

Subacute Thyroiditis from COVID-19 Infection: A Case Report and Review of Literature

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Established Facts

- Coronavirus disease 2019 is an ongoing pandemic that has many atypical presentations.
- Subacute thyroiditis can be triggered by multiple viral infections.

Novel Insights

- Coronavirus disease 2019 (COVID-19) due to severe-acute-respiratory-syndrome-coronavirus-2 (virus) can lead to subacute thyroiditis.
- Subacute thyroiditis due to COVID-19 shows a good response to anti-inflammatory and corticosteroid therapy.
- There are multiple potential peripheral and central mechanisms by which COVID-19 infection may lead to subacute thyroiditis.

Keywords

COVID-19 · SARS-CoV-2 · Subacute thyroiditis · Thyroid tests

Abstract

Introduction: The novel severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) virus has led to the ongoing Coronavirus disease 2019 (COVID-19) disease pandemic. There are increasing reports of extrapulmonary clinical features of COVID-19, either as initial presentations or sequelae of disease. We report a patient diagnosed with subacute thyroiditis precipitated by COVID-19 infection, as well as review the literature of similar cases. **Case Presentation:** A 41-year-old female with no significant personal or family

history of endocrinologic disorders presented with clinical features of thyroiditis that began after COVID-19 infection. Clinical, laboratory, and radiologic findings were indicative of subacute thyroiditis. Workup for potential triggers other than SARS-CoV-2 was negative. **Discussion/Conclusion:** We compared the clinical and diagnostic findings of our patient with other well-documented cases of subacute thyroiditis presumed to be triggered by SARS-CoV-2 viral infection. We also reviewed the literature related to the potential mechanisms leading to thyroiditis. Clinicians must be aware of the possibility of thyroid dysfunction after COVID-19 infection. Early recognition and timely anti-inflammatory therapy help in successful management.

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Introduction

In December 2019, the WHO was notified about cases of pneumonia of unknown etiology originating in Wuhan, Hubei province, China [1]. The novel virus, named severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2), was isolated on January 7, 2020 [1]. The acute respiratory disease, renamed Coronavirus disease 2019 (COVID-19), was declared a pandemic by the WHO on March 11, 2020 [2]. As of July 16, 2020, >13.3 million cases with >580,000 deaths have been reported globally [3].

The initial reported symptoms of COVID-19 in China were primarily respiratory symptoms associated with bilateral ground glass pulmonary opacities on radiographic imaging [4]. Since then, COVID-19 has been shown to cause extrapulmonary manifestations (gastrointestinal, hepatobiliary, pancreatic, cardiovascular, ocular, and neurologic), either as the initial presentation or as sequelae [5, 6].

In this article, we report a patient diagnosed with subacute thyroiditis that was precipitated by COVID-19 infection. We also review the literature of similar cases.

Case Report

A 41-year-old Caucasian woman presented to the emergency room (ER) with worsening pain and swelling of her anterior neck for 6 weeks and persistent fevers for 3 weeks. Four weeks prior to onset of symptoms, she experienced several days of fever, cough, and coryza. At that time, reverse transcriptase-PCR (rtPCR) by nasopharyngeal swab was positive for SARS-CoV-2, confirming COVID-19 infection. She reported complete resolution of symp-

toms after a 5-day course of oral azithromycin and supportive therapy.

Two weeks after symptom resolution, she noted a gradually worsening painful anterior neck mass with radiation to her jaw, associated with odynophagia. This was followed 3 weeks later by fevers, chills, and diaphoresis. She endorsed a 6 kg unintentional weight loss, fatigue, alopecia, heat intolerance, irritability, headaches, bilateral hand tremors, and palpitations. Her primary care physician prescribed 2 courses of oral antibiotics (7 days of oral levofloxacin followed by 5 days of oral amoxicillin), without relief. Respiratory viral panel nasopharyngeal testing was negative. Acetaminophen provided temporary symptom relief.

Thyroid function tests (TFTs) revealed a low thyroid-stimulating hormone (TSH) with normal T3 uptake (Table 1). Repeat TFTs showed low TSH and elevated thyroid hormone levels, suggestive of thyrotoxicosis (Table 1). A thyroid ultrasound revealed a heterogenous thyroid gland (right lobe: 4.3 × 2.3 × 1.6 cm; left lobe 4.3 × 1.9 × 1.4 cm) with bilateral patchy ill-defined hypoechoic areas, suggestive of subacute thyroiditis. No cervical lymphadenopathy was noted. Due to persistent symptoms of odynophagia, neck swelling, and fevers, she presented to the ER.

In the ER, she was febrile (39.5°C) with a heart rate of 112 beats/min. Her remaining vital signs were normal. She had a diffusely tender thyroid gland with no cervical lymphadenopathy. She was tachycardic but with a regular rhythm and clear pulmonary examination. Her deep tendon reflexes were hyperactive.

Admission laboratories noted WBC count 5.79 × 10⁹/L, hemoglobin 91 g/L, and platelet count 310 × 10⁹/L. Renal and hepatic function were unremarkable. She had elevated inflammatory markers with an erythrocyte sedimentation rate 107 mm/h (0–15 mm/h) and a C-reactive protein 36.4 mg/L (0–4 mg/L). Urine pregnancy test was negative. Repeat TFTs confirmed an excess of circulating thyroid hormones (Table 1). Chest radiography revealed clear lungs and computed tomography of chest/abdomen/pelvis showed no acute pathology.

Past medical history was significant for supraventricular tachycardia treated with ablation (May 2019), anxiety, depression, treated *Helicobacter pylori* infection (treated 2016), anemia, surgically corrected scoliosis, and gastroesophageal reflux disease. She was

Table 1. TFTs at multiple time-points during the patient's illness

Laboratory tests (normal ranges)	Dates of TFT				
	May 12, 2020	May 21, 2020	May 28, 2020	June 2, 2020	June 8, 2020
TSH (0.7–4.20 mIU/L)	↓0.018	↓<0.008	↓0.01	↓0.01	↓<0.01
tT4 (59.34–154.8 nmol/L)	–	↑222.91	–	↑305.73	↑268.32
ftT4 (11.61–23.22 pmol/L)	–	–	↑60.63	↑63.21	–
tT3 (1.232–3.08 nmol/L)	–	2.60	↑3.39	↑4.10	↑3.37
T3Up (32–48%)	45.3%	–	–	–	–
TSI (0–0.55 IU/L)	–	–	<0.1	–	–
TSHrAb (0–1.75 IU/L)	–	–	<1.10	–	–
TPOAb (≤34.9 IU/mL)	–	–	–	↑96.71	–

TSH, thyroid-stimulating hormone; TFT, thyroid function test; COVID-19, Coronavirus disease 2019; TPOAb, thyroperoxidase antibody; TSHrAb, TSH-receptor antibody; TSI, thyroid-stimulating immunoglobulin; T3Up, tri-iodothyronine uptake; tT4, total thyroxine; tT3, total tri-iodothyronine. Bolded values indicate abnormal laboratory test results.

born in an urban area of Uzbekistan and migrated to the USA in 1994. She resided in Long Island, New York, with her husband and children. She denied any history of smoking, vaping, alcohol, or recreational drug use. There was no recent use of amiodarone, intravenous contrast, or lithium. She denied any recent travel. Family history was significant for breast cancer in female relatives. There was no reported history of thyroid disease or connective tissue disorders in the family.

Urinalysis and urine culture were negative. Repeat COVID-19 rtPCR testing was negative, and she tested positive for COVID-19 IgG antibodies. HIV and Quantiferon tests were negative. Blood cultures revealed no growth.

Her clinical presentation was suggestive of thyroiditis. Given her recent COVID-19 infection, this raised the suspicion of a subacute thyroiditis triggered by COVID-19. Thyroid-stimulating immunoglobulin and TSH-receptor antibody testing was negative, with positive thyroperoxidase antibodies (Table 1). She was started on oral ibuprofen 600 mg every 6 h and prednisone 40 mg daily. She reported marked symptom relief with resolution of fever and was discharged home after 2 days of hospitalization.

On outpatient follow-up approximately 1 week later (June 8, 2020), she reported symptom resolution and improvement in TFTs (Table 1). She completed a 4-week corticosteroid taper and reported complete symptom resolution at her last outpatient follow-up visit 45 days from hospital discharge.

Discussion/Conclusion

Subacute thyroiditis (also known as subacute granulomatous, subacute nonsuppurative, giant cell, and painful/de Quervain's thyroiditis) is an uncommon cause of thyrotoxicosis. It is seen more often in women [7] and is typically characterized by a painful tender thyroid gland, with pain radiating to the ear, as well as systemic symptoms (fevers, malaise, and anorexia) [8].

It is a self-limiting illness with 3 distinct phases: an initial thyrotoxic phase, followed by hypothyroidism, and then recovery of thyroid function over weeks to months [8]. The exact cause of subacute thyroiditis is not known. Multiple viruses (such as measles, mumps, rubella, coxsackie, adenovirus, chickenpox, cytomegalovirus, Epstein Barr virus, HIV, Hepatitis E, and influenza) have been postulated to trigger onset of disease, either through direct injury or indirectly through its circulating viral genome or virus-specific antibodies [8, 9].

Subacute thyroiditis is primarily a clinical diagnosis supported by laboratory testing and imaging [7, 8]. The clinical features are correlated with a combination of test results – elevated erythrocyte sedimentation rate and C-reactive protein; low TSH; elevated thyroid hormone levels (T4 and T3) and thyroglobulin concentrations; with an absent/low positive titer of circulating thyroperoxidase and thyroglobulin antibodies [8]. Anti-inflammatory

agents are the first line of therapy, with corticosteroids used in more severe cases [8].

At that time our patient presented, there were only a few other reported cases of subacute thyroiditis after COVID-19 infection worldwide (Table 2) [10–13]. All prior cases of subacute thyroiditis due to COVID-19 occurred in women with no (or minor) medical comorbidities. Both our patient and Dr. Brancatella's patient [10] reported symptoms occurring *after* 2 weeks of infection with SARS-CoV-2; 1 patient [13] had symptoms 6 weeks *after* infection; while 2 other patients had *concurrent* diagnoses of COVID-19 and thyroiditis [11, 12]. All patients had laboratory findings of thyrotoxicosis and ultrasound findings suggestive of subacute thyroiditis. All patients responded favorably to anti-inflammatory and corticosteroid therapy.

The exact mechanisms by which SARS-CoV-2 causes thyroid dysfunction are not known. We reviewed and compared certain mechanisms noted with SARS virus:

1. *Inflammatory response, apoptosis, and local damage* – SARS-CoV produced a profound host inflammatory response [14] and induction of apoptosis through expression of several viral proteins [15–17]. In an autopsy study of 5 SARS patients performed in 2007, follicular epithelial damage and cellular apoptosis were noted, in the absence of neutrophilic or lymphoid infiltration [18]. Apoptotic cells have been found in liver and thyroid tissue of SARS-CoV patients [19]. In SARS-CoV-2 patients, an inflammatory infiltrate has been noted in many tissues including the thyroid [20], supporting the potential role of inflammation.
2. *Direct viral replication* – both SARS-CoV and SARS-CoV-2 viral genomes have been documented in patient sera [21]. SARS-CoV was not isolated in the thyroid but was noted in the infiltrating inflammatory cells [22, 23]. Other viral infections associated with thyroiditis have been associated with the presence of virus-like particles in the thyroid tissue [9]. Although SARS-CoV-2 has not yet been isolated in the thyroid, the possibility of direct viral damage has not been ruled out.
3. *Interactions with ACE2 receptor* – Angiotensin-converting enzyme 2 (ACE2) receptors are expressed in multiple organs other than the lungs, including the thyroid [24, 25]. ACE2 is believed to play a crucial role in the pathogenesis of lung injury due to coronavirus-es [26]. Thus, ACE2 receptors in the thyroid may serve as another mechanism of injury.
4. *Potential central mechanism* – SARS patients were noted to have altered thyroid hormone levels and thyroid

Table 2. Comparative clinical and laboratory features of subacute thyroiditis cases believed to occur after COVID-19 infection

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	41F	18F	41F	69F	43F
Time duration between COVID-19 infection and features of thyroiditis	~ 14 days	14 days	Concurrent illness	Concurrent illness (S/o thyrotoxicosis noted on day 5 of hospitalization)	~Six weeks
Clinical features	Tender neck swelling, odynophagia, neck pain, fevers, fatigue, hand tremors, palpitations	Fevers, fatigue, palpitations, anterior neck pain radiating to jaw	Fevers, neck pain, tender thyroid, pharyngitis, left TMJ tenderness	Fever, cough, dyspnea, palpitations, insomnia, agitation	Fever, tender anterior cervical region, fatigue, tremors, palpitations
COVID-19 rtPCR testing [#]	(-)	(-)	(+)	(+)	na
COVID-19 antibody testing [#] (+)		na	na	na	(+)
Inflammatory markers [#]	ESR 107 mm/h CRP 36.4 mg/L	ESR 90 mm/h CRP 69 mg/L	ESR 134 mm/h CRP 101 mg/L	na	na
TFT	Thyrotoxic* normal T3Up (+) TPOAb (-) TSI (-) TSHrAb	Thyrotoxic* sTg detected (low-level) (-) TPOAb (-) TSHrAb (+) TgAb	Thyrotoxic* (-) TPOAb (-) TSHrAb (-) TgAb	Thyrotoxic* ↑sTg (-) TPOAb (-) TSHrAb (-) TgAb	Thyrotoxic* ↑sTg (-) TPOAb (-) TSHrAb (-) TgAb
Thyroid ultrasound findings	1. Heterogenous thyroid gland 2. Bilateral patchy ill-defined hypoechoic areas	Multiple diffuse hypoechoic areas	1. Heterogenous thyroid parenchyma 2. Relative diffuse decrease of vascularity	1. Enlarged hypoechoic thyroid 2. Decreased vascularity 3. Known 30-mm homogenous nodule in right lobe (with peripheral vascularization)	Diffusely enlarged and hypoechoic thyroid gland (thyroid scintigraphy showed markedly reduced 99 mTc-pertechnetate uptake)
Treatment	1. Ibuprofen 600 mg PO q6h 2. Prednisone 40 mg/d PO (followed by taper)	Prednisone 25 mg/d PO (followed by taper)	1. HCQ 200 mg PO q12 h × 5 days 2. Prednisolone 16 mg/d PO (followed by taper)	1. HCQ 2. Methimazole (later discontinued) 3. Methylprednisolone IV × 3 days 4. Prednisone 25 mg/d PO (followed by taper)	Prednisone 25 mg/d PO (followed by taper)
Reference	Current case	10	11	12	13

COVID-19, Coronavirus disease 2019; CRP, C-Reactive protein; ESR, erythrocyte sedimentation rate; fT4, free thyroxine; Hgb, hemoglobin; HCQ, hydroxychloroquine; IV, intravenous; na, not available; NSAIDs, non-steroidal anti-inflammatory drugs; PO, oral; q6h, every 6 h; q12h, every 12 h; rtPCR, reverse transcriptase-PCR; sTg, serum thyroglobulin; sTgAb, serum thyroglobulin antibodies; TMJ, temporomandibular joint; TPOAb, thyroperoxidase antibody; TSH, thyroid-stimulating hormone; TSHrAb, TSH-receptor antibody; TSI, thyroid-stimulating immunoglobulin; T3Up, tri-iodothyronine uptake; tT4, total thyroxine; tT3, total tri-iodothyronine; TFT, thyroid function test. [#] Indicates results of testing performed at the time of thyroiditis diagnosis. * Thyrotoxic: Thyroid hormone test results in following pattern: †TSH; †tT3 or †tT3; †tT4; †tT4.

dysfunction [27, 28]. A previous study reported decreased thyroid hormone levels and a decreased TSH [27] – the decreased hormone levels could be explained by the pathologic findings of follicular destruction. However, the low TSH level could be secondary to hypothalamus-pituitary dysfunction – this is reinforced by the findings of central hypothyroidism and central hypocortisolism in SARS patients [28, 29]. Thus, to summarize, SARS-CoV was postulated to induce thyroid dysfunction through both local thyroid tissue destruction and central mechanisms. It is unclear whether SARS-CoV-2 will follow similar mechanisms.

Our patient had the clinical manifestations and laboratory findings of thyrotoxicosis, with imaging supportive of subacute thyroiditis. The time frame of appearance and evolution of symptoms fits with the known disease course of subacute thyroiditis – a gradual onset over 1–2 weeks, with fluctuating intensity for 3–6 weeks [8]. COVID-19 diagnosis was noted by outpatient rtPCR testing prior to illness and later confirmed by serologic testing. Other in-

fectious causes and triggers of subacute thyroiditis were ruled out through a broad inpatient and outpatient infectious workup. The prompt response to anti-inflammatory and steroid therapy further strengthens our suspicion of COVID-19 as the cause.

With the rapidly expanding knowledge of the late sequelae of COVID-19 infection [5, 6], we report a case of subacute thyroiditis occurring due to infection by SARS-CoV-2. Given the high prevalence of COVID-19 in the community, the possibility of coincidental detection of SARS-CoV-2 virus in our patient who subsequently developed subacute thyroiditis cannot be completely ruled out. Further research is needed to elicit this potential link, the mechanisms of thyroid injury as well as the long-term outcomes.

Clinicians must be aware of the possibility of thyroid dysfunction and subacute thyroiditis after COVID-19 infection due to SARS-CoV-2. Early recognition and timely anti-inflammatory therapy can help in successful management of the disease.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The research met our institutional definition of a case report (a medical chart review of 3 or fewer patients), and thus, institutional research board review was not needed. Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding Sources

The authors report no external funding sources.

Author Contributions

All authors (Akshay Khatri, Esti Charlap, and Angela Kim) were involved in the inpatient clinical care of the patient. Akshay Khatri was involved in creation of the initial draft, literature review, and subsequent modifications of the case report draft. Esti Charlap was involved in modification of the case report draft. Angela Kim was involved in literature review and modification of the case report draft. All authors reviewed and approved the final submitted draft.

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