Differences in Clinical Aspects Between Subacute Thyroiditis Associated with COVID-19 Vaccines and Classical Subacute Thyroiditis

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ABSTRACT

Subacute thyroiditis (SAT) developed after SARS-CoV-2 vaccines has been less studied. We aimed to compare classical SAT and SAT developed after SARS-CoV-2 vaccines in the context of clinical aspects. Adults with SAT detected in 90 days of COVID-19 vaccination (CoronaVac or Pfizer/BioNTech) were grouped as Vac-SAT. Those with a history of SARS-CoV-2 or upper respiratory tract infection in 6 months before the vaccination, or vaccination with another antiviral vaccine after COVID-19 vaccination were excluded. Those with SAT detected before COVID-19 pandemic were grouped as Classical-SAT. Of total (n = 85), female/male (54/31) ratio and age [43 (23–65)] were similar in Vac-SAT (n = 23) and Classical-SAT (n = 62). Duration between vaccine and SAT was 45 (7–90) days, and similar in CoronaVac-SAT (n = 5) and BioNTech-SAT (n = 18). SAT-duration was 28 (10–150) days, and higher in Vac-SAT than in Classical-SAT (p = 0.023). SAT was developed after the 1st dose vaccine in minority in CoronaVac-SAT (n = 2) and BioNTech-SAT (n = 3) (p = 0.263). Previous LT4 use, and TSH elevation after resolution were more frequent in Vac-SAT than in Classical-SAT (p = 0.027 and p = 0.041). We included a considerable number of patients with SAT occurred after COVID-19 vaccines. We cannot provide clear evidence regarding the association of COVID-19 vaccines with SAT. SAT associated with CoronaVac or BioNTech seems unlikely to be occurred after the 1st dose, and to have a longer duration, more likely to be associated with previous LT4 use and lead TSH elevation after resolution than Classical-SAT. TSH should be followed-up after the resolution of SAT detected after COVID-19 vaccination.

Introduction

COVID-19 pandemic was declared by World Health Organization on March 11, 2020, and it has affected more than 386 million people by February 2022 [1]. The frequency and severity of COVID-19 infection have been associated both with glycemic status and obesity in many studies [2–4]. Investigations analyzing also the association of other endocrine disorders, affecting gonads, thyroid or adrenal glands, have been conducted so far [5–8]. Various associations of COVID-19 infection with the thyroid gland, such as subacute granulomatous thyroiditis (SAT) or Graves' disease, have been reported during the pandemic [7, 9, 10].

Subacute granulomatous thyroiditis (SAT) is destructive thyroiditis characterized by neck pain, and classically results from post-viral inflammatory response developed a few weeks after measles, mumps, adenovirus, and probably SARS-CoV-2 infection [10, 11]. Besides, several reports showed that SAT might occur after vaccination with influenza or hepatitis B vaccines [12–17]. Mass vaccination schedules to fight the COVID-19 pandemic provided administration of more than 142 million doses of various types of COVID-19 vaccines in Türkiye, and more than 10 billion doses worldwide [1, 18]. Vaccination against COVID-19 has been continued since January 2021, in our country, Türkiye, by mRNA (BioNTech) and inactive (CoronaVac) vaccines [18]. A lot of cases of SAT developed after the COVID-19 vaccination have been observed and reported worldwide and from Türkiye [19–23].

A systematic analysis of 51 cases with SAT developed after various types of SARS-CoV-2 vaccine showed that median age was 39.5 years, median time duration elapsed after the vaccine 10 days, and corticosteroid was used in more than half the patients [23]. The number of studies investigating the comparison of classical SAT with SAT developed after the SARS-CoV-2 vaccine is limited [24].

We aimed to investigate the differences in clinical, demographic, radiological and laboratory parameters between the patients with classical SAT and those with SAT developed after SARS-CoV-2 vaccines.

Patients and Methods

Study population

Adult patients who were referred to the Adult Endocrinology Clinics of the Zonguldak Bülent Ecevit University Medical Faculty between September 2018 and January 2022 and who exhibited SAT were included in this study. This observational, retrospective cohort study was approved by the Ethics Committee of our institution (Zonguldak Bülent Ecevit University Medical Faculty, Noninterventional Clinical Researches Ethics Committee; approval number 2021/20/10) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

The adult patients in whom SAT was diagnosed in the first 90 days after COVID-19 vaccination were included and defined as in the Vac-SAT group. SAT was detected both after CoronaVac (CoronaVac, Sinovac Life Sciences, and Beijing) and the mRNA vaccine (Pfizer/BioNTech). We defined them as CoronaVac-SAT and BioNTech-SAT groups. Those with a history of the upper respiratory tract or SARS-CoV-2 infection (proved by a PCR test) in 6 months before the vaccination or vaccination with another antiviral vaccine in time between COVID-19 vaccination and the diagnosis of SAT were excluded.

The adult patients in whom classical SAT was detected after upper respiratory tract infection before the COVID-19 pandemic, between September 2018 and December 2019, were defined as the Classical-SAT group.

The diagnosis of SAT was based on clinical symptoms and signs, laboratory parameters, and sonography findings [25]. We did not perform radioiodine or technetium imaging study. Younger subjects (<18-year-old) or those for whom data were missing were excluded. The demographic, clinical, laboratory and radiological features were compared between Vac-SAT and Classical-SAT groups, and between CoronaVac-SAT, BioNTech-SAT, and Classical-SAT groups.

Clinical evaluation

Basic demographic information (age, sex) and clinical characteristics [symptoms, the vaccine dose after which SAT was occurred (1st vs. subsequent), the brand name of vaccine (CoronaVac vs. BioNTech), type 2 diabetes mellitus (T2D, absent vs. present), hypertension (HT, absent vs. present)] were recorded. The time duration between the onset of symptoms of SAT and the vaccination was defined as "Vac-to-SAT" (days). This parameter was not defined for the Classical-SAT group. The duration between the onset of symptoms and the remission of SAT was defined as SAT-duration (days). Symptoms were grouped as follows: Group 1 included any inflammatory symptoms such as dolor (neck pain), local redness or temperature; Group 2 asthenia; Group 3 neck swelling, or visible or palpable nodule; Group 4 any symptoms of thyrotoxicosis (palpitation, sweating, weight loss); Group 5 compressive symptoms [new-onset difficulty in swallowing, dyspnea (in the absence of other possible causes), or hoarseness]. The previous history of LT4 use (absent vs. present) or ATD (absent vs. present) was analyzed.

Laboratory tests

We measured erythrocyte sedimentation rate (ESR, at 1st hour, mm/h), C-reactive protein (CRP, mg/l), complete blood count (CBC), TSH (thyroid stimulating hormone (TSH, mIU/l), free T4 (fT4, ng/dl), free T3 (pg/ml), anti-thyroid peroxidase (ATPO, IU/ml), anti-thyroglobulin (ATG, IU/ml), and TSH-receptor antibody (TRAB, IU/l).

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were defined as neutrophil count or platelet count divided by lymphocyte count, respectively.

All laboratory measurements were performed at the time of diagnosis of SAT. ESR and CRP were measured also after the symptoms and signs of SAT subsided, to detect if the SAT had been resolved or not. Thyroid function tests (TSH, fT4, and fT3) were measured also both at the resolution of SAT and one month later than the resolution if they had been completely normalized or TSH elevation had persisted.

The reference ranges in our laboratory were used to determine the upper and lower limits of normal for all laboratory parameters (ESR, 0–20 mm/h; CRP, 0–8 mg/l; TSH, 0.27–4.20 mIU/l; fT4, 0.93–1.70 ng/dl; fT3, 2–4.40 pg/ml; ATPO, 0–75 IU/ml; ATG, 0–150 IU/ml; TRAB, <1.75 IU/l; WBC, 3600–10200/mm^3; neutrophil, 1700–7600/mm^3; lymphocyte, 1000–3200/mm^3; hemoglobin, 13–16.3 g/dl for male, 12.5–16 g/dl for female; platelet, 152–348 × 10^3/mm^3; MCV 73–96.2 fl; MPV, 7.4–11.4 fl). We grouped the patients also according to ATPO (negative vs. positive vs. unknown), ATG (negative vs. positive vs. unknown), TRAB (negative vs. positive vs. unknown) and ESR and CRP (both normal/at least one elevated).

Sonography

Thyroid sonography (TS) was performed by the same endocrinologist skilled in TS using a 7.5 MHz linear transducer of a SONOACE

R3 ultrasound machine (Samsung Medison Co., Korea 2015). We showed characteristic sonographic findings of SAT such as ill-defined diffuse or focal hypoechoic area without formation of round mass on the multiple planes of sonography in all participants [26]. There was a low vascular flow on Doppler sonography. We grouped the patients according to TS findings as unilateral versus bilateral.

Management and follow-up

The patients with SAT were treated with anti-inflammatory agents such as NSAID (Nonsteroidal anti-inflammatory drug) alone or methylprednisolone (MP) together with NSAID. MP was indicated in the patients whose clinical improvement could not be observed in 3 days of NSAID treatment [27]. MP, if prescribed, was discontinued gradually after the resolution of SAT.

All patients were followed up based on clinical symptoms, signs and laboratory findings every 2 weeks. Resolution of SAT was defined as relief of symptoms and signs together with the normalization of inflammatory markers in serum (ESR and CRP) [27]. Resolution of symptoms and normalization of laboratory parameters such as ESR, CRP, TSH, and fT4 suggested the diagnosis of SAT retrospectively.

TSH, fT4, and fT3 levels were measured at the resolution of SAT and at 4 weeks later. Temporary hypothyroidism, if developed after the resolution of SAT, was not treated with LT4 if the symptoms regarding hypothyroidism were mild or absent. Hypothyroidism was treated with LT4 if the symptoms of hypothyroidism were moderate or severe, or if TSH was elevated to higher than 10 mIU/l.

We grouped the patients both according to TSH elevation (absent vs. present), and LT4 requirement (absent vs. present) after the resolution of SAT.

Statistical analysis

SPSS software (ver. 22.0; IBM Corporation, Armonk, NY, USA) was used for all analyses. The Shapiro-Wilk test was used to assess the normality of the data. When comparing two independent groups in terms of quantitative measures, Mann–Whitney U-tests were used. When comparing more than two independent groups in terms of quantitative measures, the Kruskal Wallis test was used. Pearson's chi-squared tests were used to compare categorical variables. Spearman's (Rho) correlation was used to analyze the correlations of variables with each other. Quantitative variables are reported as the median (minimum-maximum) in the tables. Categorical variables are reported as numbers (n) and percentages (%), and p-values < 0.05 were taken to indicate statistical significance.

Results

Of total (n = 85), there were 23 patients in the Vac-SAT group, of which 18 was in BioNTech-SAT and 5 in CoronaVac-SAT, and 62 patients in the Classical-SAT group. Age was similar among groups. Median Vac-to-SAT-duration was 45 (7–90) days, and similar in CoronaVac-SAT and BioNTech-SAT groups. Median SAT-duration was 28 (10–150) days in total; it was higher in the Vac-SAT group than in the Classical-SAT group (p = 0.023), and highest in BioNTech-SAT, lowest in the Classical-SAT group (p = 0.016). There was a significant difference in ESR between the 3 groups (p = 0.019), and it was higher in Classical-SAT than in BioNTech-SAT. Median MCV was higher in the Vac-SAT group than in the Classical-SAT group (p = 0.033). CRP, other CBC parameters, NLR, PLR, TSH, fT4 and fT3 were similar among the groups (▶ **Table 1**).

Of total, the female/male ratio was 63.5/36.5 % (54/31), and similar between the groups. SAT was developed after 1st dose of vaccine in 5 patients in Vac-SAT (n = 23), 2 patients in CoronaVac-SAT, and 3 patients in BioNTech-SAT groups (p = 0.263). T2D was present only in the BioNTech-SAT group (p < 0.001). LT4 history was more frequent in Vac-SAT than in Classical-SAT (p = 0.027) but was present at a similar frequency in CoronaVac-SAT and BioNTech-SAT groups (p = 0.602). The number of patients with both normal ESR and CRP was 3 in the BioNTech-SAT group and 2 in the Classical-SAT group. TSH elevation was more frequent in the Vac-SAT group (p = 0.041) (▶ **Table 2**). No patients did have active thyroid dysfunction indicating a need for LT4 or ATD just before the diagnosis of SAT. Only 1 patient in Vac-SAT group did show a course of persistent SAT after 1st and 2nd doses of CoronaVac. One patient in Vac-SAT group did have a previous history of classical SAT developed 2 years ago. In 2 patients who developed SAT after 3rd dose of vaccine, 1st and 2nd doses of vaccine were CoronaVac but SAT developed after BioNTech applied as a 3rd dose in total. We grouped these patients as in BioNTech-SAT group and defined them as they developed SAT after subsequent doses of vaccine. Graves' disease was not occurred after the resolution of SAT in any patients in Vac-SAT or Classical-SAT groups.

SAT-duration was negatively correlated with PLR and fT4 level in the Classical-SAT group. ESR, CRP, NLR and PLR was positively correlated with fT4 level in the Classical-SAT group. TSH was negatively correlated with ESR and NLR in the Classical-SAT group. fT3 was positively correlated with NLR and PLR in the Classical-SAT group. SAT-duration was negatively correlated with MCV in the Vac-SAT group. Vac-to-SAT was not correlated with any parameter in the Vac-SAT group. NLR and PLR were positively correlated with fT4 level in the Vac-SAT group (▶ **Table 3**).

Discussion

We found that SAT might be occurred in about six weeks of the COVID-19 vaccines, mostly after 2nd or subsequent doses of the vaccine, and resolved after 4 weeks. ESR was higher in Classical-SAT, but SAT-duration was longer in Vac-SAT. The previous history of LT4 use, and TSH-elevation was more frequent in Vac-SAT than in Classical-SAT. The history of T2D was present only in BioNTech-SAT. Inflammatory markers were positively correlated with fT4 level, but not with Vac-to-SAT or SAT-duration.

Subacute granulomatous thyroiditis (SAT) is an inflammatory thyroiditis led by various viral infections and antiviral vaccines as reported in the literature [11–17]. Immune hyperactivation may play a role in the development of classical SAT and may be a possible mechanism in the development of SAT associated with SARS-CoV-2 infection [7, 9–11, 24]. SARS-CoV-2 enters the cells via human angiotensin-converting enzyme 2 (ACE2) and uses transmembrane serine protease 2 receptors (TMPRSS2) for S-protein priming [28]. The thyroid gland expresses ACE2 mRNA and TMPRSS2 [29]. Besides viral cytotoxicity, thyroid damage may have resulted from immune response in SARS-CoV-2 infection [29, 30].

▶ **Table 1** Demographic, clinical, and laboratory parameters of the participants and comparison between the groups.

Parameters	Vac-SAT CoronaVac-SAT (n = 5)	BioNTech-SAT (n = 18)	Vac-SAT (n = 23)	p1	Classical-SAT (n = 62)	p2	p3	Total (n = 85)
	Median (Min–Max)				Median (Min–Max)			Median (Min–Max)
Age	44 (34–49)	41.5 (23–62)	42 (23–62)	0.852	43 (26–65)	0.886	0.976	43 (23–65)
Vac-to-SAT (days)	52 (15–90)	40 (7–90)	45 (7–90)	0.708	NA	NA	NA	NA
SAT-duration (days)	70 (45–120)	37 (15–150)	45 (15–150)	0.077	28 (10–120)	**0.023**	**0.016**	**28 (10–150)**
ESR (mm/hour)	68 (34–125)	42 (4–76)	45 (4–125)	0.109	59.5 (14–127)	**0.047**	**0.019**	**55 (4–127)**
CRP (mg/l)	26.9 (18.6–120)	23.5 (3.8–62.2)	25 (3.8–120)	0.180	41.5 (1.3–296)	0.062	0.079	38.7 (1.3–296)
WBC (/mm^3)	8900 (6900–9100)	7400 (4700–16800)	7600 (4700–16800)	0.941	8500 (4600–21600)	0.243	0.506	8400 (4600–21600)
Neutrophil (/mm^3)	4900 (4400–7000)	4250 (3000–15200)	4400 (3000–15200)	0.455	5900 (2200–12700)	0.150	0.336	5700 (2200–15200)
Lymphocyte (/mm^3)	1900 (1500–3300)	1800 (1000–4200)	1800 (1000–4200)	0.709	2100 (100–6300)	0.344	0.625	2000 (100–6300)
Hb (g/dl)	12.2 (9.2–12.8)	13.1 (10.1–14.7)	12.8 (9.2–14.7)	0.052	12.55 (8.6–14.9)	0.600	0.144	12.7 (8.6–14.9)
Platelet (× 10^3/mm^3)	273 (247–444)	312 (160–587)	312 (160–587)	0.823	311.5 (162–535)	0.808	0.938	312 (160–587)
MCV (fl)	80.6 (77.8–86.9)	88.1 (81.2–92.2)	87.8 (77.8–92.2)	**0.014**	84.2 (70.4–91.4)	**0.033**	**0.005**	**85 (70.4–92.2)**
MPV (fl)	8.1 (7.4–9.3)	8.5 (6.6–10.4)	8.3 (6.6–10.4)	0.478	8.2 (6.7–17.6)	0.638	0.668	8.2 (6.6–17.6)
NLR	2.31 (1.48–4.67)	2.29 (1.28–15.2)	2.31 (1.28–15.2)	0.709	2.94 (1.1–79)	0.546	0.829	2.72 (1.1–79)
PLR	164.66 (82.73–233.68)	167.34 (58.28–327.27)	164.66 (58.28–327.27)	0.881	153.33 (48.91–3600)	0.449	0.744	163.12 (48.91–3600)
TSH (mIU/l)	0.05 (0.0–0.24)	0.96 (0.0–12.24)	0.24 (0.0–12.24)	0.167	0.04 (0.0–4.8)	0.153	0.149	0.05 (0.0–12.24)
fT4 (ng/dl)	1.88 (1.19–2.05)	1.47 (0.55–5.37)	1.54 (0.55–5.37)	0.412	1.78 (0.73–5.2)	0.116	0.256	1.67 (0.55–5.37)
fT3 (pg/ml)	4.16 (2.94–5.10)	3.68 (0.51–15.53)	3.78 (0.51–15.53)	0.823	4.31 (1.73–16.63)	0.163	0.378	4.16 (0.51–16.63)

SAT: Subacute granulomatous thyroiditis; Min: Minimum; Max: Maximum; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cell; Hb: Hemoglobin; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; NA: Not applicable; p1: Difference between CoronaVac-SAT and BioNTech-SAT; p2: Difference between Vac-SAT and Classical-SAT; p3: Difference between CoronaVac-SAT and BioNTech-SAT and Classical-SAT.

▶ **Table 2** Demographic, clinical, and laboratory parameters of the participants and comparison between the groups.

	Vac-SAT				Classical-SAT (n = 62)	Total (n = 85)		
Parameters	**CoronaVac-SAT (n = 5)**	**BioNTech-SAT (n = 18)**	**Vac-SAT (n = 23)**	**p1**		**p2**	**p3**	
	n (%)				**n (%)**			**n (%)**
Sex (female/male)	3/2 (60/40)	9/9 (50/50)	12/11 (52.2/47.8)	0.692	42/20 (67.7/32.3)	0.185	0.382	54/31 (63.5/36.5)
Vaccine dose (1st/subsequent)	2/3 (40/60)	3/15 (16.7/83.3)	5/18 (21.7/78.3)	0.263	NA	NA	NA	5/18 (21.7/78.3)
Vaccine Brand Name (CoronaVac/BioNTech)	NA	NA	5/18 (21.7/78.3)	NA	NA	NA	NA	5/18 (21.7/78.3)
T2D (absent/present)	5/0 (100/0)	14/4 (77.8/22.2)	19/4 (82.6/17.4)	0.246	62/0 (100/0)	**0.001**	**<0.001**	81/4 (95.3/4.7)
HT (absent/present)	5/0 (100/0)	14/4 (77.8/22.2)	19/4 (82.6/17.4)	0.246	58/4 (93.5/6.5)	0.125	0.099	77/8 (90.6/9.4)
Previous LT4 use (absent/present)	4/1 (80/20)	16/2 (88.9/11.1)	20/3 (87/13)	0.602	61/1 (98.4/1.6)	**0.027**	0.062	81/4 (95.3/4.7)
Previous ATD use (absent/present)	5/0 (100/0)	17/1 (94.4/5.6)	22/1 (95.7/4.3)	0.590	57/5 (91.9/8.1)	0.552	0.764	79/6 (92.9/7.1)
Symptoms (absent/present)								
Group 1	0/5 (0/100)	0/18 (0/100)	0/23 (0/100)	NA	8/54 (12.9/87.1)	0.070	0.194	8/77 (9.4/90.6)
Group 2	0/5 (0/100)	5/13 (27.8/72.2)	5/18 (21.7/78.3)	0.183	18/44 (29/71)	0.501	0.371	23/62 (27.1/72.9)
Group 3	5/0 (100/0)	16/2 (88.9/11.1)	21/2 (91.3/8.7)	0.435	48/14 (77.4/22.6)	0.146	0.296	69/16 (81.2/18.8)
Group 4	2/3 (40/60)	12/6 (66.7/33.3)	14/9 (60.9/39.1)	0.280	41/21 (66.1/33.9)	0.652	0.491	55/30 (64.7/35.3)
Group 5	4/1 (80/20)	15/3 (83.3/16.7)	19/4 (82.6/17.4)	0.862	55/7 (88.7/11.3)	0.457	0.743	74/11 (87.1/12.9)
TS (unilateral/bilateral)	0/5 (0/100)	6/12 (33.3/66.7)	6/17 (26.1/73.9)	0.133	22/40 (35.5/64.5)	0.413	0.267	28/57 (32.9/67.1)
ESR + CRP (both normal/at least one elevated)	0/5 (0/100)	3/15 (16.6/83.3)	3/20 (13/87)	0.328	2/60 (3.2/96.8)	0.087	0.087	5/80 (5.9/94.1)
ATPO (negative/positive/unknown)	5/0/0 (100/0/0)	8/3/7 (44.4/16.7/38.9)	13/3/7 (56.5/13/30.5)	0.195	30/8/24 (48.4/12.9/38.7)	0.848	0.446	43/11/31 (50.6/12.9/36.5)
ATG (negative/positive/unknown)	1/2/2 (20/40/40)	5/3/10 (27.8/16.7/55.5)	6/5/12 (26.1/21.7/52.2)	0.387	27/6/29 (43.5/9.7/46.8)	0.070	0.119	33/11/41 (38.8/13/48.2)
TRAB (negative/positive/unknown)	0/0/5 (0/0/100)	5/1/12 (27.8/5.5/66.7)	5/1/17 (21.7/4.4/73.9)	NA	14/3/45 (22.6/4.8/72.6)	0.957	0.957	19/4/62 (22.3/4.7/73)
Treatment (NSAID/NSAID + MP)	1/4 (20/80)	10/8 (55.5/44.5)	11/12 (47.8/52.2)	0.159	17/45 (27.4/72.6)	0.075	0.067	28/57 (32.9/67.1)
TSH-elevation (absent/present)	1/4 (20/80)	9/9 (50/50)	10/13 (43.5/56.5)	0.231	42/20 (67.7/32.3)	**0.041**	0.060	52/33 (61.2/38.8)
LT4 requirement (absent/present)	4/1 (80/20)	11/7 (61.1/38.9)	15/8 (65.2/34.8)	0.433	47/15 (75.8/24.2)	0.329	0.436	62/23 (72.9/27.1)

SAT: Subacute granulomatous thyroiditis; T2D: Type 2 diabetes mellitus; HT: Hypertension; LT4:Levothyroxine; TS: Thyroid sonography; ESR: Erythrocyte sedimentation rate; CRP:C-reactive protein; ATD: Antithyroid drug; ATPO: Anti-thyroid peroxidase; ATG: Anti-thyroglobulin; TRAB: TSH receptor antibody; NSAID: Nonsteroidal anti-inflammatory drug; MP: Methylprednisolone; NA: Not applicable; p1: Difference between CoronaVac-SAT and BioNTech-SAT; p2: Difference between Vac-SAT and Classical-SAT; p3: Difference between CoronaVac-SAT and BioNTech-SAT and Classical-SAT.

▶ **Table 3** Correlation of clinical parameters in Classical–SAT and Vac–SAT.

	Classical-SAT (n = 62)						**Vac-SAT (n = 23)**						
Parameters	**Age**	**SAT-duration**	**ESR**	**CRP**	**NLR**	**PLR**	**Age**	**Vac-to-SAT**	**SAT-duration**	**ESR**	**CRP**	**NLR**	**PLR**
	Rho (p)							**Rho (p)**					
Vac-to-SAT	NA	NA	NA	NA	NA	NA	0.144 (0.511)	1					
SAT-duration	−0.201 (0.117)	1					−0.034 (0.878)	0.234 (0.282)	1				
ESR	0.019 (0.882)	−0.197 (0.125)	1				−0.076 (0.729)	0.140 (0.525)	0.324 (0.132)	1			
CRP	0.088 (0.494)	−0.160 (0.213)	**0.714 (<0.001)**	1			−0.339 (0.114)	0.104 (0.638)	0.306 (0.156)	**0.663 (0.001)**	1		
NLR	−0.179 (0.165)	−0.094 (0.469)	0.220 (0.086)	**0.270 (0.034)**	1		−0.310 (0.150)	0.261 (0.228)	0.002 (0.992)	0.177 (0.418)	0.339 (0.114)	1	
PLR	−0.126 (0.330)	**−0.288 (0.023)**	0.065 (0.616)	0.035 (0.785)	**0.737 (<0.001)**	1	−0.239 (0.273)	0.038 (0.863)	0.058 (0.792)	0.122 (0.580)	0.221 (0.311)	**0.777 (<0.001)**	1
MCV	−0.114 (0.378)	0.093 (0.473)	−0.088 (0.495)	0.008 (0.954)	−0.013 (0.919)	−0.088 (0.496)	−0.064 (0.771)	−0.215 (0.326)	**−0.449 (0.032)**	−0.131 (0.550)	−0.294 (0.173)	−0.264 (0.223)	−0.244 (0.261)
MPV	0.025 (0.846)	−0.014 (0.915)	−0.076 (0.557)	−0.059 (0.646)	−0.224 (0.080)	−0.244 (0.056)	0.066 (0.765)	0.184 (0.401)	−0.308 (0.152)	**−0.471 (0.023)**	**−0.587 (0.003)**	−0.028 (0.898)	−0.263 (0.225)
TSH	0.091 (0.479)	0.151 (0.241)	**−0.353 (0.005)**	−0.225 (0.079)	**−0.278 (0.029)**	−0.228 (0.075)	0.179 (0.415)	−0.154 (0.483)	−0.111 (0.615)	−0.136 (0.537)	−0.283 (0.190)	−0.374 (0.079)	**−0.542 (0.008)**
fT4	−0.184 (0.151)	**−0.260 (0.041)**	**0.379 (0.002)**	**0.267 (0.036)**	**0.324 (0.010)**	**0.338 (0.007)**	−0.217 (0.319)	0.103 (0.641)	0.061 (0.782)	0.000 (0.998)	0.193 (0.378)	0.284 (0.190)	0.356 (0.096)
fT3	**−0.352 (0.005)**	−0.167 (0.195)	0.177 (0.168)	0.154 (0.234)	**0.295 (0.020)**	**0.370 (0.003)**	**−0.448 (0.032)**	−0.007 (0.974)	−0.075 (0.735)	0.041 (0.852)	0.091 (0.680)	**0.425 (0.043)**	**0.424 (0.044)**

SAT: Subacute granulomatous thyroiditis; ESR: Erythrocyte sedimentation rate; CRP:C-reactive protein; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NA: Not applicable.

Molecular mimicry, as demonstrated by the homology between thyroid peroxidase and epitopes of SARS-CoV-2, may initiate immune response [30]. Several case reports suggest a cause-and-effect relationship between SAT and SARS-CoV-2 infection. Limited studies compared classical SAT with vaccine-SAT [24]. However, it is difficult to prove that SARS-CoV-2 vaccines were responsible for SAT developed after these vaccines.

The median age in our study was 43, and similar among the groups. Albeit insignificant, the percentage of female patients was a little bit higher in Classical-SAT than in Vac-SAT. We showed that Vac-SAT was developed mostly (78.3 %) after the 2nd or subsequent doses of the vaccines. Albeit insignificant, the ratio of SAT developed after the 1st dose was a little bit higher in CoronaVac-SAT (40 %) than in BioNTech-SAT (16.7 %) group. However, 2 patients included in BioNTech-SAT group were vaccinated with CoronaVac as 1st and 2nd doses, but SAT vas developed after BioNTech applied as a 3rd dose in total. We defined them as they developed SAT after subsequent doses of vaccine. In one study analyzing both classical SAT and SAT associated with COVID-19 or COVID-19 vaccines, SAT was developed after 2 doses of CoronaVac in 4, 1 dose of BioNTech in 2 patients [24]. A systematic review showed that the ratio of SAT developed after the 1st dose of vaccine was 51 % in mRNA, 88.9 % in a viral vector, 33.3 % in inactivated virus vaccine groups, and 58 % in total (n = 50) (p = 0.701) [23]. In an analysis of 15 patients with SAT associated with COVID-19 vaccines, approximately half of the patients were diagnosed after the 1st dose of the vaccine [31]. They showed also that three patients were diagnosed after the 2nd dose of vaccine, but the 1st dose was CoronaVac, the 2nd dose BioNTech. Providing clinical knowledge is difficult in this context because different vaccination programs have been performed in various countries. The duration between two consecutive doses of vaccines, the ratio of various types of vaccines in the same population, access to vaccines and vaccination schedule in different age and/or risk groups may differ among the countries and vary in time in the same region. Besides systematic reviews, the analysis of the national databases will give more information about the post-vaccine inflammatory conditions.

Classical SAT has been known to be developed 2–8 weeks after upper respiratory tract viral infections [25]. It was reported to emerge 3–5 weeks after SARS-CoV-2 infection [21]. Previous reports showed that SAT might be developed in 2 days to 8 weeks after antiviral vaccines against influenza, H1N1 or hepatitis B [12–17]. We observed that Vac-SAT occurred in 7–90 days after the vaccination. Ippolito et al. showed that the onset of SAT was 4–14 days after the COVID-19 vaccines [23]. Bahçecioğlu et al. showed that SAT might be developed 1–12 weeks after the COVID-19 vaccines [24]. Oğuz et al. revealed that the median duration of time between vaccination and the symptoms was 7 (1–15) days, and the median diagnostic delay was 3 (max:13) weeks [31]. Definition of time duration in which SAT developed after the COVID-19 vaccines may be diagnosed is not clear, and vary in the case reports [23, 24, 31]. It is important to exclude the cases with other antiviral vaccines administered simultaneously or in 90 days before SAT, and those with a history of another viral infection detected again in a similar time period.

Inflammatory symptoms and asthenia were the most frequent symptoms in SAT in our study. Symptoms of thyrotoxicosis or possible compression of neck structures were the least frequent symptoms. The distribution of symptoms was similar in the study groups.

In our study, ratio of previous LT4 use was one eighth in Vac-SAT, and it was more frequent in Vac-SAT than in Classical-SAT. Previous ATD use was present in the minority of the patients. It may be proposed that suggesting previous destruction, history of previous LT4 use may be associated with the development of SAT. However, the number of patients with a history of previous LT4 use is actually low. Analysis of a large population of classical SAT revealed that the frequency of positivity of ATPO was found as 7.8 % [32]. In another study, it was found a little bit higher as 11.8 % [33]. We could not measure thyroid autoantibodies in all patients, but at least one of them was positive in approximately one fifth of the patients in Vac-SAT, and no difference was found among the groups. Therefore, evaluation of autoimmunity of the subjects with or without previous history of LT4 or ATD may be incorrect in the present study. The frequency of thyroid autoantibodies was approximately 20 % in one systematic analysis, and less in the other one, which analyzed SAT associated with COVID-19 vaccines [23, 31]. Autoantibody positivity was shown as an inconsistent finding in the patients with hypothyroidism that occurred after the resolution of SAT associated with COVID-19 vaccines [19, 21]. We found that TSH was elevated in more than half the Vac-SAT group after the resolution of SAT. TSH elevation was more frequent in Vac-SAT than in Classical-SAT. We prescribed LT4 in one third of the patients in Vac-SAT, and one forth in classical SAT. LT4 treatment was indicated in 61.5 % of the patients with TSH elevation in Vac-SAT, and 75 % of those in the Classical- SAT group. LT4 prescription was based on the ATA guideline [25]. TSH elevation after the remission of Vac-SAT has been less analyzed in the previous studies [24, 31]. In one systemic review, hypothyroidism was detected in one fourth of the patients after remission of SAT associated with COVID-19 vaccine, and LT4 was found to be indicated in approximately 60 % of them [23]. The ratio of LT4 prescription in that analysis was half that in the present study [23]. It was mentioned about that some cases included in that review could not be monitored regarding thyroid function tests after the remission. To determine the need for LT4 treatment, the patients with vaccine SAT should be observed at certain intervals with measurement of thyroid function. No cases of Graves' disease were detected after the remission of vaccine SAT in our study. Oğuz et al. showed a case of SAT associated with the vaccine who developed Graves' disease after the remission [31]. That patient did not have any previous history of thyroid disease or autoimmunity. In another report, hypothyroidism was detected in a patient without thyroid autoimmunity [19]. We previously reported a case with positive thyroid autoimmunity in which overt hypothyroidism occurred after the remission of SAT developed after CoronaVac [21]. That patient was followed-up with persistent SAT. In the present study, one patient in Vac-SAT group did have a previous history of classical SAT 2 years ago, but thyroid autoantibody status of the patient was not known. The association between thyroid autoimmunity and the outcome of SAT associated with COVID-19 vaccines may be clearly explained in a large future study including the cases with all known autoimmune status of the thyroid gland. The history of T2D was positive only in 4 patients in the BioNTech-SAT group, but HT in both BioNTech- and Classical-SAT groups. We consider that the differences may be a result of the low

number of participants included in the study, rather than a tendency of the presence of T2D or HT in Vac-SAT. No analysis has been conducted regarding the association between T2D or HT and SAT developed after COVID-19 vaccines.

As in classical SAT, acute phase reactants were found to be elevated in SAT developed after COVID-19 vaccines [23, 24, 31]. ESR is an indirect measure of acute phase response and increased in systemic and localized inflammatory situations such as SAT [27]. Our findings suggest that acute phase reactants, either ESR or CRP or both might be elevated in the vast majority of the patients both in Classical-SAT or Vac-SAT groups. We found that, albeit statistically insignificant, ESR was a little bit higher in CoronaVac-SAT than in BioNTech-SAT, or the Classical-SAT. ESR was higher in Classical-SAT than in the Vac-SAT group, and the difference was more prominent between Classical-SAT and BioNTech-SAT. However, other inflammatory markers such as CRP, NLR or PLR were found similar in Classical-SAT and Vac-SAT groups. Three patients in the BioNTech-SAT group and 2 in the Classical-SAT group were observed that neither ESR nor CRP was elevated. Systematic analysis of case reports showed that ESR and/or CRP was elevated in more than 80 % in SAT associated with COVID-19 vaccines [23, 31]. The ratio of findings of normal ESR or CRP was shown as similar in SAT groups associated with distinct types of vaccines [23, 31]. In one study, ESR and CRP were found similar in classical SAT and SAT associated with COVID-19 vaccines, and also in SAT developed after SARS-CoV-2 infection [24]. Our finding regarding ESR may not carry significance in a clinical manner. Interestingly, ESR and CRP remain unaffected in the minority of the patients in the present study. We previously reported a case of persistent SAT associated with CoronaVac who did not have prominent elevations in ESR or CRP [21]. In that case, ESR was elevated at the 1st referral of the patient after the 1st dose of CoronaVac, but CRP was elevated especially in the 2nd referral (persistence) after the 2nd dose of the vaccine [21]. Actually, in the present study, we did measure ESR and CRP but failed to measure the other indicators of acute phase response such as interleukin-1, interferon-gamma, tumor necrosis factor-alpha, complement components, or fibrinogen. Larger series are necessary to analyze if there is a difference in inflammatory markers between the patients with SAT developed after the vaccine, and those with classical SAT. We calculated NLR and PLR which were similarly increased in Vac-SAT and Classical-SAT groups. Cengiz et al. investigated NLR and PLR in classical SAT and found a mean NLR of 2.78 and PLR of 173, which were similar to those in our study [34]. We showed that NLR and PLR were correlated with fT3 levels both in Vac-SAT and Classical-SAT, but not with ESR or CRP in Vac-SAT.

Thyroid sonography is an important clinical clue in the diagnosis of SAT [27]. We showed the heterogeneous patchy area of thyroiditis, which is tender during a sonographic examination, in all subjects included. SAT is generally emerged in one lobe and then involves the contralateral thyroid lobe [27]. Sonographic evidence of bilateral involvement of the thyroid gland has been a prominent feature in vaccine SAT [21, 22, 24, 31]. We showed that bilaterality in sonography was similar in Vac-SAT and Classical-SAT groups, and was detected as more than 70 % in Vac-SAT. The diagnosis of SAT is mainly based on clinical and laboratory findings, supported by thyroid sonography. Hence, the utility of thyroid scintigraphy has been diminished [27]. We did perform thyroid technetium scintigraphy in some cases with Classical-SAT previously, but not in any patients with Vac-SAT.

NSAID may be the first choice in the management of SAT associated with COVID-19 vaccines, as in classical SAT, however, corticosteroid could be needed if treatment with NSAID is inadequate [27]. In our study, we treated all patients with NSAID alone or together with MP. MP was necessary for half of the patients in Vac-SAT, and in approximately 70 % of those in Classical-SAT. Suggesting, a similar finding was shown in a previous report [31]. The use of MP was similar among the groups in our study. Steroid was found to be needed in about 40 % of the patients with classical SAT in a previous large cohort [32]. Bahçecioğlu et al. showed that one third of the patients with SAT developed after COVID-19 vaccines were given MP, and the ratio of need for MP was similar among the groups [24]. However, clinical findings in some cases with SAT were reported to be subsided without any treatment [23, 31].

It is known that inflammatory findings and thyrotoxicosis subside generally in 2–8 weeks [25, 27]. The patients with SAT should be followed-up after the resolution of SAT as regards the development of possible hypothyroidism or recurrence. We revealed that the median duration of SAT was 45 days in Vaccine-SAT which was higher than in Classical SAT (28 days). The difference was more prominent between CoronaVac-SAT and Classical SAT, but no difference was found between the vaccine groups. Bahçecioğlu et al. showed that the duration of treatment in vaccine-related SAT was 4.5 weeks, and significantly lower than classical SAT ($p < 0.05$) [24]. Time from the onset of SAT to the remission was found up to 20 weeks in another study [31]. Duration of treatment in vaccine-related SAT was reported as 8–12 weeks in other case series [35]. We previously reported the duration of SAT as 4–14 weeks in the patients with SAT developed either after BioNTech or CoronaVac [21, 22]. We observed that SAT developed after the 1st dose of CoronaVac persisted after the 2nd dose in a patient up to a total of > 90 days [21]. In one study analyzing classical SAT, recurrence was found as approximately 20 % [32]. Recurrent SAT also was reported both after the mRNA vaccine and inactive vaccine [31, 36].

Strength and limitations

We analyzed the clinical, diagnostic and follow-up features of SAT that occurred after COVID-19 vaccines in a relatively large study population, and compared Vac-SAT with classical SAT. We showed that SAT occurred after COVID-19 vaccines might have a longer duration comparing classical SAT, and more likely lead to TSH elevation. Based on single center experience, we did not analyze the frequency of Vac-SAT in our country. We analyzed Vac-SAT associated only either with CoronaVac or BioNTech, but not with other COVID-19 vaccines. We could not screen other respiratory viral infections at the diagnosis of SAT but excluded them based on the history. We could not measure the inflammatory markers other than ESR or CRP.

Conclusions

We included a relatively larger population with SAT that occurred after COVID-19 vaccines. Our findings suggest that COVID-19 vaccines may be associated with SAT, but do not provide clear evidence. SAT associated with CoronaVac or BioNTech seems to be

more likely associated with the previous history of LT4 use, have a longer duration, and lead to more frequent TSH elevation than classical SAT. The clinicians should be alert as regards to follow-up TSH levels during the resolution of SAT that occurred after COVID-19 vaccines and later then. Larger studies including longer follow-up duration may clearly reveal the differences in the clinical aspects between SAT associated with COVID-19 vaccines and classical SAT.

Conflict of Interest

The authors declare that they have no conflict of interest.

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