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Case Report

Graves' Thyrotoxicosis Following SARS-CoV-2 Infection

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ABSTRACT

Objective: Graves' disease is an autoimmune thyroid disease that is thought to develop following environmental exposure in patients with genetic predisposition. Our objective is to present the first report of Graves' disease onset immediately following recovery from mild coronavirus disease 2019 (COVID-19), a close temporal occurrence that should be studied further.

Methods: We describe the clinical course and laboratory features, including thyroid function studies, antibody testing, and polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2.

Results: A 21-year-old woman with prediabetes, obesity, asthma, and gastroesophageal reflux disease presented to the emergency department reporting 3 days of tachycardia, palpitations, anxiety, and shortness of breath. Laboratory investigation revealed a thyroid-stimulating hormone level of 0.01 (0.30-5.00) mcIU/mL with a free thyroxine level of 3.8 (0.6-1.6) ng/dL, prompting endocrinology consultation. On physical examination, she had mild diffuse thyromegaly without tenderness and a history, which included hypothyroidism in her mother. Antibody testing results demonstrated thyroid-stimulating immunoglobulin and thyrotropin receptor antibody levels of 2.6 (<1.3) thyroid-stimulating immunoglobulin index and 17 (0.00-1.75) IU/L, respectively. Sixteen days before presenting to the ED, she was diagnosed with COVID-19 by polymerase chain reaction test after reporting typical symptoms, including fever. Infectious symptoms resolved within 10 days. She achieved clinical and laboratory improvements with a combination of methimazole and beta blocker therapy.

Conclusion: This case documents the occurrence of Graves' thyrotoxicosis following mild symptomatic COVID-19. Whether the preceding infection is coincidental or contributed to GD development requires definitive studies. This presentation may align with the theory of a viral link in the development of autoimmune thyroid disease in those with genetic predisposition.

Introduction

Graves' disease (GD) is an autoimmune syndrome of hyperthyroidism typically accompanied by an enlarged thyroid gland and occasionally ocular and dermatologic manifestations. The excess stimulation of thyroid-stimulating hormone (TSH) receptors by thyroid receptor antibodies generates an unregulated production and secretion of thyroid hormone, resulting in clinical thyrotoxicosis.[1] Current research supports genetic susceptibility and epigenetic modulation as key factors in the pathogenesis of GD, with contribution from environmental factors, including exposure to iodine, medications, stress, smoking, and certain viral infections.[2,3]

We describe a previously unreported case of GD development in a close temporal occurrence to coronavirus disease 2019 (COVID-19) infection.

Case Report

A 21-year-old female healthcare worker presented to the emergency department (ED) for 3 days of progressively worsening tachycardia with palpitations, anxiety, and shortness of breath. Six days prior to the ED visit, she had a complete resolution of symptoms from mild COVID-19, which included fever, cough, myalgias, and anosmia. Diagnosis had been confirmed with positive oropharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). She did not require hospitalization or

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; GD, Graves' disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T4, thyroxine; TSH, thyroid-stimulating hormone.

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Table
Clinical Laboratory Results

Measure	Reference range	5 years prior[a]	1 year prior[a]	Day 16[b]	Day 24[b]	Day 58[b]	Day 107[b]	Day 137[b]	Day 171[b]
FT4, ng/dL	0.6-1.6			3.6	3.8	3.2	1.4	1.4	1.0
FT3, pg/mL	2.2-3.9				15.2				
TSH, mcIU/mL	0.30-5.00	2.14	1.41	0.01	<0.01	<0.01	0.01	0.01	0.03
TRAb, IU/L	0.00-1.75				17				
TSI, TSI index	≤1.3				2.6				

Abbreviations: FT3 = free triiodothyronine; FT4 = free thyroxine; TSH = thyrotropin; TRAb = TSH receptor antibodies; TSI = thyroid-stimulating immunoglobulin.
[a] Prior to COVID-19 diagnosis.
[b] Following COVID-19 diagnosis.

treatment for COVID-19 beyond intermittent over the counter analgesic use. Further medical history includes mild intermittent asthma, gastroesophageal reflux disease, and class-I obesity as well as prediabetes managed with lifestyle modifications. Family history includes diabetes in both parents and hypothyroidism in her mother.

ED records reviewed note that the patient presented with a warm and flushed appearance, tachycardic at 120 to 140/min, with shortness of breath, and mild anxiety. She was afebrile. Initial blood pressure was 150/93 mm Hg, with an oxygen saturation of 100%. Electrocardiogram was obtained, which demonstrated sinus tachycardia, and interpreted as otherwise normal by attending physicians. She was given 5 mg of oral diazepam, and a stat chest computed tomography with angiography was performed owing to suspicion of pulmonary embolism or parenchymal disease. The radiologist interpreted this study as within normal limits; it revealed that an incidental intrapulmonary lymph node, with no evidence of pulmonary embolism or right heart strain, no pleural effusions, and no pneumothorax. Laboratory testing was also performed, and complete blood count showed white blood cell, neutrophil, hemoglobin, and platelet counts of 10.26 $\times$ 10^3/μL (4.00-10.80 $\times$ 10^3/μL), 70.8% (35.0%-80.0%), 13.5 (12.0-16.0) g/dL, and 288 $\times$ 10^3/μL (140-400 $\times$ 10^3/μL), respectively. Comprehensive metabolic panel revealed glucose, sodium, potassium, and creatinine levels of 114 (70-99) mg/dL, 138 (134-146) mmol/L, 4.2 (3.4-5.0) mmol/L, and 0.50 (0.50-1.10) mg/dL, respectively. Point of care urine pregnancy test was negative. High-sensitivity troponin assay was <6 (<14) ng/L. Following the intravenous administration of a benzodiazepine as well as 2 L of normal saline and 1000 mg of acetaminophen, the patient reported improvement in symptoms; however, she remained tachycardic at 115/min. This prompted consideration for thyroid abnormality, and thyroid function tests were obtained. Results of the thyroid studies were pending at the time of discharge from the ED and were only available the following day, demonstrating a TSH level of 0.01 (0.30-5.00) mcIU/mL with a free thyroxine (T4) level of 3.8 (0.6-1.6) ng/dL. These results were conveyed to our endocrinology practice, and she was scheduled for an urgent consultation. Notably, the patient had normal TSH results 1 and 5 years prior to presentation (Table). At follow-up, the patient reported palpitations and shortness of breath with minimal exertion as well as heat intolerance with excessive sweating and increased anxiety. On physical exam, she was tachycardic. Mild diffuse thyromegaly without tenderness was present as well as fine bilateral hand tremors and hyperreflexia. No ocular or dermatologic symptoms were observed. Laboratory test results revealed TSH, free T4, free triiodothyronine , thyroid-stimulating immunoglobulin, and thyrotropin receptor antibody levels of <0.01 (0.30-5.00) mcIU/mL, 3.6 (0.6-1.6) ng/dL, 15.2 (2.2-3.9) pg/mL, 2.6 (<1.3) thyroid-stimulating immunoglobulin index, and 17 (0.00-1.75 IU/L) IU/L, respectively (Table). A thyroid scan with radioactive iodine uptake was not pursued. Her symptoms were initially managed with a selective beta blocker twice daily, and following results of the antibody testing, methimazole was prescribed. Thyroid function tests 1 month later were similar with TSH (0.1 [0.30-5.00] mcIU/mL) and free T4 (3.2 [0.6-1.6 ng/dL] ng/dL), prompting an increase in the methimazole dose to 30 mg daily. Three months after the diagnosis of GD, the patient came to the office for follow-up. Clinically euthyroid on exam, her TSH level was 0.01 (0.30-5.00) mcIU/mL with a free T4 level of 1.4 (0.6-1.6) ng/dL. The patient continues to be medically managed with thionamide titration and plans a trial discontinuation of the beta blocker.

Discussion

We report the development of GD in a patient very recently recovered from a mild SARS-CoV-2 infection. Previous testing of thyroid function was normal, and she had no clinical signs or symptoms of hyperthyroidism prior to her illness with COVID-19. Whether COVID-19 contributes to the development of GD, or the occurrence is coincidental, requires definitive studies. The relationship between GD and viral triggers has yet to be conclusively established despite suggestive epidemiologic evidence. Studies have proposed various potential mechanisms for GD development, such as antigen exposure, molecular mimicry, cytokine release, and inflammatory response.[4–6] Case reports have documented GD following subacute thyroiditis, a viral infection of the thyroid.[7,8] Severe acute respiratory syndrome coronavirus, the virus responsible for severe acute respiratory syndrome, was found to cause extensive damage to the thyroid glands. Furthermore, clinicians have linked subacute thyroiditis with SARS-CoV-2, the related novel coronavirus responsible for COVID-19.[9–12] Though stress related to the infection may be an independent trigger unrelated to the specific viral syndrome, this is considered less likely, given the mild nature of initial illness. Family history in this case also supports the theory of genetic predisposition with external triggers.

Conclusion

This is the first case report, of which we are aware, suggesting SARS-CoV-2 as a potential viral trigger for the development of GD. This finding reinforces the need to better elucidate the relationship between viral infection and autoimmune thyroid disease as well as the direct effects of coronaviruses on the thyroid.

Disclosure

The authors have no multiplicity of interest to disclose.

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