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

Özür

Keywords: Subacute thyroiditis; COVID-19 vaccines; COVID-19

Anahtar kelimeler: Subakut tiroidit; COVID-19 aşısı; 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.

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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 glucocorticoid therapy. 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

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 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 C-reactive 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, hypoechochogenicity, 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 clinical 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, nausea, vomiting, palpitation, tremor, 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).
On thyroid sonography, diffuse hypoechogenicity and heterogeneity 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

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**Table 1. Laboratory parameters of the patient.**

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Previous (2 years before referral)</th>
<th>First referral (0th day)</th>
<th>First control (14th day)</th>
<th>Second referral (45th day)</th>
<th>Follow-up (97th day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (0-20 mm/hour)</td>
<td>NA</td>
<td>38</td>
<td>27</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>CRP (0-8 mg/L)</td>
<td>NA</td>
<td>7.8</td>
<td>8.1</td>
<td>13.2</td>
<td>4.4</td>
</tr>
<tr>
<td>WBC (3,600-10,200/mm³)</td>
<td>NA</td>
<td>6,160</td>
<td>7,000</td>
<td>6,400</td>
<td>6,300</td>
</tr>
<tr>
<td>PMNL (43.5-73.5%)</td>
<td>NA</td>
<td>61.4</td>
<td>56.4</td>
<td>60.2</td>
<td>53</td>
</tr>
<tr>
<td>TSH (0.27-4.20 mIU/L)</td>
<td>3.33</td>
<td>2.33</td>
<td>1.66</td>
<td>2.45</td>
<td>30.08</td>
</tr>
<tr>
<td>FT4 (0.93-1.70 ng/dL)</td>
<td>1.18</td>
<td>1.34</td>
<td>0.96</td>
<td>1.14</td>
<td>0.87</td>
</tr>
<tr>
<td>FT3 (2-4.40 pg/mL)</td>
<td>3.54</td>
<td>NA</td>
<td>NA</td>
<td>5.32</td>
<td>3.36</td>
</tr>
<tr>
<td>Anti-TPO (0-75 IU/mL)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>106</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Tg (0-150 IU/mL)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>265</td>
<td>NA</td>
</tr>
<tr>
<td>FBG (70-110 mg/dL)</td>
<td>NA</td>
<td>111</td>
<td>NA</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>HbA1c (4-5.7%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.4</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>NA</td>
<td>0.94</td>
<td>1.02</td>
<td>105</td>
<td>93</td>
</tr>
<tr>
<td>ALT (0-41 U/L)</td>
<td>NA</td>
<td>16</td>
<td>18</td>
<td>12</td>
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</tr>
<tr>
<td>AST (0-40 U/L)</td>
<td>NA</td>
<td>20</td>
<td>19</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>COVID-19 PCR</td>
<td>NA</td>
<td>Negative</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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 A1c; eGFR: Estimated glomerular filtration rate; ALT: Alanine transaminase; AST: Aspartate transaminase; PCR: Polymerase chain reaction; NA: Not available.

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**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 anti-inflammatory drugs and/or glucocorticoids, and sometimes a beta-blocker is added to relieve the symptoms of thyrotoxicosis (26). These medications also decrease the symp-
Symptoms 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 used in treatment (38). 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 explain the occurrence of SAT after 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.
Source of Finance

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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