

Case Report

A case report of Graves' disease following SARS-CoV-2 infection

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ABSTRACT

SARS-CoV-2 pandemic has had significant impacts on the world. The longer the pandemic continues the more we learn about the virus behind it and the post-infection complications. SARS-CoV-2 infections have been associated with immune dysfunction and thyroid disease. The spectrum of thyroid disease reported spans from subacute thyroiditis to Hashimoto's thyroiditis. We report a 16-years-old patient whose COVID-19 infection was followed by multiple complications including the appearance of symptomatic Graves' disease. Laboratory analysis was significant for elevated TSH, low free thyroxine, and antibodies consistent with the diagnosis of Graves' disease. This is the first case of Graves' disease after COVID-19 infection to be reported and the first case of thyroid dysfunction secondary to COVID-19 infection reported in the pediatric population. The spectrum of thyroid and autoimmune disease following COVID-19 is discussed. Further research into the underlying pathology behind COVID-19 infection and immune dysfunction will lead to expedited diagnosis and improved patient outcomes.

Keywords: COVID-19, SARS-CoV-2, Thyrotoxicosis, Autoimmune, Graves' disease, Hyperthyroidism

INTRODUCTION

The COVID-19 pandemic has been a once-in-a-generation event that has impacted nearly every facet of life for billions of people around the globe. Even though it has been more than a year since the pandemic began, we are still just seeing the beginnings of the ripples SARS-CoV-2 has left in its wake.

In addition to the primary infections and lives lost due to the virus, a slew of post-viral illness is being reported in all age groups around the world. Among these are numerous auto-immune conditions including diseases affecting the thyroid. This case report describes a case of Graves' disease in a pediatric patient with several other post-COVID sequelae.¹⁻²⁰

This is the first known case report linking Graves' disease with COVID-19 in any patient population.

CASE REPORT

A 16-years-old male was admitted to the hospital fall 2020 because of shortness of breath, chest pain and anxiety. Patient was in his usual state of good health until two months before admission, when he developed diminished sense of smell, cough, chills, nausea, and fatigue. Nasal pharyngeal SARS-CoV2 PCR swab was positive. After seven days the patient improved and briefly returned to his usual state of good health. However, 19 days after symptom onset his temperature rose to 39.7°C and he developed myalgia, nausea, vomiting and shortness of breath.

Five days later he was seen in the emergency department for shortness of breath. His blood pressure was 146/78 mmHg, heart rate was 98, oxygen saturation was 98%. On examination, he was in no acute distress, and his lungs were clear. Complete blood count, complete metabolic panel, and troponin were all within normal limits. Rapid

test for influenza A and B were negative. D-dimer was elevated at 0.55 (normal<0.27). Computerized tomography of the chest did not demonstrate infiltrates or pulmonary embolism. He was treated with ondansetron and discharged home.

He continued to have fatigue, headache, dizziness with exertion, and temperatures at home of 37.2-38.0°C. Three weeks prior to admission (six weeks after symptom onset) his blood pressure was 150/82 mmHg. Echocardiogram showed thickened anterior mitral valve leaflet with normal function, mild central aortic valve regurgitation, normal left ventricular systolic function, and no pericardial effusion. Electrocardiogram showed sinus tachycardia with short PR interval. Lisinopril was prescribed.

Two weeks before admission he developed tremor and anterior neck pain. One week before admission blood pressure was 150/94 mmHg, heart rate was 106 beats per minute. Erythrocyte sedimentation rate (ESR) was 12.0 mm/hr (normal=0.0-15.0) and C-reactive protein (CRP) was <0.10 mg/dl (normal range=0.00-0.50).

On the day of admission, he returned to the emergency department with complaints of shortness of breath, chest pain, and worsening anxiety. He reported ongoing tremor but denied abdominal pain, headache, diarrhoea, vomiting, or rash. His immunizations were up to date. He was a student at a local high school, and he denied using tobacco, alcohol, or illicit drugs. On examination, he was afebrile, blood pressure was 137/80 mmHg, heart rate 107 beats per minute, respiratory rate 20 breaths per minute, oxygen saturation 98% on room air. He was alert, oriented, and cooperative during the examination. His thyroid was enlarged and tender. He had no proptosis. The lungs were clear to auscultation. He had tremor in both hands.

Laboratory analysis revealed a thyroid stimulating hormone (TSH) level of <0.005 mcunit/ml (normal=0.27-4.20) and free thyroxine level of >7.77 ng/dl (normal=0.93-1.70) which was consistent with hyperthyroidism. As part of further evaluation, the following antibodies were ordered but did not result for several days: thyrotropin receptor antibody 7.12 IU/l (normal=0.00-1.75), thyroid peroxidase antibody 247 IU/ml (normal≤34), thyroglobulin antibody 306 IU/ml (normal≤115). Additional lab data show in Table 1.

Chest radiograph revealed no acute cardiopulmonary findings. Thyroid ultrasound demonstrated diffuse enlargement with heterogenous echogenicity of bilateral thyroid lobes and isthmus with multiple small hypoechoic nodules. No focal calcification or discrete lesion. Given his laboratory findings, a diagnosis of thyrotoxicosis secondary to Graves' disease was made. Methimazole and propranolol were prescribed.

Two months after discharge he was much improved without syncope, presyncope, chest pain, palpitations, exercise intolerance, or shortness of breath.

Table 1: Additional laboratory data.

Laboratory data	Reference range	On admission
Hemoglobin (g/dl)	13.5-17.5	14.7
Hematocrit (%)	38.8-50.0	42.7
White blood cell count (per mm³)	3.50-10.50	5.82
Creatinine (mg/dl)	0.70-1.20	0.50
Albumin (g/dl)	3.2-4.5	4.6
TSH (mcunit/ml)	0.27-4.20	<0.005
Free thyroxine (ng/dl)	0.93-1.70	>7.77
T4 (mcg/dl)	4.5-11.7	24.9
Total T3 (ng/ml)	0.8-2.0	6.5
Free T3 (pg/ml)	2.0-4.4	>32.5
Thyroid peroxidase antibody	≤34	247
Thyroglobulin antibody (IU/ml)	≤115	306
Thyrotropin receptor antibody (IU/ml)	0.00-1.75	7.12
TSI-mayo	<1.3	4.7
Troponin T (ng/ml)	0.00-0.01	<0.01
D-Dimer (mcg/ml FEU)	0.00-0.50	0.36

DISCUSSION

Graves' disease is an autoimmune condition associated with activating autoantibodies that target the TSH receptor. The antibodies activate the receptor leading to excess production of thyroid hormone and hyperthyroidism. There are multiple causes of hyperthyroidism, but Graves' disease is the most common. Our patient demonstrated symptoms of hyperthyroidism including palpitations, tachycardia, tremor, and increased anxiety. The diagnosis of Graves' disease is based on a combination of clinical and biochemical findings.²¹ Our patient had suppressed TSH levels that were undetectable, elevated thyroid hormone levels, and thyrotropin receptor antibodies, which in addition to his clinical findings confirm the diagnosis of Graves' disease. Prompt and accurate diagnosis of Graves' disease is crucial because unrecognized and untreated Graves' disease can have deleterious consequences. Accuracy of diagnosis is also critical as Graves' disease is just one of the many etiologies of hyperthyroidism and the primary treatment can potentially have serious side effects.

SARS-CoV-2 and the resulting COVID-19 pandemic have affected millions worldwide. Several types of thyroid disease have been associated with SARS-CoV-2 infections. The most frequently cited thyroid complication of COVID-19 is subacute thyroiditis (SAT); therefore SARS-CoV-2 joins the long list of viruses linked to SAT.^{1-4,6,9,13-16} Our patient had neck pain, a cardinal feature of SAT. However, it was not his primary complaint, and neck pain has also been reported with Graves' disease.^{22,23} Further, he did not have elevations of inflammatory

markers such as CRP and ESR generally associated with SAT. SARS-CoV-2 has been associated with other thyroid disease. Thyrotoxicosis was present in 20% of COVID-19 patients in one case series of hospitalized, non-ICU patients.¹⁰ One case report describes Hashimoto's thyroiditis and hypothyroidism associated with COVID-19.¹⁷ We believe this is the first case report of a patient who developed Graves' disease after COVID-19, and also the first case report highlighting the association of thyrotoxicosis or Graves' disease with COVID-19 in the pediatric population.

A growing body of evidence suggests that SARS-CoV-2 infection may precede the appearance of autoimmune and autoinflammatory disorders.⁸ The underlying pathophysiology behind this relationship is unclear, but has been proposed to be a consequence of transient immunosuppression in which self-tolerance is lost, and an inappropriate form of immune reconstitution.⁵ COVID-19 infection has been associated with Guillain-Barre, antiphospholipid syndrome, systemic lupus erythematosus, autoimmune hemolytic anemia, and immune thrombocytopenic purpura.^{11,12,18-20} In children, the most well-known autoinflammatory disorder associated with COVID-19 is Multisystem Inflammatory Syndrome in Children (MIS-C).⁷ Our patient had features of MIS-C, including prolonged temperature elevation and multi-organ cardiac and gastrointestinal involvement. However, his ESR and CRP were normal, and therefore he did not meet the criteria for laboratory evidence of inflammation in MIS-C.⁷ Given the known association between COVID-19 and other forms of thyroid dysfunction and post-COVID-19 autoimmune disorders, it is reasonable to conclude that the development of Graves' disease was related to his COVID-19 illness.

CONCLUSION

This is the first reported case of Graves' disease related to COVID-19 and highlights an important complication of COVID-19 infection that clinicians should consider to avoid delay in diagnosis. Our report adds to the growing body of evidence linking COVID-19 with subsequent presentation of autoimmune conditions. Further research and reports on the association between COVID-19 and its various complications would improve our understanding of the illness and ultimately lead to improved diagnostics, treatment, and patient outcomes.

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