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Review

# Subacute Thyroiditis and Graves' Disease Possibly Associated with Sars-CoV-2 Infection: Presentation of Two Cases and Review of the Current Data

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**ABSTRACT**

The severe acute respiratory syndrome coronavirus 2 has been identified as the cause of a pandemic of respiratory illness in Wuhan, China. Coronavirus disease 2019 may cause mild disease with nonspecific signs and symptoms such as fever, cough, myalgia, and fatigue or severe pneumonia with respiratory failure and sepsis. It is not clear whether coronavirus disease 2019 has an effect on the thyroid gland. Evidence support that patients with coronavirus disease 2019 who are followed up in the intensive care unit may develop temporary thyroid dysfunction as non-thyroidal illness syndrome. Until now, 22 cases of subacute thyroiditis and 5 Graves' diseases potentially related to severe acute respiratory syndrome coronavirus 2 infection have been presented in the literature. Herein, we present 2 cases with subacute thyroiditis and Graves' diseases potentially related to severe acute respiratory syndrome coronavirus 2 infection in the context of the review of the literature. Physicians should be aware of the possible relationship between thyroid dysfunction and coronavirus disease 2019.

**Keywords:** COVID-19, Graves' disease, SARS-CoV-2, subacute thyroiditis, thyroid

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has already become a pandemic just a few months after it was first detected in China.[1] The virus penetrates the body via upper respiratory mucous membranes and then spreads to the lungs. After a 2- to 14-day incubation period, most COVID-19 patients develop mild to moderate sickness (fever, cough, myalgia, and fatigue) or viral pneumonia. However, some patients experience serious diseases characterized by respiratory failure, acute respiratory distress, sepsis, myocarditis, and acute renal damage, even multi-organ failure.[2] However, it is not explicitly defined how the endocrine system is affected by this virus although there are some studies showing some endocrine deteriorations in patients with COVID-19. Researchers have looked into the possibility of thyroid dysfunction among the various extra-pulmonary manifestations. For viral and host cell membrane fusion, SARS-receptor CoV-2's-binding domain uses angiotensin-converting enzyme 2 (ACE2) of the host. The pancreas, thyroid, testis, ovary, adrenal glands, and pituitary express ACE2.[2,3] There is no convincing evidence that COVID-19 individuals, whether symptomatic or not, get thyroid dysfunction as a result of infection.

Herein, we present 2 cases with thyrotoxicosis which may be potentially related to SARS-CoV-2 infection in the context of the review of the limited literature on this subject.

## CASE 1

A 32-year-old woman presented to the endocrinology outpatient clinic with symptoms of mild fever, cough, fatigue, weakness, palpitations, weight loss, and anterior neck pain radiating to the jaw and ear. In her medical history, she had SARS-CoV-2 infection 3-4 weeks ago; her nasopharyngeal real-time reverse trans criptionpolymerase chain reaction for SARS-CoV-2 was positive, and chest high-resolution computed tomography showed peripheral ground-glass areas which are typical for SARS-CoV-2-related interstitial pneumonia in bilateral lower lobes and right lung superior lobe (shown in Figure 1). Dry cough, fatigue, and weakness were present from the beginning of the COVID-19, but palpitations, weight loss, and anterior neck pain were added to her complaints about 10 days ago before admission.

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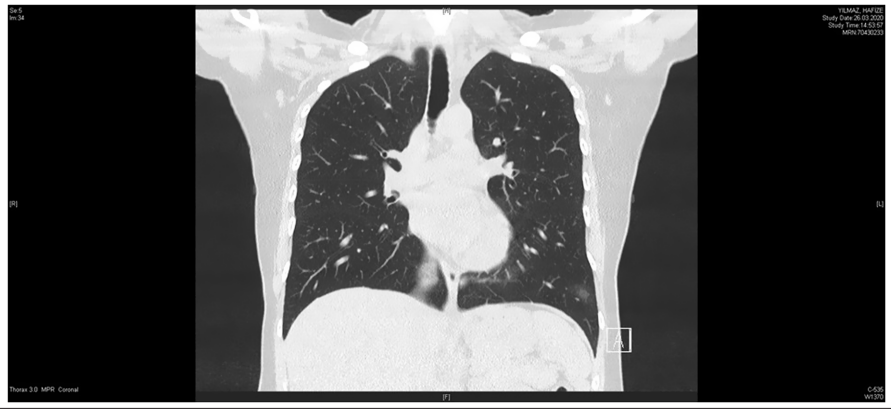
Figure 1. Chest CT shows peripheral ground-glass areas typical of SARS-CoV-2-related interstitial pneumonia in bilateral lower lobes and superior lobe of right lung. CT, computed tomography; SARS-COV-2, severe acute respiratory syndrome-coronavirus-2.



At physical examination, the patient's heart rate was 105 beats per minute, blood pressure was 130/80 mmHg, and the left lobe of the thyroid gland was markedly painful and slightly tender and enlarged on palpation. Her body temperature was 37.5°C. Other systemic examination was unremarkable. Laboratory investigations were as follows: hemoglobin 12.3 g/dL, white blood cell (WBC) 6800, neutrophil 3500, lymphocyte 280, erythrocyte sedimentation rate (ESR) 58 mm/h (<20), C-reactive protein (CRP) 2.58 mg/dL (<0.5), thyroid-stimulating hormone (TSH) <0.004 m IU/L (0.25-4.55), free triiodothyronine (T3) 7.1 pmol/L (3.5-6.5), and free thyroxine (T4) 27.5 pmol/L (11.5-22.7). Thyroid-stimulating immunoglobulin, anti-thyroglobulin (anti-TG), and anti-thyroperoxidase (anti-TPO) antibodies were negative (Table 1). The respiratory viral panel was negative. Thyroid ultrasonography revealed a widespread vascular reduction and several diffuse hypoechoic regions. Subacute thyroiditis (SAT) diagnosis was considered that might be due to SARS-CoV-2 infection. Methylprednisolone treatment was started as 32 mg per day and was gradually tapered every week for 6 weeks. After a few days on methylprednisolone, she noticed a dramatic improvement in her clinical state. The patient is still euthyroid at the third- and sixth-month visits.

## CASE 2

A 42-year-old woman was referred to cardiology outpatient clinic with laboratory results compatible with thyrotoxicosis. In her medical history, she had SARS-CoV-2 infection disease 4 weeks ago. She had mild symptoms including fever, muscle pain, and weakness. Reverse transcription-polymerase chain reaction for SARS-CoV-2 was positive. She received symptomatic treatment like paracetamol and hydroxychloroquine. But her husband stayed in the intensive care unit for 10 days due to severe COVID-19. Therefore, the family experienced serious stress during this period. She described palpitations, insomnia, agitation, and weight loss, which she had thought arose from her stressful condition, during the last 2-3 weeks.

**Main Points**

- Several patients have shown abnormalities in thyroid function after coronavirus disease 2019 (COVID-19).
- There is no convincing evidence that individuals who had COVID-19, whether symptomatic or not, may have thyroid dysfunction as a result of infection.
- Physicians should be aware of the possible relationship between thyroid disease (subacute thyroiditis, Graves' disease, etc.) and COVID-19, which should be observed by prospective studies.

The patient's heart rate was 120 beats per minute, and her blood pressure was 135/90 mmHg. Her clinical examination revealed diffusely enlarged thyroid gland and she had tremor in both hands. She did not have fever or ophthalmopathy, and other systemic examination was unremarkable.

Laboratory results were as follows: WBC 4780, ESR 20 mm/h (<25), CRP 0.4 mg/dL (0.5), TSH < 0.008 mIU/L (0.2-4.5), free T3 level 25.5 pmol/L (3.5-6.5), and free T4 level 56.3 pmol/L (11.5-22.7). Thyroid-stimulating immunoglobulin level was high (2.47 IU/L), and anti-TG and anti-TPO antibodies were negative (Table 1). Thyroid Doppler ultrasound showed diffuse increased vascularity of bilaterally enlarged thyroid lobes (peak systole > 70 cm/s) and parenchyma was heterogeneous. High radioisotope uptake (10%) was obtained with 5 mCi Tc-99 radionuclide thyroid scan (shown in Figure 2).

Graves' disease (GD) was diagnosed as potentially related to directly SARS-CoV-2 infection and/or stress factors. Methimazole (30 mg/day) and propranolol (80 mg/day) treatments were initiated.

**Clinical and Research Consequences**

Subacute thyroiditis is an inflammatory condition of the thyroid gland that generally manifests as painful thyroid enlargement. Malaise, tiredness, myalgia, arthralgia, and anterior neck discomfort spreading to the jaw and ear are common. A mild to moderate fever is common, with temperatures increasing to over 40°C at times, especially during the night. The disease's peak symptoms and signs begin in 3-4 days and diminish in a week, but

**Table 1.** Laboratory Results of the Patients

| | First Case | | Second Case | | |
|---|---|---|---|---|---|
| **Measures** | **COVID-19 Period** | **SAT Period** | **COVID-19 Period** | **Graves Period** | **Normal Range** |
| TSH (µU/mL) | 3.66 | <0.004 | 1.2 | <0.008 | 0.25-4.55 |
| FT3 (pmol/L) | NA | 7.1 | NA | 25.5 | 3.5-6.5 |
| FT4 (pmol/L) | 16.23 | 27.5 | 15.4 | 56.3 | 11.5-22.7 |
| CRP (mg/dL) | 1.04 | 2.58 | 3.5 | 0.4 | <0.5 |
| ESR (mm/sa) | 10 | 58 | 45 | 20 | <20 |
| Anti-TPO(IU/mL) | NA | 37.2 | NA | 58 | 0-60 |
| TgAb (IU/mL) | NA | 30 | NA | 40 | 0-60 |
| TSI (IU/L) | NA | 0.1 | NA | 2.47 | <0.1 |

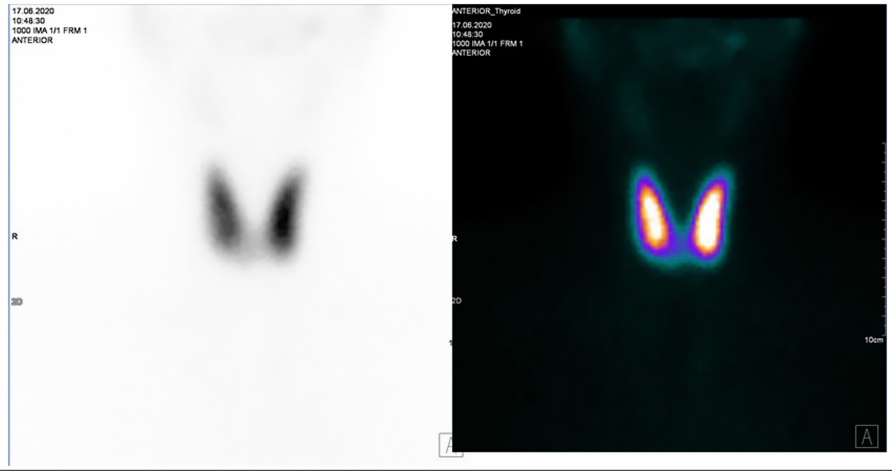
COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FT3, free triiodothyronine; FT4, free thyroxine; TgAb, thyroglobulin antibodies; TPOAb, thyroperoxidase antibodies; TSI, thyroid-stimulating immunoglobulin; SAT, subacute thyroiditis; TSH, thyrotropin; NA, not available.

the onset might take 1-2 weeks and last 3-6 weeks.[4,5] During this pandemic, it has been observed that the clinic presentation of SAT and COVID-19 may overlap making clinical and decision to treat discrimination difficult. Whether COVID-19 may trigger SAT is another matter of debate.

Subacute thyroiditis incidence is 4 times higher in women than in men, and SAT is more frequent between ages 40 and 50 years.[6,7] Several studies showed that susceptibility to the disease and recurrence risk are associated with human leukocyte antigens (HLA) mainly HLA-Bw35 and also HLAB67, HLA-B15/62, and HLA-Drw8.[8] Previous viral infections caused by viruses such as Coxsackie virus, Epstein–Barr virus, adenoviruses, influenza viruses, mumps, measles, and primary human immunodeficiency virus (about 2-6 weeks before SAT) are thought to be triggering factor for SAT.[9,10] Subacute thyroiditis is defined by elevated ESR and CRP levels, typical ultrasound findings including inhomogeneous hypo-echogenic texture with diminished vascularity and laboratory markers of thyrotoxicosis. Symptomatic treatment includes non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids in more severe cases.[4] We did not give NSAIDs to our patient including ibuprofen as it may have suppressive effect on immune response by upregulating ACE2. Paracetamol and methylprednisolone (32 mg per day) were given, and they were progressively tapered every week for 6 weeks. After 6 weeks, she had normal thyroid function and she was symptom-free.

In 2002, it was observed that the SARS epidemic caused some abnormalities in thyroid function.[11,12] Although SARS-CoV was isolated in endocrine organs including parathyroid, pituitary, pancreas, and adrenal gland, it could not be detected in thyroid, testis, ovary, and uterus.[11] Wei et al[12] showed extensive injury to the follicular epithelial cells and the para-follicular cells during autopsies of 5 SARS cases. The breakdown of the follicular epithelium and desquamation of epithelial cells into the follicular lumen were the hallmarks of follicular cell injury. The terminal deoxynucleotidyl transferase-mediated dUPT nick end–labeling (TUNEL) assay confirmed the presence of apoptosis but no inflammatory infiltration or cellular necrosis. Yao et al.[13] on the other hand, looked at pathological changes in individuals who died from SARS-CoV-2 infection by taking minimally invasive autopsies from several organs. They found lymphocytic

Figure 2. Tc-99 radionuclide thyroid scan shows high iodine uptake.



infiltration in the interstitium but no changes in thyroid follicular morphology. Neither immunohistochemistry studies nor PCR analyses detected SARS-CoV-2 in the thyroid gland tissues.[13] Rotondi et al[14] discovered that the ACE2 receptor mRNA is expressed in thyroid follicular cells via direct molecular analysis of surgical samples of thyroid tissue, suggesting them a potential target for SARS-COV-2 invasion.

During this COVID-19 pandemic, first Brancatella et al[15] introduced an 18-year-old woman with SAT diagnosis which occurred after 2 weeks of COVID-19 infection. Prednisone (25 mg/day as the starting dose) was given to the patient, and thyroid function and inflammatory markers of the patient normalized in 40 days. Ippolito et al[16] reported a 69-year-old woman with SAT during the recovery phase of COVID-19 infection following back surgery. Previously, she had a nontoxic nodular goiter and she was diagnosed with thyrotoxicosis during COVID-19. They considered a diagnosis of SAT because the patient responded to steroids but not methimazole.[16] Asfuroglu et al[17] reported a 41-year-old woman with SAT and they suggested that physicians should be aware of screening SAT patients for COVID-19. Ruggeri et al[18] described a 43-year-old woman who developed SAT with thyrotoxicosis 6 weeks after SARS-COV-2 infection. Oral prednisone (25 mg/day as the starting dose) was started on the patient and progressive remission of symptoms and signs and euthyroid status were provided after 4 weeks.[18] Brancatella et al[19] described additional 4 patients with SAT after COVID-19. Twenty-two cases of SAT potentially associated with SARS-CoV-2 infection have been reported to date.[20-28] In a recent review, SAT was found more frequent in women than in men (18 women/4 men). These patients had mild symptoms and signs including fever, myalgia, asthenia, palpitations, weight loss, and anterior neck pain or they were asymptomatic. Beta-blockers, aspirin, and glucocorticoids (prednisone 25-40 mg) were given, and their treatment was gradually discontinued over an average of 3-4 weeks. Despite a short follow-up (35 ± 12 days) period, euthyroid status was achieved after a short duration of subclinical hypothyroidism in most patients.[29]

Graves' disease is an autoimmune illness caused by thyroid autoantibodies that stimulate the production of T4, resulting in hyperthyroidism. The etiology of GD is not clear. Different environmental circumstances (i.e., infections, smoking, stress, radiation, drugs, iodine, and so on) have been suggested to promote GD, particularly in genetically sensitive individuals.[30] Valtonen et al[31] detected evidence of a recent bacterial or viral infection in the serum samples of 36% of patients with newly diagnosed GD, 67% of patients with Hashimoto's thyroiditis, and in only 10% of control subjects.[31] Several research have examined the link between GD and infectious diseases such as Yersinia, Leishmania, Mycoplasma, *Helicobacter pylori*, Foamy Viruses, Parvovirus-B19, Epstein–Barr virus, hepatitis C virus, and retroviruses such as HIV, with different results.[32] Firstly, Mateu-Salat et al[33] reported 2 cases of GD occurring after SARS-CoV-2 infection. Subsequently, Jiménez-Blanco et al[34] described 2 more cases with GD probably related to COVID-19. Pastor et al[35] presented a 45-year-old woman, with a previous history of GD who had been in long-term remission for over 4 years. She was admitted to the emergency department with a thyrotoxic crisis which was most likely caused by COVID-19.

The significance of stress in the development of hyperthyroidism in GD patients is still debated. In cross-sectional studies, stressful life events (SLE) have been shown to be more common in the months before the development of GD.[36] Vita et al[37] evaluated the relationship of SLE with the onset and outcome of GD. Patients with SLE experienced at least one exacerbation or relapse prior to each exacerbation or relapse. The patients who experienced more exacerbations or relapses lived more SLE than the patients with remission.[37] Previously, we showed that the number and impact of negative SLE in GD patients were higher when compared to healthy controls according to the Life Experience Survey.[38] Very recently, we have recommended methimazole and beta-blocker combination for initial therapy and considered dietary changes and radioactive iodine (RAI) treatment unadvisable during the COVID-19 pandemic.[39]

## CONCLUSION

In patients who had severe COVID-19 infection, changes in thyroid function may occur potentially related to COVID-19. Thyroid dysfunction has been documented during and after a COVID-19 infection; therefore, some new-onset or recurrent thyroid dysfunction is likely to be linked to a recent SARS-CoV-2 infection. Physicians should be aware of possible relationships between thyroid dysfunction and COVID-19, which should be researched by prospective studies.

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