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COVID-19 and COVID-19 vaccines-related subacute thyroiditis: analysis of a case series

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ABSTRACT

Aim: It has been indicated that COVID-19 is related to many endocrinological abnormalities. The aim of this study is to demonstrate whether there is an impact of COVID-19 and COVID-19 vaccines on development of subacute thyroiditis (SAT).

Material and Method: This retrospective single-center study includes individuals with SAT who were diagnosed between March 2020 and August 2021. Patients were evaluated for a recent Covid-19 history and SARS-CoV-2 vaccination. SAT was diagnosed based on the clinical presentation and laboratory tests; including thyroid function tests, sedimentation rate, C-reactive protein, and thyroid ultrasound. SARS-CoV-2 PCR results of patients with past COVID-19 were obtained from the Ministry of Health electronic patient data system. Type, number, and dates of vaccine doses were recorded for each participant.

Results: A total of 31 patients were included in the study. Six patients (19.4%) were diagnosed with SAT following a COVID-19 vaccination schedule. Four patients with SAT had received two inactive (CoronaVac) + one dose of mRNA vaccines (Pfizer-BioNTech). The other 2 patients had received either two doses of inactive vaccine or two doses of mRNA vaccine. Five patients were diagnosed with SAT after the second dose of the vaccine. The median interval between last vaccination dose and diagnosis of SAT was 25.8 days. In one patient, SAT developed 28 days after the mRNA vaccine. Seven patients (22.6%) were diagnosed with SAT after COVID-19 disease. The median interval from the diagnosis of COVID-19 disease to SAT was 27.3 days. All cases of post-COVID-19 and post-vaccination SAT patients exhibited similar clinical presentation and findings to idiopathic SAT.

Conclusion: Covid-19 itself and Covid-19 vaccines might let a tendency to development of subacute thyroiditis. This study has to be supported by further studies.

Keywords: COVID-19, SARS-CoV-2, subacute thyroiditis, vaccination

INTRODUCTION

Since the report of the first case in China in December 2019, the SARS-CoV-2 pandemic has resulted in above 5 million loss of lives globally, as of January 2022. Although death rates significantly decreased after the introduction of the COVID-19 vaccines, the burden of the disease and the disease related effects have remained to be a crucial matter on human life. Although COVID-19 disease is substantially diagnosed after respiratory system symptoms and many deaths are associated with lung involvement, the disease has the potential to indicate a multisystemic involvement. The clinical dimension of extrapulmonary involvement is better understood day by day. The heart, kidney, gastrointestinal system, liver, eye, skin, and central nervous system can be involved at the course of the disease (1). From a point of endocrinology, diabetes mellitus has a dual role in COVID-19; it acts as a risk factor for more severe COVID-19, and also occurs de novo after or at the course of the COVID-19 disease. However, thyroid manifestations of COVID-19 have less frequent been described compared with diabetes mellitus (1).

SARS-CoV-2 damages thyroid tissue via angiotensin converting enzyme 2 (ACE2) and transmembrane protein serin 2 (TMPRSS2) receptors which are abundant in thyroid follicular cells (2). It has also been speculated that the thyroid gland involvement by COVID-19 might be due to its anatomical proximity to the entry sites of the virus to the body. Whatever the mechanism, three different thyroid manifestations were proposed to be

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related to COVID-19: destructive (inflammatory) thyroiditis, subacute thyroiditis, and chronic lymphocytic thyroiditis (3).

Subacute thyroiditis (SAT) is a self-limiting acute inflammatory and granulomatous disorder of the thyroid gland. Influenza virus, coxsackievirus, adenovirus, HIV, mumps, measles, rubella, and cytomegalovirus have been blamed for causing SAT via direct cytopathic and/or indirect autoimmunity-triggering activity (4). Furthermore, some case reports indicates development of SAT after some kind of vaccines (5-8).

In regard of COVID-19, several SAT cases concomitantly with COVID-19 or occurred shortly after COVID-19 were reported in the recent literature (9-12). SAT and COVID-19 share many common symptoms and signs, additionally, some other factors might impact the patients' admissions to hospital for health care during pandemic and all those lead to underestimate diagnosing COVID-19 related SAT rate. Self-limiting nature of the SAT also causes in the missed cases.

Different types of vaccination have been approved by the Food and Drug Administration of the United States (FDA) and the European Medicines Agency (EMA) for COVID-19. In Turkey, an inactive vaccine (CoronaVac, Sinovac Biotech, China) and an mRNA-based vaccine BNT162b2 (Pfizer-BioNTech, Pfizer, Inc., and BioNTech) were authorized. Approximately 54% of the people have been fully vaccinated in Turkey as of 10 October 2021 (12). There are limited number of report on SAT cases occurred following COVID-19 vaccines (14-16).

Considering a large number of vaccinations throughout the world (6.46 million doses in total as of 10 October 2021) is being performed, we think vaccine-related SAT cases might have been underreported (17).

In this study, we aimed to reveal the association of COVID-19 disease and COVID-19 vaccines with the SAT development.

MATERIAL AND METHOD

Subjects and Study Design

In this retrospective single-center case-control study all adult patients who were referred to our hospital between March 2020 and August 2021 on suspicion of SAT from primary care were evaluated. The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 06.09.2021; Decision No: BŞH-28). The study was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. No informed consent form was obtained for since this is a retrospective study. The hospital database system and endocrinology charts were screened for detection of SAT cases. Exclusion criteria comprised patients with a known thyroid disorder and patients receiving thyroid drugs. We also excluded SAT patients if they had missing data.

Data Collection

All patients with suspicion of SAT were evaluated regarding prior thyroid disease, presence of neck pain and thyrotoxicosis symptoms. Physical examination signs; thyroid tenderness, volume, and texture, data about lymph nodes in anterior and posterior cervical areas were noted. Laboratory evaluation included complete blood count, erythrocyte sedimentation rate, C-reactive protein level, thyroid-stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3) concentrations. All patients had underwent thyroid and neck ultrasound (US) imaging. Thenafter they were evaluated regarding their COVID-19 vaccination status and whether they had past or ongoing COVID. The vaccinated individuals were investigated for the type of the vaccine, the number of vaccine applications, and the last vaccination date were recorded. If the patient had COVID-19 disease, we obtained information regarding of the date of infection, need for hospital or intensive care unit admission, method of how COVID-19 diagnosis was made, and treatments received.

Diagnosis of SAT

Subacute thyroiditis was diagnosed based on the typical clinical presentation of the disease and laboratory evaluation of thyroid hormone status. In a patient, the diagnosis was established on his complains including pain in the anterior neck that radiates to the jaw and/or ear, along with fatigue, malaise, fever, thyrotoxicosis symptoms, and on laboratory test result which indicated an overt thyrotoxicosis status. A tender and enlarged thyroid without any accompanying cervical adenopathy also supported the diagnosis of SAT. All patients underwent thyroid US. A heterogeneous hypoechoic pattern along with decreased vascularization is the expected US finding in patients with SAT as seen in our cases. Thyroid autoantibodies were investigated in a few patients. We did not perform thyroid scintigraphy or radioactive iodine uptake test in patients who had a typical clinical presentation for SAT. None of the included patients underwent percutaneous fine-needle aspiration of the thyroid gland.

Statistical Analysis

The Kolmogorov Smirnow test and a histogram evaluation test was used to confirm the normality of the continuous variables. Continuous variables were expressed as mean±standard deviation or median (interquartile range) depending on the distribution of the variable. Categorical variables were reported as numbers

and percentages. Based on the results of the normality test, the Mann-Whitney U test or independent samples t-test was used for the comparison of numeric variables. Analysis of categorical variables was performed with the Chi-squared test and Fisher's Exact Test. Statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). p<0.05 was accepted statistically significant with a 95% CI.

RESULTS

A total of 31 patients were evaluated in the study. The mean age was 42.6±8.9 years (min max: 26-61 years), and the majority (87.1%) of the participants were female. Mean age, sex distribution, laboratory findings, treatments and vaccination status of the patients were given in **Tables 1-3**. 13 of 31 cases of SAT (~%42) diagnosed in our hospital were related to COVID-19 disease or COVID-19 vaccination.

Table 2. Post-COVID-19 and post-vaccination SAT and administered treatments.

	Patients (n= 31)
Post-vaccination subacute thyroiditis n(%)	6 (19.4%)
Post-COVID-19 subacute thyroiditis n(%)	7 (22.6%)
Recurrent subacute thyroiditis n(%)	6 (19.4%)
Treatments for subacute thyroiditis	
None	4 (12.9%)
NSAID	11 (35.5%)
Glucocorticoids	15 (48.4%)
NSAID + Glucocorticoids	1 (3.2%)

NSAID: Nonsteroidal anti-inflammatory drug

Table 3. COVID-19 vaccination status of all SAT patients

	Vaccines (n=31)		
	1st dose	2nd dose	3rd dose
Inactivated SARS-CoV-2 vaccine	8 (25.8%)	7 (22.6%)	-
mRNA SARS-CoV-2 vaccine	19 (61.3%)	17 (54.8%)	5 (16.1%)
None	4 (12.9%)	7 (22.6%)	26 (83.9%)

Table 1. Mean age, sex distribution, and laboratory findings of the subacute thyroiditis (SAT) patients.

Parameters	Patients			p-value
	Total (n=31)	Post-COVID-19 and post-vaccination SAT (n=13)	Idiopathic SAT (n=18)	
Age (years)	42.6±8.9	45.0±11.0	40.8±6.8	0.196†
Sex (N)				
Female	27 (87.1%)	11 (84.6%)	16 (88.9%)	>0.999f
Male	4 (12.9%)	2 (15.4%)	2 (11.1%)	
TSH (μIU/mL)	0.72 (0.002-5.17)	1.39 (0.002-5.17)	0.55 (0.002-5.03)	0.303m
Free T4 (ng/dL)	1.05 (0.95-1.62)	1.05 (0.97-1.2)	1.04 (0.93-1.74)	0.814m
Free T3 (pg/mL)	3.74±1.12	3.39±0.73	3.9±1.24	0.294†
CRP (mg/dL) (normal range; 0-0.5 mg/dl)	1.64 (0.02-14.62)	1.21 (0.17-14,29)	2.05 (0.07-5.7)	0.968m
CRP in male	3.43 (0.02-14.29)	7.97 (1.64-14.29)	2.62 (0.02-5.22)	
CRP in female	1.53 (0.2-12.54)	0.97 (0.17-9.41)	2.05 (0.02-12.54)	
Sedimentation rate (mm/hour)	31.67±21.7	23.5±14.10	37.9±24.70	0.072†
Sedimentation in male (0-22)	23.25±15.84	25.5 (9.19)	21 (3-39)	
Sedimentation in female (0-29)	32.96±22.42	23.18 (15.13)	40.13±24.58	
Positive Anti-TPO (n, %)	3 (9.7%)	0	3 (16.7%)	0.245f
Positive Anti-TG (n, %)	6 (19.4%)	1 (7.7%)	5 (27.8%)	0.359f
Thyroglobulin (ng/mL)	51.6 (29.2-288.7)	79.9 (27.2-79.9)	51.6 (31.2-445)	0.844m
25(OH) Vitamin D (ng/mL)	27.9 (15.8-47.5)	32.5 (19.3-52.5)	24.9 (14.5-42.8)	0.413m
Red blood cells (million/mm³)	4.57 (4.35-4.72)	4.59 (4.51-4.66)	4.54 (4.21-4.72)	0.429m
Hemoglobin (g/dL)	13±1.2	13.1±1.3	12.9±1.2	0.672†
Hematocrit (%)	39±3.4	39.5±3.11	38.6±3.7	0.513†
MCV (fL)	85.5±5.2	85.5±4.97	85.6±5.54	0.972†
MCH (pg)	28.5±2.2	28.3±2.21	28.6±2.29	0.759†
MCHC (g/dL)	33.2±1.1	32.9±1.36	33.4±0.78	0.224†
Red cell distribution (%)	13.0±1.5	12.8±1.49	13.2±1.52	0.488†
White blood cell count (×10³/mm³)	8.57 (7.71-9.83)	8.85 (8.41-10.5)	8.18 (7.68-9.42)	0.170m
Neutrophil count (×10³/mm³)	5.28 (4.7-5.99)	5.4 (4.03-6.28)	5.28 (4.85-5.68)	0.877m
Lymphocyte count (×10³/mm³)	2.62 (1.96-3.26)	2.88 (2.06-3.54)	2.3 (1.95-3.14)	0.241m
Monocyte count (×10³/mm³)	0.63±0.23	0.71±0.27	0.58±1.86	0.118†
Eosinophil count (×10³/mm³)	0.17±0.13	0.17±0.97	0.16±0.14	0.903†
Basophil count (×10³/mm³)	0.08 (0.05-0.09)	0.08 (0.06-0.09)	0.07 (0.05-0.09)	0.309m
Platelet count (×10³/mm³)	276 (257-304)	268 (235-302)	280 (265-304)	0.564m
PDW (%)	17.6 (16.9-18.2)	16.8 (16.4-16.8)	17.6 (16.9-18.5)	0.131m
PCT %	0.21 (0.17-0.24)	0.2 (0.16-0.22)	0.21 (0.2-0.24)	0.182m

fFisher's Exact Test. mMann-Whitney U test, †Independent Samples t-test, P-values belong to comparison of variables between post-COVID-19 and post-vaccination. Not-normally distributed variables were presented as median (minimum-maximum) and normally distributed variables were presented as mean±standard deviation and n (%). Anti-TPO: Anti-thyroid peroxidase, Anti-TG: Anti-thyroglobulin, MCH: Mean Corpuscular Hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, PCT: Plateletcrit, SAT: subacute thyroiditis TSH: Thyroid-stimulating hormone.

COVID-19 Characteristics

COVID-19 diagnosis was established on positive naso-oropharyngeal swab test for SARS-CoV2 polymerase chain reaction. None of the patients required intensive care unit hospitalization for COVID-19. All of the patients with COVID-19 had been diagnosed before the initiation of COVID-19 vaccination programs. Six patients (19.4%) were exhibited the symptoms suggestive of subacute thyroiditis after the COVID-19 vaccination. Clinical and laborotary features of SAT cases regarding their vaccination and thyroid hormone status are given in **Table 4**. The median duration of the presentation with symptoms of SAT since vaccination was 25.8 days (min. 16 days, max. 35 days). In only one patient, SAT was diagnosed 28 days after the first dose of the mRNA vaccine. In patients with post-vaccination SAT, 2 patients experienced a recurrent bout of SAT. Both episodes occurred after the third dose of the vaccination (after the mRNA vaccine dose).

Sedimentation rates and C-reactive protein levels were above normal laboratory ranges as expected in SAT patients. In idiopathic SAT cases sedimentation rates was tend to be higher compared to the COVID-19 disease or vaccine-related cases (the difference was at the limit of statistical significance), p=0.055.

Seven patients (22.6%) were diagnosed with SAT following COVID-19 disease (**Table 5**). The median duration from COVID-19 to subacute thyroiditis symptoms was 27.3 days (minimum 7 days and maximum 45 days). All patients except one had two doses of mRNA vaccine. However, in patients with post-COVID-19 SAT, 2 patients experienced a recurrent SAT episode before vaccination. Individuals with number 4, 2, and 1 were treated with glucocorticoids, NSAID, and a combination of glucocorticoids and NSAID, respectively (**Table 5**).

Table 4. Patients with post-vaccination SAT

	Age	Sex	Signs and symptoms at SAT onset	Thyroid function tests	COVID-19 Vaccinations	Duration to presentation following vaccination	Subacute thyroiditis treatments	Recurrence
Patient 1	27	F	Anterior neck pain, fever	TSH: 2.13, FT4: 1.05	C+C+PB	16 days after 2nd dose, 7 days after 3rd dose	Steroid	Once
Patient 2	35	F	Anterior neck pain, tender thyroid enlargement	TSH: 1.39, FT4: 0.96	C+C+PB	30 days after 2nd dose, 7 days after 3rd dose	NSAID	Once
Patient 3	61	M	Anterior neck pain, palpitation	TSH < 0.01, FT4: 3.03	C+C+PB	28 days after 2nd dose	Steroid	None
Patient 4	61	F	Anterior neck pain, fatigue	TSH: 3.47, FT4: 0.92	C+C+PB	35 days after 2nd dose	Steroid	None
Patient 5	27	F	Anterior neck pain, pain with movement	TSH: 5.17, FT4: 1.19	C+C	20 days after 2nd dose	Steroid	None
Patient 6	45	F	Anterior neck pain, tender thyroid enlargement	TSH: 2.23, FT4: 1.03	PB+PB	28 days after 1st dose	NSAID	None

F: female, M: male, NSAID: Nonsteroidal anti-inflammatory drugs, SAT: subcute thyroiditis. Laboratory reference ranges for thyroid function tests; TSH: 0.27-4.2 µIU/mL, fT4: 0.7-1.5 ng/dL. C: CoronaVac (inactivated SARS-CoV-2 vaccine), PB: Pfizer-BioNTech (mRNA SARS-CoV-2 vaccine)

Table 5. Patients with post-COVID-19 SAT

	Age	Sex	Signs and symptoms at SAT onset	Thyroid function tests	COVID-19 Vaccinations	Time to presentation since COVID-19	Subacute thyroiditis treatments	Recurrence
Patient 1	50	F	Anterior neck pain, tender thyroid enlargement	TSH: 2.69, FT4: 0.9	PB + PB	28 days	Steroids	1
Patient 2	41	F	Anterior neck pain, tachicardy	TSH: 0.2, FT4: 1.20	---	30 days	NSAID + Steroids	2
Patient 3	50	F	Anterior neck pain, fever palpitation	TSH: 0.08, FT4: 1.04	PB + PB	7 days	Steroids	None
Patient 4	52	M	Anterior neck pain, tender thyroid enlargement, fatigue	TSH: 0.18, FT4: 0.97	PB + PB	22 days	NSAID	None
Patient 5	44	F	Anterior neck pain, fatigue	TSH: 0.72, FT4: 1.0	PB + PB	26 days	Steroids	None
Patient 6	40	F	Anterior neck pain, tender thyroid enlargement	TSH: 0.02, FT4: 1.70	PB + PB	33 days	NSAID	None
Patient 7	52	F	Anterior neck pain, pain with neck movement	TSH: 1.87, fT4: 1.16	C	45 days	Steroids	None

F: female, M: male, NSAID: Nonsteroidal anti-inflammatory drugs, SAT: subcute thyroiditis. Laboratory reference ranges for thyroid function tests; TSH: 0.27-4.2 µIU/mL, fT4: 0.7-1.5 ng/dL. C: CoronaVac (inactivated SARS-CoV-2 vaccine), PB: Pfizer-BioNTech (mRNA SARS-CoV-2 vaccine)

Thyroid Evaluation

All referred patients had a typical clinical view of SAT. Neck pain, thyroid tenderness, and painful enlargement in the thyroid gland were present in all SAT patients. The clinical presentation of SAT in patients following COVID-19 disease or COVID-19 vaccination was not different from those of idiopathic SAT patients. Thyroid US combined with Doppler US demonstrated an enlarged thyroid gland with heterogeneous parenchyma along with hypoechoic areas and diminished vascularization in the gland in cases with SAT. In post-vaccination SAT groups, one patient (patient no 3) had suppressed serum TSH value. One patient (patient no 5) had subclinical hypothyroidism while other patients were euthyroid. Four patient with post-vaccination SAT were treated with glucocorticoids, while in 2 patients, NSAID sufficed.

In patients with SAT following COVID-19 disease, only one patient (patient no 6) had overt biochemical thyrotoxicosis, whereas the other 3 patients (patient no 2, 3, and 4) had subclinical hyperthyroidism. The remaining three patients were biochemically euthyroid.

Comparison of Post-COVID-19 and Post-Vaccination SAT with Idiopathic SAT

Mean age and gender distribution were comparable in COVID-19 and vaccine related SAT patients and idiopathic ones. In the similar vein, thyroid function tests, inflammatory markers and blood counts were not different, either. **Table 1** depicts the laboratory features of the both groups.

DISCUSSION

This is one of the largest study conducted to date reporting post COVID-19 disease, and COVID-19 vaccination-related SAT cases. SAT is probably a common, and missdiagnosed endocrinological abnormality during COVID-19 management (due to shared symptoms of COVID-19 disease). SAT incidence might be higher than usual during COVID-19 pandemic since its natural etiology substantially lies on virutic origin. Here, we demonstrate that the probability of as high as a %42 incidence of SAT following a COVID-19 disease or COVID-19 vaccination.

Early reports indicating a link between COVID-19 disease and endocrinological abnormalities were emphasizing to the hyperglycemia and diabetes mellitus and their adverse outcome in COVID-19 disease (18). Kumar et al. (19) reported endocrine abnormalities COVID-19 in patients with a focus on thyroid and adrenal function. After the report of the first case of SAT related to COVID-19 by Brancatella et al. (20), several similar reports further appeared in the literature (21). Most of these reports involved single case reports with a few case series not exceeding 6 patients at most (22-24). Muller et al. (25) than announced that incidence of atypical thyroiditis in a high dependency unit went up from 0.5% in 2019 to 10% in 2020 when admission ratio to hospital was raised due to COVID-19.

It should be taken into account that these case reports might have suffered from the positive case selection bias. In addition, it was not still clear whether COVID-19 actually increased the frequency of COVID-19 cases in a given population. The attempt to answer this question came with two studies; Trimboli and colleagues (26) retrospectively evaluated SAT cases who were diagnosed during a 10-month period in an Italian-speaking region of Switzerland. The authors determined 10 SAT cases during the specified time period. Interestingly none of the cases were deemed to be related to COVID-19. However, not all patients with SAT were evaluated by PCR or serologic tests for the presence of COVID-19. In four patients, PCR tests from nasopharyngeal swabs were found to be negative. In another study, Pirola et al. (27) evaluated SAT cases retrospectively in a region that was heavily affected by COVID-19 in Italy. The researchers detected 10 cases of SAT. Of these, only one patient had a recent history of COVID-19. The authors, moreover, reported that the frequency of SAT cases did not show a significant increase after the advent of COVID-19 in their region compared with records of the previous years. However, once again, the study was retrospective in nature, and COVID-19 PCR and/or immunologic status of the patients were not reported. In contrast to the aforementioned studies, all of the SAT patients whom we deemed related to COVID-19 had PCR proof of the SARS-CoV-2 infection.

Another issue complicating the association between COVID-19 and subacute thyroiditis is the lack of direct evidence, i.e., demonstration viral tissue PCR or other infection markers in thyroid epithelial cells. Evidence regarding the direct involvement of SARS-CoV-2 in extrapulmonary tissues has been shown in human gut enterocytes (28), myocardial cells (29), and kidneys (30), among others. Poma and colleagues (31), in their autopsy study, evaluated thyroid tissues of 25 patients who were died of COVID-19. The authors could demonstrate the SARS-CoV-2 genome and antigens in 36% of the studied thyroid specimens. These patients were not specifically selected because of a clinical thyroid dysfunction related to COVID-19. The latter observation is pathophysiologically plausible considering the increased expression of ACE2 receptors, which is the main way of entry of SARS-CoV-2 into thyroid follicular epithelial cells (32,33). Though we did not evaluate tissue biopsies indicating viral genome in thyroid tissue, as far as we know, none of the reported

cases in the literature reported direct evidence of SARS-CoV-2 invasion of thyroid tissue.

In our case series, as was in the literature, there was a clear-cut latent period between the COVID-19 related symptoms and the onset of SAT-related symptoms. Anterior neck pain was the invariable symptom of the SAT patients in our series. Thus, this distinctive symptom, along with a thyroid that was tender to palpation, makes it easier to discern the onset of SAT. Thus, it is reasonable to think that autoimmune phenomena triggered by SARS-CoV-2 rather than direct viral cytopathic effect might be chiefly responsible for the development of SAT after COVID-19. Interestingly, in 2 of our SAT patients, SAT symptoms recurred after complete resolution with appropriate treatment. Repeated SARS-CoV-2 PCR tests proved to be negative in these patients, and both patients responded favorably to the repeat of their previous treatments.

In Turkey, at the beginning of the pandemic, initially, an inactive SARS-CoV-2 vaccine was available. Soon, an mRNA-based SARS-CoV-2 vaccine was also available for use. As of the time of the preparation of this manuscript, 54% of the Turkish population has been fully vaccinated (13). Vaccination (influenza and H1N1) related SAT had been previously reported (34,35). As expected from a global mass vaccination program against a respiratory pathogen, cases of SAT coincided after SARS-CoV-2 vaccination have been reported. The SAT cases were described for mRNA-based, adenovirus-vectored, and inactive SARS-CoV-2 vaccines (15, 36). However, we should emphasize the fact that the number of reported SAT cases due to SARS-CoV-2 vaccination is much fewer compared to COVID-19 related cases. Here, we report the largest-to-date case series of patients who developed SAT after vaccination for COVID-19. All but one of our patients developed SAT after the administration of an inactive SARS-CoV-2 vaccine. The median latent period between the vaccination and onset of SAT symptoms was 25.8 days. In mRNA and adenovirus-vector-based vaccine administrations, this latent period was reported to be between 2-3 weeks. However, in a report from Turkey, SAT symptoms developed 2 and 4 days after the administration of an inactive SARS-CoV-2 vaccine (14). Both in the cases reported in the literature and our own cases, the presentation, and findings of the cases with SAT were not different from those of idiopathic cases. All of the cases responded favorably to the standard treatment regiment for SAT. It has been speculated that the vaccine-related SAT cases may be a product of ASIA syndrome in which adjuvants used to enhance the immunogenicity of the vaccines may lead to unintentional activation of the immune syndrome resulting in thyroid inflammation (37).

Inflamation related markers such as sedimentation and C-reactive protein (CRP) is a nonspecific indicator of the SAT. In our cohort CRP and sedimentation levels were above references ranges as expected. However, in postCOVID-19 or COVID-19 vaccine-related groups CRP levels was similar. On the other hand sedimentation rate was highet at a border of statistical significance. This is maybe due to etiological and pathogenetic variations; such as faster recovery from COVID related disease or low activity of COVID vaccines. SAT is perhaps clinically more silent, in COVID-19-related conditions compared to idiopathic or the disease originated other than COVID-19-related conditions.

Several limitations of the current work deserve mentioned further. Although the largest of its kind, this was a single-center study with a limited number of patients. As mentioned earlier, we did not have direct tissue evidence of thyroid invasion of the virus. However, if this association were a result of the autoimmune phenomenon, as was the case in (autoimmune/inflammatory syndrome induced by adjuvants) ASIA syndrome, looking for the viral genome would be a futile effort at the local level. Since patients first presented their general practitioners and then referred when it was suspected the patients might have SAT, not all patients presented us at the same stage of their disease. This fact was also reflected by the various test results of the thyroid function and inflammatory markers. In addition, we did not have thyroid autoantibodies in all patients.

Limitations of the study: Viral causes like mumps virus, coxsackie virus, adenovirus, Ebstein-Barr virus, influenzae and cytomegalovirus are accounted for common environmental factors of subacute thyroiditis (38). In our study we did not do the assays for the mentioned viral infections since the main infectious cause in the pandemic was COVID-19.

CONCLUSION

Our present study is one of the largest study in similar studies conducted to date. We also reported both COVID-19 related, and the SARS-CoV-2 vaccination-related SAT cases together in addition to the data of idiopathic SAT cases. Our results, although lacking direct tissue evidence thereof, showed a possible association of COVID-19 and SAT development. We also reported 6 cases who developed SAT after inactive and mRNA-based SARS-CoV-2 vaccines. In our study, all COVID-19 patients had PCR evidence of the infection. In this regard, caring physicians should be aware of the possibility of the interaction between SARS-CoV-2 and the thyroid gland in the form of SAT. We still do not have enough data if SAT occurs concurrently and among the

cloud of symptoms of COVID-19 infection. At least the presence of anterior neck pain and an enlarged tender thyroid gland should direct the physician to investigate the possibility of SAT in a COVID-19 patient.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 06.09.2021; Decision No: BŞH-28).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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