


Two Cases of Severe Autoimmune Thyrotoxicosis Following SARS-CoV-2 Infection

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Abstract

Since the start of the COVID-19 pandemic, there have been multiple reports of related thyroid dysfunction, most commonly, thyroiditis. The exact mechanism for this has not been elucidated, but it is known that thyroid gland cells have both angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors, which the SARS-CoV-2 virus uses to enter cells. While SARS-CoV-2 has also been shown to precipitate other autoimmune diseases, there are only a few reported cases of new onset Graves' disease in the setting of SARS-CoV-2 infection. We report 2 patients who presented with severe thyrotoxicosis (thyroid storm and impending storm) that was likely precipitated by SARS-CoV-2 infection. Both patients had no previous history of hyperthyroidism, and potentially also developed Graves' disease after getting COVID-19. The addition of these cases to the medical literature will further highlight the fact that SARS-CoV-2 infection should be considered a causative agent for thyrotoxicosis when no other cause can be found, and that SARS-CoV-2 may be a potential trigger for autoimmune thyroid disease. It is important to know the SARS-CoV-2 status of such patients for infection control purposes, and to identify patients who may have their hospital course complicated by this disease. These cases may also help further our understanding of the etiology of autoimmune thyroid disease following a viral infection.

Keywords

COVID-19, Graves' disease, SARS-CoV-2, thyroid storm, thyrotoxicosis

Introduction

Coronavirus disease of 2019 (COVID-19) is primarily a respiratory disease; however, multi-system effects,¹ including involvement of the endocrine system have been reported.^{2–4} The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the cells via the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors, which are highly expressed in the thyroid gland.⁵ Subacute thyroiditis has been seen in relation to SARS-CoV-2 infection.^{6–9} Less commonly, COVID-19 has been reported to cause new-onset or recurrent Graves' disease,^{10–14} including thyroid storm following SARS-CoV-2 infection.^{15,16} We present 2 cases of severe auto-immune thyrotoxicosis requiring hospitalization following SARS-CoV-2 infection.

Case Presentation

Patient 1

A 27-year-old male presented to the emergency room (ER) with sudden onset confusion and aggressive behavior. He

was tremulous, febrile (temperature: 102.9°F) and tachycardic (heart rate: 172 beats/min). His blood pressure was 142/78 mmHg and oxygen saturation was 100% on room air. He did not have proptosis or lid lag and had a small goiter with no palpable nodules on thyroid exam. Laboratory findings were consistent with hyperthyroidism with thyroid stimulating hormone (TSH) of < 0.01 mIU/L (normal: 0.45–4.5 mIU/L), free thyroxine (T4) of > 7.8 ng/dL (normal: 0.8–1.8 ng/dL), and free triiodothyronine (T3) of 21.9 pg/mL (normal: 2–4.4 pg/mL) (Table 1). SARS-CoV-2 polymerase chain reaction (PCR) was positive. Urine drug screen was negative (except for benzodiazepines which he received in the ER). Chest radiograph, urinalysis, blood, and urine cultures

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Table 1. Vital Signs and Thyroid Function Tests for Patient #1 and #2.

Data (reference range)	Patient 1			Patient 2		
	Admission	Day 8 ^a	3-week follow-up	Admission	Day 2 ^a	One month follow-up
Blood pressure	142/78	127/73	—	109/54	117/85	—
Pulse	173	91	—	144	71	—
Respiratory rate	36	18	—	26	19	—
TSH (0.5-5.0 mIU/mL)	<0.01	<0.01	<0.01	<0.01	N/A	<0.01
Free T4 (0.8-1.8 ng/dL)	>7.8	7.3	2.3	>7.8	4.3	7.2
Free T3 (2.3-4.2 pg/mL)	21.9	6.4	7.5	15.4	8.8	—
TSI (≤ 0.54 IU/L)	8.43	—	—	7.77	—	—
TRAb (≤ 1.75 IU/L)	9.40	—	—	Not tested	—	—

Legend: ^aDay of discharge from the hospital.

Abbreviations: TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; TSI, thyroid Stimulating Immunoglobulin; TRAb, thyrotropin receptor antibody.

showed no evidence of infection. Computed tomography (CT) brain was normal. Thyroid stimulating immunoglobulin (TSI) and thyrotropin receptor antibody (TRAb) were both positive at 8.43 IU/L (reference range ≤ 0.54 IU/L) and 9.10 IU/L (reference range ≤ 1.75 IU/L), respectively. Thyroid ultrasound showed a diffusely enlarged, heterogeneous, hypervascular gland, consistent with Graves' disease. He had no prior personal or family history of thyroid disease, no exposure to iodinated contrast agents, and no known sick contacts. There were no available thyroid function tests prior to presentation, and he reported no weight loss, tremors, heat intolerance, anxiety, or symptoms of thyrotoxicosis prior to his presentation.

His Burch-Wartofsky score was 55 (>45 is highly suggestive of thyroid storm) prompting admission to the intensive care unit (ICU).¹⁷ He was started on an esmolol infusion at 300 mcg/kg/min (maximum dose), methimazole 60 mg once followed by 20 mg orally 3 times daily and potassium iodide solution (SSKI) 5 drops every 6 hours (started 1 hour after methimazole was given). His mental status rapidly improved and heart rate decreased to 100 to 110 beats/min in the 24 hours following these interventions. Given continued tachycardia, propranolol 60 mg orally every 6 hours was initiated while he was still receiving esmolol, along with cholestyramine 4 mg orally every 6 hours. His heart rate gradually decreased to 80 to 90 beats/min by the fifth day of hospitalization, the esmolol infusion was stopped and he was transferred out of the ICU.

On the sixth day of hospitalization, the patient's free T4 remained elevated at > 7.8 ng/dL with free T3 of 21.5 pg/mL, so methimazole was discontinued and propylthiouracil (PTU) 300 mg every 6 hours along with oral dexamethasone 2 mg every 8 hours was initiated. His circulating thyroid hormones decreased over the next 3 days (free T3 went from 14.6 to 7.3 to 6.4 pg/mL and free T4 declined to 7.3 ng/mL); PTU and dexamethasone doses were decreased to 300 mg every 8 hours, and 2 mg every 12 hours, respectively;

and cholestyramine was stopped. Given marked clinical improvement, he was discharged on methimazole 30 mg daily, atenolol 50 mg daily and SSKI 5 drops daily after a total of 8 days of hospitalization. He did not require oxygen or any specific treatment for SARS-CoV-2 during his admission.

He was seen in the outpatient endocrinology clinic for a 2-week follow-up and free T4 had improved to 2.3 ng/dL. Since he was still significantly hyperthyroid, his methimazole dose was increased to 40 mg daily. The SSKI was discontinued but he remained on atenolol.

Patient 2

A 21-year-old female with a past medical history of migraines presented to the ER with a severe headache, shortness of breath, nausea, vomiting, diarrhea, and palpitations for 1 day. She was tachycardic (heart rate: 136 beats/min), tachypneic (respiratory rate: 18 breaths/min), and hypotensive (blood pressure: 84/53 mmHg). Her temperature was 98.4°F and oxygen saturation was 99% on room air. She appeared well on physical examination in the ER; however, a formal thyroid examination was not conducted in the hospital. Laboratory studies showed leukocytosis of 34.46 (reference range: 4.22-10.33 $\times 10^9$ /L) and hyperthyroidism with TSH of <0.01 mIU/L, free T4 of >7.8 ng/dL and free T3 of 15.4 pg/mL (Table 1). No previous thyroid function tests were available, and she did not have a history of known thyroid disease. She denied any symptoms of thyrotoxicosis leading up to her hospitalization. SARS-CoV-2 PCR was positive.

Her Burch-Wartofsky score was 40 (24-44: suggestive of impending storm). She was treated with methimazole 20 mg orally 3 times daily, hydrocortisone 100 mg intravenously every 8 hours and propranolol 20 mg orally every 6 hours while inpatient. Her tachycardia resolved within 24 hours of intervention and free T4 decreased to 4.3 ng/dL, so hydrocortisone was discontinued after 2 doses.

Table 2. Hyperthyroidism Occurring in SARS-CoV-2.

Manifestation	Potential mechanisms proposed	Approximate number of cases	References
Thyroiditis post SARS-CoV-2 infection	Cytokine storm induced. Direct viral damage to the thyroid gland (potential direct entry of virus into thyroid gland using ACE-2 receptors)	At least 47 reported cases	6, 7, 8, 9
Thyroiditis post SARS-CoV-2 mRNA vaccination	Molecular mimicry between viral spike protein and autoantigens.	2 cases	22
Thyroid storm	Cytokine-storm induced. Induction of new-onset Graves' disease.	3 (including 1 case reported here)	15, 16
Graves' disease post SARS-CoV-2 infection	Dysregulated host immune response. Molecular mimicry between viral spike protein and autoantigens. Recurrence of disease previously in remission.	11 (including 2 cases reported here)	10-16
Graves' disease post SARS-CoV-2 mRNA vaccination	Molecular mimicry between viral spike protein and autoantigens. Adjuvant induced.	2	21

Abbreviation: ACE2 = angiotensin-converting enzyme 2.

She had no prior family history of thyroid disease and no known sick contacts. CT angiogram, performed after methimazole was given, did not show a pulmonary embolism or acute chest findings. Blood cultures, urine cultures, cerebrospinal fluid analysis, and HIV testing were negative for infection. TSI was positive (7.77 IU/L) confirming diagnosis of Graves' disease. She was discharged on methimazole 10 mg daily and propranolol 10 mg 3 times daily. Free T4 was still elevated (7.2 ng/dL) at her 4-week follow-up so methimazole dose was increased to 30 mg daily.

Discussion

Presented here are 2 cases of acute severe thyrotoxicosis (thyroid storm and impending storm) and new-onset Graves' disease in 2 patients with no known prior history of hyperthyroidism. The only potential precipitating factor identified in each case was SARS CoV-2 infection.

SARS-CoV-2 has been associated with multiple reports of thyroid dysfunction, including thyrotoxicosis (Table 2). A previous study investigated thyroid dysfunction in patient with COVID-19 and found the most common abnormalities were subclinical thyrotoxicosis, overt thyrotoxicosis, subclinical hypothyroidism, and overt hypothyroidism.⁹ Thirty-one patients had overt thyrotoxicosis, out of which 9 patients were tested for TRAb—all were negative. The etiology of thyrotoxicosis in these patients was thought to be either inflammatory thyroiditis driven by COVID-19 associated sustained cytokine storm, or destructive thyroiditis caused by the virus itself.⁹ Subacute thyroiditis has also been independently reported in at least 47 patients.⁶⁻⁸

There have been multiple cases of Graves' disease post COVID-19 reported in the literature. Several patients were in remission and had exacerbation of Graves' disease,^{10,11}

with 1 patient having thyroid storm.¹⁶ In other cases, patients were diagnosed with Graves' disease following SARS-CoV-2 infection.¹¹⁻¹⁴ There is 1 case reported of severe thyrotoxicosis and Graves' disease being diagnosed at the same time of SARS-CoV-2 infection, but in that case methamphetamine use may have been a confounder/trigger for thyrotoxicosis.¹⁵ We have described 2 additional patients who were diagnosed with Graves' disease post SARS-CoV-2 infection, raising the possibility of SARS-CoV-2 being a direct trigger for autoimmune thyroid disease, be it reactivation or new onset. The acute, severe thyrotoxicosis witnessed in our cases may have been driven by systemic inflammation from the SARS-CoV-2 infection. Our cases are different from most of the cases reported in the literature as Graves' disease and COVID-19 were diagnosed concurrently. It is possible that the 2 diagnoses may have occurred concurrently by chance given the high prevalence of COVID-19 in the community at that time.

SARS-CoV-2 has been associated with autoimmune diseases with reports of patients developing Guillain-Barre syndrome and systemic lupus erythematosus following infection.¹⁸ Antinuclear antibody (ANA), lupus anticoagulation, cold agglutinins, and Anti-Ro/SSA antibodies have all been associated with SARS-CoV-2 infection. There is evidence of immunoreactive epitopes in SARS-CoV-2 sharing similar sequences to host autoantigens involved in Guillain-Barre syndrome and other autoimmune diseases,¹⁸ and there is a massive heptapeptide shared between the SARS-CoV-2 spike protein and the mammalian proteasome.¹⁹ While the pathogenesis of Graves' disease has not been fully elucidated, it involves both genetic and epigenetic factors with environmental factors, including viruses, being a potential trigger for autoimmunity.²⁰ It is known that autoreactive CD4+ helper T cells which have escaped thymic and peripheral editing can

interact with MHC class II molecules presenting thyrotropin receptor peptides leading to the eventual development of the thyroid receptor stimulating antibodies that play a critical role in Graves' disease.²⁰ It is possible that COVID-19 infection could induce autoreactive CD4+ helper T cells and lead to production of thyroid receptor stimulating antibodies through either the dysregulated immune response to SARS-CoV-2 or molecular mimicry with expression of autoantigens similar to thyrotropin receptor peptides.

Interestingly, there are also 2 reported cases of Graves' disease²¹ and 1 case of thyroiditis²² that developed 3 to 10 days after injection of the Pfizer-BioNTech COVID-19 vaccine. This mRNA vaccine encodes a SARS-CoV-2 membrane-anchored spike protein,²³ giving credence to the idea of molecular mimicry driving the autoimmune thyroid disease seen post SARS-CoV-2 infection. An alternative explanation is that an adjuvant used in the vaccine could have caused such a reaction.

Conclusion

COVID-19 can be a precipitating factor for severe thyrotoxicosis requiring hospitalization, and PCR testing should be considered in hyperthyroid patients when an obvious cause cannot be identified. This may have important implications for infection control and monitoring for signs of respiratory compromise. SARS-CoV-2 may also be a potential precipitant for new onset Graves' disease. Further studies are needed to demonstrate if this is a causal relationship, and if so, what the potential mechanisms may be.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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