Persistent Subacute Thyroiditis Post SARS-CoV-2 Vaccine in a Male Patient with Positive Thyroid **Autoantibodies**

Tiroid Otoantikorları Pozitif Olan Erkek Hastada İnaktif SARS-CoV-2 Aşısından Sonra Gelişen Persistan Subakut Tiroidit

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Abstract

Subacute thyroiditis (SAT) has been recently associated with severe acute respiratory syndrome-coronavirus-2 infection or vaccines against it. We report a case of a 41-yearold male patient who developed persistent SAT after the coronavirus disease-2019 (COVID-19) vaccination. He presented with sore throat and neck pain after the first dose of the COVID-19 vaccine (CoronaVac®). There was no history of a recent viral infection. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated, thyroidstimulating hormone (TSH) and free thyroxine (fT4) were normal, COVID-19 polymerase chain reaction test was negative, and sonography showed thyroiditis in the right lobe. The symptoms resolved after treatment with methylprednisolone. However, 2 weeks after the second dose of the vaccine, the patient suffered from neck pain and hoarseness. TSH and fT4 were normal, but anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), ESR, and CRP were elevated. Sonography revealed thyroiditis in the left lobe. The patient was treated with ibuprofen. On follow-up, hypothyroidism was diagnosed, and levothyroxine started. Hence, the clinicians should suspect the possibility of SAT in the vaccinated subjects.

Keywords: Subacute thyroiditis; COVID-19 vaccines;

Özet

Subakut tiroidit (SAT), son zamanlarda şiddetli akut solunum sendromu-koronavirüs-2 enfeksiyonu veya buna karşı geliştirilen aşılarla ilişkilendirilmektedir. Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] aşılaması sonrasında persistan SAT gelişen 41 yaşında erkek hastamızı sunuyoruz. COVID-19 aşısının (CoronaVac®) ilk dozundan sonra boğaz ağrısı ve boyun ağrısı ile başvurdu. Yakın zamanda viral enfeksiyon öyküsü yoktu. Eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) yüksekti, tiroidstimüle edici hormon (TSH) ve serbest tiroksin (sT4) normaldi, COVID-19 polimeraz zincir reaksiyonu testi negatifti ve sonografide sağ lobta tiroidit mevcuttu. Metilprednizolon tedavisi ile semptomlar geriledi. Ancak aşının 2. dozundan 2 hafta sonra hasta boyun ağrısı ve ses kısıklığından yakındı. TSH ve sT4 normaldi, anti-tiroid peroksidaz, anti-tiroglobülin, ESH ve CRP yükseldi. Sonografide sol lobta tiroidit izlendi. Hasta ibuprofen ile tedavi edildi. Takipte, hipotiroidizm tanısıyla levotiroksin başlandı. Dolayısıyla klinisyenler aşılanmış kişilerde SAT olasılığını akılda tutmalıdır.

COVID-19

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was declared a pandemic on March 11, 2020, and has affected more than 236 million people by October 2021 (1). SARS-CoV-2 infection may lead to multisystem involvement.

Anahtar kelimeler: Subakut tiroidit; COVID-19 aşısı;

COVID-19

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been taking montelukast and mesalazine. The patient denied having a recent upper respiratory tract infection or pre-existing thyroid dysfunction. He had a history of COVID-19 infection eight months ago. He had a family history of Type 2 diabetes mellitus and hypertension. The patient has taken the first dose of the CoronaVac® vaccine 1 week before being referred to the hospital. Laboratory analysis revealed that erythrocyte sedimentation rate (ESR) and Creactive protein (CRP) were 27 mm/hour and 8.1 mg/L, respectively, and thyroid function tests were within normal limits (Table 1). Thyroid sonography demonstrated the presence of focal thyroiditis, hypoechogenicity, and coarsening in the right lobe of the thyroid gland. COVID-19 infection was ruled out with a negative polymerase chain reaction (PCR) test by nasopharyngeal swab. Based on these findings, SAT was diagnosed, and cefpodoxime 200 mg once daily and oral methylprednisolone 32 mg once daily were prescribed. The symptoms of the patient partially subsided, and treatment was stopped after 2 weeks. The patient did not attend clin-

ical follow-up regularly. Four weeks after cessation of the treatment, the patient presented to our clinic with complaints of neck pain, fatigue, and hoarseness. There was no history of diarrhea, vomiting, palpitation, weight loss, or heat intolerance. The patient has taken the second dose of CoronaVac® vaccine 2 weeks before visiting our clinic. On physical examination, body weight was 96.6 kg, height 183 cm, body mass index 28.8 kg/m², temperature 36.7°C, respiratory rate 12/minute, and pulse 80/minute. No visible swelling, erythema, or a local rise of temperature on the thyroid gland was observed. Mild tenderness was present on the palpation of the thyroid gland. Oropharyngeal and otological examinations were within normal limits. Examination of the other systems was unremarkable. Thyroid function tests were within normal limits with the exception of slight elevation of free triiodothyronine (fT3) level and inflammatory markers: thyroid-stimulating hormone: 2.45 mIU/L, fT4: 1.14 ng/dL, fT3: 5.32 pg/mL, ESR:17 mm/hour, CRP:13.2 mg/L, anti-thyroid peroxidase (anti-TPO): 106 IU/mL, and anti-thyroglobulin (anti-Tg): 265 IU/mL (Table 1).

Several reports suggest the possibility of association of COVID-19 with glycemic status (in diabetic and non-diabetic subjects) and obesity (2-6). Moreover, many other endocrine complications of SARS-CoV-2 infection, such as adrenal or sex hormone dysregulation or thyroid dysfunction, have been defined (2,7-9). Hashimoto's thyroiditis, Graves' disease, or subacute thyroiditis (SAT) have also been reported in patients after COVID-19 (9,10). High expression of angiotensin-converting enzyme 2 (ACE2) receptors in endocrine organs, including adrenal, pituitary, thyroid glands, and testes, may explain such complications (11-13). SAT is characterized by neck pain which may radiate to the ears, jaw, upper neck, throat, or upper chest. It can result from post-viral inflammatory response associated with coxsackievirus, mumps, measles, adenovirus, as well as with SARS-CoV-2 infection (14,15). Most of the post-covid SAT cases occur ≥14 days after the onset of respiratory symptoms (15). The majority of these patients can be managed successfully with

Apart from post-viral inflammation, SAT has also been associated with various antiviral vaccines such as influenza or hepatitis B vaccines (16-21). With mass vaccination programs running worldwide to reduce the mortality and morbidity in the COVID-19 pandemic, more than 5 billion doses of various types of COVID-19 vaccines have been administered (1). As a result, cases of SAT have also been reported after the COVID-19 vaccination (22-25).

We report a case of a patient who presented with persistent SAT, which developed after administration of inactivated COVID-19 vaccine (CoronaVac®, Sinovac Life Sciences, Beijing, Chinese).

Case Report

glucocorticoid therapy.

A 41-year-old male was referred to the Zonguldak Atatürk State Hospital, Türkiye, with complaints of sore throat and neck pain for 1 week. There were no complaints of diarrhea, nausea, vomiting, palpitation, tremor, weight loss, or heat intolerance. His past medical history was remarkable for ulcerative colitis and asthma. He had a history of avascular necrosis of the hip, for which he underwent surgery 2 years ago. He had

Persistent Subacute Thyroiditis After SARS-CoV-2 Vaccine

Laboratory	Previous	First referral	First control	Second referral	Follow-up
parameters	(2 years before referral)	(0 th day)	(14 th day)	(45 th day)	(97 th day)
ESR (0-20 mm/hour)	NA	38	27	17	3
CRP (0-8 mg/L)	NA	7.8	8.1	13.2	4.4
WBC (3,600-10,200/mm	n ³) NA	6,160	7,000	6,400	6,300
PMNL (43.5-73.5%)	NA	61.4	56.4	60.2	53
TSH (0.27-4.20 mIU/L)	3.33	2.33	1.66	2.45	30.08
fT4 (0.93-1.70 ng/dL)	1.18	1.34	0.96	1.14	0.87
fT3 (2-4.40 pg/mL)	3.54	NA	NA	5.32	3.36
Anti-TPO (0-75 IU/mL)	NA	NA	NA	106	NA
Anti-Tg (0-150 IU/mL)	NA	NA	NA	265	NA
FBG (70-110 mg/dL)	NA	111	NA	100	89
HbA1c (4-5.7%)	NA	NA	NA	NA	5.4
eGFR (mL/min)	NA	0.94	1.02	105	93
ALT (0-41 U/L)	NA	16	18	12	19
AST (0-40 U/L)	NA	20	19	17	19
COVID-19 PCR	NA	Negative	NA	NA	Negative

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cell; PMNL: Polymorphonuclear leukocyte; TSH: Thyroid-stimulating hormone; fT4: Free thyroxine; fT3: Free triiodothyronine; Anti-TPO: Anti-thyroid peroxidase; Anti-Tg: Anti-thyroglobulin; FBG: Fasting blood glucose; HbA1c: Hemoglobin A_{1C} ; eGFR: Estimated glomerular filtration rate; ALT: Alanine transaminase; AST: Aspartate transaminase; PCR: Polymerase chain reaction; NA: Not available.

On thyroid sonography, diffuse hypoechogenicity and heterogenicity of parenchyma were detected. A hypoechoic, hypovascular, subcapsular area of thyroiditis, with a size of 15.76×17.52×24 mm was detected in the left lobe of the thyroid gland (Figure 1a and 1b).

Based on clinical, laboratory, and sonographic findings, we diagnosed the patient as persistent SAT, which occurred after and was possibly associated with CoronaVac® vaccination. Ibuprofen 1,200 mg per day was prescribed. Due to mild symptoms and past medical history of avascular necrosis, glucocorticoid was not given.

The patient was re-evaluated after approximately 7 weeks. He has stopped taking ibuprofen after 4 weeks of treatment. The clinical findings, such as pain and tenderness, have been resolved. But the patient complained of fatigue, cold intolerance, weight gain (5 kg), and dry skin for 2-3

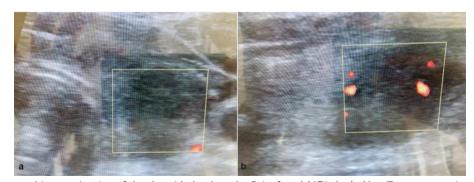


Figure 1. Sonographic examination of the thyroid gland on the 2nd referral (45th day), (**1a**: Transverse axis on the left side; **1b**: Longitudinal axis on the right side) demonstrated hypoechoic, hypovascular, subcapsular area of thyroiditis in the left lobe of the thyroid gland.

weeks. Sonographic examination revealed a reduction in the size of the subcapsular area of thyroiditis in the left lobe of the thyroid gland (Figure 2a and 2b). Laboratory evaluation showed the regression of inflammatory markers and overt primary hypothyroidism (Table 1). Oral levothyroxine was given with a gradually increasing dose: 50 mcg/day for 3 days, followed by 75 mcg/day for 3 days, and then 100 mcg/day. The patient was scheduled for re-evaluation after 4 weeks. For this case report, written consent was obtained from the Ministry of Health of Türkiye.

Discussion

Our report presents a case of persistent SAT, which was diagnosed after the first dose of CoronaVac® vaccine administration, and persisted after the second dose as well. SAT, also known as De Quervain's thyroiditis, is characterized by post-viral inflammatory disorder developing after upper respiratory tract infections (26,27). Typical clinical symptoms and signs, such as pain, increase in inflammatory markers, and sonographic findings, may aid diagnosis. Symptoms of thyrotoxicosis may also accompany the clinical picture. COVID-19 infection has been reported to be associated with several types of thyroid dysfunction, such as Hashimoto's thyroiditis or Graves' disease (10). It was demonstrated that ACE2 and transmembrane serine protease 2 expression in the thyroid gland might be responsible for thyroid involvement in COVID-19 infection (11,13). Recently, SAT has also been shown to develop after COVID-19 infection (9,28-32). There is some evidence regarding the development of SAT after antiviral vaccines also (16-21). A few case reports have demonstrated an association between SAT and inactivated, vectored, and mRNA vaccines developed against COVID-19 infection (22-25).

Massive vaccination drives have been carried out worldwide against COVID-19 (1). In Türkiye, vaccination was started in early 2021, initially in health care workers and the elderly population, and subsequently in other age groups (33). The first available vaccine was CoronaVac®, and later, other types of vaccines, such as the mRNA vaccine, were introduced. Turkish citizens were given a chance to choose one of these vaccines. Our patient opted for CoronaVac®.

A case of SAT has been reported from Türkiye where the disease manifested after the 2nd dose of the CoronaVac® vaccine in an elderly patient with no history of COVID-19 infection (22). Our patient had suffered a COVID-19 infection 8 months ago. Hence, it may raise a doubt whether the development of SAT in this patient resulted from COVID-19 infection or not. Although it is known that classically SAT occurs 2-8 weeks after an episode of upper respiratory tract infection, recent research has shown that SAT can develop 3-5 weeks after COVID-19 infection (28,34,35). Moreover, the PCR test for COVID-19 was negative in our patient both at the time of the first consultation and on follow-up. Based on these findings, we can exclude the possibility of association of SAT with prior COVID-19 infection, and we propose that the viral antigens in the vaccine triggered SAT in the present case.

SAT is usually treated with nonsteroidal antiinflammatory drugs and/or glucocorticoids, and sometimes a beta-blocker is added to relieve the symptoms of thyrotoxicosis (26). These medications also decrease the symp-

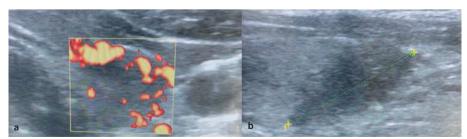


Figure 2. Sonographic examination of the thyroid gland on follow-up (97th day), (2a: Transverse axis on the left side; 2b: Longitudinal axis on the right side) demonstrated a small decrease in the size of the area of thyroiditis in the left lobe of the thyroid gland.

toms of SAT developing after COVID-19 infection (28). Ibuprofen, paracetamol, and methylprednisolone are also known to be effective in the symptomatic treatment of SAT associated with the COVID-19 vaccines (22-24). The patient was successfully treated with methylprednisolone in the first referral and with ibuprofen in the second referral. Owing to the history of avascular necrosis of the hip, beta-blocker therapy was not added to the treatment. Our case did not show clinical signs or laboratory findings suggestive of thyrotoxicosis despite a mild elevation of fT3 level in the second visit.

Previous case reports have verified that SAT can develop in the first or second week after the COVID-19 vaccination (22,24,36). In our patient, SAT occurred 1 week after the first dose of the vaccine, and he presented with persistent SAT 2 weeks after the second dose of the vaccine. Symptoms of SAT developing after the COVID-19 vaccination appear to be similar to the SAT resulting from other antiviral vaccines (24). Recurrence of SAT after its first episode can manifest both in the short-term and long-term, as presented in earlier studies (37). Recurrence can be attributed to a relatively short course of glucocorticoid therapy used in treatment (38). Although in our patient there was the persistence of clinical signs and symptoms rather than recurrence, we assume premature cessation of glucocorticoid therapy after the first episode of SAT could be responsible for this persistence.

Most of the laboratory and radiological findings in the present case (elevated inflammatory markers, hypoechoic areas on sonography) were similar to those published in previous reports on post-viral SAT or SAT developing after COVID-19 infection or the COVID-19 vaccination (22-25,28). However, contrary to the earlier studies, neither subclinical nor overt thyrotoxicosis developed in our case, albeit mild elevation of fT3 level was observed at the second patient visit. Thyroid autoantibodies might be positive in some patients with SAT (39,40). But several studies suggest that thyroid autoantibodies may be negative in most cases of SAT developing after administration of CoronaVac® or vectored vaccine (22-24,36). Though anti-TPO and anti-Tg were positive in our patient, it may be attributed to the persistence of SAT or the absence of thyrotoxicosis in this case. Overt primary hypothyroidism was detected 8 weeks after the second visit in our patient, which was treated with levothyroxine. Although, Saygili et al. has reported the development of overt primary hypothyroidism in a patient after resolution of SAT associated with inactivated COVID-19 vaccine despite negative thyroid autoantibodies (36). We attribute hypothyroidism in our patient to be associated with positive thyroid autoantibodies. In most reports, analyzing SAT associated with the COVID-19 vaccination, the patient was not either followed-up long enough to develop hypothyroidism or did not develop hypothyroidism, or an initial hypothyroid phase was followed by euthyroid state (22-24).

Several mechanisms have been proposed regarding the development of SAT after the COVID-19 vaccination (22,24). Aluminum hydroxide adjuvant in CoronaVac®, cross-reaction of SARS-CoV-2 proteins in inactivated as well as other vaccines with thyroid antigens, and genetic predisposition may exthe occurrence of SAT administration of these vaccines to some extent. Autoimmune thyroid disease may be another possible mechanism since our patient demonstrated the presence of thyroid autoantibodies.

In the future, further cases of SAT associated with either COVID-19 infection or its vaccines may emerge. Comparative studies analyzing clinical and laboratory features of such patients and patients with SAT associated with typical viral respiratory tract infections would reveal more comprehensive information about the course of the disease. In conclusion, antiviral vaccines may lead to the development of SAT. Therefore, the clinicians need to be vigilant of the possibility of SAT in the patients receiving various types of antiviral vaccines, including those against COVID-19 infection. Although the mechanism of SAT developing post-COVID-19 vaccination may be distinct from the one not associated with COVID-19 infection or its vaccination, clinical findings and treatment appear to be indistinguishable.

Authorship Contributions

All authors contributed equally while this study preparing.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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