SARS-CoV-2 vaccine-associated subacute thyroiditis

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Abstract
Purpose With coronavirus disease 2019 (COVID-19), subacute thyroiditis (SAT) cases are on the rise all over the world. COVID-19 vaccine-associated SAT cases have also been reported. In this article, we present our data on 11 vaccine-associated SAT cases.
Methods Eleven patients were included in the study. Type of the vaccines patients received, time to the occurrence of SAT after vaccination, symptoms and laboratory findings, treatment given, and response to treatment were evaluated.
Results The age of patients ranged from 26 to 73. Four of the patients were males, and seven were females. Symptoms of six patients were seen after BNT162b2 Pfizer/BioNTech COVID-19 mRNA vaccine®, and four of them after Coronavac inactivated SARS-CoV-2 vaccine®. In one patient, SAT developed after the first dose of BNT162b2, administered after two doses of Coronavac. The average time to the onset of symptoms was 22 days (15–37) after vaccination.
Conclusions The fact that both whole virus containing and genetic material containing vaccines cause SAT suggests that the trigger may be viral proteins rather than the whole viral particle. Although corticosteroids are commonly preferred in published vaccine-associated SAT cases, we preferred nonsteroidal anti-inflammatory therapy in our patients for sufficient vaccine antibody response. There is not enough information about whether patients who develop SAT can be revaccinated safely considering the ongoing pandemic. Further research is needed for a conclusion in the treatment and revaccination of these patients.

Keywords COVID-19 · Vaccination · Subacute thyroiditis · mRNA-based vaccines

Introduction
As of December 2019, the new coronavirus infection spread rapidly worldwide and was declared a pandemic by the World Health Organization (WHO) in March 2020. The cause of the infection is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease is called Coronavirus disease 2019 (COVID-19) [1, 2].

As clinical experience with COVID-19 increases, it has been observed that the disease is not limited to the upper respiratory tract and lungs but can also affect other organs. SARS-CoV-2 was found to have a high affinity for thyroid tissue. Angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2) act as receptors for SARS-CoV-2 entry into host cells [3]. With the demonstration of them in thyroid tissue, the thyroid's being a potential target for SARS-CoV-2 was better understood [4].

Subacute thyroiditis (SAT) is a self-limiting inflammatory disease manifested by pain in the thyroid lodge and thyrotoxicosis as a result of follicle destruction [5]. It is thought to occur following viral infections, especially in genetically predisposed individuals [5, 6]. A large number of SAT cases associated with COVID-19 infection have been reported. SAT is usually reported approximately 30 days after infection; however, it may co-occur with the infection in some patients [7, 8]. COVID-19-associated SAT is thought to be correlated with the viral infection and post-viral inflammatory responses, just like in other SAT cases [9].

Mass vaccination for SARS-CoV-2 started in December 2020 and as of 10 November 2021, a total of 7,160,396,495 vaccine doses have been administered globally [10]. With the increase in the frequency of vaccination worldwide,
post-vaccine SAT cases are also reported [11–13]. Along with the vaccination process in our country, we had seen 11 cases of SAT associated with the COVID-19 vaccine. In this article, we present our data on the characteristics of the administered vaccines, clinical and laboratory findings, and treatment responses of our patients.

**Subjects and methods**

Our COVID-19 vaccine-associated SAT patients diagnosed between April 2021 and September 2021 in the Endocrinology and Internal Medicine outpatient clinics were analyzed. The patients’ age and gender characteristics, type of the vaccines they received, time to the occurrence of SAT after vaccination, symptoms, treatment given, and response to treatment were evaluated. The laboratory parameters of the patients at the time of diagnosis (thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid autoantibodies), and imaging studies (ultrasound and Doppler or scintigraphy) were also evaluated. All our patients gave their written consent, and the study was approved by the local ethics committee with an approval number of E-25403353–050.99–243,706.

**Results**

The age of patients ranged from 26 to 73 years old. Four (36.3%) of the patients were male, and seven (63.6%) were female. There were two (18.1%) patients with a history of thyroid disease. Two patients had hypertension as a chronic disease.

Symptoms of 6 (54.5%) patients were seen after BNT162b2 Pfizer/BioNTech COVID-19 mRNA vaccine®; SAT was observed in two of them after the first dose, and in 4 after the second dose. In 4 of the patients (36.3%), SAT was observed after Coronavac inactivated SARS-CoV-2 vaccine®, after the first dose in one, and after the second dose in the other three patients. In one patient, SAT developed 15 days after the first dose of BNT162b2, administered after two doses of Coronavac. Of the six patients who received the BNT162b2 vaccine, 4 had a history of COVID-19 about a year before the vaccine. Patients’ symptoms appeared approximately 22 days (15–37) after vaccination. Some patients were referred to us from different clinics. The clinical features of the patients are summarized in Table 1.

All patients had suppressed TSH and elevated fT3 and fT4 levels. Elevated CRP and ESR were found in all cases. Anti-thyroglobulin antibodies (TgAb) were positive in 5 of the patients (45.4%); anti-thyroid peroxidase antibodies (TPOAb) and thyrotropin receptor antibodies (TRAb) were positive in one patient. Nasopharyngeal swab tests for SARS-CoV-2 were negative in all patients. Typical ultrasonographic characteristics of SAT were observed in 90.9% of patients. One patient (Case 5) had no ultrasonographic findings, and the diagnosis was made by scintigraphy. The laboratory and imaging characteristics of the patients are shown in Table 2.

All patients were treated with nonsteroidal anti-inflammatory drugs (NSAID), and some were administered beta-blockers. While symptomatic improvement was observed in the patients around two weeks, the average resolution time was approximately two months. In the follow-up of 4 patients (36.3%) (Cases 4,6,10 and 11), levothyroxine replacement was started due to symptomatic hypothyroidism, but we have not reached enough follow-up time to talk about permanent hypothyroidism.

One patient received the second dose of Coronavac vaccine while she was in the active phase of SAT (Case2); no worsening was observed. Three patients (Cases 1,6 and 10) received additional vaccine doses after SAT resolution, and no recurrence was observed. The majority of our patients had completed their vaccination schemes. However, two patients (Cases 4 and 7) who developed SAT after a single dose of BNT162b2 refused to be vaccinated again, even though we recommended them. Vaccination information of the patients is shown in Table 1.

**Discussion**

SAT is characterized by inflammation of the thyroid gland, usually following viral infections. Thyroid autoimmunity does not have a primary role in the development of SAT. Although the exact etiology is unknown, it is thought that the antigenic stimuli resulting from tissue damage due to viral infections and binding to HLA-B35 molecules in macrophages activate cytotoxic T lymphocytes and cause SAT [14].

Cases of COVID-19-associated and SARS-CoV-2 vaccine-associated SAT have been reported during the pandemic [7, 8, 11, 13]. In this article, we evaluated the clinical and laboratory characteristics of the additional 10 cases we saw after our first SARS-CoV-2 vaccine-associated SAT case, as well as the vaccination information of patients and our treatment results [12].

Women were in the majority among our patients, consistent with the literature. While the rates of SARS-CoV-2 vaccine-associated SAT cases reported so far were similar after the first and the second doses, we mainly observed it after the second dose. Although very rapid onset cases like the 4th day after vaccination have been reported in the literature, the shortest time from vaccination to the appearance...
|   |   |   | Pre-existing thyroid disease | Type of vaccine | Time to onset of symptoms after vaccination | Clinical features | Delay in diagnosis due to application to other clinics | Treatment | Resolution time | Need for levothyroxine | Vaccination after resolution of SAT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 67 | M | No | No | Coronavac | 19 days, after 2nd dose | Neck pain, weight loss, fever, tachycardia | No | NSAID, beta-blocker | 2 months | None | BNT162b2, 2 dose |
| 2 | 47 | F | No | No | Coronavac | 21 days, after 1st dose | Neck pain, headache, tremors, sweating | No | NSAID | 1 month | None | 2nd dose while in active phase of SAT |
| 3 | 62 | F | 1 year before | No | BNT162b2 | 1 month, after 2nd dose | Neck pain | Application to Ear Nose Throat Clinic | NSAID | 2 months | None | No |
| 4 | 44 | M | 1 year before | No | BNT162b2 | 15 days, after 1st dose | Neck pain, weight loss, fever, sweating | Application to Infectious Diseases Clinic | NSAID | 2 months | Yes | No |
| 5 | 26 | M | No | No | BNT162b2 | 37 days, after 2nd dose | Neck pain, weight loss, fever, tremors, myalgia | Application to Infectious Diseases Clinic | NSAID | 1.5 months | None | No |
| 6 | 37 | F | No | Graves' disease | Coronavac | 15 days, after 2nd dose | Neck pain, dysphagia | No | NSAID | 1 month | Yes | BNT162b2, 1 dose |
| 7 | 39 | F | 1 year before | No | BNT162b2 | 18 days, after 1st dose | Weight loss, tachycardia | Application to Cardiology Clinic | NSAID, beta-blocker | 2.5 months | None | No |
| 8 | 40 | F | No | No | BNT162b2 | 15 days, after 2nd dose | Neck pain, fever | Application to Infectious Diseases Clinic | NSAID | 2 months | None | No |
| 9 | 29 | M | No | No | Coronavac (2 doses) BNT162b2 | 15 days, after the first dose of BNT162b2, following 2 doses of Coronavac | Neck pain | No | NSAID | 2 months | None | No |
| 10 | 73 | F | No | SAT 20 years before | Coronavac | 1 month, after 2nd dose | Neck pain, tachycardia | Application to Infectious Diseases Clinic | NSAID, beta-blocker | 1 month | Yes | BNT162b2, 1 dose |
| 11 | 30 | F | 1 year before | No | BNT162b2 | 1 month, after 2nd dose | Neck pain | No | NSAID | 2 months | Yes | No |

M: male, F: female, SAT: subacute thyroiditis, NSAID: nonsteroidal anti-inflammatory drugs
Table 2 Laboratory and imaging features of the patients

|   | TSH     | fT4     | fT3     | ESR | CRP | TgAb | TPOAb | TRAb | Ultrasound and Doppler Findings                                                                 |
|---|---------|---------|---------|-----|-----|------|-------|------|-------------------------------------------------------------------------------------------------|
| 1 | <0.005  | 2.87    | 8.06    | 67  | 53.9| Negative | Negative | Negative | Heterogeneous echotexture, with poorly defined regions of decreased echogenicity and pseudonodules |
| 2 | 0.015   | 2.93    | 6.84    | 81  | 193 | Negative | Negative | Negative | Ill-defined hypoechoic areas                                                                     |
| 3 | 0.01    | 2.36    | 5.18    | 89  | 88.9| Negative | Negative | Negative | Bilateral inflammation and hipovascularity, multiple lymphadenopathy                              |
| 4 | <0.005  | 3.74    | 9.55    | 72  | 38.4| Negative | Negative | Negative | Hypoechoic and heterogeneous areas with blurred margins                                           |
| 5 | 0.01    | 2.59    | 4.62    | 82  | 78  | Negative | Negative | Negative | No significant alteration in ultrasonography, reduced 99mTc-perthecenate uptake                   |
| 6 | 0.018   | 0.942   | 6.63    | 79  | 27  | >4000  | >4000  | >30    | Bilateral enlarged thyroid gland, irregularly demarcated hypoechoic areas, decreased vascularity    |
| 7 | <0.005  | 2.04    | 5.11    | 89  | 34  | 222    | Negative | Negative | Hypoechoic and heterogeneous areas with blurred margins, poorly vascularization                   |
| 8 | <0.005  | 3.05    | 6.59    | 51  | 51.8| 542    | Negative | Negative | Inflammation and pseudonodularity                                                                |
| 9 | 0.07    | 4.29    | 11      | 33  | 43.3| Negative | Negative | Negative | Heterogeneous gland with bilateral patchy ill-defined hypoechoic areas                            |
| 10| 0.01    | 2.32    | 4.22    | 83  | 109 | Negative | Negative | Negative | Reduction in gland size, but bilateral inflammation                                               |
| 11| 0.024   | 0.27    | 9.03    | 79  | 125.4| 125.4  | Negative | Negative | Multiple diffuse hypoechoic areas, decreased vascularity                                           |

TSH thyroid stimulating hormone (0.27–4.2 uIU/ml) fT4 free thyroxine (0.93–1.70 ng/dL) fT3 free triiodothyronine (2.3–4.5 pg/mL) ESR erythrocyte sedimentation rate (0–20 mm/h). C-reactive Protein (0–5 mg/L) TgAb Anti-thyroglobulin antibodies (0–115 IU/mL) TPOAb Thyroid peroxidase antibodies (0–34 IU/mL) TRAb TSH receptor autoantibodies (0–1,5 U/L)

of SAT symptoms was 15 days among our cases. The time to remission of thyrotoxicosis was similar to the literature.

In the management of SAT, NSAIDs are recommended in mild symptomatic cases, while corticosteroids are indicated in severe cases [5, 15, 16]. Most clinicians and researchers prefer steroids first, including most published vaccine-related SAT cases. We initially chose NSAID therapy in our patients. Reduced SARS-CoV-2 vaccine immunogenicity is shown in patients receiving immunosuppressive therapy, including corticosteroids [17]. Because of the self-limiting nature of SAT and the absence of absolute corticosteroid indication, we preferred NSAID treatment to avoid suppressive effects of the corticosteroids on the anti-SARS-CoV-2 antibody response expected from the vaccine.

Graves' disease occurrence following SAT has been reported in a limited number of patients in the literature [5, 18–20]. One of our patients (Case 6) was diagnosed with Graves’ disease five months ago and was under methimazole treatment. Although the patient’s neck pain was not prominent initially, elevated ESR and CRP and newly developed hypergammaglobulinemia were detected in the laboratory tests. SAT is suspected due to these clinical findings and the recent vaccination history. When ultrasonographic examination of the thyroid was performed, bilateral ill-defined hypoechoic areas and decreased vascularity in Doppler were observed, unlike the previous hypervascularity at the time of initial diagnosis of Graves’ disease. Meanwhile, the patient developed neck pain, but since she did not accept, scintigraphic evaluation and fine-needle aspiration biopsy could not be performed. Although decreased vascularity may be due to anti-thyroid treatment, NSAID therapy was started with a preliminary diagnosis of SAT. The patient was found to have polyclonal hypergammaglobulinemia. Acute and chronic infections, malignancies, and rheumatological diseases were excluded through the investigations performed. All thyroid autoantibodies of the patient were found to be in higher titers. Since there may be temporary autoantibody positivity in SAT due to the release of thyroid antigens from the destructed follicles, polyclonal hypergammaglobulinemia is thought to be related to autoantibody release [5, 21]. During the follow-up, her inflammatory markers improved, and shortly after that, the patient developed hypothyroidism; thus, methimazole treatment was stopped, and levothyroxine replacement was started. The clinical course of the patient and the improvement in inflammatory markers supported our diagnosis of SAT. After resolution, she had a single dose of BNT162b2 vaccine very recently and is under close follow-up for recurrence.

Cases of recurrent SAT have also been reported [22, 23]. One of our patients (Case 10) had a history of SAT about 20 years ago and was on levothyroxine replacement therapy because of permanent hypothyroidism. The patient developed SAT about one month after the second dose of CoronaVac. After the diagnosis of SAT, the levothyroxine treatment was discontinued. The patient’s symptoms regressed in about a month with the NSAID treatment, and hypothyroidism came back after resolution. The patient was vaccinated with a dose of BNT162b2 on July 8, 2021, after SAT remission, and no recurrence was observed.
While some studies detect the SARS-CoV-2 genome in the thyroid, some do not [24, 25]. Apart from direct viral effects, post-viral inflammatory responses are also thought to play an essential role in thyroid damage due to COVID-19 [9]. Since there is no live virus in the body, vaccine-associated SAT is most likely to occur by immune-mediated responses. SAT cases seen with different vaccines from different countries have been reported. Among these, there are cases of SAT with inactivated virus vaccine Coronavac, viral vector vaccine Astra Zeneca (Vaxzevria), mRNA vaccines BNT162b2, and Moderna (Spikevax) [11–13, 26]. There are different views for the pathophysiology of vaccine-associated SAT. While some researchers suggest that whole virus or viral particles in the vaccine cause SAT due to cross-interaction with thyroid cell antigens, others put forward the adjuvant in the vaccine as the trigger. The fact that both whole virus-containing and genetic material-containing vaccines cause SAT suggests that the trigger may be viral proteins rather than the whole viral particle.

Spike protein is a common stimulant for cellular and humoral immune responses in the functioning of both mRNA vaccines and whole virus vaccines. The mRNA vaccines enable our cells to produce spike protein, and the whole virus vaccines contain it in an inactive form. It is possible to say that the spike protein can trigger SAT in susceptible individuals by binding to the HLA-B35 molecule in macrophages and activating cytotoxic T lymphocytes. This activation may be the reason for the destruction in thyroid follicular cells, rich in ACE-2 receptors to which spike proteins bind. The neutralization of spike protein by the anti-spike antibodies may have a role in the self-limitation of thyroid damage. ACE-2 and TMPRSS2 are more expressed in the thyroid than in the lung tissue, and women have been found to express them higher than men [27]. Although the higher incidence of SAT in women has been mostly associated with the higher incidence of autoimmune pathologies in the literature, we presume that the high expression of ACE-2 and TMPRSS2 may have a role in explaining female predominance for SAT cases related to SARS-CoV-2 infection and vaccination.

Another etiologic factor that has been suggested to play a role in vaccine-associated SAT pathogenesis is the adjuvants in the vaccine. Adjuvants are substances that enhance the immunogenicity of the vaccine, and autoimmune inflammatory changes depending on them are thought to trigger SAT. There is a lack of evidence supporting the existence of autoimmune syndromes induced by adjuvants (ASIA) [28, 29]. Despite that, this opinion is supported by many authors who published SARS-CoV-2 vaccine-associated SAT case reports. The term ‘subacute autoimmune thyroiditis’ was used in the article by Bragazzi et al. [30]. 41 HPV vaccine-associated thyroiditis cases are mentioned in the article, but it is understood that these cases have autoimmune thyroiditis when reading more in detail. In addition, there is no direct referral with ASIA syndrome in the other SAT case reports associated with influenza and HBV vaccines mentioned in the article. Since influenza vaccines are without adjuvant, evaluating SAT as a component of ASIA syndrome would not be appropriate even if it exists [31, 32]. Through the SAT cases reported with non-adjuvanted COVID-19 vaccines (BNT162b2, Moderna), it has become more apparent that the underlying cause of SAT could not be the adjuvant [11, 26, 33].

There is insufficient data on the optimum management of SARS-CoV-2 vaccine-associated SAT cases. We observed that the course of vaccine-associated SAT was not different from other types of SAT and the resolution times were similar when NSAID was given instead of corticosteroids. For the immune response expected from the vaccine to be sufficient, it would be more appropriate to evaluate the NSAID option in the management of vaccine-associated SAT. Considering the ongoing pandemic, patients who have developed vaccine-associated SAT may need to be revaccinated, and there is not enough clinical experience about the safe revaccination of these patients. Whether the same vaccine can be applied or a switch to a different type will be needed is another question. In line with the options offered by the vaccination program in our country, the accessibility of the vaccines, and our recommendations, one of our patients completed her schedule with the same vaccine (Case 2), and three patients were administered a different type of vaccine for a booster after completing their schemes with one type (Cases 1,6,10). None of them developed recurrence. However, due to the small sample size, our experience is not at a strong evidence level for being a clinical recommendation; therefore, more comprehensive reporting is needed on this issue. Considering the morbidity and mortality of COVID-19, we believe that it would be appropriate to act in line with the recommendations for the general population when revaccination of patients who develop vaccine-associated SAT is required.

The single-center nature of our study is a limitation; thus, we do not have sufficient epidemiological data on SARS-CoV-2 vaccine-associated SAT. However, at least to make a rough estimation about its’ frequency, we would like to express that we have 10 cases between March 2019 and March 2020 (in the one-year period before the COVID-19 pandemic). In addition, when we have a look at the last 20 months from the onset of the pandemic, we had 5 cases of SAT that are not associated with COVID-19 infection or vaccine, and two that occurred after COVID-19 infection. COVID-19 vaccination in our country started in January 2021 and reached 117 million total doses as of 9 November 2021. The number of people who received at least one dose of vaccine in our city was approximately 590,000, while the number of those who received two doses was around 501,000 by the end of
Written consent was obtained from committee of Eskisehir Osmangazi University with an approval number all participants.

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