OXFORD

Oxford Medical Case Reports, 2023, **5**, 195–197
https://doi.org/10.1093/omcr/omad050
Case Report

Acute febrile illness in a teenage female with history of Graves' disease

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Abstract

Thyroid storm is a rare, life-threatening condition that is usually precipitated by Graves' disease in children and adolescents. COVID-19 (SARS-CoV-2) can cause multisystem inflammatory syndrome in children (MIS C), which shares some features of Graves' disease. We present a case of acute thyroid storm following SARS-CoV-2 infection in a 16-year-old female with poorly controlled Graves' disease. She initially presented to the emergency department for fever and palpitations. Initial laboratory results suggested thyroid storm, for which she was started on propranolol. She remained tachycardic with new gallop rhythm on exam. An echocardiogram demonstrated a depressed left ventricular ejection fraction and mild pulmonary hypertension. Her SARS-CoV-2 antibodies were positive. She was started on intravenous immunoglobulin for suspected MIS-C. She responded to combined treatment of thyroid storm and MIS-C. She was discharged home on propranolol, methimazole, cholestyramine and aspirin.

INTRODUCTION

We present a 16-year-old female with history of Graves' disease who presented to the emergency department (ED) with 3-day history of palpitations, fevers and one-day history of chest pain. On exam, she had a tender goiter and was tremulous. Due to SARS-CoV-2 infection one-month prior, additional laboratory evaluation for MIS-C was performed. Our case report describes her hospital course and convalescence.

CASE REPORT

Our patient was first diagnosed with Graves' disease at 15 years of age; initial labs showed suppressed thyroid stimulation hormone (TSH), elevated free thyroxine (Free T4) and a positive thyroid stimulating immunoglobulin (TSI). She received methimazole 20 mg/day and atenolol 50 mg/day. She did not achieve euthyroidism after five months of therapy due to poor medication adherence. One month prior to admission, she presented to the ED for fevers, myalgias and sore throat. Laboratory demonstrated positive COVID-19 (SARS-CoV-2) antigen screen. Her TSH and free T4 were < 0.015 μIU/mL and > 6.99 ng/dL, respectively. Medication compliance was reinforced.

At the current ED visit, she had normal mentation and denied any gastrointestinal symptoms. She was febrile to 39.2°C with a heart rate of 170 BPM and blood pressure of 145/72 mm Hg. Initial labs (Table 1) showed elevated AST/ALT, suppressed TSH and elevated free T4/free T3. On exam, she had a tender goiter and appeared tremulous. Based on the Burch-Wartofsky Point Scale (Score > 45) and a Japanese Thyroid Association (Score > 5), the patient met clinical criteria for possible thyroid storm [1]. Endocrinology was consulted, and her beta-blocker was changed from atenolol to propranolol (20 mg TID). Cardiology was consulted due to tachycardia and hypertension. An electrocardiogram demonstrated sinus tachycardia. Due to history of SARS-CoV-2 infection, additional laboratory evaluation for MIS-C was performed per our hospital's MIS-C evaluation guidelines, which are derived from the Children's Hospital of Philadelphia's and the American College of Rheumatology guidelines [2]. MIS-C labs are indicated in Tables 1 and 2. She received IV morphine sulfate, normal saline bolus and ibuprofen with a decrease in heart rate to 132 BPM. She was then admitted to the inpatient service on methimazole 40 mg daily (0.6 mg/kg/day), propranolol 20 mg TID (1 mg/kg/day), with the addition of Lugol's iodine (0.6 mg/kg/day) and cholestyramine 4 mg BID (0.1 g/kg/day) for possible thyroid storm.

She remained tachycardic with a new gallop rhythm on exam. Chest x-ray demonstrated mild cardiomegaly without airspace disease. An echocardiogram demonstrated an estimated left ventricular ejection fraction (LVEF) of 45–50% (normal $> 55\%$), slightly echogenic proximal coronary arteries with mild ectasia and trace pericardial effusion. Laboratory tests were serially monitored which demonstrated an up-trending Troponin I, BNP, C reactive protein and D dimer. She received a hydrocortisone bolus of 100 mg IV followed by 25 mg IV every 6 hours

Received: January 10, 2023. **Revised:** March 8, 2023. **Accepted:** March 31, 2023

Table 1. Initial laboratory findings

Initial labs	Value	Reference ranges
TSH	< 0.015 μIU/mL	Normal low > 0.5 μIU/mL and normal high < 4.5 μIU/mL
Free T4	> 6.99 ng/mL	Norma low > 0.8 ng/mL and normal high < 2.00 ng/dL
Free T3	> 30 pg/mL	Normal low > 2.18 pg/mL and normal high < 3.98 pg/mL
BNP	20.0 pg/mL	Normal high < 100 pg/mL
Troponin-I	0.078 ng/mL	Normal high < 0.034 ng/mL
SARS-CoV-2 antibodies	46.30 index value	Normal < 0.99
CRP	23.3 mg/L	Normal high < 9 mg/L
ESR	58 mm/hr	Normal high < 20 mm/hr
Absolute lymphocyte count	2.81 thou/μL	Normal low > 1.3 thou/μL and normal high < 5.94 thou/μL
LDH	820 unit/L	Normal low > 340 unit/L and normal high < 670 unit/L
AST	105 unit/L	Normal low > 5 unit/L and normal high < 30 unit/L
ALT	118 unit/L	Normal low > 10 unit/L and normal high < 35 unit/L
Ferritin	120 ng/mL	Normal low > 10 ng/mL and normal high < 70 ng/mL
Fibrinogen	554 mg/dL	Normal low > 181 mg/dL and normal high < 445 mg/dL
D Dimer	0.68 mcg FEU/mL	Normal high < 0.44 mcg FEU/mL

Table 2. Hospital summary

Hospital day	Clinical course
Day 1	Admitted for thyroid storm versus MIS-C, started on propranolol and methimazole per endocrinology
	Cardiology consulted for concerns cardiac dysfunction secondary to thyrotoxicosis
Day 2	New gallop rhythm. Troponin I and BNP stable
	COVID 19 (SARS-CoV-2) antibodies elevated
	Started on cholestyramine, Lugol's iodine and given hydrocortisone for worsening thyroid storm
	Acutely worsened requiring oxygen and transferred to PICU
	Stat echocardiogram performed. LVEF 45–50%
Day 3	Troponin I and BNP trended up. Troponin peaked at 1.89 ng/mL and BNP at 1215 pg/mL
	Started on BiPAP
	Chest CT angiogram ruled out pulmonary emboli
	Rheumatology consulted for MIS-C
	Started on IVIG and methylprednisolone for MIS-C
	Continued propranolol, methimazole, Lugol's iodine and cholestyramine
	Follow up echocardiogram showed LVEF of 55–60%
Day 4	Troponin and Free T4 trending downwards
	Vital signs improving and weaned to high flow nasal cannula
	Started on anakinra and aspirin for MIS-C
Day 5	Continued to improve and was transferred out of the PICU
	Clinically and labs continued to improve
Day 9	Weaned off anakinra and Lugol's Iodine
	Discharged home on prednisone, propranolol, methimazole, cholestyramine and aspirin

(60 mg/m2/day) for possible thyroid storm. She subsequently developed chest pain, shortness of breath, desaturations and worsening tachycardia requiring to the pediatric intensive care unit (PICU).

In the PICU, she was placed on BiPAP. Due to a clinical suspicion of pulmonary embolism, a chest CT angiography demonstrated bilateral consolidative opacities with pleural effusions, but no pulmonary artery emboli. She received IV furosemide with improvement of the pulmonary edema and heart failure symptoms. Rheumatology was consulted, and a clinical diagnosis of MIS-C was made. She received a one-time dose of IVIG within 24 hours from presentation. She was started on aspirin for possible MIS-C. Hydrocortisone was switched to methylprednisolone. Rheumatology started anakinra. After completion of the IVIG, a repeat echocardiogram showed improvement of LVEF to 60–65%. She continued to respond to therapy with improving troponin I and free T4 levels. Plasmapheresis for thyroid storm was considered but not required due to improvement after IVIG.

She continued to improve after transfer to the inpatient service. Her free T4, free and total T3 levels improved, and the Lugol's Iodine was discontinued, and cholestyramine was reduced to 2 mg BID. She was weaned off anakinra and transitioned from methylprednisolone to prednisone taper on day 7 of hospitalization. She was discharged on propranolol (20 mg TID), methimazole (40 mg daily), cholestyramine (2-gram BID) and aspirin (81 mg daily). Two weeks after discharge, she had a normal electrocardiogram and an echocardiogram. She underwent total thyroidectomy about ten weeks after her hospitalization with subsequent levothyroxine replacement therapy.

DISCUSSION

Thyroid storm is rare in pediatrics but has a high mortality rate of up to 10%. Multi-organ failure and congestive heart failure are the most common causes of death [3] Diagnostic criteria have been validated in adults for suspected cases of thyroid storm; however, these criteria have not been validated in children making early diagnosis difficult. [4] The principles of treating thyroid storm include treating any precipitating factors, blocking release of pre-synthesized thyroid hormone, decreasing synthesis of thyroid

hormones, reducing enterohepatic circulation of thyroid hormone, thereby decreasing peripheral effects and cardiovascular complications. [5]

There is limited information about thyroid dysfunction during acute COVID-19 infection in adults and even less in the pediatric population. In a case series of adults hospitalized with SARS-CoV-2 in non-intensive care units, 67% had normal thyroid function, while 20% had thyrotoxicosis and 5% had hypothyroidism. [6] Little is known about the underlying cause of thyroid dysfunction caused by COVID-19. There are a few case reports and abstracts where authors suggested that MIS-C developed from COVID-19 infection leading to thyrotoxicosis secondary from the inflammatory response. [7, 8] Another short article suggests that COVID-19 precipitated thyroid storm from an adrenergic response. [9] Our report is an interesting case of a patient with pre-existing thyrotoxicosis and concurrent COVID-19 infection who developed possible thyroid storm leading to MIS-C. There are multiple potential mechanisms that have been described, including COVID-19 targeting the ACE-2 receptor in the thyroid gland, which may trigger thyroiditis. There are also reports that T4 can also regulate expression of integrin B3, which may contribute to the entry of the coronavirus into thyroid gland. [10]

In conclusion, there are many overlapping features between MIS-C and thyroid storm. It is possible that her clinical course could be explained by thyroid storm alone rather than MIS-C. However, her clinical course worsened despite giving prompt and standard of care treatment of thyroid storm. Hence, the diagnosis of MIS-C was pursued and treatment with IVIG given. She had a favorable response to IVIG with rapid improvement clinically and with down trending TSI titers. It is unclear if the addition of anakinra made a meaningful change to her clinical course. A high degree of suspicion for MIS-C should be held when examining patients with symptoms of thyroid storm and an inadequate response to standard-of-care treatment. There are newer case reports.

ACKNOWLEDGEMENTS

We thank Dr. Chris McDaniel for assistance in the initial clinical care of this patient.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

No funding was secured for this study.

ETHICAL APPROVAL

No ethical approval was required.

CONSENT

Written consent was obtained from the patient for publication of their clinical history.

GUARANTOR

M.A.R., R.A. and A.L. are the guarantors of this work.

DATA AVAILABILITY STATEMENT

The authors confirm that the data available within the manuscript support the findings. There is more data available from the corresponding author, if requests are reasonable.

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