Case Report
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Subacute Thyroiditis Secondary to SARS-CoV-2 Infection; Case Studies from Turkey

SARS-CoV-2 Enfeksiyonuna Sekonder Gelişen Subakut Tiroidit; Türkiye'den Vaka Serisi

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Abstract

Coronavirus disease-2019 (COVID-19) has infected more than 100 million people globally, with the pandemic still showing a quick increase in number. We reported five new cases in Turkey, where subacute thyroiditis was developed after the COVID-19 infection. Our study included three females and two male patients aged between 27 and 51 with a mean age of 39. Out of the five, four patients had a mild COVID-19 infection, and one patient had mild COVID-19 pneumonia. After 18-25 days of the disappearance of COVID-19 symptoms, subacute thyroiditis was developed in patients. Laboratory tests such as thyroid hormones and, especially, free thyroxin showed high levels while the thyroid-stimulating hormone was found to be low. The thyroid-stimulating hormone receptor antibody, anti-thyroid peroxidase, and anti-thyroglobulin antibodies were negative in all patients while the inflammatory markers were high. Thyroid ultrasound showed diffuse hypoechoic areas and diffused enlargement. There was no iodine uptake observed in the thyroid scintigraphy. The patients were diagnosed with subacute thyroiditis and prescribed oral prednisolone therapy. After a few days of starting the treatment, symptoms disappeared in all patients, and after four weeks of the onset of subacute thyroiditis symptoms, inflammatory markers turned to normal range in all patients. Therefore, physicians should consider subacute thyroiditis in the differential diagnosis of thyroid dysfunction during and after COVID-19 infection.

Keywords: Thyroid; COVID-19; subacute thyroiditis

Özet

Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] dünya çapında 100 milyondan fazla insanı enfekte etti ve bu pandemi süreci hâlâ hızla artıyor. COVID-19 enfeksiyonu sonrası gelişen 5 yeni subakut tiroidit olgusunu Türkiye'den sunuyoruz. Hastaların 3'ü kadın iken 2'si erkekti. Hastalar, 27-51 yaş aralığındaydı ve ortalama yaşı 39'du. Hastalardan 4'ünde hafif COVID-19 enfeksiyonu, 1'inde COVID-19 pnömonisi mevcuttu. COVID-19 hastalığının semptomlarının geçmesinden 18-25 gün sonra hastalarda subakut tiroidit semptomları başlamıştı. Laboratuvar testleri değerlendirildiğinde, tiroid hormonları, özellikle serbest tiroksin değeri yüksekti, tiroid stimülen hormon ise düşük bulundu. Tiroid stimülen hormon reseptör antikoru, antitiroid peroksidaz antikoru ve antitiroglobulin antikoru tüm hastalarda negatif saptandı. İnflamatuar belirteçler ise yüksek saptandı. Hastalara yapılan tiroid ultrasonunda yaygın hipoekoik alanlar ve diffüz büyüme saptandı. Tüm hastaların tiroid sintigrafisinde iyot tutulumu saptanmadı. Hastalara subakut tiroidit tanısı konuldu ve oral prednizolon tedavisi başlandı. Tedaviye başladıktan birkaç gün sonra tüm hastalarda semptomlar kayboldu. Subakut tiroidit semptomlarının başlamasından 4 hafta sonra, tüm hastalarda inflamatuar belirteçler normal aralığa döndü. Sonuç olarak, doktorlar COVID-19 enfeksiyonu sırasında ve sonrasında tiroid disfonksiyonunun ayırıcı tanısında subakut tiroiditi dikkate almalıdır.

Anahtar kelimeler: Tiroid; COVID-19; subakut tiroidit

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Introduction

Subacute thyroiditis (SAT) is a self-limiting inflammatory thyroid disease presented by thyroid dysfunction, fever, and neck pain (1). SAT usually develops after the occurrence of viral upper respiratory tract infection. A lot of viruses have been responsible for it, such as coxsackie, influenza, adenovirus, and less frequently cytomegalovirus, and Epstein-Barr virus (2). Coronavirus disease-2019 (COVID-19) has infected more than 100 million people globally, with the pandemic still quickly increasing. There have been reports of ten cases of SAT secondary to COVID-19 infection (3-9), and we have reported five new cases of SAT in Turkey that developed after a COVID-19 infection.

Case Reports

Case 1

On August 1, a 51 years old female patient was presented with odynophagia, myalgia, and anosmia. However, the patient did not complain about the upper respiratory tract. A nasopharyngeal swab test for COVID-19 was positive and symptomatic treatment was prescribed for the slight disease, which completely resolved in the next few days. After 18 days of her first presentation, the patient complained of fatigue, strong neck pain spreading to the right jaw and ear. Laboratory tests demonstrated a high erythrocyte sedimentation rate (ESR) of 52 mm/hr and c reactive protein (CRP) of 36 mg/L. The thyroid tests were compatible with thyrotoxicosis with the thyroid-stimulating hormone (TSH) showing a value of 0.11 U/L (0.3-4.2), free T4 (FT4) was 2.21 ng/dL (0.89-1.76), and free T3 (FT3) was 4.19 pg/mL (2.3-4.2). The anti-thyroid thyroglobulin (Anti Tg) was found to be 27 IU/mL (0-111), while the anti-thyroid peroxidase (Anti TPO) was found to be 14 IU/mL (0-34), and thyroid-stimulating hormone receptor antibody (TSI) was <0.1 IU/L (<0.1). The thyroid ultrasound demonstrated a widely enlarged and hypoechogenic thyroid gland. No iodine uptake was observed in thyroid scintigraphy. The patient was diagnosed with SAT, and nonsteroidal anti-inflammatory (NSAI) therapy was initiated. Although NSAI therapy was used for ten days, the patient's complaints did not disappear. Hence, oral prednisolone treatment was started in the patient (a beginning dose of 40 mg/day was used with gradual tapering of the dose). After the corticosteroid therapy, the symptoms and signs of the patients showed rapid improvement. After six weeks of starting steroid therapy, all thyroid function tests returned to normal.

Case 2

On July 28, a 39 years old male patient was presented with mild fever, cough, and dyspnea. A nasopharyngeal swab test for COVID-19 was found to be positive, and the chest high-resolution computed tomography demonstrated bilateral ground-glass areas specific for COVID-19 associated with interstitial pneumonia. Medical treatment was performed with hydroxychloroquine, favipiravir, and nasal oxygen therapy during the hospitalization. The swab tests for COVID-19 taken on the tenth and eleventh days of the treatment were found to be negative, and the patient was discharged. After 22 days of his initial presentation, the patient was presented with palpitations, tachycardia, sweating, and neck pain. Laboratory tests demonstrated a high ESR of 72 mm/hr and CRP of 48 mg/L. The thyroid tests were compatible with thyrotoxicosis showing the value of TSH as 0.05 U/L (0.3-4.2), FT4 as 2.89 ng/dL (0.89-1.76), and FT3 as 4.75 pg/mL (2.3-4.2). The anti-Tg was found to be 48 IU/mL (0-111), anti-TPO was 2.53 IU/mL (0-34), and TSI was <0.1 IU/L (<0.1). The thyroid ultrasound demonstrated multiple diffuse hypoechoic areas with no iodine uptake observed in thyroid scintigraphy. He was diagnosed with SAT and prescribed NSAI therapy. Since symptoms and signs did not improve after NSAI treatment, oral prednisolone treatment was started. After four weeks of starting the steroid therapy, the patient's complaints were resolved, and thyroid function tests returned to normal.

Case 3

On July 26, a 31 years old female patient was presented with a slight upper respiratory tract infection. A nasopharyngeal swab test for COVID-19 was found to be positive and symptomatic treatment was prescribed for the slight disease, which completely re-

solved in the next few days. However, after 25 days of her first presentation, the patient complained of palpitations, fever (38.5 C), fatigue, and strong neck pain spreading to the right jaw. Laboratory tests demonstrated high ESR (42 mm/hr) and CRP (12 mg/L) values, and the thyroid tests were compatible with thyrotoxicosis with TSH showing a value of 0.06 U/L (0.3-4.2), FT4 was 2.35 ng/dL (0.89-1.76), and FT3 was 4.28 pg/mL (2.3-4.2). The anti-Tg was found to be 18.6 IU/mL (0-111), anti-TPO was 18.6 IU/mL (0-34), and TSI was <0.1 IU/L (<0.1). Thyroid ultrasound demonstrated a widely enlarged and hypoechogenic thyroid gland with no iodine uptake observed in thyroid scintigraphy. SAT was diagnosed, and NSAI treatment was prescribed. One week later, the patient was presented again as the complaints continued. Oral prednisolone treatment was given to the patient (a beginning dose of 40 mg/day was given with gradual tapering of the dose). After the corticosteroid therapy, the symptoms and signs showed rapid improvements. After five weeks of starting the steroid therapy, all the thyroid function tests returned to normal.

Case 4

On September 25, a 27 years old female patient was presented with myalgia, weakness, and fever. A nasopharyngeal swab test for COVID-19 was found to be positive and symptomatic treatment was prescribed for the slight disease, which completely resolved in the next few days. The swab tests for COVID-19 taken on the tenth and eleventh days were found to be negative. After 20 days of her first presentation, the patient was again presented with fatigue and anterior neck pain. Laboratory tests demonstrated high ESR (27 mm/hr) and CRP (13.9 mg/L) values while the thyroid tests were compatible with thyrotoxicosis showing values of TSH as 0.21 U/L (0.3-4.2), FT4 was 2.13 ng/dL (0.89-1.76), and FT3 was 4.48 pg/mL (2.3-4.2). The anti-Tg value was found to be 21 IU/mL (0-111), while anti-TPO was 7.5 IU/mL (0-34), and TSI was <0.1 IU/L (<0.1). Further, a thyroid ultrasound was performed, showing multiple hypoechoic areas with no iodine uptake observed in the thyroid scintigraphy. Later, the patient was diagnosed with SAT and prescribed NSAI therapy. Since the patient's complaints continued even after the NSAI treatment, the oral steroid treatment was started. After five weeks of starting the steroid treatment, all of the patient's complaints resolved, with thyroid function tests returning to normal.

Case 5

On September 30, a 47 years old male patient was presented with mild fever, myalgia, and cough. A nasopharyngeal swab test for COVID-19 was positive, while the chest high-resolution computed tomography was normal. Medical treatment was performed with hydroxychloroquine. The swab tests for COVID-19 taken on the ninth and tenth days of the treatment were found to be negative. However, after 24 days of the initial presentation, the patient was presented with tachycardia, mild fever, and neck pain. Laboratory tests demonstrated high ESR (50 mm/hr) and CRP (46.7 mg/L) values while the thyroid tests were compatible with euthyroid showing a TSH value of 0.39 U/L (0.3-4.2) while FT4 was 1.27 ng/dL (0.89-1.76), and FT3 was 3.45 pg/mL (2.3-4.2). The anti-Tg value was 11 IU/mL (0-111), while anti-TPO was 28 IU/mL (0-34), and TSI was <0.1 IU/L (<0.1). The thyroid ultrasound demonstrated a widely enlarged and hypoechogenic thyroid gland with no iodine uptake observed in thyroid scintigraphy. SAT was diagnosed, and NSAI therapy was prescribed. Since his complaints continued even after the treatment, steroid treatment was also started. After the steroid therapy, the patient's complaints were resolved.

Discussion

SAT etiology and pathogenesis are not fully understood. However, it is a general belief that this disease is caused by a viral infection. The most commonly associated viruses with the disease include coxsackie, influenza, adenovirus, or less frequently cytomegalovirus and Epstein-Barr virus (1, 2). Autopsy studies have been conducted during the 2002 epidemic showing thyroid damage in patients with COVID-19 infection (10), and since then, the incidence of SAT associated with COVID-19 appears to be in-

creasing (3-9). The receptor-binding domains of COVID-19 are recognized by the human angiotensin-converting enzyme-2 receptor (ACE-2-R) (11). Apart from the lungs, the gene expression profiling revealed high expression of ACE-2-R in the thyroid and other tissues, suggesting possible COVID-19 infection of the thyroid (12). The incidence of SAT is 4.9 cases/100,000 people in a year with a mean age of 46 years and a female to male ratio of 3.5:1 (13). The first symptom of SAT is neck pain, often radiating to the upper neck. Upon palpation, the thyroid is found to be enlarged, sensitive, and painful. In the thyroid tests, acute phase thyrotoxicosis is observed, followed by euthyroidism, hypothyroidism, and normalization of thyroid function within three months (1). Though the diagnosis of SAT is often based on clinical grounds, laboratory tests and neck imaging are helpful (14), with a significant increase in inflammatory markers also being common. In the early phase of the disease, high levels of free T4 and T3 are detected with low concentrations of TSH. TSI is usually absent, whereas anti-TPO Ab and anti-Tg Ab are positive in some patients. Thyroid ultrasound shows bilateral, diffuse, or focally hypoechogenic areas associated. The radioiodine study shows low radionuclide uptake. The clinical course of SAT is usually mild and self-limiting, but in severe cases, steroids or NSAI drugs are also used in the treatment (13).

In the review of literature, ten SAT cases (7 cases from Italy, 1 case from Mexico, 1 case from the Philippines, and 1 case from Turkey) were reported to be developed after the COVID-19 infection. In this article, we reported five cases in Turkey with the development of SAT after the COVID-19 infection.

We included three females and two males, aged between 27 and 51, with a mean age of 39 (Table 1). All the reported cases in the literature were women between the ages of 18 and 69, and the mean age was 39.7 (3-9). Generally, the cases that developed SAT after COVID-19 were mostly women (Female/Male: 15/2) in middle age.

Four of our patients had mild COVID-19 infection, and one patient had mild COVID-19 pneumonia. Nine out of ten previously reported cases showed mild COVID-19 infection, while one case displayed pneumonia (3-9). The possibility of developing SAT after COVID-19 infection may be higher in the mild cases of COVID-19.

SAT developed in patients after 18-25 days of the disappearance of COVID-19 symptoms (Table 1). In previously reported cases of SAT, the time between the diagnosis of COVID-19 and the onset of symptoms ranged between 5 and 36 days (3-9). It is indicated that SAT is observed after the first six weeks of the COVID-19 infection.

Laboratory tests such as thyroid hormones and, especially, the free thyroxin were found to be high, while the TSH was found to be low in four of our patients. In our fifth patient, thyroid hormones were within the normal limits. In the early stages of subacute thyroiditis, thyroid hormones may be normal. Also, TSI, anti-TPO, and anti-Tg antibodies were found to be negative in all patients. Typical for SAT, inflammatory markers were elevated in all the patients. The thyroid ultrasound showed multiple diffuse hypoechoic areas, while the thyroid scintigraphy showed no iodine uptake, consistent with the acute phase of the SAT (Table 1).

Our patients were diagnosed with SAT and were prescribed 40 mg/day oral prednisone therapy. Symptoms disappeared in all patients after one week of starting the treatment. Four weeks after the onset of SAT symptoms, inflammatory markers returned to normal range in all patients.

We recommend a routine evaluation of thyroid function in patients with COVID-19 since SAT associated with COVID-19 may develop later on. As a result, physicians should consider SAT in the differential diagnosis of thyroid dysfunction during and after COVID-19 infection.

Compliance with Ethical Standards

Ethical Approval All procedures performed during this retrospective study were following the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical committee approval is not required for case reports.

Informed Consent Signed consent was obtai

Table 1. Biochemical and imaging results of the patients.

	CASE-1	CASE-2	CASE-3	CASE-4	CASE-5
Year	51	39	31	27	47
Gender	F	M	F	F	M
Pre-COVID thyroid functions	TSH: 1.81	TSH: 2.41	TSH: 0.99	TSH: 1.43	TSH: 2.08
Time from COVID to sat	18	22	25	20	24
COVID symptoms	Mild	Mild pneumonia	Mild	Mild	Mild
ESR(mm/hr)	52	72	42	27	50
CRP					
(<0.5 mg/L)	36	48	12	13.9	46.7
TSH					
(0.3-4.2 U/L)	0.11	0.05	0.06	0.21	0.39
FT4					
(0.89-1.76 g/dL)	2.21	2.89	2.35	2.13	1.27
FT3					
(2.3-4.2 pg/mL)	4.19	4.79	4.28	4.48	3.45
ANTI-TPO					
(0-34 U/mL)	14	2.53	18.6	7.5	28
ANTI-TG (0-111 U/mL)	27	48	18	21	11
TSI(<0.1 IU/L)	0.1	0.1	0.1	0.1	0.1
US	diffusely enlarged and hypoechogenic thyroid	multiple, diffuse hypoechoic areas	multiple hypoechoic areas	multiple hypoechoic areas	multiple, diffuse hypoechoic areas

ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; TSH: Thyroid-stimulating hormone; Anti TPO: Anti-thyroid peroxidase; Anti TG: Anti-thyroid thyroglobulin; TSI: Thyroid-stimulating hormone receptor antibody

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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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