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COVID-19 Pandemisiyle Artış Gösteren Subakut Tiroidit

Subacute Thyroiditis Exacerbated by the COVID-19 Pandemic

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ÖZ

Amaç: Bu çalışmada SARS-CoV-2 virüsü ile subakut tiroidit (SAT) arasındaki etiyolojik ilişkiyi değerlendirmek ve bu iki antitenin benzer klinik özelliklere sahip olabileceğine dikkat çekmek amaçlandı.

Materyal ve Metot: Ülkemizde Coronavirus disease-19 (COVID-19) salgınının 4. ayında; klinik ve laboratuvar özelliklerine göre SAT şüphesi olan 5 hasta boyun ultrasonografi (USG) için kliniğimize sevk edildi. Bu olguların geçmiş tıbbi öyküsü, temas öyküsü ve COVID-19 Polimeraz Zincir Reaksiyonu (PCR) test sonuçları değerlendirildi.

Bulgular: Subfebril ateş, boğaz ağrısı, boğazda yanma hissi, yutma güçlüğü hastaların başvuru semptomlarıydı. Tüm olgularda anormal tiroid hormon değerleri ve yüksek eritrosit sedimantasyon hızı/C-reaktif proteini (CRP) değerleri vardı. USG'de dört hastada tiroid bezi hacmi artmıştı. Belirgin demarkasyon nodülü saptanmayan tüm hastalarda tiroid parankiminde hipovaskülarize heterojen hipoekoik düzensiz alanlar gözlendi. Ultrason elastografisinde parankimal heterojenite ve sertlik saptandı. PCR testi negatif olan olguların düşük doz kontrastsız toraks bilgisayarlı tomografi bulguları (BT) normaldi.

Sonuç: Etiyolojisinde viral ajanlar sıklıkla suçlanan subakut tiroidit SARS-CoV-2 ile de ilişkili olabilir. Subakut tiroidit ve COVID-19 enfeksiyonu arasındaki klinik ve laboratuvar bulgularının benzerliği tanısal zorluklar yaratabilir.

Anahtar Kelimeler: COVID-19, elastografi, SARS-CoV -2, subakut tiroidit, ultrasonografi

ABSTRACT

Objective: It was aimed to evaluate the etiological relationship between the SARS-CoV-2 virus and subacute thyroiditis (SAT). We also wanted to point out the fact that these two entities may have similar clinical features.

Materials and Methods: During the 4th month of the Coronavirus disease-19 (COVID-19) pandemic in our country; five patients were referred to our clinic for neck ultrasonography (USG) with a suspected diagnosis of SAT based on clinical and laboratory features. Past medical history, contact history, and COVID-19 Polyerase Chain Reaction (PCR) test results of these cases were evaluated.

Results: Subfebrile fever, sore throat, burning sensation in the throat, difficulty in swallowing were the presenting symptoms of the patients. All cases had abnormal thyroid hormone values and elevated erythrocyte sedimentation rate/C-Reactive Protein (CRP) values. USG showed increased thyroid gland volume in four patients. Hypovascularized heterogeneous hypoechoic patchy areas in thyroid parenchyma were observed in all patients without discrete nodules. Ultrasound elastography revealed parenchymal heterogeneity and stiffness. Low-dose non-contrast chest computerized tomography (CT) findings was normal with negative Polymerase chain reaction (PCR) test results in patients.

Conclusion: Subacute thyroiditis, which is often accused by viral agents in etiology, may also be associated with SARS-CoV-2. The similarity of clinical and laboratory findings between subacute thyroiditis and COVID-19 infection may pose diagnostic challenges.

Keywords: COVID-19, elastography, SARS-CoV-2, subacute thyroiditis, ultrasonography

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INTRODUCTION

Subacute thyroiditis (SAT) is a rare, self-limiting clinical condition that usually occurs after viral infections, and the etiology is unknown in the majority of cases.[1,2] It is more common in women and in the 40-50 age range.[2,3] The common presenting symptoms are fever, weakness, sore throat extending to the ear and jaw, painful swelling in the neck.[2] On physical examination, tenderness and warmth can be detected during neck palpation. In the acute period, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values are generally elevated high secondary to inflammation. SAT generally shows the triphasic fluctuation in thyroid hormone values as hyperthyroidism, hypothyroidism, and euthyroidism. Although most of these cases become euthyroid, permanent hypothyroidism may occur in the long term in a small number of cases.[4]

Although the diagnosis of SAT is usually based on clinical and laboratory findings, ultrasonography (USG) is frequently used in routine practice as a supportive diagnostic method.[5,6] Grayscale ultrasonography findings include increased thyroid gland size with heterogeneous, hypoechoic, nodular-patchy areas with decreased vascularization on Doppler sonography.[4,7] Elastography shows markedly elevated stiffness with heterogeneous parenchymal color-coding, with elasticity values typically higher than thyroid malignancies.[8] Treatment is often symptomatic and is based on the disease stage. Analgesic and anti-inflammatory medication usually alleviate patient symptoms while beta-blockers can be used for thyrotoxicosis findings.[9]

Although the etiology of subacute thyroiditis is not fully understood, it is the most accepted view is that viral agents activate the immune system, causing autoimmune reactions after a certain latent period and destroying the thyroid glands with these antibodies. Like other viral agents, the SARS-CoV-2 virus, which can cause multisystem and multiorgan involvement and exacerbate the immune system, causing intense cytokine release (cytokine storm), is very likely to cause autoimmune events and affect the thyroid gland in this way. This may then cause the activation of autoimmune diseases such as subacute thyroiditis. It is also possible for a condition of essentially autoimmune origin to arise, such as subacute thyroiditis.[10-14]

In this study, we aimed to highlight that SARS-CoV -2 may play a role in the etiology of subacute thyroiditis, which usually manifests clinically within a few weeks to months following upper respiratory tract infection or other viral infections. We also wanted to emphasize that SAT should be kept in mind in the clinical differential diagnosis of COVID-19 during the pandemic period.

MATERIALS AND METHODS

This study was performed by the Acıbadem University Medical Research Ethics Committee (Date: 06.08.2020, decision no: 2020/17), and verbal informed consent form was obtained from all patients. This study was conducted according to the World Medical Association Declaration of Helsinki.

Patients who underwent neck USG with a prediagnosis of SAT in our clinic between June 14 and July 14, 2020 were included in the study. Clinical findings of the patients (fever, dry cough, sore throat, difficulty in swallowing, neck sensitivity, palpitations, tremor, irritability, sleep disorders, appetite disorders), laboratory findings [hemoglobin (Hb), hematocrit (Htc), leukocyte, neutrophil, lymphocyte, neutrophil/lymphocyte ratio (N/L), CRP, ESR], thyroid hormone panel [TSH, fT3, fT4, anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg) antibodies] were recorded. Grayscale and Doppler sonography features [volume, parenchymal heterogeneity, nodule, perithyroidal lymph node, vascularization] with elastography features [parenchymal heterogeneity, Vmean, Vmax, velocity standard deviation (VSD)] were evaluated on USG. The clinical history and relevant lab/imaging findings of these cases were evaluated in terms of COVID-19 [history of contact, clinical findings, chest x-ray, chest computed tomography (CT) examination, PCR].

All sonographic and elastographic examinations were performed with the same device (General Electric Healthcare 2016, LOGIQ S8, XDclear) by the same radiologist. The ML6-15 probe was used for grayscale, and the 9L probe for elastography. Reference values of thyroid volumes were based on the study by Seker et al.[15] (13 ± 6.27 ml). Gland vascularization was evaluated with the color Doppler feature of the device. For shear wave elastography (SWE), 2D shear software from the same device was used. The probe was placed with a gel pad precisely in the neck area, without any pressure on the skin during measurements. The patients were asked to hold their breath for 5 seconds during elastography. After the SWE stabilized, the sample box was placed in the middle of the hypoechoic areas. The region of interest (ROI) area was standardized not to exceed 0.5 cm^2 and measurements were taken from the middle of the heterogeneous area in the sample box. The Vmean, Vmax, and VSD values were automatically calculated in m/s and recorded by the device. Elastographical evaluations and measurements were made separately for both lobes.

Statistical Analysis: SPSS 21 (SPSS Inc., IBM company, Chicago) program was used for statistical analysis. Descriptive data were presented as mean, standard deviation, minimum and maximum values, frequency and ratio. As the overall number of cases

was relatively small, no inferential statistical analysis was undertaken.

RESULTS

Five patients were included in the study. All cases were female with a mean age of 46±12.68 (29-61y). All patients had subfebrile fever, tenderness in the neck, and difficulty in swallowing at the time of admission. The demographic and clinical characteristics of the cases are shown in Table 1.

The CRP and ESR values were elevated in all cases and the N/L rates were high in two cases. In three cases, there was a significant decrease in TSH value with high fT3 and fT4 values. TSH was high in one case, although fT3 and fT4 values were normal. In the other case, all values including TSH were normal. Details of the laboratory features of the cases are shown in Table 2.

Table 1. Demographic data and clinical symptoms of patients.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Age	39	29	55	46	61
Gender	F	F	F	F	F
Comorbidity	-	-	Breast cancer	-	-
Smoking	-	-	-	-	-
COVID-19 contact history	+	-	-	+	-
PA chest X-ray, Thorax CT	(no feature)			(no feature)	-
rRT-PCR	Negative	-	-	Negative	-
Fever	+	+	+	+	+
Cough	+	+	-	+	-
Sore throat	+	+	+	+	+
Difficulty in swallowing	+	+	+	+	+
Fullness in the throat	+	-	+	+	+
Tremor	+	-	+	-	+
Palpitation	+	-	+	-	+
Sleeping disorders	+	-	-	-	+
Duration of symptoms (day)	25	35	45	40	20

COVID-19, coronavirus disease 2019; CT, Computed tomography; PA, Posterior anterior; rRT-PCR, real-time reverse-transcriptase polymerase chain reaction.

Table 2. Laboratory values and thyroid hormone panel of the cases.

	Reference values	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Casa 5**
Hemoglobin (g/dL)	11.9 - 14.9	10.9	13.4	9.6	11.4	-
Hematocrit (%)	35.5 - 44.2	32.7	37.5	29.5	35.1	-
Leukocyte (x10^3/uL)	4.06 - 10.6	8.35	5.88	10.69	7.63	-
Neutrophil (x10^3/uL)	1.9 - 7.0	6.56	3.2	8.67	5.1	-
Lymphocyte (x10^3/uL)	1.3 - 3.76	1.07	1.81	1.29	1.77	-
N/L ratio	<3.13	6.15	1.77	6.72	2.88	-
C-reactive protein (mg/dL)	<0.50	9.75	11.2	36	2.47	-
ESR (mm/sa)	<20	80	91	122	41	101
TSH (uIU/mL)	0.25 - 4.55	0.017	9.52	0.015	1.21	0.06
FT3 (pmol/L)	3.5 - 6.5	11.6	5.63	9.76	3.97	7.11
FT4 (pmol/L)	11.5 - 22.7	41.48	16.51	35.04	11.97	26.55
Anti-TG (pmol/L)	0 - 60	58.4	417	52.6	33.8	15
Anti-TPO (IU/mL)	0 - 60	22.9	1300	33.7	28	47

N/L, Neutrophil/Lymphocyte; ESR, Erythrocyte sedimentation rate; TSH, Thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase.

Ultrasonography revealed parenchymal heterogeneity in all cases, and increase in thyroid gland volumes in all cases except for a single case (Figure 1a). Within the parenchyma, there were heterogeneous hypoechoic patchy and nodular areas that did not give specific boundaries. There were multiple subcentimetric lymph nodes with a reactive appearance adjacent to the thyroid gland parenchyma in all cases (Figure 1b).

In Doppler sonography, heterogeneous hypoechoic areas were hypovascular in all cases (Figure 2a). In SWE evaluation, heterogeneous color coding and increased velocity values were detected supporting parenchymal heterogeneity and increased stiffness in all patients (Figure 2b).

The average elasticity values were: right lobe Vmean: 2.88±0.37 m/sec, Vmax: 6.53±0.83 m/sec, Vsd: 1.18±0.43; left lobe Vmean: 2.89±0.58 m/sec, Vmax: 6.0±2.67 m/sec, Vsd: 0.97±0.55. Grayscale ultrasonography, Doppler sonography, and shear wave elastography features of cases are shown in Table 3. The cases were questioned retrospectively in terms of clinical complaints, contact history, and PCR results for COVID-19. There was suspicious contact history in two cases (one is a hospital staff). These two cases were assessed for COVID-19 since they had suspicious symptoms in the previous months. Chest radiographs and low-dose non-contrast chest CT were normal. The PCR results of the cases were negative.

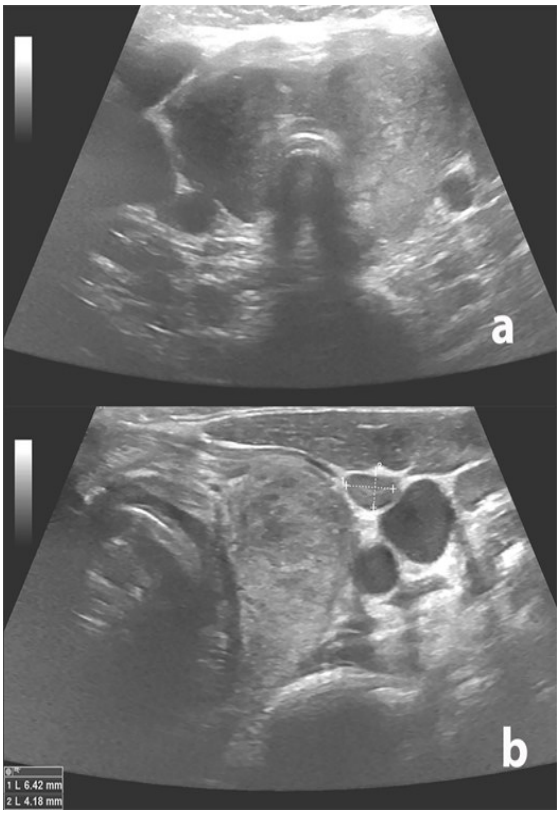

Figure 1. a) Gray scale image of the thyroid gland in subacute thyroiditis; b) Perithyroidal lymphadenopathy.

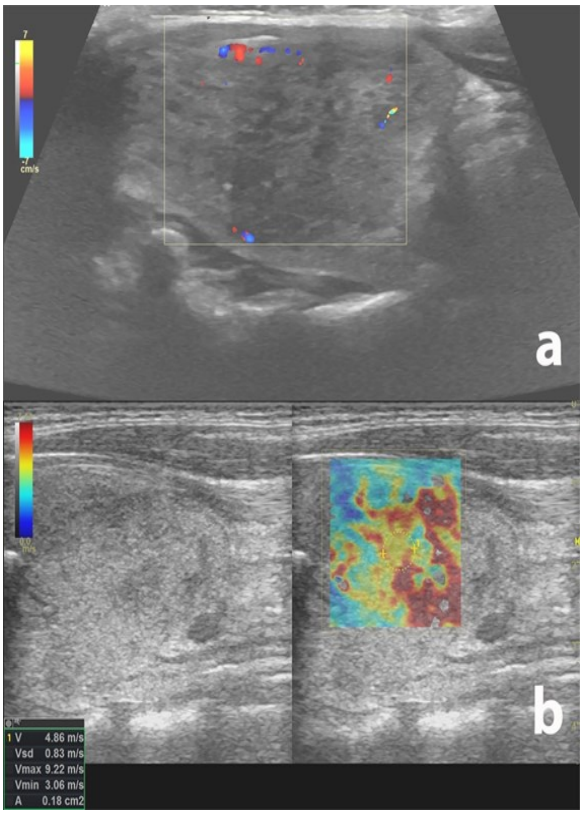

Figure 2. Doppler and elastography examination of the thyroid gland parenchyma. a) Hypovascularity of the same thyroid tissue in color Doppler sonography; b) Parenchymal patchy heterogeneity and increased stiffness in elastographic examination.

Table 3. Grayscale ultrasonography, doppler sonography, and shear wave elastography features of cases.

	Case 1	Case 2	Case 3	Case 4	Case 5
R lobe volume (ml)	10.66	4.8	6.8	8.2	9.2
L lobe volume (ml)	11.24	3.2	14.8	5.7	6.2
Total volume (ml)	21.9	8	21.6	13.9	15.4
Hypovascularization	+	+	+	+	+
Thyroid nodule	-	-	-	-	-
Perithyroidal LN	+	+	+	+	+
SWE	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous
R-Vmean (m/sn)	3.39	2.74	3.07	2.85	2.39
R-Vmax (m/sn)	6.78	6.9	7.45	5.22	6.31
R-VSD	1.15	1.1	1.89	0.69	1.1
L-Vmean (m/sn)	3.45	2.19	3.4	2.38	3.04
L-Vmax (m/sn)	8	2.63	9.25	4.39	5.76
L-VSD	1.45	0.23	1.54	0.62	1.02

LN, lymph node; R, right; L, left; SWE, shear wave elastography; VSD, velocity standard deviation.

DISCUSSION AND CONCLUSION

The SARS-CoV-2 infection that started in China in late 2019 became a global health problem lead to a pandemic in a short amount of time. SARS-CoV-2 started in China in late 2019 and has affected the whole world by causing a pandemic in a short time.[16] The common presenting symptoms of viral infection include patients mainly present with symptoms of upper respiratory tract infection such as fever, dry cough, sore throat, and weakness.[17,18] Previous studies have reported that the virus progresses more severely in immunosuppressive, elderly, and male patients who have comorbid diseases.[16-18] It has higher mortality rates compared to other viral agents, due to severe acute complications such as ARDS, sepsis, and multiorgan failure.[16-18] However, the subacute and late complications of the disease have not been clarified yet.

SAT is a benign clinical condition with unknown etiology that usually occurs within weeks to months after exposure to viral agents especially with upper respiratory tract infections such as influenza, Ebstein Barr virus (EBV), adenovirus, cytomegalovirus (CMV), Coxsackievirus A-B.[1,19] Also, SARS-CoV-2 too, which mainly affects the respiratory tract, The SARS-CoV-2, which also affects the respiratory tract, may cause SAT like other agents that are held responsible for the disease. Two different cases with SAT, who were evaluated in relation to SARS-CoV-2, have been reported in two recent publications.[20,21] This situation caught our attention at a similar time frame. SAT, which is a rare clinical condition, was encountered in five patients in the last month in our clinic. Although the disease is generally known to increase seasonally in the summer following a latent period after exposure to the viral agent, in our clinic, this high frequency for SAT has never been detected in such a short amount of time.[3] The high incidence of SAT during the pandemic suggests that the disease may be associated with SARS-CoV-2. Also, four months have passed since the first case of the virus was detected in our country and this interval is consistent with the latent period of the disease. Although COVID-19 PCR was negative in our cases, it did not affect our suspicion as to the causative etiology of SARS-CoV-2 for SAT. The PCR sensitivity may vary depending on the time of sampling, method of sampling, and the person taking the sample. The false negativity rate can be quite high as 40-70%.[22,23] The fact that no radiological feature in terms of COVID-19 was detected in our cases does not refute our findings as CT may be negative in very early stages of the disease.[23,24] According to the literature, we also know that some patients may have the disease without showing any radiological or clinical findings.[22,25] In addition, considering the average age of our patients, there is a possibility that they underwent the disease asymptomatically.[26,27] Therefore, although our cases did not show any COVID-19 related clinical or radiological findings in the past months, SARS-CoV-2 was a suspected factor in these patients. Similarly, the detection of widespread follicular damage and parenchymal destructions in the thyroid gland in the autopsy series after the SARS pandemic in 2002-2003 strengthens the relationship between SAT and SARS-CoV-2.[28,29] Moreover, many case reports and case series showing the relationship between SARS-CoV-2 and subacute thyroiditis have been published in the literature so far [10-14]. This relationship is so strong that there are cases that develop subacute thyroiditis even after vaccination.[30] The most common symptoms in subacute thyroiditis cases developing after COVID-19 is fever and sore throat (81%) as in other agents[11] Therefore, it is difficult to diagnose SARS-CoV-2-associated subacute thyroiditis based on symptoms

alone. In this case, it should be considered in patients with recent COVID-19 infection, those with a history of contact with people diagnosed with COVID-19, and those who have been vaccinated against SARS-CoV-2 . It mustn't be developed immediately after the disease, but after a certain latent period like other agents.

Apart from all these, another point that should be emphasized is that both diseases can present with similar complaints of nonspecific upper respiratory tract infection, and the laboratory findings can be similar as well. In this respect, SAT should be kept in mind and included in the clinical differential diagnosis in patients with a pre-diagnosis of COVID-19 without specific laboratory and radiological imaging findings specific to the disease.

In conclusion, subacute thyroiditis is a clinical entity that usually occurs after a latent period following viral infections. The SARS-CoV-2 may cause subacute thyroiditis or autoimmune diseases like other viral agents. Subacute thyroiditis may clinically mimic SARS-CoV-2. Due to the similarity of clinical and laboratory findings, subacute thyroiditis should be considered in the differential diagnosis of COVID-19 infection, and SARS-CoV-2 should be considered as an etiologic agent for subacute thyroiditis.

Ethics Committee Approval: This study was performed after it was approved by the Acıbadem Healthcare Institutions Medical Research Ethics Committee (Date: 06.08.2020, decision no: 2020/17).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – DETS; Supervision – DY.; Materials – DETS; Data Collection and Processing – DETS; Analysis and Interpretation – DETS, DY; Writing – DETS, DY.

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