16 mg/day and propranolol 25 mg/12h were started on March 1, 2021. Then, her neck pain and palpitation complaints disappeared within a day. Thyroid function tests during follow-up are shown in Table 1. The patient is still being followed up in the 4th week of treatment with methylprednisolone 8 mg/day.

Case 2: On her physical examination, her heart rate was 84/min, body temperature was 36.7°C. There was bilateral sensitivity of the thyroid gland on palpation. The nasopharyngeal swab PCR test for SARS-CoV-2 was negative. The thyroid function test was compatible with thyrotoxicosis. Anti-Tg, anti-TPO, and TRAB were negative, and ESR was in the normal range. Thyroid USG revealed bilateral focal hypoechoic areas with decreased blood flow (Figure 1B). Based on clinical symptoms and laboratory examinations, the patient's diagnosis was considered to be subacute thyroiditis. Methylprednisolone 16 mg/day and propranolol 25 mg twice a day were started. Then, methylprednisolone treatment was weekly tapered according to the patient's clinic, and her complaints regressed significantly. She did not get the second dose of the vaccine. During follow-up, after reducing the methylprednisolone dose to 4 mg/day, the patient's complaints of myalgia and neck pain reappeared, and the dose of glucocorticoid treatment was increased. The patient still has no complaints with 8 mg/day methylprednisolone treatment in the 10th week of his treatment.

Case 3: Physical examination was unremarkable, except for mild tenderness on palpation over the right lobe of the thyroid gland. Thyroid USG showed bilateral hypoechoic areas with irregular borders and reduced blood flow in Doppler USG (Figure 1C). Her laboratory examination was unremarkable, and thyroid antibodies were negative (Table 1). Subacute thyroiditis was considered with the patient's clinic and ultrasound findings. She has been followed up without treatment. During follow-up, she rarely needed paracetamol for neck pain. At the 4th week control visit, her right lobe of the thyroid gland was palpated as quite sensitive and enlarged. Her control laboratory examination revealed thyrotoxicosis and an elevated level of ESR (Table 2). She was diagnosed with subacute thyroiditis and was followed up without treatment since her pain was not severe. At the 8th week control visit, the patient became wholly asymptomatic, and her thyroid function returned to normal.

Discussion

The COVID-19 vaccination program has begun in Turkey with the emergency use approval on January 14, 2021, upon receiving the interim analyses results of the phase III study (17) of CoronaVac®. CoronaVac® is the inactivated SARS-CoV-2 vaccine, and the side effects and adverse reactions in phase I / II studies were pain, redness, swelling at the injection site, and allergic reactions; cough and fever (18,19). No subacute thyroiditis case has been reported to date. Here, we present three cases who were diagnosed with subacute thyroiditis after CoronaVac® administration.

Angiotensin-converting enzyme-2 receptors are abundantly expressed in many endocrine organs (20), and emerging evidence suggests that COVID-19 can lead to hypothalamic involvement and functional hypopituitarism (2,21), adrenal necrosis and hemorrhage (22,23), beta-cell and gonadal dysfunctions (2,24), and thyroid inflammation, including autoimmune and subacute thyroiditis (3-5). Possible pathogenic mechanisms of SARS COV-2 damage to endocrine organs may include direct virus entry into cells and cell destruction, cellular dysfunction caused by inflammation, and immune/antibody-mediated hormonal dysfunction (2,20). Subacute thyroiditis is characterized by painful inflammation in the thyroid gland and usually develops 2-8 weeks after a viral infection (6). The pathogenesis of subacute thyroiditis is not clear yet, but it develops in genetically predisposed individuals who carry certain human leukocyte antigen haplotypes (25).

Adjuvants in vaccines are intentionally used as immunogenicity enhancing agents to induce the adaptive immune responses. Aluminum hydroxide is used in the vaccines along with the viral antigens as an adjuvant because of its ability to enhance the immune responses with the use of reduced amounts of antigens (26). However, adjuvants can trigger adverse

immune reactions in genetically predisposed individuals, causing ASIA syndrome (27). Since the first definition of ASIA syndrome in 2011, most reported cases have occurred following vaccines mainly directed to HPV, HBV, and influenza (28). Post-vaccination ASIA syndrome might lead to endocrinopathies, but limited cases have been reported in the literature (reviewed in (9)). These were cases of type-1 diabetes, premature ovarian failure, autoimmune thyroiditis, adrenal insufficiency, and subacute thyroiditis. Subacute thyroiditis has been described mostly after vaccines for HPV and Influenza, and the symptoms have occurred two days to 2 months after vaccinations (9-15). All reported cases except one were negative for thyroid antibodies and all patients recovered completely.

CoronaVac® is a conventional killed whole virus vaccine prepared with the method used for various vaccines for decades. It is created from African green monkey kidney cells (WHO Vero 10-87 cells) inoculated with SARS-CoV-2. After the incubation period, the virus is harvested, inactivated with propiolactone, and absorbed onto aluminum hydroxide. The aluminum hydroxide complex is diluted in sodium chloride, phosphate-buffered saline, and water. CoronaVac® is given in two injections, 2 or 4 weeks apart. After injecting the vaccine, an immune response that can neutralize the virus is generated against the S protein (a part of the SARS-CoV-2 S spike) (18,19). In the present cases, subacute thyroiditis has developed five days after the first dose of CoronaVac® or 4 and 7 days after the second dose, respectively. The onset of symptoms due to subacute thyroiditis was similar to cases reported after other vaccines (9-15). In addition, our cases were negative for thyroid antibodies, and they did not have any history of thyroid disease or preceding upper respiratory system infection or COVID-19. Their laboratory test results were compatible with destructive thyroiditis. Postpartum thyroiditis can be included in the differential diagnosis since two of the cases are in the breastfeeding period. However, postpartum thyroiditis was ruled out because the clinical features of the cases included painful thyroid inflammation, thyroid

antibodies were negative, and typical ultrasonographic findings for subacute thyroiditis were detected. Thus, aluminum hydroxide, the CoronaVac® adjuvant compound, may have induced subacute thyroiditis as a phenomenon of post-vaccination ASIA syndrome.

Furthermore, it was shown that SARS-CoV-2 spike protein, nucleoprotein, and membrane protein all cross-reacted with thyroid peroxidase, and many thyroid peroxidase peptide sequences shared homology or similarity with sequences in various SARS-CoV-2 proteins (29). Recently, Graves' disease was reported in two female healthcare workers who received a SARS-CoV-2 vaccine (Pfizer-BioNTech), composed of a nucleoside RNA encoding a modified SARS-CoV-2 spike protein (16). They developed clinical manifestation three days after vaccination and were previously healthy. These findings support that antibodies generated against SARS-CoV-2 can promote autoimmune thyroiditis. It is possible that SARS-CoV-2 proteins in CoronaVac® and other vaccines cross-react with thyroid target proteins due to molecular mimicry, and this may be an additional factor that facilitates the triggering of ASIA syndrome.

In most cases after vaccination, symptoms of thyroiditis appear in the first few days (9-16). One possible reason may be that the concentration of viral proteins reaches its peak within a few days after vaccination and triggers autoimmunity (8,16). The postpartum period is an immunological rebound time from the selective immunosuppression of pregnancy (30); therefore, being in the postpartum period may be a facilitating factor for the development of ASIA syndrome, especially for case 3, who was in the fifth postpartum month. The clinical course of subacute thyroiditis after vaccination may be mild (13), as in case 3, and the recovery time may be shorter than post-viral cases (11,12). The clinical features of subacute thyroiditis according to different etiologies are summarized in Table 2.

Post-vaccination ASIA syndrome has been rarely reported despite mass vaccination. Possible causes of underreporting include various confounding and masking factors in the diagnosis of ASIA syndrome (9), the self-limiting nature of most cases (11-13), and the lack of awareness among clinicians. Nevertheless, further data are needed on whether the observed association between SARS-CoV-2 vaccination and subacute thyroiditis is causal. Moreover, COVID-19 has been leading to millions of disabilities and deaths worldwide, and the risks of COVID-19 outweigh the minor risks of the vaccine; therefore, vaccination should continue unabated.

To the best of our knowledge, this is the first report of subacute thyroiditis as a phenomenon of ASIA syndrome after inactivated COVID-19 vaccination. The development of subacute thyroiditis may occur within a few days after the vaccination. Being in the postpartum period may be a facilitating factor for the development of ASIA syndrome. Post-vaccination ASIA syndrome appears to be a rare phenomenon and can be challenging to diagnose due to confounding factors, especially during the COVID-19 pandemic. Therefore, clinicians should be aware that subacute thyroiditis may develop after inactive SARS-CoV-2 vaccination.

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Statement of Ethics

All subjects have given their written informed consent to publish their case (including publication of images).

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

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Figure Legend

Figure 1. Thyroid ultrasonography images of cases. (A) Focal hypoechoic areas with decreased blood flow on Doppler USG in both thyroid lobes (arrows). (B) Bilateral focal hypoechoic areas with decreased blood flow on Doppler USG (arrows). (C) A patchy ill-defined hypoechoic area in the right lobe and diffuse hypoechoic area in the isthmus and a small focal hypoechoic area in the left lobe with decreased blood flow on Doppler USG (arrows).

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Table 1: Laboratory tests results of cases

	Case 1	Case 2	Case 3
At diagnosis			
TSH (0.38-5.33 mIU/L)	0.473	0.01	0.9
ft4 (7.86-14.41 pmol/L)	14.1	5.2	13.85
ft3 (3.8-6 pmol/L)	6.15	11.8	6.05
Anti TPO (0-9 IU/mL)	1.2	1.2	4.1
Anti Tg (0-4 IU/mL)	<0.9	<0.9	<0.9
TRAB (<1.5 IU/L)	<1.5	<1.5	<1.5
WBC (4.1-11/10 ³ mm ³)	9.9	9.7	6.3
ESR (<20 mm/h)	53	19	25
CRP (<5 mg/L)	100.5	6	2.4
On follow-up (4th week)			
TSH (0.38-5.33 mIU/L)	2.27	<0.015	0.018
ft4 (7.86-14.41 pmol/L)	14.8	25.85	26.1
ft3 (3.8-6 pmol/L)	5.3	8.02	6.99
WBC (4.1-11/10 ³ mm ³)	11.1	9.7	7.8
ESR (0-25 mm/h)	28	16	44
CRP (<5 mg/L)	13.1	5.3	NA

TSH: Thyroid stimulating hormone. ft4: Free thyroxine. ft3: Free triiodothyronine. Anti TPO: Thyroid peroxidase antibody. Anti Tg: Anti-thyroglobulin antibody. TRAB: TSH receptor antibodies. WBC: white blood cell. ESR: erythrocyte sedimentation rate. C-reactive protein. NA: not assessed

Table 2: Comparison of Subacute Thyroiditis Clinic According to Etiologies

	Classical SAT (Post-viral)	SAT After COVID-19 Infection	*SAT After Vaccinations	SAT After SARS-Cov-2 Vaccination
Onset of symptoms	2-8 weeks	2-3 weeks	2 days - 8 weeks	4-7 days
Need of glucocorticoid	Often	Often	Commonly	Commonly
Recovery duration (week)	8-16	4-8	1-8	ND

SAT: Subacute thyroiditis. ND: Not determined. * after HPV, HBV, and influenza vaccinations.

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Figure 1

